



Clinical trial results:

A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects With Severe Familial Hypercholesterolemia

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2011-005400-15 |
| Trial protocol | BE GR CZ GB ES IT NL |
| Global end of trial date | 11 May 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 22 November 2018 |
| First version publication date | 22 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20110271 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01624142 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Amgen Inc. |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320 |
| Public contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------|
| Analysis stage | Final |
| Date of interim/final analysis | 11 May 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to characterize the safety and tolerability of long-term administration of evolocumab (AMG 145) among subjects with severe familial hypercholesterolemia.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and Food and Drug Administration (FDA) regulations/guidelines.

The Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) for this study reviewed the study protocol, amendments, and the informed consent form (ICF). No subjects were recruited into the study and no investigational product was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 01 June 2012 |
| 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 | Canada: 37 |
| Country: Number of subjects enrolled | United States: 32 |
| Country: Number of subjects enrolled | Belgium: 12 |
| Country: Number of subjects enrolled | Czech Republic: 28 |
| Country: Number of subjects enrolled | France: 20 |
| Country: Number of subjects enrolled | Greece: 2 |
| Country: Number of subjects enrolled | Israel: 5 |
| Country: Number of subjects enrolled | Italy: 25 |
| Country: Number of subjects enrolled | Lebanon: 1 |
| Country: Number of subjects enrolled | Netherlands: 23 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Brazil: 25 |
| Country: Number of subjects enrolled | Australia: 10 |
| Country: Number of subjects enrolled | Hong Kong: 1 |
| Country: Number of subjects enrolled | Japan: 9 |
| Country: Number of subjects enrolled | New Zealand: 11 |

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | South Africa: 31 |
| Worldwide total number of subjects | 300 |
| EEA total number of subjects | 138 |

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) | 14 |
| Adults (18-64 years) | 240 |
| From 65 to 84 years | 46 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 43 centers in Canada, South Africa, Czech Republic, Netherlands, USA, France, Spain, Italy, Belgium, Australia, New Zealand, United Kingdom, Japan, Israel, Greece, Lebanon, Brazil, and Hong Kong between 01 June 2012 and 19 March 2015.

Pre-assignment

Screening details:

A total of 246 participants enrolled directly in Study 20110271 and 54 participants rolled over from Study 20110233 (NCT01588496).

Results are reported separately for participants with homozygous familial hypercholesterolemia (HoFH) and non-HoFH severe familial hypercholesterolemia (FH) (ie, all those not meeting the protocol criteria for HoFH).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | Yes |
| Arm title | HoFH |

Arm description:

Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) levels.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Evolocumab |
| Investigational medicinal product code | AMG 145 |
| Other name | Repatha |
| Pharmaceutical forms | Solution for injection, Solution for injection in pre-filled pen, Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Evolocumab 420 mg via subcutaneous injection, initially administered either once a month (QM) (non-apheresis subjects) or once every 2 weeks (Q2W) (apheresis subjects).

| | |
|-----------|-----------|
| Arm title | Severe FH |
|-----------|-----------|

Arm description:

Participants with severe (non-HoFH) familial hypercholesterolemia (FH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound PCSK9 levels.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Evolocumab |
| Investigational medicinal product code | AMG 145 |
| Other name | Repatha |
| Pharmaceutical forms | Solution for injection, Solution for injection in pre-filled pen, Solution for injection in cartridge |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Evolocumab 420 mg via subcutaneous injection, initially administered either once a month (QM) (non-apheresis subjects) or once every 2 weeks (Q2W) (apheresis subjects).

| Number of subjects in period 1 | HoFH | Severe FH |
|---------------------------------------|------|-----------|
| Started | 106 | 194 |
| Completed | 74 | 178 |
| Not completed | 32 | 16 |
| Adverse event, serious fatal | 3 | 6 |
| Consent withdrawn by subject | 14 | 4 |
| Study Closure | 12 | 6 |
| Other | 1 | - |
| Lost to follow-up | 2 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | HoFH |
|-----------------------|------|

Reporting group description:

Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) levels.

| | |
|-----------------------|-----------|
| Reporting group title | Severe FH |
|-----------------------|-----------|

Reporting group description:

Participants with severe (non-HoFH) familial hypercholesterolemia (FH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound PCSK9 levels.

| Reporting group values | HoFH | Severe FH | Total |
|---|--------|-----------|-------|
| Number of subjects | 106 | 194 | 300 |
| Age Categorical | | | |
| Baseline characteristics for parent study rollover subjects are defined at the parent study baseline. | | | |
| Units: Subjects | | | |
| <=18 years | 14 | 0 | 14 |
| Between 18 and 65 years | 88 | 152 | 240 |
| >=65 years | 4 | 42 | 46 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.3 | 54.7 | |
| standard deviation | ± 14.4 | ± 11.9 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 54 | 78 | 132 |
| Male | 52 | 116 | 168 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 1 |
| Asian | 13 | 3 | 16 |
| Black or African American | 0 | 6 | 6 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 85 | 179 | 264 |
| Other | 7 | 4 | 11 |
| Mixed Race | 0 | 2 | 2 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 5 | 22 | 27 |
| Not Hispanic or Latino | 101 | 172 | 273 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Low-density Lipoprotein Cholesterol (LDL-C) Concentration | | | |
| Units: mg/dL | | | |
| arithmetic mean | 329.0 | 192.7 | |

| | | | |
|--|---------|---------|---|
| standard deviation | ± 136.7 | ± 64.6 | - |
| Non-high-density Lipoprotein Cholesterol (non-HDL-C) Concentration Units: mg/dL | | | |
| arithmetic mean | 350.5 | 222.1 | |
| standard deviation | ± 138.4 | ± 68.3 | - |
| Lipoprotein (a) Concentration Units: nmol/L | | | |
| arithmetic mean | 104.7 | 127.1 | |
| standard deviation | ± 100.6 | ± 142.8 | - |
| Apolipoprotein B Concentration Units: mg/dL | | | |
| arithmetic mean | 200.7 | 139.2 | |
| standard deviation | ± 69.9 | ± 35.6 | - |
| Total Cholesterol/HDL-C Ratio Units: ratio | | | |
| arithmetic mean | 11.473 | 6.055 | |
| standard deviation | ± 6.312 | ± 2.397 | - |
| Apolipoprotein B/Apolipoprotein A1 Ratio Units: ratio | | | |
| arithmetic mean | 1.984 | 1.023 | |
| standard deviation | ± 0.950 | ± 0.355 | - |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | HoFH |
| Reporting group description: | |
| Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) levels. | |
| Reporting group title | Severe FH |
| Reporting group description: | |
| Participants with severe (non-HoFH) familial hypercholesterolemia (FH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound PCSK9 levels. | |

Primary: Number of Participants with Adverse Events

| | |
|--|---|
| End point title | Number of Participants with Adverse Events ^[1] |
| End point description: | |
| The severity of each adverse event (AE) was graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) grading scale, where grade 1 = mild AE, grade 2 = moderate AE, grade 3 = severe AE, grade 4 = life-threatening AE and grade 5 = death due to AE. | |
| End point type | Primary |
| End point timeframe: | |
| From first dose of study drug in Study 20110271 up to 30 days after the last dose or until the end of study date, whichever was earlier; median duration of treatment was 48.7 months. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal hypothesis testing was conducted. The primary clinical hypothesis was that long-term exposure of evolocumab would be safe and well tolerated in subjects with severe familial hypercholesterolemia.

| End point values | HoFH | Severe FH | | |
|--|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: participants | | | | |
| All adverse events (AEs) | 94 | 174 | | |
| Adverse events ≥ grade 2 | 76 | 143 | | |
| Adverse events ≥ grade 3 | 38 | 68 | | |
| Adverse events ≥ grade 4 | 4 | 14 | | |
| Serious adverse events (SAEs) | 29 | 57 | | |
| AEs Leading to discontinuation of evolocumab | 3 | 8 | | |
| Fatal adverse events | 2 | 5 | | |
| Device-related adverse events | 6 | 18 | | |

Statistical analyses

Secondary: Percent Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C)

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Low-density Lipoprotein Cholesterol (LDL-C) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|---------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 87, 183) | -20.42 (-38.25 to -8.28) | -54.95 (-66.67 to -44.55) | | |
| Week 6 (n = 83, 166) | -18.32 (-36.09 to -4.16) | -67.57 (-79.54 to -53.93) | | |
| Week 8 (n = 94, 187) | -20.28 (-37.81 to -8.44) | -55.03 (-68.58 to -42.07) | | |
| Week 12 (n = 104, 191) | -18.26 (-36.06 to -7.76) | -57.11 (-68.00 to -42.80) | | |
| Week 16 (n = 102, 188) | -23.15 (-39.23 to -7.87) | -57.53 (-67.99 to -44.95) | | |
| Week 20 (n = 101, 185) | -25.37 (-45.99 to -8.96) | -57.26 (-67.48 to -44.68) | | |
| Week 24 (n = 99, 191) | -21.84 (-41.39 to -8.11) | -57.10 (-67.05 to -43.70) | | |
| Week 36 (n = 94, 187) | -26.79 (-46.44 to -8.28) | -56.08 (-68.70 to -44.47) | | |
| Week 48 (n = 93, 197) | -25.50 (-44.79 to -4.43) | -59.67 (-69.14 to -47.88) | | |
| Week 60 (n = 88, 186) | -27.26 (-44.58 to -4.28) | -57.13 (-68.42 to -42.65) | | |
| Week 72 (n = 85, 184) | -27.11 (-51.06 to -12.03) | -55.73 (-70.52 to -42.76) | | |
| Week 84 (n = 82, 180) | -27.96 (-50.29 to -7.96) | -56.02 (-68.49 to -42.18) | | |
| Week 96 (n = 82, 180) | -22.47 (-46.53 to -8.12) | -57.10 (-69.53 to -41.66) | | |
| Week 108 (n = 82, 181) | -26.15 (-44.58 to -5.62) | -60.57 (-69.47 to -43.15) | | |
| Week 120 (n = 82, 184) | -26.66 (-43.43 to -7.42) | -56.76 (-69.48 to -41.70) | | |
| Week 132 (n = 81, 177) | -28.25 (-48.23 to -9.42) | -55.25 (-68.17 to -39.89) | | |
| Week 144 (n = 79, 180) | -28.33 (-49.27 to -10.33) | -56.48 (-69.26 to -40.69) | | |
| Week 156 (n = 80, 181) | -23.65 (-47.66 to -11.05) | -55.38 (-69.48 to -41.03) | | |

| | | | | |
|------------------------|---------------------------|---------------------------|--|--|
| Week 168 (n = 76, 171) | -29.52 (-51.35 to -4.41) | -54.77 (-67.16 to -36.42) | | |
| Week 180 (n = 74, 166) | -25.66 (-53.71 to -9.87) | -54.08 (-71.53 to -37.55) | | |
| Week 192 (n = 74, 147) | -30.12 (-53.23 to -11.81) | -52.19 (-66.79 to -33.99) | | |
| Week 204 (n = 75, 129) | -29.62 (-47.43 to -6.11) | -59.59 (-70.50 to -39.06) | | |
| Week 216 (n = 68, 96) | -32.22 (-46.65 to -8.97) | -50.62 (-67.73 to -32.31) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Non-high-density Lipoprotein Cholesterol (non-HDL-C)

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in Non-high-density Lipoprotein Cholesterol (non-HDL-C) |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|---------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 88, 183) | -19.62 (-35.54 to -7.84) | -50.00 (-59.92 to -39.88) | | |
| Week 6 (n = 85, 168) | -18.17 (-33.88 to -4.29) | -59.76 (-70.50 to -49.23) | | |
| Week 8 (n = 94, 188) | -20.29 (-35.94 to -9.28) | -50.61 (-58.49 to -37.91) | | |
| Week 12 (n = 105, 192) | -17.05 (-32.03 to -6.99) | -50.25 (-61.49 to -38.63) | | |
| Week 16 (n = 102, 188) | -21.73 (-37.81 to -7.88) | -51.31 (-59.76 to -40.40) | | |
| Week 20 (n = 101, 188) | -24.09 (-43.06 to -7.76) | -50.76 (-59.44 to -38.67) | | |
| Week 24 (n = 100, 192) | -21.88 (-38.81 to -9.54) | -51.12 (-60.67 to -38.52) | | |
| Week 36 (n = 95, 190) | -22.43 (-44.08 to -6.22) | -49.65 (-61.00 to -38.26) | | |
| Week 48 (n = 94, 190) | -24.08 (-43.47 to -3.98) | -51.12 (-61.58 to -42.11) | | |
| Week 60 (n = 89, 189) | -24.81 (-42.96 to -2.67) | -49.73 (-61.61 to -38.00) | | |

| | | | | |
|------------------------|---------------------------|---------------------------|--|--|
| Week 72 (n = 85, 188) | -25.88 (-48.21 to -9.47) | -48.94 (-61.14 to -36.08) | | |
| Week 84 (n = 83, 184) | -21.00 (-42.68 to -7.45) | -49.50 (-62.07 to -35.14) | | |
| Week 96 (n = 83, 184) | -21.10 (-42.84 to -7.85) | -49.53 (-63.80 to -36.86) | | |
| Week 108 (n = 83, 186) | -24.17 (-43.01 to -5.69) | -52.86 (-61.20 to -38.11) | | |
| Week 120 (n = 82, 185) | -23.21 (-40.37 to -6.23) | -49.45 (-60.48 to -35.91) | | |
| Week 132 (n = 82, 182) | -26.39 (-40.28 to -7.19) | -49.49 (-60.95 to -33.66) | | |
| Week 144 (n = 81, 183) | -25.38 (-45.55 to -8.08) | -49.81 (-61.69 to -33.88) | | |
| Week 156 (n = 80, 184) | -22.35 (-45.47 to -10.50) | -50.15 (-60.81 to -36.11) | | |
| Week 168 (n = 76, 176) | -27.97 (-48.82 to -4.36) | -47.93 (-60.71 to -31.01) | | |
| Week 180 (n = 74, 167) | -26.32 (-49.82 to -8.62) | -48.43 (-62.22 to -33.06) | | |
| Week 192 (n = 75, 151) | -27.61 (-49.49 to -9.29) | -44.50 (-57.71 to -29.77) | | |
| Week 204 (n = 75, 131) | -27.22 (-45.14 to -5.73) | -50.84 (-64.12 to -36.03) | | |
| Week 216 (n = 68, 98) | -31.40 (-42.75 to -9.67) | -45.30 (-61.45 to -26.32) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Lipoprotein (a)

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Lipoprotein (a) |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|---------------------------------------|------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 87, 183) | -11.11 (-27.50 to 0.0) | -20.49 (-39.84 to -11.61) | | |
| Week 6 (n = 85, 169) | -8.97 (-24.21 to 3.76) | -24.42 (-45.95 to -9.38) | | |
| Week 8 (n = 94, 188) | -9.95 (-25.00 to 3.23) | -21.51 (-39.84 to -9.09) | | |

| | | | | |
|------------------------|--------------------------|---------------------------|--|--|
| Week 12 (n = 105, 192) | -7.69 (-21.64 to 6.83) | -24.40 (-40.28 to -9.09) | | |
| Week 16 (n = 103, 188) | -8.93 (-25.00 to 4.76) | -23.08 (-38.88 to -7.62) | | |
| Week 20 (n = 100, 188) | -13.52 (-29.36 to 0.00) | -22.21 (-39.34 to -5.98) | | |
| Week 24 (n = 100, 192) | -10.46 (-23.75 to 1.00) | -25.99 (-41.81 to -9.09) | | |
| Week 36 (n = 95, 190) | -15.14 (-28.18 to 0.00) | -24.26 (-41.30 to -7.85) | | |
| Week 48 (n = 94, 189) | -13.17 (-30.51 to 0.00) | -26.32 (-41.94 to -10.49) | | |
| Week 60 (n = 90, 189) | -13.04 (-35.00 to 2.86) | -24.05 (-41.97 to -7.63) | | |
| Week 72 (n = 86, 188) | -17.43 (-37.19 to 5.88) | -24.23 (-43.96 to -6.81) | | |
| Week 84 (n = 84, 184) | -14.12 (-36.73 to 0.63) | -24.12 (-44.05 to -8.02) | | |
| Week 96 (n = 83, 184) | -17.24 (-33.33 to 0.49) | -31.28 (-47.33 to -13.34) | | |
| Week 108 (n = 83, 186) | -21.43 (-42.50 to 0.00) | -32.44 (-48.65 to -12.69) | | |
| Week 120 (n = 82, 186) | -20.16 (-33.25 to 0.00) | -31.22 (-45.00 to -11.40) | | |
| Week 132 (n = 82, 182) | -19.15 (-37.68 to 0.00) | -29.32 (-49.82 to -12.29) | | |
| Week 144 (n = 81, 183) | -23.64 (-47.06 to 0.00) | -30.36 (-48.17 to -11.92) | | |
| Week 156 (n = 80, 184) | -18.40 (-42.14 to -2.33) | -28.10 (-47.35 to -9.09) | | |
| Week 168 (n = 76, 176) | -22.94 (-41.01 to -0.49) | -23.96 (-45.64 to -9.09) | | |
| Week 180 (n = 74, 168) | -17.29 (-43.83 to 0.00) | -26.23 (-46.01 to -8.83) | | |
| Week 192 (n = 75, 151) | -22.78 (-44.44 to 0.00) | -20.00 (-37.75 to -2.44) | | |
| Week 204 (n = 75, 131) | -16.33 (-38.46 to 3.95) | -14.29 (-34.38 to 10.00) | | |
| Week 216 (n = 68, 98) | -14.06 (-36.07 to 4.08) | -0.67 (-23.64 to 23.81) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Apolipoprotein B

| | |
|--|--|
| End point title | Percent Change from Baseline in Apolipoprotein B |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216 | |

| End point values | HoFH | Severe FH | | |
|---------------------------------------|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 88, 183) | -16.91 (-31.67 to -6.81) | -43.84 (-54.59 to -34.40) | | |
| Week 6 (n = 85, 169) | -16.25 (-27.82 to -1.96) | -56.70 (-67.23 to -46.11) | | |
| Week 8 (n = 94, 188) | -17.57 (-32.00 to -6.24) | -43.95 (-55.69 to -31.55) | | |
| Week 12 (n = 105, 192) | -13.11 (-26.87 to -3.49) | -45.78 (-55.16 to -32.65) | | |
| Week 16 (n = 102, 188) | -18.65 (-34.77 to -8.35) | -45.72 (-55.23 to -35.39) | | |
| Week 20 (n = 101, 188) | -22.60 (-39.05 to -5.03) | -45.16 (-53.93 to -33.18) | | |
| Week 24 (n = 100, 192) | -20.09 (-33.04 to -3.97) | -44.87 (-55.32 to -31.01) | | |
| Week 36 (n = 95, 190) | -16.48 (-36.43 to -2.56) | -43.33 (-55.12 to -29.10) | | |
| Week 48 (n = 94, 190) | -15.90 (-33.60 to -4.15) | -45.38 (-55.40 to -33.93) | | |
| Week 60 (n = 90, 189) | -15.99 (-38.12 to -0.27) | -44.81 (-56.07 to -31.33) | | |
| Week 72 (n = 86, 188) | -20.70 (-42.02 to -3.17) | -44.07 (-55.61 to -32.72) | | |
| Week 84 (n = 84, 184) | -19.52 (-35.66 to -0.09) | -43.87 (-55.50 to -32.13) | | |
| Week 96 (n = 83, 184) | -15.07 (-36.34 to -3.67) | -42.31 (-57.65 to -29.89) | | |
| Week 108 (n = 83, 186) | -19.45 (-36.07 to 5.03) | -46.30 (-55.41 to -32.21) | | |
| Week 120 (n = 82, 185) | -21.58 (-33.33 to -1.57) | -44.33 (-54.68 to -30.00) | | |
| Week 132 (n = 82, 181) | -22.44 (-35.70 to -3.75) | -43.48 (-54.90 to -28.22) | | |
| Week 144 (n = 81, 183) | -21.24 (-41.89 to -3.55) | -41.64 (-54.36 to -27.85) | | |
| Week 156 (n = 80, 184) | -18.30 (-36.66 to -5.63) | -44.04 (-55.16 to -29.73) | | |
| Week 168 (n = 76, 176) | -20.38 (-41.58 to -2.81) | -40.20 (-52.22 to -25.78) | | |
| Week 180 (n = 74, 168) | -19.51 (-39.73 to -3.02) | -41.58 (-54.70 to -24.57) | | |
| Week 192 (n = 75, 151) | -19.38 (-39.63 to -2.63) | -37.02 (-52.06 to -21.08) | | |
| Week 204 (n = 75, 131) | -21.64 (-36.15 to -5.48) | -43.19 (-56.81 to -28.81) | | |
| Week 216 (n = 68, 98) | -22.68 (-35.34 to -4.51) | -35.95 (-53.05 to -23.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Total Cholesterol/HDL-C Ratio

| | |
|-----------------|---|
| End point title | Percent Change from Baseline in Total Cholesterol/HDL-C Ratio |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|---------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 88, 183) | -21.32 (-38.45 to -10.36) | -43.49 (-53.07 to -33.78) | | |
| Week 6 (n = 85, 168) | -23.25 (-35.54 to -7.14) | -52.38 (-60.97 to -42.29) | | |
| Week 8 (n = 94, 188) | -23.93 (-35.26 to -5.42) | -43.44 (-51.21 to -34.81) | | |
| Week 12 (n = 105, 192) | -21.20 (-34.98 to -9.31) | -44.75 (-53.20 to -35.12) | | |
| Week 16 (n = 102, 188) | -24.01 (-36.52 to -8.86) | -45.31 (-52.38 to -34.95) | | |
| Week 20 (n = 101, 188) | -24.69 (-36.39 to -4.29) | -43.07 (-51.89 to -33.54) | | |
| Week 24 (n = 100, 192) | -23.53 (-38.59 to -9.10) | -43.79 (-52.96 to -34.28) | | |
| Week 36 (n = 95, 190) | -27.16 (-42.86 to -9.12) | -42.69 (-53.01 to -30.99) | | |
| Week 48 (n = 94, 190) | -26.54 (-43.73 to -8.03) | -44.68 (-54.47 to -33.90) | | |
| Week 60 (n = 89, 189) | -22.80 (-45.57 to -5.13) | -43.82 (-54.01 to -32.46) | | |
| Week 72 (n = 85, 188) | -24.79 (-42.72 to -9.47) | -42.64 (-54.28 to -30.73) | | |
| Week 84 (n = 83, 184) | -22.62 (-41.45 to -6.24) | -43.16 (-53.15 to -27.42) | | |
| Week 96 (n = 83, 184) | -23.00 (-38.97 to -10.33) | -42.46 (-54.03 to -31.69) | | |
| Week 108 (n = 83, 186) | -25.03 (-41.12 to -4.98) | -43.68 (-53.91 to -32.90) | | |
| Week 120 (n = 82, 185) | -25.40 (-42.55 to -6.92) | -42.42 (-54.18 to -30.87) | | |
| Week 132 (n = 82, 182) | -25.66 (-41.29 to -5.10) | -42.14 (-53.54 to -30.15) | | |
| Week 144 (n = 81, 183) | -27.79 (-44.96 to -6.39) | -43.40 (-54.91 to -28.80) | | |
| Week 156 (n = 80, 184) | -25.52 (-45.62 to -9.87) | -43.85 (-53.49 to -29.86) | | |

| | | | | |
|------------------------|---------------------------|---------------------------|--|--|
| Week 168 (n = 76, 176) | -26.30 (-46.28 to -8.75) | -41.59 (-52.67 to -24.39) | | |
| Week 180 (n = 74, 167) | -29.53 (-47.74 to -7.54) | -40.13 (-54.50 to -28.99) | | |
| Week 192 (n = 75, 151) | -27.79 (-47.16 to -12.15) | -38.24 (-53.80 to -25.34) | | |
| Week 204 (n = 75, 131) | -27.32 (-42.19 to -7.20) | -43.13 (-57.50 to -31.50) | | |
| Week 216 (n = 68, 98) | -30.92 (-42.09 to -8.93) | -40.78 (-52.60 to -26.46) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio

| | |
|-----------------|--|
| End point title | Percent Change from Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|---------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percent change | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Week 4 (n = 88, 183) | -23.06 (-39.88 to -6.22) | -46.79 (-57.95 to -37.69) | | |
| Week 6 (n = 85, 169) | -21.38 (-36.90 to -10.11) | -59.77 (-68.35 to -48.98) | | |
| Week 8 (n = 94, 188) | -21.53 (-36.51 to -4.66) | -47.82 (-57.87 to -37.07) | | |
| Week 12 (n = 105, 192) | -16.67 (-30.72 to -4.37) | -48.63 (-59.21 to -38.16) | | |
| Week 16 (n = 102, 188) | -22.52 (-42.86 to -8.97) | -48.98 (-58.13 to -39.59) | | |
| Week 20 (n = 101, 188) | -25.41 (-41.87 to -12.43) | -49.12 (-57.11 to -38.09) | | |
| Week 24 (n = 100, 192) | -22.97 (-38.08 to -8.99) | -49.92 (-58.44 to -37.29) | | |
| Week 36 (n = 95, 190) | -26.86 (-41.04 to -7.69) | -49.02 (-58.10 to -35.67) | | |
| Week 48 (n = 94, 190) | -25.96 (-43.38 to -12.26) | -49.35 (-59.34 to -38.98) | | |
| Week 60 (n = 90, 189) | -24.31 (-44.46 to -6.67) | -48.57 (-59.11 to -35.94) | | |

| | | | | |
|------------------------|---------------------------|---------------------------|--|--|
| Week 72 (n = 86, 188) | -23.63 (-45.15 to -10.89) | -48.94 (-60.36 to -38.76) | | |
| Week 84 (n = 84, 184) | -24.09 (-43.12 to -4.16) | -49.47 (-59.73 to -34.54) | | |
| Week 96 (n = 83, 184) | -24.75 (-45.92 to -8.61) | -48.45 (-60.40 to -36.17) | | |
| Week 108 (n = 83, 186) | -26.03 (-41.27 to -4.78) | -50.18 (-60.18 to -37.84) | | |
| Week 120 (n = 82, 185) | -26.45 (-44.21 to -12.32) | -49.75 (-59.38 to -36.17) | | |
| Week 132 (n = 82, 181) | -24.26 (-47.15 to -7.81) | -48.54 (-58.39 to -32.01) | | |
| Week 144 (n = 81, 183) | -28.09 (-48.50 to -7.81) | -47.44 (-59.12 to -33.82) | | |
| Week 156 (n = 80, 184) | -27.21 (-46.95 to -12.25) | -49.10 (-59.29 to -35.31) | | |
| Week 168 (n = 76, 176) | -32.16 (-47.39 to -12.53) | -44.46 (-56.03 to -30.06) | | |
| Week 180 (n = 74, 168) | -28.70 (-48.45 to -9.71) | -45.13 (-58.67 to -30.84) | | |
| Week 192 (n = 75, 151) | -27.50 (-50.49 to -10.22) | -43.40 (-56.45 to -28.14) | | |
| Week 204 (n = 75, 131) | -28.04 (-46.84 to -12.13) | -49.71 (-60.22 to -35.16) | | |
| Week 216 (n = 68, 98) | -28.37 (-41.15 to -11.76) | -44.00 (-56.69 to -31.29) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a 15% or Greater Reduction in LDL-C

| | |
|-----------------|---|
| End point title | Percentage of Participants with a 15% or Greater Reduction in LDL-C |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and weeks 4, 6, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and 216

| End point values | HoFH | Severe FH | | |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 194 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Week 4 (n = 87, 183) | 62.1 | 98.9 | | |
| Week 6 (n = 83, 166) | 51.8 | 98.2 | | |
| Week 8 (n = 94, 187) | 57.4 | 97.9 | | |
| Week 12 (n = 104, 191) | 56.7 | 99.0 | | |
| Week 16 (n = 102, 188) | 63.7 | 97.3 | | |

| | | | | |
|------------------------|------|------|--|--|
| Week 20 (n = 101, 185) | 64.4 | 98.9 | | |
| Week 24 (n = 99, 191) | 66.7 | 96.3 | | |
| Week 36 (n = 94, 187) | 62.8 | 97.3 | | |
| Week 48 (n = 93, 187) | 60.2 | 97.9 | | |
| Week 60 (n = 88, 186) | 60.2 | 94.1 | | |
| Week 72 (n = 85, 184) | 69.4 | 94.0 | | |
| Week 84 (n = 82, 180) | 65.9 | 93.9 | | |
| Week 96 (n = 82, 180) | 65.9 | 94.4 | | |
| Week 108 (n = 82, 181) | 61.0 | 96.1 | | |
| Week 120 (n = 82, 184) | 64.6 | 91.8 | | |
| Week 132 (n = 81, 177) | 61.7 | 92.7 | | |
| Week 144 (n = 79, 180) | 72.2 | 93.3 | | |
| Week 156 (n = 80, 181) | 68.8 | 93.4 | | |
| Week 168 (n = 76, 171) | 59.2 | 93.6 | | |
| Week 180 (n = 74, 166) | 63.5 | 93.4 | | |
| Week 192 (n = 74, 147) | 66.2 | 91.8 | | |
| Week 204 (n = 75, 129) | 65.3 | 93.8 | | |
| Week 216 (n = 68, 96) | 70.6 | 88.5 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug in Study 20110271 up to 30 days after the last dose or until the end of study date, whichever was earlier; median duration of treatment was 48.7 months.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------|
| Reporting group title | HoFH |
|-----------------------|------|

Reporting group description:

Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) levels.

| | |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Participants received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound PCSK9 levels.

| | |
|-----------------------|-----------|
| Reporting group title | Severe FH |
|-----------------------|-----------|

Reporting group description:

Participants with severe (non-HoFH) familial hypercholesterolemia (FH) received 420 mg evolocumab every month (participants not on lipid apheresis) or every 2 weeks (participants on lipid apheresis) for up to 5 years. Participants could switch dosing regimens at week 12 or 24 based on LDL-C and serum unbound PCSK9 levels.

| Serious adverse events | HoFH | Total | Severe FH |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 106 (27.36%) | 86 / 300 (28.67%) | 57 / 194 (29.38%) |
| number of deaths (all causes) | 2 | 7 | 5 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma pancreas | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Breast cancer in situ | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Colon cancer metastatic subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Invasive lobular breast carcinoma subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to liver subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ovarian germ cell teratoma subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small cell lung cancer subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Vascular disorders | | | |
| Aortic stenosis | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 5 / 300 (1.67%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery occlusion | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral artery stenosis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion spontaneous | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest discomfort | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 6 / 300 (2.00%) | 5 / 194 (2.58%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Complication associated with device | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 4 / 300 (1.33%) | 3 / 194 (1.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Uterine prolapse | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleuritic pain | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 2 / 300 (0.67%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac stress test abnormal | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Liver function test abnormal | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Troponin increased | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula site haemorrhage | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Arteriovenous fistula thrombosis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fall | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fracture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 2 / 300 (0.67%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cerebrovascular arteriovenous malformation | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|------------------|-----------------|
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 4 / 300 (1.33%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 11 / 300 (3.67%) | 7 / 194 (3.61%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 12 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 3 / 300 (1.00%) | 3 / 194 (1.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve disease | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Coronary artery disease | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 106 (2.83%) | 4 / 300 (1.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 5 / 300 (1.67%) | 4 / 194 (2.06%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 6 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supravalvular aortic stenosis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Carotid artery occlusion | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia with Lewy bodies | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolic stroke | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 2 / 300 (0.67%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 2 / 300 (0.67%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Macular degeneration | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Macular hole | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingival cyst | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 2 / 300 (0.67%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Hepatic cyst | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-alcoholic steatohepatitis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 2 / 300 (0.67%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal infarct | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 2 / 300 (0.67%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscle atrophy | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Posture abnormal | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 300 (0.33%) | 0 / 194 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 2 / 300 (0.67%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 2 / 300 (0.67%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteomyelitis chronic | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 3 / 300 (1.00%) | 2 / 194 (1.03%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 300 (0.33%) | 1 / 194 (0.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | HoFH | Total | Severe FH |
|---|-------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 80 / 106 (75.47%) | 214 / 300 (71.33%) | 134 / 194 (69.07%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 9 / 300 (3.00%) | 3 / 194 (1.55%) |
| occurrences (all) | 13 | 16 | 3 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 10 / 300 (3.33%) | 4 / 194 (2.06%) |
| occurrences (all) | 11 | 16 | 5 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 106 (8.49%) | 24 / 300 (8.00%) | 15 / 194 (7.73%) |
| occurrences (all) | 9 | 25 | 16 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 16 / 300 (5.33%) | 12 / 194 (6.19%) |
| occurrences (all) | 4 | 21 | 17 |
| Headache | | | |
| subjects affected / exposed | 17 / 106 (16.04%) | 33 / 300 (11.00%) | 16 / 194 (8.25%) |
| occurrences (all) | 18 | 41 | 23 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 19 / 300 (6.33%) | 15 / 194 (7.73%) |
| occurrences (all) | 5 | 21 | 16 |

| | | | |
|---|------------------|------------------|-------------------|
| Fatigue | | | |
| subjects affected / exposed | 8 / 106 (7.55%) | 27 / 300 (9.00%) | 19 / 194 (9.79%) |
| occurrences (all) | 9 | 32 | 23 |
| Influenza like illness | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 12 / 300 (4.00%) | 10 / 194 (5.15%) |
| occurrences (all) | 3 | 15 | 12 |
| Injection site bruising | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 14 / 300 (4.67%) | 10 / 194 (5.15%) |
| occurrences (all) | 6 | 16 | 10 |
| Injection site pain | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 11 / 300 (3.67%) | 5 / 194 (2.58%) |
| occurrences (all) | 8 | 14 | 6 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 14 / 300 (4.67%) | 11 / 194 (5.67%) |
| occurrences (all) | 3 | 15 | 12 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 7 / 106 (6.60%) | 14 / 300 (4.67%) | 7 / 194 (3.61%) |
| occurrences (all) | 8 | 16 | 8 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 106 (6.60%) | 29 / 300 (9.67%) | 22 / 194 (11.34%) |
| occurrences (all) | 12 | 40 | 28 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 19 / 300 (6.33%) | 14 / 194 (7.22%) |
| occurrences (all) | 9 | 23 | 14 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 10 / 106 (9.43%) | 10 / 300 (3.33%) | 0 / 194 (0.00%) |
| occurrences (all) | 11 | 11 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 29 / 300 (9.67%) | 23 / 194 (11.86%) |
| occurrences (all) | 6 | 34 | 28 |
| Back pain | | | |

| | | | |
|-----------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed | 9 / 106 (8.49%) | 26 / 300 (8.67%) | 17 / 194 (8.76%) |
| occurrences (all) | 10 | 28 | 18 |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 19 / 300 (6.33%) | 15 / 194 (7.73%) |
| occurrences (all) | 6 | 31 | 25 |
| Myalgia | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 30 / 300 (10.00%) | 24 / 194 (12.37%) |
| occurrences (all) | 7 | 38 | 31 |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 15 / 300 (5.00%) | 11 / 194 (5.67%) |
| occurrences (all) | 5 | 18 | 13 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 106 (3.77%) | 20 / 300 (6.67%) | 16 / 194 (8.25%) |
| occurrences (all) | 5 | 30 | 25 |
| Gastroenteritis | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 18 / 300 (6.00%) | 12 / 194 (6.19%) |
| occurrences (all) | 8 | 21 | 13 |
| Influenza | | | |
| subjects affected / exposed | 17 / 106 (16.04%) | 38 / 300 (12.67%) | 21 / 194 (10.82%) |
| occurrences (all) | 24 | 47 | 23 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 17 / 106 (16.04%) | 53 / 300 (17.67%) | 36 / 194 (18.56%) |
| occurrences (all) | 38 | 95 | 57 |
| Sinusitis | | | |
| subjects affected / exposed | 7 / 106 (6.60%) | 14 / 300 (4.67%) | 7 / 194 (3.61%) |
| occurrences (all) | 9 | 16 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 18 / 106 (16.98%) | 35 / 300 (11.67%) | 17 / 194 (8.76%) |
| occurrences (all) | 39 | 63 | 24 |
| Urinary tract infection | | | |
| subjects affected / exposed | 8 / 106 (7.55%) | 20 / 300 (6.67%) | 12 / 194 (6.19%) |
| occurrences (all) | 11 | 25 | 14 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 17 July 2012 | <ul style="list-style-type: none">• adjusted the study title to be more reflective of the actual study population• added a study acronym• clarified that laboratory data were blinded for subjects coming from a blinded (or blinded portion) of a parent study• added an optional apheresis substudy• increased the sample size from 75 subjects to 125 based on new subject interest in the study• added a screening period for either subjects who do not come from a parent study or for parent study subjects who do not roll over into Study 20110271 within 3 days• changed the dosage and dosing schedule to accommodate the eclectic subject population• updated the evolocumab background section with new data based on the phase 2 interim analysis• decreased the frequency of anti-evolocumab antibody collection after year 1• updated the subject inclusion criteria• highlighted that any time a subject has 2 consecutive LDL-C values < 25 mg/dL, the DMC was notified.• highlighted that vitamin E values were blinded• updated the safety reporting timelines as well as the pregnancy and lactation language per Amgen's most recent template• divided the schedule of assessments into 3 groups: rollover subjects, non-rollover non-apheresis subjects, and apheresis subjects |
| 07 December 2012 | <ul style="list-style-type: none">• updated the at-home dosing information• changed the dosing terminology from Q4W to QM• added an additional secondary endpoint• added more flexible dosing language for subjects who enter Study 20110271 from Study 20110233• highlighted that lipid lowering concomitant medications cannot be adjusted during the first 12 weeks of the study |
| 16 September 2013 | <ul style="list-style-type: none">• added Lp(a) as a secondary endpoint• updated the exploratory endpoints• expanded eligible population to include patients with severe FH, without requiring HoFH or specific types of mutations• increased the sample size to 250 subjects to accommodate additional high need subjects• excluded subjects using lomitapide and CETP inhibitors• added AI/pen and AMD language• clarified dose adjustment language• updated the safety reporting section with Amgen's new template language• added CEC language• updated the study schemas• updated the background section• added additional criteria for withholding IP• removed the apheresis substudy |
| 15 April 2014 | <ul style="list-style-type: none">• updated the sample size to 310 subjects• updated the number of sites from 45 to 50• updated the dosing language• updated the analyte table to include eGFR and serum hCG |
| 11 May 2015 | <ul style="list-style-type: none">• removed the external DMC following the DMC's expressed preference to not review open-label, uncontrolled safety data.• added measurements of height, weight and Tanner staging for adolescent subjects; definition of 'adolescent' was also provided. |

| | |
|------------------|---|
| 02 December 2015 | <ul style="list-style-type: none"> • clarified end of study language to specify the study will end when the last patient has completed assessments at week 260. • updated criteria for possible drug-induced liver injury. • clarified language regarding product complaints. • allowed for additional pregnancy testing at the discretion of the investigator. • corrected Tanner Staging criteria for males. |
|------------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported