Clinical trial results:
Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomised, double-blind, placebo-controlled trial

Summary

EudraCT number	2011-005906-32
Trial protocol	DE BE GB DK ES NL AT
Global end of trial date	21 September 2017

Results information

Result version number	v1 (current)
This version publication date	22 February 2021
First version publication date	22 February 2021

Trial information

Trial identification

Sponsor protocol code	WAKE-UP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01525290
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center Hamburg-Eppendorf
Sponsor organisation address	Martinistr. 52, Hamburg, Germany, 20246
Public contact	Götz Thomalla, University Medical Center Hamburg-Eppendorf, +49 40741050137, thomalla@uke.de
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2017
Global end of trial reached?	Yes
Global end of trial date	21 September 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective is to test efficacy and safety of MRI-based intravenous thrombolysis with Alteplase in patients waking up with stroke symptoms or patients with unknown symptom onset.

Protection of trial subjects:

See trial protocol

Background therapy:

See trial protocol

Evidence for comparator:

See trial protocol

Actual start date of recruitment	01 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Spain: 45
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 47
Country: Number of subjects enrolled	Denmark: 144
Country: Number of subjects enrolled	France: 62
Country: Number of subjects enrolled	Germany: 162
Worldwide total number of subjects	503
EEA total number of subjects	468

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	308
From 65 to 84 years	195
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first enrolment: 12.10.2012, Date of last completed: 21.09.2017
The treatment has been initiated as soon as possible within 60 minutes of the end of the MRI examination.

Pre-assignment

Screening details:

1362 patients underwent screening at 61 centers in eight European countries. Of these patients, 859 were excluded, including 455 who had no mismatch between findings on MRI diffusion-weighted imaging and FLAIR and 15 for whom thrombectomy was planned.

Pre-assignment period milestones

Number of subjects started	1362[1]
Number of subjects completed	503

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not meet inclusion criteria: 859

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1362 patients have been screened for the inclusion in the trial WAKE-UP, only 503 patients could be enrolled as the others did not meet the inclusion and exclusion criteria.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active treatment

Arm description:

Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the active treatment, Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) have been given.

Arm type	Active comparator
Investigational medicinal product name	Actilyse
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes)

Arm title	Placebo

Arm description:

Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the placebo, matching placebo 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) was given

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes)

Number of subjects in period 1	Active treatment	Placebo
Started	254	249
Completed	246	244
Not completed	8	5
Lost to follow-up	8	5

Baseline characteristics

Reporting groups	
Reporting group title	Active treatment
Reporting group description:	
Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the active treatment, Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) have been given.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the placebo, matching placebo 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) was given	

Reporting group values	Active treatment	Placebo	Total
Number of subjects	254	249	503
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)	103	92	195
From 65-84 years	151	157	308
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	65.3	65.2	
standard deviation	± 11.2	± 11.9	-
Gender categorical Units: Subjects			
Female	89	89	178
Male	165	160	325

End points

End points reporting groups

Reporting group title	Active treatment
Reporting group description:	
Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the active treatment, Alteplase 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) have been given.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomized 1:1 to either active treatment (Alteplase, rtPA, Acitlyse®) or placebo. In this arm, the placebo, matching placebo 0.9 mg per kilogram of body weight (with 10% as bolus, the remainder by infusion over 60 minutes) was given	

Primary: MRS 0-1

End point title	MRS 0-1
End point description:	
Primary endpoint will be "favourable outcome" defined by a score of 0-1 on the modified Rankin Scale (MRS) 90 days after stroke	
End point type	Primary
End point timeframe:	
90 days after stroke	

End point values	Active treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	249		
Units: 0-1				
number (not applicable)				
Favorable Outcome (mRS 0- 1) at 90 days – no. (%)	116	91		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description:	
Unconditional logistic-regression model	
Comparison groups	Active treatment v Placebo
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	2.36

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse Events were reported regularly, all Serious Adverse Events were reported to the Trial Safety desk from trial sites within 48 hours.

Adverse event reporting additional description:

SAE was assessed for seriousness, causality and expectedness. Suspected Unexpected Serious Adverse Reactions were directly reported to Eudravigilance EVCTM.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Blood and lymphatic system disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Cardiac disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Congenital, familial and genetic disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Eye disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Gastrointestinal disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	General disorders and administration site conditions

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Hepatobiliary disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Immune system disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Infections and infestations

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Injury, poisoning and procedural complications

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Investigations

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Musculoskeletal and connective tissue disorders

Reporting group description:

Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.

Reporting group title	Neoplasms benign, malignant and unspecified (incl cy)

Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Nervous system disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Psychiatric disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Renal and urinary disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Reproductive system and breast disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Respiratory, thoracic and mediastinal disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Social circumstances
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Surgical and medical procedures
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	
Reporting group title	Vascular disorders
Reporting group description:	
Subjects affected by non-serious adverse events cannot be reported, therefore 0 has been entered.	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Subjects affected by non-serious adverse events have not been recorded in this study.

Serious adverse events	Blood and lymphatic system disorders	Cardiac disorders	Congenital, familial and genetic disorders
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 254 (0.39%)	9 / 254 (3.54%)	2 / 254 (0.79%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	5	0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 254 (0.39%)	9 / 254 (3.54%)	2 / 254 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 9	0 / 2
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Eye disorders	Gastrointestinal disorders	General disorders and administration site conditions
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 254 (0.00%)	2 / 254 (0.79%)	8 / 254 (3.15%)

number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	1	2
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	0 / 254 (0.00%)	2 / 254 (0.79%)	8 / 254 (3.15%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Hepatobiliary disorders	Immune system disorders	Infections and infestations
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	5 / 254 (1.97%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	0	4
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	5 / 254 (1.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Injury, poisoning and procedural complications	Investigations	Musculoskeletal and connective tissue disorders
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 254 (1.57%)	0 / 254 (0.00%)	2 / 254 (0.79%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	4 / 254 (1.57%)	0 / 254 (0.00%)	2 / 254 (0.79%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Neoplasms benign, malignant and unspecified (incl cy)	Nervous system disorders	Psychiatric disorders
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 254 (0.39%)	34 / 254 (13.39%)	1 / 254 (0.39%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	1	5	0

Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 254 (0.39%)	34 / 254 (13.39%)	1 / 254 (0.39%)
occurrences causally related to treatment / all	0 / 1	0 / 34	0 / 1
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Renal and urinary disorders	Reproductive system and breast disorders	Respiratory, thoracic and mediastinal disorders
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 254 (1.18%)	1 / 254 (0.39%)	5 / 254 (1.97%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	0	1
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	3 / 254 (1.18%)	1 / 254 (0.39%)	5 / 254 (1.97%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

Serious adverse events	Social circumstances	Surgical and medical procedures	Vascular disorders
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 254 (0.39%)	10 / 254 (3.94%)	3 / 254 (1.18%)
number of deaths (all causes)	13	13	13
number of deaths resulting from adverse events	0	0	1
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 254 (0.39%)	10 / 254 (3.94%)	3 / 254 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 10	0 / 3
deaths causally related to treatment / all	0 / 13	0 / 13	0 / 13

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

Non-serious adverse events	Blood and lymphatic system disorders	Cardiac disorders	Congenital, familial and genetic disorders
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Eye disorders	Gastrointestinal disorders	General disorders and administration site conditions
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Hepatobiliary disorders	Immune system disorders	Infections and infestations
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Injury, poisoning and procedural complications	Investigations	Musculoskeletal and connective tissue disorders
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Neoplasms benign, malignant and unspecified (incl cy)	Nervous system disorders	Psychiatric disorders
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Renal and urinary disorders	Reproductive system and breast disorders	Respiratory, thoracic and mediastinal disorders
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

Non-serious adverse events	Social circumstances	Surgical and medical procedures	Vascular disorders
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 254 (0.00%)	0 / 254 (0.00%)	0 / 254 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2015	Amendment due to a new German Summary of Product Characteristics (SmPC, Fachinformation) for Actilyse® provided by the manufacturer. Next to minor changes as to the frequency of adverse events and editorial changes, the new SmPC comprises new information concerning patients under oral anticoagulation therapy. Therefore, the section relating to clinical exclusion criteria in the protocol was adapted in line with the new SmPC. The wording as to the use of anticoagulants as clinical exclusion criterion was modified adding further new oral anticoagulants and specifying the effective use of oral anticoagulants as clinical exclusion criterion. Additionally it was added that the use of Actilyse® can be considered in patients using vitamin K-antagonists when appropriate tests of anti-coagulant activity show no clinically relevant activity. The DSMB has evaluated that these new information are not relevant as to the risk or benefit of Actilyse®, thus the new SmPC does not change the overall risk-benefit-evaluation for Actilyse®.

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.

It was decided to stop the trial with 503 randomised patients as the funding from the EU ended. The overall appraisal was that with >500 patients randomized the trial should have sufficient power to demonstrate a beneficial treatment effect.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29766770