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

Summary

EudraCT number	2014-002823-86
Trial protocol	ES
Global end of trial date	30 April 2018

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021
Summary attachment (see zip file)	ENCHANTED tPA arm results (ENCHANTEDmain resultsNEJMMay2016.pdf) ENCHANTED tPA arm results supplementary materials (nejmoa1515510_appendix.pdf) ENCHANTED BP arm results (ENCHANTED BP arm main result_Lancet.pdf) ENCHANTED BP arm results supplementary materials (ENCHANTED BP arm main result_Lancet_appendix.pdf)

Trial information

Trial identification

Sponsor protocol code	ENCHANTED

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The George Institute for Global health
Sponsor organisation address	Level 10, King George V Building, 83-117 Missenden Rd , Camperdown NSW , Australia, 2050
Public contact	Enrique Peña, Institut de Recerca HSCSP, 34 935537636, epenag@santpau.cat
Scientific contact	Enrique Peña, Institut de Recerca HSCSP, 02 8052 4549 , xchen@thegeorgeinstitute.org.au

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	01 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	30 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if:
- Compared with standard dose i.v. rtPA, low-dose rtPA is at least as effective (not inferior) on the major clinical outcome of death or disability at 3 months (i.e. corresponding null hypothesis is that low-dose is inferior to standard dose rtPA);
- Compared with standard guideline-based BP management, early intensive BP lowering is superior in reducing the risk of the major clinical outcome of death or disability at 3 months (i.e. corresponding null hypothesis is that there is no difference in treatments on this outcome).

Protection of trial subjects:

An independent data and safety monitoring committee monitored progress of the trial every 6 months. Responsibilitiies of the DSMB included: Monitor blinded response variables and serious adverse events for early dramatic benefits or potential harmful effects using the approach developed by Sir Richard Peto for safety monitoring and providing reports to the sponsor on recommendations to continue or temporarily halt recruitment to the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2012
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	Australia: 59
Country: Number of subjects enrolled	Brazil: 394
Country: Number of subjects enrolled	Chile: 143
Country: Number of subjects enrolled	China: 2985
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	United Kingdom: 970
Country: Number of subjects enrolled	Vietnam: 357
Worldwide total number of subjects	5493
EEA total number of subjects	71

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)	5493
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between March 3, 2012, and April 30, 2018, 2227 patients were randomly allocated to treatment groups.
Patients recruited into the ENCHANTED study were from 110 sites in 15 countries (Australia, Brazil, Chile, China, Colombia, Hong Kong, India, Italy, Korea, Singapore, Spain, Taiwan, Thailand, United Kingdom, Vietnam).

Pre-assignment

Screening details:

Adult patients (aged ≥18 years) with acute ischaemic stroke and systolic blood pressure 150 mm Hg or more were eligible if they fulfilled standard criteria for thrombolysis with intravenous alteplase, and if the treating clinician had uncertainty over the benefit and risk of the intensity of blood pressure control during and for up to 72 h.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study used a blinded outcome evaluation

Arms

Are arms mutually exclusive?	Yes
Arm title	Low dose rtPA

Arm description: -

Arm type	quasifactorial

No investigational medicinal product assigned in this arm

Arm title	Standard dose rtPA

Arm description: -

Arm type	quasifactorial
Investigational medicinal product name	Alteplase
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Injection

Dosage and administration details:

Participants were randomly assigned to receive either a standard dose of intravenous alteplase (0.9 mg per kilogram of estimated, or measured, body weight; 10% as a bolus and 90% as an infusion over a period
of 60 minutes; maximum dose, 90 mg) or a low dose (0.6 mg per kilogram, 15% as a bolus and 85% as an infusion over a period of 60 minutes; maximum dose, 60 mg), to be commenced within 4.5 hours after symptom onset.

Arm title	BP arm intensive

Arm description: -

Arm type	quasifactorial

No investigational medicinal product assigned in this arm

Arm title	BP arm standard

Arm description: -

Arm type	quasifactorial

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Low dose rtPA	Standard dose rtPA	BP arm intensive
Started	1654	1643	1081
Completed	1607	1599	1072
Not completed	47	44	9
other	47	44	9

Number of subjects in period 1	BP arm standard
Started	1115
Completed	1108
Not completed	7
other	7

Baseline characteristics

Reporting groups	
Reporting group title	Low dose rtPA
Reporting group description: -	
Reporting group title	Standard dose rtPA
Reporting group description: -	
Reporting group title	BP arm intensive
Reporting group description: -	
Reporting group title	BP arm standard
Reporting group description: -	

Reporting group values	Low dose rtPA	Standard dose rtPA	BP arm intensive
Number of subjects	1654	1643	1081
Age categorical Units: Subjects			
Adults (18-64 years)	1654	1643	1081
Age continuous Units: years			
median	68	67	67
inter-quartile range (Q1-Q3)	58 to 76	58 to 76	58 to 76
Gender categorical Units: Subjects			
Female	634	614	401
Male	1020	1029	680

Reporting group values	BP arm standard	Total	
Number of subjects	1115	5493	
Age categorical Units: Subjects			
Adults (18-64 years)	1115	5493	
Age continuous Units: years			
median	67		
inter-quartile range (Q1-Q3)	58 to 76	-	
Gender categorical Units: Subjects			
Female	434	2083	
Male	681	3410	

Subject analysis sets	
Subject analysis set title	Primary outcome BP arm
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The prespecified primary outcome, assessed at 90 days in the intention-to-treat population, was a shift in measures
of functioning according to the full range of scores on the mRS

Subject analysis set title	Primary outcome rtPA arm

Subject analysis set type	Intention-to-treat

Subject analysis set description:

Scores on the modified Rankin scale for assessment of the primary outcome

Reporting group values	Primary outcome BP arm	Primary outcome rtPA arm	
Number of subjects	2180	3206	
Age categorical Units: Subjects			
Adults (18-64 years)	2180	3206	
Age continuous Units: years			
median	1.01	1.0	
inter-quartile range (Q1-Q3)	0.87 to 1.17	0.89 to 1.13	
Gender categorical Units: Subjects			
Female	614	634	
Male	1566	2572	

End points

End points reporting groups

Reporting group title	Low dose rtPA
Reporting group description: -	
Reporting group title	Standard dose rtPA
Reporting group description: -	
Reporting group title	BP arm intensive
Reporting group description: -	
Reporting group title	BP arm standard
Reporting group description: -	
Subject analysis set title	Primary outcome BP arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The prespecified primary outcome, assessed at 90 days in the intention-to-treat population, was a shift in measures of functioning according to the full range of scores on the mRS	
Subject analysis set title	Primary outcome rtPA arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Scores on the modified Rankin scale for assessment of the primary outcome	

Primary: modified rankin scale

End point title	modified rankin scale
End point description:	
The prespecified primary outcome was the combined end point of death or disability at 90 days, which was defined by scores of 2 to 6 on the modified Rankin scale	
End point type	Primary
End point timeframe:	
90 days	

End point values	Low dose rtPA	Standard dose rtPA	BP arm intensive	BP arm standard
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1607	1599	1072	1108
Units: score				
number (not applicable)				
2-6 of the mRS	855	817	498	532

Statistical analyses

Statistical analysis title	Primary outcome analysis rtPa arm dose
Comparison groups	Low dose rtPA v Standard dose rtPA v BP arm intensive v BP arm standard

Number of subjects included in analysis	5386
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.25
Variability estimate	Standard deviation

Statistical analysis title	Primary outcome analysis BP arm
Comparison groups	Low dose rtPA v Standard dose rtPA v BP arm intensive v BP arm standard
Number of subjects included in analysis	5386
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.11

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: enrolment to 90 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4.1

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

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: The study collected serious adverse events and SUSARs only.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Change in the statistical considerations and sample size of the study as follows: Statistical considerations A sample size of 3300 (1650 per group) for arm [A] (i.e. rtPA dose) will provide (i) >90% power to detect non-inferiority (relative margin 14% [i.e. relative risk 1.14], absolute margin rate 6.5%) of low-dose rtPA on the primary outcome (one-sided α = 0.025), and (ii) ≥80% power to detect plausible 40% reductions in risks of sICH with low-dose rtPA (2-sided α = 0.05) with 5% drop-out. A sample size of 2304 (1152 per group) for arm [B] (i.e. BP lowering intensities) will provide ≥90% power to detect superiority of intensive BP lowering on the primary outcome and any ICH(2-sided α = 0.05) with 5% drop-out. Given overlap of approximately 800 patients in the combined arms [A] and [B], an expected total of 4800 patients will participate in the study. A total of 100+ sites are required, most in Asia (approximately 60 sites) and Australia/New Zealand, Europe (approximately 40 sites), and South America (approximately 30 sites), to achieve the sample of 4800 patients ([50%] from Asia) over 4 years (av. 6 patients per site per year). Also, amendment to the BP target for the BP arm of the study as follows: Systolic BP ≥150 mmHg; no definite indication or contraindication to rapid intensive BP lowering to 130-140mmHg systolic target. Other administrative changes
16 February 2017	Addition of: Reason for this Protocol amendment from version 4.0 to version 5.0: The rtPA dose arm of the study addressing questions (1) and (3) concluded with a publication of the results in May 2016. The BP intensity arm of the study is ongoing, and the protocol has been modified to reflect changes. Change of secondary aims: Other secondary aims are to define the effects of the treatments on symptomatic and any ICH; good outcome (mRS 0-1), death or major disability (mRS 3-6); separately on death and disability (mRS 3-5); Explaining that the arm A of low- vs standard-dose rtPA has now closed;

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported