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Tenecteplase in Wake-up Ischaemic Stroke Trial

Submission date
17/02/2016

Recruitment status
No longer recruiting

Registration date
31/05/2016

Overall study status
Completed

Last Edited
22/12/2022

Condition category
Circulatory System

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
In an acute ischemic stroke, the blood supply to part of the brain is cut off by a blood clot. The clot-busting drug alteplase is the only approved drug treatment for acute ischaemic stroke, but must be given within 4.5 hours of symptom onset. Unfortunately, at least 20% of patients currently wake up with their stroke symptoms - called ‘wake up stroke’. These patients are currently not eligible for clot-busting treatment, but it is likely that their stroke happened just before awakening. In this study we will be using the newer clot-busting drug tenecteplase, which is likely to improve the blood supply to the brain more quickly, so promoting a better recovery. The aim of this study is to find out whether treatment with tenecteplase is more effective than the usual care, specifically whether it reduces the risk of poor functional outcome 3 months later. Patients also undergo a scan to look for bleeding or significant brain damage that has already resulted from the stroke. The researchers propose to use a CT scan, which all patients with stroke have on coming into hospital. Other studies testing clot-busting treatment in ‘wake up’ stroke are using more complex brain scans, which can delay treatment and are not routinely available in all hospitals. The researchers therefore also aim to determine whether CT scan findings can identify patients who benefit from this treatment.

Who can participate?
‘Wake up’ stroke patients (i.e., with stroke symptoms on awakening that were not present before they went to sleep)

What does the study involve?
Participants are randomly allocated to either usual care or usual care plus tenecteplase. The results of all routine tests are recorded, and participants have additional assessments of their recovery at 7 days after stroke (or hospital discharge) and at 3 months. These are intended to assess whether the treatment improves outcome and is safe.

What are the possible benefits and risks of participating?
It is hoped (and expected) that the study will result in better long-term outcomes for the 20% of patients who currently are excluded from clot-busting treatment because they wake up with their stroke. The researchers have good reasons to believe that tenecteplase can dissolve the blood clot and thereby reduce the injury to the brain. However, this cannot be guaranteed. The information from this study may help to treat future patients better. Because tenecteplase works to help dissolve a clot, the most common side effect is bleeding. Such bleeding may be

small and harmless, like increased bleeding after blood sampling, while others may be serious, like bleeding in the brain (intracranial hemorrhage). Intracranial hemorrhage can also occur in patients who are not treated with clot-busting treatment, but treatment with tenecteplase increases the risk. Previous studies have shown that the risk of dying from intracranial hemorrhage is about 4% (one extra death for every 25th patient who receives clot-busting treatment). This means that clot-busting treatment may reduce the chance of being disabled as a result of the stroke, but that it may also increase the risk of having an intracranial hemorrhage.

Where is the study run from?
The study will be conducted in Norway, Sweden, Denmark, Finland, Estonia, Lithuania and the UK

When is the study starting and how long is it expected to run for?
September 2016 to January 2022 (updated 08/06/2021, previously: March 2021)

Who is funding the study?
National Association for Public Health (Norway)

Who is the main contact?
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Study website
https://twist.uit.no

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2014-000096-80

IRAS number

ClinicalTrials.gov number
NCT03181360

Secondary identifying numbers
160204

Study information

Scientific Title
Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST): a randomised controlled trial of thrombolytic treatment with tenecteplase for acute ischaemic stroke upon awakening

Acronym
TWIST

Study objectives
The trial aims to answer the following questions:
1. Can thrombolytic treatment with tenecteplase given within 4.5 hours of wake-up reduce the risk of poor functional outcome at 3 months?
2. Can findings on plain CT and CT angiography (and CT perfusion at selected centres) identify patients who benefit from such treatment, compared to patients without such findings?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Norway: Norwegian Research Ethics Committee, 10/02/2016, ref: 2015/1070/REK nord
2. Lithuania: Lithuanian Bioethics Committee, 06/09/2016
3. Sweden: EPN Lund, 21/06/2016, ref: Dnr 2016/359
4. UK: NHS Health Research Authority - East Midlands - Leicester Central Research Ethics Committee, 13/10/2016, ref: 16/EM/0322
5. Finland: Joint Authority/Ethical Committees Coordinating Ethics Committee, 01/06/2016, ref: 145/13/03/00/16
6. Estonia: Research Ethics Committee of the University of Tartu, 30/06/2016, ref: 2601T
7. Denmark: De Videnskabsetiske Komiteer, 23/09/2016, ref: H-16031906

Study design
Randomised controlled open-label trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Acute ischaemic stroke upon awakening

Interventions
Patients will be randomly allocated to tenecteplase 0.25 mg/kg plus best standard treatment vs best standard treatment alone.

Treatment with open tenecteplase
The total dose of tenecteplase is 0.25 mg per kg of body weight (maximum 25 mg). The dose shall be given as an intravenous bolus.

Control treatment (open design)
Patients randomised to control shall not be given tenecteplase or any other thrombolytic agent.

Both arms will receive best standard care. If the patient is given tenecteplase, then aspirin or other antiplatelet drugs shall not be given until 24 hours after termination of infusion. If the patient was allocated to control, he/she will receive aspirin as soon as possible after randomisation. All patients shall avoid intra-arterial interventions for proximal cerebral artery occlusions, unless there is a clear indication, as judged by the investigator. The duration of the follow-up period is 3 months. During this period, all patients should be treated according to standard clinical guidelines, at the discretion of the clinician.

Clinical visits: These will be performed on day 1 and on the day of discharge or day 7 (whichever occurs first). Outcome assessors will be blinded to the assigned treatment group.

Plain CT and CT angiography (if possible): All patients will undergo plain CT and CT angiography (if possible) before randomisation, and again at 24±6 hours after randomisation. CT perfusion will be performed at selected centres.

The Trial Coordinating Centre will contact patients (or their carers) via telephone and/or mail at 3 months follow-up, blinded to the treatment that the patients received. We may also need to contact the patients' general practitioners and local hospitals to get information from the patients' medical records. We will collect data by using record linkage with data from central registries such as national patient registries and the cause-of-death registries in the participating countries.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
Functional outcome (defined by the mRS) at 3 months

Secondary outcome measures
Clinical events:
1. Intracranial haemorrhage during the first 7 days
2. Stroke progression during the first 7 days
3. Recurrent ischaemic stroke during the first 7 days
4. Death from all cause during the first 7 days and during 3 months' follow-up

Clinical outcomes:
Barthel Index score, EuroQol score, and Mini Mental State Examination (MMSE) scores at 3 months

Health-economic variables:
Costs related to:
1. Length of hospital stay
2. Nursing home care after discharge
3. Re-hospitalisations during first 3 months

Overall study start date
01/09/2016

Completion date
01/01/2022

Eligibility

Key inclusion criteria
1. Stroke symptoms on awakening that were not present before sleep
2. Clinical diagnosis of stroke with limb weakness with NIHSS score >5, or dysphasia
3. Treatment with tenecteplase is possible within 4.5 hours of awakening
4. Written consent from the patient, non-written consent from the patient (witnessed by non-participating health care personnel), or written consent from the nearest family member

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
500

Total final enrolment
578

Key exclusion criteria
1. Age <18 years
2. Findings on plain CT that indicate that the patient is unlikely to benefit from treatment:

2.1. Infarction comprising more than >1/3 of the middle cerebral artery territory on plain CT
2.2. Intracranial haemorrhage, structural brain lesions which can mimic stroke (e.g. cerebral tumour)
3. Patient will be treated with intra-arterial interventions for proximal cerebral artery occlusion
4. High risk of bleeding, e.g.:
4.1. Major surgery, trauma or gastrointestinal or urinary tract haemorrhage within the previous 21 days, or arterial puncture at a non-compressible site within the previous 7 days
4.2. Any known defect in coagulation, e.g. current use of vitamin K antagonist with an INR > 1.7, or other oral anticoagulants, or heparins
4.3. Known defect of clotting or platelet function (but patients on antiplatelet agents can be included)
4.4. Ischaemic stroke in previous 2 weeks, previous intracranial haemorrhage, or known arteriovenous malformation or aneurysm
5. Persistent blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg), despite blood pressure lowering treatment
6. Blood glucose < 3.0 or > 20.0 mmol/L
7. Childbearing potential, pregnancy, positive pregnancy test, breastfeeding
8. Other serious or life-threatening disease before the stroke: severe mental or physical disability (e.g. Mini Mental Status score < 20, or mRS score ≥ 3), or life expectancy less than 12 months
9. Patient unavailability for follow-up (e.g. no fixed address)

Date of first enrolment
12/07/2017

Date of final enrolment
31/12/2020

Locations

Countries of recruitment
Denmark

Estonia

Finland

Lithuania

Norway

Sweden

Switzerland

United Kingdom

Study participating centre

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NO-9038

Sponsor information

Organisation
University Hospital of North Norway

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-
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Sponsor type
Hospital/treatment centre

ROR
https://ror.org/030v5kp38

Funder(s)

Funder type
Other

Funder Name
Norwegian Public Health Association

Funder Name
KLINBEFORSK (Norwegian National Programme for Clinical Therapy Research)

Funder Name
British Heart Foundation

Alternative Name(s)

the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Schweizerische Herzstiftung

Alternative Name(s)
Swiss Heart Foundation, Fondation Suisse de Cardiologie, Fondazione Svizzera di Cardiologia, HerzstiftungCH

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
Switzerland

Results and Publications

Publication and dissemination plan
The trial will be published in accordance with the CONSORT guidelines and will be presented by a writing committee on behalf of the investigators. All participating centres and collaborators will be acknowledged in the main publication. The primary results and results of any substudies will be presented at international meetings and in public media.

All trial data and procedures will be available for audit and inspection.

All patients will be assigned a unique code number. The patient data will be linked to this number, and the patients' names or other personal identifiers will not be included in the database. The patient database will be kept on a separate, secure computer. The code will be stored on another, secure computer, and will be deleted 15 years after the results of the trial have been published. The trial's procedures for data protection will conform to the Norwegian applicable regulatory requirements, and to the conditions set by the Norwegian Data Inspectorate.

Intention to publish date
01/09/2022

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		14/01/2021	23/05/2022	Yes	No
Statistical Analysis Plan		19/05/2022	23/05/2022	Yes	No
Results article	primary outcome data	19/12/2022	22/12/2022	Yes	No
HRA research summary			28/06/2023	No	No