Clinical trial results:
Efficacy and Safety Study of Desmoteplase to Treat Acute Ischemic Stroke (DIAS-4)

Summary

EudraCT number	2008-005539-14
Trial protocol	BE SE FI IE DK GB IT EE ES
Global end of trial date	07 October 2014

Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016

Trial information

Trial identification

Sponsor protocol code	012649A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00856661
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@lundbeck.com , H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com
Scientific contact	LundbeckClinicalTrials@lundbeck.com , H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 October 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2014
Global end of trial reached?	Yes
Global end of trial date	07 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether desmoteplase is effective and safe in the treatment of patients with acute ischaemic stroke when given within 3 to 9 hours from onset of stroke symptoms.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2008) and ICH Good Clinical Practice (1996)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Denmark: 11
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Finland: 12
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Canada: 19
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Thailand: 3
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 86
Country: Number of subjects enrolled	Vietnam: 5
Country: Number of subjects enrolled	South Africa: 1

Worldwide total number of subjects	270
EEA total number of subjects	123

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)	84
From 65 to 84 years	182
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Desmoteplase

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Desmoteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

90 µg/kg bodyweight, IV, single bolus over 1 to 2 minutes on 1st day

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

IV, single bolus over 1 to 2 minutes on 1st day

Number of subjects in period 1	Desmoteplase	Placebo
Started	135	135
Treated	126	131
Completed	108	106
Not completed	27	29
Consent withdrawn by subject	1	2
Physician decision	8	5

Death	15	18
Lost to follow-up	1	3
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Desmoteplase
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Desmoteplase	Placebo	Total
Number of subjects	135	135	270
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)	42	42	84
From 65-84 years	90	92	182
85 years and over	3	1	4
Age continuous Units: years			
arithmetic mean	69.1	68.2	
standard deviation	± 11.1	± 12.5	-
Gender categorical Units: Subjects			
Female	72	69	141
Male	63	66	129
Race Units: Subjects			
Black or African American	11	9	20
White	111	115	226
Asian	7	6	13
Other	6	5	11

End points

End points reporting groups

Reporting group title	Desmoteplase
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Modified Rankin Scale Score (mRS) (Percentage of Participants With mRS Scores 0-2)

End point title	Modified Rankin Scale Score (mRS) (Percentage of Participants With mRS Scores 0-2)

End point description:

The mRS is a clinician-rated scale designed to provide a global assessment of the patients' dependency after stroke. The scale consists of a single item measuring the patient's function based on the ability to perform daily activities. The patient is rated on a 7-point scale from 0 to 6, where a score of 5 corresponds to severe disability, and 6 to death. Assessment of a pre-stroke mRS score is based on an interview addressing the status of the patient prior to the stroke

End point type	Primary

End point timeframe:

Day 90

End point values	Desmoteplase	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	128		
Units: percentage				
number (not applicable)	41.9	35.9		

Statistical analyses

Statistical analysis title	Modified Rankin Scale Score (mRS)

Statistical analysis description:

Statistical Analysis 1 for Modified Rankin Scale Score (mRS) (Percentage of Participants With mRS Scores 0-2). All patients who were treated and had at least one valid post-baseline assessment of the mRS. As death is a valid outcome on the mRS, patients who died within 90 days after IMP administration were included. If no assessment was available for last observation carried forward after baseline, the mRS score was set to 5 if alive, or 6, if otherwise = death

Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.229
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.45

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	2.64

Secondary: National Institutes of Health Stroke Scale (NIHSS) Score

End point title	National Institutes of Health Stroke Scale (NIHSS) Score

End point description:

The NIHSS is a clinician-rated, 15-item scale designed to assess the severity of stroke-related neurological deficits: level of consciousness, eye movements, visual fields, facial symmetry, motor strength (arm and leg), coordination, sensation, language (aphasia and dysarthria), and neglect. Each item is rated on a 3-, 4-, or 5-point scale ranging from 0 (normal) to the maximum score (extremely severe symptoms). The total score of the 15 items ranges from 0 to 42, where lower scores indicate less impairment. Results are shown as percentage of participants with NIHSS Score <=1 or NIHSS Decrease >=8

End point type	Secondary

End point timeframe:

90 days

End point values	Desmoteplase	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	128		
Units: percent				
number (not applicable)	49.2	50.8		

Statistical analyses

Statistical analysis title	Statistical Analysis for NIHSS Score

Statistical analysis description:

Statistical Analysis for National Institutes of Health Stroke Scale (NIHSS) Score. (Percentage of Participants With NIHSS Score <=1 or NIHSS Decrease >=8. Two and three patients from the desmoteplase and placebo group, respectively, had no valid functional assessment done. Hence, the full analysis set consisted of 124 and 128 patients, respectively.

Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9401
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.62

Secondary: Composite of mRS & NIHSS Response

End point title	Composite of mRS & NIHSS Response
End point description:	
Percentage of Participants With mRS Scores 0-2 and NIHSS score <= 1 or NIHSS Decrease >= 8.	
End point type	Secondary
End point timeframe:	
Day 90	

End point values	Desmoteplase	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	128		
Units: percent				
number (not applicable)	32.3	28.9		

Statistical analyses

Statistical analysis title	Statistical Analysis for Composite of mRS & NIHSS
Statistical analysis description:	
Percentage of Participants With mRS Scores 0-2 and NIHSS score <= 1 or NIHSS score Decrease >= 8. All patients treated, who had at least one valid post-baseline assessment of the mRS and with a baseline NIHSS score of 8 to 24. If no assessment was available for last observation carried forward after baseline, the mRS score was set to 5 if the patient was known to be alive, or 6, if otherwise = dead.	
Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5076
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.18

Secondary: Modified Ranking Scale Score (Using the Ordinal Scale)

End point title	Modified Ranking Scale Score (Using the Ordinal Scale)

End point description:

The mRS is a clinician-rated scale designed to provide a global assessment of the patients' dependency after stroke. The scale consists of a single item measuring the patient's function based on the ability to perform daily activities. The patient is rated on a 7-point scale from 0 to 6, where a score of 5 corresponds to severe disability, and 6 to death. Assessment of a pre-stroke mRS score is based on an interview addressing the status of the patient prior to the stroke

End point type	Secondary

End point timeframe:

Day 90

End point values	Desmoteplase	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	128		
Units: Scores on a scale				
least squares mean (standard error)	3.02 (± 0.14)	3.12 (± 0.15)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Modified Ranking Scale

Statistical analysis description:

Statistical Analysis for Modified Ranking Scale Score (Using the Ordinal Scale). All patients treated, who had at least one valid post-baseline assessment of the mRS. As death is a valid outcome on the mRS, patients who died within 90 days after IMP administration were included

Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	252
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6146
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.75

Adverse events

Adverse events information	
Timeframe for reporting adverse events: First dose to follow-up	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: IV, single bolus over 1 to 2 minutes 3-9 hours after symptoms onset	
Reporting group title	Desmoteplase
Reporting group description: 90 ug/kg, IV, single bolus over 1 to 2 minutes 3-9 hours after symptoms onset	

Serious adverse events	Placebo	Desmoteplase	
Total subjects affected by serious adverse events			
subjects affected / exposed	56 / 131 (42.75%)	61 / 126 (48.41%)	
number of deaths (all causes)	18	14	
number of deaths resulting from adverse events	3	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac valve fibroelastoma			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 131 (0.76%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site phlebitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	2 / 131 (1.53%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 131 (2.29%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 131 (0.76%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory acidosis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 131 (0.76%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 131 (0.00%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 131 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood culture positive			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	4 / 131 (3.05%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nih stroke scale score increased			
subjects affected / exposed	4 / 131 (3.05%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			

subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory rate increased			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 131 (0.76%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 131 (3.05%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			
subjects affected / exposed	1 / 131 (0.76%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 131 (0.76%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	

Cardiac failure			
subjects affected / exposed	0 / 131 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	2 / 131 (1.53%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	2 / 131 (1.53%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	6 / 131 (4.58%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	1 / 3	0 / 0	
Brain stem stroke			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery occlusion			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 131 (0.76%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depressed level of consciousness			

subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand mal convulsion			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	2 / 131 (1.53%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 131 (0.00%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	5 / 131 (3.82%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	2 / 131 (1.53%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
subjects affected / exposed	6 / 131 (4.58%)	10 / 126 (7.94%)	
occurrences causally related to treatment / all	2 / 6	3 / 11	
deaths causally related to treatment / all	1 / 3	1 / 3	
Syncope			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 131 (0.00%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia of chronic disease			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coagulopathy			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deficiency anaemia			
subjects affected / exposed	0 / 131 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			

subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Leukopenia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 131 (0.76%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pernicious anaemia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Pupils unequal			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 131 (1.53%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Endocarditis bacterial			
subjects affected / exposed	1 / 131 (0.76%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 131 (0.76%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pneumonia bacterial			
subjects affected / exposed	4 / 131 (3.05%)	5 / 126 (3.97%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Pulmonary sepsis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 131 (1.53%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 131 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 131 (0.76%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 131 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Desmoteplase	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 131 (81.68%)	98 / 126 (77.78%)	
Investigations			
Blood potassium decreased			
subjects affected / exposed	4 / 131 (3.05%)	8 / 126 (6.35%)	
occurrences (all)	4	8	
Nih stroke scale score increased			

subjects affected / exposed	10 / 131 (7.63%)	8 / 126 (6.35%)	
occurrences (all)	10	9	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 131 (6.87%)	3 / 126 (2.38%)	
occurrences (all)	9	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 131 (10.69%)	16 / 126 (12.70%)	
occurrences (all)	14	16	
Hypotension			
subjects affected / exposed	7 / 131 (5.34%)	4 / 126 (3.17%)	
occurrences (all)	7	4	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	13 / 131 (9.92%)	11 / 126 (8.73%)	
occurrences (all)	13	11	
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 131 (16.79%)	22 / 126 (17.46%)	
occurrences (all)	22	26	
Stroke in evolution			
subjects affected / exposed	7 / 131 (5.34%)	7 / 126 (5.56%)	
occurrences (all)	7	7	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 131 (0.76%)	11 / 126 (8.73%)	
occurrences (all)	1	12	
Pain			
subjects affected / exposed	7 / 131 (5.34%)	7 / 126 (5.56%)	
occurrences (all)	7	7	
Pyrexia			
subjects affected / exposed	11 / 131 (8.40%)	8 / 126 (6.35%)	
occurrences (all)	12	8	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	32 / 131 (24.43%)	30 / 126 (23.81%)	
occurrences (all)	32	30	
Diarrhoea			
subjects affected / exposed	8 / 131 (6.11%)	6 / 126 (4.76%)	
occurrences (all)	8	6	
Nausea			
subjects affected / exposed	14 / 131 (10.69%)	12 / 126 (9.52%)	
occurrences (all)	15	12	
Vomiting			
subjects affected / exposed	13 / 131 (9.92%)	7 / 126 (5.56%)	
occurrences (all)	14	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 131 (6.11%)	11 / 126 (8.73%)	
occurrences (all)	9	11	
Depressive symptom			
subjects affected / exposed	13 / 131 (9.92%)	13 / 126 (10.32%)	
occurrences (all)	13	13	
Insomnia			
subjects affected / exposed	11 / 131 (8.40%)	15 / 126 (11.90%)	
occurrences (all)	11	15	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	7 / 131 (5.34%)	6 / 126 (4.76%)	
occurrences (all)	7	6	
Urinary retention			
subjects affected / exposed	8 / 131 (6.11%)	3 / 126 (2.38%)	
occurrences (all)	8	5	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 131 (5.34%)	9 / 126 (7.14%)	
occurrences (all)	8	9	
Infections and infestations			
Pneumonia bacterial			

subjects affected / exposed	7 / 131 (5.34%)	3 / 126 (2.38%)	
occurrences (all)	7	3	
Urinary tract infection			
subjects affected / exposed	4 / 131 (3.05%)	8 / 126 (6.35%)	
occurrences (all)	4	8	
Urinary tract infection bacterial			
subjects affected / exposed	26 / 131 (19.85%)	22 / 126 (17.46%)	
occurrences (all)	30	27	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	12 / 131 (9.16%)	9 / 126 (7.14%)	
occurrences (all)	12	9	
Hyperglycaemia			
subjects affected / exposed	1 / 131 (0.76%)	7 / 126 (5.56%)	
occurrences (all)	1	7	
Hypokalaemia			
subjects affected / exposed	20 / 131 (15.27%)	18 / 126 (14.29%)	
occurrences (all)	21	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2012	The main rationale for the protocol amendment was the introduction of the Post-follow-up visits, up to 2 years after IMP administration. Also, the timing of the post-dose ECG was moved from 24 hours after IMP administration to be done within 4 hours after IMP administration
18 October 2013	The main rationale for the protocol amendment was adding reads to study design: "...At each site, two consecutive subjects with a baseline NIHSS score of 4-10 cannot be randomised. Hence, one or more subject(s) with a baseline NIHSS score of 11-24 must be randomised following each subject randomised with a baseline NIHSS score of 4-10." Also, the primary and secondary endpoints were additionally analyzed in the subgroup of subjects with a baseline NIHSS score of 8-24. The exploratory analysis of the primary outcome measure, mRS using ordinal logistic regression, was changed to a secondary analysis. The primary outcome measure, mRS, was also analyzed in the subgroup of subjects with time from stroke onset to treatment ≤7hours and >7 hours

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated October 2014. The recruitment into DIAS4 was stopped as the result of DIAS 3 indicated that the study was unlikely to reach its primary endpoint with the current protocol

Notes: