Clinical trial results:
Double-blind, Randomized, Multicenter, Placebo-controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-cholesterol (LDL-C) Reduction, as Add-on to Diet and Lipid-lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)

Summary

EudraCT number	2014-002277-11
Trial protocol	CZ BE ES IT Outside EU/EEA GR NL GB AT HU SI PT PL NO RO
Global end of trial date	25 November 2019

Results information

Result version number	v1 (current)
This version publication date	07 June 2020
First version publication date	07 June 2020

Trial information

Trial identification

Sponsor protocol code	20120123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02392559
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-PIP01-05
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	25 November 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab compared with placebo, when added to standard of care, on percent change from baseline in LDL-C in pediatric subjects 10 to 17 years of age with HeFH.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations, and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 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	United States: 5
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Netherlands: 22
Country: Number of subjects enrolled	Norway: 8
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: 5
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Turkey: 2
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: 2
Worldwide total number of subjects	158
EEA total number of subjects	97

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)	39
Adolescents (12-17 years)	119
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 24 March 2016 to 30 May 2019 at 8 research centers in North America, 30 research centers in Europe, 6 research centers in Latin America, and 3 research centers in Asia Pacific.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio to receive 24 weeks of monthly (QM) evolocumab or placebo. Randomization was stratified by screening low-density lipoprotein cholesterol (LDL-C; < 160 mg/dL vs ≥ 160 mg/dL) and age (< 14 years vs ≥ 14 years).

Pre-assignment period milestones

Number of subjects started	158
Number of subjects completed	157

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized, not dosed: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Matching subcutaneous injection QM

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Each QM administration of investigational product consists of 3 injections of placebo in 1.0 mL (administration by prefilled AI/Pen) for a total of 3.0 mL placebo administered.

Arm title	EvoMab 420 mg QM

Arm description:

Evolocumab subcutaneous injection QM

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

Dosage and administration details:

Each QM administration of investigational product consists of 3 injections of 140 mg evolocumab in 1.0 mL (administration by prefilled AI/Pen) for a total of 3.0 mL (420 mg evolocumab) administered.

Number of subjects in period 1[1]	Placebo	EvoMab 420 mg QM
Started	53	104
Completed	53	104

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 enrolled and randomized participant was not dosed.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Matching subcutaneous injection QM	
Reporting group title	EvoMab 420 mg QM
Reporting group description: Evolocumab subcutaneous injection QM	

Reporting group values	Placebo	EvoMab 420 mg QM	Total
Number of subjects	53	104	157
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	13.7	13.7	
standard deviation	± 2.5	± 2.3	-
Sex: Female, Male Units:			
Female	27	61	88
Male	26	43	69
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	6	13
Not Hispanic or Latino	46	98	144
Race/Ethnicity, Customized Units: Subjects			
Asian	0	2	2
Black (or African American)	0	2	2
White	44	89	133
Other, Not Specified	9	11	20
Stratification Factor: Age Group Units: Subjects			
< 14 years	25	48	73
≥ 14 years	28	56	84
Stratification Factor: Screening LDL-C Level Units: Subjects			
< 160 mg/dL	16	33	49
≥ 160 mg/dL	37	71	108
LDL-C Units: mg/dL			
arithmetic mean	183.0	185.0	
standard deviation	± 47.2	± 45.0	-
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Units: mg/dL			

arithmetic mean	200.2	203.8	
standard deviation	± 48.2	± 47.3	-
Total Cholesterol/HDL-C Ratio			
Units: ratio			
arithmetic mean	5.517	5.702	
standard deviation	± 1.492	± 1.791	-
Apolipoprotein B (ApoB)			
participants with an assessment at baseline (n=154)			
Units: mg/dL			
arithmetic mean	119.4	123.3	
standard deviation	± 27.9	± 27.1	-
ApoB/Apolipoprotein A1 (ApoA1) Ratio			
participants with an assessment at baseline (n=154)			
Units: ratio			
arithmetic mean	0.938	0.970	
standard deviation	± 0.255	± 0.302	-
Systolic Blood Pressure			
Units: mmHg			
arithmetic mean	112.0	110.8	
standard deviation	± 12.1	± 11.5	-
Diastolic Blood Pressure			
Units: mmHg			
arithmetic mean	67.2	66.3	
standard deviation	± 8.7	± 7.7	-
Heart Rate			
Units: beats per minute			
arithmetic mean	74.3	74.5	
standard deviation	± 11.7	± 11.1	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Matching subcutaneous injection QM	
Reporting group title	EvoMab 420 mg QM
Reporting group description: Evolocumab subcutaneous injection QM	

Primary: Percent Change From Baseline to Week 24 in LDL-C	
End point title	Percent Change From Baseline to Week 24 in LDL-C
End point description: Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from interactive voice response system [IVRS]), scheduled visit and the interaction of treatment with scheduled visit as covariates. The model uses an unstructured covariance.	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-6.23 (± 3.08)	-44.53 (± 2.17)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-38.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.54
upper limit	-31.06

Variability estimate	Standard error of the mean
Dispersion value	3.66

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [1]
Method	sequential testing/Hochberg procedure

Notes:

[1] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Mean Percent Change from Baseline to Mean of Weeks 22 and 24 in LDL-C

End point title	Mean Percent Change from Baseline to Mean of Weeks 22 and 24 in LDL-C

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

End point type	Secondary

End point timeframe:

Baseline, Week 22, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-5.87 (± 2.66)	-47.95 (± 1.92)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-42.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.34
upper limit	-35.83
Variability estimate	Standard error of the mean
Dispersion value	3.17

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [2]
Method	sequential testing/Hochberg procedure

Notes:

[2] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Change From Baseline to Week 24 in LDL-C

End point title	Change From Baseline to Week 24 in LDL-C

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: mg/dL				
least squares mean (standard error)	-9.0 (± 6.2)	-77.5 (± 4.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM

Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [3]
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-68.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.1
upper limit	-54
Variability estimate	Standard error of the mean
Dispersion value	7.3

Notes:

[3] - Treatment difference uses placebo as the reference.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	sequential testing/Hochberg procedure

Notes:

[4] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Percent Change From Baseline to Week 24 in Non-HDL-C

End point title	Percent Change From Baseline to Week 24 in Non-HDL-C

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-6.14 (± 2.87)	-41.19 (± 2.01)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-35.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.79
upper limit	-28.3
Variability estimate	Standard error of the mean
Dispersion value	3.41

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	sequential testing/Hochberg procedure

Notes:

[5] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Percent Change From Baseline to Week 24 in Apoliprotein-B (ApoB)

End point title	Percent Change From Baseline to Week 24 in Apoliprotein-B (ApoB)

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-2.37 (± 2.70)	-34.85 (± 1.88)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-32.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.82
upper limit	-26.13
Variability estimate	Standard error of the mean
Dispersion value	3.21

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [6]
Method	sequential testing/Hochberg procedure

Notes:

[6] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Percent Change From Baseline to Week 24 in Total Cholesterol/HDL-C Ratio

End point title	Percent Change From Baseline to Week 24 in Total Cholesterol/HDL-C Ratio

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-4.66 (± 2.60)	-34.96 (± 1.82)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-30.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.4
upper limit	-24.21
Variability estimate	Standard error of the mean
Dispersion value	3.09

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	sequential testing/Hochberg procedure

Notes:

[7] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Percent Change From Baseline to Week 24 in ApoB:ApoA1 Ratio

End point title	Percent Change From Baseline to Week 24 in ApoB:ApoA1 Ratio

End point description:

Least squares mean is from the repeated measures model which includes treatment group, stratification factors of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.

End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: percent change				
least squares mean (standard error)	-0.63 (± 2.80)	-37.02 (± 1.95)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	repeated measures model
Parameter estimate	treatment difference
Point estimate	-36.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.97
upper limit	-29.8
Variability estimate	Standard error of the mean
Dispersion value	3.33

Statistical analysis title	Statistical Analysis 2
Comparison groups	Placebo v EvoMab 420 mg QM
Number of subjects included in analysis	157
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [8]
Method	sequential testing/Hochberg procedure

Notes:

[8] - Adjusted p-value based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints.

Secondary: Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation (DC), Fatal TEAEs, and Device-Related TEAEs

End point title	Number of Participants With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs, TEAEs Leading to Discontinuation (DC), Fatal TEAEs, and Device-Related TEAEs

End point description:

An adverse event (AE) is defined as any untoward medical occurrence that does not necessarily have a causal relationship with study treatment. An SAE is defined as an adverse event that: is fatal; is a life threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or other medically important serious event. Events were graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading scale (1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death). Events were defined as treatment emergent if they occurred after the first dose of study drug and up to and including 30 days after the last dose or the end of study date, whichever is earlier.

End point type	Secondary

End point timeframe:

From first dose of study drug up to and including 30 days after the last dose or end of study date (Week 24), whichever was earlier. Mean (SD) duration on study was 5.664 (0.278) and 5.608 (0.137) months for Placebo and EvoMab arms, respectively.

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: participants				
All TEAEs	34	64		
Grade ≥ 2 TEAEs	22	46		
Grade ≥ 3 TEAEs	0	4		
Grade ≥ 4 TEAEs	0	0		
Serious TEAEs	0	1		
TEAEs Leading to DC of Study Drug	0	1		
Serious TEAEs Leading to DC of Study Drug	0	0		
Non-Serious TEAEs Leading to DC of Study Drug	0	1		
Fatal TEAEs	0	0		
Device-Related TEAEs	2	3		
Device-Related Grade ≥ 2 TEAEs	0	0		
Device-Related Grade ≥ 3 TEAEs	0	0		
Device-Related Grade ≥ 4 TEAEs	0	0		
Serious Device-Related TEAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Maximum Post-Baseline Laboratory Toxicities of Grade ≥ 3

End point title	Number of Participants With Maximum Post-Baseline Laboratory Toxicities of Grade ≥ 3

End point description:

Laboratory toxicity grading was based on NCI CTCAE grading; Grade 3 indicates severe toxicity and

Grade 4 indicates life-threatening toxicity. Values representing a worsening from baseline are shown.

End point type	Secondary

End point timeframe:
Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: participants				
High Total Bilirubin - Grade 3	1	0		
High Total Cholesterol - Grade 3	1	1		
High Uric Acid - Grade 3	2	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Systolic Blood Pressure

End point title	Change From Baseline Over Time in Systolic Blood Pressure

End point description:

End point type	Secondary

End point timeframe:
Baseline, Week 4, Week 12, Week 20, Week 22, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: mmHg				
arithmetic mean (standard deviation)				
Change at Week 4	-0.1 (± 11.3)	-0.7 (± 9.4)		
Change at Week 12	-0.6 (± 10.3)	0.3 (± 9.6)		
Change at Week 20	-2.1 (± 7.7)	0.1 (± 10.1)		
Change at Week 22	1.0 (± 10.9)	1.1 (± 10.0)		
Change at Week 24	-0.6 (± 11.4)	0.6 (± 10.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Diastolic Blood Pressure

End point title	Change From Baseline Over Time in Diastolic Blood Pressure

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12, Week 20, Week 22, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: mmHg				
arithmetic mean (standard deviation)				
Change at Week 4	-2.5 (± 9.5)	-1.5 (± 7.3)		
Change at Week 12	-2.2 (± 10.0)	0.5 (± 8.9)		
Change at Week 20	-3.3 (± 7.6)	-0.6 (± 7.7)		
Change at Week 22	-1.5 (± 9.3)	2.9 (± 8.0)		
Change at Week 24	-0.5 (± 9.0)	0.3 (± 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline Over Time in Heart Rate

End point title	Change From Baseline Over Time in Heart Rate

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12, Week 20, Week 22, Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	104		
Units: beats per minute				
arithmetic mean (standard deviation)				
Change at Week 4	2.1 (± 11.0)	0.1 (± 10.8)		
Change at Week 12	-0.5 (± 11.5)	-1.3 (± 10.2)		
Change at Week 20	-1.1 (± 10.3)	1.1 (± 11.5)		
Change at Week 22	1.3 (± 13.5)	-0.6 (± 11.3)		
Change at Week 24	0.2 (± 13.0)	-1.8 (± 11.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Testing Positive for Anti-Evolocumab Antibodies

End point title	Number of Participants Testing Positive for Anti-Evolocumab Antibodies

End point description:

End point type	Secondary

End point timeframe:

up to Week 24

End point values	Placebo	EvoMab 420 mg QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	104		
Units: participants				
Binding antibody positive at anytime		0		
Neutralizing antibody positive at anytime		0		

Notes:

[9] - Participants receiving evolocumab only were assessed.

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Evolocumab Concentrations Over Time

End point title	Serum Evolocumab Concentrations Over Time[10]

End point description:

End point type	Secondary

End point timeframe:

Week 12, Week 22, Week 24

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: Serum concentration assessments are limited to participants who received evolocumab.

End point values	EvoMab 420 mg QM			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 12	22400 (± 14700)			
Week 22	64900 (± 34400)			
Week 24	25800 (± 19200)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Fatal AEs: from first dose date to the end of study date (Week 24). Non-fatal AEs: from first dose of study drug up to and including 30 days after the last dose or end of study date, whichever was earlier.

Adverse event reporting additional description:

Mean (SD) duration on study was 5.664 (0.278) and 5.608 (0.137) months for the Placebo and EvoMab arms, respectively.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	EvoMab 420 mg QM

Reporting group description:

Evolocumab subcutaneous injection QM

Reporting group title	Placebo QM

Reporting group description:

Matching subcutaneous injection QM

Serious adverse events	EvoMab 420 mg QM	Placebo QM	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 104 (0.96%)	0 / 53 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	EvoMab 420 mg QM	Placebo QM	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 104 (39.42%)	19 / 53 (35.85%)	
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 104 (0.96%)	2 / 53 (3.77%)	
occurrences (all)	1	3	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 104 (10.58%)	1 / 53 (1.89%)	
occurrences (all)	17	1	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	3 / 104 (2.88%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	3 / 104 (2.88%)	3 / 53 (5.66%)	
occurrences (all)	3	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 104 (2.88%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 104 (1.92%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Oropharyngeal pain			
subjects affected / exposed	7 / 104 (6.73%)	0 / 53 (0.00%)	
occurrences (all)	8	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 104 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	5 / 104 (4.81%)	4 / 53 (7.55%)	
occurrences (all)	5	4	
Influenza			
subjects affected / exposed	6 / 104 (5.77%)	2 / 53 (3.77%)	
occurrences (all)	6	5	
Nasopharyngitis			

subjects affected / exposed	12 / 104 (11.54%)	6 / 53 (11.32%)	
occurrences (all)	14	6	
Rhinitis			
subjects affected / exposed	0 / 104 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Upper respiratory tract infection			
subjects affected / exposed	6 / 104 (5.77%)	1 / 53 (1.89%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2015	• added hematology, urinalysis, and anti-evolocumab antibody assessments at week 12 • added exclusion of apheresis subjects to synopsis • added documentation of historical lipid therapies • added assessments of cognitive function to schedule of assessments and as an exploratory endpoint • clarification that the calculation of sample size accounts for 20% of randomized subjects discontinuing investigational product prior to completion of the study • deleted the exploratory endpoint of "categorical change from baseline in high sensitivity C-reactive protein"
01 September 2015	• added explicit exclusion of homozygous familial hypercholesterolemia subjects • added adverse device effects (ADE) and disease-related events (DRE) as safety assessments • removed cogstate neurocognitive battery as an exploratory endpoint and added it as a other safety endpoint. • added low-fat diet as background therapy to be maintained throughout the study • added explicit exclusion subjects receiving lipid apheresis • added definition of product complaints to the schedule of assessments • added the primary estimand • added statistical methodology for reporting vital signs, antibody data, and pharmacokinetic data

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported