# 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)<br>ENCHANTED tPA arm results supplementary materials (nejmoa1515510_appendix.pdf)<br>ENCHANTED BP arm results (ENCHANTED BP arm main result_Lancet.pdf)<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 1654 | 1643 | 1081 |
| Age continuous<br>Units: years | | | |
| median | 68 | 67 | 67 |
| inter-quartile range (Q1-Q3) | 58 to 76 | 58 to 76 | 58 to 76 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 634 | 614 | 401 |
| Male | 1020 | 1029 | 680 |

| Reporting group values | BP arm standard | Total | |
|---|---|---|---|
| Number of subjects | 1115 | 5493 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 1115 | 5493 | |
| Age continuous<br>Units: years | | | |
| median | 67 | | |
| inter-quartile range (Q1-Q3) | 58 to 76 | - | |
| Gender categorical<br>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<br>Units: Subjects | | | |
| Adults (18-64 years) | 2180 | 3206 | |
| Age continuous<br>Units: years | | | |
| median | 1.01 | 1.0 | |
| inter-quartile range (Q1-Q3) | 0.87 to 1.17 | 0.89 to 1.13 | |
| Gender categorical<br>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:<br>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.<br>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).<br><br>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.<br>Other administrative changes |
| 16 February 2017 | Addition of:<br>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.<br><br>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);<br><br>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