Clinical trial results:
REVEAL: Randomized EValuation of the Effects of Anacetrapib through Lipid-modification. A large-scale, randomized placebo-controlled trial of the clinical effects of anacetrapib among people with established vascular disease

Summary

EudraCT number	2010-023467-18
Trial protocol	GB SE DK FI DE IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	14 September 2018
First version publication date	14 September 2018

Trial information

Trial identification

Sponsor protocol code	CTSUREVEAL1

Additional study identifiers

ISRCTN number	ISRCTN48678192
ClinicalTrials.gov id (NCT number)	NCT01252953
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LE
Public contact	REVEAL Study team, CTSU, Nuffield Department of Population Health, +44 01865743743, reveal@ndph.ox.ac.uk
Scientific contact	Martin Landray, CTSU, Nuffield Department of Population Health, +44 01865743743, martin.landray@ndph.ox.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	Interim
Date of interim/final analysis	15 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of lipid modification using anacetrapib 100mg daily versus placebo on the time to first "major coronary event" (defined as the occurrence of coronary death, myocardial infarction or coronary revascularization procedure) during the scheduled treatment period.

Protection of trial subjects:

At each visit details of hospital admissions, other Serious Adverse Events, unexplained muscle pain or weakness, and non-serious adverse events attributed to study treatment were sought. Liver function was also checked at each follow-up visit.
Participants were provided with a 24-hour Freefone number should they wish to discuss trial-related medical problems outside of the normal working hours.

Background therapy:

Atorvastatin 10mg, 20mg or 80mg
In China, atorvastatin 10mg or 20mg daily was used. Elsewhere the dose was 20mg or 80mg.

Evidence for comparator:

When used either as monotherapy or in combination with a statin, the CETP inhibitor anacetrapib more than doubles HDL cholesterol concentration and also reduces non-HDL cholesterol concentration. In early phase studies completed prior to initiation of REVEAL, anacetrapib was well tolerated and had no effects on blood pressure or aldosterone levels. The REVEAL trial set out to assess whether the lipid changes produced by anacetrapib would reduce the risk of vascular events when used in addition to effective doses of a statin.

Actual start date of recruitment	22 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 844
Country: Number of subjects enrolled	Sweden: 861
Country: Number of subjects enrolled	United Kingdom: 8381
Country: Number of subjects enrolled	Denmark: 1850
Country: Number of subjects enrolled	Finland: 613
Country: Number of subjects enrolled	Germany: 1529
Country: Number of subjects enrolled	Italy: 1660
Country: Number of subjects enrolled	United States: 5330
Country: Number of subjects enrolled	Canada: 752
Country: Number of subjects enrolled	China: 8629

Worldwide total number of subjects	30449
EEA total number of subjects	15738

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)	13277
From 65 to 84 years	16779
85 years and over	393

Subject disposition

Recruitment

Recruitment details:

49,787 participants attended a screening visit after which 38,246 entered the run-in period and subsequently 30,449 were randomized between August 2011 and October 2013.

Pre-assignment

Screening details:

Successfully screened participants were entered into a run-in period. Attendees were discouraged from continuing to randomization if it was thought unlikely they would be able to continue attending follow-up visits for at least 4-5years.
During run-in participants were issued atorvastatin (1 tablet/day) and placebo anacetrapib (1 tablet/day).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The trial was placebo controlled.
Access to randomized data was available to an unblinded statistician and the Data Monitoring Committee. Lipid results were not accessible during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Anacetrapib

Arm description:

Experimental drug

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

Dosage and administration details:

100mg daily

Arm title	Placebo

Arm description:

Placebo anacetrapib

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

Dosage and administration details:

Placebo anacetrapib 100mg daily

Number of subjects in period 1	Anacetrapib	Placebo
Started	15225	15224
Completed	15187	15186
Not completed	38	38
Consent withdrawn by subject	16	17
Lost to follow-up	22	21

Baseline characteristics

Reporting groups	
Reporting group title	Anacetrapib
Reporting group description: Experimental drug	
Reporting group title	Placebo
Reporting group description: Placebo anacetrapib	

Reporting group values	Anacetrapib	Placebo	Total
Number of subjects	15225	15224	30449
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6634	6643	13277
From 65-84 years	0	0	0
85 years and over	0	0	0
From 65 to 69 years	3380	3377	6757
70 years and over	5211	5204	10415
Age continuous Units: years			
arithmetic mean	67	67	
standard deviation	± 8	± 8	-
Gender categorical Units: Subjects			
Female	2456	2459	4915
Male	12769	12765	25534
Systolic blood pressure (mmHg) Units: Subjects			
< 125	5678	5760	11438
≥ 125 < 140	4819	4740	9559
≥ 140	4728	4724	9452
Diastolic blood pressure (mmHg) Units: Subjects			
< 75	5656	5790	11446
≥ 75 < 85	5408	5277	10685
≥ 85	4161	4157	8318
Region Units: Subjects			
Europe	7863	7875	15738
North America	3048	3034	6082

China	4314	4315	8629
Body-mass index (kg/m²)			
The body-mass index is the weight in kilograms divided by the square of the height in meters.			
Units: Subjects			
< 25	3447	3361	6808
≥ 25 < 30	6949	6995	13944
≥ 30	4829	4868	9697
LDL cholesterol (mmol/L) Units: Subjects			
< 1.4	5023	5077	10100
≥ 1.4 < 1.7	4529	4582	9111
≥ 1.7	5559	5442	11001
Missing	114	123	237
Non-HDL cholesterol (mmol/L) Units: Subjects			
< 2.2	5642	5701	11343
≥ 2.2 < 2.6	4782	4730	9512
≥ 2.6	4687	4670	9357
Missing	114	123	237
HDL cholesterol (mmol/L) Units: Subjects			
< 0.9	4583	4590	9173
≥ 0.9 < 1.1	5324	5146	10470
≥ 1.1	5204	5365	10569
Missing	114	123	237
Glomerular filtration rate (ml/min/1.73m²)			
The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.			
Units: Subjects			
< 60	1655	1698	3353
≥ 60	13570	13526	27096
Systolic blood pressure Units: mm Hg			
arithmetic mean	131.3	131.1	
standard deviation	± 18.5	± 18.5	-
Diastolic blood pressure Units: mm Hg			
arithmetic mean	78.1	78.0	
standard deviation	± 10.9	± 11	-
Body-mass index			
The body-mass index is the weight in kilograms divided by the square of the height in meters.			
Units: kg/m²			
arithmetic mean	28.6	28.6	
standard deviation	± 5.0	± 5.1	-
LDL cholesterol Units: mmol/L			
arithmetic mean	1.58	1.57	
standard deviation	± 0.39	± 0.39	-
Non-HDL cholesterol Units: mmol/L			
arithmetic mean	2.37	2.37	

standard deviation	± 0.49	± 0.49	-
HDL cholesterol			
Units: mmol/L			
arithmetic mean	1.04	1.04	
standard deviation	± 0.25	± 0.25	-
Glomerular filtration rate			
The estimated glomerular filtration rate was calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).			
Units: ml/min/1.73m²			
arithmetic mean	83	83	
standard deviation	± 17	± 17	-

End points

End points reporting groups	
Reporting group title	Anacetrapib
Reporting group description:	
Experimental drug	
Reporting group title	Placebo
Reporting group description:	
Placebo anacetrapib	

Primary: Major coronary event	
End point title	Major coronary event
End point description:	
Primary assessment involves an intention-to-treat comparison among all randomized participants of the effects of allocation to anacetrapib versus placebo on major coronary events (defined as the occurrence of coronary death, myocardial infarction or coronary revascularization procedure) during the scheduled treatment period. Data reported is for first major coronary event.	
End point type	Primary
End point timeframe:	
Randomized treatment phase during median follow-up period of 4.1years	

End point values	Anacetrapib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15225	15224		
Units: Events	1640	1803		

Statistical analyses

Statistical analysis title	Major coronary event
Comparison groups	Anacetrapib v Placebo
Number of subjects included in analysis	30449
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.004
Method	Logrank
Parameter estimate	Rate Ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.97

Notes:

[1] - Time to first event

Secondary: Major atherosclerotic event

End point title	Major atherosclerotic event

End point description:

Major atherosclerotic events (defined as coronary death, myocardial infarction or presumed ischaemic stroke; the key secondary outcome)
Secondary assessments involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the scheduled treatment period.

End point type	Secondary

End point timeframe:

Randomized treatment phase during median follow-up period of 4.1years

End point values	Anacetrapib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15225	15224		
Units: Events	1383	1483		

Statistical analyses

Statistical analysis title	Major atherosclerotic events
Comparison groups	Anacetrapib v Placebo
Number of subjects included in analysis	30449
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.052
Method	Logrank
Parameter estimate	Rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1

Notes:

[2] - Time to first event

Secondary: Presumed ischaemic stroke

End point title	Presumed ischaemic stroke

End point description:

Presumed ischaemic stroke (i.e. not known to be haemorrhagic).
Secondary assessments involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the scheduled treatment period.

End point type	Secondary

End point timeframe:

Randomized treatment phase during median follow-up period of 4.1years

End point values	Anacetrapib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15225	15224		
Units: Events	485	489		

Statistical analyses

Statistical analysis title	Presumed ischaemic stroke
Comparison groups	Anacetrapib v Placebo
Number of subjects included in analysis	30449
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Rate ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.12

Notes:

[3] - Time to first event
In accordance with the data analysis plan, if the outcome of a major atherosclerotic event did not reach significance, there was no hypothesis testing for presumed ischaemic stoke, so no P value is given.

Secondary: Major vascular event

End point title	Major vascular event

End point description:

Major vascular events (defined as coronary death, myocardial infarction, coronary revascularization or presumed ischaemic stroke).
Secondary assessments involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the scheduled treatment period

End point type	Secondary

End point timeframe:

Randomized treatment phase during median follow-up period of 4.1years

End point values	Anacetrapib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15225	15224		
Units: Events	2068	2214		

Statistical analyses

Statistical analysis title	Major vascular event
Comparison groups	Anacetrapib v Placebo
Number of subjects included in analysis	30449
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.02
Method	Logrank
Parameter estimate	Rate ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	0.99

Notes:

[4] - Time to first event

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomized treatment phase during median follow-up period of 4.1years

Adverse event reporting additional description:

All serious adverse events were reported on the electronic case report form together with non-serious adverse events that were thought to be related to the randomized study treatment (nSARs).
Further tabulations of adverse events have been published at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1706444/suppl_file/nejmoa1706444_appendix_2.html

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Anacetrapib

Reporting group description:

Experimental drug

Reporting group title	Placebo

Reporting group description:

Placebo anacetrapib

Serious adverse events	Anacetrapib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8898 / 15225 (58.44%)	8912 / 15224 (58.54%)	
number of deaths (all causes)	1122	1155	
number of deaths resulting from adverse events	1122	1155	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	1323 / 15225 (8.69%)	1295 / 15224 (8.51%)	
occurrences causally related to treatment / all	0 / 1810	1 / 1770	
deaths causally related to treatment / all	0 / 331	1 / 331	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	346 / 15225 (2.27%)	352 / 15224 (2.31%)	
occurrences causally related to treatment / all	0 / 399	0 / 393	
deaths causally related to treatment / all	0 / 18	0 / 18	
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	3409 / 15225 (22.39%)	3478 / 15224 (22.85%)	
occurrences causally related to treatment / all	1 / 5051	0 / 5241	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	691 / 15225 (4.54%)	736 / 15224 (4.83%)	
occurrences causally related to treatment / all	0 / 781	0 / 838	
deaths causally related to treatment / all	0 / 203	0 / 210	
Immune system disorders			
Immune system disorder			
subjects affected / exposed	12 / 15225 (0.08%)	29 / 15224 (0.19%)	
occurrences causally related to treatment / all	0 / 12	1 / 29	
deaths causally related to treatment / all	0 / 0	0 / 1	
Social circumstances			
Social circumstances			
subjects affected / exposed	501 / 15225 (3.29%)	516 / 15224 (3.39%)	
occurrences causally related to treatment / all	0 / 769	0 / 778	
deaths causally related to treatment / all	0 / 2	0 / 0	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	49 / 15225 (0.32%)	56 / 15224 (0.37%)	
occurrences causally related to treatment / all	0 / 53	0 / 59	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	606 / 15225 (3.98%)	605 / 15224 (3.97%)	
occurrences causally related to treatment / all	0 / 791	1 / 813	
deaths causally related to treatment / all	0 / 52	1 / 41	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	104 / 15225 (0.68%)	111 / 15224 (0.73%)	
occurrences causally related to treatment / all	0 / 117	0 / 124	
deaths causally related to treatment / all	0 / 5	0 / 8	

Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	217 / 15225 (1.43%)	238 / 15224 (1.56%)	
occurrences causally related to treatment / all	2 / 251	0 / 268	
deaths causally related to treatment / all	0 / 5	0 / 9	
Investigations			
Investigations			
subjects affected / exposed	1105 / 15225 (7.26%)	1135 / 15224 (7.46%)	
occurrences causally related to treatment / all	0 / 1421	0 / 1419	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	753 / 15225 (4.95%)	777 / 15224 (5.10%)	
occurrences causally related to treatment / all	0 / 889	0 / 918	
deaths causally related to treatment / all	0 / 26	0 / 23	
Congenital, familial and genetic disorders			
Congenital, familial and genetic disorders			
subjects affected / exposed	9 / 15225 (0.06%)	4 / 15224 (0.03%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	2568 / 15225 (16.87%)	2766 / 15224 (18.17%)	
occurrences causally related to treatment / all	0 / 4120	1 / 4280	
deaths causally related to treatment / all	0 / 263	0 / 295	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	1399 / 15225 (9.19%)	1455 / 15224 (9.56%)	
occurrences causally related to treatment / all	0 / 1789	0 / 1822	
deaths causally related to treatment / all	0 / 90	0 / 97	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			

subjects affected / exposed	188 / 15225 (1.23%)	182 / 15224 (1.20%)	
occurrences causally related to treatment / all	0 / 219	0 / 210	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Ear and labrinth disorders			
subjects affected / exposed	114 / 15225 (0.75%)	91 / 15224 (0.60%)	
occurrences causally related to treatment / all	0 / 121	0 / 99	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	204 / 15225 (1.34%)	232 / 15224 (1.52%)	
occurrences causally related to treatment / all	0 / 235	0 / 264	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	813 / 15225 (5.34%)	788 / 15224 (5.18%)	
occurrences causally related to treatment / all	2 / 1012	3 / 976	
deaths causally related to treatment / all	0 / 20	0 / 20	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	84 / 15225 (0.55%)	97 / 15224 (0.64%)	
occurrences causally related to treatment / all	1 / 93	2 / 109	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	415 / 15225 (2.73%)	398 / 15224 (2.61%)	
occurrences causally related to treatment / all	0 / 516	3 / 470	
deaths causally related to treatment / all	0 / 8	0 / 8	
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	50 / 15225 (0.33%)	49 / 15224 (0.32%)	
occurrences causally related to treatment / all	0 / 50	0 / 51	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders			
subjects affected / exposed	438 / 15225 (2.88%)	432 / 15224 (2.84%)	
occurrences causally related to treatment / all	2 / 508	0 / 501	
deaths causally related to treatment / all	0 / 1	0 / 1	
Infections and infestations			
Infections and infestations			
subjects affected / exposed	1559 / 15225 (10.24%)	1537 / 15224 (10.10%)	
occurrences causally related to treatment / all	0 / 2097	2 / 2152	
deaths causally related to treatment / all	0 / 96	0 / 91	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	642 / 15225 (4.22%)	687 / 15224 (4.51%)	
occurrences causally related to treatment / all	0 / 774	0 / 820	
deaths causally related to treatment / all	0 / 1	0 / 2	

Frequency threshold for reporting non-serious adverse events: 0.01 %

Non-serious adverse events	Anacetrapib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	826 / 15225 (5.43%)	827 / 15224 (5.43%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	1 / 15225 (0.01%)	0 / 15224 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	3 / 15225 (0.02%)	1 / 15224 (0.01%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	31 / 15225 (0.20%)	33 / 15224 (0.22%)	
occurrences (all)	32	38	
Immune system disorders			

Immune system disorders			
subjects affected / exposed	2 / 15225 (0.01%)	4 / 15224 (0.03%)	
occurrences (all)	2	4	
Social circumstances			
Social circumstances			
subjects affected / exposed	0 / 15225 (0.00%)	1 / 15224 (0.01%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	9 / 15225 (0.06%)	8 / 15224 (0.05%)	
occurrences (all)	9	8	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	27 / 15225 (0.18%)	31 / 15224 (0.20%)	
occurrences (all)	28	33	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	18 / 15225 (0.12%)	26 / 15224 (0.17%)	
occurrences (all)	22	28	
Investigations			
Investigations			
subjects affected / exposed	62 / 15225 (0.41%)	54 / 15224 (0.35%)	
occurrences (all)	64	59	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	5 / 15225 (0.03%)	5 / 15224 (0.03%)	
occurrences (all)	6	5	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	12 / 15225 (0.08%)	7 / 15224 (0.05%)	
occurrences (all)	13	7	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	121 / 15225 (0.79%)	106 / 15224 (0.70%)	
occurrences (all)	134	112	

Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	6 / 15225 (0.04%)	6 / 15224 (0.04%)	
occurrences (all)	6	6	
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	6 / 15225 (0.04%)	8 / 15224 (0.05%)	
occurrences (all)	6	8	
Eye disorders			
Eye disorders			
subjects affected / exposed	4 / 15225 (0.03%)	11 / 15224 (0.07%)	
occurrences (all)	4	11	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	200 / 15225 (1.31%)	192 / 15224 (1.26%)	
occurrences (all)	230	220	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	4 / 15225 (0.03%)	4 / 15224 (0.03%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	71 / 15225 (0.47%)	66 / 15224 (0.43%)	
occurrences (all)	76	69	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	9 / 15225 (0.06%)	9 / 15224 (0.06%)	
occurrences (all)	9	10	
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	0 / 15225 (0.00%)	1 / 15224 (0.01%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	330 / 15225 (2.17%)	343 / 15224 (2.25%)	
occurrences (all)	413	427	

Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	 30 / 15225 (0.20%) 33	 31 / 15224 (0.20%) 32	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 45 / 15225 (0.30%) 46	 41 / 15224 (0.27%) 43	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2016	The Steering Committee agreed the following changes to the protocol: 1. Cancel any formal interim review of efficacy by the Data Monitoring Committee prior to 3 years' median follow-up. (The interim review of efficacy originally scheduled to take place at 2.5 years after median randomization, was cancelled and has been removed from the protocol; section 2.5.2.2). 2. Revise the secondary assessments (section 2.3.1.2) to: (i) Major atherosclerotic events (defined as coronary death, myocardial infarction or presumed ischaemic stroke; the key secondary outcome); (ii) Presumed ischaemic stroke; and (iii) Major vascular events (defined as coronary death, myocardial infarction, coronary revascularization or presumed ischaemic stroke); 3. Make minor changes to the tertiary assessments (section 2.3.1.4) Power calculations for the new secondary endpoints have been added, based on the number of participants who have been randomized and the blinded event rates observed to date (section 2.4.3). A brief summary of relevant information that has emerged since the study background and rationale (section 1.1) were written has been added (section 1.2). A small number of administrative changes and clarifications have also been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28454801

http://www.ncbi.nlm.nih.gov/pubmed/28847206