



## 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      |
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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:

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### 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         |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1</b> | 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/m <sup>2</sup> )  |        |        |       |
| 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/1.73m <sup>2</sup> )   |        |        |       |
| 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/m <sup>2</sup>  |        |        |       |
| 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/1.73m <sup>2</sup>   |        |        |   |
| 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 <sup>[1]</sup>  |
| 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 <sup>[2]</sup> |
|---------------|----------------------|

|         |         |
|---------|---------|
| 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 <sup>[3]</sup>      |
| 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 stroke, 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

|   |                       |
|---|-----------------------|
| <b>Statistical analysis title</b>       | Major vascular event  |
| Comparison groups                       | Anacetrapib v Placebo |
| Number of subjects included in analysis | 30449                 |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | other <sup>[4]</sup>  |
| 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](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

| <b>Serious adverse events</b>                                       | Anacetrapib              | Placebo                  |  |
|---|--------------------------|--------------------------|--|
| Total subjects affected by serious adverse events                   |                          |                          |  |
| subjects affected / exposed   | 8898 / 15225<br>(58.44%) | 8912 / 15224<br>(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<br>(8.69%)  | 1295 / 15224<br>(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<br>(2.27%)   | 352 / 15224<br>(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<br>(22.39%) | 3478 / 15224<br>(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<br>(4.54%)   | 736 / 15224<br>(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<br>(3.29%)   | 516 / 15224<br>(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<br>(3.98%)   | 605 / 15224<br>(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<br>(0.68%)   | 111 / 15224<br>(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<br>(1.43%)   | 238 / 15224<br>(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<br>(7.26%)  | 1135 / 15224<br>(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<br>(4.95%)   | 777 / 15224<br>(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<br>(16.87%) | 2766 / 15224<br>(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<br>(9.19%)  | 1455 / 15224<br>(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<br>(1.23%) | 182 / 15224<br>(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<br>(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<br>(1.34%) | 232 / 15224<br>(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<br>(5.34%) | 788 / 15224<br>(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<br>(2.73%) | 398 / 15224<br>(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<br>(2.88%)   | 432 / 15224<br>(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<br>(10.24%) | 1537 / 15224<br>(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<br>(4.22%)   | 687 / 15224<br>(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 %

| <b>Non-serious adverse events</b>                                   | Anacetrapib            | Placebo                |  |
|---|------------------------|------------------------|--|
| Total subjects affected by non-serious adverse events               |                        |                        |  |
| subjects affected / exposed   | 826 / 15225<br>(5.43%) | 827 / 15224<br>(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<br>subjects affected / exposed<br>occurrences (all)  | 2 / 15225 (0.01%)<br>2     | 4 / 15224 (0.03%)<br>4     |  |
| Social circumstances<br>Social circumstances<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15225 (0.00%)<br>0     | 1 / 15224 (0.01%)<br>1     |  |
| Reproductive system and breast disorders<br>Reproductive system and breast disorders<br>subjects affected / exposed<br>occurrences (all)               | 9 / 15225 (0.06%)<br>9     | 8 / 15224 (0.05%)<br>8     |  |
| Respiratory, thoracic and mediastinal disorders<br>Respiratory, thoracic and mediastinal disorders<br>subjects affected / exposed<br>occurrences (all) | 27 / 15225 (0.18%)<br>28   | 31 / 15224 (0.20%)<br>33   |  |
| Psychiatric disorders<br>Psychiatric disorders<br>subjects affected / exposed<br>occurrences (all)   | 18 / 15225 (0.12%)<br>22   | 26 / 15224 (0.17%)<br>28   |  |
| Investigations<br>Investigations<br>subjects affected / exposed<br>occurrences (all)   | 62 / 15225 (0.41%)<br>64   | 54 / 15224 (0.35%)<br>59   |  |
| Injury, poisoning and procedural complications<br>Injury, poisoning and procedural complications<br>subjects affected / exposed<br>occurrences (all)   | 5 / 15225 (0.03%)<br>6     | 5 / 15224 (0.03%)<br>5     |  |
| Cardiac disorders<br>Cardiac disorders<br>subjects affected / exposed<br>occurrences (all)   | 12 / 15225 (0.08%)<br>13   | 7 / 15224 (0.05%)<br>7     |  |
| Nervous system disorders<br>Nervous system disorders<br>subjects affected / exposed<br>occurrences (all)   | 121 / 15225 (0.79%)<br>134 | 106 / 15224 (0.70%)<br>112 |  |

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 11 January 2016 | <p>The Steering Committee agreed the following changes to the protocol:</p> <ol style="list-style-type: none"><li>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).</li><li>2. Revise the secondary assessments (section 2.3.1.2) to:<ol style="list-style-type: none"><li>(i) Major atherosclerotic events (defined as coronary death, myocardial infarction or presumed ischaemic stroke; the key secondary outcome);</li><li>(ii) Presumed ischaemic stroke; and</li><li>(iii) Major vascular events (defined as coronary death, myocardial infarction, coronary revascularization or presumed ischaemic stroke);</li></ol></li><li>3. Make minor changes to the tertiary assessments (section 2.3.1.4)</li></ol> <p>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).</p> <p>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).</p> <p>A small number of administrative changes and clarifications have also been made.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

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

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