Clinical trial results:
A phase III, randomized, open-label, 500-subject clinical trial of minimally invasive surgery plus rt-PA in the treatment of intracerebral haemorrhage.

Summary

EudraCT number	2013-002818-12
Trial protocol	GB HU ES DE
Global end of trial date	28 January 2019

Results information

Result version number	v1 (current)
This version publication date	23 October 2019
First version publication date	23 October 2019

Trial information

Trial identification

Sponsor protocol code	ICH02

Additional study identifiers

ISRCTN number	ISRCTN81927110
ClinicalTrials.gov id (NCT number)	NCT01827046
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 8523

Notes:

Sponsors

Sponsor organisation name	Newcastle University
Sponsor organisation address	Wolfson Research Centre, Newcastle upon Tyne, United Kingdom, NE4 5PL
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Scientific contact	Dr Barbara Gregson, Newcastle University, +44 01912085793, barbara.gregson@ncl.ac.uk
Sponsor organisation name	Johns Hopkins University
Sponsor organisation address	750 East Pratt Street, 16th Floor, Baltimore, United States, 21202
Public contact	Daniel Hanley, MD, Johns Hopkins University, +1 410-361-7999, dhanley@jhmi.edu
Scientific contact	Daniel Hanley, MD, Johns Hopkins University, +1 410-361-7999, dhanley@jhmi.edu

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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 September 2018
Global end of trial reached?	Yes
Global end of trial date	28 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show whether minimally invasive surgery (MIS) plus recombinant tissue plasminogen activator (rt-PA) for three days improves outcome at six months as compared to standard medical treatment in patients with spontaneous bleeding in the brain (with no underlying cause)(ICH). It will also show whether early use of MIS+rt-PA for three days is safe for the treatment of ICH relative to rates of mortality, rebleeding, and infection in the medically treated subject at 30 days.

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	01 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, 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	Australia: 4
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	China: 10
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	United States: 393

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 16
Worldwide total number of subjects	499
EEA total number of subjects	78

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)	295
From 65 to 84 years	199
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Recruitment and randomization occurred at 78 hospitals in USA, Canada, Europe, Australia, and Asia

Pre-assignment

Screening details:

After screening for eligibility, patients were randomised using a computer-generated number sequence with a block size of four or six to centrally randomise patients to image-guided MISTIE treatment (1·0 mg alteplase every 8 h for up to nine doses) or standard medical care.

Period 1

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

Blinding implementation details:

Study personnel were masked to outcome, which was determined by an adjudication committee masked to treatment allocation

Arms

Are arms mutually exclusive?	Yes
Arm title	MIS plus rt-PA management

Arm description:

Subjects randomized to the Minimally Invasive Surgery (MIS) plus rt-PA management arm will undergo minimally invasive surgery followed by up to 9 doses of 1.0 mg of rt-PA

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

Dosage and administration details:

Up to 9 doses of 1.0 mg of rt-PA will be administered through the catheter that was placed directly into the intracerebral hemorrhage using minimally invasive surgery.

Arm title	Medical Management

Arm description:

Subjects randomized to medical management will receive the standard medical therapies for the treatment of intracerebral hemorrhage, which includes ICU care only and no planned surgical intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	MIS plus rt-PA management	Medical Management
Started	250	249
Completed	249	240
Not completed	1	9
Consent withdrawn by subject	-	4

Lost to follow-up	1	5

Baseline characteristics

Reporting groups	
Reporting group title	MIS plus rt-PA management
Reporting group description:	
Subjects randomized to the Minimally Invasive Surgery (MIS) plus rt-PA management arm will undergo minimally invasive surgery followed by up to 9 doses of 1.0 mg of rt-PA	
Reporting group title	Medical Management
Reporting group description:	
Subjects randomized to medical management will receive the standard medical therapies for the treatment of intracerebral hemorrhage, which includes ICU care only and no planned surgical intervention.	

Reporting group values	MIS plus rt-PA management	Medical Management	Total
Number of subjects	250	249	499
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)	146	149	295
From 65-84 years	104	95	199
85 years and over	0	5	5
Age continuous Units: years			
median	62	62	
inter-quartile range (Q1-Q3)	52 to 70	53 to 71	-
Gender categorical Units: Subjects			
Female	91	103	194
Male	159	146	305
Race Units: Subjects			
American Indian or alaska Native	1	1	2
Asian	12	18	30
Native Hawaiian or other Pacifiec Islander	0	3	3
Black or African american	46	41	87
White	190	184	374
More than one race	0	2	2
Unknown or Not reported	1	0	1
Region of enrollment Units: Subjects			
Australia	2	2	4
Canada	3	4	7

China	5	5	10
Germany	4	4	8
Spain	10	12	22
Great Britain	16	16	32
Hungary	8	8	16
Israel	3	4	7
United States	199	194	393
Tobacco use Units: Subjects			
Yes	50	39	89
No	200	210	410
Cocaine use Units: Subjects			
Yes	11	9	20
No	239	240	479
On anticoagulants Units: Subjects			
Yes	24	10	34
No	226	239	465
Use of Hormone replacement therapy Units: Subjects			
Yes	1	3	4
No	249	246	495
Hyperlipidaemia medication compliant Units: Subjects			
Yes	96	93	189
No	154	156	310
On antiplatelet therapy Units: Subjects			
Yes	67	77	144
No	183	172	355
History of diabetes Units: Subjects			
Yes	72	67	139
No	178	182	360
History of hypertension Units: Subjects			
Yes	241	240	481
No	9	9	18
Other cardiovascular disease Units: Subjects			
Yes	38	34	72
No	212	215	427
GCS score at randomisation			
Glasgow Coma Scale (GCS) scores range from 15 (fully conscious) to 3 (Deep coma)			
Units: Subjects			
3-8	64	63	127
9-12	111	108	219
13-15	75	78	153
Ventilated at randomisation Units: Subjects			

Yes	107	102	209
No	143	147	290
mRS score before stroke			
Measure Description: Score 0 = No symptoms. Score 1 = Having symptoms but no significant disability, and is able to carry out all usual activities			
Units: Subjects			
No symptoms	230	233	463
Having symptoms but no significant disability	20	16	36
Clot location			
Units: Subjects			
Deep	163	144	307
Lobar	87	105	192
NIHSS score at randomisation			
NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The maximum possible score is 42, with the minimum score being 0. Stroke severity is scored in the following way:0=No stroke symptoms,1-4=Minor stroke, 5-15=Moderate stroke,16- 20=Moderate to severe stroke, 21-42=Severe stroke			
Units: Units on a scale			
median	19	19	
inter-quartile range (Q1-Q3)	15 to 23	15 to 23	-
Diagnostic CT at presentation - IntraCerebral Hemorrhage (ICH) volume			
Units: mL			
median	42.7	41.5	
inter-quartile range (Q1-Q3)	30.4 to 54.5	30.9 to 55.3	-
Diagnostic CT at presentation - IntraVentricular Hemorrhage (IVH) volume			
Units: mL			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 1.7	0 to 1.9	-
Stability CT (last CT before randomisation) - IntraCerebral Hemorrhage (ICH) volume			
Units: mL			
median	45.8	45.3	
inter-quartile range (Q1-Q3)	35.4 to 59.6	35.4 to 57.2	-
Stability CT (last CT before randomisation) - IntraVentricular Hemorrhage (IVH) volume			
Units: mL			
median	0.3	0.4	
inter-quartile range (Q1-Q3)	0 to 3.1	0 to 3.2	-
Systolic blood pressure at presentation			
Units: mm Hg			
median	177	176	
inter-quartile range (Q1-Q3)	155 to 208	158 to 200	-
Diastolic blood pressure at presentation			
Units: mm Hg			
median	99	98	
inter-quartile range (Q1-Q3)	85 to 113	84 to 114	-
Systolic blood pressure at randomisation			
Units: mm Hg			

median	138	138	
inter-quartile range (Q1-Q3)	130 to 148	131 to 148	-
Diastolic blood pressure at randomisation			
Units: mm Hg			
median	70	69	
inter-quartile range (Q1-Q3)	63 to 78	60 to 77	-
Time from stroke to diagnostic CT			
Units: Hours			
median	2.2	1.9	
inter-quartile range (Q1-Q3)	1.1 to 6.0	1.2 to 4.8	-
Time from stroke to stability CT			
Units: Hours			
median	36.4	36.3	
inter-quartile range (Q1-Q3)	23.4 to 52.6	23.6 to 48.6	-

End points

End points reporting groups

Reporting group title	MIS plus rt-PA management

Reporting group description:

Subjects randomized to the Minimally Invasive Surgery (MIS) plus rt-PA management arm will undergo minimally invasive surgery followed by up to 9 doses of 1.0 mg of rt-PA

Reporting group title	Medical Management

Reporting group description:

Subjects randomized to medical management will receive the standard medical therapies for the treatment of intracerebral hemorrhage, which includes ICU care only and no planned surgical intervention.

Primary: 1.Dichotomized, Adjudicated Modified Rankin Scale Score 0-3 vs. 4-6 at 365 Days Post Ictus (Adjusted)

End point title	1.Dichotomized, Adjudicated Modified Rankin Scale Score 0-3 vs. 4-6 at 365 Days Post Ictus (Adjusted)

End point description:

Dichotomized, adjudicated, cross-sectional modified Rankin Scale (mRS) score 0-3 vs. 4-6 at 365 days post-ictus, adjusting for baseline (pre-randomization) variables used in covariate adaptive randomization as well as the clinically established severity variables IVH size and ICH location (lobar or deep). Ictus refers to symptom onset.
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-No symptoms at all, 1=No significant disability, 2=Slight disability, 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:

Day 365

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249[1]	240[2]		
Units: Number of participants				
mRS 0-3	110	100		
mRS 4-6	139	140		

Notes:

[1] - Includes participants with mRS scores available at day 365.

[2] - Includes participants with mRS scores available at day 365.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management

Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	10.7

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted for age, GCS, stability ICH volume, stability IVH volume, ICH deep location	
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	489
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Multivariate Logit Model
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	12

Secondary: 2. Dichotomized Extended Glasgow Outcome Scale (eGOS) Score UGR-US vs. LS-Death at 365 Days Post Ictus (Adjusted)

End point title	2. Dichotomized Extended Glasgow Outcome Scale (eGOS) Score UGR-US vs. LS-Death at 365 Days Post Ictus (Adjusted)

End point description:

Dichotomized, cross-sectional extended Glasgow Outcome Scale (eGOS) score upper good recovery (UGR) through upper severe disability (US) vs. lower severe disability (LS) through death at 365 days post ictus, adjusting for baseline (pre-randomization) variables used in covariate adaptive randomization as well as the clinically established severity variables IVH size and ICH location (lobar or deep).
The eGOS 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 as: 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. Dichotomous variable coding is as follows: 1=codes 4-8, 0=codes 1-3.

End point type	Secondary

End point timeframe:

Day 365

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244[3]	234[4]		
Units: Number of participants				
eGOS UGR-US (4-8)	94	84		
eGOS LS-Death (1-3)	150	150		

Notes:

[3] - Those with non-missing mRS scores at 365 days post ictus

[4] - Those with non-missing mRS scores at 365 days post ictus

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.11

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Multivariate logit model adjusted for age, GCS, stability ICH volume, stability IVH volume and ICH deep location	
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Multivariate Logit Model
Parameter estimate	Risk difference (RD)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.97

Secondary: 3. All Cause Mortality Longitudinally From Ictus to 365 Days (Adjusted)	
End point title	3. All Cause Mortality Longitudinally From Ictus to 365 Days (Adjusted)
End point description: By group comparison of mortality from ictus to 365 days adjusted for baseline severity.	
End point type	Secondary
End point timeframe: Day 365	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of participants	48	62		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08
Method	Logrank

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Adjusted Cox proportional Hazard adjusted for age, GCS, Stability ICH volume, Stability IVH volume, ICH deep location, diabetes, cardiovascular disease and race.	
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	Adjusted cox proportional hazard
Parameter estimate	Cox proportional hazard
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.98

Secondary: 4. Clot Removal (Amount of Residual Blood)

End point title	4. Clot Removal (Amount of Residual Blood)

End point description:

Relationship between clot removal as an Area Under the Curve (AUC) clot assessment that estimates the time-averaged clot volume from ictus to end of treatment (EOT i.e. 24 hours after last dose) as AUC clot exposure and
functional outcome (proportion 0-3 Modified Rankin Scale (mRS)).

End point type	Secondary

End point timeframe:

24 hours after last dose

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[5]	239[6]		
Units: 10mL x days				
arithmetic mean (standard deviation)				
mRS 0-3	2.69 (± 1.11)	4.11 (± 1.35)		
mRS 4-6	3.32 (± 1.33)	5.26 (± 1.82)		

Notes:

[5] - Includes patients who survived through the dosing period

[6] - Includes patients who survived through the dosing period

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Medical Management v MIS plus rt-PA management
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Logit model
Parameter estimate	Odds ratio (OR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.8

Statistical analysis title	Statistical Analysis 2
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	0.78

Secondary: 5. Patient Disposition: Home Days Over 365 Days Time From Ictus.	
End point title	5. Patient Disposition: Home Days Over 365 Days Time From Ictus.
End point description:	
By group comparison of cumulative days at home during the 365 days post ictus.	
End point type	Secondary
End point timeframe:	
During 365 days of follow-up	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166[7]	157[8]		
Units: Days				
median (inter-quartile range (Q1-Q3))	306 (237 to 329)	300 (232 to 328)		

Notes:

[7] - Includes only patients with cumulative home days at any time during the 365 days of followup.

[8] - Includes only patients with cumulative home days at any time during the 365 days of followup.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management

Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Wilcoxon (Mann-Whitney)

Secondary: 6. Patient Disposition: Patient Location at 365 Days Post Ictus (i.e., Good vs. Bad Location) (Adjusted)

End point title	6. Patient Disposition: Patient Location at 365 Days Post Ictus (i.e., Good vs. Bad Location) (Adjusted)

End point description:

Patient disposition: By group comparison of residential location at day 365 post ictus adjusted for baseline severity. Good locations refers to home and rehabilitation; and bad locations refers to acute care, long-term care and death.

End point type	Secondary

End point timeframe:

Day 365

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	201[9]	178[10]		
Units: Number of participants				
Good location	163	151		
Bad location	87	98		

Notes:

[9] - Includes patients who were alive and not lost to follow-up at day 365

[10] - Includes patients who were alive and not lost to follow-up at day 365

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	379
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.11

Secondary: 7. Dichotomized, Adjudicated, Cross-sectional Modified Rankin Scale (mRS) Score 0-3 vs. 4-6 180 Days Post Ictus (Adjusted)

End point title	7. Dichotomized, Adjudicated, Cross-sectional Modified Rankin Scale (mRS) Score 0-3 vs. 4-6 180 Days Post Ictus (Adjusted)

End point description:

Dichotomized, adjudicated, cross-sectional modified Rankin Scale (mRS) score 0-3 vs. 4-6 at 180 days post-ictus, adjusting for baseline (pre-randomization) variables used in covariate adaptive randomization as well as the clinically established severity variables IVH size and ICH location (lobar or deep).
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	Secondary

End point timeframe:

Day 180 post ictus

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250[11]	243[12]		
Units: Number of participants				
mRS 0-3	99	93		
mRS 4-6	151	150		

Notes:

[11] - Includes patients who were not lost to followup at day 180

[12] - Includes patients who were not lost to followup at day 180

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.07

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:	
Multivariate logit model adjusted for age, GCS, Stability ICH volume, Stability IVH volume, ICH deep location	
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.94

Secondary: 8. Dichotomized Extended Glasgow Outcome Scale (eGOS) Score UGR-US vs. LS-Death at 180 Days Post Ictus (Adjusted)

End point title	8. Dichotomized Extended Glasgow Outcome Scale (eGOS) Score UGR-US vs. LS-Death at 180 Days Post Ictus (Adjusted)

End point description:

Dichotomized, cross-sectional extended Glasgow Outcome Scale (eGOS) score upper good recovery (UGR) through upper severe disability (US) vs. lower severe disability (LS) through death at 180 days post ictus, adjusting for baseline (pre-randomization) variables used in covariate adaptive randomization as well
as the clinically established severity variables IVH size and ICH location (lobar or deep).
The eGOS 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 as: 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. Dichotomous variable coding is as follows: 1=codes 4-8, 0=codes 1-3.

End point type	Secondary

End point timeframe:

Day 180 post ictus

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	243[13]		
Units: Number of participants				
eGOS UGR-US (4-8)	81	76		
eGOS LS-Death (1-3)	169	167		

Notes:

[13] - Includes patients not lost to followup at day 180

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.09

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Multivariate logit model adjusted for age, GCS, Stability ICH volume, Stability IVH volume, ICH deep location	
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.35
Method	Multivariate Logit Model
Parameter estimate	Odds ratio (OR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.97

Secondary: 9.Type and Intensity of ICU Management: ICU Days	
End point title	9.Type and Intensity of ICU Management: ICU Days
End point description:	
By group comparison of cumulative number of days in the Intensive Care Unit (ICU) in a hospital	
End point type	Secondary
End point timeframe:	
Up to 365 days	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	240[14]	238[15]		
Units: Days				
median (inter-quartile range (Q1-Q3))	10 (7 to 17)	10 (5 to 16)		

Notes:

[14] - Includes patients with cumulative ICU days during the 365 days of follow-up

[15] - Includes patients with cumulative ICU days during the 365 days of follow-up

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	478
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Median test

Secondary: 10. Type and Intensity of ICU Management: Hospital Days

End point title	10. Type and Intensity of ICU Management: Hospital Days
End point description:	
By group comparison of total number of days in the hospital	
End point type	Secondary
End point timeframe:	
Up to 365 days	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Days				
median (inter-quartile range (Q1-Q3))	17 (13 to 27)	17 (10 to 25)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.75
Method	Median test

Secondary: 11. EQ-VAS

End point title	11. EQ-VAS

End point description:

By group comparison of EQ-VAS at day 365 post ictus. The EuroQol Visual Analogue Scale (EQ-VAS) is a self-reported measure of health status. It is a marked scale where subjects 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:

Day 365

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183[16]	164[17]		
Units: Score on a scale				
median (inter-quartile range (Q1-Q3))	70 (50 to 80)	70 (50 to 80)		

Notes:

[16] - Includes patients who survived or were not lost to followup through 365 days

[17] - Includes patients who survived or were not lost to followup through 365 days

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	347
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	Wilcoxon (Mann-Whitney)

Secondary: 12. EuroQol 5 Dimensional Scale (EQ-5D)

End point title	12. EuroQol 5 Dimensional Scale (EQ-5D)

End point description:

By group comparison of EQ-5D at day 365 post ictus. The EuroQol 5 Dimensional Scale (Eq-5D) is a self-reported measure of health status. It is arranged to assess domains related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, codes were 1=no problems, 2=some problems, 3=extreme problems, and 9=unknown. Having a problem in at least 1 domain was coded as 1 (originally represented by 2 or 3) and no problems as 0 (originally represented by 1)

End point type	Secondary

End point timeframe:

Day 365

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192[18]	170[19]		
Units: Number of participants				
Any problem	176	155		
No problem	16	15		

Notes:

[18] - Includes patients who survived or were not lost to followup through 365 days

[19] - Includes patients who survived or were not lost to followup through 365 days

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Chi-squared

Secondary: 13. First-week (Operative) Mortality

End point title	13. First-week (Operative) Mortality

End point description:

Mortality and Safety events: By group comparison of mortality within the first 7 days post randomization.

End point type	Secondary

End point timeframe:

Day 7

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of participants	1	10		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Chi-squared

Secondary: 14. All Cause Mortality

End point title	14. All Cause Mortality
End point description:	
By group comparison of mortality from all causes within the first 30 days post randomization.	
End point type	Secondary
End point timeframe:	
Day 30	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of participants	23	37		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Chi-squared

Secondary: 15. Adjudicated Symptomatic Brain Bleeding Within 72 Hours After Last Dose

End point title	15. Adjudicated Symptomatic Brain Bleeding Within 72 Hours After Last Dose
End point description:	
By group comparison of the percentage of subjects experiencing one or more adjudicated symptomatic brain bleeding events within the first 30 days post randomization.	
End point type	Secondary
End point timeframe:	
72 hours after last dose	

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of participants	6	3		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Chi-squared

Secondary: 16. Adjudicated Bacterial Brain Infection

End point title	16. Adjudicated Bacterial Brain Infection

End point description:

By group comparison of the percentage of subjects experiencing one or more adjudicated brain bacterial infection events within the first 30 days post randomization.

End point type	Secondary

End point timeframe:

Day 30

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of participants	2	0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management

Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Chi-squared

Secondary: 17. Total Serious Adverse Events (SAE) at 30 Days

End point title	17. Total Serious Adverse Events (SAE) at 30 Days

End point description:

By group comparison of the total number of adjudicated serious adverse events that occurred within the first 30 days post randomization.

End point type	Secondary

End point timeframe:

Day 30

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of events	123	136		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	MIS plus rt-PA management v Medical Management
Number of subjects included in analysis	499
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Chi-squared

Secondary: 18. Number of Adverse Events (AEs) Within the First 30 Days Post Ictus

End point title	18. Number of Adverse Events (AEs) Within the First 30 Days Post Ictus

End point description:

By group comparison of the total number of adjudicated adverse events (AE) across all coded organ systems that occurred within the first 30 days post ictus.

End point type	Secondary

End point timeframe:

Day 30

End point values	MIS plus rt-PA management	Medical Management		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	250	249		
Units: Number of events	477	378		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
30 days post ictus	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	MIS plus rt-PA management
Reporting group description:	
Subjects randomized to the Minimally Invasive Surgery (MIS) plus rt-PA management arm will undergo minimally invasive surgery followed by up to 9 doses of 1.0 mg of rt-PA	
Reporting group title	Medical Management
Reporting group description:	
Subjects randomized to medical management will receive the standard medical therapies for the treatment of intracerebral hemorrhage, which includes ICU care only and no planned surgical intervention.	

Serious adverse events	MIS plus rt-PA management	Medical Management	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 250 (30.00%)	84 / 249 (33.73%)	
number of deaths (all causes)	48	62	
number of deaths resulting from adverse events	24	38	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	3 / 250 (1.20%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			

subjects affected / exposed	6 / 250 (2.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	3 / 250 (1.20%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	17 / 250 (6.80%)	33 / 249 (13.25%)	
occurrences causally related to treatment / all	14 / 41	0 / 62	
deaths causally related to treatment / all	1 / 1	0 / 8	
General disorders and administration site conditions			
General disorders			
subjects affected / exposed	13 / 250 (5.20%)	26 / 249 (10.44%)	
occurrences causally related to treatment / all	1 / 13	0 / 27	
deaths causally related to treatment / all	1 / 12	0 / 25	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	3 / 250 (1.20%)	4 / 249 (1.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 2	
Respiratory, thoracic and mediastinal disorders			
Resoiratory, thoracic and mediastinal disorders			
subjects affected / exposed	26 / 250 (10.40%)	14 / 249 (5.62%)	
occurrences causally related to treatment / all	0 / 40	0 / 25	
deaths causally related to treatment / all	0 / 8	0 / 1	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

REnal and urinary disorders			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	2 / 250 (0.80%)	4 / 249 (1.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	1 / 250 (0.40%)	0 / 249 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MIS plus rt-PA management	Medical Management	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	205 / 250 (82.00%)	169 / 249 (67.87%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	1 / 250 (0.40%)	1 / 249 (0.40%)	
occurrences (all)	1	2	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	14 / 250 (5.60%)	13 / 249 (5.22%)	
occurrences (all)	39	29	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	17 / 250 (6.80%)	12 / 249 (4.82%)	
occurrences (all)	53	42	
Immune system disorders			

Immune system disorders			
subjects affected / exposed	0 / 250 (0.00%)	1 / 249 (0.40%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	30 / 250 (12.00%)	33 / 249 (13.25%)	
occurrences (all)	67	62	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	6 / 250 (2.40%)	5 / 249 (2.01%)	
occurrences (all)	14	13	
Investigations			
Investigations			
subjects affected / exposed	1 / 250 (0.40%)	7 / 249 (2.81%)	
occurrences (all)	12	20	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	1 / 250 (0.40%)	2 / 249 (0.80%)	
occurrences (all)	4	3	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	3 / 250 (1.20%)	5 / 249 (2.01%)	
occurrences (all)	15	11	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	108 / 250 (43.20%)	47 / 249 (18.88%)	
occurrences (all)	216	107	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 250 (0.80%)	0 / 249 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	5 / 250 (2.00%)	7 / 249 (2.81%)	
occurrences (all)	12	17	
Hepatobiliary disorders			

Hepatobiliary disorders subjects affected / exposed occurrences (all)	0 / 250 (0.00%) 0	2 / 249 (0.80%) 2	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	0 / 250 (0.00%) 0	1 / 249 (0.40%) 3	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	3 / 250 (1.20%) 5	2 / 249 (0.80%) 5	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	2 / 250 (0.80%) 3	0 / 249 (0.00%) 0	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	9 / 250 (3.60%) 16	25 / 249 (10.04%) 41	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	3 / 250 (1.20%) 17	6 / 249 (2.41%) 20	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 July 2015	In this amendment, there are a large number of administrative clarifications; the results of other studies that have now reported have been incorporated – they do not alter the trial; the inclusion and exclusion criteria have been amended slightly removing the upper age limit, and adding etiological exclusions, and medication exclusions; a longer stability time between catheter placement and drug administration is required.; further MRI sequences have been added to the imaging. The optional substudies investigate whether certain factors observed on imaging are related to perioperative bleeding and outcome after this treatment; the relationship between inflammatory mediators and haematoma volume and outcome and finally whether specific genotypes are associated with outcome. In addition two further UK sites have been added since the initial acceptance was obtained. The contact name and address for the legal representative of the sponsor in the UK has also changed.

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/30739747