



## Clinical trial results:

### A pilot, phase IIb, randomised, multicentre trial of Argatroban in combination with recombinant tissue plasminogen activator for acute stroke

#### Summary

EudraCT number	2012-002319-25
Trial protocol	GB
Global end of trial date	07 April 2015

#### Results information

Result version number	v1 (current)
This version publication date	15 August 2016
First version publication date	15 August 2016

#### Trial information

##### Trial identification

Sponsor protocol code	HSC-MS-11-0464
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01464788
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne, United Kingdom,
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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	30 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2015
Global end of trial reached?	Yes
Global end of trial date	07 April 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To estimate overall treatment benefit (improvement in disability) among stroke patients treated with rt-PA (alteplase) who are randomised to also receive either low-dose Argatroban, high-dose Argatroban or neither.

Protection of trial subjects:

Since Argatroban is a drug that prevents blood clotting there was an additional risk of an increase in bleeding complications. Bleeding may have occurred at any site in the body the most serious being a bleed inside the brain. Bleeding in the brain causing deterioration is a known risk of thrombolytic treatment for stroke occurring in 3% of patients. Whether this risk of bleeding is increased with Argatroban is unclear and was one of the main focuses of the trial. Patients were monitored continuously throughout the treatment infusion and the treatment discontinued in the event of any suspected bleeding. Participants were informed of the side effects of the study medication in the patient information leaflet and verbally when the study was explained.

The side effects of Argatroban on the unborn foetus or nursing infant are unknown at this time. Therefore female patients of childbearing potential underwent a blood pregnancy test prior to receiving treatment.

Patients received an extra CT angiogram if participating in the study compared to standard care. The radiation dose for this scan has been reviewed by a medical physics expert and a clinical radiation expert and considered as clinically appropriate as part of the study. Participants were informed of this additional radiation dose in the patient information sheet.

Participants had blood samples taken. Venepuncture has a small risk of discomfort and bruising, but was carried out by experienced staff to minimise this risk. The study procedures were carried out in selected hospitals in the UK with experienced research staff who had access to emergency facilities & equipment as required.

Background therapy:

Patients who have had an ischaemic stroke and admitted to the Accident and Emergency Department or Acute Stroke Unit by their treating physician receive IV Recombinant tissue plasminogen activator (rt-PA or Alteplase) as per standard treatment, provided they are able to be treated within 3 hours of the onset of their stroke symptoms (or <4.5 hours according to each site's local standard).

Evidence for comparator: -

Actual start date of recruitment	20 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	United Kingdom: 25
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	90
EEA total number of subjects	25

Notes:

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**Subjects enrolled per age group**

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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)	37
From 65 to 84 years	39
85 years and over	14

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited over the following periods:

UK: 01 April 2013 through 07 April 2015

USA: 20 December 2011 through 15 March 2015

### Pre-assignment

Screening details:

Patients who met the inclusion criteria received a head CT scan prior to initiation of rt-PA and the Argatroban infusion. If available, patients also underwent intracranial vessel imaging performed before or immediately after IV-tPA bolus (but before Argatroban bolus). Patients could not be randomised until after the CTA demonstrated an occlusion.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor <sup>[1]</sup>

Blinding implementation details:

The study was carried out by unblinded caregivers. Every effort was made by treating physician and nursing staff to not divulge the treatment arm. This is especially true for patients enrolled into the Argatroban arms. Patients and family members were not told whether they received the high or low-dose regimen unless they asked. All endpoint assessments were performed by investigators blinded to the treatment arm.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Low-dose Argatroban + usual care IV-rt-PA

Arm description:

Low-dose Argatroban (1.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA

Arm type	Active comparator
Investigational medicinal product name	Exembol
Investigational medicinal product code	
Other name	Argatroban
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

Dosage and administration details:

1.0g/kg/min continuous infusion of Argatroban x 48 hours, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion titrated to achieve an aPTT of 1.75 times baseline - not to exceed 10 g/kg/min PLUS usual care IV-rt-PA.

<b>Arm title</b>	High-dose Argatroban + usual care IV-rt-PA
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Arm description:

High-dose Argatroban (3.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA

Arm type	Active comparator
Investigational medicinal product name	Exembol
Investigational medicinal product code	
Other name	Argatroban
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous use

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**Dosage and administration details:**

High-dose Argatroban 3.0g/kg/min continuous infusion of Argatroban X 48 hours, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion will be titrated to achieve an aPTT of 2.25 times baseline - not to exceed 10 g/kg/min PLUS usual care IV-rt-PA

<b>Arm title</b>	Intravenous-rt-PA alone
Arm description: Intravenous-rt-PA alone (usual care).	
Arm type	Usual care
No investigational medicinal product assigned in this arm	

**Notes:**

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The study was carried out by unblinded caregivers. Every effort was made by treating physician and nursing staff to not divulge the treatment arm. This is especially true for patients enrolled into the Argatroban arms. Patients and family members were not told whether they received the high or low-dose regimen unless they asked. All endpoint assessments were performed by investigators blinded to the treatment arm.

Number of subjects in period 1	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone
Started	30	31	29
Completed	30	31	29

## Baseline characteristics

### Reporting groups

Reporting group title	Low-dose Argatroban + usual care IV-rt-PA
Reporting group description:	Low-dose Argatroban (1.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA
Reporting group title	High-dose Argatroban + usual care IV-rt-PA
Reporting group description:	High-dose Argatroban (3.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA
Reporting group title	Intravenous-rt-PA alone
Reporting group description:	Intravenous-rt-PA alone (usual care).

Reporting group values	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone
Number of subjects	30	31	29
Age categorical			
all subjects had to be 18 years of age or older at the time of enrollment			
Units: Subjects			
Adults (18-64 years)	11	13	13
From 65-84 years	14	15	10
85 years and over	5	3	6
Age continuous			
Units: years			
arithmetic mean	70.9	67.1	68.9
standard deviation	± 15.1	± 13.4	± 15.4
Gender categorical			
Units: Subjects			
Female	13	15	12
Male	17	16	17

Reporting group values	Total		
Number of subjects	90		
Age categorical			
all subjects had to be 18 years of age or older at the time of enrollment			
Units: Subjects			
Adults (18-64 years)	37		
From 65-84 years	39		
85 years and over	14		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	40		
Male	50		



## End points

### End points reporting groups

Reporting group title	Low-dose Argatroban + usual care IV-rt-PA
Reporting group description: Low-dose Argatroban (1.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA	
Reporting group title	High-dose Argatroban + usual care IV-rt-PA
Reporting group description: High-dose Argatroban (3.0g/kg/min continuous infusion of Argatroban, preceded by a 100 g/kg bolus administered over 3-5 minutes Infusion) + usual care IV-rt-PA	
Reporting group title	Intravenous-rt-PA alone
Reporting group description: Intravenous-rt-PA alone (usual care).	

### Primary: Excellent functional outcome as measured by the percentage of patients with a 0 or 1 on the modified Rankin Scale (mRS)

End point title	Excellent functional outcome as measured by the percentage of patients with a 0 or 1 on the modified Rankin Scale (mRS)
End point description: Excellent functional outcome as measured by the percentage of patients with a 0 or 1 on the modified Rankin Scale (mRS).	
End point type	Primary
End point timeframe: Day 90.	

End point values	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	31 <sup>[1]</sup>	29	
Units: Relative Risk				
number (not applicable)				
mRS 0-1	9	10	6	
mRS 2-6	21	21	23	

Notes:

[1] - One subject was lost to follow-up, but the endpoint was imputed.

### Statistical analyses

Statistical analysis title	low dose compared to tPA at 90 day mRS
Comparison groups	Low-dose Argatroban + usual care IV-rt-PA v Intravenous-rt-PA alone



Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.417 <sup>[3]</sup>
Method	Poisson regression
Parameter estimate	Relative Risk
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	3.56
Variability estimate	Standard error of the mean

Notes:

[2] - 1) Results are from unadjusted analysis

2) A similar unadjusted Bayesian analysis was performed using a neutral prior of: RR=1.0 and 95% credible intervals of 0.3-3.0.

The posterior results were: RR=1.15 and 95% CrI 0.56-2.34.

[3] - relative risk of Low dose compared to tPA

<b>Statistical analysis title</b>	High dose compared to tPA at 90 day mRS
Comparison groups	Intravenous-rt-PA alone v High-dose Argatroban + usual care IV-rt-PA
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.321 <sup>[5]</sup>
Method	Poisson regression
Parameter estimate	Relative Risk
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	3.75
Variability estimate	Standard error of the mean

Notes:

[4] - 1) Results are from unadjusted analysis

2) A similar unadjusted Bayesian analysis was performed using a neutral prior of: RR=1.0 and 95% credible intervals of 0.3-3.0.

The posterior results were: RR=1.23 and 95% CrI 0.61-2.51.

[5] - relative risk of High dose compared to tPA

## Secondary: Symptomatic Intracranial Hemorrhage

End point title	Symptomatic Intracranial Hemorrhage
End point description:	
Primary safety outcome was incidence of symptomatic intracerebral hemorrhage (sICH).	
End point type	Secondary
End point timeframe:	
Baseline through end of treatment (48-hours)	

<b>End point values</b>	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	30	31 <sup>[6]</sup>	29	
Units: Relative Risk				
number (not applicable)	4	2	3	

Notes:

[6] - 1 Subject was lost to follow-up

## Statistical analyses

<b>Statistical analysis title</b>	Low dose compared to tPA
Statistical analysis description:	
Relative Risk > 1.0 indicates higher risk of symptomatic intracranial hemorrhage compared to the control group (rt-PA alone).	
Comparison groups	Low-dose Argatroban + usual care IV-rt-PA v Intravenous-rt-PA alone
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.724
Method	Poisson Regression
Parameter estimate	Relative Risk
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	5.26
Variability estimate	Standard error of the mean

<b>Statistical analysis title</b>	high dose compared to tPA
Statistical analysis description:	
A relative risk (RR) <1.0 indicates a lower risk of symptomatic ICH compared to control group (rt-PA alone).	
Comparison groups	Intravenous-rt-PA alone v High-dose Argatroban + usual care IV-rt-PA
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5394
Method	Poisson Regression
Parameter estimate	Relative Risk
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	3.47
Variability estimate	Standard error of the mean

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline to day 90.

Adverse event reporting additional description:

AEs regardless of whether thought to be associated with the study or IMP under investigation were graded by the Investigator and recorded on the Electronic Case Report Form. An AE form was completed for any Intracranial Haemorrhage (ICH). A haemorrhage was labelled as symptomatic by either the local principal investigator or the safety monitor.

Assessment type	Systematic
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### Dictionary used

Dictionary name	As reported
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Dictionary version	1.0
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### Reporting groups

Reporting group title	Low-dose Argatroban + usual care IV-rt-PA
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Reporting group description: -

Reporting group title	High-dose Argatroban + usual care IV-rt-PA
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Reporting group description: -

Reporting group title	Intravenous-rt-PA alone
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Reporting group description: -

<b>Serious adverse events</b>	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 30 (50.00%)	15 / 31 (48.39%)	14 / 29 (48.28%)
number of deaths (all causes)	5	3	5
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac Disorders			
subjects affected / exposed	0 / 30 (0.00%)	2 / 31 (6.45%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Nervous system disorders	Additional description: Includes: symptomatic intracranial hemorrhage, neurological worsening, cerebral edema/brain herniation, seizures, etc.		
subjects affected / exposed	9 / 30 (30.00%)	10 / 31 (32.26%)	9 / 29 (31.03%)
occurrences causally related to treatment / all	5 / 11	5 / 10	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Blood - Circulation System			

subjects affected / exposed	0 / 30 (0.00%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Electrolyte imbalance			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 30 (16.67%)	3 / 31 (9.68%)	5 / 29 (17.24%)
occurrences causally related to treatment / all	5 / 5	3 / 3	5 / 5
deaths causally related to treatment / all	5 / 5	3 / 3	5 / 5
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	1 / 30 (3.33%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary			
subjects affected / exposed	4 / 30 (13.33%)	4 / 31 (12.90%)	3 / 29 (10.34%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Genitourinary			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Musculoskeletal			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
subjects affected / exposed	2 / 30 (6.67%)	1 / 31 (3.23%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Low-dose Argatroban + usual care IV-rt-PA	High-dose Argatroban + usual care IV-rt-PA	Intravenous-rt-PA alone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 30 (90.00%)	25 / 31 (80.65%)	20 / 29 (68.97%)
General disorders and administration site conditions			
Dental			
subjects affected / exposed	0 / 30 (0.00%)	1 / 31 (3.23%)	0 / 29 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Immune system disorder			
subjects affected / exposed	2 / 30 (6.67%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Pulmonary			
subjects affected / exposed	8 / 30 (26.67%)	0 / 31 (0.00%)	4 / 29 (13.79%)
occurrences (all)	11	0	4
Psychiatric disorders			
Psychological disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 31 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac Disorders			
subjects affected / exposed	5 / 30 (16.67%)	7 / 31 (22.58%)	9 / 29 (31.03%)
occurrences (all)	5	8	9
Nervous system disorders			

Nervous System disorders subjects affected / exposed occurrences (all)	16 / 30 (53.33%) 18	7 / 31 (22.58%) 10	4 / 29 (13.79%) 5
Blood and lymphatic system disorders Blood system - Electrolyte Imbalance subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 31 (3.23%) 1	0 / 29 (0.00%) 0
Blood - circulation system subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 31 (6.45%) 2	0 / 29 (0.00%) 0
Hematologic subjects affected / exposed occurrences (all)	Additional description: Anemia, hematuria, leukopenia, leukocytosis, etc.		
	3 / 30 (10.00%) 3	3 / 31 (9.68%) 3	4 / 29 (13.79%) 5
Ear and labyrinth disorders Ear, Nose and Throat (ENT) subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 31 (3.23%) 1	0 / 29 (0.00%) 0
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 6	8 / 31 (25.81%) 9	0 / 29 (0.00%) 0
Skin and subcutaneous tissue disorders Skin and Subcutaneous tissue subjects affected / exposed occurrences (all)	9 / 30 (30.00%) 11	6 / 31 (19.35%) 8	4 / 29 (13.79%) 5
Renal and urinary disorders Genitourinary subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 31 (3.23%) 1	1 / 29 (3.45%) 1
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1	1 / 31 (3.23%) 1	1 / 29 (3.45%) 1
Musculoskeletal and connective tissue disorders Musculoskeletal disorder subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 7	5 / 31 (16.13%) 5	3 / 29 (10.34%) 3
Infections and infestations			

Infections and infestations subjects affected / exposed occurrences (all)	7 / 30 (23.33%) 9	10 / 31 (32.26%) 12	6 / 29 (20.69%) 6
Metabolism and nutrition disorders Electrolyte imbalance subjects affected / exposed occurrences (all)	6 / 30 (20.00%) 8	2 / 31 (6.45%) 2	3 / 29 (10.34%) 4



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2015	On 07-Apr-2015 a decision to halt enrolment was the result of four landmark randomized clinical trials demonstrating the efficacy of endovascular therapy. Although each trial utilized slightly different eligibility criteria, the overwhelming majority of patients enrolled in these studies would be eligible for enrolment into the ARTSS2, but the current ARTSS2 protocol lists endovascular therapy as an exclusion criterion. As a result of these positive trials, the landscape of acute ischemic stroke (AIS) therapy has now changed dramatically. The role of embolectomy for stroke is now established and consequently, on-going reperfusion clinical trials that prohibit endovascular therapy such as ARTSS2 are no longer feasible and must adjust. A notice of substantial amendment was submitted to the MHRA on 13/04/2015.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 April 2015	A temporary halt to the trial as detailed in the substantial amendment dated 13/04/2015.	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Endpoint results are for unadjusted analyses only. Final results reported in presentations and manuscript will include both the adjusted and unadjusted results.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26278031>