Clinical trial results:
Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732 and LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia

Summary

EudraCT number	2013-002572-40
Trial protocol	IT ES BE NL GB NO CZ FI AT DE DK PT RO HU BG
Global end of trial date	30 June 2017

Results information

Result version number	v1 (current)
This version publication date	15 July 2018
First version publication date	15 July 2018

Trial information

Trial identification

Sponsor protocol code	LTS13463

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01954394
WHO universal trial number (UTN)	U1111-1143-3810
Other trial identifiers	ODYSSEY OLE : Other Identifier

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	28 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in subjects with heterozygous familial hypercholesterolemia (heFH) who have completed one of the following studies: EFC12492, R727-CL-1112, EFC12732 & LTS11717.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

All subjects received a stable dose of statin (rosuvastatin, simvastatin or atorvastatin) with or without other lipid-modifying therapy (LMT) as clinically indicated throughout the duration of study.

Evidence for comparator: -

Actual start date of recruitment	17 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 133
Country: Number of subjects enrolled	Norway: 57
Country: Number of subjects enrolled	Portugal: 2
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 52
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czech Republic: 76
Country: Number of subjects enrolled	Denmark: 27
Country: Number of subjects enrolled	Finland: 7
Country: Number of subjects enrolled	France: 75
Country: Number of subjects enrolled	Germany: 7

Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Canada: 49
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	South Africa: 167
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	986
EEA total number of subjects	553

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	772
From 65 to 84 years	212
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 177 centers in 24 countries. Overall, 986 subjects who completed study EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500), EFC12732 (NCT01617655) and LTS11717 (NCT01507831) were enrolled between December 2013 and December 2014.

Pre-assignment

Screening details:

The Day 1 visit of this study was: the end of treatment visit of the 78-week treatment period for subjects who completed EFC12492, R727-CL-1112 and EFC12732; and the end of study visit i.e. 8 weeks after completion of the 78-week treatment period for subjects who completed LTS11717.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Alirocumab: All Subjects

Arm description:

All subjects who received alirocumab/placebo in the parent studies and received alirocumab 75 mg or 150 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to stable LMT for up to 168 additional weeks in this study.

Arm type	Experimental
Investigational medicinal product name	Alirocumab
Investigational medicinal product code	SAR236553, REGN727
Other name	Praluent
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Alirocumab administered as SC injection in the abdomen, thigh, or outer area of upper arm by self-injection or by another designated person.

Number of subjects in period 1	Alirocumab: All Subjects
Started	986
Treated	985
Completed	899
Not completed	87
Adverse Event	33
Other than specified above	31
Poor compliance to protocol	14
Related to Study Drug administration	4
Enrolled but not treated	1
Subject Moved	4

Baseline characteristics

Reporting groups	
Reporting group title	Alirocumab: All Subjects
Reporting group description:	
All subjects who received alirocumab/placebo in the parent studies and received alirocumab 75 mg or 150 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to stable LMT for up to 168 additional weeks in this study.	

Reporting group values	Alirocumab: All Subjects	Total	
Number of subjects	986	986	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.4		
standard deviation	± 11.9	-	
Gender categorical Units: Subjects			
Female	436	436	
Male	550	550	
Ethnicity Units: Subjects			
Hispanic or Latino	39	39	
Not Hispanic or Latino	940	940	
Unknown or Not Reported	7	7	
Race/Ethnicity, Customized Units: Subjects			
White	939	939	
Black or African American	4	4	
Asian	8	8	
American Indian or Alaska Native	3	3	
Native Hawaiian or Other Pacific Islander	1	1	
Other	11	11	
White/Black or African American	11	11	
White/Asian	7	7	
White/American Indian or Alaska Native	1	1	
Black or African American/Asian	1	1	
Calculated low- density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL-C = Total cholesterol - High-density lipoprotein cholesterol - [Triglyceride/5]). This parameter was evaluated at the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717).			
Units: mg/dL			
arithmetic mean	152.0		
standard deviation	± 53.2	-	
Calculated LDL-C in mmol/L			

This parameter was evaluated at the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717).			
Units: mmol/L			
arithmetic mean	3.936		
standard deviation	± 1.379	-	

Subject analysis sets

Subject analysis set title	Placebo to Alirocumab 75 or 150 mg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 weeks in subjects who received placebo in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and low-density lipoprotein cholesterol (LDL-C) values.

Subject analysis set title	Alirocumab to Alirocumab 75 or 150 mg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 additional weeks in subjects who received Alirocumab in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and LDL-C values.

Reporting group values	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Number of subjects	330	655	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.8	54.1	
standard deviation	± 11.4	± 12.1	
Gender categorical			
Units: Subjects			
Female	148	287	
Male	182	368	
Ethnicity			
Units: Subjects			
Hispanic or Latino	12	27	
Not Hispanic or Latino	317	623	
Unknown or Not Reported	1	5	
Race/Ethnicity, Customized			
Units: Subjects			
White	310	628	
Black or African American	2	2	
Asian	2	6	
American Indian or Alaska Native	1	2	

Native Hawaiian or Other Pacific Islander	1	0	
Other	4	7	
White/Black or African American	6	5	
White/Asian	2	5	
White/American Indian or Alaska Native	1	0	
Black or African American/Asian	1	0	
Calculated low- density lipoprotein cholesterol (LDL-C) in mg/dL			
Calculated LDL-C in mg/dL from Friedewald formula (LDL-C = Total cholesterol - High-density lipoprotein cholesterol - [Triglyceride/5]). This parameter was evaluated at the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717).			
Units: mg/dL			
arithmetic mean	148.8	153.5	
standard deviation	± 48.8	± 55.3	
Calculated LDL-C in mmol/L			
This parameter was evaluated at the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717).			
Units: mmol/L			
arithmetic mean	3.854	3.977	
standard deviation	± 1.265	± 1.432	

End points

End points reporting groups

Reporting group title	Alirocumab: All Subjects

Reporting group description:

All subjects who received alirocumab/placebo in the parent studies and received alirocumab 75 mg or 150 mg subcutaneous (SC) injection every 2 weeks (Q2W) added to stable LMT for up to 168 additional weeks in this study.

Subject analysis set title	Placebo to Alirocumab 75 or 150 mg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 weeks in subjects who received placebo in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and low-density lipoprotein cholesterol (LDL-C) values.

Subject analysis set title	Alirocumab to Alirocumab 75 or 150 mg Q2W
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 additional weeks in subjects who received Alirocumab in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and LDL-C values.

Primary: Percentage of Subjects Who Experienced Adverse Events (AEs)

End point title	Percentage of Subjects Who Experienced Adverse Events

End point description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of alirocumab in this study up to the last dose of alirocumab received in this study +70 days). Clinically significant lab and vital sign abnormalities were to be reported as AEs. Analysis performed on all enrolled subjects who received at least one dose or part of a dose of alirocumab in this study.

End point type	Primary

End point timeframe:

Up to 10 weeks after last study drug administration (maximum of 176 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Safety analyses were descriptive in nature.

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	985	330	655	
Units: percentage of subjects				
number (not applicable)				
Any AE	86.2	83.9	87.3	
Any Serious AE	21.5	20.6	22.0	

Any AE leading to treatment discontinuation	3.4	3.0	3.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Calculated LDL-C at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Percent Change From Baseline in Calculated LDL-C at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. Modified ITT (mITT) population: all enrolled and treated subjects with 1 baseline (from parent study) and at least 1 post-baseline calculated LDL-C value on-treatment. Here, "Number analysed"(n) = subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n= 917, 306, 611)	-44.2 (± 27.8)	-44.9 (± 25.9)	-43.8 (± 28.7)	
Week 24 (n= 926, 305, 621)	-46.9 (± 28.7)	-46.9 (± 27.5)	-46.9 (± 29.3)	
Week 48 (n= 918, 309, 609)	-46.9 (± 28.6)	-45.6 (± 28.0)	-47.5 (± 28.8)	
Week 72 (n= 887, 293, 594)	-47.4 (± 26.8)	-47.7 (± 23.5)	-47.3 (± 28.4)	
Week 96 (n= 711, 236, 475)	-47.9 (± 26.8)	-47.4 (± 23.8)	-48.2 (± 28.2)	
Week 120 (n= 540, 188, 352)	-46.8 (± 28.8)	-47.4 (± 24.0)	-46.6 (± 31.1)	
Week 144 (n= 198, 69, 129)	-48.5 (± 25.0)	-46.5 (± 25.8)	-49.6 (± 24.6)	
Week 168 (n= 10, 4, 6)	-48.8 (± 17.8)	-43.6 (± 13.4)	-52.2 (± 20.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Calculated LDL-C (mg/dL) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Absolute Change From Baseline in Calculated LDL-C (mg/dL) at

	Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: mg/dL				
arithmetic mean (standard deviation)				
Week 8 (n= 917, 306, 611)	-67.0 (± 48.0)	-66.8 (± 45.6)	-67.1 (± 49.2)	
Week 24 (n= 926, 305, 621)	-71.9 (± 51.4)	-70.3 (± 49.5)	-72.7 (± 52.4)	
Week 48 (n= 918, 309, 609)	-71.9 (± 52.8)	-67.8 (± 49.7)	-73.9 (± 54.3)	
Week 72 (n= 887, 293, 594)	-73.7 (± 51.4)	-71.2 (± 44.5)	-74.9 (± 54.5)	
Week 96 (n= 711, 236, 475)	-74.0 (± 52.2)	-70.2 (± 45.9)	-75.9 (± 55.0)	
Week 120 (n= 540, 188, 352)	-74.2 (± 55.2)	-72.3 (± 45.6)	-75.2 (± 59.7)	
Week 144 (n= 198, 69, 129)	-81.6 (± 55.4)	-73.1 (± 50.0)	-86.2 (± 57.8)	
Week 168 (n= 10, 4, 6)	-86.1 (± 42.4)	-66.1 (± 24.7)	-99.4 (± 48.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Calculated LDL-C (mmol/L) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Absolute Change From Baseline in Calculated LDL-C (mmol/L) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: mmol/L				
arithmetic mean (standard deviation)				
Week 8 (n= 917, 306, 611)	-1.735 (± 1.242)	-1.729 (± 1.180)	-1.738 (± 1.273)	
Week 24 (n= 926, 305, 621)	-1.863 (± 1.332)	-1.821 (± 1.282)	-1.883 (± 1.356)	
Week 48 (n= 918, 309, 609)	-1.861 (± 1.368)	-1.757 (± 1.286)	-1.914 (± 1.405)	
Week 72 (n= 887, 293, 594)	-1.908 (± 1.332)	-1.843 (± 1.154)	-1.940 (± 1.411)	
Week 96 (n= 711, 236, 475)	-1.916 (± 1.353)	-1.818 (± 1.190)	-1.965 (± 1.426)	
Week 120 (n= 540, 188, 352)	-1.923 (± 1.428)	-1.874 (± 1.180)	-1.949 (± 1.546)	
Week 144 (n= 198, 69, 129)	-2.114 (± 1.436)	-1.894 (± 1.294)	-2.232 (± 1.498)	
Week 168 (n= 10, 4, 6)	-2.229 (± 1.098)	-1.712 (± 0.641)	-2.574 (± 1.252)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) Over Time

End point title	Percentage of Subjects Reaching Calculated LDL-C <100 mg/dL (2.59 mmol/L) Over Time

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percentage of subjects				
number (not applicable)				
Baseline (n= 974, 323, 651)	11.7	12.1	11.5	
Week 8 (n= 969, 321, 648)	81.1	71.0	86.1	

Week 24 (n= 926, 305, 621)	76.1	77.0	75.7	
Week 48 (n= 918, 309, 609)	76.8	77.7	76.4	
Week 72 (n= 887, 293, 594)	79.4	82.9	77.6	
Week 96 (n= 711, 236, 475)	77.6	79.2	76.8	
Week 120 (n= 540, 188, 352)	77.2	78.2	76.7	
Week 144 (n= 198, 69, 129)	73.7	72.5	74.4	
Week 168 (n= 10, 4, 6)	80.0	75.0	83.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) Over Time

End point title	Percentage of Subjects Reaching Calculated LDL-C <70 mg/dL (1.81 mmol/L) Over Time

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percentage of subjects				
number (not applicable)				
Baseline (n= 974, 323, 651)	1.1	0.9	1.2	
Week 8 (n= 969, 321, 648)	60.1	47.4	66.4	
Week 24 (n= 926, 305, 621)	53.2	53.4	53.1	
Week 48 (n= 918, 309, 609)	52.7	51.1	53.5	
Week 72 (n= 887, 293, 594)	54.5	57.0	53.2	
Week 96 (n= 711, 236, 475)	55.3	53.0	56.4	
Week 120 (n= 540, 188, 352)	51.5	52.7	50.9	
Week 144 (n= 198, 69, 129)	47.5	46.4	48.1	
Week 168 (n= 10, 4, 6)	40.0	50.0	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Calculated LDL-C <70 mg/dL (1.81mmol/L) and/or ≥50% Reduction in Calculated LDL-C From Baseline (if Calculated LDL-C≥70 mg/dL [1.81mmol/L]) Over Time

End point title	Percentage of Subjects With Calculated LDL-C <70 mg/dL (1.81mmol/L) and/or ≥50% Reduction in Calculated LDL-C From Baseline (if Calculated LDL-C≥70 mg/dL [1.81mmol/L]) Over Time

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percentage of subjects				
number (not applicable)				
Baseline (n= 974, 323, 651)	1.1	0.9	1.2	
Week 8 (n= 969, 321, 648)	61.3	49.5	67.1	
Week 24 (n= 926, 305, 621)	54.2	54.1	54.3	
Week 48 (n= 918, 309, 609)	53.7	52.1	54.5	
Week 72 (n= 887, 293, 594)	55.4	57.3	54.4	
Week 96 (n= 711, 236, 475)	56.1	53.0	57.7	
Week 120 (n= 540, 188, 352)	53.1	53.2	53.1	
Week 144 (n= 198, 69, 129)	48.0	46.4	48.8	
Week 168 (n= 10, 4, 6)	40.0	50.0	33.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Percent Change From Baseline in Non-High Density Lipoprotein Cholesterol (Non-HDL-C) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n= 928, 310, 618)	-37.8 (± 26.0)	-38.1 (± 24.8)	-37.6 (± 26.6)	
Week 24 (n= 935, 310, 625)	-40.5 (± 27.1)	-40.6 (± 25.5)	-40.4 (± 27.9)	
Week 48 (n= 926, 310, 616)	-40.3 (± 26.9)	-39.7 (± 25.5)	-40.6 (± 27.6)	
Week 72 (n= 891, 294, 597)	-40.5 (± 25.3)	-40.8 (± 22.6)	-40.3 (± 26.5)	
Week 96 (n= 721, 240, 481)	-40.3 (± 25.6)	-39.9 (± 23.5)	-40.5 (± 26.6)	
Week 120 (n= 546, 188, 358)	-39.5 (± 27.3)	-41.4 (± 22.1)	-38.4 (± 29.7)	
Week 144 (n= 202, 70, 132)	-41.1 (± 23.6)	-39.8 (± 22.9)	-41.8 (± 24.0)	
Week 168 (n= 10, 4, 6)	-44.9 (± 16.1)	-40.7 (± 12.3)	-47.7 (± 18.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total-cholesterol at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Percent Change From Baseline in Total-cholesterol at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n= 928, 310, 618)	-27.7 (± 20.2)	-27.9 (± 19.3)	-27.7 (± 20.7)	

Week 24 (n= 935, 310, 625)	-30.1 (± 21.2)	-30.1 (± 20.3)	-30.2 (± 21.6)	
Week 48 (n= 926, 310, 616)	-29.7 (± 21.2)	-29.0 (± 20.5)	-30.0 (± 21.6)	
Week 72 (n= 891, 294, 597)	-30.0 (± 19.9)	-29.9 (± 18.0)	-30.1 (± 20.8)	
Week 96 (n= 721, 240, 481)	-29.6 (± 20.2)	-28.9 (± 18.3)	-29.9 (± 21.1)	
Week 120 (n= 546, 188, 358)	-29.0 (± 21.0)	-30.2 (± 17.2)	-28.4 (± 22.8)	
Week 144 (n= 202, 70, 132)	-30.5 (± 18.8)	-29.1 (± 18.2)	-31.3 (± 19.1)	
Week 168 (n= 10, 4, 6)	-36.4 (± 13.3)	-32.3 (± 12.4)	-39.1 (± 14.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in High Density Lipoprotein Cholesterol (HDL-C) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Percent Change From Baseline in High Density Lipoprotein Cholesterol (HDL-C) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n= 928, 310, 618)	6.3 (± 17.3)	5.6 (± 17.1)	6.6 (± 17.3)	
Week 24 (n= 935, 310, 625)	5.8 (± 17.1)	5.7 (± 17.4)	5.8 (± 16.9)	
Week 48 (n= 926, 310, 616)	7.2 (± 18.7)	7.1 (± 17.8)	7.2 (± 19.2)	
Week 72 (n= 891, 294, 597)	7.0 (± 19.1)	6.7 (± 17.6)	7.2 (± 19.9)	
Week 96 (n= 721, 240, 481)	7.2 (± 18.7)	7.2 (± 18.8)	7.2 (± 18.7)	
Week 120 (n= 546, 188, 358)	8.1 (± 18.6)	8.0 (± 18.4)	8.1 (± 18.7)	
Week 144 (n= 202, 70, 132)	8.8 (± 23.0)	8.8 (± 19.2)	8.8 (± 24.8)	
Week 168 (n= 10, 4, 6)	-2.8 (± 17.1)	-6.6 (± 26.2)	-0.3 (± 9.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Fasting Triglycerides (TGs) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point title	Percent Change From Baseline in Fasting Triglycerides (TGs) at Weeks 8, 24, 48, 72, 96, 120, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 8, 24, 48, 72, 96, 120, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 8 (n= 927, 309, 618)	3.5 (± 44.9)	3.4 (± 40.5)	3.5 (± 47.0)	
Week 24 (n= 932, 308, 624)	0.9 (± 44.0)	0.6 (± 39.9)	1.0 (± 45.9)	
Week 48 (n= 925, 309, 616)	3.7 (± 67.2)	0.8 (± 37.5)	5.1 (± 78.0)	
Week 72 (n= 889, 293, 596)	3.8 (± 43.0)	4.3 (± 43.3)	3.6 (± 42.9)	
Week 96 (n= 718, 239, 479)	9.2 (± 54.5)	9.1 (± 53.2)	9.3 (± 55.2)	
Week 120 (n= 545, 187, 358)	6.7 (± 44.8)	-1.2 (± 35.3)	10.8 (± 48.5)	
Week 144 (n= 201, 70, 131)	6.8 (± 45.9)	5.0 (± 38.0)	7.7 (± 49.8)	
Week 168 (n= 10, 4, 6)	-15.0 (± 24.6)	-22.1 (± 21.9)	-10.3 (± 27.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Lipoprotein (a) at Weeks 48, 96, 144 and 168

End point title	Percent Change From Baseline in Lipoprotein (a) at Weeks 48, 96, 144 and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 48, 96, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 48 (n= 913, 307, 606)	-22.6 (± 97.6)	-15.0 (± 158.4)	-26.4 (± 40.2)	
Week 96 (n= 713, 239, 474)	-18.9 (± 146.9)	-13.9 (± 171.7)	-21.4 (± 132.7)	
Week 144 (n= 198, 69, 129)	-28.5 (± 34.3)	-20.1 (± 46.1)	-33.0 (± 25.0)	
Week 168 (n= 10, 4, 6)	-29.6 (± 15.6)	-30.3 (± 18.2)	-29.2 (± 15.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein-B (Apo-B) at Weeks 48, 96, 144, and 168

End point title	Percent Change From Baseline in Apolipoprotein-B (Apo-B) at Weeks 48, 96, 144, and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 48, 96, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 48 (n= 915, 308, 607)	-37.5 (± 22.9)	-36.9 (± 21.7)	-37.8 (± 23.4)	
Week 96 (n= 713, 238, 475)	-37.6 (± 22.3)	-36.9 (± 20.9)	-38.0 (± 22.9)	
Week 144 (n= 198, 69, 129)	-35.9 (± 21.2)	-33.9 (± 20.9)	-36.9 (± 21.3)	
Week 168 (n= 10, 4, 6)	-41.1 (± 16.5)	-38.0 (± 9.0)	-43.1 (± 20.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1) at Weeks 48, 96, 144, and 168

End point title	Percent Change From Baseline in Apolipoprotein A-1 (Apo A-1) at Weeks 48, 96, 144, and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 48, 96, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: percent change				
arithmetic mean (standard deviation)				
Week 48 (n= 915, 308, 607)	5.7 (± 16.3)	5.6 (± 14.5)	5.8 (± 17.2)	
Week 96 (n= 713, 238, 475)	8.3 (± 14.5)	7.8 (± 15.4)	8.5 (± 14.1)	
Week 144 (n= 198, 69, 129)	10.6 (± 17.8)	11.2 (± 16.3)	10.2 (± 18.7)	
Week 168 (n= 10, 4, 6)	2.7 (± 13.2)	0.9 (± 19.3)	3.9 (± 9.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 48, 96, 144, and 168

End point title	Absolute Change From Baseline in Apo B/Apo A-1 Ratio at Weeks 48, 96, 144, and 168

End point description:

Baseline here corresponds to the baseline in the parent study (EFC12492, R727-CL-1112, EFC12732 or LTS11717). Post-baseline on-treatment data was obtained from Week 8 onwards up to Week 168 in this study. mITT population. Here, "n" signifies subjects evaluable at specified time-points. This number decreased significantly with visit because of the possibility to switch to commercial alirocumab.

End point type	Secondary

End point timeframe:

Parent Baseline, Weeks 48, 96, 144, and 168

End point values	Alirocumab: All Subjects	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	974	323	651	
Units: ratio				
arithmetic mean (standard deviation)				
Week 48 (n= 915, 308, 607)	-0.354 (± 0.286)	-0.340 (± 0.245)	-0.361 (± 0.304)	
Week 96 (n= 713, 238, 475)	-0.363 (± 0.256)	-0.340 (± 0.228)	-0.375 (± 0.268)	
Week 144 (n= 198, 69, 129)	-0.389 (± 0.379)	-0.342 (± 0.242)	-0.414 (± 0.433)	
Week 168 (n= 10, 4, 6)	-0.447 (± 0.238)	-0.370 (± 0.161)	-0.498 (± 0.280)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (Week 176 post-treatment follow-up visit) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that is AEs that developed/worsened during the 'treatment-emergent period' (the time from the first dose of alirocumab in this study up to the day of last dose of alirocumab received in this study + 70 days).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo to Alirocumab 75 or 150 mg Q2W

Reporting group description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 weeks in subjects who received placebo in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and LDL-C values.

Reporting group title	Alirocumab to Alirocumab 75 or 150 mg Q2W

Reporting group description:

Alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 additional weeks in subjects who received Alirocumab in the parent studies. Subjects from parent study EFC12732 (NCT01617655) started with alirocumab 150 mg Q2W and subjects from parent studies EFC12492 (NCT01623115), R727-CL-1112 (NCT01709500) and LTS11717 (NCT01507831) started with alirocumab 75 mg Q2W. Alirocumab doses could be either up-titrated from 75 to 150 mg Q2W or down-titrated from 150 to 75 mg Q2W from Week 12 or maintained according to the investigator judgement and LDL-C values.

Reporting group title	Alirocumab: All Subjects

Reporting group description:

All subjects who received alirocumab/placebo in the parent studies and received alirocumab 75 mg or 150 mg SC injection Q2W added to stable LMT for up to 168 additional weeks in this study.

Serious adverse events	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	Alirocumab: All Subjects
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 330 (20.61%)	144 / 655 (21.98%)	212 / 985 (21.52%)
number of deaths (all causes)	4	7	11
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Adenocarcinoma Of Colon			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Basal Cell Carcinoma			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign Pancreatic Neoplasm			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Transitional Cell Carcinoma Recurrent			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast Cancer Recurrent			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Lymphocytic Leukaemia Stage 0			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Adenoma			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Cancer			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Cancer Metastatic			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hodgkin's Disease			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Ductal Breast Carcinoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive Lobular Breast Carcinoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal Papilloma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lobular Breast Carcinoma In Situ			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Adenocarcinoma			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic Leukaemia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Melanoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic Glioma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Adenoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cancer Stage Iii			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary Cystadenoma Lymphomatosum			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phyllodes Tumour			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer Metastatic			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate Cancer Stage Ii			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Cancer Metastatic			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary Gland Adenoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of Skin			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Air Embolism			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Aneurysm			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Aortic Dissection			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Hypertension			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac Artery Occlusion			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent Claudication			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Hypertension			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic Shock			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral Artery Stenosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 330 (0.30%)	2 / 655 (0.31%)	3 / 985 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Malaise			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-Cardiac Chest Pain			
subjects affected / exposed	2 / 330 (0.61%)	4 / 655 (0.61%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden Cardiac Death			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Vascular Stent Occlusion			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Bartholin's Cyst			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian Cyst			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine Polyp			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal Dysplasia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Pulmonary Oedema			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute Respiratory Failure			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dyspnoea			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Hypertension			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary Oedema			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Alcohol Withdrawal Syndrome			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium Tremens			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed Mood			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major Depression			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal Ideation			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anticoagulation Drug Level Above Therapeutic			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart Rate Irregular			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases Increased			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight Decreased			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcohol Poisoning			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal Bite			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropod Bite			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Valve Replacement Complication			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral Neck Fracture			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional Overdose			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Injuries			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle Rupture			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haemorrhage			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural Haemorrhage			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road Traffic Accident			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid Haemorrhage			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Subdural Haematoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon Rupture			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal Burn			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic Vertebral Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Limb Fracture			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Bypass Dysfunction			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Graft Thrombosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound Dehiscence			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hereditary Non-Polyposis Colorectal Cancer Syndrome			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute Myocardial Infarction			
subjects affected / exposed	2 / 330 (0.61%)	4 / 655 (0.61%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Angina Pectoris			
subjects affected / exposed	6 / 330 (1.82%)	8 / 655 (1.22%)	14 / 985 (1.42%)
occurrences causally related to treatment / all	0 / 6	0 / 8	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Unstable			
subjects affected / exposed	4 / 330 (1.21%)	5 / 655 (0.76%)	9 / 985 (0.91%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Disease			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Disease Mixed			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic Valve Stenosis			
subjects affected / exposed	2 / 330 (0.61%)	1 / 655 (0.15%)	3 / 985 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis Coronary Artery			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			

subjects affected / exposed	1 / 330 (0.30%)	3 / 655 (0.46%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	2 / 330 (0.61%)	2 / 655 (0.31%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 2
Cardiac Failure Congestive			
subjects affected / exposed	3 / 330 (0.91%)	1 / 655 (0.15%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Disease			
subjects affected / exposed	2 / 330 (0.61%)	4 / 655 (0.61%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Occlusion			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Stenosis			
subjects affected / exposed	3 / 330 (0.91%)	3 / 655 (0.46%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary Artery Thrombosis			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Cardiomyopathy			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Incompetence			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral Valve Stenosis			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	2 / 330 (0.61%)	3 / 655 (0.46%)	5 / 985 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Pericarditis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal Angina			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular Tachycardia			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Dysfunction			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	1 / 330 (0.30%)	3 / 655 (0.46%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Amnesia			
subjects affected / exposed	2 / 330 (0.61%)	0 / 655 (0.00%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid Arteriosclerosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical Radiculopathy			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic Cerebral Infarction			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Focal Dyscognitive Seizures			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normal Pressure Hydrocephalus			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory Loss			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 330 (0.30%)	6 / 655 (0.92%)	7 / 985 (0.71%)
occurrences causally related to treatment / all	0 / 1	1 / 6	1 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic Encephalopathy			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient Ischaemic Attack			
subjects affected / exposed	0 / 330 (0.00%)	6 / 655 (0.92%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 7	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Dementia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic Anaemia			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Acute Vestibular Syndrome			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo Positional			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Corneal Decompensation			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Open Angle Glaucoma			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic Ischaemic Neuropathy			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Detachment			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Tear			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal Vein Occlusion			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal Pain			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Barrett's Oesophagus			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis Ischaemic			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum Intestinal			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Polyps			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis Haemorrhagic			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus Hernia			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Internal Hernia			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Acute			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Chronic			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Haemorrhage			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal Ulcer Haemorrhage			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small Intestinal Obstruction			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical Hernia			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic Steatosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular Injury			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hypersensitivity Vasculitis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash Generalised			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute Kidney Injury			
subjects affected / exposed	2 / 330 (0.61%)	2 / 655 (0.31%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 330 (0.30%)	3 / 655 (0.46%)	4 / 985 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Colic			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Impairment			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Pain			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Incontinence			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Acquired Claw Toe			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Pain			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture Pain			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 330 (0.30%)	5 / 655 (0.76%)	6 / 985 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Pain			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck Pain			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 330 (0.61%)	5 / 655 (0.76%)	7 / 985 (0.71%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain In Extremity			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid Arthritis			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator Cuff Syndrome			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Column Stenosis			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter Site Infection			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 330 (0.00%)	3 / 655 (0.46%)	3 / 985 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium Difficile Colitis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal Abscess			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis Bacterial			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device Related Sepsis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gastroenteritis			
subjects affected / exposed	1 / 330 (0.30%)	1 / 655 (0.15%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma Infection			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	0 / 330 (0.00%)	2 / 655 (0.31%)	2 / 985 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung Infection			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal Abscess			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 330 (0.61%)	3 / 655 (0.46%)	5 / 985 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pneumonia Pseudomonal			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Abscess			

subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative Wound Infection			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stitch Abscess			
subjects affected / exposed	1 / 330 (0.30%)	0 / 655 (0.00%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Myocarditis			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 Diabetes Mellitus			
subjects affected / exposed	0 / 330 (0.00%)	1 / 655 (0.15%)	1 / 985 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo to Alirocumab 75 or 150 mg Q2W	Alirocumab to Alirocumab 75 or 150 mg Q2W	Alirocumab: All Subjects
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 330 (55.45%)	366 / 655 (55.88%)	549 / 985 (55.74%)
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 330 (3.94%)	37 / 655 (5.65%)	50 / 985 (5.08%)
occurrences (all)	13	39	52
General disorders and administration site conditions			
Influenza Like Illness			
subjects affected / exposed	12 / 330 (3.64%)	40 / 655 (6.11%)	52 / 985 (5.28%)
occurrences (all)	17	48	65
Injection Site Reaction			
subjects affected / exposed	26 / 330 (7.88%)	28 / 655 (4.27%)	54 / 985 (5.48%)
occurrences (all)	66	148	214
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	19 / 330 (5.76%)	43 / 655 (6.56%)	62 / 985 (6.29%)
occurrences (all)	21	52	73
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	34 / 330 (10.30%)	53 / 655 (8.09%)	87 / 985 (8.83%)
occurrences (all)	37	59	96
Back Pain			
subjects affected / exposed	26 / 330 (7.88%)	56 / 655 (8.55%)	82 / 985 (8.32%)
occurrences (all)	29	65	94
Myalgia			
subjects affected / exposed	15 / 330 (4.55%)	44 / 655 (6.72%)	59 / 985 (5.99%)
occurrences (all)	18	47	65
Pain In Extremity			
subjects affected / exposed	18 / 330 (5.45%)	31 / 655 (4.73%)	49 / 985 (4.97%)
occurrences (all)	18	38	56
Infections and infestations			

Bronchitis			
subjects affected / exposed	19 / 330 (5.76%)	41 / 655 (6.26%)	60 / 985 (6.09%)
occurrences (all)	23	45	68
Influenza			
subjects affected / exposed	34 / 330 (10.30%)	61 / 655 (9.31%)	95 / 985 (9.64%)
occurrences (all)	40	73	113
Upper Respiratory Tract Infection			
subjects affected / exposed	31 / 330 (9.39%)	71 / 655 (10.84%)	102 / 985 (10.36%)
occurrences (all)	44	104	148
Urinary Tract Infection			
subjects affected / exposed	21 / 330 (6.36%)	28 / 655 (4.27%)	49 / 985 (4.97%)
occurrences (all)	28	37	65
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	51 / 330 (15.45%)	93 / 655 (14.20%)	144 / 985 (14.62%)
occurrences (all)	70	123	193

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2014	1. Clarified inclusion criterion I01. 2. Updated language on cardiovascular events to be reported to the CEC for adjudication and included a clarification on cerebrovascular events. 3. Updated language on collection of partner pregnancy as per other protocol in the ODYSSEY phase 3 program. 4. Categorization of AEs (updated language on how to record injection site reactions that were not related to IMP).
10 July 2015	1. Prolongation of the study duration by 1 year to allow patients in most countries to benefit from commercial alirocumab. 2. Removal of the Clinical Events Committee (cardiovascular events adjudication): since this study was a non-comparative study, there were no purposes in having the CV events adjudicated, and thus the process was discontinued. 3. Termination of Steering Committee activities on 31 December 2015 since most of the phase 3a studies were completed. 4. Possibility to add an Interim analysis in order to either be able to answer potential Health Authorities requests or to provide analyses for scientific purposes. 5. Removal of the specific ADA monitoring after the follow-up visit. 6. Modification of personal data collection: collection of racial origin as this information was needed for creatinine clearance calculation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported