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European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits

Submission date 17/07/2013	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 22/10/2013	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 08/04/2019	**Condition category** Circulatory System	[_] Individual participant data

Plain English summary of protocol

Background and study aims
The only approved medical treatment for stroke patients is thrombolysis treatment (dissolving blood clots) with the drug Alteplase within a 4.5-hour time-window from the start of symptoms. Thus patients with a longer or unknown time-window cannot be treated with Alteplase. This study aims to find out about the beneficial effect of treatment with Alteplase in such patients based on a careful selection with MRI techniques.

Who can participate?
Patients with symptoms of an acute stroke between 4.5 and 9 hours after symptom onset or with unknown time-window (e.g. waking up with symptoms).

What does the study involve?
Patients will be randomly allocated to either receive Alteplase or placebo (dummy). The drug or the placebo will be injected through their veins for one hour. Patients will be followed up at 3 months.

What are the possible benefits and risks of participating?
Possible benefits are reduced disability because of the reduction of the stroke size. The main risk of any thrombolytic therapy is hemorrhage with deterioration of the nervous system.

Where is the study run from?
Around 30 centers in Austria, Czech Republic, France, Germany, Italy, Spain and the UK will participate.

When is the study starting and how long is it expected to run for?
The study will start in late 2014 and run until 2016.

Who is funding the study?
This study is funded by Boehringer Ingelheim (Germany).

Who is the main contact?
Prof. Dr Werner Hacke
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2012-003609-80

Protocol serial number
Version 1.0, 15 May 2013

Study information

Scientific Title
European Cooperative Acute Stroke Study-4: Extending the time for thrombolysis in emergency neurological deficits a double-blind, placebo-controlled randomized study

Acronym
ECASS 4

Study objectives
To test the hypothesis that ischemic stroke patients with significant penumbral mismatch at 4.5-9 hours post onset of stroke or after waking with symptoms of stroke ("wake up stroke") will have improved clinical outcomes when given intravenous rt-PA (alteplase) compared to patients treated with placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
For Germany (which is the lead country) ethics committee of the Medical Faculty of the University Hospital Heidelberg; 20/09/2013; Ref: AFmu-328/2013

Study design
Double-blind placebo-controlled randomized multi-center study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Stroke

Interventions
Patients will be randomized on a 1:1 basis to either receive Alteplase (0.9 mg/kg bw, not more than 90 mg) or placebo.
Route of intervention: Intravenous (iv.)
Duration: 1 hour
Follow-up: 3 months

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Alteplase

Primary outcome(s)
Categorical shift in the modified Rankin Scale (mRS) at day 90

Key secondary outcome(s))
1. Disability at day 90, dichotomized as a favorable outcome (mRS) 0-1 vs 2 - 6
2. Change in at least 11 National Institute of Health Stroke Scale (NIHSS) points or reaching 0 or 1 on this scale at day 1 and day 90
3. Reperfusion at 12-24 hours after treatment
4. Recanalization at 12-24 hours after treatment
5. Infarct growth on diffusion-weighted imaging (DWI) within 12-24 hours after treatment
6. NIHSS score at day 7
7. Barthel Index (BI) at day 90
8. Montreal Cognitive Assessment (MoCA) score at day 90

Completion date
31/08/2016

Eligibility

Key inclusion criteria
1. Patients presenting with acute ischemic stroke
2. Patient or legally acceptable representative has given written informed consent. An

independent witness may sign the consent form if the patient is able to give verbal consent but unable to sign
3. Patients, male and female, aged 18 years or over
4. Treatment onset within 4.5 and 9 hours after stroke onset or patients waking up with stroke symptoms and unclear time window
5. National Institutes of Health Stroke Scale (NIHSS) score of 4 to 26 with clinical signs of hemispheric infarction
6. Penumbral mismatch imaging via local assessment following predefined criteria using standardized criteria including a perfusion volume (PWI) to infarct core (DWI) ratio of ≥ 1.2, and a minimum perfusion lesion volume of 20 ml

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Intracranial hemorrhage (ICH) identified by CT or MRI
2. Rapidly improving symptoms, particularly if, in the opinion of the investigator, the improvement is likely to result in the patient having an NIHSS score of <4 at randomization
3. Pre-stroke modified Rankin Scale (mRS) score of >1 (indicating previous disability)
4. Contraindication to imaging with MRI
5. Infarct core >1/3 MCA territory qualitatively or >100 ml quantitatively (determined by DWI lesion on MRI)
6. Participation in any investigational study in the previous 30 days
7. A life expectancy of less than 3 months
8. Any condition that, in the opinion of the investigator, could impose hazards to the patient if study therapy is initiated or affect the participation of the patient in the study (this applies to patients with severe microangiopathy such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura)
9. Pregnant (clinically evident) or breastfeeding women
10. Previous stroke within the three months prior to randomization
11. Recent history (in the opinion of the investigator) or clinical presentation of ICH, subarachnoid hemorrhage (SAH), arterio-venous (AV) malformation, aneurysm or cerebral neoplasm
12. Current use of oral anticoagulants and a prolonged prothrombin time (INR > 1.6) or any activated partial thromboplastin (aPTT) time exceeding 1.5-times the normal range or prolonged Thrombin-Time (TT), indicating the potential use of Dabigatran-Etexilate
13. Use of heparin, except for low-dose subcutaneous heparin, within 48 hours prior to randomization
14. Use of glycoprotein IIb-IIIa inhibitors within 72 hours prior to randomization

15. Clinically significant hypoglycemia
16. Uncontrolled hypertension defined by blood pressure > 185 mmHg systolic or >110 mmHg diastolic on at least two separate occasions at least 10 minutes apart, or requiring aggressive treatment to reduce the blood pressure to within these limits. The definition of aggressive treatment is left to the discretion of the investigator
17. Hereditary or acquired hemorrhagic diathesis
18. Gastrointestinal or urinary bleeding within 21 days prior to randomization
19. Major surgery within 14 days prior to randomization which poses a risk in the opinion of the investigator
20. Exposure to a thrombolytic agent within 72 hours prior to randomization

Date of first enrolment
01/09/2013

Date of final enrolment
31/08/2016

Locations

Countries of recruitment
United Kingdom

Czech Republic

France

Germany

Italy

Study participating centre
Head of Neurology
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Sponsor information

Organisation
Ruprecht-Karls-University Heidelberg (Germany)

ROR
https://ror.org/038t36y30

Funder(s)

Funder type
Industry

Funder Name
Boehringer Ingelheim (Germany)

Alternative Name(s)
Boehringer Ingelheim Pharmaceuticals, Inc., Boehringer Ingelheim International GmbH, BI, BIPI

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2019		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes