



## 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
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##### 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:

<b>Subjects enrolled per age group</b>	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	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

<b>Arm title</b>	Mipomersen
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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  $\geq$  50 kg) or 160 mg (for subjects weighed  $<$ 50 kg) once a week.

<b>Number of subjects in period 1</b>	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
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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 standard deviation	49.3 ± 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) <sup>[1]</sup>
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#### 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  $\geq 6$  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
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#### 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)			
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## 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) <sup>[2]</sup>
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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  $\geq 6$  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
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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 <sup>[3]</sup>
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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  $\geq 6$  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
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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) <sup>[4]</sup>
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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  $\geq 6$  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
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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)			
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## 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
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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  $\geq 6$  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
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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)
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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  $\geq 6$  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
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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)
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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  $\geq 6$  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
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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)
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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  $\geq 6$  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
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End point timeframe:

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

<b>End point values</b>	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)
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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  $\geq 6$  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
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End point timeframe:

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

<b>End point values</b>	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)
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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  $\geq 6$  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
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End point timeframe:

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

<b>End point values</b>	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)
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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  $\geq 6$  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
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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  $\geq 6$  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  $\geq 6$  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:	
<p>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 <math>\geq 6</math> 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 <math>&lt; 6</math> 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.</p>	
End point type	Secondary
End point timeframe:	
Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)	

<b>End point values</b>	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
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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  $\geq 6$  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
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End point timeframe:

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

<b>End point values</b>	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
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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  $\geq 6$  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
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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  $\geq 6$  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  $\geq 6$  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)	

<b>End point values</b>	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
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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  $\geq 6$  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
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End point timeframe:

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

<b>End point values</b>	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:	
<p>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 <math>\geq 6</math> 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 <math>&lt; 6</math> 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.</p>	
End point type	Secondary
End point timeframe:	
Baseline up to End of treatment; 24 weeks post treatment (up to 4.5 years)	

<b>End point values</b>	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
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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  $\geq 6$  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
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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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17
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### Reporting groups

Reporting group title	Mipomersen
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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		
<b>Vascular disorders</b>			
<b>Aortic Aneurysm</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Aortic Stenosis</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Femoral Artery Occlusion</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Peripheral Artery Dissection</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Surgical and medical procedures</b>			
<b>Ileostomy</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>General disorders and administration site conditions</b>			
<b>Chest Pain</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Device Malfunction</b>			
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		
<b>Gastrointestinal Anastomotic Leak</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Coronary Artery Restenosis</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Extradural Haematoma</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
<b>Acute Coronary Syndrome</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Acute Myocardial Infarction</b>			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Angina Pectoris</b>			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
<b>Aortic Valve Stenosis</b>			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Angina Unstable</b>			

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

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

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

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

Flushing			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	4		
Infarction			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hypertensive Crisis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Intermittent Claudication			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
Peripheral Coldness			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Orthostatic Hypotension			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Subclavian Artery Stenosis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Phlebitis			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Peripheral Vascular Disorder			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	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 occurrences (all)	3 / 141 (2.13%) 5		
Injection Site Hypoaesthesia subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 4		
Injection Site Induration subjects affected / exposed occurrences (all)	31 / 141 (21.99%) 62		
Injection Site Hypersensitivity subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 5		
Injection Site Macule subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 21		
Injection Site Lymphadenopathy subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Injection Site Inflammation subjects affected / exposed occurrences (all)	12 / 141 (8.51%) 25		
Injection Site Nodule subjects affected / exposed occurrences (all)	9 / 141 (6.38%) 22		
Injection Site Oedema subjects affected / exposed occurrences (all)	19 / 141 (13.48%) 84		
Injection Site Pain subjects affected / exposed occurrences (all)	102 / 141 (72.34%) 807		
Injection Site Mass subjects affected / exposed occurrences (all)	14 / 141 (9.93%) 88		
Injection Site Pallor subjects affected / exposed occurrences (all)	3 / 141 (2.13%) 15		

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

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

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

subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Pruritus Genital subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 2		
Prostatitis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Testicular Cyst subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Uterine Prolapse subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Uterine Haemorrhage subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vaginal Discharge subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vaginal Haemorrhage subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Vulvovaginal Burning Sensation subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Vulvovaginal Dryness subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Respiratory, thoracic and mediastinal disorders			
Bronchial Hyperreactivity subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 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 occurrences (all)	2 / 141 (1.42%) 3		
Productive Cough subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 4		
Sinus Disorder subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Respiratory Tract Congestion subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Sinus Congestion subjects affected / exposed occurrences (all)	6 / 141 (4.26%) 8		
Rhinorrhoea subjects affected / exposed occurrences (all)	8 / 141 (5.67%) 9		
Upper Respiratory Tract Congestion subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 4		
Sleep Apnoea Syndrome subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Wheezing subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Psychiatric disorders			
Abnormal Sleep-Related Event subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Confusional State subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Anxiety subjects affected / exposed occurrences (all)	6 / 141 (4.26%) 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 occurrences (all)	2 / 141 (1.42%) 2		
Electrocardiogram T Wave Abnormal subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Electrocardiogram St Segment Depression subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Heart Rate Increased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Electrocardiogram Abnormal subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Gamma-Glutamyltransferase Increased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Haematocrit Decreased subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 4		
Haemoglobin Decreased subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
International Normalised Ratio Increased subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Liver Function Test Abnormal subjects affected / exposed occurrences (all)	3 / 141 (2.13%) 3		
Hepatic Enzyme Increased subjects affected / exposed occurrences (all)	6 / 141 (4.26%) 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 occurrences (all)	1 / 141 (0.71%) 1		
Red Blood Cells Urine Positive subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Scan Myocardial Perfusion Abnormal subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Red Blood Cell Schistocytes Present subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Weight Increased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Urine Analysis Abnormal subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Transaminases Increased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Weight Decreased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
White Blood Cell Count Decreased subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Injury, poisoning and procedural complications			
Animal Scratch subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Ankle Fracture subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Back Injury			

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

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

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

subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
<b>Cardiac disorders</b>			
Angina Pectoris subjects affected / exposed occurrences (all)	14 / 141 (9.93%) 19		
Atrial Fibrillation subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 4		
Aortic Valve Disease subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Aortic Valve Incompetence subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Bradycardia subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Coronary Artery Disease subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Extrasystoles subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Atrioventricular Block Second Degree subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Myocardial Ischaemia subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Palpitations subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 7		
Supraventricular Extrasystoles subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 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		
<b>Nervous system disorders</b>			
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 occurrences (all)	1 / 141 (0.71%) 1		
Restless Legs Syndrome subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Presyncope subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Sciatica subjects affected / exposed occurrences (all)	3 / 141 (2.13%) 3		
Syncope subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 4		
Sinus Headache subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 6		
Somnolence subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Transient Ischaemic Attack subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Viith Nerve Paralysis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Tremor subjects affected / exposed occurrences (all)	8 / 141 (5.67%) 9		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	9 / 141 (6.38%) 11		
Thrombocytopenia subjects affected / exposed occurrences (all)	5 / 141 (3.55%) 5		

Leukopenia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	3 / 141 (2.13%)		
occurrences (all)	4		
<b>Ear and labyrinth disorders</b>			
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		
<b>Eye disorders</b>			
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	1 / 141 (0.71%)		
occurrences (all)	1		
Rectal Haemorrhage			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Pancreatic Duct Dilatation			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Proctitis Ulcerative			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Periodontal Disease			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Retching			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	13 / 141 (9.22%)		
occurrences (all)	21		
Umbilical Hernia			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	5 / 141 (3.55%)		
occurrences (all)	5		
Tooth Impacted			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
Vomiting Projectile			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	2		
Hepatobiliary disorders			
Cholecystitis Chronic			

subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Biliary Cyst</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Cholelithiasis</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Cholecystitis Acute</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Hepatic Cyst</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Hepatic Fibrosis</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Hepatomegaly</b> subjects affected / exposed occurrences (all)	9 / 141 (6.38%) 9		
<b>Hepatic Steatosis</b> subjects affected / exposed occurrences (all)	17 / 141 (12.06%) 19		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Alopecia</b> subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
<b>Cold Sweat</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Dermatitis Acneiform</b> subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
<b>Dermatitis Contact</b> subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 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		
Onychoclasia			
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		
<b>Nephrolithiasis</b>			
subjects affected / exposed	2 / 141 (1.42%)		
occurrences (all)	2		
<b>Micturition Urgency</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Nephropathy</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Proteinuria</b>			
subjects affected / exposed	6 / 141 (4.26%)		
occurrences (all)	8		
<b>Pollakiuria</b>			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
<b>Pyelocaliectasis</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Pyuria</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Renal Cyst</b>			
subjects affected / exposed	4 / 141 (2.84%)		
occurrences (all)	4		
<b>Renal Failure</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Stress Urinary Incontinence</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Urinary Tract Disorder</b>			
subjects affected / exposed	1 / 141 (0.71%)		
occurrences (all)	1		
<b>Urge Incontinence</b>			

subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	19 / 141 (13.48%) 26		
Arthritis subjects affected / exposed occurrences (all)	4 / 141 (2.84%) 5		
Back Pain subjects affected / exposed occurrences (all)	24 / 141 (17.02%) 34		
Bunion subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Bone Pain subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Bursitis subjects affected / exposed occurrences (all)	2 / 141 (1.42%) 2		
Chondrocalcinosis Pyrophosphate subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Cervical Spinal Stenosis subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 1		
Coccydynia subjects affected / exposed occurrences (all)	1 / 141 (0.71%) 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	<p>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.</p> <p>- Included that subjects must establish sufficient sustained efficacy throughout the treatment period per Investigator judgment, such as <math>\geq 15\%</math> LDL-C reduction from the subject's primary study baseline value, regardless of dosing regimen.</p> <p>- 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).</p> <p>- Included additional post-dose serial PK blood samples for the purpose of further exploring the PK profile after mipomersen administration.</p>
12 September 2011	<p>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.</p> <p>- Blood samples collected at the visits specified on the schedule of events and stored specifically for hepatic biomarker testing.</p>

Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported