Clinical trial results:
An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 301012 in Patients with Familial Hypercholesterolemia or Severe-Hypercholesterolemia

Summary

EudraCT number	2005-003450-10
Trial protocol	GB
Global end of trial date	15 September 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	301012-CS6

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00694109
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street, Cambridge, MA, United States, 02142
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	21 November 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and efficacy of extended dosing with ISIS 301012 (mipomersen) in subjects with familial hypercholesterolemia or severe hypercholesterolemia on concomitant lipid-lowering therapy.

Protection of trial subjects:

Pediatric Subjects: The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child.
Adult 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: -	
Evidence for comparator: -	
Actual start date of recruitment	01 April 2008
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	Brazil: 5
Country: Number of subjects enrolled	Canada: 34
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 75
Worldwide total number of subjects	142
EEA total number of subjects	2

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)	7
Adults (18-64 years)	114
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 33 centers in 7 countries. A total of 144 subjects were enrolled in the study. 1 subject never received study drug. 2 of the enrolled subjects came from a phase 2 study and its extension and consequently had very different treatment from the other treated subjects, and thus were excluded from all summary tables.

Pre-assignment

Screening details:

Subjects who successfully completed ISIS 301012--CS5 (NCT00607373), ISIS 301012- CS7 (NCT00706849), ISIS 301012-CS17 (NCT00694109) or MIPO3500108 (NCT00794664) with an acceptable safety profile were eligible for study.

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	Mipomersen

Arm description:

Mipomersen for up to 4 years (depending on subject's consent). Subjects were followed for additional 24 week post-treatment.

Arm type	Experimental
Investigational medicinal product name	Mipomersen sodium
Investigational medicinal product code	ISIS 301012
Other name	Kynamro®
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mipomersen sodium 200 mg (for subjects weighed ≥ 50 kg) or 160 mg (for subjects weighed <50 kg) once a week.

Number of subjects in period 1	Mipomersen
Started	142
Treated	141
Consented 2 years additional treatment	42
Completed consented length of treatment	60
Completed	25
Not completed	117
Consented but did not receive additional treatment	3
Not consented for additional 2 years of treatment	18
Physician decision	3
Pregnancy	1

Adverse event	74
Unspecified	2
Enrolled but not treated	1
Withdrawal by subject	13
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Mipomersen
Reporting group description:	
Mipomersen for up to 4 years (depending on subject's consent). Subjects were followed for additional 24 week post-treatment.	

Reporting group values	Mipomersen	Total	
Number of subjects	142	142	
Age categorical Units: Subjects			
Age continuous			
Number of subjects analysed for this parameter are 141.			
Units: years			
arithmetic mean	49.3		
standard deviation	± 15.3	-	
Gender categorical Units: Subjects			
Female	57	57	
Male	84	84	
Not Available	1	1	

End points

End points reporting groups

Reporting group title	Mipomersen

Reporting group description:

Mipomersen for up to 4 years (depending on subject's consent). Subjects were followed for additional 24 week post-treatment.

Primary: Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C)

End point title	Percent Change From Baseline in Low Density Lipoprotein Cholesterol (LDL-C)[1]

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Primary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

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: No formal statistical analysis was planned to be performed .

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-28.5 (-31.9 to -25.1)			
week 52 (n = 111)	-27 (-31.2 to -22.8)			
week 76 (n = 66)	-27.3 (-33 to -21.6)			
week 104 (n = 57)	-27.9 (-33.9 to -21.8)			
week 130 (n = 42)	-21.9 (-31.1 to -12.7)			
week 156 (n = 30)	-21.4 (-31.2 to -11.7)			
week 182 (n = 26)	-23.6 (-36.6 to -10.6)			
week 208 (n = 27)	-26.3 (-36.4 to -16.2)			
week 234 (n = 17)	-22.5 (-34.3 to -10.6)			

24 weeks post last dose (n=117)	1.6 (-2.6 to 5.9)			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Apolipoprotein B (Apo B)

End point title	Percent Change From Baseline in Apolipoprotein B (Apo B)[2]

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Primary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

Notes:

[2] - 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: No formal statistical analysis was planned to be performed .

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-28.9 (-32 to -25.8)			
week 52 (n = 111)	-28.1 (-32 to -24.2)			
week 76 (n = 66)	-30.3 (-34.7 to -26)			
week 104 (n = 57)	-31.2 (-36.5 to -25.9)			
week 130 (n = 43)	-29.1 (-35.7 to -22.5)			
week 156 (n = 30)	-30.2 (-38.1 to -22.2)			
week 182 (n = 26)	-31.1 (-39.9 to -22.2)			
week 208 (n = 27)	-33.3 (-40.8 to -25.9)			
week 234 (n = 17)	-31.4 (-38.7 to -24.1)			
24 weeks post last dose (n=117)	-3.46 (-6.9 to 0)			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Total Cholesterol

End point title	Percent Change From Baseline in Total Cholesterol[3]

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Primary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

Notes:

[3] - 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: No formal statistical analysis was planned to be performed .

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-21.7 (-24.4 to -18.9)			
week 52 (n = 111)	-20.4 (-23.9 to -16.8)			
week 76 (n = 66)	-20.1 (-24.6 to -15.5)			
week 104 (n = 57)	-19.8 (-24.8 to -14.7)			
week 130 (n = 43)	-14.9 (-22.1 to -7.8)			
week 156 (n = 30)	-14.4 (-22.3 to -6.6)			
week 182 (n = 26)	-14.3 (-25 to -3.5)			
week 208 (n = 27)	-16.5 (-24.2 to -8.8)			
week 234 (n = 17)	-12.5 (-21.5 to -3.4)			
24 weeks post last dose (n=117)	1.94 (-1.5 to 5.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change From Baseline in Non High-Density Lipoprotein Cholesterol (Non-HDL-C)

End point title	Percent Change From Baseline in Non High-Density Lipoprotein Cholesterol (Non-HDL-C)[4]

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Primary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

Notes:

[4] - 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: No formal statistical analysis was planned to be performed .

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-27.2 (-30.4 to -24.1)			
week 52 (n = 111)	-25.4 (-29.5 to -21.3)			
week 76 (n = 66)	-25 (-30.4 to -19.7)			
week 104 (n = 57)	-26.2 (-32 to -20.4)			
week 130 (n = 43)	-20.7 (-29.1 to -12.3)			
week 156 (n = 30)	-20 (-29.6 to -10.3)			
week 182 (n = 26)	-21.7 (-34.7 to -8.7)			
week 208 (n = 27)	-23.9 (-33.7 to -14.1)			
week 234 (n = 17)	-19.9 (-31.5 to -8.2)			

24 weeks post last dose (n=117)	2.5 (-1.8 to 6.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Triglycerides

End point title	Percent Change From Baseline in Triglycerides

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-20.1 (-33.1 to -1.2)			
week 52 (n = 111)	-7.9 (-31.5 to 16.9)			
week 76 (n = 66)	-10.2 (-27.7 to 13.8)			
week 104 (n = 57)	-12.5 (-37.1 to 7.2)			
week 130 (n = 43)	-10.9 (-36 to 10)			
week 156 (n = 30)	-10.4 (-23.8 to 12.7)			
week 182 (n = 26)	-12.9 (-27.4 to -1.6)			
week 208 (n = 27)	-13.9 (-40 to 33)			
week 234 (n = 17)	1.3 (-15.4 to 15.7)			
24 weeks post last dose (n=117)	2.1 (-17.2 to 27.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in lipoprotein (a)

End point title	Percent Change From Baseline in lipoprotein (a)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n = 130)	-20.5 (-39.3 to -3.6)			
week 52 (n = 111)	-19 (-33.3 to 0)			
week 76 (n = 66)	-17.9 (-33.3 to -0.5)			
week 104 (n = 57)	-16.6 (-36.1 to 0)			
week 130 (n = 43)	-15.8 (-31.3 to 0)			
week 156 (n = 30)	-9.1 (-33.8 to 7.3)			
week 182 (n = 26)	-9 (-27.2 to 7.6)			
week 208 (n = 27)	-9.9 (-32.5 to 4.1)			
week 234 (n = 17)	-18.3 (-31.6 to -4.8)			
24 weeks post last dose (n=117)	0 (-6 to 5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL Particles' Size (Total)

End point title	Percent Change From Baseline in LDL Particles' Size (Total)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	-26.77 (-32.7 to -20.8)			
week 104 (n=47)	-27.77 (-35.3 to -20.3)			
week 156 (n=20)	-25.1 (-40.3 to -9.9)			
week 208 (n=19)	-32.65 (-44.9 to -20.4)			
End of treatment (n=139)	-22.63 (-27 to -18.3)			
24 weeks post last dose (n=115)	6.11 (0.8 to 11.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL Particles' Size (Large)

End point title	Percent Change From Baseline in LDL Particles' Size (Large)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug.

Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	-5.01 (-16.8 to 6.8)			
week 104 (n=47)	-14.32 (-27 to -1.6)			
week 156 (n=20)	-27.04 (-40.6 to -13.4)			
week 208 (n=19)	-22.67 (-41.6 to -3.8)			
End of treatment (n=139)	-2.94 (-13.2 to 7.3)			
24 weeks post last dose (n=115)	6.19 (-6.1 to 18.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL Particles' Size (Medium)

End point title	Percent Change From Baseline in LDL Particles' Size (Medium)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	-9.5 (-31.8 to 12.8)			
week 104 (n=47)	11.09 (-42.2 to 64.4)			
week 156 (n=20)	-19.62 (-57.3 to 18)			
week 208 (n=19)	-15.82 (-62 to 30.4)			
End of treatment (n=139)	-5.65 (-30.3 to 19)			
24 weeks post last dose (n=115)	46.92 (5.6 to 88.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL Particles' Size (Small)

End point title	Percent Change From Baseline in LDL Particles' Size (Small)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	-8.79 (-33.7 to 16.2)			
week 104 (n=47)	1.72 (-43.9 to 47.4)			
week 156 (n=20)	-18.95 (-58.8 to 20.9)			

week 208 (n=19)	-27.95 (-67.9 to 12)			
End of treatment (n=139)	-5.17 (-29.2 to 18.8)			
24 weeks post last dose (n=115)	51.94 (7.7 to 96.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in LDL Particles' Size (Very Small)

End point title	Percent Change From Baseline in LDL Particles' Size (Very Small)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	-5.05 (-32.2 to 22.2)			
week 104 (n=47)	-0.11 (-44.4 to 44.2)			
week 156 (n=20)	-18.7 (-59.2 to 21.8)			
week 208 (n=19)	-30.77 (-69.3 to 7.8)			
End of treatment (n=139)	0.75 (-28 to 29.5)			
24 weeks post last dose (n=115)	60.22 (7.5 to 112.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL Particles' Size (Large)

End point title	Percent Change From Baseline in HDL Particles' Size (Large)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 52 (n=89)	160.8 (-38.3 to 359.9)			
week 104 (n=47)	43.23 (-12.2 to 98.7)			
week 156 (n=20)	58.26 (-38 to 154.6)			
week 208 (n=19)	61.76 (-41.6 to 165.2)			
End of treatment (n=134)	121.16 (-17.3 to 259.6)			
24 weeks post last dose (n=110)	85.93 (-7.3 to 179.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL Particles' Size (Medium)

End point title	Percent Change From Baseline in HDL Particles' Size (Medium)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=44)	154.77 (2.8 to 306.8)			
week 104 (n=28)	176.14 (-68.6 to 420.9)			
week 156 (n=9)	21.24 (-65.1 to 107.6)			
week 208 (n=8)	838.32 (-1109.3 to 2785.9)			
End of treatment (n=68)	388.16 (94.5 to 681.8)			
24 weeks post last dose (n=56)	233.78 (7.9 to 459.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in HDL Particles' Size (Small)

End point title	Percent Change From Baseline in HDL Particles' Size (Small)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	1.83 (-7.3 to 10.9)			
week 104 (n=47)	-9.81 (-17.7 to -2)			
week 156 (n=20)	-14.18 (-25.1 to -3.2)			
week 208 (n=19)	-11.47 (-20 to -2.9)			
End of treatment (n=139)	0.44 (-6.9 to 7.7)			
24 weeks post last dose (n=115)	8.31 (0.6 to 16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Intermediate Density Lipoprotein Particles' Size

End point title	Percent Change From Baseline in Intermediate Density Lipoprotein Particles' Size

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=79)	-9.9 (-45.6 to 25.8)			
week 104 (n=40)	-27.35 (-66.5 to 11.8)			
week 156 (n=16)	155.42 (-90.1 to 401)			

week 208 (n=15)	32.88 (-104 to 169.8)			
End of treatment (n=122)	24.66 (-28.4 to 77.8)			
24 weeks post last dose (n=101)	57.46 (15.2 to 99.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Very Low Density Lipoprotein (VLDL) Particles' Size (Large) and Chylomicron Particles' Size

End point title	Percent Change From Baseline in Very Low Density Lipoprotein (VLDL) Particles' Size (Large) and Chylomicron Particles' Size

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=86)	109.23 (33.7 to 184.8)			
week 104 (n=46)	107.5 (-10.2 to 225.2)			
week 156 (n=19)	123.42 (-113 to 359.8)			
week 208 (n=18)	241.76 (-241.5 to 725.1)			
End of treatment (n=132)	86.75 (28.4 to 145.1)			
24 weeks post last dose (n=110)	90.82 (21.8 to 159.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in VLDL Particles' Size (Medium)

End point title	Percent Change From Baseline in VLDL Particles' Size (Medium)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=88)	70.81 (2.1 to 139.5)			
week 104 (n=47)	97.74 (-21 to 216.5)			
week 156 (n=20)	172.46 (5.3 to 339.7)			
week 208 (n=19)	98.7 (-71.3 to 268.7)			
End of treatment (n=136)	63.25 (12.1 to 114.4)			
24 weeks post last dose (n=113)	99.57 (16.8 to 182.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in VLDL Particles' Size (Small)

End point title	Percent Change From Baseline in VLDL Particles' Size (Small)

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	49.51 (-41.1 to 140.4)			
week 104 (n=47)	30.48 (-75.1 to 136.1)			
week 156 (n=20)	9.34 (-48.3 to 67)			
week 208 (n=19)	-30.36 (-49.8 to -10.9)			
End of treatment (n=139)	31.27 (-27.3 to 89.8)			
24 weeks post last dose (n=115)	32.14 (-5.3 to 69.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Total VLDL Particles' Size and Chylomicron Particles' Size

End point title	Percent Change From Baseline in Total VLDL Particles' Size and Chylomicron Particles' Size

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	140			
Units: Percent Change				
arithmetic mean (confidence interval 95%)				
week 52 (n=91)	19.94 (-36.7 to 74.6)			
week 104 (n=47)	-14.25 (-36.4 to 7.9)			
week 156 (n=20)	3.48 (-27.5 to 34.5)			
week 208 (n=19)	-18.66 (-43.6 to 6.3)			
End of treatment (n=139)	12.82 (-25.5 to 51.2)			
24 weeks post last dose (n=115)	19.69 (3.2 to 36.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in C-Reactive Protein

End point title	Change From Baseline in C-Reactive Protein

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with c-reactive protein assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: mg/L				
arithmetic mean (confidence interval 95%)				
week 26 (n=130)	0.67 (-0.8 to 2.1)			
week 52 (n=111)	-0.37 (-1.4 to 0.6)			
week 76 (n=84)	-1.05 (-2 to -0.1)			

week 104 (n=58)	0.12 (-0.8 to 1)			
week 130 (n=42)	-0.18 (-1.1 to 0.8)			
week 156 (n=30)	0.02 (-0.5 to 2.1)			
week 182 (n=31)	0.73 (0.1 to 1.4)			
week 208 (n=27)	0.2 (-0.5 to 0.9)			
week 234 (n=18)	0.53 (-0.5 to 1.5)			
End of treatment (n=140)	0.41 (-0.6 to 1.4)			
24 weeks post last dose (n=116)	0.09 (-0.9 to 1.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Apolipoprotein A-1

End point title	Percent Change From Baseline in Apolipoprotein A-1

End point description:

Baseline was defined as the last value prior to receiving the first dose of mipomersen in this study (for subjects randomized to placebo in their index study and for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered >=6 months from their last dose of mipomersen in their index study), or the last value prior to receiving the first dose of mipomersen in their index study (for subjects randomized to mipomersen in their index study and their first dose of mipomersen in this study was administered <6 months from their last dose of mipomersen in their index study). Safety set: all enrolled subjects who received at least 1 injection of study drug. Here n=subjects with lipid parameter assessment at specified time.

End point type	Secondary

End point timeframe:

Baseline up to Week 234; 24 weeks post treatment (up to 4.5 years)

End point values	Mipomersen			
Subject group type	Reporting group			
Number of subjects analysed	141			
Units: percent change				
arithmetic mean (confidence interval 95%)				
week 26 (n=130)	-1.01 (-3.8 to 1.7)			
week 52 (n=111)	-1.59 (-4.7 to 1.6)			
week 76 (n=66)	-3.73 (-7.9 to 0.5)			
week 104 (n=57)	-4.33 (-9.1 to 0.4)			
week 130 (n=43)	-1.37 (-6.1 to 3.4)			

week 156 (n=30)	-5.55 (-11.2 to 0)			
week 182 (n=26)	-3.17 (-9.4 to 3.1)			
week 208 (n=27)	-2.19 (-7.2 to 2.8)			
week 234 (n=17)	3.68 (-3 to 10.3)			
24 weeks post last dose (n = 117)	-0.67 (-3.5 to 2.2)			

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 (59.7 months) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events and death are treatment-emergent that is AEs that developed/worsened and death that occurred during the 'on treatment period' (from the start of study drug in this study up to 24 weeks post-treatment)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Mipomersen

Reporting group description:

Mipomersen for up to 4 years (depending on subject's consent). Subjects were followed for additional 24 week post-treatment.

Serious adverse events	Mipomersen		
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 141 (25.53%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast Cancer			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal Cancer			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous Cell Carcinoma			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic Aneurysm			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic Stenosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Femoral Artery Occlusion			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral Artery Dissection			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Ileostomy			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device Malfunction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Non-Cardiac Chest Pain			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Contrast Media Allergy			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary Hypertension			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Alcoholism			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle Fracture			

subjects affected / exposed	2 / 141 (1.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal Anastomotic Leak				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Restenosis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extradural Haematoma				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Coronary Syndrome				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute Myocardial Infarction				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Aortic Valve Stenosis				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina Unstable				

subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Congestive				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Coronary Artery Disease				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Myocardial Infarction				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Supraventricular Tachycardia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dementia Alzheimer's Type				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Amnesia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	2 / 141 (1.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Arachnoid Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial Seizures			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Splenic Haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulum Intestinal			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Glomerulonephritis Membranous			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Neck Pain			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Mipomersen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	141 / 141 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal Cell Carcinoma			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
Benign Breast Neoplasm			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Lipoma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Seborrhoeic Keratosis			

subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Melanocytic Naevus			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Skin Papilloma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Thyroid Neoplasm			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vascular disorders			
Aortic Arteriosclerosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Aortic Aneurysm			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Aortic Dilatation			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Aortic Stenosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Aortic Calcification			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	8 / 141 (5.67%)		
occurrences (all)	9		
Hot Flush			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
Haematoma			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		

Flushing subjects affected / exposed occurrences (all)	3 / 141 (2.13%) 4		
Infarction subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Hypertensive Crisis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Intermittent Claudication subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Hypotension subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Peripheral Coldness subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 2		
Orthostatic Hypotension subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Pallor subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Subclavian Artery Stenosis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Phlebitis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Peripheral Vascular Disorder subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
General disorders and administration site conditions			

Asthenia				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	10			
Chest Discomfort				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Chest Pain				
subjects affected / exposed	9 / 141 (6.38%)			
occurrences (all)	9			
Chills				
subjects affected / exposed	27 / 141 (19.15%)			
occurrences (all)	103			
Cyst				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Device Breakage				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Exercise Tolerance Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Facial Pain				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Device Failure				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Feeling Cold				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Discomfort				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gait Disturbance				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			

Influenza Like Illness				
subjects affected / exposed	70 / 141 (49.65%)			
occurrences (all)	282			
Fatigue				
subjects affected / exposed	38 / 141 (26.95%)			
occurrences (all)	93			
Injection Site Discolouration				
subjects affected / exposed	55 / 141 (39.01%)			
occurrences (all)	144			
Injection Site Bruising				
subjects affected / exposed	72 / 141 (51.06%)			
occurrences (all)	316			
Injection Site Discomfort				
subjects affected / exposed	14 / 141 (9.93%)			
occurrences (all)	55			
Injection Site Atrophy				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Injection Site Erythema				
subjects affected / exposed	117 / 141 (82.98%)			
occurrences (all)	822			
Injection Site Eczema				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Injection Site Exfoliation				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Injection Site Extravasation				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	3			
Injection Site Haematoma				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Injection Site Haemorrhage				
subjects affected / exposed	17 / 141 (12.06%)			
occurrences (all)	35			

Injection Site Hypertrophy				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	5			
Injection Site Hypoaesthesia				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	4			
Injection Site Induration				
subjects affected / exposed	31 / 141 (21.99%)			
occurrences (all)	62			
Injection Site Hypersensitivity				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	5			
Injection Site Macule				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	21			
Injection Site Lymphadenopathy				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Injection Site Inflammation				
subjects affected / exposed	12 / 141 (8.51%)			
occurrences (all)	25			
Injection Site Nodule				
subjects affected / exposed	9 / 141 (6.38%)			
occurrences (all)	22			
Injection Site Oedema				
subjects affected / exposed	19 / 141 (13.48%)			
occurrences (all)	84			
Injection Site Pain				
subjects affected / exposed	102 / 141 (72.34%)			
occurrences (all)	807			
Injection Site Mass				
subjects affected / exposed	14 / 141 (9.93%)			
occurrences (all)	88			
Injection Site Pallor				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	15			

Injection Site Papule				
subjects affected / exposed	7 / 141 (4.96%)			
occurrences (all)	34			
Injection Site Paraesthesia				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Injection Site Pruritus				
subjects affected / exposed	46 / 141 (32.62%)			
occurrences (all)	206			
Injection Site Swelling				
subjects affected / exposed	31 / 141 (21.99%)			
occurrences (all)	157			
Injection Site Recall Reaction				
subjects affected / exposed	10 / 141 (7.09%)			
occurrences (all)	15			
Injection Site Reaction				
subjects affected / exposed	12 / 141 (8.51%)			
occurrences (all)	48			
Injection Site Rash				
subjects affected / exposed	16 / 141 (11.35%)			
occurrences (all)	54			
Injection Site Warmth				
subjects affected / exposed	19 / 141 (13.48%)			
occurrences (all)	47			
Injection Site Vesicles				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Injection Site Urticaria				
subjects affected / exposed	10 / 141 (7.09%)			
occurrences (all)	28			
Non-Cardiac Chest Pain				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	5			
Malaise				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			

Localised Oedema subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Local Swelling subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Oedema Peripheral subjects affected / exposed occurrences (all)	10 / 141 (7.09%) 10		
Pain subjects affected / exposed occurrences (all)	13 / 141 (9.22%) 41		
Pyrexia subjects affected / exposed occurrences (all)	25 / 141 (17.73%) 38		
Temperature Intolerance subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vaccination Site Pain subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Swelling subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Tenderness subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Xerosis subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Vessel Puncture Site Bruise subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Immune system disorders Hypersensitivity			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Seasonal Allergy			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	4		
Serum Sickness			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Erectile Dysfunction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Dyspareunia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Breast Mass			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Amenorrhoea			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	3		
Menopausal Symptoms			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Ovarian Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Menstruation Delayed			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Pelvic Pain			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Pruritus Genital			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Prostatitis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Testicular Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Uterine Prolapse			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Uterine Haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vaginal Discharge			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vaginal Haemorrhage			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Vulvovaginal Burning Sensation			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vulvovaginal Dryness			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Bronchial Hyperreactivity			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Dysphonia			

subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Cough				
subjects affected / exposed	15 / 141 (10.64%)			
occurrences (all)	22			
Dyspnoea				
subjects affected / exposed	12 / 141 (8.51%)			
occurrences (all)	14			
Dyspnoea Exertional				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	5			
Epistaxis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	16			
Hypoxia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Paranasal Sinus Hypersecretion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Hiccups				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Nasal Congestion				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	4			
Painful Respiration				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Oropharyngeal Pain				
subjects affected / exposed	13 / 141 (9.22%)			
occurrences (all)	18			
Pneumonia Aspiration				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Rhinitis Allergic				

subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Productive Cough			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	4		
Sinus Disorder			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Respiratory Tract Congestion			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Sinus Congestion			
subjects affected / exposed	6 / 141 (4.26%)		
occurrences (all)	8		
Rhinorrhoea			
subjects affected / exposed	8 / 141 (5.67%)		
occurrences (all)	9		
Upper Respiratory Tract Congestion			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
Sleep Apnoea Syndrome			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Wheezing			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Psychiatric disorders			
Abnormal Sleep-Related Event			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Confusional State			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	6 / 141 (4.26%)		
occurrences (all)	8		

Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	8 / 141 (5.67%)		
occurrences (all)	8		
Libido Decreased			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Panic Attack			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	9 / 141 (6.38%)		
occurrences (all)	9		
Stress			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	5		
Investigations			
Albumin Urine Present			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Aspartate Aminotransferase Increased			
subjects affected / exposed	21 / 141 (14.89%)		
occurrences (all)	23		
Alanine Aminotransferase Increased			
subjects affected / exposed	26 / 141 (18.44%)		
occurrences (all)	33		
Beta 2 Microglobulin Urine Increased			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Blood Bicarbonate Decreased			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Blood Alkaline Phosphatase Increased			

subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	4			
Blood Potassium Increased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Blood Creatine Phosphokinase Increased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Blood Creatinine Increased				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	6			
Blood Uric Acid Increased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Blood Phosphorus Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Body Temperature Increased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Blood Testosterone Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Blood Pressure Increased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Carotid Bruit				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Cardiac Murmur				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	4			
C-Reactive Protein Increased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			

Electrocardiogram T Wave Inversion				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Electrocardiogram T Wave Abnormal				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Electrocardiogram St Segment Depression				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Heart Rate Increased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Electrocardiogram Abnormal				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gamma-Glutamyltransferase Increased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Haematocrit Decreased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	4			
Haemoglobin Decreased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
International Normalised Ratio Increased				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Liver Function Test Abnormal				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Hepatic Enzyme Increased				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	7			
Multiple Gated Acquisition Scan Abnormal				

subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Lymph Node Palpable				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Liver Scan Abnormal				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Platelet Count Decreased				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	9			
Lymphocyte Count Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Mycobacterium Tuberculosis Complex Test Positive				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Peripheral Pulse Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Nuclear Magnetic Resonance Imaging Abnormal				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Red Blood Cell Count Decreased				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Prothrombin Time Prolonged				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Red Blood Cell Acanthocytes Present				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Protein Urine Present				

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Red Blood Cells Urine Positive			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Scan Myocardial Perfusion Abnormal			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Red Blood Cell Schistocytes Present			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Weight Increased			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Urine Analysis Abnormal			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Transaminases Increased			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Weight Decreased			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
White Blood Cell Count Decreased			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Animal Scratch			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Ankle Fracture			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Back Injury			

subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Arthropod Sting				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Brain Contusion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Arthropod Bite				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	5			
Contusion				
subjects affected / exposed	9 / 141 (6.38%)			
occurrences (all)	15			
Concussion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Epicondylitis				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Fractured Coccyx				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Excoriation				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	3			
Jaw Fracture				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Fall				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	3			
Incisional Hernia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gastrointestinal Anastomotic Leak				

subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Injury				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Kidney Contusion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Laceration				
subjects affected / exposed	7 / 141 (4.96%)			
occurrences (all)	7			
Ligament Sprain				
subjects affected / exposed	8 / 141 (5.67%)			
occurrences (all)	8			
Post Procedural Contusion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Muscle Strain				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	4			
Limb Injury				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Meniscus Injury				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Procedural Vomiting				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Radius Fracture				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Procedural Pain				
subjects affected / exposed	9 / 141 (6.38%)			
occurrences (all)	10			
Post-Traumatic Pain				

subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Repetitive Strain Injury				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Road Traffic Accident				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Scratch				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Spinal Compression Fracture				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	3			
Splenic Haematoma				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Sunburn				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Suture Related Complication				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Thermal Burn				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	6			
Tibia Fracture				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Tooth Fracture				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Vaccination Complication				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Wound				

subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	14 / 141 (9.93%)		
occurrences (all)	19		
Atrial Fibrillation			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
Aortic Valve Disease			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Aortic Valve Incompetence			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Bradycardia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Coronary Artery Disease			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Extrasystoles			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Atrioventricular Block Second Degree			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Myocardial Ischaemia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	7		
Supraventricular Extrasystoles			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		

Tachycardia			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Ventricular Extrasystoles			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Ventricular Dysfunction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Nervous system disorders			
Burning Sensation			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Carotid Artery Stenosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Carpal Tunnel Syndrome			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Cluster Headache			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Cognitive Disorder			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	10 / 141 (7.09%)		
occurrences (all)	11		
Dizziness Postural			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Dysgeusia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Headache			

subjects affected / exposed	35 / 141 (24.82%)			
occurrences (all)	81			
Hypoaesthesia				
subjects affected / exposed	7 / 141 (4.96%)			
occurrences (all)	8			
Lethargy				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	11			
Loss Of Consciousness				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Morton's Neuralgia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Migraine With Aura				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Migraine				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	6			
Nerve Compression				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Paraesthesia				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Orthostatic Intolerance				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Neuropathy Peripheral				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Post Herpetic Neuralgia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Neuralgia				

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Restless Legs Syndrome			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Sciatica			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Syncope			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
Sinus Headache			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	6		
Somnolence			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Transient Ischaemic Attack			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Viith Nerve Paralysis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	8 / 141 (5.67%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 141 (6.38%)		
occurrences (all)	11		
Thrombocytopenia			
subjects affected / exposed	5 / 141 (3.55%)		
occurrences (all)	5		

Leukopenia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Ear Discomfort			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Ear Pain			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Eustachian Tube Dysfunction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Vertigo			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Eye disorders			
Cataract			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	6		
Arcus Lipoides			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Dry Eye			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Diplopia			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Eye Irritation			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Eye Swelling			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Eye Pain			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Eyelid Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Halo Vision			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Vitreous Floaters			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vision Blurred			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		
Presbyopia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Ocular Hyperaemia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal Hernia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Abdominal Distension			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	3		

Abdominal Discomfort				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	3			
Anal Haemorrhage				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Abdominal Pain				
subjects affected / exposed	14 / 141 (9.93%)			
occurrences (all)	24			
Abdominal Pain Upper				
subjects affected / exposed	7 / 141 (4.96%)			
occurrences (all)	9			
Dental Caries				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Abdominal Pain Lower				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	5			
Colitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Bezoar				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	7			
Diverticulum				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Diverticulum Intestinal				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Diarrhoea				
subjects affected / exposed	21 / 141 (14.89%)			
occurrences (all)	37			

Dyspepsia				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	7			
Faeces Soft				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Faecal Incontinence				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Dysphagia				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Gastric Ulcer				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Food Poisoning				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Gastritis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Flatulence				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gastrooesophageal Reflux Disease				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Gastritis Erosive				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gingival Recession				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Hiatus Hernia				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			

Haematochezia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Haemorrhoids				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Hypoaesthesia Oral				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Intestinal Obstruction				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Lip Blister				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Lip Swelling				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Inguinal Hernia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Oesophageal Dilatation				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Mouth Ulceration				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	37 / 141 (26.24%)			
occurrences (all)	105			
Odynophagia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Oesophagitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			

Oesophageal Spasm subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Rectal Haemorrhage subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Pancreatic Duct Dilatation subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Proctitis Ulcerative subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Periodontal Disease subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Retching subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vomiting subjects affected / exposed occurrences (all)	13 / 141 (9.22%) 21		
Umbilical Hernia subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Toothache subjects affected / exposed occurrences (all)	5 / 141 (3.55%) 5		
Tooth Impacted subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vomiting Projectile subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 2		
Hepatobiliary disorders Cholecystitis Chronic			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Biliary Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Cholelithiasis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Cholecystitis Acute			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hepatic Cyst			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hepatic Fibrosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hepatomegaly			
subjects affected / exposed	9 / 141 (6.38%)		
occurrences (all)	9		
Hepatic Steatosis			
subjects affected / exposed	17 / 141 (12.06%)		
occurrences (all)	19		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Cold Sweat			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Dermatitis Acneiform			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Dermatitis Contact			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		

Blister				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Dermatitis				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Ecchymosis				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	10			
Dry Skin				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Dermatitis Allergic				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	4			
Hair Growth Abnormal				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	5			
Eczema				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Erythema				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Lipodystrophy Acquired				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Ingrowing Nail				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Ingrown Hair				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Intertrigo				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			

Macule				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Petechiae				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Onychoclasis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pain Of Skin				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pruritus				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	18			
Pruritus Generalised				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Pigmentation Disorder				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Rash Papular				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Rash Maculo-Papular				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Rash				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	11			
Rash Erythematous				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	3			
Scab				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			

Rash Vesicular			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Rash Pruritic			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Skin Lesion			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Skin Hyperpigmentation			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	6 / 141 (4.26%)		
occurrences (all)	8		
Skin Plaque			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Xanthoma			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Xanthelasma			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Renal and urinary disorders			
Bladder Discomfort			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Albuminuria			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	4		
Haematuria			
subjects affected / exposed	6 / 141 (4.26%)		
occurrences (all)	6		
Dysuria			

subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Nephrolithiasis				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Micturition Urgency				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Nephropathy				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Proteinuria				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	8			
Pollakiuria				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Pyelocaliectasis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pyuria				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Renal Cyst				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Renal Failure				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Stress Urinary Incontinence				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Urinary Tract Disorder				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Urge Incontinence				

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 141 (13.48%)		
occurrences (all)	26		
Arthritis			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	5		
Back Pain			
subjects affected / exposed	24 / 141 (17.02%)		
occurrences (all)	34		
Bunion			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Bone Pain			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Bursitis			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Cervical Spinal Stenosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Coccydynia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Costochondritis			

subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Exostosis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Fibromyalgia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Dupuytren's Contracture				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Flank Pain				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Intervertebral Disc Degeneration				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Fracture Pain				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Muscle Atrophy				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Haemarthrosis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Joint Effusion				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Joint Swelling				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Muscular Weakness				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	5			
Muscle Spasms				

subjects affected / exposed	8 / 141 (5.67%)			
occurrences (all)	13			
Muscle Tightness				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Muscle Twitching				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Musculoskeletal Discomfort				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Musculoskeletal Chest Pain				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			
Musculoskeletal Pain				
subjects affected / exposed	7 / 141 (4.96%)			
occurrences (all)	8			
Myalgia				
subjects affected / exposed	33 / 141 (23.40%)			
occurrences (all)	53			
Osteoarthritis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Neck Pain				
subjects affected / exposed	6 / 141 (4.26%)			
occurrences (all)	8			
Musculoskeletal Stiffness				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	5			
Osteopenia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pain In Jaw				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pain In Extremity				

subjects affected / exposed	14 / 141 (9.93%)		
occurrences (all)	19		
Plantar Fasciitis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Spinal Osteoarthritis			
subjects affected / exposed	5 / 141 (3.55%)		
occurrences (all)	8		
Soft Tissue Atrophy			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Rotator Cuff Syndrome			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	7		
Temporomandibular Joint Syndrome			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Tendon Pain			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Infections and infestations			
Abscess Limb			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Asymptomatic Bacteriuria			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Acarodermatitis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Acute Sinusitis			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		

Anal Abscess				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	10 / 141 (7.09%)			
occurrences (all)	16			
Conjunctivitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Bronchopneumonia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Cellulitis				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Ear Infection				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	5			
Cystitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Eye Infection				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	5			
Diverticulitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Folliculitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Furuncle				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			

Genital Herpes Simplex				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gastrointestinal Infection				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gastrointestinal Viral Infection				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	9			
Helicobacter Gastritis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Gastroenteritis Viral				
subjects affected / exposed	5 / 141 (3.55%)			
occurrences (all)	5			
H1n1 Influenza				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Giardiasis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Herpes Zoster				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Kidney Infection				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Influenza				
subjects affected / exposed	17 / 141 (12.06%)			
occurrences (all)	23			
Laryngitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Lower Respiratory Tract Infection				
subjects affected / exposed	3 / 141 (2.13%)			
occurrences (all)	3			

Localised Infection				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Nasopharyngitis				
subjects affected / exposed	28 / 141 (19.86%)			
occurrences (all)	54			
Otitis Externa				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Oral Herpes				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Otitis Media Acute				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Onychomycosis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			
Paronychia				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			
Pharyngitis Streptococcal				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	3			
Post Procedural Infection				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Respiratory Tract Infection				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	4 / 141 (2.84%)			
occurrences (all)	4			

Pneumonia				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Sinusitis				
subjects affected / exposed	20 / 141 (14.18%)			
occurrences (all)	35			
Skin Bacterial Infection				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Tinea Cruris				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Sinobronchitis				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Tooth Abscess				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Tinea Versicolour				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	1			
Tooth Infection				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Urinary Tract Infection				
subjects affected / exposed	23 / 141 (16.31%)			
occurrences (all)	37			
Upper Respiratory Tract Infection				
subjects affected / exposed	27 / 141 (19.15%)			
occurrences (all)	34			
Viral Infection				
subjects affected / exposed	2 / 141 (1.42%)			
occurrences (all)	2			
Vaginal Infection				
subjects affected / exposed	1 / 141 (0.71%)			
occurrences (all)	2			

Wound Infection			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Wound Sepsis			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Decreased Appetite			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	5		
Dehydration			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Glucose Tolerance Impaired			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Gout			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Iron Deficiency			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	3		
Vitamin B12 Deficiency			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Type 2 Diabetes Mellitus			

subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vitamin D Deficiency			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 August 2007	It included the following changes: - The dose regimen was changed from 200 mg every other week with dose-titration to effect to 200 mg once a week without the option to dose-titrate to effect. - In addition, it reduced the treatment period from 2 years to 6 months in accordance with the extension of the treatment period in the studies that were to roll into this open-label extension study. - It also modified the protocol to include subjects who completed study ISIS 301012-CS7. - Other modifications were made to maintain consistency between this study and other ongoing mipomersen clinical trials. The background information for the drug was updated to reflect the status of the mipomersen development program and to be consistent with the Investigator's Brochure. - Minor changes were also made to improve the overall clarity of the original protocol.
17 July 2008	It included the following changes: - This amendment indicated that sponsorship was transferred from Isis Pharmaceuticals, Inc. to the Genzyme Corporation. - The safety reporting information was updated to provide contact information for the Genzyme Pharmacovigilance Department. - Modifications were made to extend dosing of mipomersen from 26 weeks to 52 weeks for the purpose of obtaining additional long-term safety and efficacy data. - Minor changes were also made to improve the overall clarity of the protocol and to align the text with the Investigator's Brochure.
24 August 2009	It included the following changes: Dosing of mipomersen was extended from 52 weeks to 104 weeks for the purpose of obtaining additional long-term safety and efficacy data. - Included subjects who completed study MIPO3500108, which expanded the population to include subjects with severe hypercholesterolemia. The title of the study was updated to reflect this change. - Safety monitoring and stopping rules were revised to reflect information from the larger safety database. - This amendment also allowed for temporary dose adjustment for liver chemistry elevations, as well as for injection site reactions and constitutional symptoms leading the subject to consider discontinuation from the study. - Added a new section to the protocol recommending magnetic resonance imaging (MRI) or computed tomography (CT) scanning if clinically indicated. - This amendment noted that additional pharmacokinetic (PK) samples were to be drawn (not just for trough levels), in order to determine peak mipomersen levels after dosing. - Minor changes were also made to improve the overall clarity of the protocol and to align the text with the Investigator's Brochure.
17 February 2010	It included the following changes: - Included MRI assessments of liver fat fraction at approximately 6-month intervals during the study. These MRI assessments were added to provide further characterization of potential changes in liver fat with long-term treatment with mipomersen. - In addition, it included a metabolomics analysis, which was added to help in understanding the cellular mechanisms underlying any imaging findings observed. - Other changes included minor changes to safety monitoring rules and clarifications made to study conduct and corrections to minor inconsistencies.

18 May 2011	It included the following changes: - Extended dosing from 2 years to 4 years or until mipomersen was commercially available (whichever came first) for the purpose of obtaining additional long-term safety and efficacy data. - Included that subjects must establish sufficient sustained efficacy throughout the treatment period per Investigator judgment, such as ≥15% LDL-C reduction from the subject's primary study baseline value, regardless of dosing regimen. - Dose adjustment instructions were modified to align with current development plans for mipomersen, specifically, to offer an alternative dosing regimen (70 mg thrice per week) for subjects with intolerable injection site reactions or flu-like symptoms with the 200 mg per week injections and to extend the dose interval for subjects with liver enzyme elevations (200 mg every other week). - Included additional post-dose serial PK blood samples for the purpose of further exploring the PK profile after mipomersen administration.
12 September 2011	It included following changes:- Biopsy data collected in order to evaluate whether hepatic abnormalities were present in subjects who had already completed, or were expected to complete, more than 2 years of treatment. - Blood samples collected at the visits specified on the schedule of events and stored specifically for hepatic biomarker testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported