



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Evinacumab in Patients with Homozygous Familial Hypercholesterolemia

#### Summary

EudraCT number	2017-001388-19
Trial protocol	DE FR AT CZ GR IT
Global end of trial date	17 March 2020

#### Results information

Result version number	v1
This version publication date	03 October 2020
First version publication date	03 October 2020

#### Trial information

##### Trial identification

Sponsor protocol code	R1500-CL-1629
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03399786
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002298-PIP01-17
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 March 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 March 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) using evinacumab 15 milligrams per kilogram (mg/kg) intravenously (IV) in comparison to placebo after 24 weeks in subjects with homozygous familial hypercholesterolemia (HoFH).

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following: Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines; Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; Applicable laws and regulations.

Background therapy:

Study treatment was added on to the subjects' stable background lipid modifying therapy. Subjects were on a maximally tolerated statin, ezetimibe, and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor antibody unless the subject had a documented history of tolerability issues, little or no response to therapy, or other documented reason.

Evidence for comparator: -

Actual start date of recruitment	18 January 2018
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	Australia: 4
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Japan: 10
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	South Africa: 8
Country: Number of subjects enrolled	Ukraine: 8
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	65
EEA total number of subjects	22

Notes:

<b>Subjects enrolled per age group</b>	
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)	2
Adults (18-64 years)	55
From 65 to 84 years	8
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted at 30 centers that enrolled subjects in 11 countries in Europe, Asia, North America, and Australia. Randomization was stratified by apheresis treatment status and by region (Japan, Rest of the World [ROW]).

### Pre-assignment

Screening details:

A total of 75 subjects were screened and 65 subjects randomized. There were 10 subjects that were considered screen failures; 8 subjects violated eligibility criteria and 2 subjects withdrew consent.

### Period 1

Period 1 title	Double-blind treatment period (DBTP)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

(day 1 to week 20)

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo IV Q4W
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Arm description:

Subjects received IV infusion of placebo matched to evinacumab every 4 weeks (Q4W) from day 1 to week 20 in the double-blind treatment period (DBTP).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of placebo matched to evinacumab Q4W from day 1 to week 20.

<b>Arm title</b>	Evinacumab 15 mg/kg IV Q4W
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Arm description:

Subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from day 1 to week 20 in the double-blind treatment period (DBTP).

Arm type	Experimental
Investigational medicinal product name	Evinacumab
Investigational medicinal product code	REGN1500
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from day 1 to week 20.

Number of subjects in period 1	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W
Started	22	43
Completed	21	43
Not completed	1	0
Consent withdrawn by subject	1	-

## Period 2

Period 2 title	Open-label treatment period (OLTP)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Evinacumab 15 mg/kg IV Q4W
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Arm description:

All subjects who completed the double-blind treatment period received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from week 24 to week 44 in the open-label treatment period (OLTP).

Arm type	Experimental
Investigational medicinal product name	Evinacumab
Investigational medicinal product code	REGN1500
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

All subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from week 24 to week 44.

Number of subjects in period 2	Evinacumab 15 mg/kg IV Q4W
Started	64
Completed	62
Not completed	2
Noncompliance with protocol by the subject	1
Pregnancy	1

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo IV Q4W
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Reporting group description:

Subjects received IV infusion of placebo matched to evinacumab every 4 weeks (Q4W) from day 1 to week 20 in the double-blind treatment period (DBTP).

Reporting group title	Evinacumab 15 mg/kg IV Q4W
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Reporting group description:

Subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from day 1 to week 20 in the double-blind treatment period (DBTP).

Reporting group values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W	Total
Number of subjects	22	43	65
Age categorical			
Units: Subjects			
≥12 to <18	1	1	2
≥18 to <45	16	23	39
≥45 to <65	5	11	16
≥65 to <75	0	7	7
≥75	0	1	1
Age continuous			
Units: years			
arithmetic mean	36.7	44.3	
standard deviation	± 11.52	± 16.78	-
Gender categorical			
Units: Subjects			
Male	11	19	30
Female	11	24	35
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	20	38	58
Not Reported	1	4	5
Race			
Units: Subjects			
White	17	31	48
Black or African American	0	2	2
Asian	4	6	10
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Reported	0	2	2
Other	1	2	3
Calculated Low-density Lipoprotein Cholesterol (LDL-C)			
Units: Milligrams per Deciliter (mg/dL)			
arithmetic mean	246.5	259.5	
standard deviation	± 153.71	± 172.40	-
Apolipoprotein B (Apo B)			

Units: mg/dL arithmetic mean standard deviation	175.9 ± 98.76	169.1 ± 82.75	-
Non-high-density Lipoprotein Cholesterol (non-HDL-C) Units: mg/dL arithmetic mean standard deviation	269.9 ± 157.81	281.9 ± 172.61	-
Total Cholesterol (TC) Units: mg/dL arithmetic mean standard deviation	315.9 ± 150.44	325.6 ± 170.76	-
Fasting Triglycerides (TG) Units: mg/dL arithmetic mean standard deviation	144.1 ± 144.54	113.1 ± 68.39	-
Lipoprotein A (Lp[a]) Units: Nanomoles per Liter (nmol/L) arithmetic mean standard deviation	103.4 ± 109.43	111.3 ± 114.40	-
Apolipoprotein CIII (Apo CIII) Units: mg/dL arithmetic mean standard deviation	9.7 ± 5.23	9.2 ± 4.00	-

## End points

### End points reporting groups

Reporting group title	Placebo IV Q4W
Reporting group description: Subjects received IV infusion of placebo matched to evinacumab every 4 weeks (Q4W) from day 1 to week 20 in the double-blind treatment period (DBTP).	
Reporting group title	Evinacumab 15 mg/kg IV Q4W
Reporting group description: Subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from day 1 to week 20 in the double-blind treatment period (DBTP).	
Reporting group title	Evinacumab 15 mg/kg IV Q4W
Reporting group description: All subjects who completed the double-blind treatment period received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from week 24 to week 44 in the open-label treatment period (OLTP).	

### Primary: Percent Change in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Week 24 (Intent-to-Treat [ITT] Estimand)

End point title	Percent Change in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Week 24 (Intent-to-Treat [ITT] Estimand)
End point description: Percent change was calculated as $100 \times (\text{calculated LDL-C value at Week 24} - \text{calculated LDL-C value at baseline}) / \text{calculated LDL-C value at baseline}$ . The baseline LDL-C value was the last calculated LDL-C value obtained before the first dose of double-blind-study drug. The calculated LDL-C at week 24 was the LDL-C value obtained within the week 24 efficacy analysis window, regardless of adherence to treatment and subsequent therapies (intent-to-treat [ITT] estimand). The ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	
End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	1.9 ( $\pm$ 6.5)	-47.1 ( $\pm$ 4.6)		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
Statistical analysis description: Confidence interval (CI) with p-value was based on-treatment group difference of least squares (LS) means using mixed-effect model repeat measurement (MMRM), randomization strata, treatment/strata/baseline value-by-time point interaction and continuous fixed covariates of baseline	



calculated LDL-C value.

Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeat Measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65
upper limit	-33.1
Variability estimate	Standard error of the mean
Dispersion value	8

### Secondary: Percent Change in Apolipoprotein B (Apo B) from Baseline to Week 24 (ITT Estimand)

End point title	Percent Change in Apolipoprotein B (Apo B) from Baseline to Week 24 (ITT Estimand)
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End point description:

Percent change in Apo B from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	-4.5 (± 4.8)	-41.4 (± 3.3)		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
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Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. CI with p-value was based on-treatment group difference of LS means using MMRM, randomization strata, treatment/strata/baseline value-by-time point interaction and continuous fixed covariates of baseline calculated Apo B value.

Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeat Measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-36.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.6
upper limit	-25.2
Variability estimate	Standard error of the mean
Dispersion value	5.9

### Secondary: Percent Change in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Week 24 (ITT Estimand)

End point title	Percent Change in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Week 24 (ITT Estimand)
End point description:	
Percent change from baseline in non-HDL-C at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	2.0 (± 5.4)	-49.7 (± 3.8)		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
Statistical analysis description:	
A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. CI with p-value was based on-treatment group difference of LS means using MMRM, randomization strata, treatment/strata/baseline value-by-time point interaction and continuous fixed covariates of baseline calculated non-HDL-C value.	
Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeat Measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-51.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-64.8
upper limit	-38.5
Variability estimate	Standard error of the mean
Dispersion value	6.6

### Secondary: Percent Change in Total Cholesterol (TC) from Baseline to Week 24 (ITT Estimand)

End point title	Percent Change in Total Cholesterol (TC) from Baseline to Week 24 (ITT Estimand)
End point description:	
Percent change in TC from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	1.0 (± 4.2)	-47.4 (± 3.0)		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
Statistical analysis description:	
A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. CI with p-value was based on-treatment group difference of LS means using MMRM, randomization strata, treatment/strata/baseline value-by-time point interaction and continuous fixed covariates of baseline calculated TC value.	
Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeat Measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-48.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.7
upper limit	-38.1
Variability estimate	Standard error of the mean
Dispersion value	5.1

### Secondary: Percentage of Subjects with $\geq 30\%$ Reduction in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24 (ITT Estimand)

End point title	Percentage of Subjects with $\geq 30\%$ Reduction in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24 (ITT Estimand)
End point description:	Percentage of subjects who achieved reduction in calculated LDL-C $\geq 30\%$ at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).
End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	18.2	83.7		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
Statistical analysis description:	A 2-sided hierarchical testing procedure was used for secondary endpoints in pre-specified order to control type I error. Testing sequence continued only when previous endpoint was statistically significant at 0.05. Multiple imputation addressed missing data at week 24. Combined estimate for odds ratio obtained by Rubin's formulae. Logistic regression models stratified by randomized strata include fixed categorical effect of treatment group & continuous fixed covariate of baseline calculated LDL-C.
Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	< 0.0001
Method	Logistic Regression Models Analyses
Parameter estimate	Odds ratio (OR)
Point estimate	25.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	110.5

Notes:

[1] - A 2-step multiple imputation method addressed missing values (seeds = 1629 & 9261 with number of imputations = 100 in first and number of imputation=1 in second step).

### Secondary: Percentage of Subjects with $\geq 50\%$ Reduction in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24 (ITT Estimand)

End point title	Percentage of Subjects with $\geq 50\%$ Reduction in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) at Week 24 (ITT Estimand)
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End point description:

Percentage of subjects who achieved reduction in calculated LDL-C  $\geq 50\%$  at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

At Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	4.5	55.8		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
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Statistical analysis description:

A 2-sided hierarchical testing procedure was used for secondary endpoints in pre-specified order to control type I error. Testing sequence continued only when previous endpoint was statistically significant at 0.05. Multiple imputation addressed missing data at week 24. Combined estimate for odds ratio obtained by Rubin's formulae. Logistic regression models stratified by randomized strata include fixed categorical effect of treatment group & continuous fixed covariate of baseline calculated LDL-C.

Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[2]</sup>
P-value	= 0.0028
Method	Logistic Regression Models Analyses
Parameter estimate	Odds ratio (OR)
Point estimate	24.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	195.6

Notes:

[2] - A 2-step multiple imputation method addressed missing values (seeds = 1629 & 9261 with number of imputations = 100 in first and number of imputation=1 in second step).

### Secondary: Absolute Change in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Week 24 (ITT Estimand)

End point title	Absolute Change in Calculated Low-Density Lipoprotein Cholesterol (LDL-C) from Baseline to Week 24 (ITT Estimand)
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End point description:

Absolute change in calculated LDL-C from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Milligrams per Deciliter (mg/dL)				
least squares mean (standard error)	-2.6 (± 17.6)	-134.7 (± 12.4)		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
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Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. CI with p-value was based on-treatment group difference of LS means using MMRM, randomization strata, treatment/strata/baseline value-by-time point interaction and continuous fixed covariates of baseline calculated LDL-C value.

Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed-effect Model Repeat Measure (MMRM)
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-132.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-175.3
upper limit	-88.9
Variability estimate	Standard error of the mean
Dispersion value	21.5

### Secondary: Percentage of Subjects Who Met United States (US) Apheresis Eligibility Criteria at Week 24 (ITT Estimand)

End point title	Percentage of Subjects Who Met United States (US) Apheresis Eligibility Criteria at Week 24 (ITT Estimand)
End point description:	
US apheresis eligibility criteria included subjects who had inadequate response to diet and LMTs after 6 months of treatment and with Functional Homozygous familial hypercholesterolemia (HoFH) or Heterozygous familial hypercholesterolemia (HeFH) (with 0-1 risk factor) with LDL-C $\geq$ 300 mg/dL (7.77 mmol/L). Percentage of subjects who met US apheresis eligibility criteria at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	
End point type	Secondary
End point timeframe:	
At Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	22.7	7.0		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
Statistical analysis description:	
A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Combined estimate for odds ratio was obtained by using Rubin's formulae. Logistic regression models stratified the fixed categorical effect of treatment group and the continuous fixed covariate of baseline calculated LDL-C value.	

Comparison groups	Evinacumab 15 mg/kg IV Q4W v Placebo IV Q4W
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
P-value	= 0.0845
Method	Logistic Regression Models Analyses
Parameter estimate	Odds ratio (OR)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.3

Notes:

[3] - A 2-step multiple imputation method addressed missing values (seeds = 1629 & 9261 with number of imputations = 100 in first and number of imputation=1 in second step).

### **Secondary: Percentage of Subjects with Low-Density Lipoprotein Cholesterol (LDL-C) <100 milligrams per deciliter (mg/dL) (2.59 millimoles per liter [mmol/L]) at Week 24 (ITT Estimand)**

End point title	Percentage of Subjects with Low-Density Lipoprotein Cholesterol (LDL-C) <100 milligrams per deciliter (mg/dL) (2.59 millimoles per liter [mmol/L]) at Week 24 (ITT Estimand)
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End point description:

Percentage of subjects with LDL-C value <100 mg/dL (2.59 mmol/L) in the DBTP at Week 24 was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analysed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

At Week 24

<b>End point values</b>	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	22.7	46.5		

### **Statistical analyses**

<b>Statistical analysis title</b>	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
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Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Combined estimate for odds ratio was obtained by using Rubin's formulae. Logistic regression models stratified the fixed categorical effect of treatment group and the continuous fixed covariate of baseline calculated LDL-C value.

Comparison groups	Evinacumab 15 mg/kg IV Q4W v Placebo IV Q4W
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Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	= 0.0203 <sup>[5]</sup>
Method	Logistic Regression Models Analyses
Parameter estimate	Odds ratio (OR)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	24.9

Notes:

[4] - A 2-step multiple imputation method addressed missing values (seeds = 1629 & 9261 with number of imputations = 100 in first and number of imputation=1 in second step).

[5] - The p-value is nominal for descriptive purpose only due to statistical hypothesis testing terminated previously.

### Secondary: Percentage of Subjects Who Met European Union (EU) Apheresis Eligibility Criteria at Week 24 (ITT Estimand)

End point title	Percentage of Subjects Who Met European Union (EU) Apheresis Eligibility Criteria at Week 24 (ITT Estimand)
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End point description:

EU apheresis eligibility criteria included subjects who had inadequate response to diet and Lipid modifying therapies (LMTs) after 3 months of treatment, Primary prevention: Subjects with Familial hypercholesterolemia (FH) with LDL-C >160 mg/dL (4.2 mmol/L) and Cardiovascular (CV) events in close relatives. Secondary prevention: Subjects with progressive CV events with LDL-C > 120 to 130 mg/dL (3.1-3.4 mmol/L). Percentage of subjects who met EU apheresis eligibility criteria at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

At Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	77.3	32.6		

### Statistical analyses

Statistical analysis title	Placebo IV Q4W, Evinacumab 15 mg/kg IV Q4W
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Statistical analysis description:

A 2-sided hierarchical testing procedure was used for the secondary endpoints in a pre-specified order to control type I error. The hierarchical testing sequence continued only when the previous endpoint was statistically significant at 0.05 level. Combined estimate for odds ratio was obtained by using Rubin's formulae. Logistic regression models stratified the fixed categorical effect of treatment group and the continuous fixed covariate of baseline calculated LDL-C value.

Comparison groups	Placebo IV Q4W v Evinacumab 15 mg/kg IV Q4W
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
P-value	= 0.0004 <sup>[7]</sup>
Method	Logistic Regression Models Analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.3

Notes:

[6] - A 2-step multiple imputation method addressed missing values (seeds = 1629 & 9261 with number of imputations = 100 in first and number of imputation=1 in second step).

[7] - The p-value is nominal for descriptive purpose only due to statistical hypothesis testing terminated previously.

### Secondary: Percentage of Subjects with Calculated Low-Density Lipoprotein Cholesterol (LDL-C) <70 mg/dL (1.81 mmol/L) at Week 24 (ITT Estimand)

End point title	Percentage of Subjects with Calculated Low-Density Lipoprotein Cholesterol (LDL-C) <70 mg/dL (1.81 mmol/L) at Week 24 (ITT Estimand)
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End point description:

Percentage of subjects with LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

At Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percentage of Subjects				
number (not applicable)	4.5	27.9		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Fasting Triglycerides (TG) from Baseline to Week 24 (ITT Estimand)

End point title	Percent Change in Fasting Triglycerides (TG) from Baseline to Week 24 (ITT Estimand)
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**End point description:**

Percent change from baseline in TG at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	-4.6 (± 7.0)	-55.0 (± 3.1)		

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percent Change in Lipoprotein A (Lp[a]) from Baseline to Week 24 (ITT Estimand)**

End point title	Percent Change in Lipoprotein A (Lp[a]) from Baseline to Week 24 (ITT Estimand)
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**End point description:**

Percent change in Lp(a) from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	-3.6 (± 5.8)	-5.5 (± 4.0)		

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Absolute Change in Apolipoprotein B (Apo B) from Baseline to Week 24 (ITT Estimand)**

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End point title	Absolute Change in Apolipoprotein B (Apo B) from Baseline to Week 24 (ITT Estimand)
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End point description:

Absolute change in Apo B from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

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End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: mg/dL				
least squares mean (standard error)	-8.0 (± 9.1)	-74.4 (± 6.3)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Absolute Change in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Week 24 (ITT Estimand)**

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End point title	Absolute Change in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Week 24 (ITT Estimand)
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End point description:

Absolute change in non-HDL-C from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).

End point type	Secondary
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End point timeframe:

Baseline, Week 24

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End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: mg/dL				
least squares mean (standard error)	-0.4 ( $\pm$ 17.4)	-148.0 ( $\pm$ 12.3)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute Change in Total Cholesterol (TC) from Baseline to Week 24 (ITT Estimand)

End point title	Absolute Change in Total Cholesterol (TC) from Baseline to Week 24 (ITT Estimand)
End point description:	
Absolute change in TC from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	
End point type	Secondary
End point timeframe:	
Baseline, Week 24	

End point values	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: mg/dL				
least squares mean (standard error)	-0.4 ( $\pm$ 17.2)	-161.6 ( $\pm$ 12.2)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Apolipoprotein CIII (Apo CIII) from Baseline to Week 24 (ITT Estimand)

End point title	Percent Change in Apolipoprotein CIII (Apo CIII) from Baseline to Week 24 (ITT Estimand)
End point description:	
Percent change in Apo CIII from baseline at Week 24 in the DBTP was reported; value obtained regardless of adherence to study treatment and subsequent therapies (ITT estimand). ITT population included all randomized subjects who received at least one dose or part of a dose of double-blind study drug. Subjects in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as randomized subject group).	

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

<b>End point values</b>	Placebo IV Q4W	Evinacumab 15 mg/kg IV Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	43		
Units: Percent Change				
least squares mean (standard error)	5.8 (± 5.5)	-84.1 (± 3.9)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up until end of study (Week 68) regardless of seriousness or relationship to investigational product (IP).

Adverse event reporting additional description:

Adverse events were presented as Double-blind Safety Set and Open-label Safety Set combined. Arm assignments for subjects in Safety Set were based on actual treatment received, such that 1 subject assigned to Placebo arm who inadvertently received evinacumab 15mg/kg was included in DBTP: Evinacumab 15mg/kg arm for purpose of safety analysis.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	22

### Reporting groups

Reporting group title	Evinacumab 15 mg/kg IV Q4W
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Reporting group description:

Subjects received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from day 1 to week 20 in the double-blind treatment period (DBTP). All subjects who completed the double-blind treatment period received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from week 24 to week 44 in the open-label treatment period (OLTP).

Reporting group title	Placebo IV Q4W
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Reporting group description:

Subjects received IV infusion of placebo matched to evinacumab every 4 weeks (Q4W) from day 1 to week 20 in the double-blind treatment period (DBTP). All subjects who completed the double-blind treatment period received IV infusion of evinacumab at a dose of 15 mg/kg Q4W from week 24 to week 44 in the open-label treatment period (OLTP).

Serious adverse events	Evinacumab 15 mg/kg IV Q4W	Placebo IV Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 44 (20.45%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Cardiac procedure complication			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery restenosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			



subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrocalcinosis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urosepsis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Evinacumab 15 mg/kg IV Q4W	Placebo IV Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 44 (81.82%)	18 / 21 (85.71%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 44 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 44 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 44 (15.91%)	5 / 21 (23.81%)	
occurrences (all)	12	8	

General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	6 / 44 (13.64%)	0 / 21 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	2 / 44 (4.55%)	2 / 21 (9.52%)	
occurrences (all)	9	3	
Diarrhoea			
subjects affected / exposed	3 / 44 (6.82%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Nausea			
subjects affected / exposed	4 / 44 (9.09%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Dental caries			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Cough			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 44 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Muscle spasms			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	9 / 44 (20.45%)	5 / 21 (23.81%)	
occurrences (all)	12	8	
Urinary tract infection			
subjects affected / exposed	1 / 44 (2.27%)	2 / 21 (9.52%)	
occurrences (all)	1	3	
Gastroenteritis			
subjects affected / exposed	3 / 44 (6.82%)	0 / 21 (0.00%)	
occurrences (all)	3	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2017	1. Added EuroQol-5D (EQ-5D) and Hospital Anxiety and Depression Scale (HADS) Quality of Life (QOL) questionnaires and an EQ-5D and HADS objective and exploratory endpoint to allow assessment of quality of life in this population. 2. Added Lipid Panel and Specialty Lipid Panel assessments and assessments of hematology, blood chemistry, and creatinine phosphokinase for the follow-up period. 3. Added a criterion excluding patients with LDL-C level <70 mg/dL as that was the goal for FH subjects. 4. Updated anti-drug antibody (ADA) variables and added a statement for follow-up of subjects positive in the ADA assay. 5. Added ADA sample at week 4. 6. Modified timing of one assessment for weight and one assessment for Pharmacokinetics (PK).
21 June 2018	1. Expanded Risk/Benefit section to include risk/benefit assessment of the combination of Evinacumab and Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, including alirocumab for the treatment of subjects with homozygous familial hypercholesterolemia (HoFH). 2. Clarified that subjects enrolling from R727-CL-1628 (2017-000351-95) will continue to receive alirocumab 150 mg every 2 weeks (Q2W).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported