Clinical trial results:
A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Subjects With Heterozygous Familial Hypercholesterolemia

Summary

EudraCT number	2012-001365-32
Trial protocol	ES NL SE GB DE
Global end of trial date	19 December 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	31 July 2015

Trial information

Trial identification

Sponsor protocol code	20110117

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01763918
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	19 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 December 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 (SC) every other week (EOW)and once monthly (QM), compared with placebo, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in subjects with heterozygous familial hypercholesterolemia (HeFH).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 February 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	Canada: 55
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Netherlands: 50
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 15
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Australia: 14
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	South Africa: 41

Worldwide total number of subjects	331
EEA total number of subjects	166

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)	282
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Men and women 18 to 80 years old with a diagnosis of heterozygous familial hypercholesterolemia (HeFH) on stable doses of an approved statin with fasting low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL were eligible for this study. The first participant enrolled on 07 February 2013 and the last participant enrolled 03 September 2013.

Pre-assignment

Screening details:

Participants received subcutaneous placebo corresponding to the once monthly dose volume during a 6-week screening period. Those who completed the screening period and met final eligibility criteria were randomized 1:1:2:2 into 4 treatment groups. Randomization was stratified by LDL-C level (< 160 mg/dL vs ≥ 160 mg/dL) and ezetimibe use.

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) 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

Arm title	Placebo QM

Arm description:

Participants received placebo subcutaneous injection once every month (QM) 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

Arm title	Evolocumab Q2W

Arm description:

Participants received 140 mg evolocumab by subcutaneous injection once every 2 weeks for up to 12 weeks.

Arm type	Experimental

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

Dosage and administration details:
Administered by subcutaneous injection

Arm title	Evolocumab QM

Arm description:
Participants received 420 mg evolocumab by subcutaneous injection once a month for up to 12 weeks.

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

Dosage and administration details:
Administered by subcutaneous injection

Number of subjects in period 1	Placebo Q2W	Placebo QM	Evolocumab Q2W
Started	55	55	111
Received Treatment	54	55	110
Completed	49	54	101
Not completed	6	1	10
Consent withdrawn by subject	2	1	1
Sponsor Decision	4	-	9

Number of subjects in period 1	Evolocumab QM
Started	110
Received Treatment	110
Completed	108
Not completed	2
Consent withdrawn by subject	2
Sponsor Decision	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Participants received placebo subcutaneous injection once every 2 weeks (Q2W) for up to 12 weeks.	
Reporting group title	Placebo QM
Reporting group description:	
Participants received placebo subcutaneous injection once every month (QM) 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 for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month for up to 12 weeks.	

Reporting group values	Placebo Q2W	Placebo QM	Evolocumab Q2W
Number of subjects	55	55	111
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.1	46.8	52.3
standard deviation	± 14.1	± 12.1	± 12.6
Gender, Male/Female Units: participants			
Female	25	24	45
Male	30	31	66
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	4
Black or African American	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
White	51	49	100
Other	2	3	6
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	54	55	111
Stratification Factor: Low-Density Lipoprotein Cholesterol (LDL-C) Level Units: Subjects			
< 160 mg/dL	35	35	70
≥ 160 mg/dL	20	20	41
Baseline Ezetimibe Use			

Units: Subjects			
No	22	21	43
Yes	33	34	68
LDL-C Concentration			
Data are provided for the full analysis set (all randomized participants who received at least 1 dose of investigational product)			
Units: mg/dL			
arithmetic mean	151.1	151.5	161.4
standard deviation	± 36.5	± 42.5	± 51
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	175.4	175.4	187.4
standard deviation	± 43.9	± 45.9	± 56.7
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	114.3	110.3	119
standard deviation	± 29.8	± 21.7	± 30.7
Total cholesterol/HDL-C Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	4.695	4.844	5.159
standard deviation	± 1.905	± 1.435	± 2.031
Apolipoprotein B/Apolipoprotein A1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	0.815	0.851	0.888
standard deviation	± 0.264	± 0.249	± 0.322
Lipoprotein(a) Concentration			
Data are provided for the full analysis set			
Units: nmol/L			
median	44	87	77.5
inter-quartile range (Q1-Q3)	24 to 105	36 to 219	29 to 205.5
Triglyceride Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	95.8	102	118.5
inter-quartile range (Q1-Q3)	74.5 to 143	79 to 151	86.5 to 160.5
Very Low-Density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	23.1	23.9	25.9
standard deviation	± 10.7	± 10.5	± 11.8
HDL-C Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	53.2	49.1	50.4
standard deviation	± 16.5	± 12.7	± 16.1

Reporting group values	Evolocumab QM	Total	
Number of subjects	110	331	
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	51.9		
standard deviation	± 12	-	
Gender, Male/Female Units: participants			
Female	46	140	
Male	64	191	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	8	16	
Black or African American	1	3	
Native Hawaiian or Other Pacific Islander	0	0	
White	98	298	
Other	3	14	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	2	
Not Hispanic or Latino	109	329	
Stratification Factor: Low-Density Lipoprotein Cholesterol (LDL-C) Level Units: Subjects			
< 160 mg/dL	70	210	
≥ 160 mg/dL	40	121	
Baseline Ezetimibe Use Units: Subjects			
No	43	129	
Yes	67	202	
LDL-C Concentration			
Data are provided for the full analysis set (all randomized participants who received at least 1 dose of investigational product)			
Units: mg/dL			
arithmetic mean	153.6		
standard deviation	± 43.3	-	
Non-High-Density Lipoprotein Cholesterol (non-HDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	178.5		
standard deviation	± 45.8	-	
Apolipoprotein B Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	114.9		
standard deviation	± 25.5	-	

Total cholesterol/HDL-C Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	4.842		
standard deviation	± 1.801	-	
Apolipoprotein B/Apolipoprotein A1 Ratio			
Data are provided for the full analysis set			
Units: ratio			
arithmetic mean	0.85		
standard deviation	± 0.331	-	
Lipoprotein(a) Concentration			
Data are provided for the full analysis set			
Units: nmol/L			
median	61		
inter-quartile range (Q1-Q3)	17 to 194	-	
Triglyceride Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
median	112.5		
inter-quartile range (Q1-Q3)	84.5 to 156.5	-	
Very Low-Density Lipoprotein Cholesterol (VLDL-C) Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	24.9		
standard deviation	± 11.7	-	
HDL-C Concentration			
Data are provided for the full analysis set			
Units: mg/dL			
arithmetic mean	51.9		
standard deviation	± 16	-	

End points

End points reporting groups	
Reporting group title	Placebo Q2W
Reporting group description:	
Participants received placebo subcutaneous injection once every 2 weeks (Q2W) for up to 12 weeks.	
Reporting group title	Placebo QM
Reporting group description:	
Participants received placebo subcutaneous injection once every month (QM) 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 for up to 12 weeks.	
Reporting group title	Evolocumab QM
Reporting group description:	
Participants received 420 mg evolocumab by subcutaneous injection once a month for up to 12 weeks.	

Primary: Percent Change From Baseline in LDL-C at Week 12	
End point title	Percent Change From Baseline in LDL-C at Week 12
End point description:	
Calculated LDL-C was determined based on the Friedewald equation.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-2.02 (± 2.49)	5.53 (± 3.25)	-61.25 (± 1.77)	-55.74 (± 2.25)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Statistical analysis description:	
Within each dose frequency, the null hypothesis was that there was no mean difference in the percent change from baseline at week 12 or 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

Number of subjects included in analysis	164
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	-59.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.11
upper limit	-53.35
Variability estimate	Standard error of the mean
Dispersion value	2.98

Notes:

[1] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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

Statistical analysis description:

Within each dose frequency, the null hypothesis was that there was no mean difference in the percent change from baseline at week 12 or 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	165
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	-61.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69
upper limit	-53.55
Variability estimate	Standard error of the mean
Dispersion value	3.91

Notes:

[2] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 LDL-C at Weeks 10 and 12

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

End point description:

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

End point type	Primary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-1.08 (± 2.41)	2.3 (± 2.41)	-61.23 (± 1.71)	-63.25 (± 1.7)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W

Statistical analysis description:

Within each dose frequency, the null hypothesis was that there was no mean difference in the percent change from baseline at week 12 or 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
Number of subjects included in analysis	164
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	-60.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.83
upper limit	-54.46
Variability estimate	Standard error of the mean
Dispersion value	2.88

Notes:

[3] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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

Statistical analysis description:

Within each dose frequency, the null hypothesis was that there was no mean difference in the percent change from baseline at week 12 or 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	165
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	-65.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.27
upper limit	-59.83
Variability estimate	Standard error of the mean
Dispersion value	2.9

Notes:

[4] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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
End point description:	
Calculated LDL-C was determined based on the Friedewald equation.	
End point type	Secondary
End point timeframe:	
Baseline and Weeks 10 and 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: mg/dL				
least squares mean (standard error)	-6.5 (± 4.2)	-1.3 (± 4.1)	-101.7 (± 3)	-98.8 (± 2.9)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-95.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-105.1
upper limit	-85.2
Variability estimate	Standard error of the mean
Dispersion value	5

Notes:

[5] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-97.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-107.1
upper limit	-87.7
Variability estimate	Standard error of the mean
Dispersion value	4.9

Notes:

[6] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: mg/dL				
least squares mean (standard error)	-8.5 (± 4.2)	4.1 (± 5.2)	-101.3 (± 3)	-87.2 (± 3.6)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-92.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-102.9
upper limit	-82.8
Variability estimate	Standard error of the mean
Dispersion value	5.1

Notes:

[7] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-91.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-103.8
upper limit	-78.9
Variability estimate	Standard error of the mean
Dispersion value	6.3

Notes:

[8] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 with LDL-C < 70 mg/dL (1.8 mmol/L) at Weeks 10 and 12

End point title	Mean Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Weeks 10 and 12

End point description:

Mean low density lipoprotein-cholesterol response (low density lipoprotein-cholesterol < 70 mg/dL [1.8 mmol/L])

End point type	Secondary

End point timeframe:

Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percentage of participants				
number (confidence interval 95%)	1.9 (0.3 to 9.9)	1.9 (0.3 to 9.8)	67 (57.7 to 75.1)	80.4 (71.9 to 86.8)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	78.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	66.9
upper limit	85.1

Notes:

[9] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and ezetimibe use. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	65.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	52.8
upper limit	73.4

Notes:

[10] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and ezetimibe use. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Secondary: Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at

Week 12	
End point title	Percentage of Participants with LDL-C < 70 mg/dL (1.8 mmol/L) at Week 12
End point description:	
Low density lipoprotein-cholesterol response (low density lipoprotein-cholesterol < 70 mg/dL [1.8 mmol/L]).	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percentage of participants				
number (confidence interval 95%)	2 (0.3 to 10.3)	2.2 (0.4 to 11.3)	68.3 (58.8 to 76.4)	63.1 (53.5 to 71.8)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [11]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	60.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	47.6
upper limit	69.8

Notes:

[11] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and ezetimibe use. Multiplicity adjusted p-value is significant if less than the familywise error rate of 0.05.

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Treatment Difference
Point estimate	66.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	53.7
upper limit	74.6

Notes:

[12] - Cochran-Mantel Haenszel test stratified by baseline LDL-C and ezetimibe use. 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 (non-HDL-C) at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	0.21 (± 2.29)	2.72 (± 2.21)	-55.79 (± 1.63)	-57.28 (± 1.56)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.41
upper limit	-50.59
Variability estimate	Standard error of the mean
Dispersion value	2.74

Notes:

[13] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-60.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.24
upper limit	-54.77
Variability estimate	Standard error of the mean
Dispersion value	2.65

Notes:

[14] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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-HDL-C at Week 12

End point title	Percent Change From Baseline in non-HDL-C at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-1.39 (± 2.4)	5.29 (± 2.94)	-56.19 (± 1.71)	-49.67 (± 2.04)

Statistical analyses

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

Number of subjects included in analysis	164
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	-54.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.47
upper limit	-49.12
Variability estimate	Standard error of the mean
Dispersion value	2.87

Notes:

[15] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-54.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.95
upper limit	-47.96
Variability estimate	Standard error of the mean
Dispersion value	3.54

Notes:

[16] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-0.19 (± 2.1)	2.21 (± 1.97)	-49.58 (± 1.48)	-52.76 (± 1.36)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [17]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.32
upper limit	-44.46
Variability estimate	Standard error of the mean
Dispersion value	2.5

Notes:

[17] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [18]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-54.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.58
upper limit	-50.38
Variability estimate	Standard error of the mean
Dispersion value	2.33

Notes:

[18] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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:	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-0.67 (± 2.32)	4.6 (± 2.7)	-49.75 (± 1.63)	-44.81 (± 1.8)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [19]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.55
upper limit	-43.63
Variability estimate	Standard error of the mean
Dispersion value	2.76

Notes:

[19] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [20]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.41

Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.73
upper limit	-43.1
Variability estimate	Standard error of the mean
Dispersion value	3.19

Notes:

[20] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 the Total Cholesterol/HDL-C Ratio at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in the Total Cholesterol/HDL-C Ratio at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	0.86 (± 2.05)	4.14 (± 2.13)	-45.74 (± 1.45)	-45.02 (± 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	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [21]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-46.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.43
upper limit	-41.76
Variability estimate	Standard error of the mean
Dispersion value	2.45

Notes:

[21] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [22]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-49.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.21
upper limit	-44.11
Variability estimate	Standard error of the mean
Dispersion value	2.56

Notes:

[22] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 the Total Cholesterol/HDL-C Ratio at Week 12

End point title	Percent Change From Baseline in the Total Cholesterol/HDL-C Ratio at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	0.12 (± 2.19)	7.11 (± 3.13)	-45.95 (± 1.56)	-38.32 (± 2.15)

Statistical analyses

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

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-46.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51.27
upper limit	-40.88
Variability estimate	Standard error of the mean
Dispersion value	2.63

Notes:

[23] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	Repeated measures linear effects model
Parameter estimate	LS Mean Treatment Difference
Point estimate	-45.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.86
upper limit	-37.98
Variability estimate	Standard error of the mean
Dispersion value	3.77

Notes:

[24] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	0.78 (± 2.21)	1.65 (± 2.35)	-52.39 (± 1.56)	-53.91 (± 1.6)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-53.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.35
upper limit	-47.99
Variability estimate	Standard error of the mean
Dispersion value	2.62

Notes:

[25] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-55.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-61.08
upper limit	-50.05
Variability estimate	Standard error of the mean
Dispersion value	2.79

Notes:

[26] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	1.54 (± 2.49)	4.23 (± 3.66)	-52.74 (± 1.75)	-45.31 (± 2.42)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-54.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.16
upper limit	-48.41
Variability estimate	Standard error of the mean
Dispersion value	2.97

Notes:

[27] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-49.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.14
upper limit	-40.96
Variability estimate	Standard error of the mean
Dispersion value	4.35

Notes:

[28] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	7.34 (± 2.97)	5.35 (± 2.95)	-24.03 (± 2.09)	-25.65 (± 2.07)

Statistical analyses

Statistical analysis title	Evolocumab QM vs Placebo QM
Comparison groups	Placebo QM v Evolocumab QM
Number of subjects included in analysis	165
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	-31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.91
upper limit	-24.09
Variability estimate	Standard error of the mean
Dispersion value	3.5

Notes:

[29] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-31.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38.33
upper limit	-24.41
Variability estimate	Standard error of the mean
Dispersion value	3.52

Notes:

[30] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 Lipoprotein (a) at Week 12

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	8.68 (± 3.27)	6.69 (± 3.16)	-22.89 (± 2.31)	-21.55 (± 2.17)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-31.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.28
upper limit	-23.87
Variability estimate	Standard error of the mean
Dispersion value	3.9

Notes:

[31] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-28.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.61
upper limit	-20.88
Variability estimate	Standard error of the mean
Dispersion value	3.73

Notes:

[32] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 Triglycerides at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Triglycerides at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	9.09 (± 3.02)	7.49 (± 3.26)	-13.27 (± 2.14)	-9.25 (± 2.27)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-22.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.48
upper limit	-15.24
Variability estimate	Standard error of the mean
Dispersion value	3.6

Notes:

[33] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-16.74

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.43
upper limit	-9.05
Variability estimate	Standard error of the mean
Dispersion value	3.89

Notes:

[34] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 Triglycerides at Week 12

End point title	Percent Change From Baseline in Triglycerides at Week 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	3.5 (± 3.51)	6.43 (± 4.15)	-16.09 (± 2.49)	-5.13 (± 2.84)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-19.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.92
upper limit	-11.26
Variability estimate	Standard error of the mean
Dispersion value	4.22

Notes:

[35] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-11.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.38
upper limit	-1.74
Variability estimate	Standard error of the mean
Dispersion value	4.97

Notes:

[36] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 HDL-C at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in HDL-C at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-0.45 (± 1.7)	-2.86 (± 1.84)	7.93 (± 1.2)	6.62 (± 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	164
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	8.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.36
upper limit	12.4
Variability estimate	Standard error of the mean
Dispersion value	2.04

Notes:

[37] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	9.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.1
upper limit	13.85
Variability estimate	Standard error of the mean
Dispersion value	2.21

Notes:

[38] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 HDL-C at Week 12

End point title	Percent Change From Baseline in HDL-C at Week 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	-1.15 (± 1.91)	-3.73 (± 2.35)	8.05 (± 1.35)	5.35 (± 1.62)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.66
upper limit	13.74
Variability estimate	Standard error of the mean
Dispersion value	2.3

Notes:

[39] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	9.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.48
upper limit	1466
Variability estimate	Standard error of the mean
Dispersion value	2.83

Notes:

[40] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Weeks 10 and 12

End point title	Mean Percent Change From Baseline in Very Low-Density Lipoprotein Cholesterol (VLDL-C) at Weeks 10 and 12

End point description:

End point type	Secondary

End point timeframe:

Baseline and Weeks 10 and 12

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	8.66 (± 2.9)	6.34 (± 3.27)	-13.97 (± 2.06)	-9.2 (± 2.27)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-22.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.46
upper limit	-15.81
Variability estimate	Standard error of the mean
Dispersion value	3.46

Notes:

[41] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-15.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.25
upper limit	-7.84
Variability estimate	Standard error of the mean
Dispersion value	3.9

Notes:

[42] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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 VLDL-C at Week 12

End point title	Percent Change From Baseline in VLDL-C at Week 12
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Placebo Q2W	Placebo QM	Evolocumab Q2W	Evolocumab QM
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	54	55	110	110
Units: percent change				
least squares mean (standard error)	3.73 (± 3.5)	4.1 (± 4.17)	-17.25 (± 2.48)	-5.06 (± 2.84)

Statistical analyses

Statistical analysis title	Evolocumab Q2W vs Placebo Q2W
Comparison groups	Placebo Q2W v Evolocumab Q2W
Number of subjects included in analysis	164
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	-20.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.29
upper limit	-12.66
Variability estimate	Standard error of the mean
Dispersion value	4.21

Notes:

[43] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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	165
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	-9.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.01
upper limit	0.68
Variability estimate	Standard error of the mean
Dispersion value	4.98

Notes:

[44] - The model includes treatment group, baseline LDL-C and ezetimibe use, 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.

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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

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	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.	

Serious adverse events	Placebo Q2W	Placebo QM	Evolocumab Q2W
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 54 (3.70%)	3 / 55 (5.45%)	3 / 110 (2.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 110 (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
Colonoscopy abnormal			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 110 (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
Endoscopy gastrointestinal abnormal			

subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 110 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 110 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 110 (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			
Inguinal hernia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 110 (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
Pancreatitis acute			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 110 (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			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 110 (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
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 110 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 110 (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

Serious adverse events	Evolocumab QM		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 110 (3.64%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colonoscopy abnormal			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endoscopy gastrointestinal abnormal			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo Q2W	Placebo QM	Evolocumab Q2W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 54 (9.26%)	10 / 55 (18.18%)	17 / 110 (15.45%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	0 / 110 (0.00%)
occurrences (all)	1	3	0
Headache			
subjects affected / exposed	1 / 54 (1.85%)	3 / 55 (5.45%)	4 / 110 (3.64%)
occurrences (all)	2	4	10
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 55 (1.82%)	7 / 110 (6.36%)
occurrences (all)	1	1	8
Back pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	2 / 110 (1.82%)
occurrences (all)	0	1	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	3 / 55 (5.45%)	8 / 110 (7.27%)
occurrences (all)	2	3	8

Non-serious adverse events	Evolocumab QM		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 110 (21.82%)		

Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	 4 / 110 (3.64%) 4 5 / 110 (4.55%) 6		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 1 / 110 (0.91%) 1 6 / 110 (5.45%) 6		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 11 / 110 (10.00%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2012	- added testing for prior or existing HCV infection in high risk individuals and evaluation of viral load in those who show evidence thereof - clarified that subjects with known sensitivity to the "active substances or the excipients" were excluded - added urine pregnancy testing at day 1, week 4, and week 8 for women of childbearing potential - implemented minor error corrections
10 October 2012	- added the RUTHERFORD-2 study acronym and short title - added new evolocumab formulation and autoinjectors to allow administration of investigational product in a 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 - 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 - made other minor clarifications and error corrections
10 December 2012	- 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 - made other minor clarifications and error corrections

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported