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

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON44426

Source
ToetsingOnline

Brief title
WAKE-UP

Condition

- Other condition
- Central nervous system vascular disorders

Synonym
cerebrovascular accident, stroke

Health condition

acute ischemische beroerte

Research involving
Human

Sponsors and support

Primary sponsor: University Medical Center Hamburg-Eppendorf
Source(s) of monetary or material Support: EU FP-7 grant

Intervention

Keyword: MRI-based thrombolysis, wake-up stroke

Outcome measures

Primary outcome

Primary Efficacy endpoint :

- "Favourable Outcome" defined by a score of 0-1 on the Modified Ranking Scale

(MRS) 90 (+/-10) days after stroke

Primary Safety Endpoints :

- Mortality 90 (+/-10) days after stroke

- Death or dependency 90 (+/-10) days after stroke (MRS 4-6)

Secondary outcome

Secondary efficacy endpoints :

- Global Outcome Score (combination of MRS0-1, NIHSS 0-1, Barthel Index 95-100,

Glasgow Coma Scale 1) 90 (+/-10) days after stroke

- Categorical shift in MRS 90 (+/-10) days after stroke

- Responder analysis relating MRS 90 (+/-10) days after stroke to baseline

NIHSS score : "response" defined by NIHSS<7 = MRS 0; NIHSS 8-14 = MRS 0-1 ;

NIHSS>14 = MRS 0-2

- Infarct volume after 22-36 hours

- Depressive symptoms 90 (+/-10) dyays after stroke (Beck Depression Inventory)

- Functional Health Status and Quality of Life 90 (+/-10) days after stroke

(EQ-5D)

- Use of health care system resources 90 (+/-10) days after stroke)

Secondary Safety endpoints :

- Symptomatic intracranial haemorrhage (SICH) as defined in SITS-MOST

- SICH as defined in ECASS II

- SICH as defined in NINDS

- Parenchymal haemorrhage type 2 (PH-2)

- 22-36 hours after treatment

Study description

Background summary

Wake-Up is an European collaborative research project launched by a consortium of academic and SME partners destined to improve the treatment of strole patients. The core of Wake-Up is an investigator-initiated randomized controlled trial of MRI-based thrombolysis in patients waking up with strole symptoms.
The Wake-Up consortium brings together leading stroke researchers from European academic institutions, highly specialized SME partners, and patient organizations providing a wide range of clinical and scientific expertise in stroke , image processing and the conduct of clinical trials.

Study objective

The ,aim of Wake-Up is to provide a new safe and effective treatment option for acute stroke patients waking up with stroke symptoms or patients with unknown symptom onset. Every year about 2milion patients suffer a stroke in the EU and up to 20% of stroke patients wake-up with stroke symptoms. Currently these patients are excluded from thrombolysis which is the only approved specific treatment available for acute stroke.
The core of Wake-Up is an investigator-initiated, randomized, placebo-controlled trial designed to test the efficacy and saftey of MRI-based intravenous thrombolysis in patients with wake-up stroke.
The trial will be accompanied by research to develop automated storke MRI analysis and activities to increase the public awareness of acute stroke.

Study design

Controlled
Randomised
Double blind
Parallel group
Placebo controlled

Intervention

In this trial we will use modern multiparametric MRI techniques applying a new diagnostic algorithm to identify patients likely to benefit from treatment. We will enroll 800 patients iof which 400 will receive intravenous tissue

plasminogen activator (Alteplase) and 400 will receive placebo.

Study burden and risks

not applicable

Contacts

Public
University Medical Center Hamburg-Eppendorf

Martinistr. 52
HAMBURG 20246
DE
Scientific
University Medical Center Hamburg-Eppendorf

Martinistr. 52
HAMBURG 20246
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Clinical Inclusion Criteria
- Clinical diagnosis of acute ischemic stroke with unknown symptom onset (e.g., stroke symptoms recognized on
awakening)

- Last known well (without neurological symptoms) >4.5 hours of treatment initiation
- Measurable disabling neurological deficit (defined as an impairment of one or more of the following: language, motor
function, cognition, gaze, vision, neglect)
- Age 18-80 years
-Treatment can be started within 4.5 hours of symptom recognition (e.g., awakening)
- Written informed consent by patient or proxy ;Imaging Inclusion Criteria:
- Acute stroke MRI including diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR)
completed and showing a pattern of *DWI-FLAIR-mismatch*, i.e. acute ischemic lesion visibly on DWI (*positive
DWI*) but no marked parenchymal hyperintensity visible on FLAIR (*negative FLAIR*) indicative of an acute ischemic
lesion *4.5 hours of age

Exclusion criteria

Clinical Exclusion Criteria
- Planned or anticipated treatment with endovascular reperfusion strategies (e.g. intra-arterial thrombolysis,
mechanical recanalization techniques)
- Pre-stroke disability (inability to carry out all daily activities, requiring some help or supervision, i.e. slight disability
corresponding to an MRS score >1)
- Participation in any investigational study in the previous 30 days
- Severe stroke by clinical assessment (e.g. NIHSS >25)
- Hypersensitivity to Alteplase or any of the excipients
- Pregnancy or lactating (formal testing needed in woman of childbearing potential; childbearing potential is assumed
in women up to 55 years of age)
- Significant bleeding disorder at present or within past 6 months
- Known haemorrhagic diathesis
- Manifest or recent severe or dangerous bleeding
- Known history of or suspected intracranial haemorrhage
- Suspected subarachnoid haemorrhage (even if CT is negative) or condition after subarachnoid haemorrhage from
aneurysm
- History of CNS damage (e.g. neoplasm, aneurysm, intracranial or spinal surgery)
- Recent (within 10 days) traumatic external heart massage, obstetrical delivery, recent puncture of a
non-compressible blood-vessel
- Current use of anticoagulants (e.g. Phenprocoumon, Warfarin, new anticoagulants such as Dabigatran) or current
use of heparin and elevated thromboplastin time (low-dose subcutaneous heparin is allowed)
- Platelet count <100.000/mm3 (<100G/l)

- Blood glucose <50 or >400 mg/dl (<2.8 or 22.2 mmol/l)
- Severe uncontrolled hypertension, i.e. systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg
or requiring aggressive medication to maintain blood pressure within these limits (routine medical treatment is allowed to lower the blood pressure below these limits)
- Manifest or recent bacterial endocarditis, pericarditis
- Manifest or recent acute pancreatitis
- Documented ulcerative gastrointestinal disease during the last 3 months, oesophageal varices, arterial aneurysm, arterial/venous malformations
- Neoplasm with increased bleeding risk
- Manifest severe liver disease including hepatic failure, cirrhosis, portal hypertension and active hepatitis
- Major surgery or significant trauma in past 3 months
- Stroke within 30 days
- Life expectancy 6 months or less by judgement of the investigator
- Any condition associated with a significantly increased risk of severe bleeding not mentioned above
- Any contraindication to MRI (e.g. cardiac pacemaker);Imaging Exclusion Criteria:
- Poor MRI quality precluding interpretation according to the study protocol
- Any sign of intracranial haemorrhage on baseline MRI
- FLAIR showing a marked parenchymal hyperintensity in a region corresponding to the acute DWI lesion inidicative of
an acute ischemic lesion with a high likelihood of being > 4.5 hours old
- Large DWI lesion volume > 1/3 of the MCA or >50% of the anterior cerebral artery (ACA) or posterior cerebral artery (PCA) territory (visual inspection) or >100 ml
- Any MRI findings indicative of a high risk of symptomatic intracranial haemorrhage related to potential IV-tPA treatment in the judgement of the investigator

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-04-2016
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Actilyse
Generic name:	Alteplase
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	12-11-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	23-11-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	21-01-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	16-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	22-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-04-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-005906-32-NL
ClinicalTrials.gov	NCT01525290
CCMO	NL49677.100.14