Clinical trial results:
Open-label, Single-arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous (HAUSER-OLE)

Summary

EudraCT number	2015-002276-25
Trial protocol	DE GB NO HU AT BE CZ GR ES NL PT SI PL IT RO
Global end of trial date	01 June 2021

Results information

Result version number	v1 (current)
This version publication date	18 November 2021
First version publication date	18 November 2021

Trial information

Trial identification

Sponsor protocol code	20120124

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02624869
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001268-PIP01-12
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	01 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to describe the safety and tolerability of 80 weeks of subcutaneous (SC) evolocumab when added to standard of care in children 10 to 17 years of age with familial hypercholesterolemia.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
The study protocol and all amendments, the informed consent form, and any accompanying materials provided to the subjects were reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each study center.
The investigator or his/her designee informed the subject or legally acceptable representative of all aspects pertaining to the subject's participation in the study and obtained written informed consent from the subject or legally acceptable representative before any screening procedures were performed or any investigational product(s) were administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2016
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: 17
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 1
Country: Number of subjects enrolled	Slovenia: 1
Country: Number of subjects enrolled	Spain: 4

Country: Number of subjects enrolled	Switzerland: 3
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Brazil: 20
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	South Africa: 8
Worldwide total number of subjects	163
EEA total number of subjects	94

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)	35
Adolescents (12-17 years)	120
Adults (18-64 years)	8
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 46 centers in 23 countries (Australia, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Greece, Hungary, Italy, Malaysia, Netherlands, Norway, Poland, Portugal, Russia, Slovenia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and United States of America).

Pre-assignment

Screening details:

This study enrolled participants with heterozygous familial hypercholesterolemia (HeFH) who had completed the parent study 20120123 (EudraCT #: 2014-002277-11) without experiencing a treatment-related serious adverse event or children 10 to 17 years of age with a diagnosis of homozygous familial hypercholesterolemia (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	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM

Arm description:

Participants with heterozygous familial hypercholesterolemia (HeFH) who had received placebo in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks (QM) for up to 80 weeks.

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

Dosage and administration details:

Administered once a month by subcutaneous injection

Arm title	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM

Arm description:

Participants with heterozygous familial hypercholesterolemia who had received evolocumab in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.

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

Dosage and administration details:

Administered once a month by subcutaneous injection

Arm title	HoFH: Evolocumab 420 mg QM

Arm description:

Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab

administered by subcutaneous injection every 4 weeks for up to 80 weeks.

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

Dosage and administration details:

Administered once a month by subcutaneous injection

Number of subjects in period 1	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM
Started	49	101	13
Received Study Drug	49	101	12
Completed	48	98	11
Not completed	1	3	2
Consent withdrawn by subject	1	3	1
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM
Reporting group description:	
Participants with heterozygous familial hypercholesterolemia (HeFH) who had received placebo in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks (QM) for up to 80 weeks.	
Reporting group title	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM
Reporting group description:	
Participants with heterozygous familial hypercholesterolemia who had received evolocumab in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.	
Reporting group title	HoFH: Evolocumab 420 mg QM
Reporting group description:	
Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.	

Reporting group values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM
Number of subjects	49	101	13
Age Categorical			
Eight HeFH participants were 18 years old at the time of rollover into Study 20120124, however all were ≤ 17 years old at the time of enrollment into the parent study 20120123.			
Units: participants			
2 - 11 years	11	18	6
12 - 17 years	37	76	7
18 - 64 years	1	7	0
Age Continuous			
Units: years			
arithmetic mean	13.8	14.2	12.4
standard deviation	± 2.5	± 2.4	± 2.0
Sex: Female, Male			
Units: participants			
Female	24	59	2
Male	25	42	11
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	7	6	0
Not Hispanic or Latino	42	95	13
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	2	2
Black or African American	0	2	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	40	86	9
Other	9	11	2

Region Units: Subjects			
North America	8	12	0
Europe	33	65	7
Latin America	8	18	0
Asia Pacific	0	6	6
Low-density Lipoprotein Cholesterol (LDL-C) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set which includes all participants with HeFH from parent Study 20120123 who were enrolled and dosed as well as all participants with HoFH who were enrolled and dosed in this study (49, 101, and 12 subjects in each arm respectively).			
Units: mg/dL			
arithmetic mean	184.0	184.4	426.0
standard deviation	± 48.3	± 45.2	± 166.4
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set (49, 101, and 12 subjects in each arm respectively).			
Units: mg/dL			
arithmetic mean	201.0	203.4	443.7
standard deviation	± 49.3	± 47.5	± 170.8
Apolipoprotein B (ApoB) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set with available baseline data (47, 100, and 12 subjects in each arm respectively).			
Units: mg/dL			
arithmetic mean	119.1	123.1	250.1
standard deviation	± 28.1	± 27.4	± 84.9
Total Cholesterol/High-density Lipoprotein Cholesterol (HDL-C) Ratio			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set (49, 101, and 12 subjects in each arm respectively).			
Units: ratio			
arithmetic mean	5.546	5.716	14.707
standard deviation	± 1.541	± 1.809	± 7.891
Apolipoprotein B/Apolipoprotein A1 Ratio			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set with available baseline data (47, 100, and 12 subjects in each arm respectively).			
Units: ratio			
arithmetic mean	0.943	0.972	2.388
standard deviation	± 0.265	± 0.306	± 1.036

Reporting group values	Total		
Number of subjects	163		
Age Categorical			
Eight HeFH participants were 18 years old at the time of rollover into Study 20120124, however all were ≤ 17 years old at the time of enrollment into the parent study 20120123.			
Units: participants			
2 - 11 years	35		
12 - 17 years	120		
18 - 64 years	8		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	85		
Male	78		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	13		
Not Hispanic or Latino	150		
Unknown or Not Reported	0		
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Black or African American	2		
Native Hawaiian or Other Pacific Islander	0		
White	135		
Other	22		
Region			
Units: Subjects			
North America	20		
Europe	105		
Latin America	26		
Asia Pacific	12		
Low-density Lipoprotein Cholesterol (LDL-C) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set which includes all participants with HeFH from parent Study 20120123 who were enrolled and dosed as well as all participants with HoFH who were enrolled and dosed in this study (49, 101, and 12 subjects in each arm respectively).			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1.			

Data are provided for the full analysis set (49, 101, and 12 subjects in each arm respectively).			
Units: mg/dL arithmetic mean standard deviation	- 	 	
Apolipoprotein B (ApoB) Concentration			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set with available baseline data (47, 100, and 12 subjects in each arm respectively).			
Units: mg/dL arithmetic mean standard deviation	- 	 	
Total Cholesterol/High-density Lipoprotein Cholesterol (HDL-C) Ratio			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set (49, 101, and 12 subjects in each arm respectively).			
Units: ratio arithmetic mean standard deviation	- 	 	
Apolipoprotein B/Apolipoprotein A1 Ratio			
For participants with HeFH who rolled over from parent study 20120123, baseline values are defined as parent study baseline concentrations; for de novo participants with HoFH, baseline values are defined as the mean of the two most recent non-missing concentrations measured through the central laboratory prior to or on Study Day 1. Data are provided for the full analysis set with available baseline data (47, 100, and 12 subjects in each arm respectively).			
Units: ratio arithmetic mean standard deviation	- 	 	

End points

End points reporting groups

Reporting group title	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM
Reporting group description:	
Participants with heterozygous familial hypercholesterolemia (HeFH) who had received placebo in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks (QM) for up to 80 weeks.	

Reporting group title	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM
Reporting group description:	
Participants with heterozygous familial hypercholesterolemia who had received evolocumab in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.	

Reporting group title	HoFH: Evolocumab 420 mg QM
Reporting group description:	
Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.	

Primary: Number of Participants with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs)[1]
End point description:	
An adverse event is defined as any untoward medical occurrence in a clinical trial participant, not necessarily having a causal relationship with study treatment. A serious AE is as an AE that met at least 1 of the following criteria: • fatal; • life threatening; • required in-patient hospitalization or prolongation of existing hospitalization; • resulted in persistent or significant disability/incapacity; • congenital anomaly/birth defect; • other medically important serious event. AEs were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0: Grade 1: Mild; asymptomatic or mild symptoms; Grade 2: Moderate; minimal, local or noninvasive intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; Grade 4: Life-threatening consequences; urgent intervention indicated; Grade 5: Death related to AE.	

End point type	Primary
End point timeframe:	
From first dose of evolocumab in this study up to and including 30 days after the last dose or up to the end of study date, whichever was earlier; up to 80 weeks.	

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: Statistical analyses in this open-label study were descriptive in nature. No statistical inference or missing value imputation was planned.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	101	12	
Units: participants				

Any treatment-emergent adverse event (TEAE)	36	69	7	
TEAE ≥ Grade 2	25	56	5	
TEAE ≥ Grade 3	4	2	2	
TEAE ≥ Grade 4	0	1	0	
Serious adverse events	2	2	2	
TEAE leading to discontinuation of evolocumab	0	0	0	
Fatal adverse events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Low-density Lipoprotein Cholesterol (LDL-C) in HeFH Participants

End point title	Percent Change from Baseline to Week 80 in Low-density Lipoprotein Cholesterol (LDL-C) in HeFH Participants[2]

End point description:

For HeFH participants baseline was defined as the baseline value of the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	88		
Units: percent change				
arithmetic mean (standard error)	-36.01 (± 4.28)	-34.96 (± 3.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in LDL-C in HoFH Participants

End point title	Percent Change from Baseline to Week 80 in LDL-C in HoFH Participants[3]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent change				
median (inter-quartile range (Q1-Q3))	-14.29 (-40.61 to 3.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Non-HDL-C in HeFH Participants

End point title	Percent Change from Baseline to Week 80 in Non-HDL-C in HeFH Participants[4]

End point description:

For HeFH participants baseline was defined as the baseline value of the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	88		
Units: percent change				
arithmetic mean (standard error)	-32.37 (± 3.96)	-31.95 (± 2.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Non-HDL-C in HoFH

Participants	
End point title	Percent Change from Baseline to Week 80 in Non-HDL-C in HoFH Participants[5]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent change				
median (inter-quartile range (Q1-Q3))	-13.03 (-40.68 to 2.69)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Apolipoprotein B in HeFH Participants

End point title	Percent Change from Baseline to Week 80 in Apolipoprotein B in HeFH Participants[6]

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	87		
Units: percent change				
arithmetic mean (standard error)	-27.10 (± 3.32)	-24.15 (± 2.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Apolipoprotein B in HoFH Participants

End point title	Percent Change from Baseline to Week 80 in Apolipoprotein B in HoFH Participants[7]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent change				
median (inter-quartile range (Q1-Q3))	-19.17 (-33.33 to 11.59)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Total Cholesterol/HDL-C Ratio in HeFH Participants

End point title	Percent Change from Baseline to Week 80 in Total Cholesterol/HDL-C Ratio in HeFH Participants[8]

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	88		
Units: percent change				
arithmetic mean (standard error)	-28.78 (± 3.48)	-28.32 (± 2.47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Apolipoprotein B / Apolipoprotein A1 Ratio in HeFH Participants

End point title	Percent Change from Baseline to Week 80 in Apolipoprotein B / Apolipoprotein A1 Ratio in HeFH Participants[9]

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	87		
Units: percent change				
arithmetic mean (standard error)	-31.00 (± 3.66)	-29.89 (± 2.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Total Cholesterol/HDL-C Ratio in HoFH Participants

End point title	Percent Change from Baseline to Week 80 in Total Cholesterol/HDL-C Ratio in HoFH Participants[10]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent change				
median (inter-quartile range (Q1-Q3))	3.71 (-41.17 to 7.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 80 in Apolipoprotein B/Apolipoprotein A1 Ratio in HoFH Participants

End point title	Percent Change from Baseline to Week 80 in Apolipoprotein B/Apolipoprotein A1 Ratio in HoFH Participants[11]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: percent change				
median (inter-quartile range (Q1-Q3))	-2.96 (-35.71 to 9.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in LDL-C in HeFH Participants

End point title	Change from Baseline to Week 80 in LDL-C in HeFH Participants[12]

End point description:

For HeFH participants baseline was defined as the baseline value of the parent study 20120123.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	88		
Units: mg/dL				
arithmetic mean (standard error)	-67.2 (± 8.2)	-63.1 (± 5.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in LDL-C in HoFH Participants

End point title	Change from Baseline to Week 80 in LDL-C in HoFH Participants[13]

End point description:

For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results are reported separately for subjects with HeFH and HoFH.

End point values	HoFH: Evolocumab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg/dL				
median (inter-quartile range (Q1-Q3))	-36.5 (-180.5 to 16.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Estradiol Levels

End point title	Change from Baseline to Week 80 in Estradiol Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	23	54	2	
Units: pmol/L				
arithmetic mean (standard error)	131.3 (± 45.3)	48.2 (± 58.1)	283.0 (± 130.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Testosterone Levels

End point title	Change from Baseline to Week 80 in Testosterone Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	34	7	
Units: nmol/L				
arithmetic mean (standard error)	5.282 (± 1.567)	3.230 (± 1.167)	2.916 (± 0.984)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Follicle Stimulating Hormone (FSH) Levels

End point title	Change from Baseline to Week 80 in Follicle Stimulating Hormone (FSH) Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	91	10	
Units: IU/L				
arithmetic mean (standard error)	1.88 (± 0.90)	0.60 (± 0.37)	1.18 (± 0.35)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Luteinizing Hormone (LH) Levels

End point title	Change from Baseline to Week 80 in Luteinizing Hormone (LH) Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary
End point timeframe: Baseline and week 80	

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	92	10	
Units: IU/L				
arithmetic mean (standard error)	2.88 (± 1.51)	1.04 (± 0.95)	1.76 (± 0.84)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Adenocorticotropic Hormone (ACTH) Levels

End point title	Change from Baseline to Week 80 in Adenocorticotropic Hormone (ACTH) Levels
End point description: For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124). Results are reported for the full analysis set with available data.	
End point type	Secondary
End point timeframe: Baseline and week 80	

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	84	11	
Units: pmol/L				
arithmetic mean (standard error)	0.78 (± 0.55)	0.55 (± 0.61)	-0.75 (± 1.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Dehydroepiandrosterone Sulfate (DHEA-S) Levels

End point title	Change from Baseline to Week 80 in Dehydroepiandrosterone Sulfate (DHEA-S) Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	89	11	
Units: µmol/L				
arithmetic mean (standard error)	1.051 (± 0.222)	0.956 (± 0.126)	0.944 (± 0.247)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Cortisol Levels

End point title	Change from Baseline to Week 80 in Cortisol Levels

End point description:

For HeFH participants baseline was defined as the baseline value in the parent study 20120123. For HoFH participants baseline was defined as the baseline value in this study (20120124).
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	43	90	11	
Units: nmol/L				
arithmetic mean (standard error)	29.81 (± 28.34)	51.18 (± 25.19)	57.26 (± 56.11)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Liver Function Test Abnormalities at Week 80

End point title	Number of Participants with Liver Function Test Abnormalities at Week 80

End point description:

Liver function tests included alanine aminotransferase (ALT) levels, aspartate aminotransferase (AST) levels and total bilirubin levels.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	91	10	
Units: participants				
ALT or AST > 3 x ULN	0	0	0	
ALT or AST > 5 x ULN	0	0	0	
Total bilirubin > 2 x ULN	0	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormalities in Levels of Creatine Kinase (CK) at Week 80

End point title	Number of Participants with Abnormalities in Levels of Creatine Kinase (CK) at Week 80

End point description:

The number of participants with levels of creatine kinase greater than 5 times the upper limit of normal (ULN) and greater than 10 times the ULN, measured by the central laboratory.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	45	90	10	
Units: participants				
CK > 5 x ULN	0	0	1	
CK > 10 x ULN	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 80 in Carotid Intima-media Thickness (cIMT)

End point title	Change from Baseline to Week 80 in Carotid Intima-media Thickness (cIMT)

End point description:

Carotid intima-media thickness measures the thickness of the intima and media, the inner two layers of the carotid artery, and is used to determine the extent of plaque buildup in the walls of the arteries (atherosclerosis) supplying blood to the head.
CIMT was measured by ultrasonography and analyzed at a core laboratory.
The largest values measured in the left common carotid artery (LCCA) and the right common carotid artery (RCCA) are averaged in this analysis.
Results are reported for the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	59	7	
Units: mm				
arithmetic mean (standard error)	-0.019 (± 0.007)	-0.012 (± 0.006)	0.006 (± 0.032)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Height at Weeks 24, 48, and 80

End point title	Change from Baseline in Height at Weeks 24, 48, and 80

End point description:

Results are reported for the full analysis set with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 24, 48, and 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	101	12	
Units: cm				
arithmetic mean (standard error)				
Females: Baseline (n = 24, 59, 2)	158.1 (± 2.3)	157.9 (± 1.3)	149.4 (± 7.1)	
Females: Change at week 24 (n = 21, 55, 2)	2.8 (± 0.7)	2.0 (± 0.4)	1.6 (± 1.1)	
Females: Change at week 48 (n = 22, 55, 2)	4.2 (± 1.0)	2.8 (± 0.5)	1.4 (± 2.4)	
Females: Change at week 80 (n = 24, 56, 2)	4.0 (± 1.7)	3.4 (± 0.7)	2.4 (± 3.9)	
Males: Baseline (n = 25, 42, 10)	158.2 (± 3.0)	163.7 (± 1.9)	158.9 (± 4.8)	
Males: Change at week 24 (n = 23, 40, 10)	3.4 (± 0.5)	3.8 (± 0.5)	3.8 (± 0.8)	
Males: Change at week 48 (n = 23, 39, 9)	6.2 (± 0.8)	6.2 (± 0.7)	5.3 (± 1.2)	
Males: Change at week 80 (n = 21, 36, 9)	9.3 (± 1.5)	9.0 (± 1.1)	9.2 (± 1.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Weight at Weeks 24, 48, and 80

End point title	Change from Baseline in Weight at Weeks 24, 48, and 80

End point description:

Results are reported for the full analysis set with available data at each time point.

End point type	Secondary

End point timeframe:

Baseline and weeks 24, 48, and 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	101	12	
Units: kg				
arithmetic mean (standard error)				
Females: Baseline (n = 24, 59, 2)	52.8 (± 2.9)	57.0 (± 2.0)	42.7 (± 1.3)	
Females: Change at week 24 (n = 21, 55, 2)	3.3 (± 0.8)	2.3 (± 0.6)	3.4 (± 2.1)	
Females: Change at week 48(n= 22, 54, 2)	4.3 (± 1.1)	3.5 (± 0.7)	4.7 (± 5.3)	
Females: Change at week 80 (n = 24, 56, 2)	5.6 (± 1.3)	5.2 (± 0.8)	5.5 (± 4.2)	
Males: Baseline (n = 25, 42, 10)	54.1 (± 3.6)	61.0 (± 3.2)	51.7 (± 4.9)	
Males: Change at week 24 (n = 23, 40, 10)	4.4 (± 0.9)	4.6 (± 0.7)	4.6 (± 0.9)	
Males: Change at week 48 (n = 23, 39, 9)	6.8 (± 1.3)	7.4 (± 1.0)	7.6 (± 1.2)	
Males: Change at week 80 (n = 21, 36, 9)	10.9 (± 1.6)	11.2 (± 1.4)	10.6 (± 2.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Change in Tanner Staging from Baseline to Week 80

End point title	Number of Participants with Change in Tanner Staging from Baseline to Week 80

End point description:

Pubertal growth and sexual maturity was assessed separately for males and females using the 5 Tanner stages where stage 1 = prepubertal and stage 5 = mature.
Results are reported for the full analysis set.

End point type	Secondary

End point timeframe:

Baseline and week 80

End point values	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	101	12	
Units: participants				
Males: Staging by genital size	13	20	6	
Males: Staging by pubic hair	14	21	6	
Females: Staging by breast development	11	27	1	

Females: Staging by pubic hair	11	26	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of evolocumab in this study up to and including 30 days after the last dose or up to the end of study date, whichever was earlier; up to 80 weeks.

Adverse event reporting additional description:

Serious adverse events and other adverse events are reported for all participants who received at least one dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM

Reporting group description:

Participants with heterozygous familial hypercholesterolemia (HeFH) who had received placebo in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks (QM) for up to 80 weeks.

Reporting group title	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM

Reporting group description:

Participants with heterozygous familial hypercholesterolemia who had received evolocumab in the parent study received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.

Reporting group title	HoFH: Evolocumab 420 mg QM

Reporting group description:

Participants with homozygous familial hypercholesterolemia (HoFH) received 420 mg evolocumab administered by subcutaneous injection every 4 weeks for up to 80 weeks.

Serious adverse events	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 49 (4.08%)	2 / 101 (1.98%)	2 / 12 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arteriovenous fistula aneurysm			
subjects affected / exposed	0 / 49 (0.00%)	0 / 101 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	1 / 49 (2.04%)	0 / 101 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anorexia nervosa			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 101 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 49 (2.04%)	0 / 101 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 101 (0.00%)	0 / 12 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	HeFH (Placebo in Parent Study): Evolocumab 420 mg QM	HeFH (Evolocumab in Parent Study): Evolocumab 420 mg QM	HoFH: Evolocumab 420 mg QM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 49 (55.10%)	45 / 101 (44.55%)	7 / 12 (58.33%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Lipoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 101 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 49 (0.00%)	0 / 101 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 49 (8.16%)	9 / 101 (8.91%)	1 / 12 (8.33%)
occurrences (all)	7	16	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 49 (8.16%)	3 / 101 (2.97%)	0 / 12 (0.00%)
occurrences (all)	4	3	0
Influenza like illness			
subjects affected / exposed	5 / 49 (10.20%)	8 / 101 (7.92%)	0 / 12 (0.00%)
occurrences (all)	8	10	0
Injection site erythema			
subjects affected / exposed	4 / 49 (8.16%)	1 / 101 (0.99%)	0 / 12 (0.00%)
occurrences (all)	11	2	0
Injection site haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Pyrexia			
subjects affected / exposed	5 / 49 (10.20%)	1 / 101 (0.99%)	0 / 12 (0.00%)
occurrences (all)	7	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 49 (2.04%)	5 / 101 (4.95%)	1 / 12 (8.33%)
occurrences (all)	1	6	1
Nausea			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	2 / 12 (16.67%)
occurrences (all)	0	1	6
Oropharyngeal pain			
subjects affected / exposed	4 / 49 (8.16%)	5 / 101 (4.95%)	0 / 12 (0.00%)
occurrences (all)	5	5	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 49 (0.00%)	3 / 101 (2.97%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Psychiatric disorders			
Attention deficit hyperactivity disorder			
subjects affected / exposed	2 / 49 (4.08%)	2 / 101 (1.98%)	1 / 12 (8.33%)
occurrences (all)	2	2	1
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 101 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	3 / 49 (6.12%)	7 / 101 (6.93%)	0 / 12 (0.00%)
occurrences (all)	3	9	0
Influenza			
subjects affected / exposed	0 / 49 (0.00%)	3 / 101 (2.97%)	1 / 12 (8.33%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	8 / 49 (16.33%)	14 / 101 (13.86%)	0 / 12 (0.00%)
occurrences (all)	10	20	0
Otitis media			
subjects affected / exposed	0 / 49 (0.00%)	1 / 101 (0.99%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Tonsillitis			
subjects affected / exposed	0 / 49 (0.00%)	4 / 101 (3.96%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	3 / 49 (6.12%) 3	6 / 101 (5.94%) 6	1 / 12 (8.33%) 2
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	0 / 49 (0.00%) 0	3 / 101 (2.97%) 3	1 / 12 (8.33%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 September 2015	• Added safety endpoint of incidence of abnormal neurological examination at week 80. • Changed endpoint of change from baseline in cognitive function at week 80 as assessed by Cogstate battery from an exploratory endpoint to a safety endpoint. • Added that adverse device effects and disease related events would be collected at every study visit. • Added collection of sample for assessment of fasting vitamins A, D, E, and K levels. • Deleted papilla elevation from tanner stages (sexual maturity ratings) for stage 1 male genital size.
22 June 2016	• Clarified primary endpoint timepoint at week 80. • Added language that defines baseline lab values for rollover and de novo subjects. • Clarified eligibility criteria; rollover subjects should not have experienced treatment related serious adverse events in Study 20120123. • Updated schedule of assessments and study procedures: - allowed for a 4 week screening window for rollover subjects and for those subjects who exceed the 4-week window noted which procedures must be redone; - updated collection points for creatinine kinase; - added additional analytes for urinalysis; - removed thyroid stimulating hormone (TSH) as an analyte.
26 April 2017	• Updated the number of sites expected. • Added AMD product information and option for device use. • Clarified enrollment should be on day 1 or as close as possible to day 1 and no earlier than 5 days prior to day 1. • Aligned safety definitions and reporting procedures with current protocol template.
27 May 2020	• Added interim analysis for all enrolled subjects. • Updated number of subjects expected to roll over from Study 20120123 into Study 20120124. • Aligned with current protocol template: - removed language regarding the collection of disease related events; - removed details from study monitoring and data collection to restrict Amgen (or designee) correcting obvious data errors in the clinical trial database.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported