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/Apoliprotein 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

No statistical analyses for this end point

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	• 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	• 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	• 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	• 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	• 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	• 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