

**Clinical trial results:****Phase II, randomized, pharmacokinetic, dose finding, and dose frequency determination using rt-PA in intraventricular hemorrhage****Summary**

EudraCT number	2004-000919-26
Trial protocol	GB FI
Global end of trial date	21 August 2008

Results information

Result version number	v1 (current)
This version publication date	26 March 2020
First version publication date	26 March 2020

Trial information**Trial identification**

Sponsor protocol code	IVH05
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Additional study identifiers

ISRCTN number	ISRCTN47341677
ClinicalTrials.gov id (NCT number)	NCT00650858
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johns Hopkins University
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Sponsor organisation name	Newcastle upon Tyne Hospitals NHS Trust
Sponsor organisation address	RVI, Queen Victoria Road, Newcastle upon Tyne, United Kingdom, NE1 4LPE
Public contact	Jane Varey, Newcastle upon Tyne Hospitals NHS Trust, 0191 2825959, Trust.R&D@nuth.nhs.uk
Scientific contact	Jane Varey, Newcastle upon Tyne Hospitals NHS Trust, 0191 2825959, Trust.R&D@nuth.nhs.uk

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	31 August 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2008
Global end of trial reached?	Yes
Global end of trial date	21 August 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

CLEAR IVH, a Phase II dose-finding study, tested the ability of different doses of recombinant tissue plasminogen activator (rt-PA, Cathflo®; Genentech, Inc.) to lyse intraventricular blood clots. Subjects experiencing spontaneous intracerebral hemorrhage (ICH) with intraventricular hemorrhage (IVH) extension were enrolled according to protocol. Major selection criteria were: 1) presence of ICH \leq 30cc; 2) acute obstructive hydrocephalus secondary to large intraventricular hemorrhage; and 3) stability of IVH and ICH size over a 6-hour period of observation with CT scanning. Pregnant women and children were not enrolled. There were no major changes to the protocol; minor changes included an increased enrollment time window and clarifications to dosage discontinuation rules.

Protection of trial subjects:

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 6 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 6 month follow-up period
9. All infections reported to the safety and monitoring committee for an independent assessment of clinical significance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 January 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Canada: 3

Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	United States: 47
Worldwide total number of subjects	52
EEA total number of subjects	2

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)	39
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began for protocol stage 1 in August 2005 and ended for protocol stage 2 on February 6, 2008. Subjects were screened by clinical stroke service personnel in the Emergency Department or by direct transfer from an outside hospital.

Pre-assignment

Screening details:

Major selection criteria were: 1) presence of ICH \leq 30cc; 2) acute obstructive hydrocephalus secondary to large intraventricular hemorrhage; and 3) stability of IVH and ICH size over a 6-hour period of observation with CT scanning. Pregnant women and children were not enrolled.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Comparator: 0.3 mg rt-PA q12h

Arm description:

In stage 1 of the protocol, dose finding, subjects were randomized to either this 0.3 mg dose arm or the 1.0 mg dose arm. Subjects in this arm (0.3 mg) received up to 8 doses of 0.3 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Arm type	Active comparator
Investigational medicinal product name	rt-PA
Investigational medicinal product code	
Other name	Activase, Cathflo
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraventricular use

Dosage and administration details:

0.3 mg and 1.0 mg of rt-PA (Cathflo) were administered every 12 hours (dose finding) and every 8 hours (dose frequency) via the intraventricular catheter to treat intraventricular hemorrhage.

Arm title	Active Comparator: 1.0 mg rt-PA q12h
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Arm description:

In stage 1 of the protocol, dose finding, subjects were randomized to either this 1.0 mg dose arm or the 0.3 mg dose arm. Subjects in this arm (1.0 mg) received up to 8 doses of 1.0 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Arm type	Active comparator
Investigational medicinal product name	rt-PA
Investigational medicinal product code	
Other name	Activase, Cathflo
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraventricular use

Dosage and administration details:

1.0 mg of rt-PA (Cathflo) were administered every 12 hours (dose finding) and every 8 hours (dose frequency) via the intraventricular catheter to treat intraventricular hemorrhage.

Arm title	Experimental: 1.0 mg rt-PA q8h
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Arm description:

In stage 2 of the protocol, dose frequency, subjects received up to 8 doses of 1.0 mg of rt-PA (Cathflo) every 8 hours through the intraventricular catheter to treat intraventricular hemorrhage.

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

Dosage and administration details:

Subjects received up to 8 doses of 1.0 mg of rt-PA (Cathflo) every 8 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Number of subjects in period 1	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h
Started	8	8	36
Completed	8	8	36

Baseline characteristics

Reporting groups

Reporting group title	Active Comparator: 0.3 mg rt-PA q12h
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Reporting group description:

In stage 1 of the protocol, dose finding, subjects were randomized to either this 0.3 mg dose arm or the 1.0 mg dose arm. Subjects in this arm (0.3 mg) received up to 8 doses of 0.3 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Reporting group title	Active Comparator: 1.0 mg rt-PA q12h
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Reporting group description:

In stage 1 of the protocol, dose finding, subjects were randomized to either this 1.0 mg dose arm or the 0.3 mg dose arm. Subjects in this arm (1.0 mg) received up to 8 doses of 1.0 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Reporting group title	Experimental: 1.0 mg rt-PA q8h
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Reporting group description:

In stage 2 of the protocol, dose frequency, subjects received up to 8 doses of 1.0 mg of rt-PA (Cathflo) every 8 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Reporting group values	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h
Number of subjects	8	8	36
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)	7	6	26
From 65-84 years	1	2	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.6	57.3	57.0
standard deviation	± 9.8	± 8.3	± 10.2
Gender categorical Units: Subjects			
Female	3	4	11
Male	5	4	25
Region of Enrollment Units: Subjects			
United States	8	8	31
Canada	0	0	3
Germany	0	0	1
United Kingdom	0	0	1

Reporting group values	Total		
Number of subjects	52		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	39		
From 65-84 years	13		
85 years and over	0		
Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	18		
Male	34		
Region of Enrollment Units: Subjects			
United States	47		
Canada	3		
Germany	1		
United Kingdom	1		

End points

End points reporting groups

Reporting group title	Active Comparator: 0.3 mg rt-PA q12h
Reporting group description:	In stage 1 of the protocol, dose finding, subjects were randomized to either this 0.3 mg dose arm or the 1.0 mg dose arm. Subjects in this arm (0.3 mg) received up to 8 doses of 0.3 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.
Reporting group title	Active Comparator: 1.0 mg rt-PA q12h
Reporting group description:	In stage 1 of the protocol, dose finding, subjects were randomized to either this 1.0 mg dose arm or the 0.3 mg dose arm. Subjects in this arm (1.0 mg) received up to 8 doses of 1.0 mg rt-PA every 12 hours through the intraventricular catheter to treat intraventricular hemorrhage.
Reporting group title	Experimental: 1.0 mg rt-PA q8h
Reporting group description:	In stage 2 of the protocol, dose frequency, subjects received up to 8 doses of 1.0 mg of rt-PA (Cathflo) every 8 hours through the intraventricular catheter to treat intraventricular hemorrhage.

Primary: 1. Primary: 30-day Mortality

End point title	1. Primary: 30-day Mortality
End point description:	The number of subjects who died at or before the 30-day follow-up visit were determined as a measure of safety. If more than 50% of the subjects died at or before the 30-day follow-up visit, the study would have been stopped for full DSMB review.
End point type	Primary
End point timeframe:	30 days

End point values	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	36	
Units: Number of participants	1	1	6	

Statistical analyses

Statistical analysis title	Difference by group for 30-Day mortality
Comparison groups	Active Comparator: 0.3 mg rt-PA q12h v Active Comparator: 1.0 mg rt-PA q12h v Experimental: 1.0 mg rt-PA q8h

Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Primary: 2. Primary: Incidence of Bacterial Ventriculitis, Meningitis

End point title	2. Primary: Incidence of Bacterial Ventriculitis, Meningitis
End point description:	The incidence of bacterial ventriculitis/meningitis was recorded to determine the safety of intraventricular administration of rt-PA. If 30% or more subjects experienced this event, the study would have been stopped for full DSMB review.
End point type	Primary
End point timeframe:	30 days

End point values	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	36	
Units: Number of participants	0	1	1	

Statistical analyses

Statistical analysis title	Difference by group for 30-Day ventriculitis
Comparison groups	Active Comparator: 1.0 mg rt-PA q12h v Experimental: 1.0 mg rt-PA q8h v Active Comparator: 0.3 mg rt-PA q12h
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.525
Method	Fisher exact

Primary: 3. Primary: Rate of symptomatic Bleeding Events

End point title	3. Primary: Rate of symptomatic Bleeding Events
End point description:	The rate of symptomatic brain bleeding events were recorded to determine the safety of intraventricular administrations of rt-PA. If 35% or more subjects experienced a symptomatic bleeding event prior to the 30-day follow-up visit, the study would have been stopped for a full DSMB review.
End point type	Primary

End point timeframe:

30 days

End point values	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	36	
Units: Number of participants	0	0	2	

Statistical analyses

Statistical analysis title	Difference by group for 30-Day bleeding
Comparison groups	Active Comparator: 0.3 mg rt-PA q12h v Active Comparator: 1.0 mg rt-PA q12h v Experimental: 1.0 mg rt-PA q8h
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: 4. Secondary: Average Daily Percentage Clot Size Resolution Over the First 3 Days

End point title	4. Secondary: Average Daily Percentage Clot Size Resolution Over the First 3 Days
End point description:	Daily IVH clot volume resolution, as a percentage of stability CT IVH volume, averaged over the first 3 days, determined by CT scans
End point type	Secondary
End point timeframe:	3 days

End point values	Active Comparator: 0.3 mg rt-PA q12h	Active Comparator: 1.0 mg rt-PA q12h	Experimental: 1.0 mg rt-PA q8h	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	8	36	
Units: Percent of stability CT volume resolved				
arithmetic mean (full range (min-max))	22.19 (8 to 66)	24.20 (0 to 72)	19.99 (0 to 60)	

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Secondary: 90 Day Follow-up Modified Rankin Scale (mRS) Score

End point title	5. Secondary: 90 Day Follow-up Modified Rankin Scale (mRS) Score ^[1]
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End point description:

End point type	Secondary
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End point timeframe:

90 Days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is the median mRS score at 90 days for one treatment arm and there is no comparison group to provide a statistical result.

End point values	Experimental: 1.0 mg rt-PA q8h			
Subject group type	Reporting group			
Number of subjects analysed	36			
Units: mRS Score				
median (full range (min-max))	4.3 (0 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Secondary: 90 Day Follow-Up Glasgow Outcome Scale (GOS) Score

End point title	6. Secondary: 90 Day Follow-Up Glasgow Outcome Scale (GOS) Score ^[2]
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End point description:

90 day follow-up visit GOS score. The GOS is a scale used to determine the degree of recovery from patients with brain injury. There are five categories: 1. Dead, 2. Vegetative State, 3. Severe Disability, 4. Moderate Disability and 5. Good Recovery. (Stage 1 patients only had 30 day scores, Stage 2 patients had 30 day, 90 day and 180 day scores collected)

End point type	Secondary
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End point timeframe:

90 Days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is the median GOS score at 90 days for one treatment arm and there is no comparison group to provide a statistical result.

End point values	Experimental: 1.0 mg rt-PA q8h			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[3]			
Units: GOS Score				
median (full range (min-max))	2.3 (0 to 4)			

Notes:

[3] - Analyzed only those with non-missing GOS score

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Secondary: 180 Day Follow-Up Modified Rankin Scale (mRS) Score

End point title	7. Secondary: 180 Day Follow-Up Modified Rankin Scale (mRS) Score ^[4]
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End point description:

180 day follow-up visit mRS score. 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 to 6: 0. No Symptoms, 1. No Significant Disability, 2. Slight Disability, 3. Moderate Disability, 4. Moderately Severe Disability, 5. Severe Disability and 6. Dead.

(Stage 1 patients only had 30 day scores, Stage 2 patients had 30 day, 90 day and 180 day scores collected)

End point type	Secondary
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End point timeframe:

180 Days

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This is the median mRS score at 180 days for one treatment arm and there is no comparison group to provide a statistical result.

End point values	Experimental: 1.0 mg rt-PA q8h			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[5]			
Units: mRS Score				
median (full range (min-max))	4.0 (0 to 6)			

Notes:

[5] - Analyzed only those with non-missing mRS score

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Secondary: 180 Day Follow-Up Glasgow Outcome Scale (GOS) Score

End point title	8. Secondary: 180 Day Follow-Up Glasgow Outcome Scale (GOS) Score ^[6]
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End point description:

180 day follow-up visit GOS score. The GOS is a scale used to determine the degree of recovery from patients with brain injury. There are five categories: 1. Dead, 2. Vegetative State, 3. Severe Disability, 4. Moderate Disability and 5. Good Recovery.

(Stage 1 patients only had 30 day scores, Stage 2 patients had 30 day, 90 day and 180 day scores)

collected)

End point type	Secondary
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End point timeframe:
180 Days

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This is the median GOS score at 180 days for one treatment arm and there is no comparison group to provide a statistical result.

End point values	Experimental: 1.0 mg rt-PA q8h			
Subject group type	Reporting group			
Number of subjects analysed	35 ^[7]			
Units: GOS Score				
median (full range (min-max))	2.3 (0 to 4)			

Notes:

[7] - Analysed only those with non-missing data

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During follow-up period

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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Reporting groups

Reporting group title	0.3 mg rt-PA q12h
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Reporting group description:

0.3 mg of rt-PA (Cathflo) was administered every 12 hours (dose finding)

Reporting group title	1.0 mg rt-PA q12h
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Reporting group description:

1.0 mg of rt-PA (Cathflo) was administered every 12 hours (dose finding)

Reporting group title	1.0 mg rt-PA q8h
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Reporting group description:

1.0 mg of rt-PA (Cathflo) was administered every 8hours (dose frequency)

Serious adverse events	0.3 mg rt-PA q12h	1.0 mg rt-PA q12h	1.0 mg rt-PA q8h
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	2 / 8 (25.00%)	11 / 36 (30.56%)
number of deaths (all causes)	1	1	10
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac Arrest			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hemorrhage new catheter tract >5 mm with mas effect, symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus, Communicating			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
ICH Hemorrhage, new symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IVH Hemorrhage enlargement - asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IVH Hemorrhage enlargement - symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IVH hemorrhage, new symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventriculitis, Bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ventriculitis, Non-Bacterial subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory, thoracic and mediastinal disorders			
Accidental Extubation subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suspected cardiac or pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheal stricture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ventilatory failure, mechanical			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	0.3 mg rt-PA q12h	1.0 mg rt-PA q12h	1.0 mg rt-PA q8h
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	8 / 8 (100.00%)	32 / 36 (88.89%)
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
Bradycardia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 36 (0.00%)
occurrences (all)	0	1	0

Congestive Heart Failure subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 36 (0.00%) 0
Hypertension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	3 / 8 (37.50%) 4	1 / 36 (2.78%) 1
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	2 / 36 (5.56%) 2
Nervous system disorders			
Brain Edema / Swelling subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	3 / 36 (8.33%) 3
CSF Leak subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 8 (25.00%) 2	0 / 36 (0.00%) 0
Cerebral Infarction subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	5 / 36 (13.89%) 5
Cerebral infarction, extension subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	0 / 36 (0.00%) 0
Decreased Level of consciousness subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	2 / 8 (25.00%) 2	7 / 36 (19.44%) 12
Encephalopathy subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Headache subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	3 / 36 (8.33%) 4
Hemorrhage enl, cath tract >5mm w/o mass, asymptomatic subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	2 / 8 (25.00%) 2	2 / 36 (5.56%) 2
Hemorrhage enlargement, catheter tract > 5 mm with mass effect, asymptomatic			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Hemorrhage, new catheter tract <= 5 mm, asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	3 / 8 (37.50%)	2 / 36 (5.56%)
occurrences (all)	0	3	2
Hemorrhage, new catheter tract > 5 mm with mass effect, asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Hemorrhage, new catheter tract > 5 mm with mass effect, symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Herniation, Brain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Hydrocephalus, Obstructive			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Hydrocephalus, communicating			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
ICH hemorrhage enlargement, asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
ICH hemorrhage, new asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
ICH hemorrhage, new symptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
IVH hemorrhage enlargement - asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	4
Increased midline shift			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Intracranial hypertension			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	2 / 36 (5.56%)
occurrences (all)	5	2	4
Peri-hemorrhagic ischemic change			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
SAH Hemorrhage, new asymptomatic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Siezure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
Ventriculitis, bacterial			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 36 (5.56%)
occurrences (all)	0	1	4
Ventriculitis, nonbacterial			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	8 / 36 (22.22%)
occurrences (all)	0	1	9
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
Bacteremia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	4
Hyperglycemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Hypokalemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	3 / 36 (8.33%)
occurrences (all)	0	1	3
Hyponatremia			

subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2	0 / 8 (0.00%) 0	0 / 36 (0.00%) 0
Hypoxemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Increased Blood Urea Nitrogen subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
General disorders and administration site conditions			
Fever of unknown origin subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3	4 / 8 (50.00%) 4	8 / 36 (22.22%) 8
Respiratory, thoracic and mediastinal disorders			
Adult Respiratory Distress Syndrome subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	1 / 36 (2.78%) 1
Aspiration subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 36 (0.00%) 0
Atelectasis subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	3 / 36 (8.33%) 3
Pleural effusion subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	2 / 36 (5.56%) 2
Pneumonia subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	1 / 8 (12.50%) 1	9 / 36 (25.00%) 9
Pneumonia, aspiration subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 8 (0.00%) 0	3 / 36 (8.33%) 3
Pulmonary edema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Tracheitis			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Ventilatory failure subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	2 / 36 (5.56%) 2
Skin and subcutaneous tissue disorders Decubitus ulcer subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Renal and urinary disorders Acute Renal Failure subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	1 / 8 (12.50%) 1	0 / 36 (0.00%) 0
Diarrhea subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	3 / 36 (8.33%) 3
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	2 / 8 (25.00%) 2	4 / 36 (11.11%) 4
Infections and infestations Skin Exanthema subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1
Metabolism and nutrition disorders Edema (metabolic causes) subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 8 (0.00%) 0	1 / 36 (2.78%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2005	<p>Substantial Amendment</p> <p>The Notice of Acceptance was for the dose frequency phase of this study but at that time the dose finding stage had not been analysed. The dose finding phase has now been completed and a decision made about the dose level. For this phase the dose level will be 1.0mg.</p> <p>Following on from completion of the dose finding phase and from experience in that phase the project team at Johns Hopkins have made some amendments to the protocol. These were submitted to the appropriate ethical committee who requested further changes. These have all been incorporated in the attached documents. Documents enclosed include</p> <p>Notification of Amendment Form Updated Request for Authorisation Form Summary of changes from original Request for Authorisation Form Protocol Version 5.2 dated 24 October 2005 Summary of changes from protocol version 4.1 dated 15/03/2005 to protocol version 5.2 dated 24/10/2005.</p>
24 August 2006	<p>Substantial Amendment 2</p> <p>The proposed number of patients in the first tier of the dose-frequency stage of this study has been recruited and the initial data have been analysed. A decision has been made by the Data and Safety Monitoring Board and the Steering Committee that more data are needed to further evaluate the 1.0mg q8hr dose. The current tier has therefore been expanded from 12 patients to 24.</p> <p>To date no patients have been recruited in the UK.</p> <p>The Protocol has not been amended and there are no changes to the information provided in the Request for Authorisation Form. However I enclose the following documents:</p> <p>Notification of Amendment Form Safety Report : Stage 2 Dose Tier 1 Results Letter from DSMB</p>

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/22382155>

<http://www.ncbi.nlm.nih.gov/pubmed/21940973>

<http://www.ncbi.nlm.nih.gov/pubmed/22474059>

<http://www.ncbi.nlm.nih.gov/pubmed/23370203>

<http://www.ncbi.nlm.nih.gov/pubmed/23463422>

<http://www.ncbi.nlm.nih.gov/pubmed/26228884>