Dual thrombolytic therapy with mutant pro-urokinase (m-pro-urokinase, HisproUK) and low dose alteplase for ischemic stroke

Published: 26-02-2019
Last updated: 12-04-2024

To test the safety and preliminary efficacy of a dual acute thrombolytic treatment consisting of a small intravenous (IV) bolus of alteplase followed by IV infusion of m-pro-urokinase against usual treatment with IV alteplase in patients presenting...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON55848

Source
ToetsingOnline

Brief title
DUMAS

Condition

- Central nervous system vascular disorders
- Embolism and thrombosis

Synonym
brain infarction, Ischemic Stroke

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Thrombolytic Science International (TSI)

Intervention

Keyword: Hemorrhage, Ischemic stroke, Randomized clinical trial, Thrombolytic treatment

Outcome measures

Primary outcome

The primary outcome is any post-intervention intracranial haemorrhage on MRI according to the Heidelberg Bleeding Classification within 24-48 hours of study drug administration.

Secondary outcome

Secondary clinical outcomes

- Score on the National Institute of Health Stroke Scale (NIHSS) assessed at 24 hours and at 5-7 days post-treatment.

- Improvement of at least 4 points on NIHSS at 24 hours compared to baseline, or (near) complete recovery (NIHSS 0 or 1).

- Score on the modified Rankin Scale (mRS) assessed at 30 days (-7 days to +14 days) post-treatment.

- All possible dichotomizations of the mRS as assessed at 30 days (-7 days to +14 days) post-treatment. This includes complete recovery (mRS 0 vs 1-6), excellent functional outcome (mRS 0-1 vs 2-6), good functional outcome (mRS 0-3 vs 4-6), and handicapped survival (mRS 0-4 vs 5-6) and survival in any condition (mRS 0-5 vs 6).

Secondary neuroimaging outcomes

- Infarct volume measured with MRI (DWI) at 24-48 hours post-treatment.

- Change (pre-treatment vs. post-treatment) in abnormal perfusion volume based on TTP/MTT maps measured with CT perfusion at baseline and MRI at 24-48 hours post treatment.

Secondary blood biomarker outcomes

- Secondary blood biomarkers of thrombolysis at 1 hour, 3 hours and 24 hours after treatment, including d-dimeres and fibrinogen.

- Change in blood biomarkers of thrombolysis from baseline to 24 hours, including d-dimeres and fibrinogen.

Safety outcomes

- Symptomatic intracranial hemorrhage (sICH) according to the Heidelberg Bleeding Classification within the follow-up period defined by the last follow-up contact at 30 days5

- Death from any cause including intracranial hemorrhage within 30 days (-7 days or +14 days) (this is equivalent to handicapped survival (mRS 0-4 vs 5-6) and survival in any condition (mRS 0-5 vs 6).

- Major extracranial hemorrhage according to the ISTH criteria within 24 hours of study drug administration.

Study description

Background summary

Recombinant tissue plasminogen activator alteplase is the only FDA-approved thrombolytic agent for thrombolytic treatment of ischemic stroke. Its effectiveness is limited and the occurrence of intra- and extracerebral hemorrhage is a major limitation. Dual thrombolytic therapy with low dose alteplase pre-treatment followed by a mutant pro-urokinase (m-pro-urokinase, HisproUK), which does not lyse hemostatic fibrin, has a significant potential to be safer and more efficacious than the FDA-approved regimen of standard dose alteplase alone.

Study objective

To test the safety and preliminary efficacy of a dual acute thrombolytic treatment consisting of a small intravenous (IV) bolus of alteplase followed by IV infusion of m-pro-urokinase against usual treatment with IV alteplase in patients presenting with ischemic stroke.

Study design

This is a multicentre, phase II, , randomized clinical trial with open-label treatment, adaptive design for dose optimization and blinded outcome assessment, comparing low dose IV alteplase + two different dosages of IV m-pro-urokinase with usual thrombolytic treatment.

Intervention

Bolus of IV alteplase (5 mg) followed by continuous IV infusion of the study medication: m-pro-urokinase 40 mg/hr during 60 minutes (initial dose). Depending on results of interim analyses, the alternate dose may be revised to a lower dose (30 mg/hr during 60 minutes) or a higher dose (50mg/hr during 60 minutes). Usual care consists of a bolus of IV alteplase followed by continuous infusion of alteplase in a total dose of 0.9 mg/kg with a maximum of 90 mg.

Study burden and risks

M-pro-urokinase has an improved safety profile and similar effectiveness as alteplase in ex- and in-vivo experimental studies as well as in a clinical study in myocardial infarction. The informed consent procedure takes on average one hour, both in proxies and in stroke patients themselves. For every 15 minutes of delay of IV thrombolytic treatment, the likelihood of a good functional outcome is reduced by 1% (absolute risk difference). We will therefore defer consent and ask for written informed consent as early as deemed appropriate according to the treating physician.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015CN
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Wytemaweg 80
Rotterdam 3015CN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- A clinical diagnosis of acute ischemic stroke;
- A score of at least 1 on the NIH Stroke Scale;
- CT or MRI ruling out intracranial hemorrhage;
-Treatment is possible
o within 4.5 hours from symptom onset or last seen well, or
o between 4.5 to 12 hours from symptom onset or last seen well, if the infarct core is less than 25 mL and a penumbra is at least the same size as the infarct core (i.e. total ischemic volume/infarct core mismatch >= 2.0),5 or 3)
* In case of lacunar syndrome,25 if there is a diffusion-weighted imaging and FLAIR mismatch4;*
- Meet the criteria for standard treatment for IV alteplase according to national guidelines;

- Contra-indication for an MRI scan (e.g., an MRI incompatible pacemaker and metal foreign bodies)
- Age of 18 years or older;
- Written informed consent (deferred).

Exclusion criteria

- Candidate for endovascular thrombectomy (i.e., no proximal intracranial large artery occlusion on CTA or MRA)
- Contra-indication for treatment with IValteplase
- Pre-stroke disability which interferes with the assessment of functional outcome at 30 days, i.e. mRS > 2.
- Known pregnancy or if pregnancy cannot be excluded, i.e. adequate use of any contraceptive method (e.g. intrauterine devices) or sterilization of the subject herself
- Participation in medical or surgical intervention trials other than DUMAS (or MR ASAP/ARTEMIS)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-08-2019
Enrollment:	240
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	HisproUK
Generic name:	mutant pro-urokinase

Ethics review

Approved WMO Date:	26-02-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-05-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	05-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-04-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2018-004448-42-NL
CCMO	NL68252.078.18
Other	NL7409 (NTR7634) en NCT04256473