



## Clinical trial results: Theophylline Effect in Acute Ischemic Stroke Trial Summary

EudraCT number	2013-001989-42
Trial protocol	DK
Global end of trial date	12 March 2018

### Results information

Result version number	v1 (current)
This version publication date	02 October 2020
First version publication date	02 October 2020

### Trial information

#### Trial identification

Sponsor protocol code	TEA-Stroke
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#### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 4, Aalborg, Denmark, 9000
Public contact	TEA-Stroke Information Desk, Aalborg University Hospital, 45 97 66 22 71, aalborguh@rn.dk
Scientific contact	TEA-Stroke Information Desk, Aalborg University Hospital, 45 97 66 22 71, aalborguh@rn.dk

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	31 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate safety and efficacy of add-on Teofylin treatment to standard thrombolytic therapy in patients with MR-proved acute ischemic stroke. The study is designed as a randomized controlled trial comparing add-on Teofylin to placebo. The main interests are to demonstrate the tissue effect of Teofylin by measuring the infarct growth assessed by multimodal MRI as well as improved early clinical outcome

Protection of trial subjects:

Possibility to withdraw informed consent.

GCP-monitoring of adverse events and laboratory parameters

Independent data safety monitoring board

Background therapy:

Thrombolytic therapy with 0.9mg/kg alteplase and mechanical thrombectomy after institutional standard of care and national guidelines for acute stroke treatment

Evidence for comparator:

Theophylline

Actual start date of recruitment	08 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	23
From 65 to 84 years	39
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

1573 patients were treated with thrombolysis at the 2 recruiting sites, 1216 patients were screened for the TEA-Stroke Trial by an investigator, 64 patients were finally randomized to the trial .

### Pre-assignment

Screening details:

1216 patients were screened, 67 patients were enrolled, 3 patients did not fulfilled the MRI inclusion criteria, 64 were finally randomized to the trial

### Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Web-based randomization

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Theophylline
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Arm description:

10 mL of theophylline (Teofylamin 22 mg/mL containing 20 mg of theophylline monohydrate and 5.5 mg of solubilized ethylene-diamine hydrate)

Arm type	Active comparator
Investigational medicinal product name	Theophylline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Teofylamin 22 mg/mL containing 20 mg of theophylline monohydrate and 5.5 mg of solubilized ethylene-diamine hydrate as short intravenous infusion over 15 minutes

<b>Arm title</b>	Placebo
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Arm description:

10 mL of physiological saline solution

Arm type	Placebo
Investigational medicinal product name	physiological saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mL of physiological saline solution as short intravenous infusion over 15 minutes

<b>Number of subjects in period 1</b>	Theophylline	Placebo
Started	33	31
Completed	33	31

## Baseline characteristics

### Reporting groups

Reporting group title	Theophylline
Reporting group description: 10 mL of theophylline (Teofylamin 22 mg/mL containing 20 mg of theophylline monohydrate and 5.5 mg of solubilized ethylene-diamine hydrate)	
Reporting group title	Placebo
Reporting group description: 10 mL of physiological saline solution	

Reporting group values	Theophylline	Placebo	Total
Number of subjects	33	31	64
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)	12	11	23
From 65-84 years	20	19	39
85 years and over	1	1	2
Gender categorical Units: Subjects			
Female	13	12	25
Male	20	19	39

## End points

### End points reporting groups

Reporting group title	Theophylline
Reporting group description: 10 mL of theophylline (Teofylamin 22 mg/mL containing 20 mg of theophylline monohydrate and 5.5 mg of solubilized ethylene-diamine hydrate)	
Reporting group title	Placebo
Reporting group description: 10 mL of physiological saline solution	

### Primary: Early clinical improvement

End point title	Early clinical improvement
End point description: Change in NIHSS from baseline to 24 hour follow-up	
End point type	Primary
End point timeframe: 24 hour follow-up	

End point values	Theophylline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	31		
Units: point				
arithmetic mean (standard deviation)	4.7 (± 5.6)	1.3 (± 7.5)		

### Statistical analyses

Statistical analysis title	primary endpoint
Comparison groups	Theophylline v Placebo
Number of subjects included in analysis	64
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.025 <sup>[1]</sup>
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - After correction for multiplicity (Bonferroni technique)

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**Other pre-specified: Proportion of infarct growth**

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End point title	Proportion of infarct growth
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End point description:

Infarct growth at 24-hour follow-up was defined by the proportion of co-registered DWI lesion at 24-hour follow-up not present at baseline  $[(\text{DWI follow-up} - \text{DWI baseline}) / \text{DWI baseline} \times 100\%]$

End point type	Other pre-specified
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End point timeframe:

24 hour follow-up

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End point values	Theophylline	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	30 <sup>[2]</sup>		
Units: %				
arithmetic mean (standard deviation)	141.6 (± 126.5)	104.1 (± 62.5)		

Notes:

[2] - MRI follow-up at 24 h was not possible in 1 patient

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**Statistical analyses**

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

3 month

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	unknown
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Dictionary version	1
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### Reporting groups

Reporting group title	Theophylline
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Theophylline	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 33 (9.09%)	15 / 31 (48.39%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Vascular disorders			
Systemic vascular event			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Carotid surgery			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological deterioration			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 33 (3.03%)	5 / 31 (16.13%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
General disorders and administration site conditions			
Trauma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GI-bleeding			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (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			
Pneumonia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 33 (0.00%)	3 / 31 (9.68%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	3 / 3	
Skin and subcutaneous tissue disorders			
Hematoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Theophylline	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 33 (87.88%)	24 / 31 (77.42%)	
Cardiac disorders			
Artrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 33 (9.09%)	1 / 31 (3.23%)	
occurrences (all)	3	1	
Nervous system disorders			
Neurological deterioration			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 33 (6.06%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
cephalgia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Sleep apnoea syndrome			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
affected general condition			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 33 (9.09%)	2 / 31 (6.45%)	
occurrences (all)	3	2	
Trauma			
alternative assessment type: Systematic			

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0	
Immune system disorders allergic reaction subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	2 / 31 (6.45%) 2	
Gastrointestinal disorders Nausea, vomiting, obstipation alternative assessment type: Systematic subjects affected / exposed occurrences (all)  GI bleeding alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3  0 / 33 (0.00%) 0	2 / 31 (6.45%) 2  1 / 31 (3.23%) 1	
Skin and subcutaneous tissue disorders Hematoma alternative assessment type: Systematic subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 31 (9.68%) 3	
Psychiatric disorders Depression alternative assessment type: Systematic subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	0 / 31 (0.00%) 0	
Infections and infestations Infection or fever subjects affected / exposed occurrences (all)	10 / 33 (30.30%) 10	9 / 31 (29.03%) 9	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 January 2015	Change of inclusion criterion NIHSS $\geq 6$ to NIHSS $\geq 4$ : The inclusion criterion NIHSS was lowered from 6 to 4 the majority of patients have less severe stroke and the severe stroke patients often are not able to give informed consent. The National Institute of Health Stroke Scale (NIHSS) measures the severity of stroke (NIHSS 0-4 corresponds to mild stroke symptoms, NIHSS 5-15 to moderate, NIHSS 16-20 to moderate to severe, and NIHSS $\geq 20$ corresponds to severe stroke).
24 February 2016	Change of method to assess the inclusion criteria perfusion/diffusion mismatch: In the TEA-Stroke protocol, a semi-automatic in-house software was chosen to assess the MRI perfusion/diffusion-mismatch. Unfortunately, several potential trial candidates were excluded, as the semi-automatic calculation was not possible in time for technical reasons. The visual assessment of the perfusion/diffusion-mismatch based on the MRI-scanner software was allowed, if the semi-automatic calculation might not be available in time.
20 June 2016	Change of inclusion criteria and extension of study period: The delayed start of recruitment and the unexpected low recruitment rate made it necessary to extend the trial period to 1st February 2019, as the permission for the TEA-Stroke study will finish the 31th August 2016. The technical challenging and time consuming inclusion criterion "perfusion/diffusion-mismatch" was removed to improve the recruitment rate. Visit 2 at 2-3 hours after treatment with the trial medication was removed, as MRI was mainly performed at visit 2 to demonstrate the acute change of perfusion. An interim analysis was scheduled after inclusion of 60 patients

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 December 2017	After 3.5 years of recruitment, the steering committee decided to stop the clinical trial due to low recruitment rate. The scheduled interim analysis was omitted in favor of a post hoc final analysis.	-

Notes:

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31008285>

