Clinical trial results:
Clot lysis: evaluating accelerated resolution of intraventricular hemorrhage Phase III

Summary

EudraCT number	2008-006916-39
Trial protocol	GB ES DE
Global end of trial date	13 January 2016

Results information

Result version number	v1 (current)
This version publication date	17 October 2019
First version publication date	17 October 2019

Trial information

Trial identification

Sponsor protocol code	IVH06

Additional study identifiers

ISRCTN number	ISRCTN70157009
ClinicalTrials.gov id (NCT number)	NCT00784134
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 8523

Notes:

Sponsors

Sponsor organisation name	Newcastle University, Neurosurgical Trials Unit
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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	15 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 January 2016
Global end of trial reached?	Yes
Global end of trial date	13 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To define precisely the long-term effects of lysing ventricular blood clots with rt-PA on the functional outcomes of cerebral hemorrhage patients. We propose to test if this intervention promotes a recovery of function, as defined as a modified Rankin score of < 3 at 180 days post ictus, by facilitating more rapid clot resolution as compared to treatment with extraventricular drainage (EVD) with placebo.

Protection of trial subjects:

1. Adherence to inclusion and exclusion criteria during screening
2. Explaining potential risks to participants during informed consent
3. Ethical / Institutional Review Board and DSMB team to evaluate safety of the study drug
4. Subject confidentiality
5. Human Subjects Research Training completed for all study staff.
6. Women who become pregnant during the follow-up period will be followed through 12 month visit to document clinical and functional outcome but no CT scans will be done.
7. All subjects stabilized for at least 6 hours prior to the first dose of test article.
8. All adverse events monitored throughout the initial hospitalization and during the 12 month follow-up period
9. All infections will be reported to the safety and monitoring committee for an independent assessment of clinical significance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 370

Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Israel: 37
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	500
EEA total number of subjects	76

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)	354
From 65 to 84 years	146
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants aged 18–80 years with known symptom onset within 24 h of the initial CT scan confirming intraventricular haemorrhage and 3rd or 4th ventricle obstruction were recruited to participate in the study.

Pre-assignment

Screening details:

Eligibility criteria included supratentorial intracerebral haemorrhage volume 30 mL or less, measured by the ABC/2 method,18,19 and clot stability (no measured expansion >5 mL) on repeat CT scan at least 6 h after extraventricular drain placement

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Alteplase

Arm description:

Administration of alteplase via the intraventricular catheter
1.0 mg of alteplase will be administered via the intraventricular catheter every 8 hours for up to 12 doses
Other Names: Cathflo Activase, rt-PA

Arm type	Experimental
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	rtPA, Cathflo Activase
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraventricular use

Dosage and administration details:

1.0 mg of alteplase will be administered via the intraventricular catheter every 8 hours for up to 12 doses

Arm title	Saline Placebo

Arm description:

1 ml of normal saline administered via the intraventricular catheter
Normal saline: 1 ml of normal saline will be administered via the intraventricular catheter every 8 hours for up to 12 doses

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraventricular use

Dosage and administration details:

1 ml of normal saline administered via the intraventricular catheter

Number of subjects in period 1	Alteplase	Saline Placebo
Started	249	251
Completed	246	245
Not completed	3	6
Lost to follow-up	3	6

Baseline characteristics

Reporting groups	
Reporting group title	Alteplase
Reporting group description:	
Administration of alteplase via the intraventricular catheter 1.0 mg of alteplase will be administered via the intraventricular catheter every 8 hours for up to 12 doses Other Names: Cathflo Activase, rt-PA	
Reporting group title	Saline Placebo
Reporting group description:	
1 ml of normal saline administered via the intraventricular catheter Normal saline: 1 ml of normal saline will be administered via the intraventricular catheter every 8 hours for up to 12 doses	

Reporting group values	Alteplase	Saline Placebo	Total
Number of subjects	249	251	500
Age categorical 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)	182	172	354
From 65-84 years	67	79	146
85 years and over	0	0	0
Age continuous Units: years			
median	59	59	
inter-quartile range (Q1-Q3)	51 to 66	51 to 67	-
Gender categorical Units: Subjects			
Female	105	117	222
Male	144	134	278
Race Units: Subjects			
American Indian or Alaskan Native	0	1	1
Asian	7	7	14
Native Hawaiian or Other Pacific Islander	3	1	4
Black or African American	92	78	170
White	144	161	305
More than one race	0	1	1
Unknown or Not reported	3	2	5
Region of enrollment Units: Subjects			
Canada	3	6	9

Hungary	7	6	13
United States	190	180	370
Brazil	1	3	4
United Kingdom	4	4	8
Israel	13	24	37
Switzerland	1	3	4
Germany	21	18	39
Spain	9	7	16

End points

End points reporting groups

Reporting group title	Alteplase

Reporting group description:

Administration of alteplase via the intraventricular catheter
1.0 mg of alteplase will be administered via the intraventricular catheter every 8 hours for up to 12 doses
Other Names: Cathflo Activase, rt-PA

Reporting group title	Saline Placebo

Reporting group description:

1 ml of normal saline administered via the intraventricular catheter
Normal saline: 1 ml of normal saline will be administered via the intraventricular catheter every 8 hours for up to 12 doses

Primary: 1. Participants With Modified Rankin Scale (mRS) <=3 - Dichotomized Analysis

End point title	1. Participants With Modified Rankin Scale (mRS) <=3 - Dichotomized Analysis

End point description:

Analysis modified on September 29, 2015 to account for adaptive randomization. The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from: 0=No symptoms at all, 1=No significant disability, 2=Slight disability, 3=Moderate disability, 4=Moderately severe disability, 5=Severe disability and 6=death. The dichotomized scores are as follows: 0-3=No symptoms to moderate disability requiring some assistance; 4-6=Moderately severe disability requiring complete assistance to death.
All the non-missing mRS scores at 180 days were analyzed. Number and proportions reported refer to number of participants with Modified Rankin Score 0-3

End point type	Primary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[1]	245[2]		
Units: Number of participants	117	110		

Notes:

[1] - All patients with non-missing data at 180 days were analysed

[2] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo

Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.554
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.027
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.062
upper limit	0.115

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Multivariable logit model adjusted for age, GCS, thalamus, stability ICH volume and stability IVH volume.	
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.87

Primary: 2. Participant Score on the Modified Rankin Scale (mRS) - Ordinal Analysis	
End point title	2. Participant Score on the Modified Rankin Scale (mRS) - Ordinal Analysis
End point description:	

End point type	Primary
End point timeframe:	
180 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[3]	245[4]		
Units: Unit of measure				
median (inter-quartile range (Q1-Q3))	4 (3 to 5)	4 (3 to 6)		

Notes:

[3] - All patients with non-missing data at 180 days were analysed

[4] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.484
Method	Generalized ordered Logit model
Parameter estimate	Odds ratio (OR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.25

Notes:

[5] - Generalized ordered logit model adjusted for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical) compares odds ratio for mRS score > K v. <= K for K = 1 - 4; Alt v. Sal.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	< 0.001
Method	Generalized ordered Logit model
Parameter estimate	Odds ratio (OR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.71

Notes:

[6] - The same generalized ordered logit model, adjusting for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical), compares odds ratio for mRS score greater than 5 versus mRS score
equal or less than 5 (dead versus alive).

Primary: 3. Participants With Modified Rankin Scale (mRS) <=4 - Dichotomized Analysis

End point title	3. Participants With Modified Rankin Scale (mRS) <=4 - Dichotomized Analysis

End point description:

The modified Rankin Scale (mRS) is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from: 0=No symptoms at all, 1=No significant disability, 2=Slight disability, 3=Moderate disability, 4=Moderately severe disability, 5=Severe disability and 6=death. Dichotomized scores are: 0-4=No symptoms to moderately severe disability requiring some assistance; 5-6=Severe disability requiring complete assistance to death.

End point type	Primary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[7]	245[8]		
Units: Number of participants	158	151		

Notes:

[7] - All patients with non-missing data at 180 days were analysed

[8] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.552
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.059
upper limit	0.111

Statistical analysis title	Statistical Analysis 2
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35 [9]
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.9

Notes:

[9] - Multivariable logit model adjusting for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical).

Primary: 4. Random Effects Assessment of Site Effect on Modified Rankin Scale (mRS) <= 3

End point title	4. Random Effects Assessment of Site Effect on Modified Rankin Scale (mRS) <= 3

End point description:

Dichotomized, adjudicated, cross-sectional modified Rankin Scale (mRS) score 0-3 vs. 4-6 at 180 days post-ictus. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from: 0=No symptoms at all, 1=No significant disability, 2=Slight disability, 3=Moderate disability, 4=Moderately severe disability, 5=Severe disability and 6=death. Dichotomized scores are: 0-3=No symptoms to moderate disability requiring some assistance; 4-6=Moderately severe disability requiring complete assistance to death

End point type	Primary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[10]	245[11]		
Units: Number of participants	117	110		

Notes:

[10] - All patients with non-missing data at 180 days were analysed

[11] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.428 [12]
Method	Random Effects Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.8

Notes:

[12] - Random effects model with site as random effect adjusted for age GCS, thalamus, stability ICH volume and stability IVH volume (categorical).

Primary: 5.Longitudinal Assessment of Participants With Modified Rankin Scale (mRS) <=3

End point title	5.Longitudinal Assessment of Participants With Modified Rankin Scale (mRS) <=3

End point description:

Comparing longitudinal modified Rankin Scale (mRS) scores 0-3 at Day 30 and Day 180. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death). It is scored from: 0=No symptoms at all, 1=No significant disability, 2=Slight disability, 3=Moderate disability, 4=Moderately severe disability, 5=Severe disability and 6=death. Dichotomized scores are: 0-3=No symptoms to moderate disability requiring some assistance; 4-6=Moderately severe disability requiring complete assistance to death.

End point type	Primary

End point timeframe:

30 days and 180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[13]	245[14]		
Units: Number of participants				
Day 30	50	41		
Day 180	110	117		

Notes:

[13] - All patients with non-missing data at 30 days and 180 days were analysed

[14] - All patients with non-missing data at 30 days and 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Logit mRS scores 0-3 at 30 days	
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.384 [15]
Method	Generalized Estimating Equation
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	2.1

Notes:

[15] - Generalized estimating equation model adjusting for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical)

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Logit mRS scores 0-3 at 180 days	
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.964 [16]
Method	Generalized Estimating Equation model
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.64

Notes:

[16] - Generalized estimating equation model adjusting for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical).

Secondary: 6. All Cause Mortality

End point title	6. All Cause Mortality
End point description:	
All cause mortality among all patients that were enrolled in CLEAR III were analyzed	
End point type	Secondary
End point timeframe:	
180 Days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Numberof participants	46	73		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	Logrank

Secondary: 7. Clot Removal (Amount of Residual Blood)	
End point title	7. Clot Removal (Amount of Residual Blood)
End point description: Change in blood volume measured between stability scan and end of treatment scan	
End point type	Secondary
End point timeframe: 72 hours	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: odds ratio per time -weighted mL				
number (not applicable)	0.96	0.97		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	AUC/Logit Model

Secondary: 8. Intensity of Critical Care Management - Hospital Days	
End point title	8. Intensity of Critical Care Management - Hospital Days
End point description: Intensity of critical care management as measured by hospital length of stay.	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number				
median (inter-quartile range (Q1-Q3))	23 (17 to 31)	24 (16 to 31)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771
Method	Kruskal-wallis

Secondary: 9. Intensity of Critical Care Management - ICU Days	
End point title	9. Intensity of Critical Care Management - ICU Days
End point description: Intensity of critical care management as measured by ICU length of stay.	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number				
median (inter-quartile range (Q1-Q3))	14 (11 to 21)	15 (12 to 22)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	Kruskal-wallis

Secondary: 10. Intensity of Critical Care Management - ICP Management	
End point title	10. Intensity of Critical Care Management - ICP Management
End point description: Intensity of critical care management as measured by frequency of ICP >20 mmHg events	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of events of ICP >20mmHg	24	26		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Generalized Linear Models

Secondary: 11. Intensity of Critical Care Management - Mechanical Ventilation	
End point title	11. Intensity of Critical Care Management - Mechanical Ventilation
End point description: Intensity of Critical Care Management as measured by Mechanical Ventilation	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants with ventilation	184	192		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.501
Method	Chi-squared

Secondary: 12. Intensity of Critical Care Management - Pressors

End point title	12. Intensity of Critical Care Management - Pressors
End point description: Intensity of critical care management as measured by pressors	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	60	63		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.795
Method	Chi-squared

Secondary: 13. Intensity of Critical Care Management - Shunts

End point title	13. Intensity of Critical Care Management - Shunts
End point description: Intensity of critical care management as measured by shunts	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	46	44		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.784
Method	Chi-squared

Secondary: 14. Intensity of Critical Care Management - All Infections

End point title	14. Intensity of Critical Care Management - All Infections
End point description: Intensity of Critical Care Management as measure by all infections	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	120	127		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.592
Method	Chi-squared

Secondary: 15. Intensity of Critical Care Management - Pneumonia

End point title	15. Intensity of Critical Care Management - Pneumonia
End point description:	
Intensity of Critical Care Management as measured by Pneumonia	
End point type	Secondary
End point timeframe:	
30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	65	82		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	Chi-squared

Secondary: 16. Intensity of Critical Care Management - All Infections

End point title	16. Intensity of Critical Care Management - All Infections
End point description:	
Intensity of critical care management as measured by all infections at 180 days	
End point type	Secondary
End point timeframe:	
180 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	124	141		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.152
Method	Chi-squared

Secondary: 17. Safety/Mortality - Mortality Within 30 Days

End point title	17. Safety/Mortality - Mortality Within 30 Days
End point description: Frequency of mortality within 30 days	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	22	36		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo

Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.055
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-0.055
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.111
upper limit	0.008

Secondary: 18. Safety/Mortality - Bacterial Brain Infections Within 30 Days

End point title	18. Safety/Mortality - Bacterial Brain Infections Within 30 Days
End point description: Frequency of bacterial brain infections within 30 days	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	17	26		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Saline Placebo v Alteplase
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.202
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-0.035
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.084
upper limit	0.014

Secondary: 19. Safety/Mortality - Systematic Bleeds Within 72 Hours	
End point title	19. Safety/Mortality - Systematic Bleeds Within 72 Hours
End point description: Frequency of systematic bleeds within 72 hours	
End point type	Secondary
End point timeframe: 72 hours	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	6	5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.022
upper limit	0.03

Secondary: 20. Safety/Mortality - Systematic Bleeds Within 30 Days	
End point title	20. Safety/Mortality - Systematic Bleeds Within 30 Days
End point description: Frequency of bacterial brain infections, symptomatic brain bleeds, and mortality.	
End point type	Secondary
End point timeframe: 30 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	9	8		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.028
upper limit	0.036

Secondary: 21. Adverse and Serious Adverse Events

End point title	21. Adverse and Serious Adverse Events
End point description:	
Assessment of number of adverse and serious adverse events by treatment group.	
End point type	Secondary
End point timeframe:	
180 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	114	151		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-0.144
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	-0.057

Secondary: 22. Predicting Hazards of Death by Treatment Group

End point title	22. Predicting Hazards of Death by Treatment Group
End point description:	
Cox Proportional Hazards Model is used to predict the hazards ratio by treatment group.	
End point type	Secondary
End point timeframe:	
180 days	

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	251		
Units: Number of participants	46	73		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [17]
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.86

Notes:

[17] - Adjusted Cox Proportional Hazards Model adjusting for age, GCS, thalamus, stability ICH volume and stability IVH volume (categorical).

Secondary: 23. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Race (African-American)

End point title	23. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Race (African-American)

End point description:

Assessment of modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90[18]	75[19]		
Units: Number of participants	49	36		

Notes:

[18] - All African American patients with non-missing data were analysed

[19] - All African American patients with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.41
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.088
upper limit	0.217

Secondary: 24. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3

Proportion by Race (White)

End point title	24. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Race (White)

End point description:

Assessment of modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[20]	158[21]		
Units: Number of participants	62	66		

Notes:

[20] - All White patients with non-missing data were analysed

[21] - All White patients with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.781
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.096
upper limit	0.128

Secondary: 25. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Gender (Female)

End point title	25. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Gender (Female)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[22]	114[23]		
Units: Number of participants	49	52		

Notes:

[22] - All female patients with non-missing data were analysed

[23] - All female patients with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.773
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.113
upper limit	0.152

Secondary: 26. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Gender (Male)

End point title	26. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Gender (Male)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143[24]	131[25]		
Units: Number of participants	68	58		

Notes:

[24] - All male patients with non-missing data were analysed

[25] - All male patients with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.587
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.032
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.151

Secondary: 27. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Age (65 Years or Under)

End point title	27. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Age (65 Years or Under)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[26]	167[27]		
Units: Number of participants	96	87		

Notes:

[26] - All patients 65 years and under with non-missing data were analysed

[27] - All patients 65 years and under with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.121

Secondary: 28. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Age (Over 65 Years)

End point title	28. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Age (Over 65 Years)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67[28]	78[29]		
Units: Number of participants	21	23		

Notes:

[28] - All patients over 65 years with non-missing data were analysed

[29] - All patients over 65 years with non-missing data were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.808
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.019

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.132
upper limit	0.169

Secondary: 29. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by IVH Size (Less Than 20ml)

End point title	29. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by IVH Size (Less Than 20ml)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109[30]	108[31]		
Units: Number of participants	60	63		

Notes:

[30] - All patients with non-missing data and IVH size less than 20ml were analysed

[31] - All patients with non-missing data and IVH size less than 20ml were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.625
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.033
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.165
upper limit	0.099

Secondary: 30. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3

Proportion by IVH Size (20-50ml)

End point title	30. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by IVH Size (20-50ml)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[32]	109[33]		
Units: Number of participants	52	42		

Notes:

[32] - All patients with non-missing data and IVH size 20-50ml were analysed

[33] - All patients with non-missing data and IVH size 20-50ml were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.087
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.043
upper limit	0.218

Secondary: 31. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by IVH Size (Greater Than 50ml)

End point title	31. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by IVH Size (Greater Than 50ml)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27[34]	28[35]		
Units: Number of participants	5	5		

Notes:

[34] - All patients with non-missing data and IVH size greater than 50ml were analysed

[35] - All patients with non-missing data and IVH size greater than 50ml were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.949
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.0066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.197
upper limit	0.211

Secondary: 32. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Location (Thalamic)

End point title	32. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Location (Thalamic)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147[36]	139[37]		
Units: Number of participants	57	52		

Notes:

[36] - All patients with non-missing data and thalamic clot location were analysed

[37] - All patients with non-missing data and thalamic clot location were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.812
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.098
upper limit	0.126

Secondary: 33. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Location (Non-Thalamic)

End point title	33. Sub-Group Analyses - Difference in Modified Rankin Scale (mRS) 0-3 Proportion by Location (Non-Thalamic)

End point description:

Assessment of Modified Rankin Scale (mRS) score 0-3 compared by race, gender, age, IVH size, and ICH location. The mRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. It is scored from 0 (perfect health without symptoms) to 6 (death).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[38]	106[39]		
Units: Number of participants	60	58		

Notes:

[38] - All patients with non-missing data and non-thalamic clot location were analysed

[39] - All patients with non-missing data and non-thalamic clot location were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.059
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.194

Secondary: 34. Functional Status - Barthel Index

End point title	34. Functional Status - Barthel Index

End point description:

Assessment of NIHSS, Barthel Index, eGOS (dichotomy and ordinal) by group. The Barthel Index (BI) assesses ten functional tasks of daily living, and each task provides a measure for level of independence. Scores range from 0 and 100, with a higher score indicating greater independence.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197[40]	170[41]		
Units: Barthel score				
arithmetic mean (standard deviation)	65.2 (± 37.7)	69.5 (± 35.1)		

Notes:

[40] - All patients with non-missing data at 180 days were analysed

[41] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	367
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	Wilcoxon (Mann-Whitney)

Secondary: 35. Functional Status - Participants With Extended Glasgow Outcome (eGOS) Score >=Upper Severe Disability

End point title	35. Functional Status - Participants With Extended Glasgow Outcome (eGOS) Score >=Upper Severe Disability

End point description:

Assessment of NIHSS, Barthel Index, eGOS (dichotomy and ordinal) by group. The extended Glasgow Outcome Scale (eGOS) is a global scale for functional outcome with eight categories: 1 - Death, 2 - Vegetative State, 3 - Lower Severe Disability, 4 - Upper Severe Disability, 5 - Lower Moderate Disability, 6 - Upper Moderate Disability, 7 - Lower Good Recovery, 8 - Upper Good Recovery.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241[42]	241[43]		
Units: % of participants with score>=4	95	77		

Notes:

[42] - All patients with non-missing data at 180 days were analysed

[43] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.087
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.075
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.16

Statistical analysis title	Statistical Analysis 2
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064 [44]
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.43

Notes:

[44] - Adjusted Multivariable Logit Model comparing eGOS scores of Upper Severe Disability or greater versus Lower Severe Disability and worse; Alteplase versus Saline

Statistical analysis title	Statistical Analysis 3
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.336 [45]
Method	Generalized ordered Logit model
Parameter estimate	Odds ratio (OR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.89

Notes:

[45] - Adjusted generalized ordered logit model odds ratios for eGOS scores of Moderate Disability or worse
versus Good Recovery; Alteplase versus Saline

Statistical analysis title	Statistical Analysis 4
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	482
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783 [46]
Method	Generalized ordered Logit model
Parameter estimate	Odds ratio (OR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.52

Notes:

[46] - Adjusted generalized ordered logit model odds ratios for eGOS scores of Upper Severe Disability or worse versus Moderate Disability + Good Recovery; Alteplase versus Saline

Secondary: 36. Functional Status - National Institutes of Health Stroke Scale (NIHSS)

End point title	36. Functional Status - National Institutes of Health Stroke Scale (NIHSS)

End point description:

Assessment of NIHSS, Barthel Index, eGOS (dichotomy and ordinal) by group. The National Institutes of Health Stroke Scale (NIHSS) is a 15-item scale that assesses language, motor function, sensory loss, consciousness, visual fields, extraocular movements, coordination, neglect, and speech. It is scored

from 0 (no stroke symptoms) to 42 (severe stroke).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[47]	158[48]		
Units: NIHSS score				
median (inter-quartile range (Q1-Q3))	3 (0 to 9)	2 (0 to 7)		

Notes:

[47] - All patients with non-missing data at 180 days were analysed

[48] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Wilcoxon (Mann-Whitney)

Secondary: 37. Quality of Life - Stroke Impact Scale (SIS) - Strength

End point title	37. Quality of Life - Stroke Impact Scale (SIS) - Strength

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of
daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[49]	165[50]		
Units: SIS score				
arithmetic mean (standard deviation)	54.97 (± 35.37)	58.75 (± 34.36)		

Notes:

[49] - All patients with non-missing data at 180 days were analysed

[50] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	t-test, 2-sided

Secondary: 38. Quality of Life - Stroke Impact Scale (SIS) - Mobility

End point title	38. Quality of Life - Stroke Impact Scale (SIS) - Mobility

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of
daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[51]	165[52]		
Units: SIS score				
arithmetic mean (standard deviation)	58.3 (± 38.6)	60.1 (± 36.05)		

Notes:

[51] - All patients with non-missing data at 180 days were analysed

[52] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	t-test, 2-sided

Secondary: 39. Quality of Life - Stroke Impact Scale (SIS) - Hand Function

End point title	39. Quality of Life - Stroke Impact Scale (SIS) - Hand Function

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of
daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180- days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[53]	165[54]		
Units: SIS score				
arithmetic mean (standard deviation)	53.41 (± 41.86)	56.52 (± 39.69)		

Notes:

[53] - All patients with non-missing data at 180 days were analysed

[54] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.478
Method	t-test, 2-sided

Secondary: 40. Quality of Life - Stroke Impact Scale (SIS) - Activities of Daily Living

End point title	40. Quality of Life - Stroke Impact Scale (SIS) - Activities of Daily Living

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of
daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a

scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[55]	165[56]		
Units: SIS score				
arithmetic mean (standard deviation)	59.33 (± 37.9)	61.19 (± 34.98)		

Notes:

[55] - All patients with non-missing data at 180 days were analysed

[56] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.634
Method	t-test, 2-sided

Secondary: 41. Quality of Life - Stroke Impact Scale (SIS) - Communication

End point title	41. Quality of Life - Stroke Impact Scale (SIS) - Communication

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[57]	165[58]		
Units: SIS score				
arithmetic mean (standard deviation)	76.02 (± 31.47)	79.6 (± 26.76)		

Notes:

[57] - All patients with non-missing data at 180 days were analysed

[58] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.255
Method	t-test, 2-sided

Secondary: 42. Quality of Life - Stroke Impact Scale (SIS) - Thinking

End point title	42. Quality of Life - Stroke Impact Scale (SIS) - Thinking

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[59]	165[60]		
Units: SIS score				
arithmetic mean (standard deviation)	58.48 (± 33.11)	62.68 (± 31.18)		

Notes:

[59] - All patients with non-missing data at 180 days were analysed

[60] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo

Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	t-test, 2-sided

Secondary: 43. Quality of Life - Stroke Impact Scale (SIS) - Emotion

End point title	43. Quality of Life - Stroke Impact Scale (SIS) - Emotion

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[61]	163[62]		
Units: SIS score				
arithmetic mean (standard deviation)	73.14 (± 19.62)	73.45 (± 20.24)		

Notes:

[61] - All patients with non-missing data at 180 days were analysed

[62] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882
Method	t-test, 2-sided

Secondary: 44. Quality of Life - Stroke Impact Scale (SIS) - Participation

End point title	44. Quality of Life - Stroke Impact Scale (SIS) - Participation

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:
180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[63]	163[64]		
Units: SIS score				
arithmetic mean (standard deviation)	47.46 (± 33.01)	49.58 (± 33.03)		

Notes:

[63] - All patients with non-missing data at 180 days were analysed

[64] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	349
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.551
Method	t-test, 2-sided

Secondary: 45. Quality of Life - Stroke Impact Scale (SIS) - Recovery	
End point title	45. Quality of Life - Stroke Impact Scale (SIS) - Recovery

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. The Stroke Impact Scale (SIS) covers 8 dimensions of stroke outcomes: strength, hand function, activities of daily living/instrumental activities of daily living, mobility, communication, emotion, memory and thinking, participation. It is scored on a scale of 0 to 100 for each dimension, with higher scores indicating better self-reported health.

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	185[65]	162[66]		
Units: SIS score				
arithmetic mean (standard deviation)	60.04 (± 26.42)	63.44 (± 25.44)		

Notes:

[65] - All patients with non-missing data at 180 days were analysed

[66] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	t-test, 2-sided

Secondary: 46. Quality of Life - EuroQol Visual Analogue Scale (EQ-VAS)

End point title	46. Quality of Life - EuroQol Visual Analogue Scale (EQ-VAS)

End point description:

Assessment of SIS and EuroQol Visual Analog Scale by group. EuroQol Visual Analogue Scale (EQ-VAS) is a self-reported measure of health status. It is a marked scale where individuals draw a line to indicate their health, with end points of 0 (the worst health you can imagine) and 100 (the best health you can imagine).

End point type	Secondary

End point timeframe:

180 days

End point values	Alteplase	Saline Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177[67]	160[68]		
Units: EuroQol score				
arithmetic mean (standard deviation)	62.8 (± 26.0)	65.1 (± 23.3)		

Notes:

[67] - All patients with non-missing data at 180 days were analysed

[68] - All patients with non-missing data at 180 days were analysed

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Alteplase v Saline Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.376
Method	t-test, 2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 180 days since symptom onset	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	Alteplase
Reporting group description: Administration of alteplase via the intraventricular catheter Alteplase: 1.0 mg of alteplase will be administered via the intraventricular catheter every 8 hours for up to 12 doses	
Reporting group title	Saline Placebo
Reporting group description: 1 ml of normal saline administered via the intraventricular catheter Normal saline: 1 ml of normal saline will be administered via the intraventricular catheter every 8 hours for up to 12 doses	

Serious adverse events	Alteplase	Saline Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	114 / 249 (45.78%)	151 / 251 (60.16%)	
number of deaths (all causes)	46	73	
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	6 / 249 (2.41%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

PEG tube complication			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Cerebrovascular death (Brain death)			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death due to index bleeding event			
subjects affected / exposed	10 / 249 (4.02%)	21 / 251 (8.37%)	
occurrences causally related to treatment / all	0 / 10	0 / 21	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 249 (0.40%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death NOS			
subjects affected / exposed	6 / 249 (2.41%)	8 / 251 (3.19%)	
occurrences causally related to treatment / all	0 / 6	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Adult respiratory distress syndrome			

subjects affected / exposed	3 / 249 (1.20%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	2 / 249 (0.80%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COPD			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 249 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryneal oedema			
subjects affected / exposed	1 / 249 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	17 / 249 (6.83%)	13 / 251 (5.18%)	
occurrences causally related to treatment / all	0 / 19	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	1 / 249 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 249 (2.81%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	12 / 249 (4.82%)	17 / 251 (6.77%)	
occurrences causally related to treatment / all	0 / 12	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	4 / 249 (1.61%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnea			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal mucositis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
INR increased			
subjects affected / exposed	0 / 249 (0.00%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Platelet count decreased			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy bleeding			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asystole			
subjects affected / exposed	2 / 249 (0.80%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caridac arrest			
subjects affected / exposed	5 / 249 (2.01%)	9 / 251 (3.59%)	
occurrences causally related to treatment / all	1 / 5	0 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
Congestive heart failure			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure			
subjects affected / exposed	0 / 249 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercardiac clot			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 249 (0.00%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachydysrhythmia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Takotsubo syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered mental status			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anoxic brain damage			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anoxic brain injury			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			

subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain and catheter related infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brainstorming/autonomic dysfunction			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 249 (0.00%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular death			
subjects affected / exposed	2 / 249 (0.80%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	2 / 2	1 / 6	
deaths causally related to treatment / all	2 / 2	1 / 1	
Cognitive disturbance			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death due to index bleeding event			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	7 / 249 (2.81%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	1 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diencephalic storming			

subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema cerebral			
subjects affected / exposed	3 / 249 (1.20%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extensor posturing			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herniation			
subjects affected / exposed	1 / 249 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus, communicating			
subjects affected / exposed	14 / 249 (5.62%)	13 / 251 (5.18%)	
occurrences causally related to treatment / all	0 / 14	3 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus, obstructive			
subjects affected / exposed	1 / 249 (0.40%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intracranial abscess			

subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemmorhage: Catheter Tract, Enlargement			
subjects affected / exposed	2 / 249 (0.80%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage: Catheter Tract, new			
subjects affected / exposed	8 / 249 (3.21%)	7 / 251 (2.79%)	
occurrences causally related to treatment / all	8 / 8	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemmorhage: Hematoma, subdural			
subjects affected / exposed	1 / 249 (0.40%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercranial hemorrhage: subarachnoid space, new			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage: Tissue, enlargement			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage: Tissue, new			
subjects affected / exposed	2 / 249 (0.80%)	5 / 251 (1.99%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage: Ventricular system, enlargement			

subjects affected / exposed	3 / 249 (1.20%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial hemorrhage: Ventricular system, new			
subjects affected / exposed	2 / 249 (0.80%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Intracranial hypertension			
subjects affected / exposed	9 / 249 (3.61%)	8 / 251 (3.19%)	
occurrences causally related to treatment / all	3 / 9	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemia cerobrovascular			
subjects affected / exposed	3 / 249 (1.20%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	2 / 249 (0.80%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible cerebral vasoconstriction vs vasculitis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 249 (1.20%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	4 / 249 (1.61%)	4 / 251 (1.59%)	
occurrences causally related to treatment / all	3 / 4	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	
VP shunt dysfunction			

subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplasm or DIND			
subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculitis, bacterial			
subjects affected / exposed	3 / 249 (1.20%)	10 / 251 (3.98%)	
occurrences causally related to treatment / all	0 / 3	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculitis, non-bacterial			
subjects affected / exposed	4 / 249 (1.61%)	3 / 251 (1.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 249 (0.80%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colonic perforation			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Hemorrhage			
subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal hemorrhage			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric hemorrhage			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroparesis			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal hemorrhage			
subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Swollen tongue			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			

subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrahepatic cholestasis of unknown etiology			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash acneiform			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal failure			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial nephritis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal calculi			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal insufficiency			
subjects affected / exposed	6 / 249 (2.41%)	6 / 251 (2.39%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Chest wall pain			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle weakness, left-sided			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial infection			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal infection			
subjects affected / exposed	0 / 249 (0.00%)	2 / 251 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	11 / 249 (4.42%)	7 / 251 (2.79%)	
occurrences causally related to treatment / all	0 / 13	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tracheitis			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 249 (1.20%)	8 / 251 (3.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculitis, bacterial			
subjects affected / exposed	1 / 249 (0.40%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculitis, non-bacterial			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection, non-neurologic			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 249 (0.40%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus, Type I			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatremia			
subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycemia			

subjects affected / exposed	2 / 249 (0.80%)	0 / 251 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			
subjects affected / exposed	0 / 249 (0.00%)	1 / 251 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Alteplase	Saline Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	165 / 249 (66.27%)	178 / 251 (70.92%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	21 / 249 (8.43%)	20 / 251 (7.97%)	
occurrences (all)	21	20	
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	6 / 249 (2.41%)	12 / 251 (4.78%)	
occurrences (all)	7	13	
Hydrocephalus, communicating			
subjects affected / exposed	24 / 249 (9.64%)	33 / 251 (13.15%)	
occurrences (all)	24	33	
Intracranial hemorrhage: Catheter tract, new			
subjects affected / exposed	34 / 249 (13.65%)	39 / 251 (15.54%)	
occurrences (all)	37	47	
Intracranial hypertension			
subjects affected / exposed	39 / 249 (15.66%)	42 / 251 (16.73%)	
occurrences (all)	53	50	
Seizure			
subjects affected / exposed	13 / 249 (5.22%)	16 / 251 (6.37%)	
occurrences (all)	14	20	
General disorders and administration site conditions			

Fever			
subjects affected / exposed	72 / 249 (28.92%)	67 / 251 (26.69%)	
occurrences (all)	76	74	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	41 / 249 (16.47%)	53 / 251 (21.12%)	
occurrences (all)	41	53	
Infections and infestations			
Bacteremia			
subjects affected / exposed	13 / 249 (5.22%)	6 / 251 (2.39%)	
occurrences (all)	13	7	
Urinary tract infection			
subjects affected / exposed	36 / 249 (14.46%)	23 / 251 (9.16%)	
occurrences (all)	38	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2010	The proposed changes were as follows: • Vital signs will be recorded on the trial data capture forms less frequently (every 4 hours instead of hourly). • Follow up changes: GOS will be computed from the GOSe and not collected separately at follow up visit. EQ-SD will be collected at the 90 and 270 day telephone interviews. MMSE will be administered to all patients at days 30, 180 and 365. • Exclusion criteria changes: patients with Moya Moya disease will be excluded. Patients with INR greater than 1.3 and abnormal aPTT will also be excluded. (The INR change is due to the acceptable INR being lowered from 1.7 lo 1.3. • Acquisition of a CT angiogram is now a required part of the protocol. • Data will be captured using the VISION/Prelude EDC system. • Daily laboratory assessments of PT, fibrinogen, plasminogen and d-dimer will not take place. Fibrinogen and plasminogen will only be collected once prior to first dose. Only serum WBC,Hct, platelet count, INR, aPTTand CSF labs will be collected on a daily basis. • The need to culture the IVC tip is no longer required because the CSF is being cultured. • All quality assurance monitoring of subject data will be done remotely using the VISION/Prelude EDC system. • Analysis of video recordings of the outcome assessment of the modified Rankin scale will be undertaken by researchers from Glasgow University
13 January 2011	The proposed changes were as follows: • There has been a change in the management of the study in that the randomisation algorithm has been changed from a block randomisation to adaptive block randomisation. Details are enclosed. • The lead Neurosurgery department location in the UK has moved: Newcastle upon Tyne Hospitals NHS Foundation Trust has moved the Neurosciences Directorate from the Newcastle General Hospital to the Royal Victoria Infirmary • The Coordinating centre location has moved from the Newcastle General Hospital building to a University building: Neurosurgical Trials Unit, 3-4 Claremont Terrace, Newcastle upon Tyne NE2 4AE.
03 February 2011	The proposed change was a change of address of the site of the drug importer.
15 May 2011	The proposed changes were: • Addition of a new site in the UK: Salford • Updated protocol: this includes changes previously notified; an additional outcome measure; clarification of when the first dose may be given if patient safety requires additional stabilising time; a slight increase in the maximum permitted INR during screening and dosing (this will be formally analysed after the next 100 patients to ensure that it is does not significantly alter the safety of the subjects); permit the use of heparin during the acute treatment period to comply with standard of care policies (this will be formally analysed after the next 100 patients to check whether it significantly alters the safety of subjects); increased stability period from 12 to 24 hours being consistent with study training. • CTA file has been converted from version 7, additional fields completed, Prelude Dynamics has been moved from "Central Technical Facilities" classification to "Organisations to whom sponsor has transferred" as being more appropriate and Newcastle University has been added as undertaking these submissions.

23 April 2013	Currently this trial uses Cathflo Activase from Genentech imported from the USA and distributed to sites in Europe by Mawdsleys. A problem has arisen with respect to drug supply and it has become necessary to obtain the tP-A from an alternative source for use from 1st May 2013. Although this may be temporary it would be appropriate to arrange that the drug can be used from either source from now on. This alternative source is Boehringer Ingelheim based in Germany (Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Strasse 173, 55216 Ingelheim am Rhein) and the product is Actilyse Cathflo 2mg (ATC code B01AD02) with a marketing authorisation number 79189.00.00. Mawdsleys will remain responsible for the importation and distribution of drug to recruiting hospitals. The most recent version of the protocol does not specify the source of the drug. At present we only have the SPC available in German but this will be translated into English for distribution to sites. Appropriate labels have been developed by Mawdsley.
15 May 2013	Updated protocol includes mostly administrative clarifications. There are also some administrative corrections and changes to remove product line references, making the protocol generic, changes in timing of CT scans to align with current training and practice, amendment to exclude patients taking Dabigatran, extending the permitted interventions for DVT prophylaxis to include enoxaparin as well as other LMWH.
29 July 2014	The proposed amendment is to additionally exclude patients taking Apixaban or Rivaroxaban as well as Dabigatran.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28081952