Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk

Summary

EudraCT number	2016-003189-16
Trial protocol	EE BG SK
Global end of trial date	05 March 2020

Results information

Result version number	v2 (current)
This version publication date	02 July 2021
First version publication date	20 March 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	R727-CL-1532

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03694197
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc, 001 844-734-6643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc, 001 844-734-6643, 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	Final
Date of interim/final analysis	05 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the effect on mental state (known as "neurocognitive function") with use of Praluent.

Protection of trial subjects:

This clinical study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

Background therapy:

Background treatment with lipid modifying therapies (LMT) was allowed for all subjects (those who are using concomitant statins and for those who are not). The background LMT dose remained stable throughout the entire study, from screening to the end of study visit.

Evidence for comparator: -

Actual start date of recruitment	02 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 157
Country: Number of subjects enrolled	Chile: 67
Country: Number of subjects enrolled	Estonia: 42
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Mexico: 157
Country: Number of subjects enrolled	Russian Federation: 284
Country: Number of subjects enrolled	South Africa: 386
Country: Number of subjects enrolled	Ukraine: 358
Country: Number of subjects enrolled	United States: 690
Worldwide total number of subjects	2176
EEA total number of subjects	199

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	1229
From 65 to 84 years	945
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 2176 subjects were randomized across 169 sites in Bulgaria, Chile, Estonia, Japan, Mexico, Russian Federation, South Africa, Ukraine, and the United States.

Pre-assignment

Screening details:

Subjects who met the eligibility criteria were randomized in 1:1 ratio into 2 treatment groups: placebo and alirocumab. Randomization was stratified by age (less than [<] 65 or greater than or equal to [>=] 65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received subcutaneous (SC) injections of placebo matched to alirocumab every 2 weeks (Q2W) up to 94 weeks.

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

Dosage and administration details:

Placebo-matching alirocumab

Arm title	Alirocumab 75 Q2W/Up150 Q2W

Arm description:

Subjects received SC injections of alirocumab at a dose of 75 milligrams (mg) Q2W and up-titrated to 150 mg Q2W at Week 12 in a blinded fashion (if LDL-C ≥ 50 mg/dL at Week 8) up to 94 weeks.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SUB74847
Other name	Praluent
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

75mg Q2W up to 150mg Q2W

Number of subjects in period 1	Placebo	Alirocumab 75 Q2W/Up150 Q2W
Started	1088	1088
Randomized and treated	1085	1086
Completed	890	919
Not completed	198	169
Physician decision	4	4
Consent withdrawn by subject	64	33
Adverse event, non-fatal	64	67
Non-disclosed	16	12
Poor Compliance to Protocol	30	26
Study Terminated by Sponsor	4	3
Related to IMP Administration	3	6
Subject Moved	10	16
Discont'd After Randomization, Prior to Treatment	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received subcutaneous (SC) injections of placebo matched to alirocumab every 2 weeks (Q2W) up to 94 weeks.	
Reporting group title	Alirocumab 75 Q2W/Up150 Q2W
Reporting group description:	
Subjects received SC injections of alirocumab at a dose of 75 milligrams (mg) Q2W and up-titrated to 150 mg Q2W at Week 12 in a blinded fashion (if LDL-C ≥ 50 mg/dL at Week 8) up to 94 weeks.	

Reporting group values	Placebo	Alirocumab 75 Q2W/Up150 Q2W	Total
Number of subjects	1088	1088	2176
Age categorical			
Safety population (SAF) included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered (SAF population of subjects: Placebo=1084; Alirocumab=1087)			
Units: Subjects			
<45 years	26	23	49
>=45 to <65 years	587	589	1176
>=65 to <75 years	374	369	743
>=75	97	106	203
Subjects not included in SAF	4	1	5
Age Continuous			
Safety population (SAF) included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered (SAF population of subjects: Placebo=1084; Alirocumab=1087)			
Units: years			
arithmetic mean	62.7	62.6	
standard deviation	± 9.02	± 8.88	-
Sex: Female, Male			
Safety population (SAF) included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered (SAF population of subjects: Placebo=1084; Alirocumab=1087)			
Units: Subjects			
Female	459	448	907
Male	625	639	1264
Subjects not included in SAF	4	1	5
Ethnicity (NIH/OMB)			
Safety population (SAF) included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered (SAF population of subjects: Placebo=1084; Alirocumab=1087)			
Units: Subjects			
Hispanic or Latino	137	142	279
Not Hispanic or Latino	945	943	1888
Unknown or Not Reported	2	2	4
Subjects not included in SAF	4	1	5
Race/Ethnicity, Customized			
Race; Safety population (SAF) included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered (SAF population of subjects: Placebo=1084; Alirocumab=1087)			

Units: Subjects			
White	888	886	1774
Black or African American	86	77	163
Asian	19	28	47
American Indian or Alaska Native	11	16	27
Native Hawaiian or Other Pacific Islander	0	0	0
Other	80	80	160
Subjects not included in SAF	4	1	5

CANTAB Cognitive Domain Spatial Working Memory (SWM) Strategy Raw Score			
Cambridge Neuropsychological Test Automated Battery (CANTAB) SWM task assessed cognitive domain of executive function. Colored boxes were shown on a screen. A token was hidden in a box. Subjects touched boxes to search for token until #of tokens found = #of boxes. SWM strategy index is #of times search began w/ a different box. Baseline score = last score before 1st dose. Raw score ranges from 4 to 28; high score = inefficient strategy. Primary safety population (subjects w/ SWM score at baseline and at least 1 score during treatment period (Placebo=1035; Alirocumab=1051))			
Units: Units on a Scale			
arithmetic mean	15.9	16.0	
standard deviation	± 5.03	± 5.11	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received subcutaneous (SC) injections of placebo matched to alirocumab every 2 weeks (Q2W) up to 94 weeks.	
Reporting group title	Alirocumab 75 Q2W/Up150 Q2W
Reporting group description:	
Subjects received SC injections of alirocumab at a dose of 75 milligrams (mg) Q2W and up-titrated to 150 mg Q2W at Week 12 in a blinded fashion (if LDL-C ≥ 50 mg/dL at Week 8) up to 94 weeks.	

Primary: Change From Baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) Cognitive Domain Spatial Working Memory (SWM) Strategy Z-Score at Week 96

End point title	Change From Baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) Cognitive Domain Spatial Working Memory (SWM) Strategy Z-Score at Week 96
End point description:	
CANTAB SWM task assessed cognitive domain of executive function. Colored boxes were shown on a computer screen. One at a time, a token was hidden in a box (never same box twice). Instructions were to touch boxes to search for token. Search continued until # of tokens found was = to # of boxes. SWM strategy index represents # of times a subject began a search with a different box. Z-score represents standardized measure of how far an individual deviated from study cohort average at baseline. A higher Z-score reflects better performance. Primary safety population (subjects from safety population who had an SWM strategy score at baseline & at least 1 score measured during treatment-emergent adverse event (TEAE) period (first double-blind treatment dose to last dose of double-blind treatment + 70 days). Subjects analyzed according to treatment actually received.	
End point type	Primary
End point timeframe:	
Week 96	

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1035	1051		
Units: Z-score				
least squares mean (standard error)	-0.180 (± 0.027)	-0.200 (± 0.027)		

Statistical analyses

Statistical analysis title	Alirocumab 75 Q2W/Up150 Q2W, Placebo
Statistical analysis description:	
Change at Week 96	
Comparison groups	Alirocumab 75 Q2W/Up150 Q2W v Placebo

Number of subjects included in analysis	2086
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.6055 [2]
Method	Mixed-effect Model Repeated Measures
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.055

Notes:

[1] - Upper confidence interval (CI) limit was compared to the noninferiority margin, which was 0.2%, and noninferiority was declared if the upper CI limit was below the noninferiority margin.
[2] - P-value was taken from mixed-effect model with repeated measures (MMRM) analysis.

Secondary: Change From Baseline in CANTAB Cognitive Domain SWM Strategy Raw Score at Week 96

End point title	Change From Baseline in CANTAB Cognitive Domain SWM Strategy Raw Score at Week 96

End point description:

CANTAB SWM task assessed cognitive domain of executive function. Colored boxes were shown on a screen. A token was hidden in one of the boxes (never same box twice). Instructions were to touch boxes to search for token until number of tokens found equaled number of boxes. SWM strategy index represents number of times a search began with a different box. Lower change from baseline raw scores reflect better SWM performance (i.e. less impairment). Primary safety population included subjects from the safety population who had an assessment of the SWM strategy score at baseline, and at least 1 score measured during the treatment-emergent adverse event (TEAE) period. The TEAE period is defined as the first double-blind treatment dose to last dose of double-blind treatment + 70 days (10 weeks). Subjects were analyzed according to the treatment actually received.

End point type	Secondary

End point timeframe:

Week 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	868	901		
Units: Units on a Scale				
arithmetic mean (standard deviation)	-0.9 (± 4.49)	-1.0 (± 4.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Calculated Low-density Lipoprotein Cholesterol (LDL-C) at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Calculated Low-density Lipoprotein Cholesterol (LDL-C) at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in calculated LDL-C at Week 12, 24, 48, 72, and 96 was reported. LDL-C was measured using conventional units milligram per deciliter (mg/dL). Intent-to-treat (ITT) population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	0.6 (± 1.0)	-49.6 (± 0.9)		
Percent change at Week 24	3.0 (± 1.0)	-54.2 (± 1.0)		
Percent change at Week 48	2.8 (± 1.1)	-51.4 (± 1.1)		
Percent change at Week 72	2.4 (± 1.2)	-50.4 (± 1.2)		
Percent change at Week 96	4.0 (± 1.3)	-46.2 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein (Apo) B at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Apolipoprotein (Apo) B at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in Apo B at Week 12, 24, 48, 72, and 96 was reported. Apo B was measured using conventional units mg/dL. ITT population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	0.8 (± 0.7)	-36.7 (± 0.7)		
Percent change at Week 24	2.1 (± 0.8)	-40.9 (± 0.8)		
Percent change at Week 48	1.1 (± 0.8)	-39.0 (± 0.8)		
Percent change at Week 72	0.2 (± 0.9)	-39.1 (± 0.8)		
Percent change at Week 96	1.4 (± 0.9)	-36.4 (± 0.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Non-High-Density Lipoprotein Cholesterol (non-HDL-C) at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in non-HDL-C at Week 12, 24, 48, 72, and 96 was reported. Non-HDL-C was measured using conventional units mg/dL. ITT population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	0.7 (± 0.8)	-40.4 (± 0.8)		
Percent change at Week 24	2.2 (± 0.9)	-44.0 (± 0.9)		
Percent change at Week 48	1.7 (± 0.9)	-41.1 (± 0.9)		
Percent change at Week 72	1.7 (± 1.0)	-40.6 (± 1.0)		
Percent change at Week 96	2.5 (± 1.1)	-37.0 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total Cholesterol (Total-C) at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Total Cholesterol (Total-C) at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in calculated Total-C at Week 12, 24, 48, 72, and 96 was reported. Total-C was measured using conventional units mg/dL. ITT population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	-0.3 (± 0.6)	-29.6 (± 0.6)		
Percent change at Week 24	1.5 (± 0.6)	-31.8 (± 0.6)		
Percent change at Week 48	1.1 (± 0.7)	-29.6 (± 0.7)		
Percent change at Week 72	1.1 (± 0.7)	-29.0 (± 0.7)		
Percent change at Week 96	1.8 (± 0.7)	-26.5 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lipoprotein a [Lp(a)] at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Lipoprotein a [Lp(a)] at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in Lp(a) at Week 12, 24, 48, 72, and 96 was reported. Lp(a) was measured using conventional units mg/dL. ITT Population was used. The two-step multiple imputation procedure is used to address missing values in the randomized population. In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	-3.3 (± 0.8)	-22.4 (± 0.8)		
Percent change at Week 24	-0.5 (± 0.9)	-24.7 (± 0.9)		
Percent change at Week 48	-1.4 (± 1.0)	-24.3 (± 1.0)		
Percent change at Week 72	-1.7 (± 1.0)	-25.1 (± 1.0)		
Percent change at Week 96	4.8 (± 1.1)	-17.7 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in High-Density Lipoprotein Cholesterol (HDL-C) at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in HDL-C at Week 12, 24, 48, 72, and 96 was reported. HDL-C was measured using conventional units mg/dL. ITT population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	0.6 (± 0.5)	5.9 (± 0.5)		
Percent change at Week 24	3.8 (± 0.6)	9.0 (± 0.6)		
Percent change at Week 48	3.8 (± 0.6)	9.2 (± 0.6)		
Percent change at Week 72	4.4 (± 0.7)	10.3 (± 0.6)		
Percent change at Week 96	5.5 (± 0.7)	10.8 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Triglycerides (TG) at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Triglycerides (TG) at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in TG at Week 12, 24, 48, 72, and 96 was reported. TG was measured using conventional units mg/dL. ITT population was used. The two-step multiple imputation procedure is used to address missing values in the randomized population. In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	0.7 (± 1.0)	-11.0 (± 1.0)		
Percent change at Week 24	-1.8 (± 1.0)	-12.9 (± 1.0)		
Percent change at Week 48	-1.8 (± 1.1)	-11.3 (± 1.1)		
Percent change at Week 72	-2.1 (± 1.1)	-12.3 (± 1.1)		
Percent change at Week 96	-2.7 (± 1.1)	-11.9 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein (Apo) A-1 at Week 12, 24, 48, 72, and 96

End point title	Percent Change From Baseline in Apolipoprotein (Apo) A-1 at Week 12, 24, 48, 72, and 96

End point description:

Percent change from baseline in Apo A-1 at Week 12, 24, 48, 72, and 96 was reported. Apo A-1 was measured using conventional units mg/dL. ITT population included all subjects with availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (i.e. baseline) and within

1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window. ITT population analyzed according to treatment group allocated by randomization (as-randomized).

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percent Change				
least squares mean (standard error)				
Percent change at Week 12	-1.3 (± 0.4)	1.7 (± 0.4)		
Percent change at Week 24	2.9 (± 0.4)	6.1 (± 0.4)		
Percent change at Week 48	4.7 (± 0.4)	7.7 (± 0.4)		
Percent change at Week 72	4.4 (± 0.4)	7.8 (± 0.4)		
Percent change at Week 96	4.2 (± 0.4)	7.5 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Reached Low-Density Lipoprotein Cholesterol (LDL-C) Level Less Than (<) 70 mg/dL (1.81 Millimoles per Liter [mmol/L]) at Week 12, 24, 48, 72, and 96

End point title	Percentage of Subjects Who Reached Low-Density Lipoprotein Cholesterol (LDL-C) Level Less Than (<) 70 mg/dL (1.81 Millimoles per Liter [mmol/L]) at Week 12, 24, 48, 72, and 96

End point description:

Percentage of subjects who reached LDL-C level < 70 mg/dL (1.81 mmol/L) at Week 12, 24, 48, 72, and 96 were reported. ITT population was used. The two-step multiple imputation procedure is used to address missing values in the randomized population. In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percentage of Subjects				
number (not applicable)				
Week 12	10.3	69.4		
Week 24	8.4	74.7		
Week 48	10.7	71.4		
Week 72	11.3	69.7		
Week 96	10.7	64.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Reached Low-Density Lipoprotein Cholesterol (LDL-C) Level Less Than (<) 50 mg/dL (1.29 mmol/L) at Week 12, 24, 48, 72, and 96

End point title	Percentage of Subjects Who Reached Low-Density Lipoprotein Cholesterol (LDL-C) Level Less Than (<) 50 mg/dL (1.29 mmol/L) at Week 12, 24, 48, 72, and 96

End point description:

Percentage of subjects who reached LDL-C level < 50 mg/dL (1.29 mmol/L) at Week 12, 24, 48, 72, and 96 were reported. ITT population was used. The two-step multiple imputation procedure is used to address missing values in the randomized population. In the first step, the monotone missing pattern is induced in the multiply-imputed data. In the second step, the missing data at subsequent visits are imputed using the regression method for continuous variables.

End point type	Secondary

End point timeframe:

Week 12, 24, 48, 72, and 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1051	1058		
Units: Percentage of Subjects				
number (not applicable)				
Week 12	1.7	45.6		
Week 24	2.0	56.9		
Week 48	2.1	51.3		
Week 72	2.5	52.1		
Week 96	2.4	46.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An Adverse Event (AE) was any untoward medical occurrence in a subject administered a study drug which may or may not have a causal relationship with the study drug. TEAE was defined as AEs that developed or worsened/became serious during on-treatment period (time from the first double-blind study treatment injection up to 70 days after the last double-blind study treatment injection). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in any of the following outcomes: death, life-threatening, required initial or prolonged in-subject hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or considered as medically important event. Any TEAE included subjects with both serious and non-serious AEs. Safety analysis set (SAF) (included all subjects randomized and exposed to at least 1 dose of study drug, regardless of the amount of treatment administered)

End point type	Secondary

End point timeframe:

Up to Week 96

End point values	Placebo	Alirocumab 75 Q2W/Up150 Q2W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1084	1087		
Units: Subjects				
Subjects with any TEAEs	857	866		
Subjects with any Serious TEAEs	216	189		
Subjects with any TEAE leading to death	17	13		
TEAE leading to treatment discontinuation	59	64		

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 to the end of study (Week 96) regardless of seriousness or relationship to investigational product (IP).

Adverse event reporting additional description:

Safety population included all subjects randomized and exposed to at least one dose of study drug, regardless of the amount of treatment administered. Subjects were analyzed according to the treatment received (placebo or Praluent 75 mg Q2W/up-titrate 150 mg Q2W).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received subcutaneous (SC) injections of placebo matched to alirocumab every 2 weeks (Q2W) up to 94 weeks.

Reporting group title	Alirocumab 75 Q2W/Up150 Q2W

Reporting group description:

Subjects received SC injections of alirocumab at a dose of 75 milligrams (mg) Q2W and up-titrated to 150 mg Q2W at Week 12 in a blinded fashion (if LDL-C ≥ 50 mg/dL at Week 8) up to 94 weeks.

Serious adverse events	Placebo	Alirocumab 75 Q2W/Up150 Q2W	
Total subjects affected by serious adverse events			
subjects affected / exposed	216 / 1084 (19.93%)	189 / 1087 (17.39%)	
number of deaths (all causes)	24	17	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	3 / 1084 (0.28%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer stage III			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			

subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acinic cell carcinoma of salivary gland			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign neoplasm of epididymis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer stage II			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant melanoma			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 1084 (0.09%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer stage I			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer metastatic			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder neoplasm			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer stage IV			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of the cervix			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 1084 (0.65%)	6 / 1087 (0.55%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	3 / 1084 (0.28%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 1084 (0.28%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 1084 (0.28%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 1084 (0.18%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			

subjects affected / exposed	2 / 1084 (0.18%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paget-Schroetter syndrome			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker replacement			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	3 / 1084 (0.28%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 1084 (0.18%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 1084 (0.18%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Fatigue			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site haematoma			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 1084 (0.09%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Vascular stent occlusion			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-graft endoleak			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Homicide			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 1084 (0.28%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Female genital tract fistula			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix haemorrhage uterine			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erectile dysfunction			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic obstruction			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	4 / 1084 (0.37%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 1084 (0.37%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	4 / 1084 (0.37%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	3 / 1084 (0.28%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			

subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Somatic symptom disorder			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	2 / 1084 (0.18%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal injury			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery restenosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary bypass thrombosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated incisional hernia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary bypass stenosis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Vestibulocerebellar syndrome			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	16 / 1084 (1.48%)	14 / 1087 (1.29%)	
occurrences causally related to treatment / all	0 / 17	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	13 / 1084 (1.20%)	5 / 1087 (0.46%)	
occurrences causally related to treatment / all	0 / 16	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	10 / 1084 (0.92%)	11 / 1087 (1.01%)	
occurrences causally related to treatment / all	0 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	8 / 1084 (0.74%)	6 / 1087 (0.55%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	7 / 1084 (0.65%)	5 / 1087 (0.46%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute coronary syndrome			
subjects affected / exposed	4 / 1084 (0.37%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 1084 (0.37%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 1084 (0.37%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure acute			
subjects affected / exposed	3 / 1084 (0.28%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	3 / 1084 (0.28%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 1084 (0.18%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conduction disorder			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frederick's syndrome			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia paroxysmal			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	5 / 1084 (0.46%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	4 / 1084 (0.37%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 1084 (0.28%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	3 / 1084 (0.28%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	2 / 1084 (0.18%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar stroke			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 1084 (0.09%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multifocal motor neuropathy			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic haematoma			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoclonal B-cell lymphocytosis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Amaurosis fugax			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 1084 (0.00%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 1084 (0.18%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal incarcerated hernia			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyclic vomiting syndrome			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal vascular malformation haemorrhagic			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal mass			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oroantral fistula			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 1084 (0.18%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic skin ulcer			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 1084 (0.37%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 1084 (0.28%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 1084 (0.18%)	6 / 1087 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back disorder			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis reactive			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriatic arthropathy			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 1084 (0.46%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 1084 (0.37%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 1084 (0.28%)	4 / 1087 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	3 / 1084 (0.28%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue haemorrhagic fever			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysentery			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 1084 (0.09%)	3 / 1087 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sinusitis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic fever with renal syndrome			

subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 1084 (0.00%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	2 / 1084 (0.18%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 1084 (0.18%)	2 / 1087 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 1084 (0.09%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	1 / 1084 (0.09%)	0 / 1087 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic syndrome			
subjects affected / exposed	0 / 1084 (0.00%)	1 / 1087 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Alirocumab 75 Q2W/Up150 Q2W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	387 / 1084 (35.70%)	366 / 1087 (33.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	73 / 1084 (6.73%)	64 / 1087 (5.89%)	
occurrences (all)	93	81	
Nervous system disorders			
Headache			
subjects affected / exposed	85 / 1084 (7.84%)	71 / 1087 (6.53%)	
occurrences (all)	123	83	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	71 / 1084 (6.55%)	60 / 1087 (5.52%)	
occurrences (all)	82	66	
Infections and infestations			
Bronchitis			
subjects affected / exposed	65 / 1084 (6.00%)	60 / 1087 (5.52%)	
occurrences (all)	72	78	
Influenza			
subjects affected / exposed	69 / 1084 (6.37%)	63 / 1087 (5.80%)	
occurrences (all)	77	69	
Nasopharyngitis			
subjects affected / exposed	89 / 1084 (8.21%)	82 / 1087 (7.54%)	
occurrences (all)	117	98	
Urinary tract infection			
subjects affected / exposed	46 / 1084 (4.24%)	61 / 1087 (5.61%)	
occurrences (all)	65	78	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2016	The purpose of this amendment was to incorporate changes made based on feedback received from the FDA and to address inconsistencies in the original version.
08 August 2016	The overall purpose of this amendment was to address inconsistencies, provide clarifications and correct errors as follows: To correct and replace EudraCT number - To clarify that the last study drug administration is week 94 and not week 96 - To revise the total number of site locations from up to 600 to up to 300 - To add study milestones - To add the proportion of patients reaching LDL-C <50 (1.29 mmol/L) mg/dL as a secondary efficacy endpoint because it is the criterion for dose adjustment - To clarify gonadal hormone levels for female and male patients - To add GDS-S and MoCA to the Schedule of Events table - To add that limited clinical data are available on the impact of very low circulating LDL on neurocognitive function - To allow study drug administration prior to performing study assessments at visit 4 - To allow unscheduled neurocognitive testing during visits when a neurocognitive AE is reported and the CANTAB test is not planned or in the case of early treatment discontinuation - To modify reasons for permanent discontinuation of study drug - Add new onset of diabetes as an AE of interest - To revise the list of AE causality evaluation factors for the "not related" category - To more precisely define Neurocognitive Events of Special Interest - To add electronic systems used to process and/or collect data - To clarify that the sponsor may not implement a change in the design or operation of the protocol/ICF without a heath authority and/or IRB/EC approved amendment
10 January 2017	The main purpose of this amendment was to incorporate the following changes requested during the regulatory review via the Voluntary Harmonization Procedure (VHP): Added a history of serious allergic reactions and severe hepatic impairment as exclusion criteria - Provide the list of highly effective contraception methods in accordance with recommendations of the Clinical Trial Facilitation Group (CTFG) - Describe the procedure to be followed if emergency unblinding of a patient by the investigator is required during the study - Indicate that any patient with 2 consecutive LDL-C levels that are increased >25% compared to the randomization visit LDL-C level may receive rescue treatment if no reason for LDL-C levels above the threshold value can be determined - Add mild cognitive impairment and dementia as reasons for potential permanent discontinuation of study drug - Define what constitutes the end of the study

17 May 2017	The following changes were made to the protocol: Added coronary calcium scan as a clarification of possible diagnostic methods to document history of coronary heart disease - Revised exclusion criteria to enhance enrollment (#5), to provide a definition for "as needed" (pro re nata [PRN]) use (#6), to provide comprehensive list of exclusionary medications (#6), to clarify "hyperthyroidism/or hypothyroidism" (#8), and to remove history of serious allergic reactions (such as anaphylaxis) as this is not included in the approved drug labeling (#11) - Clarified procedures to follow if emergency unblinding is required - Added collection of menstrual cycle data in the study to facilitate meaningful analysis of reproductive hormone data - Clarified the visits (days on which blood samples are not collected) when study drug may be administered prior to study assessments to provide more flexibility in drug administration - Added collection of a laboratory sample for hepatitis B surface antigen and hepatitis C antibody at the end-of-study visit - Removed the requirement that patients be identified by their initials on case report forms (CRFs) and other documents submitted to the sponsor to preserve patient confidentiality - Removed gabapentin from the list of exclusionary medications since use of gabapentin won't impact interpretation of study endpoints - Provided a more comprehensive list of medications for calculating the anticholinergic burden (ACB)
17 July 2018	The main purpose of this amendment was to correct that optional laboratory evaluations are mandatory. Other minor edits and corrections were also made: Corrected that certain laboratory evaluations should be performed at the end of study visit even in the absence of clinically relevant abnormal values in these parameters at previous visits - Clarified that medication history to be collected is limited to medication history related to lipid-modifying therapy - Clarified definition of non-high density lipoprotein - Specified that research samples should be serum and plasma - Specified that adverse events of special interest (AESI) should be reported

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported