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ARTSS-2: A pilot, phase IIb, randomised, multicentre, safety and activity trial of Argatroban in combination with TPA (Alteplase) Stroke Study

Submission date
18/01/2013

Registration date
23/01/2013

Last Edited
20/01/2020

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Circulatory System

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

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
13646

Study information

Scientific Title
ARTSS-2: A pilot, phase IIb, randomised, multi-center trial of Argatroban in combination with recombinant tissue plasminogen activator for acute stroke

Acronym
ARTSS-2

Study objectives
A pilot, phase IIb, randomised, multicentre trial of Argatroban in combination with recombinant tissue plasminogen activator for acute stroke.

Recombinant tissue plasminogen activator (rtPA), the only proven treatment for acute ischemic stroke, fails to reperfuse the brain in most patients with large thrombi. In a Phase IIa low dose safety study (n=65), conducted by University of Texas Houston, delivering Argatroban with rtPA indicated that both drugs appear safe when delivered concomitantly and recanalisation rates were greater than with historical controls.

The purpose of the trial is to estimate the overall treatment benefit (improvement in disability) among stroke patients treated with rtPA (Alteplase) who are randomised to receive either lowdose Argatroban, highdose Argatroban or neither.

This study will provide evidence based hypotheses and data needed to design a larger definitive trial. The study will be conducted in six hospitals across the UK and will recruit males and females over 18 years of age with acute ischemic stroke.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North West Greater Manchester South, 24/07/2012, ref:12/NW/0425

Study design
Pilot phase IIb randomised multicentre trial

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 to request a patient information sheet

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

Interventions
Three treatment arms (n=35 each) will be enrolled:
1. Low-dose Argatroban* (1.0µg/kg/min continuous infusion of Argatroban, preceded by a 100 µg /kg bolus administered over 3-5 minutes Infusion will be titrated to achieve an aPTT of 1.75 times baseline - not to exceed 10 µg/kg/min) + usual care IV-rt-PA;
2. High-dose Argatroban* 3.0 µg/kg/min continuous infusion of Argatroban, preceded by a 100 µg/kg bolus administered over 3-5 minutes Infusion will be titrated to achieve an aPTT of 2.25 times baseline - not to exceed 10 µg/kg/min) + usual care IV-rt-PA;
3. Intravenous-rt-PA alone (usual care).
*Argatroban infusions will continue for a maximum of 48 hours.

During the course of the treatment, patients will be evaluated via Computed Tomography (CT) angiogram, CT scans, vital signs, laboratory measurements, and neurological and unctional outcomes. Patients will also be evaluated at 24 hours following the onset of the stroke, Day 7 or discharge (whichever comes first) and at day 90.

Sponsor's EEA representative:
The Newcastle upon Tyne Hospitals NHS Foundation Trust
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Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Excellent functional outcome as measured by the percentage of patients with a 0 or 1 on the modified Rankin Scale (mRS) at day 90 as assessed by study personnel blinded to treatment

Secondary outcome measures
1. Safety as measured by the incidence of:
1.1. Symptomatic intracranial haemorrhage (sICH)

1.2. Parenchymal Haemorrhage 2 (PH-2)
1.3. Major systemic haemorrhage.
2. Rates and completeness of arterial recanalisation assessed at baseline and 2-3 hours by CT-Angiogram (CTA)
3. Neurological deficits improvement from baseline to 2 hours, 24 hours, end of Argatroban infusion, Day 7/discharge and day 90 as measured by NIHSS
4. Quality of Life obtained by standard gamble, time-trade-off method and visual analogue scale (VAS)
5. Cost and cost-effectiveness analysis
5.1 Medical costs associated with each treatment
5.2 Incremental cost-effectiveness ratio (change in cost divided by quality of life gained)

Overall study start date
01/03/2013

Completion date
31/07/2014

Eligibility

Key inclusion criteria
1. Disabling ischemic stroke symptoms with onset < 3 hours treated with IV rtPA (alteplase) by local standards*.
* or <= 4.5 hours according to local standard of care
2. Age >= 18
3. National Institutes of Health Stroke Scale (NIHSS) >= 10* or any NIHSS with an intracranial clot should be demonstrated on neurovascular imaging (TCD or CTA) in any one of the following areas: distal ICA, MCA (M1 or M2), PCA (P1 or P2), distal vertebral or basilar artery
3.1. TCD criteria: TIBI 0, 1, 2 or 3
3.2. CTAngiogram: TIMI 0 or 1
* NIHSS = 10, demonstration of clot on neuroimaging is not necessary (i.e., enrollment can proceed with noncontrast head CT alone), but if performed, a clot must be demonstrated
4. For those patients who will undergo repeat CT Angiogram at 23 hours, estimated glomerular filtration rate (eGFR) must be >= 60 mL/min/1.73m2
5. Females of childbearing potential must have a negative serum pregnancy test prior to the administration of trial medication
6. Signed (written) informed consent by the patient or the patients legal representative and/or guardian

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
UK Sample Size: 50

Key exclusion criteria
1. Patients whom the treating physician is planning (or could plan) to treat with intraarterial thrombolysis or other endovascular procedures (i.e., mechanical clot retrieval) aimed at recanalisation
2. Evidence of intracranial haemorrhage (ICH) on baseline CT scan or diagnosis of a nonvascular cause of neurologic deficit
3. NIHSS Level of Consciousness score (1a) >= 2
4. Preexisting disability with mRS >= 2
5. CT scan findings of hypoattenuation of the xray signal (hypodensity) involving >= 1/3 of the MCA territory
6. Any evidence of clinically significant bleeding, or known coagulopathy
7. INR >1.5
8. Patients with an elevated activated partial thromboplastin time (aPTT) greater than the upper limit of normal
9. Patients currently, or within the previous 24 hours, on an oral direct thrombin inhibitor
10. Heparin flush required for an IV line. Line flushes with saline only.
11. Any history of intracranial haemorrhage, known arteriovenous malformation or unsecured cerebral aneurysms
12. Significant bleeding episode within the 3 weeks before study enrollment
13. Major surgery or serious trauma in last 2 weeks
14. Patients who have had an arterial puncture at a noncompressible site, biopsy of parenchymal organ, or lumbar puncture within the last 2 weeks
15. Previous stroke, myocardial infarction (MI), post myocardial infarction pericarditis, intracranial surgery, or significant head trauma within 3 months
16. Uncontrolled hypertension (SBP > 185 mmHg or DBP >110 mmHg) that does not respond to intravenous antihypertensive agents
17. Surgical intervention (any reason) anticipated within the next 48 hours
18. Known history of clinically significant hepatic dysfunction or liver disease including a current history of alcohol abuse
19. Abnormal blood glucose <50 mg/dL (2.7 mmol/L)
20. History of primary or metastatic brain tumor
21. Current platelet count < 100,000/mm3
22. Life expectancy < 3 months
23.Patients who, in the judgment of the investigator, needs to be on concomitant (i.e., during the Argatroban infusion) anticoagulants other than Argatroban, including any form of heparin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), defibrinogenating agent, dextran, other direct thrombin inhibitors or thrombolytic agents, GPIIb/IIIa inhibitor or warfarin. [*Caveat: However, if in the judgment of the investigator a patient needs to be anticoagulated, but this can be deferred for 48 hours, then they could be included.]
24. Currently participating or has participated in any investigational drug or device study within 30 days before the first dose of study medication
25. Known hypersensitivity to Argatroban or its agents
26. Additional exclusion criteria if patient presents between 34.5 hours:
26.1. Age >80
26.2. Currently taking oral anticoagulants (regardless of INR)
26.3. A history of stroke and diabetes.
26.4. NIHSS > 25

Date of first enrolment
01/03/2013

Date of final enrolment
31/07/2014

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Newcastle Clinical Trials Unit
Newcastle Upon Tyne
United Kingdom
NE2 4HH

Sponsor information

Organisation
The University of Texas Health Science Center at Houston (USA)

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Sponsor type
University/education

Website
http://www.uthouston.edu/

ROR
https://ror.org/03gds6c39

Funder(s)

Funder type

Government

Funder Name
National Institutes of Health (USA)

Alternative Name(s)
Institutos Nacionales de la Salud, US National Institutes of Health, NIH

Funding Body Type
Government organisation

Funding Body Subtype
National government

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?
Results article	results	01/09/2015		Yes	No
HRA research summary			28/06/2023	No	No