Clinical trial results:
A randomised, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of desmoteplase in subjects with acute ischemic stroke

Summary

EudraCT number	2008-000622-40
Trial protocol	NL HU AT DE FR ES EE
Global end of trial date	07 July 2014

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	12402A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00790920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark,
Public contact	LundbeckClinicalTrials@lundbeck.com, H. Lundbeck A/S, LundbeckClinicalTrials@lundbeck.com
Scientific contact	H. Lundbeck A/S, 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	24 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2014
Global end of trial reached?	Yes
Global end of trial date	07 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of desmoteplase 90 µg/kg versus placebo in terms of favourable outcome at Day 90 in patients with acute ischemic stroke.

Protection of trial subjects:

The nature of the illness often implies impairment to understand and /or consent to participate in a study in the acute setting. Hence, consenting procedures, normally done by the patient and/or his/her legal representative, were extended to include consent by an impartial witness, a proxy (a relative), or a study-independent physician. However, this was only allowed under the conditions listed in the protocol and if allowed by local law and regulations and approved by the relevant ethics committee or IRB

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	Austria: 25
Country: Number of subjects enrolled	Estonia: 25
Country: Number of subjects enrolled	France: 35
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Hong Kong: 17
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Korea, Republic of: 52
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Thailand: 56
Country: Number of subjects enrolled	Taiwan: 50

Country: Number of subjects enrolled	Vietnam: 72
Worldwide total number of subjects	492
EEA total number of subjects	181

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)	175
From 65 to 84 years	308
85 years and over	9

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening for patients with occlusion or high-grade stenosis of the proximal cerebral arteries, and excluded patients with intracranial haemorrhage (ICH), signs of extensive infarct core, or subacute infarction.

Period 1

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

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:

Desmoteplase 90 µg/kg single bolus within 3-9 hours after the onset of stroke symptoms

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 use

Dosage and administration details:

single bolus within 3-9 hours after the onset of stroke symptoms

Number of subjects in period 1[1]	Desmoteplase	Placebo
Started	240	238
Completed	200	205
Not completed	40	33
Adverse event, serious fatal	23	22
Consent withdrawn by subject	8	2

administrative or other reasons	1	3
Lost to follow-up	8	4
Protocol deviation	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 492 patients were randomised (245 and 247 to placebo and treatment, respectively) However, only 478 (238 and 240 to placebo and treatment, respectively) were actually treated

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	240	238	478
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)	85	85	170
From 65-84 years	150	149	299
85 years and over	5	4	9
Age continuous Units: years			
arithmetic mean	67	67.7	
standard deviation	± 14.1	± 13.2	-
Gender categorical Units: Subjects			
Female	125	112	237
Male	115	126	241
Race Units: Subjects			
White	99	95	194
Black or african american	2	1	3
Asian	138	142	280
Other	1	0	1

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

End point title	Modified Rankin Scale Score

End point description:

mRS response (score of 0 to 2) at Day 90

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:

90 days

End point values	Desmoteplase	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	237		
Units: Score (%)				
number (not applicable)	51.3	49.8		

Statistical analyses

Statistical analysis title	mRS response (score 0 to 2) at Day 90
Comparison groups	Placebo v Desmoteplase
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.81

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.9

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	236	237		
Units: score (%)				
number (not applicable)	61.9	56.1		

Statistical analyses

Statistical analysis title	National Institutes of Health Stroke Scale (NIHSS)
Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.9

Secondary: mRS & NIHSS Response

End point title	mRS & NIHSS Response

End point description:

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	236	237		
Units: Score (%)				
number (not applicable)	45.8	42.2		

Statistical analyses

Statistical analysis title	mRS & NIHSS
Comparison groups	Desmoteplase v Placebo
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Odds ratio (OR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.93

Secondary: Modified Ranking Scale Score (using the ordinal scale)

End point title	Modified Ranking Scale Score (using the ordinal scale)

End point description:

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	236	237		
Units: Score				
least squares mean (standard error)	2.46 (± 0.15)	2.65 (± 0.15)		

Statistical analyses

Statistical analysis title	mRS Scores at Day 90
Comparison groups	Placebo v Desmoteplase
Number of subjects included in analysis	473
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.74

Notes:

[1] - Ordinal logistic regression

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

Serious adverse events	Desmoteplase	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 240 (26.67%)	69 / 238 (28.99%)	
number of deaths (all causes)	24	23	
number of deaths resulting from adverse events	6	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ovarian cancer metastatic			

alternative assessment type: Non-systematic			
subjects affected / exposed[1]	0 / 125 (0.00%)	1 / 112 (0.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Withdrawal of life support			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Catheter site haemorrhage			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Sudden death			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung disorder			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 240 (2.50%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pneumothorax			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			
Anxiety disorder			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac disorders			
Acute coronary syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Atrial fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 240 (1.25%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac discomfort			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Cardiac failure congestive			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Congestive cardiomyopathy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ventricular fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basilar artery thrombosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	6 / 238 (2.52%)	
occurrences causally related to treatment / all	2 / 3	3 / 6	
deaths causally related to treatment / all	1 / 2	1 / 3	
Cerebral artery occlusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 240 (2.08%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	5 / 5	4 / 4	
deaths causally related to treatment / all	1 / 1	3 / 3	
Cerebral infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epilepsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Hydrocephalus			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 240 (2.08%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudobulbar palsy			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke in evolution			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	8 / 238 (3.36%)	
occurrences causally related to treatment / all	2 / 3	2 / 8	
deaths causally related to treatment / all	1 / 1	0 / 1	
Subarachnoid haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral artery occlusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diaphragmatic hernia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric ulcer haemorrhage			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal failure acute			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Musculoskeletal and connective tissue disorders			
Spondylolisthesis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 240 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis infectious			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocarditis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 2	
Pneumonia bacterial			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 240 (0.42%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia escherichia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 240 (1.25%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Staphylococcal sepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 240 (0.83%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 240 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This Adverse Event only apply to women

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

Non-serious adverse events	Desmoteplase	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	182 / 240 (75.83%)	173 / 238 (72.69%)	
Investigations			
Nih stroke scale score increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 240 (5.42%)	11 / 238 (4.62%)	
occurrences (all)	13	12	
Vascular disorders			
Hypertension			
alternative assessment type: Non-systematic			
subjects affected / exposed	29 / 240 (12.08%)	20 / 238 (8.40%)	
occurrences (all)	32	20	
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	18 / 240 (7.50%)	18 / 238 (7.56%)	
occurrences (all)	18	19	
Nervous system disorders			
Haemorrhagic transformation stroke			
alternative assessment type: Non-systematic			

subjects affected / exposed	14 / 240 (5.83%)	16 / 238 (6.72%)	
occurrences (all)	14	17	
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	37 / 240 (15.42%)	34 / 238 (14.29%)	
occurrences (all)	39	39	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	29 / 240 (12.08%)	20 / 238 (8.40%)	
occurrences (all)	30	23	
Gastrointestinal disorders			
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	61 / 240 (25.42%)	66 / 238 (27.73%)	
occurrences (all)	62	70	
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 240 (6.25%)	14 / 238 (5.88%)	
occurrences (all)	16	14	
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 240 (6.25%)	9 / 238 (3.78%)	
occurrences (all)	15	9	
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	21 / 240 (8.75%)	24 / 238 (10.08%)	
occurrences (all)	21	26	
Psychiatric disorders			
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 240 (4.58%)	13 / 238 (5.46%)	
occurrences (all)	11	13	
Depressive symptom			
alternative assessment type: Non-systematic			

subjects affected / exposed	22 / 240 (9.17%)	17 / 238 (7.14%)	
occurrences (all)	22	17	
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 240 (9.17%)	21 / 238 (8.82%)	
occurrences (all)	22	22	
Renal and urinary disorders			
Haematuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 240 (11.25%)	27 / 238 (11.34%)	
occurrences (all)	28	27	
Infections and infestations			
Pneumonia bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 240 (5.42%)	8 / 238 (3.36%)	
occurrences (all)	14	8	
Urinary tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	30 / 240 (12.50%)	29 / 238 (12.18%)	
occurrences (all)	33	30	
Urinary tract infection bacterial			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 240 (7.08%)	24 / 238 (10.08%)	
occurrences (all)	20	24	
Metabolism and nutrition disorders			
Hypokalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	35 / 240 (14.58%)	28 / 238 (11.76%)	
occurrences (all)	36	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2009	The statistical design of the study was modified in order to align with the twin-study (12649A; DIAS-4). The original design was changed to a fixed-sample design, including an interim futility analysis without adjusting the significance level in the final analysis. With the fixed design, a two-sided test at the 0.05 level of significance was used. The sample size was increased to 400 treated patients in order to be able to detect a smaller effect size of 13% (38% desmoteplase responders versus 25% placebo responders) instead of 15%. The following was added: hierarchical ordering of endpoints, identification of the full-analysis set (FAS) as the primary analysis set, sensitivity analyses.
09 May 2012	Post-follow-up visits, up to 2 years after IMP administration, were added to explore the long-term antibody response and safety profile. Also, long-term assessments of living arrangements, quality of life, and a measure of resource utilisation were added. The timing of the post-dose ECG was moved from 24 hours after IMP administration to within 4 hours after IMP administration, as this was closer to the peak plasma concentration. Central reading of the ECGs was added. Exclusion criteria were clarified
21 September 2012	The total number of patients planned was increased from 400 to 480, to preserve the risk of a type II error at an acceptable level, as a review of blinded data showed that the overall percentage of responders in the study was higher than anticipated.
18 October 2013	Additional analyses of the primary and secondary endpoints were added to investigate the subgroup of patients with a baseline NIHSS score of 8-24. Analysis of the mRS using ordinal logistic regression was moved from the exploratory analysis to the secondary analysis. Subgroup analyses investigating the relationship between time from stroke onset to treatment and clinical outcome were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported