

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

<b>Submission date</b> 17/07/2013	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 22/10/2013	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 08/04/2019	<b>Condition category</b> Circulatory System	<input type="checkbox"/> 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  
Neurologie@med.uni-heidelberg.de

## Contact information

**Type(s)**  
Scientific

**Contact name**  
Prof Werner Hacke

**Contact details**  
Head of Neurology  
University hospital Heidelberg  
Im Neuenheimer Feld 400  
Heidelberg  
Germany  
69120

## Additional identifiers

**EudraCT/CTIS number**  
2012-003609-80

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**  
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

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use the contact details below to request a patient information sheet

**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 measure**

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

**Secondary outcome measures**

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

**Overall study start date**

01/09/2013

**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. Penumbra mismatch imaging via local assessment following predefined criteria using standardized criteria including a perfusion volume (PWI) to infarct core (DWI) ratio of  $\geq 1.2$ , and a minimum perfusion lesion volume of 20 ml

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Sex**

Both

**Target number of participants**

264

**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**

Czech Republic

France

Germany

Italy

United Kingdom

#### **Study participating centre**

**Head of Neurology**  
Heidelberg  
Germany  
69120

## **Sponsor information**

### **Organisation**

Ruprecht-Karls-University Heidelberg (Germany)

### **Sponsor details**

Medical Faculty  
Represented by Universitätsklinikum Heidelberg and its Commercial Director Ms. Irmtraut  
Gürkan  
Im Neuenheimer Feld 672  
Heidelberg  
Germany  
69120

### **Sponsor type**

University/education

### **Website**

<http://www.uni-heidelberg.de>

### **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

**Publication and dissemination plan**

Not provided at time of registration

**Intention to publish date****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?
<a href="#">Results article</a>	results	01/07/2019		Yes	No