Clinical trial results:
EuroHYP-1: European multicentre, randomised, phase III clinical trial of therapeutic hypothermia plus best medical treatment versus best medical treatment alone for acute ischaemic stroke

Summary

EudraCT number	2012-002944-25
Trial protocol	ES FI IT IE
Global end of trial date	09 May 2018

Results information

Result version number	v1 (current)
This version publication date	05 February 2020
First version publication date	05 February 2020
Summary attachment (see zip file)	Synopsis_annex1_ICH_E3 (0102_Synopsis Ergebnisbericht E3_v1.0_190424.pdf)

Trial information

Trial identification

Sponsor protocol code	EuroHyp-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01833312
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Erlangen
Sponsor organisation address	Schwabachanlage 6, Erlangen, Germany,
Public contact	Direktion, Neurologische Klinik, Universitätsklinikum Erlangen, stefan.schwab@uk-erlangen.de
Scientific contact	Direktion, Neurologische Klinik, Universitätsklinikum Erlangen, stefan.schwab@uk-erlangen.de

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	09 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2018
Global end of trial reached?	Yes
Global end of trial date	09 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether systemic cooling to a target body temperature between 34.0 and 35.0°C, started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

Protection of trial subjects:

Study participants assigned to the control group initially have their vital parameters closely monitored and also come to the study site once at the end of the follow-up phase for a final examination. The discomfort for these patients is classified as minimal; there are no study-related risks for these patients. For study participants assigned to therapeutic hypothermia by the randomisation process, the following control mechanisms and counter-measures have been implemented to minimise discomfort and risks.
1. Discomfort and shivering: Administration of pethidine and buspirone, if necessary increase in target body temperature or termination of hypothermia.
2. Opioid-induced Nausea: Administration of 5-HT3-receptor antagonists.
3. Pain from application of cooling catheter (endovascular cooling): Local anaesthesia at the puncture site, maximum 2 puncturing attempts.
4. Volume overload due to induction infusion (20 mL/kg BW): Exclusion criterion NYHA ≥III, if necessary administration of a diuretic.
5. Pneumonia: Antibiotic therapy, if necessary discontinuation of hypothermia.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	Belgium: 3
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	98
EEA total number of subjects	98

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)	25
From 65 to 84 years	73
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1. Diagnosis of acute ischaemic stroke.
2. Possibility to start therapeutic hypothermia within 6 hours after onset of stroke.
3. mRS score ≤2 prior to onset of stroke.
4. NIHSS score ≥ 6.
5. No evidence from CT or MRI of intracranial haemorrhage or tumour or encephalitis

Period 1

Period 1 title	Screening Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Assessor, Data analyst[2]

Arms

Are arms mutually exclusive?	Yes
Arm title	Hypothermia group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pethidine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Loading dose 50mg, subsequent doses 25mg, interval 30min minimum, maximum daily dose 500mg

Arm title	Control group

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.
[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.

Number of subjects in period 1	Hypothermia group	Control group
Started	49	49
Completed	49	49

Period 2	
Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[3]
Roles blinded	Data analyst, Assessor[4]

Arms	
Are arms mutually exclusive?	Yes
Arm title	Hypothermia group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Pethidine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: Loading dose 50mg, subsequent doses 25mg, interval 30min minimum, maximum daily dose 500mg	
Investigational medicinal product name	Buspirone hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: loading dose 10mg, subsequent doses 10mg, maximum daily dose 30mg	
Arm title	Control group
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.
[4] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.

Number of subjects in period 2	Hypothermia group	Control group
Started	49	49
Completed	49	49

Period 3	
Period 3 title	Post-treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[5]
Roles blinded	Assessor, Data analyst[6]

Arms	
Are arms mutually exclusive?	Yes
Arm title	Hypothermia group
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Pethidine hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details: Loading dose 50mg, subsequent doses 25mg, interval 30min minimum, maximum daily dose 500mg	
Investigational medicinal product name	Buspirone hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: loading dose 10mg, subsequent doses 10mg, maximum daily dose 30mg	
Arm title	Control group
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[5] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.
[6] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to the nature of the intervention blinding of subject and site staff was not possible but assessor of the primary endpoint and data analyst were blinded.

Number of subjects in period 3	Hypothermia group	Control group
Started	49	49
Completed	48	46
Not completed	1	3
Lost to follow-up	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Hypothermia group
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	

Reporting group values	Hypothermia group	Control group	Total
Number of subjects	49	49	98
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)	11	14	25
From 65-84 years	38	35	73
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	71.1	69.6	
standard deviation	± 12.0	± 11.8	-
Gender categorical Units: Subjects			
Female	22	21	43
Male	27	28	55
NIHSS >12			
at the time of enrollment			
Units: Subjects			
NIHSS >12	21	19	40
NIHSS <=12	28	30	58

End points

End points reporting groups	
Reporting group title	Hypothermia group
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	
Reporting group title	Hypothermia group
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	
Reporting group title	Hypothermia group
Reporting group description: -	
Reporting group title	Control group
Reporting group description: -	

Primary: Score on the mRS	
End point title	Score on the mRS
End point description: Distribution of subjects per mRS score	
End point type	Primary
End point timeframe: Day 91±14 days	

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: number of subjects				
mRS 0	3	1		
mRS 1	7	6		
mRS 2	14	11		
mRS 3	5	9		
mRS 4	4	12		
mRS 5	10	3		
mRS 6	5	4		

Statistical analyses

Statistical analysis title	mRS score
Statistical analysis description: Frequencies and percentages per mRS categories per intervention group are reported.	
Comparison groups	Hypothermia group v Control group

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.13

Secondary: Death or dependency, defined as a score on the mRS >2

End point title	Death or dependency, defined as a score on the mRS >2

End point description:

End point type	Secondary

End point timeframe:

Day 91±14 days

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: number of subjects	24	28		

Statistical analyses

Statistical analysis title	death or dependency
Comparison groups	Hypothermia group v Control group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.29
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.14

Secondary: Death	
End point title	Death
End point description:	
End point type	Secondary
End point timeframe:	
Day 91±14 days	

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	46		
Units: number of subjects	5	4		

Statistical analyses

Statistical analysis title	death
Comparison groups	Hypothermia group v Control group
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	3.81

Secondary: Score on NIHSS	
End point title	Score on NIHSS
End point description:	
End point type	Secondary
End point timeframe:	
Day 91±14 days	

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: score				
median (inter-quartile range (Q1-Q3))	3.0 (1.0 to 11.0)	3.0 (1.0 to 8.0)		

Statistical analyses

Statistical analysis title	score on NIHSS
Comparison groups	Hypothermia group v Control group
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.26
upper limit	2.86

Secondary: Brain infarct size

End point title	Brain infarct size

End point description:

End point type	Secondary

End point timeframe:

Hour 48±24 hours

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	37		
Units: mm3				
median (inter-quartile range (Q1-Q3))	37468 (13027 to 102760)	34302 (10523 to 65460)		

Statistical analyses

Statistical analysis title	Brain infarct size
Comparison groups	Hypothermia group v Control group
Number of subjects included in analysis	82
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-14695
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64212
upper limit	34823

Secondary: WHODAS 2.0 score

End point title	WHODAS 2.0 score
End point description:	
End point type	Secondary
End point timeframe:	
Day 91±14 days	

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	27		
Units: score				
median (inter-quartile range (Q1-Q3))	53.5 (5.8 to 86.5)	38.0 (12.0 to 74.0)		

Statistical analyses

Statistical analysis title	WHODAS 2.0 score
Comparison groups	Hypothermia group v Control group

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-16.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.6
upper limit	3.75

Secondary: EQ-5D-5L score

End point title	EQ-5D-5L score

End point description:

End point type	Secondary

End point timeframe:

Day 91±14 days

End point values	Hypothermia group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	46		
Units: score				
median (inter-quartile range (Q1-Q3))	70.0 (50.0 to 90.0)	67.0 (50.0 to 80.0)		

Statistical analyses

Statistical analysis title	EQ-5D-5L
Comparison groups	Hypothermia group v Control group
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.26
upper limit	2.86

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for an AE extends from the time of patient enrolment until outcome assessment [A7, Day 91±14 days] or end of trial assessment [A8], respectively, has been performed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Hypothermia group
Reporting group description: -	
Reporting group title	Control group

Reporting group description: -

Serious adverse events	Hypothermia group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 49 (36.73%)	14 / 49 (28.57%)	
number of deaths (all causes)	5	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			

subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Carotid endarterectomy			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 49 (2.04%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 49 (4.08%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	4 / 49 (8.16%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Stroke in evolution			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 49 (0.00%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Impaired healing			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (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	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	6 / 49 (12.24%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (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			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sepsis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 49 (2.04%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	1 / 49 (2.04%)	
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	Hypothermia group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 49 (73.47%)	30 / 49 (61.22%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	
occurrences (all)	6	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 49 (6.12%)	0 / 49 (0.00%)	
occurrences (all)	5	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 49 (8.16%)	5 / 49 (10.20%)	
occurrences (all)	4	5	
Nervous system disorders			

Haemorrhagic transformation stroke			
subjects affected / exposed	6 / 49 (12.24%)	1 / 49 (2.04%)	
occurrences (all)	6	1	
Headache			
subjects affected / exposed	3 / 49 (6.12%)	2 / 49 (4.08%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 49 (8.16%)	4 / 49 (8.16%)	
occurrences (all)	6	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 49 (16.33%)	6 / 49 (12.24%)	
occurrences (all)	8	7	
Nausea			
subjects affected / exposed	5 / 49 (10.20%)	1 / 49 (2.04%)	
occurrences (all)	5	1	
Vomiting			
subjects affected / exposed	5 / 49 (10.20%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	5 / 49 (10.20%)	1 / 49 (2.04%)	
occurrences (all)	7	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	5 / 49 (10.20%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	3 / 49 (6.12%)	4 / 49 (8.16%)	
occurrences (all)	4	4	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 49 (10.20%)	2 / 49 (4.08%)	
occurrences (all)	5	2	
Urinary tract infection			

subjects affected / exposed	7 / 49 (14.29%)	3 / 49 (6.12%)	
occurrences (all)	8	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 49 (6.12%)	1 / 49 (2.04%)	
occurrences (all)	4	1	
Hypokalaemia			
subjects affected / exposed	6 / 49 (12.24%)	1 / 49 (2.04%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2014	1. Prolongation of injection time span for 5-HT3 receptor antagonists 2. Surveillance of body temperature according to local practice 3. No surveillance of depth of sedation in regular time intervals 4. Hourly documentation of vital parameters 5. Permission of thrombolysis in other Hospital
29 June 2015	1. Reduction of cooling period from 24 hours to 12 hours 2. Extention of study population: NIHSS without upper limitation, permission of intravasal thrombectomy, time interval from start of thrombolysis to start of cooling from 90 to 150 minutes 3. Reduction of sample size (1500 -> 800)
24 June 2016	1. Prolongation of biomarker blood sampling by one hour 2. Introduction of 2 additional surface systems and 2 additional intravasal cooling catheters 3. Importation of buspirone from other EU member states in those member states where buspirone is no longer marketed

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.

Considerable shortfall of number of subjects recruited limits informative value of results

Notes: