Clinical trial results:
Enhanced Control of Hypertension and Thrombolysis Stroke Trial

Summary

EudraCT number	2011-005545-12
Trial protocol	GB
Global end of trial date	02 March 2019

Results information

Result version number	v1 (current)
This version publication date	02 January 2020
First version publication date	02 January 2020

Trial information

Trial identification

Sponsor protocol code	0250

Additional study identifiers

ISRCTN number	ISRCTN82387104
ClinicalTrials.gov id (NCT number)	NCT01422616
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The University of Leicester
Sponsor organisation address	University Road, Leicester, United Kingdom, LE1 7RH
Public contact	Professor T G Robinson, University of Leicester, +44 01162523182, tgr2@le.ac.uk
Scientific contact	Professor T G Robinson, University of Leicester, +44 01162523182, tgr2@le.ac.uk
Sponsor organisation name	University of Leicester
Sponsor organisation address	University Road, Leicester, United Kingdom, LE1 7RH
Public contact	Prof Thompson Robinson, University of Leicester, +44 0116 252 2962, tgr2@le.ac.uk
Scientific contact	Prof Thompson Robinson, University of Leicester, +44 0116 252 2962, tgr2@le.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overall objective is to increase the number of acute ischaemic stroke patients eligible for thrombolysis (clot-busting treatment), and to improve thrombolysis outcomes by reducing rates of bleeding into the brain (symptomatic intracerebral haemorrhage, sICH).

Therefore, the principal aims are to determine: [A] whether compared to the standard dose, low-dose rtPA is at least as effective (‘not inferior’) on death or any disability; [B] whether compared with current guideline recommended criteria for BP management, early intensive BP lowering is superior in reducing the risk of death or any disability.

Protection of trial subjects:

Exclusion criteria applied regarding contra-indication to the investigation product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 970
Country: Number of subjects enrolled	Australia: 59
Country: Number of subjects enrolled	Brazil: 254
Country: Number of subjects enrolled	Chile: 136
Country: Number of subjects enrolled	China: 2196
Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	Hong Kong: 7
Country: Number of subjects enrolled	India: 35
Country: Number of subjects enrolled	Italy: 65
Country: Number of subjects enrolled	Korea, Republic of: 362
Country: Number of subjects enrolled	Norway: 2
Country: Number of subjects enrolled	Singapore: 33
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Taiwan: 62
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Vietnam: 357

Worldwide total number of subjects	4557
EEA total number of subjects	1041

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1950
From 65 to 84 years	2310
85 years and over	297

Subject disposition

Recruitment

Recruitment details:

Low dose n= 1654
Standard dose n= 1643
Intensive BP lowering n= 1081
Standard BP lowering n= 1115

Total Recruited n=4597

First patient in date= 3 March 2012 / last patient in date = 30 April 2018

Pre-assignment

Screening details:

Patients were screen by Clinical Research Teams on stroke units at the beginning of shifts to assess eligibility for ENCHANTED. If an eligible patient was identified, the delegated medic would approach to discuss the information sheet with patient and family/legal representatives before moving to consent.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Blinding implementation details:

The 28 and 90 day evaluations will be conducted in-person or by telephone, by a trained staff member at the local site who is blind to the treatment allocation.

Arms

Are arms mutually exclusive?	No
Arm title	Low Dose Alteplase

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

0.6mg/kg

Arm title	Standard Dose Alteplase

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

0.9mg/kg

Arm title	Intensive Blood Pressure Lowering

Arm description: -

Arm type	Active comparator

Investigational medicinal product name	transdermal glyceryl trinitrate
Investigational medicinal product code	
Other name	Deponit 5
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Maximum cumulative Deponit dose to be received by participants in the ENCHANTED trial is 10mg per day.

Arm title	Standard Blood Pressure Lowering

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	transdermal glyceryl trinitrate
Investigational medicinal product code	
Other name	Deponit 5
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Maximum cumulative Deponit dose to be received by participants in the ENCHANTED trial is 10mg per day.

Number of subjects in period 1	Low Dose Alteplase	Standard Dose Alteplase	Intensive Blood Pressure Lowering
Started	1607	1599	1072
Completed	1607	1599	1072

Number of subjects in period 1	Standard Blood Pressure Lowering
Started	1108
Completed	1108

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	4557	4557	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1950	1950	
From 65-84 years	2310	2310	
85 years and over	297	297	
Gender categorical Units: Subjects			
Female	1722	1722	
Male	2835	2835	

End points

End points reporting groups

Reporting group title	Low Dose Alteplase
Reporting group description: -	
Reporting group title	Standard Dose Alteplase
Reporting group description: -	
Reporting group title	Intensive Blood Pressure Lowering
Reporting group description: -	
Reporting group title	Standard Blood Pressure Lowering
Reporting group description: -	
Subject analysis set title	Low dose alteplase
Subject analysis set type	Intention-to-treat
Subject analysis set description: low dose alteplase 0.6mg/kg	
Subject analysis set title	Standard dose alteplase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Standard-dose arm 0.9mg/kg	
Subject analysis set title	Intensive BP Lowering
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intensive BP lowering, target <140mmHg systolic	
Subject analysis set title	Standard BP Lowering
Subject analysis set type	Intention-to-treat
Subject analysis set description: Target lowering BP to <180mmHg systolic	

Primary: mRS at Day 90 in BP arms

End point title	mRS at Day 90 in BP arms
End point description: Primary outcome data were available for 1072 patients in the intensive group and 1108 in the guideline group. Functional status (mRS score distribution) at 90 days did not differ between groups (unadjusted odds ratio [OR] 1·01, 95% CI 0·87–1·17, p=0·870)	
End point type	Primary
End point timeframe: Randomisation to Day 90	

End point values	Low Dose Alteplase	Standard Dose Alteplase	Intensive Blood Pressure Lowering	Standard Blood Pressure Lowering
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1607	1599	1072	1108
Units: Scale				
number (confidence interval 95%)	1.05 (0.90 to 1.22)	1.05 (0.90 to 1.22)	1.01 (0.87 to 1.17)	1.01 (0.87 to 1.17)

End point values	Low dose alteplase	Standard dose alteplase	Intensive BP Lowering	Standard BP Lowering
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed				
Units: Scale				
number (confidence interval 95%)	1.05 (0.90 to 1.22)	1.05 (0.9 to 1.22)	1.01 (0.87 to 1.17)	1.01 (0.87 to 1.17)

Statistical analyses

Statistical analysis title	Ordinal Shift Analysis

Statistical analysis description:

Power calculations were based on the estimated treatment effects on a conventional binary assessment of poor outcome (mRS scores 3–6). Assuming poor outcomes of 43% in the intensive blood pressure lowering group and 50% in the guideline-recommended blood pressure lowering group, a sample size of 2304 (1152 per group) was estimated to provide more than 90% power (using a two-sided α=0·05) to detect a 14% relative reduction in poor outcome in the intensive group.

Comparison groups	Intensive Blood Pressure Lowering v Standard Blood Pressure Lowering
Number of subjects included in analysis	2180
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.87
Method	Regression, Logistic

Notes:

[1] - Statistical analyses were done on an intention-to-treat basis. We did shift analyses using ordinal logistic regression for the primary efficacy outcome, and dichotomous logistic regression analyses for all other outcomes.All tests were two-sided and the nominal level of α was 5%.

Primary: mRS at Day 90 in dose arms

End point title	mRS at Day 90 in dose arms

End point description:

No significant differences in the treatment effects were observed between low- and standard-dose alteplase for poor outcomes (death or disability) by age, ethnicity, or severity (all P > .37 for interaction). Similarly, the treatment effects of low-vs standard-dose alteplase on function outcome (ordinal shift of the modified Rankin Scale) in Asians (odds ratio, 1.05; 95% CI, 0.90-1.22) was consistent with non-Asians (odds ratio, 0.93; 95% CI, 0.76-1.14) (P = .32 for interaction).

End point type	Primary

End point timeframe:

Randomisation to Day 90

End point values	Low Dose Alteplase	Standard Dose Alteplase	Intensive Blood Pressure Lowering	Standard Blood Pressure Lowering
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1607	1599	1072	1108
Units: Scale				
number (confidence interval 95%)	1.05 (0.90 to 1.22)	1.05 (0.90 to 1.22)	1.01 (0.87 to 1.17)	1.01 (0.87 to 1.17)

Statistical analyses

Statistical analysis title	Ordinal Shift Analysis

Statistical analysis description:

Ordinal shift of the modified Rankin Scale.

Comparison groups	Low Dose Alteplase v Standard Dose Alteplase
Number of subjects included in analysis	3206
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.32 [3]
Method	Regression, Logistic

Notes:

[2] - The ENCHANTED trial did show that low-dose alteplase was non-inferior for overall functional recovery through ordinal analysis of the mRS and resulted in significantly less severe sICH than did standard-dose alteplase.

[3] - Insignificant p value. However, reductions in rates of ICH with low-dose alteplase, although not statistically significant by age, ethnicity or severity of stroke.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Consent to Day 90 follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Serious Adverse Events - Intensive BP Group

Reporting group description:

A serious adverse event (SAE) in human drug trials is defined as any untoward medical occurrence that at any dose

results in death,
is life-threatening
requires inpatient hospitalization or causes prolongation of existing hospitalization
results in persistent or significant disability/incapacity,
may have caused a congenital anomaly/birth defect, or
requires intervention to prevent permanent impairment or damage.

Reporting group title	Serious Adverse Event - Guideline BP Group
Reporting group description: -	
Reporting group title	Serious Adverse Event - Low Dose Alteplase Group
Reporting group description: -	
Reporting group title	Serious Adverse Event - Standard Dose Alteplase Group
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Only Serious Adverse Events were collected for this study.

Serious adverse events	Serious Adverse Events - Intensive BP Group	Serious Adverse Event - Guideline BP Group	Serious Adverse Event - Low Dose Alteplase Group
Total subjects affected by serious adverse events			
subjects affected / exposed	277 / 1081 (25.62%)	245 / 1115 (21.97%)	559 / 1654 (33.80%)
number of deaths (all causes)	102	88	141
number of deaths resulting from adverse events			
Investigations			
Other - Non Vascular			
subjects affected / exposed	18 / 1081 (1.67%)	26 / 1115 (2.33%)	39 / 1654 (2.36%)
occurrences causally related to treatment / all	0 / 18	0 / 26	0 / 39
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 16
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	2 / 1081 (0.19%)	1 / 1115 (0.09%)	2 / 1654 (0.12%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 1081 (0.28%)	3 / 1115 (0.27%)	4 / 1654 (0.24%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Intracerebral haemorrhage			
subjects affected / exposed	59 / 1081 (5.46%)	100 / 1115 (8.97%)	135 / 1654 (8.16%)
occurrences causally related to treatment / all	0 / 59	0 / 100	0 / 135
deaths causally related to treatment / all	0 / 21	0 / 22	0 / 22
Intracranial haemorrhage			
subjects affected / exposed	66 / 1081 (6.11%)	105 / 1115 (9.42%)	0 / 1654 (0.00%)
occurrences causally related to treatment / all	0 / 66	0 / 105	0 / 0
deaths causally related to treatment / all	0 / 25	0 / 24	0 / 0
Ischaemic stroke			
subjects affected / exposed	64 / 1081 (5.92%)	67 / 1115 (6.01%)	118 / 1654 (7.13%)
occurrences causally related to treatment / all	0 / 61	0 / 45	0 / 118
deaths causally related to treatment / all	0 / 25	0 / 33	0 / 61
Undifferentiated Stroke			
subjects affected / exposed	8 / 1081 (0.74%)	11 / 1115 (0.99%)	20 / 1654 (1.21%)
occurrences causally related to treatment / all	0 / 8	0 / 11	0 / 20
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Other Vascular			
subjects affected / exposed	27 / 1081 (2.50%)	23 / 1115 (2.06%)	55 / 1654 (3.33%)
occurrences causally related to treatment / all	0 / 27	0 / 23	0 / 55
deaths causally related to treatment / all	0 / 9	0 / 2	0 / 16
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	17 / 1081 (1.57%)	10 / 1115 (0.90%)	21 / 1654 (1.27%)
occurrences causally related to treatment / all	0 / 17	0 / 10	0 / 21
deaths causally related to treatment / all	0 / 11	0 / 7	0 / 7
Blood and lymphatic system disorders			

Angioedema			
subjects affected / exposed	0 / 1081 (0.00%)	1 / 1115 (0.09%)	4 / 1654 (0.24%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	40 / 1081 (3.70%)	34 / 1115 (3.05%)	63 / 1654 (3.81%)
occurrences causally related to treatment / all	0 / 40	0 / 34	0 / 63
deaths causally related to treatment / all	0 / 21	0 / 16	0 / 28
Sepsis			
subjects affected / exposed	8 / 1081 (0.74%)	21 / 1115 (1.88%)	27 / 1654 (1.63%)
occurrences causally related to treatment / all	0 / 8	0 / 21	0 / 27
deaths causally related to treatment / all	0 / 4	0 / 6	0 / 4

Serious adverse events	Serious Adverse Event - Standard Dose Alteplase Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	627 / 1643 (38.16%)		
number of deaths (all causes)	172		
number of deaths resulting from adverse events			
Investigations			
Other - Non Vascular			
subjects affected / exposed	63 / 1643 (3.83%)		
occurrences causally related to treatment / all	0 / 63		
deaths causally related to treatment / all	0 / 14		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 1643 (0.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Subarachnoid haemorrhage			
subjects affected / exposed	3 / 1643 (0.18%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		

Intracerebral haemorrhage			
subjects affected / exposed	152 / 1643 (9.25%)		
occurrences causally related to treatment / all	0 / 152		
deaths causally related to treatment / all	0 / 41		
Intracranial haemorrhage			
subjects affected / exposed	0 / 1643 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	97 / 1643 (5.90%)		
occurrences causally related to treatment / all	0 / 97		
deaths causally related to treatment / all	0 / 45		
Undifferentiated Stroke			
subjects affected / exposed	28 / 1643 (1.70%)		
occurrences causally related to treatment / all	0 / 28		
deaths causally related to treatment / all	0 / 5		
Other Vascular			
subjects affected / exposed	64 / 1643 (3.90%)		
occurrences causally related to treatment / all	0 / 64		
deaths causally related to treatment / all	0 / 14		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	19 / 1643 (1.16%)		
occurrences causally related to treatment / all	0 / 19		
deaths causally related to treatment / all	0 / 13		
Blood and lymphatic system disorders			
Angioedema			
subjects affected / exposed	6 / 1643 (0.37%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	71 / 1643 (4.32%)		
occurrences causally related to treatment / all	0 / 71		
deaths causally related to treatment / all	0 / 35		
Sepsis			
subjects affected / exposed	32 / 1643 (1.95%)		
occurrences causally related to treatment / all	0 / 32		
deaths causally related to treatment / all	0 / 12		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Serious Adverse Events - Intensive BP Group	Serious Adverse Event - Guideline BP Group	Serious Adverse Event - Low Dose Alteplase Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1081 (0.00%)	0 / 1115 (0.00%)	0 / 1654 (0.00%)

Non-serious adverse events	Serious Adverse Event - Standard Dose Alteplase Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1643 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2012	Substantial Amendment 2 - Summary of Changes A4. Mrs Wendy Gamble added as Sponsor Representative (replaces Mr Graham Hewitt) A64-1. Mrs Wendy Gamble added as Sponsor Representative (replaces Mr Graham Hewitt) A65. Confirmation of award of Project Grant from The Stroke Association of value £210,055 (replaces Pending, £210,000) A71-2. Increase to 50 UK sites (replaces 25) A72. Increase to 47 England sites (replaces 22) Part B. Section 1. PR8. Details with respect to the addition of intravenous glyceryl trinitrate as a Test IMP Part C. Addition of Research Sites
06 February 2013	Substantial Amendment 3 - Summary of Changes 1. An alteration in the wording of the Participant and Legal Representative Information Sheets at the request of Sponsor Insurers to conform to their revised standard wording. 2. Revised Participant Consent and Legal Representative Assent Forms to refer to the correct versions of the Information Sheets. 3. Altered IMP labelling for Alteplase to enable the use of 10mg and 20mg strength vials, as well as 50mg vials (MHRA only). 4. Addition of new sites, including Principal Investigators. 5. Change in Principal Investigator as participating centres.

07 February 2014	Substantial Amendment 4 - Summary of Changes 1. Amendment to the protocol 2. Revised Participant and Legal Representative Information Sheets, and Participant Consent and Legal Representative Assent Forms, both Full and Short Versions. 3. Removal of existing sites. 4. Change in Principal Investigator details at participating sites
10 September 2014	Substantial Amendment 5 - Summary of Changes 1. Revised Participant and Legal Representative Information Sheets, and Participant Consent and Legal Representative Assent Forms, Full Versions only. 2. Removal of existing sites. 3. Change in Principal Investigator details at participating site. 4. Addition of new sites. 5. Request to increase UK total recruitment to 800.
23 March 2015	Substantial Amendment 6 - Summary of Changes 1. Addition of new site 2. Deletion of site 3. Change of PI at two sites
02 September 2015	Substantial Amendment 7 - Summary of Changes 1. Deletion of 3 sites 2. Change of PI at one site 3. Request to change UK total recruitment to 970
05 November 2015	Substantial Amendment 8 - Summary of Changes 1. Deletion of sites 2. Revised Participant and Legal Representative Information Sheets, and Participant Consent and Legal Representative Assent Forms, Full and Short versions.
04 July 2016	Substantial Amendment 9 - Summary of Changes 1. Change of Principal Investigator at sites 2. Addition of BP arm site 3. Deletion of 6 rtpa arm only sites 4. Submission of the published rtpa arm results paper

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported