



Clinical trial results:

A Double-blind, Randomized, Placebo and Ezetimibe-controlled, Multicenter Study to Evaluate Safety and Efficacy of Lipid Lowering Monotherapy With AMG 145 in Subjects With a 10-Year Framingham Risk Score of 10% or Less

Summary

EudraCT number	2012-001362-15
Trial protocol	DK BE
Global end of trial date	29 October 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	20110114
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763827
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 October 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	29 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of 12 weeks of evolocumab subcutaneous monotherapy every 2 weeks and monthly, compared with placebo and ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with a 10-year Framingham risk score of 10% or less.

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	21 January 2013
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: 310
Country: Number of subjects enrolled	Canada: 42
Country: Number of subjects enrolled	Belgium: 54
Country: Number of subjects enrolled	Denmark: 119
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Australia: 44
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 13
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	615
EEA total number of subjects	198

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)	0
Adults (18-64 years)	504
From 65 to 84 years	111
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Men and women ≥ 18 to ≤ 80 years of age with fasting low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL and < 190 mg/dL and fasting triglycerides ≤ 400 mg/dL with a 10-year Framingham Risk Score of 10% or less were eligible for this study. The first participant was enrolled on 21 January 2013 and the last participant was enrolled 29 July 2013.

Pre-assignment

Screening details:

Participants received subcutaneous placebo corresponding to the once monthly dose volume during a 6 week screening period. Participants who completed the screening period and met final eligibility criteria were randomized 1:1:1:1:2:2 into 6 treatment groups. Randomization was stratified by LDL-C concentration (< 130 mg/dL or ≥ 30 mg/dL).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Q2W

Arm description:

Participants received placebo subcutaneous injection once every 2 weeks (Q2W) and placebo tablets once a day for up to 12 weeks.

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

Dosage and administration details:

Administered by subcutaneous injection

Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Self-administered orally once daily

Arm title	Placebo QM
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Arm description:

Participants received placebo subcutaneous injection once every month (QM) and placebo tablets once a day for up to 12 weeks.

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

Dosage and administration details:	
Administered by subcutaneous injection	
Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Self-administered orally once daily	
Arm title	Ezetimibe (Q2W)
Arm description:	
Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Arm type	Active comparator
Investigational medicinal product name	Placebo to Evolocumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details:	
Administered by subcutaneous injection	
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
10 mg administered orally once a day	
Arm title	Ezetimibe (QM)
Arm description:	
Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Arm type	Active comparator
Investigational medicinal product name	Placebo to Evolocumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use
Dosage and administration details:	
Administered by subcutaneous injection	
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
10 mg administered orally once a day	
Arm title	Evolocumab Q2W
Arm description:	
Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Arm type	Experimental

Investigational medicinal product name	Evolocumab
Investigational medicinal product code	AMG 145
Other name	Repatha
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Self-administered orally once daily

Arm title	Evolocumab QM
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Arm description:

Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.

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

Dosage and administration details:

Administered by subcutaneous injection

Investigational medicinal product name	Placebo to Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Self-administered orally once daily

Number of subjects in period 1	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)
Started	77	78	77
Received at Least 1 Dose of Study Drug	76	78	77
Completed	74	77	73
Not completed	3	1	4
Consent withdrawn by subject	1	-	-
Lost to follow-up	-	1	1
Decision by sponsor	2	-	3

Number of subjects in period 1	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Started	77	153	153
Received at Least 1 Dose of Study Drug	77	153	153

Completed	76	147	151
Not completed	1	6	2
Consent withdrawn by subject	-	2	-
Lost to follow-up	1	2	1
Decision by sponsor	-	2	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo Q2W
Reporting group description: Participants received placebo subcutaneous injection once every 2 weeks (Q2W) and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Placebo QM
Reporting group description: Participants received placebo subcutaneous injection once every month (QM) and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (Q2W)
Reporting group description: Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (QM)
Reporting group description: Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Evolocumab Q2W
Reporting group description: Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description: Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.	

Reporting group values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)
Number of subjects	77	78	77
Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	54.4	52.6	53.9
standard deviation	± 10.3	± 10.7	± 11.3
Gender, Male/Female Units: participants			
Female	49	47	53
Male	28	31	24
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	8	7
Black or African American	4	6	6
Native Hawaiian or Other Pacific Islander	0	1	0
White	64	63	63
Other	0	0	0
Mixed Race	0	0	1

Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	6	8	9
Not Hispanic or Latino	71	70	68
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)			
Units: Subjects			
< 130 mg/dL	23	24	22
≥ 130 mg/dL	54	54	55
LDL-C Concentration			
Data are provided for the full analysis set (all randomized participants who received at least 1 dose of investigational product (subcutaneously or orally)).			
Units: mg/dL			
arithmetic mean	139.5	144.3	143.3
standard deviation	± 21.3	± 23.9	± 23.8
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	167.4	172.8	168.8
standard deviation	± 25.8	± 31	± 28.9
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	103.7	107.3	107.2
standard deviation	± 16.8	± 19.9	± 19.7
Total Cholesterol/High-density Lipoprotein Cholesterol Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	4.148	4.444	4.055
standard deviation	± 1.311	± 1.465	± 1.082
Apolipoprotein B/Apolipoprotein A-1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	0.671	0.713	0.691
standard deviation	± 0.193	± 0.194	± 0.187
Lipoprotein(a)			
Data are provided for the full analysis set			
Units: nmol/L			
median	21	21.5	28
inter-quartile range (Q1-Q3)	9 to 49	7 to 62	11 to 120
Triglycerides			
Data are provided for the full analysis set			
Units: mg/dL			
median	113.5	118	112.5
inter-quartile range (Q1-Q3)	83.3 to 178	85.5 to 178.5	83.5 to 158
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	22.5	23.8	22.5
inter-quartile range (Q1-Q3)	16.8 to 34.3	17 to 35.5	16.5 to 32

High-density Lipoprotein Cholesterol (HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	57	54	58.5
inter-quartile range (Q1-Q3)	43.8 to 77.3	44.5 to 65.5	47 to 69.5

Reporting group values	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Number of subjects	77	153	153
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	53	52.5	52.9
standard deviation	± 12.7	± 13.7	± 12.1
Gender, Male/Female			
Units: participants			
Female	52	104	101
Male	25	49	52
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1	0	2
Asian	10	12	12
Black or African American	6	9	9
Native Hawaiian or Other Pacific Islander	0	0	0
White	60	132	129
Other	0	0	0
Mixed Race	0	0	1
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	11	14	21
Not Hispanic or Latino	66	139	132
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)			
Units: Subjects			
< 130 mg/dL	22	45	45
≥ 130 mg/dL	55	108	108
LDL-C Concentration			
Data are provided for the full analysis set (all randomized participants who received at least 1 dose of investigational product (subcutaneously or orally)).			
Units: mg/dL			
arithmetic mean	143.5	141.7	144.4
standard deviation	± 23.1	± 22.3	± 23.3
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	169.4	166.5	170.4
standard deviation	± 27.3	± 25.6	± 26.6
Apolipoprotein B Concentration			
Data are provided for the full analysis set			

Units: mg/dL			
arithmetic mean	106.2	104.5	108.3
standard deviation	± 17.8	± 17.2	± 17.9
Total Cholesterol/High-density Lipoprotein Cholesterol Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	4.335	4.17	4.175
standard deviation	± 1.118	± 1.17	± 1.071
Apolipoprotein B/Apolipoprotein A-1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	0.712	0.687	0.707
standard deviation	± 0.173	± 0.169	± 0.17
Lipoprotein(a)			
Data are provided for the full analysis set			
Units: nmol/L			
median	28	20	28
inter-quartile range (Q1-Q3)	12 to 64	7 to 58	9 to 104
Triglycerides			
Data are provided for the full analysis set			
Units: mg/dL			
median	116.5	112	119
inter-quartile range (Q1-Q3)	90 to 159	81.5 to 147.5	82.5 to 168.5
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	23.5	22.5	23.5
inter-quartile range (Q1-Q3)	18 to 31.5	16.5 to 29.5	16.5 to 33.5
High-density Lipoprotein Cholesterol (HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	53.5	53	56.5
inter-quartile range (Q1-Q3)	42 to 67.5	44.5 to 67	46.5 to 65.5
Reporting group values			
	Total		
Number of subjects	615		
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: participants			
Female	406		
Male	209		

Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	3		
Asian	58		
Black or African American	40		
Native Hawaiian or Other Pacific Islander	1		
White	511		
Other	0		
Mixed Race	2		
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	69		
Not Hispanic or Latino	546		
Stratification Factor: Low-density Lipoprotein Cholesterol (LDL-C)			
Units: Subjects			
< 130 mg/dL	181		
≥ 130 mg/dL	434		
LDL-C Concentration			
Data are provided for the full analysis set (all randomized participants who received at least 1 dose of investigational product (subcutaneously or orally)).			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Non-High-Density Lipoprotein Cholesterol (Non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Total Cholesterol/High-density Lipoprotein Cholesterol Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean			
standard deviation	-		
Apolipoprotein B/Apolipoprotein A-1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean			
standard deviation	-		
Lipoprotein(a)			
Data are provided for the full analysis set			
Units: nmol/L			
median			
inter-quartile range (Q1-Q3)	-		

Triglycerides			
Data are provided for the full analysis set			
Units: mg/dL median inter-quartile range (Q1-Q3)	-		
Very Low-density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL median inter-quartile range (Q1-Q3)	-		
High-density Lipoprotein Cholesterol (HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL median inter-quartile range (Q1-Q3)	-		

End points

End points reporting groups

Reporting group title	Placebo Q2W
Reporting group description: Participants received placebo subcutaneous injection once every 2 weeks (Q2W) and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Placebo QM
Reporting group description: Participants received placebo subcutaneous injection once every month (QM) and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (Q2W)
Reporting group description: Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Ezetimibe (QM)
Reporting group description: Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.	
Reporting group title	Evolocumab Q2W
Reporting group description: Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description: Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.	

Primary: Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Week 12

End point title	Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Week 12
End point description: Calculated LDL-C was determined based on the Friedewald equation. Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Primary
End point timeframe: Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	0.1 (\pm 1.67)	-1.34 (\pm 1.54)	-17.75 (\pm 1.67)	-18.57 (\pm 1.56)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-57.04 (\pm 1.23)	-56.12 (\pm 1.12)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and placebo, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[1]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-57.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.14
upper limit	-53.14
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[1] - The model included treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and placebo, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[2]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-54.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.46
upper limit	-51.1
Variability estimate	Standard error of the mean
Dispersion value	1.87

Notes:

[2] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[3]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-39.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.28
upper limit	-35.31
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[3] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the percent change from Baseline at Week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[4]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-37.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.24
upper limit	-33.86
Variability estimate	Standard error of the mean
Dispersion value	1.88

Notes:

[4] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Primary: Mean Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Low-density Lipoprotein Cholesterol (LDL-C) at Weeks 10 and 12
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End point description:

Calculated LDL-C was determined based on the Friedewald equation.

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Primary
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End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	-0.43 (± 1.45)	-1.41 (± 1.37)	-17.52 (± 1.46)	-19.12 (± 1.39)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-56.93 (± 1.07)	-58.81 (± 1)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and placebo, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Placebo Q2W v Evolocumab Q2W
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Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[5]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-56.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.95
upper limit	-53.04
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[5] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and placebo, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[6]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-57.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.66
upper limit	-54.14
Variability estimate	Standard error of the mean
Dispersion value	1.66

Notes:

[6] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
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Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[7]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-39.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.87
upper limit	-35.94
Variability estimate	Standard error of the mean
Dispersion value	1.76

Notes:

[7] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
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Statistical analysis description:

The null hypothesis was that there was no mean difference in the mean percent change from Baseline at Weeks 10 and 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis was that a mean difference did exist.

Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[8]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-36.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.97
upper limit	-36.42
Variability estimate	Standard error of the mean
Dispersion value	1.66

Notes:

[8] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Change From Baseline in LDL-C at Weeks 10 and 12

End point title	Mean Change From Baseline in LDL-C at Weeks 10 and 12
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End point description:

Calculated LDL-C was determined based on the Friedewald equation.

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: mg/dL				
least squares mean (standard error)	1.2 (\pm 2.3)	0 (\pm 2.1)	-23.1 (\pm 2.3)	-25.9 (\pm 2.1)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: mg/dL				
least squares mean (standard error)	-78.4 (\pm 1.7)	-81.9 (\pm 1.5)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[9]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-79.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-85
upper limit	-74.2
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[9] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[10]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-81.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-87
upper limit	-76.9
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[10] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[11]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-55.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.7
upper limit	-49.9
Variability estimate	Standard error of the mean
Dispersion value	2.7

Notes:

[11] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[12]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-56.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.1
upper limit	-51
Variability estimate	Standard error of the mean
Dispersion value	2.6

Notes:

[12] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Change From Baseline in LDL-C at Week 12

End point title	Change From Baseline in LDL-C at Week 12
End point description:	
Calculated LDL-C was determined based on the Friedewald equation. Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: mg/dL				
least squares mean (standard error)	1.9 (± 2.5)	-0.1 (± 2.4)	-23.4 (± 2.5)	-25 (± 2.4)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: mg/dL				
least squares mean (standard error)	-78.4 (± 1.9)	-77.9 (± 1.7)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[13]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-80.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-86.4
upper limit	-74.3
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[13] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[14]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-77.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.4
upper limit	-72.2
Variability estimate	Standard error of the mean
Dispersion value	2.8

Notes:

[14] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[15]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-55

Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.1
upper limit	-49
Variability estimate	Standard error of the mean
Dispersion value	3.1

Notes:

[15] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Ezetimibe (QM) v Evolocumab QM
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[16]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-52.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.5
upper limit	-47.3
Variability estimate	Standard error of the mean
Dispersion value	2.9

Notes:

[16] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percentage of Participants Who Achieved LDL-C < 70 mg/dL at Weeks 10 and 12

End point title	Mean Percentage of Participants Who Achieved LDL-C < 70 mg/dL at Weeks 10 and 12
End point description:	
Calculated LDL-C was determined based on the Friedewald equation. The analysis was performed using the full analysis set.	
End point type	Secondary
End point timeframe:	
Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 4.8)	0 (0 to 4.9)	1.3 (0.2 to 7.2)	2.8 (0.8 to 9.6)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percentage of participants				
number (confidence interval 95%)	73.6 (65.7 to 80.2)	71.3 (63.6 to 78)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[17]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	73.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	64.4
upper limit	80.2

Notes:

[17] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[18]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	71.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.2
upper limit	78

Notes:

[18] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	72.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	62.4
upper limit	78.9

Notes:

[19] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[20]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	68.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	58.3
upper limit	75.5

Notes:

[20] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percentage of Participants Who Achieved LDL-C < 70 mg/dL at Week 12

End point title	Percentage of Participants Who Achieved LDL-C < 70 mg/dL at Week 12
End point description:	
Calculated LDL-C was determined based on the Friedewald equation. Efficacy analyses were performed in the full analysis set.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percentage of participants				
number (confidence interval 95%)	1.4 (0.3 to 7.8)	0 (0 to 5.2)	1.4 (0.3 to 7.7)	1.4 (0.3 to 7.8)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percentage of participants				
number (confidence interval 95%)	72.9 (64.8 to 79.8)	65.4 (57.1 to 72.9)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[21]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	71.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	61.2
upper limit	78.4

Notes:

[21] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[22]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	65.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	55.6
upper limit	72.9

Notes:

[22] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	71.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	61.3
upper limit	78.4

Notes:

[23] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Evolocumab QM v Ezetimibe (QM)
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[24]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	64
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.5
upper limit	71.6

Notes:

[24] - Based on Cochran-Mantel Haenszel test stratified by Baseline LDL-C level. For testing, non-achievement was imputed for participants with a missing value. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Non-high-density Lipoprotein Cholesterol at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Non-high-density Lipoprotein Cholesterol at Weeks 10 and 12
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End point description:

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Secondary
End point timeframe:	
Baseline and Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	-1.41 (\pm 1.34)	1.32 (\pm 1.24)	-14.64 (\pm 1.35)	-16.48 (\pm 1.25)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-50.22 (\pm 0.99)	-51.96 (\pm 0.9)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[25]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-48.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.01
upper limit	-45.61
Variability estimate	Standard error of the mean
Dispersion value	1.63

Notes:

[25] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[26]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-53.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.23
upper limit	-50.33
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[26] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[27]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-35.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.79
upper limit	-32.38
Variability estimate	Standard error of the mean
Dispersion value	1.63

Notes:

[27] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[28]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-35.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.44
upper limit	-32.53
Variability estimate	Standard error of the mean
Dispersion value	1.5

Notes:

[28] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Non-high-density Lipoprotein Cholesterol at Week 12

End point title	Percent Change From Baseline in Non-high-density Lipoprotein Cholesterol at Week 12
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End point description:

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	-0.31 (± 1.48)	1.51 (± 1.38)	-14.89 (± 1.47)	-16.48 (± 1.39)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-50.12 (± 1.08)	-49.68 (± 1.01)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[29]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.34
upper limit	-46.27
Variability estimate	Standard error of the mean
Dispersion value	1.79

Notes:

[29] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[30]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-51.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.49
upper limit	-47.9
Variability estimate	Standard error of the mean
Dispersion value	1.67

Notes:

[30] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[31]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-35.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.74
upper limit	-31.71
Variability estimate	Standard error of the mean
Dispersion value	1.78

Notes:

[31] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[32]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.51
upper limit	-29.9
Variability estimate	Standard error of the mean
Dispersion value	1.68

Notes:

[32] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Apolipoprotein B at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Apolipoprotein B at Weeks 10 and 12
End point description:	
Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	0.05 (± 1.51)	1.54 (± 1.41)	-13.47 (± 1.52)	-14.75 (± 1.43)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-47.04 (\pm 1.12)	-49.39 (\pm 1.03)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[33]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-47.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.67
upper limit	-43.51
Variability estimate	Standard error of the mean
Dispersion value	1.82

Notes:

[33] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[34]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-50.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.27
upper limit	-47.59
Variability estimate	Standard error of the mean
Dispersion value	1.7

Notes:

[34] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[35]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.15
upper limit	-29.99
Variability estimate	Standard error of the mean
Dispersion value	1.82

Notes:

[35] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[36]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.99
upper limit	-31.28
Variability estimate	Standard error of the mean
Dispersion value	1.71

Notes:

[36] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Apolipoprotein B at Week 12

End point title	Percent Change From Baseline in Apolipoprotein B at Week 12
End point description:	
Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Secondary

End point timeframe:
Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	0.59 (\pm 1.58)	1.84 (\pm 1.53)	-13.17 (\pm 1.58)	-14.02 (\pm 1.54)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-47.21 (\pm 1.17)	-46.59 (\pm 1.12)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[37]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-47.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.56
upper limit	-44.05
Variability estimate	Standard error of the mean
Dispersion value	1.91

Notes:

[37] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[38]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-48.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.07
upper limit	-44.79
Variability estimate	Standard error of the mean
Dispersion value	1.85

Notes:

[38] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[39]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.78
upper limit	-30.3
Variability estimate	Standard error of the mean
Dispersion value	1.9

Notes:

[39] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[40]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-32.57

Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.21
upper limit	-28.92
Variability estimate	Standard error of the mean
Dispersion value	1.85

Notes:

[40] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Total Cholesterol/High-density Lipoprotein Cholesterol Ratio at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Total Cholesterol/High-density Lipoprotein Cholesterol Ratio at Weeks 10 and 12
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End point description:

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	0.44 (± 1.29)	6.42 (± 1.5)	-9.14 (± 1.29)	-11.9 (± 1.51)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-38.49 (± 0.95)	-39.41 (± 1.08)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[41]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-38.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42
upper limit	-35.86
Variability estimate	Standard error of the mean
Dispersion value	1.56

Notes:

[41] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[42]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-45.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.39
upper limit	-42.27
Variability estimate	Standard error of the mean
Dispersion value	1.81

Notes:

[42] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[43]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-29.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.43
upper limit	-26.28
Variability estimate	Standard error of the mean
Dispersion value	1.56

Notes:

[43] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[44]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-27.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.08
upper limit	-23.94
Variability estimate	Standard error of the mean
Dispersion value	1.81

Notes:

[44] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Total Cholesterol/High-density Lipoprotein Cholesterol Ratio at Week 12

End point title	Percent Change From Baseline in Total Cholesterol/High-density Lipoprotein Cholesterol Ratio at Week 12
End point description:	
Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	1.18 (± 1.39)	7.02 (± 1.67)	-10.03 (± 1.39)	-12.34 (± 1.68)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-38.45 (\pm 1.02)	-37.65 (\pm 1.21)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[45]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-39.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.97
upper limit	-36.3
Variability estimate	Standard error of the mean
Dispersion value	1.69

Notes:

[45] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[46]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-44.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.66
upper limit	-40.68
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[46] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[47]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-28.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.73
upper limit	-25.1
Variability estimate	Standard error of the mean
Dispersion value	1.68

Notes:

[47] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[48]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-25.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.31
upper limit	-21.31
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[48] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Weeks 10 and 12
End point description:	
Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.	
End point type	Secondary

End point timeframe:
Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	1.01 (\pm 1.69)	3.85 (\pm 1.77)	-13.39 (\pm 1.69)	-14.49 (\pm 1.79)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-48.12 (\pm 1.25)	-51.1 (\pm 1.29)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[49]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.12
upper limit	-45.12
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[49] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[50]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-54.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.12
upper limit	-50.78
Variability estimate	Standard error of the mean
Dispersion value	2.12

Notes:

[50] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[51]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-34.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.73
upper limit	-30.73
Variability estimate	Standard error of the mean
Dispersion value	2.03

Notes:

[51] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[52]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-36.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.81
upper limit	-32.42
Variability estimate	Standard error of the mean
Dispersion value	2.13

Notes:

[52] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12

End point title	Percent Change From Baseline in Apolipoprotein B/Apolipoprotein A1 Ratio at Week 12
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End point description:

Efficacy analyses were performed on the full analysis set. Least squares (LS) means are from a repeated measures linear effects model; missing values were not imputed.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
least squares mean (standard error)	1.12 (± 1.77)	4.51 (± 1.9)	-12.69 (± 1.77)	-14.29 (± 1.92)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
least squares mean (standard error)	-48.45 (± 1.31)	-48.26 (± 1.39)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[53]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.78
upper limit	-45.36
Variability estimate	Standard error of the mean
Dispersion value	2.14

Notes:

[53] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[54]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-52.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.28
upper limit	-48.26
Variability estimate	Standard error of the mean
Dispersion value	2.29

Notes:

[54] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[55]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-35.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.95
upper limit	-31.57
Variability estimate	Standard error of the mean
Dispersion value	2.13

Notes:

[55] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[56]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-33.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.48
upper limit	-29.45
Variability estimate	Standard error of the mean
Dispersion value	2.29

Notes:

[56] - The model includes treatment group, Baseline LDL-C level, scheduled visit and the interaction of treatment with scheduled visit. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Lipoprotein (a) at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Lipoprotein (a) at Weeks 10 and 12
End point description: Efficacy analyses were performed on the full analysis set.	
End point type	Secondary
End point timeframe: Baseline and Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	0.12 (-11.11 to 11.5)	0 (-11.82 to 8.33)	0 (-9.6 to 10.31)	-2.08 (-18.18 to 5.56)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-18.37 (-37.5 to 0)	-19.24 (-38.8 to -4.79)		

Statistical analyses

Statistical analysis title	Placebo Q2W v Evolocumab Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[57]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-18.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.28
upper limit	-11.68

Notes:

[57] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[58]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-19.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.2
upper limit	-15.28

Notes:

[58] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[59]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-18.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.39
upper limit	-12.35

Notes:

[59] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[60]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-17.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.23
upper limit	-11.08

Notes:

[60] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Lipoprotein (a) at Week 12

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 12
End point description:	
Efficacy analyses were performed on the full analysis set.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	0 (-8.51 to 17.5)	0 (-10.53 to 8.11)	0 (-9.09 to 12.5)	-2.05 (-17.19 to 8.33)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-20.41 (-39.53 to 0)	-17.82 (-38.46 to 0)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[61]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-20.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.76
upper limit	-13.06

Notes:

[61] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[62]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-17.82

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.51
upper limit	-11.12

Notes:

[62] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[63]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-20.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.13
upper limit	-12.69

Notes:

[63] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[64]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-15.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.39
upper limit	-7.14

Notes:

[64] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Triglycerides at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Triglycerides at Weeks 10 and 12
End point description:	
Efficacy analyses were performed on the full analysis set.	
End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-3.89 (-18.85 to 11.24)	4.89 (-12.71 to 31.65)	-1.46 (-15.03 to 18.41)	-3.97 (-17.65 to 10.38)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-9.16 (-24.19 to 11.03)	-15.71 (-28.2 to 6.4)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 ^[65]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-5.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.27
upper limit	2.73

Notes:

[65] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM

Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[66]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-20.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.98
upper limit	-10.2

Notes:

[66] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 ^[67]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-7.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.86
upper limit	1.45

Notes:

[67] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[68]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-11.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.19
upper limit	-2.27

Notes:

[68] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Triglycerides at Week 12

End point title	Percent Change From Baseline in Triglycerides at Week 12
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End point description:

Efficacy analyses were performed on the full analysis set.

End point type	Secondary
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End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-1.91 (-18.58 to 11.46)	2.01 (-16.62 to 33.83)	0 (-13.26 to 17.54)	-2.41 (-19.34 to 12.86)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-8.14 (-26.14 to 10.13)	-15.64 (-30.03 to 1.53)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 ^[69]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-6.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.41
upper limit	3.95

Notes:

[69] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[70]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-17.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.67
upper limit	-8.63

Notes:

[70] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027 ^[71]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-8.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.54
upper limit	1.26

Notes:

[71] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[72]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-13.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.69
upper limit	-4.77

Notes:

[72] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in Very Low-density Lipoprotein Cholesterol at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Very Low-density Lipoprotein Cholesterol at Weeks 10 and 12
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End point description:

Efficacy analyses were performed on the full analysis set.

End point type	Secondary
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End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-3.81 (-19.16 to 9.97)	4.22 (-13.6 to 27.91)	-2.69 (-16.54 to 16.67)	-3.33 (-20 to 9.52)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-8.4 (-25.43 to 10.91)	-16.17 (-28 to 5.52)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 ^[73]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-4.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	2.12

Notes:

[73] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[74]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-20.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.11
upper limit	-10.68

Notes:

[74] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082 ^[75]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-5.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.13
upper limit	2.71

Notes:

[75] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[76]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-12.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.14
upper limit	-3.54

Notes:

[76] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in Very Low-density Lipoprotein Cholesterol at Week 12

End point title	Percent Change From Baseline in Very Low-density Lipoprotein Cholesterol at Week 12
End point description:	
Efficacy analyses were performed on the full analysis set.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-1.58 (-20 to 10.53)	0 (-16.67 to 33.33)	-0.94 (-12.32 to 12.93)	-3.61 (-19.23 to 14.29)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	-9.52 (-26.83 to 10.34)	-16.33 (-30.73 to 2.51)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 ^[77]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-7.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.81
upper limit	2.92

Notes:

[77] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[78]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-16.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.64
upper limit	-7.02

Notes:

[78] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082 ^[79]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	-8.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.1
upper limit	0.94

Notes:

[79] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[80]
Method	Quade test
Parameter estimate	Median Treatment Dfference
Point estimate	-12.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.89
upper limit	-4.54

Notes:

[80] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Mean Percent Change From Baseline in High-density Lipoprotein Cholesterol at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in High-density Lipoprotein Cholesterol at Weeks 10 and 12
End point description:	
Efficacy analyses were performed on the full analysis set.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-1.64 (-8.41 to 5.03)	-4.67 (-10.63 to -0.57)	-0.92 (-10.11 to 7.29)	0 (-6.98 to 8.68)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	3.89 (-1.35 to 11.55)	3.81 (-2.56 to 11.86)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 ^[81]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.23
upper limit	8.84

Notes:

[81] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[82]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	8.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.53
upper limit	11.43

Notes:

[82] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 ^[83]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	4.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	8.78

Notes:

[83] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[84]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.77
upper limit	8.39

Notes:

[84] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percent Change From Baseline in High-density Lipoprotein Cholesterol at Week 12

End point title	Percent Change From Baseline in High-density Lipoprotein Cholesterol at Week 12
End point description:	
Efficacy analyses were performed on the full analysis set.	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)	Ezetimibe (QM)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	78	77	77
Units: percent change				
median (inter-quartile range (Q1-Q3))	-1.15 (-9.09 to 6.06)	-5.27 (-11.3 to 2.33)	-2.79 (-8.57 to 8.74)	-1.47 (-6.67 to 8.2)

End point values	Evolocumab Q2W	Evolocumab QM		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: percent change				
median (inter-quartile range (Q1-Q3))	4.76 (-2.86 to 12.82)	4.06 (-2.68 to 11.15)		

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 ^[85]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	5.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.67
upper limit	10.16

Notes:

[85] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 ^[86]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	9.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	5.32
upper limit	13.34

Notes:

[86] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Ezetimibe (Q2W)
Comparison groups	Ezetimibe (Q2W) v Evolocumab Q2W
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 ^[87]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	7.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.11
upper limit	12

Notes:

[87] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab QM vs Ezetimibe (QM)
Comparison groups	Ezetimibe (QM) v Evolocumab QM
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044 ^[88]
Method	Quade test
Parameter estimate	Median Treatment Difference
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.22
upper limit	8.84

Notes:

[88] - P-value obtained from Quade test adjusting for Baseline value. Median difference and 95% CI were obtained from McKean-Schrader algorithm. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug until 28 days after the last dose (12 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Placebo Q2W
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Reporting group description:

Participants received placebo subcutaneous injection once every 2 weeks (Q2W) and placebo tablets once a day for up to 12 weeks.

Reporting group title	Placebo QM
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Reporting group description:

Participants received placebo subcutaneous injection once every month (QM) and placebo tablets once a day for up to 12 weeks.

Reporting group title	Ezetimibe (Q2W)
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Reporting group description:

Participants received placebo subcutaneous injection once every 2 weeks and 10 mg ezetimibe orally once a day for up to 12 weeks.

Reporting group title	Ezetimibe (QM)
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Reporting group description:

Participants received placebo subcutaneous injection once a month and 10 mg ezetimibe orally once a day for up to 12 weeks.

Reporting group title	Evolocumab Q2W
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Reporting group description:

Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks and placebo tablets once a day for up to 12 weeks.

Reporting group title	Evolocumab QM
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Reporting group description:

Participants received 420 mg evolocumab by subcutaneous injection once a month and placebo tablets once a day for up to 12 weeks.

Serious adverse events	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and			

unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 78 (1.28%)	0 / 77 (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
Breast cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 76 (0.00%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Serious adverse events	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 77 (1.30%)	3 / 153 (1.96%)	1 / 153 (0.65%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 77 (0.00%)	1 / 153 (0.65%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 77 (0.00%)	0 / 153 (0.00%)	0 / 153 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 77 (1.30%)	0 / 153 (0.00%)	0 / 153 (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
Renal cancer			
subjects affected / exposed	0 / 77 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 77 (0.00%)	1 / 153 (0.65%)	0 / 153 (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
Gastrointestinal disorders			
Pancreatitis acute			
subjects affected / exposed	0 / 77 (0.00%)	0 / 153 (0.00%)	1 / 153 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 77 (0.00%)	1 / 153 (0.65%)	0 / 153 (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

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

Non-serious adverse events	Placebo Q2W	Placebo QM	Ezetimibe (Q2W)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 76 (11.84%)	4 / 78 (5.13%)	10 / 77 (12.99%)
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 76 (3.95%)	1 / 78 (1.28%)	4 / 77 (5.19%)
occurrences (all)	3	1	4
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 76 (6.58%)	1 / 78 (1.28%)	2 / 77 (2.60%)
occurrences (all)	6	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 76 (1.32%)	2 / 78 (2.56%)	4 / 77 (5.19%)
occurrences (all)	1	2	4

Non-serious adverse events	Ezetimibe (QM)	Evolocumab Q2W	Evolocumab QM
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 77 (5.19%)	12 / 153 (7.84%)	12 / 153 (7.84%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 77 (1.30%)	5 / 153 (3.27%)	5 / 153 (3.27%)
occurrences (all)	1	5	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 77 (1.30%)	4 / 153 (2.61%)	5 / 153 (3.27%)
occurrences (all)	1	4	5
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 77 (2.60%)	3 / 153 (1.96%)	3 / 153 (1.96%)
occurrences (all)	2	3	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2012	<ul style="list-style-type: none">- added testing for prior or existing HCV infection in high risk individuals and evaluation of viral load in those who showed evidence thereof- clarified that subjects with known sensitivity to the 'active substances or their excipients' were excluded- added urine pregnancy testing at day 1, week 4, and week 8 for women of childbearing potential
10 October 2012	<ul style="list-style-type: none">- added the MENDEL-2 study acronym and short title- added new evolocumab formulation and autoinjectors to allow administration of investigational product in the home-use setting- revised schedule of assessment and description of procedures in Section 7 to replace weeks 4 and 6 visits with home-use IP administration- added reporting requirements for product/device complaints- updated program status in evolocumab background section- provided instruction regarding missed ezetimibe doses- added subjects with a history of HCV infection to the HCV antibody testing and viral load monitoring, if positive- updated sections on collection and reporting of adverse events and serious adverse events, including adding device related adverse events, and the serious adverse event contingency form- moved change from baseline in VLDL-C at week 12 from tertiary to secondary endpoints- added transient ischemic attacks and non-coronary revascularization as exploratory endpoints
10 December 2012	<ul style="list-style-type: none">- added the LDL-C endpoint of mean percent change from baseline at weeks 10 and 12 as a co-primary endpoint- added the means of weeks 10 and 12 as co-secondary endpoints to all secondary endpoints- added alert threshold for elevated triglycerides- added publication references for primary result publications of phase 2 studies MENDEL and LAPLACE- introduced simplified terminology of QM dosing

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported