



Clinical trial results:

An evaluation of the effect of an angiotensin-converting enzyme (ACE) inhibitor on the growth rate of small abdominal aortic aneurysms

Summary

EudraCT number	2010-020226-17
Trial protocol	GB
Global end of trial date	01 April 2015

Results information

Result version number	v1 (current)
This version publication date	15 May 2016
First version publication date	15 May 2016

Trial information

Trial identification

Sponsor protocol code	CRO 1644
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Additional study identifiers

ISRCTN number	ISRCTN51383267
ClinicalTrials.gov id (NCT number)	NCT01118520
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Professor Neil Poulter , Imperial College London, +44 (0)20 7594 3446, n.poulter@imperial.ac.uk
Scientific contact	Professor Neil Poulter , Imperial College London, +44 (0)20 7594 3446, n.poulter@imperial.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	01 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2015
Global end of trial reached?	Yes
Global end of trial date	01 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:

To investigate the hypothesis that an ACEI-I perindopril reduces growth rate of small AAAs in a three-arm randomised placebo-controlled trial.

Secondary objectives:

To evaluate any blood pressure independent effects of perindopril on the growth rate of small AAAs.
To determine differences in AAA rupture rate and/or time taken to reach 5.5cm among the three randomised groups.

To evaluate how well perindopril is tolerated as measured by compliance, adverse events and quality of life.

To compare the repeatability of measurements of internal and external small AAA diameters.

Protection of trial subjects:

N/A

Background therapy:

N/A

Evidence for comparator:

Animal studies have suggested a potential role of the renin-angiotensin system (RAS) in AAA formation and growth. A case-control study on a group of over 15000 patients with an AAA, reported that patients who had previously received an angiotensin converting enzyme inhibitor (ACE-I) but not other antihypertensive agents were 20% less likely to present with ruptured aneurysm. Conversely, post-hoc analysis from both the UK Small Aneurysm Trial and the PHAST trial failed to show that ACE-I slow aneurysm growth. Given the, albeit inconsistent, observational evidence that RAS-blockade might restrict AAA progression or lead to a decrease in the risk of rupture, the AARDVARK (Aortic Aneurysmal Regression of Dilatation: Value of ACE-Inhibition on Risk) trial was designed.

Actual start date of recruitment	05 September 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: 224
Worldwide total number of subjects	224
EEA total number of subjects	224

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)	30
From 65 to 84 years	182
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 14 sites across England and six patient identification centres that referred potential participants to the associated research site for trial recruitment. Between 16th December 2011 and 19th April 2013, 224 patients were correctly randomised to the trial.

Pre-assignment

Screening details:

Trial eligibility was assessed at a screening visit at which demographic information, past medical history and current medication history was recorded. The most recent AAA ultrasound measurements were reviewed and written informed consent was obtained. Thereafter BP recordings and blood samples for creatinine and electrolytes were recorded.

Pre-assignment period milestones

Number of subjects started	224
Number of subjects completed	

Period 1

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

Blinding implementation details:

The trial was classified as single blind since the three tablets prescribed were not identical in appearance. Drugs were dispensed in identical opaque bottles and whilst technically patients could have investigated the composition of their prescribed trial drug, neither patients, ultrasonographers nor site investigators were aware of which tablets had been prescribed to each patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	Perindopril

Arm description:

Perindopril

Arm type	Experimental
Investigational medicinal product name	Perindopril arginine
Investigational medicinal product code	Perindopril
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Perindopril (10mgs arginine salt). One tablet at the same time each day.

Arm title	Amlodipine
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Arm description:

Amlodipine 5mg

Arm type	Active comparator
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Investigational medicinal product name	Amlodipine
Investigational medicinal product code	Amlodipine
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Amlodipine 5mg. 1 tablet at the same time each day.

Arm title	Placebo
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Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral. At the same time each day.

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: All the trial was single blind (the tablets were not over-encapsulated), in practice the trial was double-blind because neither the investigator or the patient were informed of the study drug allocation.

Number of subjects in period 1	Perindopril	Amlodipine	Placebo
Started	73	72	79
Completed	53	49	59
Not completed	20	23	20
Adverse event, serious fatal	3	3	3
Consent withdrawn by subject	8	13	8
AAA repair	9	7	9

Baseline characteristics

Reporting groups

Reporting group title	Perindopril
Reporting group description: Perindopril	
Reporting group title	Amlodipine
Reporting group description: Amlodipine 5mg	
Reporting group title	Placebo
Reporting group description: Placebo	

Reporting group values	Perindopril	Amlodipine	Placebo
Number of subjects	73	72	79
Age categorical Units: Subjects			
Age continuous			
Mean age			
Units: years			
arithmetic mean	71.6	71.5	70.7
standard deviation	± 6.9	± 6.7	± 7.5
Gender categorical Units: Subjects			
Female	2	6	5
Male	71	66	74
Use of statins Units: Subjects			
Receiving statins	53	45	48
Not receiving statins	20	27	31
Diabetes Units: Subjects			
Number of patients with diabetes	2	6	8
Number of patients without diabetes	71	66	71
Anti-platelet therapy Units: Subjects			
Receiving anti-platelet therapy	37	33	28
Not receiving anti-platelet therapy	36	39	51
Current smokers Units: Subjects			
Current smoker	21	18	17
Not current smoker	52	54	62
Past smokers Units: Subjects			
Past smoker	41	44	56
Not a past smoker	32	28	23

Systolic BP			
Systolic BP in mmHg			
Units: mmHg			
arithmetic mean	130.9	131.9	131.7
standard deviation	± 11.5	± 13	± 12.2
Diastolic BP			
Diastolic BP in mmHg			
Units: mmHg			
arithmetic mean	76.7	78	77.9
standard deviation	± 8	± 7	± 7.6
AAA external longitudinal diameter			
Units: cm			
arithmetic mean	4.05	4.03	4.06
standard deviation	± 0.65	± 0.69	± 0.67
AAA internal longitudinal diameter			
Units: cm			
arithmetic mean	3.66	3.61	3.67
standard deviation	± 0.68	± 0.71	± 0.67
AAA external transverse diameter			
Units: cm			
arithmetic mean	4.09	4.04	4.05
standard deviation	± 0.65	± 0.67	± 0.68
AAA internal transverse diameter			
Units: cm			
arithmetic mean	3.68	3.61	3.65
standard deviation	± 0.68	± 0.7	± 0.69
Height			
Units: cm			
arithmetic mean	175.9	173.7	174.4
standard deviation	± 8.3	± 8.7	± 8.5
Weight			
Units: kg			
arithmetic mean	84.3	81.2	84.3
standard deviation	± 16.6	± 13.8	± 16.1
Pack years current smokers			
Units: Years			
arithmetic mean	33.1	29.3	32.9
standard deviation	± 24	± 17.3	± 28
Pack years past smokers			
Units: Years			
arithmetic mean	42	40.5	42.2
standard deviation	± 33.8	± 36.8	± 45.5

Reporting group values	Total		
Number of subjects	224		
Age categorical			
Units: Subjects			

Age continuous			
Mean age			
Units: years			

arithmetic mean			
standard deviation	-		

Gender categorical			
Units: Subjects			
Female	13		
Male	211		
Use of statins			
Units: Subjects			
Receiving statins	146		
Not receiving statins	78		
Diabetes			
Units: Subjects			
Number of patients with diabetes	16		
Number of patients without diabetes	208		
Anti-platelet therapy			
Units: Subjects			
Receiving anti-platelet therapy	98		
Not receiving anti-platelet therapy	126		
Current smokers			
Units: Subjects			
Current smoker	56		
Not current smoker	168		
Past smokers			
Units: Subjects			
Past smoker	141		
Not a past smoker	83		
Systolic BP			
Systolic BP in mmHg			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Diastolic BP			
Diastolic BP in mmHg			
Units: mmHg			
arithmetic mean			
standard deviation	-		
AAA external longitudinal diameter			
Units: cm			
arithmetic mean			
standard deviation	-		
AAA internal longitudinal diameter			
Units: cm			
arithmetic mean			
standard deviation	-		
AAA external transverse diameter			
Units: cm			
arithmetic mean			
standard deviation	-		
AAA internal transverse diameter			

Units: cm arithmetic mean standard deviation	-		
Height Units: cm arithmetic mean standard deviation	-		
Weight Units: kg arithmetic mean standard deviation	-		
Pack years current smokers Units: Years arithmetic mean standard deviation	-		
Pack years past smokers Units: Years arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Perindopril
Reporting group description:	Perindopril
Reporting group title	Amlodipine
Reporting group description:	Amlodipine 5mg
Reporting group title	Placebo
Reporting group description:	Placebo

Primary: AAA external longitudinal diameter's growth rate

End point title	AAA external longitudinal diameter's growth rate ^[1]
End point description:	
End point type	Primary
End point timeframe:	Annual rate over the entire period with visits at 3, 6, 9, 12, 15, 18, 21, 24 months

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary endpoint was whether perindopril reduces the growth rates of small AAA. Amlodipine was a secondary comparator. Each of the active arms was compared individually against placebo.

End point values	Perindopril	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: cm				
least squares mean (standard error)	1.77 (\pm 0.02)	1.68 (\pm 0.02)		

Statistical analyses

Statistical analysis title	linear mixed models (multilevel modelling)
Statistical analysis description:	Linear mixed models (multilevel modelling) where repeated measurements are nested within subjects. We fitted a random-coefficient model adding a random slope of time to allow patients to differ in their rate of diameter growth and the interaction term between time and treatment in the fixed part to investigate the difference in growth rate between treatment groups. The primary comparison is between perindopril and placebo.
Comparison groups	Placebo v Perindopril

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.008
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.065
Variability estimate	Standard error of the mean
Dispersion value	0.029

Notes:

[2] - The differences in the slopes of modelled growth over time were not significant between perindopril and placebo

Secondary: AAA external longitudinal diameter's growth rate

End point title	AAA external longitudinal diameter's growth rate ^[3]
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End point description:

End point type	Secondary
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End point timeframe:

Annual rate over the entire period with visits at 3, 6, 9, 12, 15, 18, 21, 24 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary endpoint was whether perindopril reduces the growth rates of small AAA. Amlodipine was a secondary comparator. Each of the active arms was compared individually against placebo.

End point values	Perindopril	Amlodipine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	72		
Units: cm				
least squares mean (standard error)	1.77 (± 0.02)	1.81 (± 0.02)		

Statistical analyses

Statistical analysis title	linear mixed models (multilevel modelling)
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Statistical analysis description:

Linear mixed models (multilevel modelling) where repeated measurements are nested within subjects. We fitted a random-coefficient model adding a random slope of time to allow patients to differ in their rate of diameter growth and the interaction term between time and treatment in the fixed part to investigate the difference in growth rate between treatment groups. Secondary comparison is between perindopril and amlodipine.

Comparison groups	Perindopril v Amlodipine
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Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.056
upper limit	0.064
Variability estimate	Standard error of the mean
Dispersion value	0.031

Secondary: reaching 5.5 cm in AAA diameter

End point title	reaching 5.5 cm in AAA diameter
End point description:	
The endpoint is reaching 5.5 cm in any of the 4 measurements (the first visit when this happens even if they continue FU) or having surgery or being referred to surgery. When they have both the date considered is the one when reaching threshold unless this is at baseline	
End point type	Secondary
End point timeframe:	
the entire period with visits at 3, 6, 9, 12, 15, 18, 21, 24 months	

End point values	Perindopril	Amlodipine	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	67	77	
Units: events	6	9	11	

Attachments (see zip file)	Kaplan-Meier estimates/kaplan meier.tif
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Statistical analyses

Statistical analysis title	logrank test
Comparison groups	Perindopril v Amlodipine v Placebo
Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85 [4]
Method	Logrank

Notes:

[4] - No significant differences were found between the three treatment groups.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

5 September 2011 to 1 April 2015.

Adverse event reporting additional description:

The following adverse events (AEs) were collected as part of the study:

- Serious AEs (SAEs)
- A single diagnosis or symptom, which led to discontinuation of the trial drug.
- AE's thought to be secondary to trial medication

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19
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Reporting groups

Reporting group title	Perindopril
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Reporting group description:

Perindopril

Reporting group title	Amlodipine
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Reporting group description:

Amlodipine 5mg

Reporting group title	Placebo
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Reporting group description:

Placebo

Serious adverse events	Perindopril	Amlodipine	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 73 (26.03%)	12 / 72 (16.67%)	16 / 79 (20.25%)
number of deaths (all causes)	2	2	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	2 / 73 (2.74%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Adenocarcinoma of prostate			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Angiodysplasia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectum biopsy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Collapse			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Spinal decompression			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia repair			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe operation			

subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm repair			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysm embolisation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatectomy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate transurethral resection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgery			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bowel resection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biopsy penis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laser prostatectomy			

subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicectomy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angioplasty			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Swelling of legs			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
COPD exacerbation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shortness of breath			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Angiography			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngoscopy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystoscopy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiogram			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fractured neck of femur			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder injury			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Compression fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart block			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	2 / 79 (2.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract surgery			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual field defect			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abdominal pain			
subjects affected / exposed	2 / 73 (2.74%)	1 / 72 (1.39%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal bleed			
subjects affected / exposed	0 / 73 (0.00%)	2 / 72 (2.78%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal bleeding			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 73 (2.74%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Gallstones			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive jaundice			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic disease			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle swelling			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infections and infestations			
Chest infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cellulitis of leg			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis of arm			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Perindopril	Amlodipine	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 73 (9.59%)	8 / 72 (11.11%)	9 / 79 (11.39%)
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Heart failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 73 (4.11%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences (all)	3	1	0
Headache			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences (all)	0	1	0
Blackout			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences (all)	0	1	0
Numbness in feet			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Numbness in hands, forearms, elbows			

subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	0 / 72 (0.00%) 0	1 / 79 (1.27%) 1
General disorders and administration site conditions			
Sweating			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Feeling sick			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Feeling unwell			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Upset stomach			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Hiatus hernia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	1 / 79 (1.27%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Breathlessness			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 79 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Itchy skin			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 79 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			

Ankle swelling subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	3 / 72 (4.17%) 3	0 / 79 (0.00%) 0
Metabolism and nutrition disorders Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	0 / 73 (0.00%) 0	0 / 72 (0.00%) 0	1 / 79 (1.27%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2011	Change of IMP supplier
20 June 2011	The brand name was removed from the CTA for amlodipine besilate 5mg, so that there was flexibility of the brand used throughout the trial. This is due to possible supply issues.
13 July 2011	<p>For the first two weeks following randomisation, patients will be asked to take half doses of the IMP dispensed (ie. 5mg of perindopril, 2.5mg amlodipine and half of the placebo tablet). This is in line with standard clinical practice for perindopril that patients should not commence on the full dose. All patients will be provided with pill cutters at their randomisation visit for this purpose. After two weeks they will be instructed to uptitrate to the full dose by taking 1 full tablet per day. Participating sites in London will now only identify, recruit and screen patients. Patients will then be referred to St Mary's Hospital for all subsequent visits.</p> <p>The protocol has been updated to incorporate the changes above- protocol version 3 (01.07.2011).</p> <p>The patient information sheet has been updated to incorporate the changes above – PIS version 5</p> <p>Confirmation that indapamide and losartan are considered Non-Investigational Medicinal Products.</p> <p>Dossiers attached (note this is for consistency in our documentation only).</p> <p>The IMP label has been updated.</p>

19 December 2011	<p>Submission of new version of the patient information sheet (V6) and the addition of a patient invitation letter (V1) and a trial poster (V1).</p> <p>The contact person in section C of the CTA is now Gaia Mahalingam.</p> <p>The main amendments to the protocol are shown in the table below:</p> <p>Amendment Rationale</p> <ol style="list-style-type: none"> 1. Inclusion criteria: 3-5.4cm by Inner to Inner (ITI) or Outer to Outer (OTO) measurements Some sites routinely take ITI measurements whilst others take OTO. Both will be included and measurements of both ITI and OTO will be taken at baseline. 2. Inclusion criteria: Age limit will be dropped to include those 55 years old and above One of the study sites queried the current age range because they have several patients with AAA in their 40's and 50's. The management team decided that the age limit could be dropped to 55 yrs old but not any further to avoid inclusion of patients with connective tissue disease/genetic syndromes. 3. 12 week re-evaluation of BP at PI's discretion If a patient still has systolic BP >150 after 6 weeks on indapamide then they may be prescribed 5mg of amlodipine by their GP and re-evaluated at 12 weeks for study entry. 4. Removal of lipids at screening and update of GP letter to request lipid check. Fasting lipids limits screening visits to the morning and means the patient is asked to fast prior to signing consent. 5. Removal of use of portable ultrasound scanner as per NAAASP. Coventry will use a GE full size scanner. QC will be performed by Head Vascular Scientist at St Mary's Hospital. 6. Allow clinical bloods to be used for screening if performed within 6 weeks To avoid a repeat blood test for the patient if a sample for creatinine and electrolytes has been taken recently. 7. Clarification of window between screening and baseline The protocol is currently unclear. A two month window will be permitted. 8. Addition of visit window for each 3-monthly visit (+/- 7 days where possible)
02 April 2012	<p>Addition of 3 new sites to the AARDVARK study – Hull & East Yorkshire NHS Trust, Royal Bournemouth & Christchurch NHS Trust and Colchester Hospital University NHS Trust.</p> <p>A new version of the protocol – V5.</p> <p>A new version of the patient information sheet and consent – V7. One for sites conducting the biomarker study and the other for sites not conducting the biomarker study.</p> <p>A new version of GP letters A and B (V2)</p>

01 July 2012	<p>Addition of 10 new sites to the AARDVARK study – North West London Hospitals NHS Trust, Newcastle Upon Tyne NHS Trust, Central Manchester University Hospitals NHS Trust, Sheffield Teaching Hospitals NHS Trust, Norfolk and Norwich University Hospitals NHS Trust, York Teaching Hospitals NHS Trust, City Hospitals Sunderland NHS Trust, University Hospitals Birmingham NHS Trust, Salisbury NHS Foundation Trust and NHS Grampian.</p> <p>A new version of the protocol – V6. Clean and tracked copies attached as well as a summary of changes.</p> <p>A new version of the patient information sheet and consent – V8 (one for sites that are participating in the biomarker study and one for sites that are not).</p> <p>A new version of the patient invitation letter – V2</p> <p>A new version of GP letter A - V3</p>
01 August 2013	New version of protocol - version 7. Update to description of quality assurance procedures for clarification.

Notes:

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.

The AAAs in the trial grew slower than expected and the accuracy of ultrasound scanning was less than expected, both of which may have reduced our ability to detect small differences between groups if they were present.

Notes: