



Clinical trial results:

A Randomized, Double-Blind, Double-Dummy, Active-Controlled Study to Evaluate the Efficacy and Safety of REGN727/SAR236553 in Patients with Primary Hypercholesterolemia Who are Intolerant to Statins

Summary

EudraCT number	2012-001221-27
Trial protocol	NO IT GB AT
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	27 June 2020
First version publication date	07 August 2015
Version creation reason	• Correction of full data set Minor updates

Trial information

Trial identification

Sponsor protocol code	R727-CL-1119
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01709513
WHO universal trial number (UTN)	-
Other trial identifiers	Study Name: ODYSSEY ALTERNATIVE

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, United States, 10591
Public contact	Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.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	Interim
Date of interim/final analysis	18 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Subjects entered 24 weeks double blind treatment period. The main objective was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab in comparison with ezetimibe 10 mg orally once daily (QD) after 24 weeks in subjects with primary hypercholesterolemia (heterozygous familial hypercholesterolemia [heFH] and non-familial hypercholesterolemia [FH]) who were intolerant to statins. After completion of double blind treatment period subjects entered open label treatment period wherein all subjects received alirocumab.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy:

Lipid modifying therapies (LMT): bile acid-binding sequestrants such as cholestyramine, colestipol, and colesevelam; nicotinic acid; fenofibrate, and omega-3 fatty acids and excluded ezetimibe, statins, red yeast rice, and fibrates other than fenofibrate.

Evidence for comparator: -

Actual start date of recruitment	26 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 6
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	United States: 214
Worldwide total number of subjects	314
EEA total number of subjects	50

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)	170
From 65 to 84 years	142
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 67 sites in 8 countries. Overall, 519 subjects were screened between 28 September 2012 and 11 Aug 2013, 158 of whom were screen failures. Screen failures were mainly due to exclusion criteria met. After screening, 361 subjects entered into single blind placebo run-in period. 314 subjects were randomized.

Pre-assignment

Screening details:

Randomization was stratified according to prior history of myocardial infarction or ischemic stroke. Assignment to treatment arms was done centrally in a 2:2:1 (alirocumab:ezetimibe:atorvastatin) ratio. Endpoints were not reported for statin arm as the purpose of statin arm was only to assess the statin tolerance of population.

Period 1

Period 1 title	Double-Blind Treatment Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Atorvastatin

Arm description:

Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT.

Arm type	Statin rechallenge arm
Investigational medicinal product name	Atorvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Atorvastatin over-encapsulated tablets.

Investigational medicinal product name	Placebo (for alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo (for alirocumab) administered as a subcutaneous (SC) injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.

Arm title	Ezetimibe
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Arm description:

Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT.

Arm type	Active comparator
Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	Zetia
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details: Ezetimibe over--encapsulated tablet.	
Investigational medicinal product name	Placebo (for alirocumab)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Placebo (for alirocumab) administered as a SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.	
Arm title	Alirocumab 75 mg/up to 150 mg
Arm description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL--C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk.	
Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	REGN727/SAR236553
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Alirocumab administered as a SC injection of 1 mL into the abdomen, thigh, or outer area of the upper arm.	
Investigational medicinal product name	Placebo (for atorvastatin/ezetimibe)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Placebo matched to atorvastatin/ezetimibe over--encapsulated tablet.	

Number of subjects in period 1	Atorvastatin	Ezetimibe	Alirocumab 75 mg/up to 150 mg
Started	63	125	126
Treated	63	124	126
Completed	42	82	96
Not completed	21	43	30
Randomized but not treated	-	1	-
Adverse event	16	31	23
Unspecified	3	11	7
poor compliance to protocol	2	-	-

Baseline characteristics

Reporting groups

Reporting group title	Atorvastatin
Reporting group description: Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT.	
Reporting group title	Ezetimibe
Reporting group description: Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT.	
Reporting group title	Alirocumab 75 mg/up to 150 mg
Reporting group description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk.	

Reporting group values	Atorvastatin	Ezetimibe	Alirocumab 75 mg/up to 150 mg
Number of subjects	63	125	126
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	63.4 ± 9.5	62.8 ± 10.1	64.1 ± 9
Gender categorical Units: Subjects Female Male	28 35	58 67	56 70
Low Density Lipoprotein Cholesterol (LDL-C) in mg/dL Calculated LDL-C values were obtained using Friedewald formula. Units: mg/dL arithmetic mean standard deviation	187.3 ± 59.5	193.5 ± 70.9	191.1 ± 72.7
LDL-C in mmol/L Calculated LDL-C values were obtained using Friedewald formula. Units: mmol/L arithmetic mean standard deviation	4.85 ± 1.54	5.011 ± 1.837	4.951 ± 1.883

Reporting group values	Total		
Number of subjects	314		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean			
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standard deviation	-		
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Gender categorical			
Units: Subjects			
Female	142		
Male	172		
Low Density Lipoprotein Cholesterol (LDL-C) in mg/dL			
Calculated LDL-C values were obtained using Friedewald formula.			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
LDL-C in mmol/L			
Calculated LDL-C values were obtained using Friedewald formula.			
Units: mmol/L			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Atorvastatin
Reporting group description: Atorvastatin 20 mg QD for 24 weeks and placebo (for alirocumab) every two weeks (Q2W) for 24 weeks added to stable LMT.	
Reporting group title	Ezetimibe
Reporting group description: Ezetimibe 10 mg QD for 24 weeks and placebo for alirocumab Q2W for 24 weeks added to stable LMT.	
Reporting group title	Alirocumab 75 mg/up to 150 mg
Reporting group description: Alirocumab 75 mg Q2W for 24 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk.	

Primary: Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-Treat (ITT) Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - Intent-to-Treat (ITT) Analysis ^[1]
End point description: Calculated LDL-C values were obtained from Friedewald formula. Adjusted Least-squares (LS) means and standard errors at Week 24 were obtained from a mixed-effect model with repeated measures (MMRM) to account for missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were used in the model (ITT analysis). ITT population: all randomized subjects with one baseline and at least one post-baseline calculated LDL-C value on- or off-treatment.	
End point type	Primary
End point timeframe: From Baseline to Week 24	
Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.	

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-14.6 ($\pm$ 2.2)	-45 ($\pm$ 2.2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
Statistical analysis description: Alirocumab group was compared to the corresponding active control group using an appropriate contrast statement.	

Comparison groups	Alirocumab 75 mg/up to 150 mg v Ezetimibe
Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-30.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.6
upper limit	-24.2

Notes:

[2] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 24 - On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 24 - On-Treatment Analysis ^[3]
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End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis) . Modified ITT (mITT) population: all randomized and treated subjects with one baseline and at least one post-baseline calculated LDL-C value on-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percent change				
least squares mean (standard error)	-17.1 (± 2)	-52.2 (± 2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

A hierarchical testing procedure was used to control type I error and handle multiple secondary endpoint analyses. Testing was then performed sequentially in the order the endpoints are reported. The hierarchical testing sequence continued only when previous endpoint was statistically significant at 5% level.

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.7
upper limit	-29.5

Notes:

[4] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 12 - ITT Analysis ^[5]
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End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment (ITT analysis). ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-15.6 (± 2)	-47 (± 1.9)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
Statistical analysis description:	
Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).	
Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[6]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-31.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.9
upper limit	-26.1

Notes:

[6] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Calculated LDL-C at Week 12 - On-Treatment Analysis

End point title	Percent Change From Baseline in Calculated LDL-C at Week 12 - On-Treatment Analysis ^[7]
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End point description:

Calculated LDL-C values were obtained from Friedewald formula. Adjusted LS means and standard errors at Week 12 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first) (on-treatment analysis). mITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percent change				
least squares mean (standard error)	-18 (± 1.8)	-51.2 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-33.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-38
upper limit	-28.2

Notes:

[8] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Apolipoprotein (Apo) B at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Apolipoprotein (Apo) B at Week 24 - ITT Analysis ^[9]
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End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline Apo B value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	122		
Units: percent change				
least squares mean (standard error)	-11.2 (± 1.7)	-36.3 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[10]
Method	Mixed models analysis
Parameter estimate	LS Mean difference
Point estimate	-25.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.8
upper limit	-20.4

Notes:

[10] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Apo B at Week 24 - On-Treatment Analysis

End point title	Percent Change From Baseline in Apo B at Week 24 - On-Treatment Analysis ^[11]
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End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline Apo B value on-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	109		
Units: percent change				
least squares mean (standard error)	-14.4 (± 1.4)	-42.6 (± 1.3)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[12]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-28.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.1
upper limit	-24.4

Notes:

[12] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 24 - ITT Analysis ^[13]
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End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline non-HDL-C value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-14.6 (± 1.7)	-40.2 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75 mg/up to 150 mg v Ezetimibe
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Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[14]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.4
upper limit	-20.8

Notes:

[14] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Non-HDL-C at Week 24 - On-Treatment Analysis

End point title	Percent Change From Baseline in Non-HDL-C at Week 24 - On-Treatment Analysis ^[15]
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End point description:

Adjusted LS means and standard errors at Week 24 were obtained from MMRM model including available post-baseline on-treatment data from Week 4 to Week 24 (i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first). Subjects analyzed: subjects of the mITT population with one baseline and at least one post-baseline non-HDL-C value on-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percent change				
least squares mean (standard error)	-17.1 ($\pm$ 1.5)	-46.9 ($\pm$ 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[16]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-29.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.9
upper limit	-25.8

Notes:

[16] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Week 24 - ITT Analysis ^[17]
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End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline total-C value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-10.9 (± 1.4)	-31.8 (± 1.4)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[18]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-20.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.7
upper limit	-17

Notes:

[18] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Apo B at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Apo B at Week 12 - ITT Analysis ^[19]
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo B ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	122		
Units: percent change				
least squares mean (standard error)	-11.6 ($\pm$ 1.5)	-36.1 ($\pm$ 1.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
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Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
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Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[20]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.7
upper limit	-20.4

Notes:

[20] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Non-HDL-C at Week 12 - ITT Analysis ^[21]
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Non-HDL-C ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-15.8 (± 1.5)	-41.5 (± 1.5)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[22]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-25.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.9
upper limit	-21.5

Notes:

[22] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Total-C at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Total-C at Week 12 - ITT Analysis ^[23]
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Total-C ITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-11.6 ($\pm$ 1.2)	-32.7 ($\pm$ 1.2)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Alirocumab 75 mg/up to 150 mg v Ezetimibe
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[24]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.5
upper limit	-17.7

Notes:

[24] - Threshold for significance ≤ 0.05 .

Secondary: Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis

End point title	Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - ITT Analysis ^[25]
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End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were included in the imputation model (ITT analysis). ITT population.

End point type	Secondary
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End point timeframe:

Up to Week 24

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percentage of subjects				
number (not applicable)	4.4	41.9		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	55.2

Notes:

[26] - Threshold for significance ≤ 0.05 .

Secondary: Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis

End point title	Percentage of Very High CV Risk Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) or Moderate or High CV Risk Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 - On-Treatment Analysis ^[27]
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End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first (on-treatment analysis). mITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 24

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percentage of subjects				
number (not applicable)	5.6	51.2		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a Logistic regression model.

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[28]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	24.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.6
upper limit	71.9

Notes:

[28] - Threshold for significance ≤ 0.05 .

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT Analysis

End point title	Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - ITT Analysis ^[29]
-----------------	--

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model for handling of missing data. All available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment were included in the imputation model (ITT analysis). ITT population.

End point type	Secondary
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End point timeframe:

Up to Week 24

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percentage of subjects				
number (not applicable)	0.8	32.5		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a last observation carried forward (LOCF) approach followed by exact conditional logistic regression model.

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[30]
Method	Regression, Exact Conditional Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	71.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.1
upper limit	3022.1

Notes:

[30] - Threshold for significance ≤ 0.05 .

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis

End point title	Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 - On-Treatment Analysis ^[31]
-----------------	---

End point description:

Adjusted percentages at Week 24 were obtained from a multiple imputation approach model including available post-baseline on-treatment data from Week 4 to Week 24 i.e. up to 21 days after last injection or 3 days after the last capsule, whichever came first (on-treatment analysis). mITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

Up to Week 24

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percentage of subjects				
number (not applicable)	0.8	39		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a LOCF approach followed by exact conditional logistic regression model.

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[32]
Method	Regression, Exact Conditional Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	109.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	16.5
upper limit	4759.3

Notes:

[32] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Lipoprotein (a) at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 24 - ITT Analysis ^[33]
-----------------	---

End point description:

Adjusted means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
arithmetic mean (standard error)	-7.3 ($\pm$ 2.5)	-25.9 ($\pm$ 2.4)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant). Statistical analysis used a multiple imputation approach followed by a robust regression model.

Comparison groups	Alirocumab 75 mg/up to 150 mg v Ezetimibe
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[34]
Method	Regression, Robust
Parameter estimate	Adjusted Mean Difference
Point estimate	-18.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-11.8

Notes:

[34] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in HDL-C at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in HDL-C at Week 24 - ITT Analysis ^[35]
-----------------	---

End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population with one baseline and at least one post-baseline HDL-C value on- or off-treatment.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline to Week 24

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	6.8 (± 1.7)	7.7 (± 1.7)		

Statistical analyses

Statistical analysis title	Alirocumab 75 mg/up to 150 mg vs Ezetimibe
----------------------------	--

Statistical analysis description:

Testing according to the hierarchical testing procedure (previous endpoints were statistically significant).

Comparison groups	Ezetimibe v Alirocumab 75 mg/up to 150 mg
-------------------	---

Number of subjects included in analysis	248
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6997 ^[36]
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	5.6

Notes:

[36] - Threshold for significance ≤ 0.05 .

Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 24 - ITT Analysis ^[37]
-----------------	---

End point description:

Adjusted LS means and standard errors at Week 24 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed: subjects of the ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-3.6 ($\pm$ 2.8)	-9.3 ($\pm$ 2.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apo A-1 at Week 24 - ITT Analysis

End point title	Percent Change From Baseline in Apo A-1 at Week 24 - ITT Analysis ^[38]
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End point description:

Adjusted LS means and standard errors at Week 24 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Subjects analyzed:

subjects of the ITT population with one baseline and at least one post-baseline Apo A-1 value on- or off-treatment.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	122		
Units: percent change				
least squares mean (standard error)	2.9 ($\pm$ 1.2)	4.8 ($\pm$ 1.2)		

Statistical analyses

No statistical analyses for this end point

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

End point title	Percent Change From Baseline in Lipoprotein (a) at Week 12 - ITT Analysis ^[39]
-----------------	---

End point description:

Adjusted means and standard errors at Week 12 from from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Lipoprotein (a) ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 12

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
arithmetic mean (standard error)	-4.5 ($\pm$ 2.3)	-21.7 ($\pm$ 2.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in HDL-C at Week 12 - ITT Analysis ^[40]
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. HDL-C ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	7.6 (± 1.2)	9 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Fasting Triglycerides at Week 12 - ITT Analysis ^[41]
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End point description:

Adjusted LS means and standard errors at Week 12 from a multiple imputation approach model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Fasting triglycerides ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	126		
Units: percent change				
least squares mean (standard error)	-9.4 (± 2.6)	-8 (± 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis

End point title	Percent Change From Baseline in Apo A-1 at Week 12 - ITT Analysis ^[42]
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End point description:

Adjusted LS means and standard errors at Week 12 from MMRM model including all available post-baseline data from Week 4 to Week 24 regardless of status on- or off-treatment. Apo A-1 ITT population.

End point type	Secondary
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End point timeframe:

From Baseline to Week 24

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The main objective of the study was to compare alirocumab with ezetimibe in statin-intolerant subjects. The purpose of statin arm was only to assess whether the population was truly statin intolerant.

End point values	Ezetimibe	Alirocumab 75 mg/up to 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	122		
Units: percent change				
least squares mean (standard error)	3.9 (± 1)	5.5 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Skeletal Muscle-related Adverse Event (AE)

End point title	Percentage of Subjects Who Experienced Skeletal Muscle-related Adverse Event (AE)
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End point description:

Skeletal muscle-related adverse events were a predefined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness and muscle fatigue. Events that developed during treatment emergent adverse events period (the time from the first double-blind study treatment [injection or capsules, whichever came first] up to the day of the last double-blind injection + 70 days) are reported.

End point type	Secondary
End point timeframe:	
From Baseline up to Week 24	

End point values	Atorvastatin	Ezetimibe	Alirocumab 75 mg/up to 150 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	124	126	
Units: Percentage of Subjects				
number (not applicable)				
Any skeletal muscle-related AE	46.0	41.1	32.5	
Leading to treatment discontinuation	22.2	20.2	15.9	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to Week 24

Adverse event reporting additional description:

Treatment emergent adverse events that developed during treatment emergent adverse events period (the time from the first double-blind study treatment [injection or capsules, whichever came first] up to the day of the last double-blind injection + 70 days) are reported.

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	Atorvastatin
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Reporting group description:

Atorvastatin 20 mg QD for 24 weeks and placebo 'for aliocumab' Q2W for 22 weeks added to stable LMT.

Reporting group title	Alirocumab 75 mg/up to 150 mg
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Reporting group description:

Alirocumab 75 mg Q2W for 22 weeks and placebo for atorvastatin/ezetimibe QD for 24 weeks added to stable LMT. Alirocumab dose up-titrated to 150 mg Q2W from Week 12 when LDL-C levels ≥ 70 mg/dL (1.81 mmol/L) or ≥ 100 mg/dL (2.59 mmol/L) at Week 8, based on cardiovascular risk.

Reporting group title	Ezetimibe
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Reporting group description:

Ezetimibe 10 mg QD for 24 weeks and placebo for aliocumab Q2W for 22 weeks added to stable LMT.

Serious adverse events	Atorvastatin	Alirocumab 75 mg/up to 150 mg	Ezetimibe
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 63 (11.11%)	12 / 126 (9.52%)	10 / 124 (8.06%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Ovarian epithelial cancer			

subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Malignant melanoma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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			
Hip fracture			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Traumatic arthritis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Post procedural haematoma			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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

Atrial fibrillation			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 63 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 63 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
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 unstable			
subjects affected / exposed	1 / 63 (1.59%)	1 / 126 (0.79%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
General disorders and administration site conditions			
Non-Cardiac chest pain			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	4 / 124 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 63 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Peritoneal haemorrhage			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Nausea			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Vomiting			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (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
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Haemarthrosis			

subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Osteoarthritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 126 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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
Pyelonephritis			
subjects affected / exposed	0 / 63 (0.00%)	0 / 126 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 63 (0.00%)	1 / 126 (0.79%)	0 / 124 (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	Atorvastatin	Alirocumab 75 mg/up to 150 mg	Ezetimibe
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 63 (55.56%)	57 / 126 (45.24%)	63 / 124 (50.81%)
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	4 / 63 (6.35%)	4 / 126 (3.17%)	0 / 124 (0.00%)
occurrences (all)	4	4	0
Headache			
subjects affected / exposed	4 / 63 (6.35%)	6 / 126 (4.76%)	6 / 124 (4.84%)
occurrences (all)	4	7	8
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 5	6 / 126 (4.76%) 6	4 / 124 (3.23%) 4
Musculoskeletal and connective tissue disorders			
Myalgia subjects affected / exposed occurrences (all)	17 / 63 (26.98%) 21	31 / 126 (24.60%) 35	29 / 124 (23.39%) 35
Muscular weakness subjects affected / exposed occurrences (all)	4 / 63 (6.35%) 4	1 / 126 (0.79%) 1	2 / 124 (1.61%) 2
Arthralgia subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 5	6 / 126 (4.76%) 9	9 / 124 (7.26%) 10
Muscle spasms subjects affected / exposed occurrences (all)	7 / 63 (11.11%) 7	5 / 126 (3.97%) 7	9 / 124 (7.26%) 11
Back pain subjects affected / exposed occurrences (all)	5 / 63 (7.94%) 6	5 / 126 (3.97%) 6	7 / 124 (5.65%) 9
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 63 (3.17%) 2	8 / 126 (6.35%) 8	10 / 124 (8.06%) 12
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 63 (3.17%) 2	7 / 126 (5.56%) 7	5 / 124 (4.03%) 5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 January 2013	The purpose of this amendment was to: - Add an open-label treatment period. - Change the wording of the inclusion/exclusion criteria. - Change the schedule of events. - Make changes to reflect the addition of the open-label extension.
12 February 2013	The purpose of this amendment was to: - Add contingency language to ensure the continuity of study drug supply without interruption (in the event the manufacturer faced any performance or supply issues of the auto-injector). - Increase some visit windows to allow more scheduling flexibility. - Remove hospitalization for unanticipated coronary revascularization from the list of Clinical Events Committee (CEC) adjudication categories, and add that all coronary revascularizations would be submitted to the CEC. - Make miscellaneous administrative clarifications.
01 May 2013	The purpose of this amendment was to: - Change vitamin D status requirements. - Clarify allowable retreatment with ezetimibe after discontinuation of study drug. - Make formatting and other corrections.
07 April 2014	The purpose of this amendment was to: - Modify the primary efficacy analysis population to the ITT population for the primary and secondary efficacy endpoints, which included assessments both on study treatment and off study treatment through the analysis period. - An MMRM was to be used for the primary endpoint and for other continuous secondary endpoints anticipated to have normally distributed data. - For continuous endpoints expected to have non-normally distributed data, the robust regression method was to be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - For binary endpoints, logistic regression method was to be used to test the treatment group differences and missing data was to be handled using multiple imputation approach. - Primary and key secondary endpoints was also to be analyzed in the mITT population to assess the drug effect during the study treatment period (on treatment approach). - The lists of key and other secondary efficacy endpoints and estimands (ITT estimand or on-treatment estimand) were adjusted. - Update language on CV events to be reported to the CEC for adjudication, and clarify cerebrovascular events. - Clarify that LDL-C measured and calculated was to be performed at weeks 0 and 24. - Update language on collection of partner pregnancy data, per the ODYSSEY program. - Update categorization of AEs (update language on how to record injection site reactions that were not related to study drug). - Make minor corrections/clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported