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