



Clinical trial results:

ENOS: Efficacy of Nitric Oxide in Stroke. Estudio ENOS: Eficacia del óxido nítrico en el ictus

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2004-003870-27 |
| Trial protocol | ES DK SE GR |
| Global end of trial date | 22 October 2014 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 24 February 2019 |
| First version publication date | 24 February 2019 |
| Summary attachment (see zip file) | Effi cacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial (04001 Bath Lancet 2015.pdf) |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | RA2363 |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN99414122 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Nottingham |
| Sponsor organisation address | R&I, East Atrium Jubilee Conference Centre, Nottingham, United Kingdom, NG8 1DH |
| Public contact | Philip Bath, University of Nottingham, +44 115 823 1765, philip.bath@nottingham.ac.uk |
| Scientific contact | Angela Shone, University of Nottingham, +44 115 84 67906, angela.shone@nottingham.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 | 22 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 22 October 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 October 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 20 July 2001 |
| 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 | Spain: 8 |
| Country: Number of subjects enrolled | Sweden: 14 |
| Country: Number of subjects enrolled | Denmark: 17 |
| Country: Number of subjects enrolled | Greece: 12 |
| Country: Number of subjects enrolled | Italy: 33 |
| Country: Number of subjects enrolled | United Kingdom: 2545 |
| Country: Number of subjects enrolled | Australia: 8 |
| Country: Number of subjects enrolled | Canada: 33 |
| Country: Number of subjects enrolled | China: 103 |
| Country: Number of subjects enrolled | Egypt: 148 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Georgia: 195 |
| Country: Number of subjects enrolled | Hong Kong: 4 |
| Country: Number of subjects enrolled | India: 157 |
| Country: Number of subjects enrolled | Malaysia: 14 |
| Country: Number of subjects enrolled | Norway: 4 |
| Country: Number of subjects enrolled | New Zealand: 71 |
| Country: Number of subjects enrolled | Philippines: 16 |
| Country: Number of subjects enrolled | Poland: 123 |
| Country: Number of subjects enrolled | Romania: 217 |
| Country: Number of subjects enrolled | Singapore: 155 |
| Country: Number of subjects enrolled | Sri Lanka: 110 |

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Turkey: 14 |
| Worldwide total number of subjects | 4011 |
| EEA total number of subjects | 2983 |

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) | 1244 |
| From 65 to 84 years | 2299 |
| 85 years and over | 468 |

Subject disposition

Recruitment

Recruitment details:

Between 20th July 2001 and 14th October 2013, 4011 patients from 173 sites were enrolled across 23 countries

Pre-assignment

Screening details:

Inclusion criteria:

Within 48 hours of stroke onset with raised systolic blood pressure of 140 - 220mmHg
Patients who were taking antihypertensives were also randomised to either continue or stop their treatment

Period 1

| | |
|------------------------------|---|
| Period 1 title | Randomisation |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind ^[1] |
| Roles blinded | Subject, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | No |
| Arm title | GTN arm |

Arm description:

Treatment arm

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Glyceryl trinitrate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Impregnated pad |
| Routes of administration | Transdermal use |

Dosage and administration details:

5mg patch applied once per day for 7 days

| | |
|------------------|--------|
| Arm title | No GTN |
|------------------|--------|

Arm description:

No active treatment patch given

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| | |
|------------------|----------------------------|
| Arm title | Continue antihypertensives |
|------------------|----------------------------|

Arm description:

Continuing prior antihypertensive treatment

| | |
|---|------------------------------|
| Arm type | Continuing antihypertensives |
| No investigational medicinal product assigned in this arm | |

| | |
|------------------|------------------------|
| Arm title | Stop antihypertensives |
|------------------|------------------------|

Arm description:

Stop prior antihypertensive treatment

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Participant was blinded

| Number of subjects in period 1 | GTN arm | No GTN | Continue antihypertensives |
|--------------------------------|---------|--------|----------------------------|
| Started | 2000 | 2011 | 1053 |
| Completed | 2000 | 2011 | 1053 |

| Number of subjects in period 1 | Stop antihypertensives |
|--------------------------------|------------------------|
| Started | 1044 |
| Completed | 1044 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Day 90 |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind ^[2] |
| Roles blinded | Subject, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Day 90 follow up coordinator blinded to treatment assignments

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | GTN arm |

Arm description:

Treatment arm

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Glyceryl trinitrate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Impregnated pad |
| Routes of administration | Transdermal use |

Dosage and administration details:

5mg patch applied once per day for 7 days

| | |
|------------------|--------|
| Arm title | No GTN |
|------------------|--------|

Arm description:

No active treatment patch given

| | |
|---|----------------------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |
| Arm title | Continue antihypertensives |

Arm description:

Continuing prior antihypertensive treatment

| | |
|----------|----------------------------|
| Arm type | Continue antihypertensives |
|----------|----------------------------|

| | |
|---|------------------------|
| No investigational medicinal product assigned in this arm | |
| Arm title | Stop antihypertensives |
| Arm description: | |
| Stop prior antihypertensive treatment | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

Notes:

[2] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Participant was blinded

| Number of subjects in period 2 | GTN arm | No GTN | Continue antihypertensives |
|---------------------------------------|---------|--------|----------------------------|
| Started | 2000 | 2011 | 1053 |
| Completed | 1993 | 2002 | 1050 |
| Not completed | 7 | 9 | 3 |
| Lost to follow-up | 7 | 9 | 3 |

| Number of subjects in period 2 | Stop antihypertensives |
|---------------------------------------|------------------------|
| Started | 1044 |
| Completed | 1040 |
| Not completed | 4 |
| Lost to follow-up | 4 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------------|
| Reporting group title | GTN arm |
| Reporting group description: | |
| Treatment arm | |
| Reporting group title | No GTN |
| Reporting group description: | |
| No active treatment patch given | |
| Reporting group title | Continue antihypertensives |
| Reporting group description: | |
| Continuing prior antihypertensive treatment | |
| Reporting group title | Stop antihypertensives |
| Reporting group description: | |
| Stop prior antihypertensive treatment | |

| Reporting group values | GTN arm | No GTN | Continue antihypertensives |
|------------------------|---------|--------|----------------------------|
| Number of subjects | 2000 | 2011 | 1053 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 620 | 624 | 232 |
| From 65-84 years | 1147 | 1152 | 656 |
| 85 years and over | 233 | 235 | 165 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 70 | 70 | 73 |
| standard deviation | ± 12 | ± 12 | ± 11 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 853 | 861 | 525 |
| Male | 1147 | 1150 | 528 |

| Reporting group values | Stop antihypertensives | Total | |
|------------------------|------------------------|-------|--|
| Number of subjects | 1044 | 4011 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 240 | 1244 | |
| From 65-84 years | 663 | 2299 | |
| 85 years and over | 141 | 468 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 73 | - | |
| standard deviation | ± 11 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 504 | 1714 | |
| Male | 540 | 2297 | |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | GTN arm |
| Reporting group description: Treatment arm | |
| Reporting group title | No GTN |
| Reporting group description: No active treatment patch given | |
| Reporting group title | Continue antihypertensives |
| Reporting group description: Continuing prior antihypertensive treatment | |
| Reporting group title | Stop antihypertensives |
| Reporting group description: Stop prior antihypertensive treatment | |
| Reporting group title | GTN arm |
| Reporting group description: Treatment arm | |
| Reporting group title | No GTN |
| Reporting group description: No active treatment patch given | |
| Reporting group title | Continue antihypertensives |
| Reporting group description: Continuing prior antihypertensive treatment | |
| Reporting group title | Stop antihypertensives |
| Reporting group description: Stop prior antihypertensive treatment | |

Primary: Day 90 mRs

| | |
|--------------------------------|------------|
| End point title | Day 90 mRs |
| End point description: | |
| End point type | Primary |
| End point timeframe: Day 90 | |

| End point values | GTN arm | No GTN | Continue antihypertensives | Stop antihypertensives |
|---------------------------------------|-----------------|-----------------|----------------------------|------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1993 | 2002 | 1050 | 1040 |
| Units: score | | | | |
| median (inter-quartile range (Q1-Q3)) | 3 (2 to 4) | 3 (2 to 4) | 3 (2 to 5) | 3 (2 to 4) |

Statistical analyses

| | |
|---|------------------------------|
| Statistical analysis title | Primary outcome analysis GTN |
| Comparison groups | GTN arm v No GTN |
| Number of subjects included in analysis | 3995 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.83 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.13 |

| | |
|---|---|
| Statistical analysis title | Primary analysis - continue/stop |
| Comparison groups | Continue antihypertensives v Stop antihypertensives |
| Number of subjects included in analysis | 2090 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.55 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.22 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Up to day 90

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | All participants |
|-----------------------|------------------|

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: ENOS had a pre-specified list of adverse events for reporting

| Serious adverse events | All participants | | |
|--|-------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1022 / 4011 (25.48%) | | |
| number of deaths (all causes) | 448 | | |
| number of deaths resulting from adverse events | 448 | | |
| General disorders and administration site conditions | | | |
| Serious adverse events | | | |
| subjects affected / exposed | 1022 / 4011 (25.48%) | | |
| occurrences causally related to treatment / all | 24 / 1444 | | |
| deaths causally related to treatment / all | 0 / 448 | | |

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

| Non-serious adverse events | All participants | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 4011 (0.00%) | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|-----|
| N/A |
|-----|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25465108>