EU Clinical Trials Register

Clinical trial results:

An Open-Label Extension Study to Assess the Long-Term Safety and Efficacy of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy (FAP)

Summary

EudraCT number	2013-004561-13
Trial protocol	PT GB DE FR ES
Global end of trial date	07 January 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	ISIS420915-CS3

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02175004
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, CA 92010
Public contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760603-3804, ClinicalTrials@ionisph.com
Scientific contact	Ionis Clinical Trial Information, Ionis Pharmaceuticals, Inc., +1 760603-3804, ClinicalTrials@ionisph.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	07 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of extended dosing with ISIS 420915 in subjects with familial amyloid polyneuropathy.

Protection of trial subjects:

All subjects signed an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 June 2014
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	Portugal: 15
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 67
Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Brazil: 19
Worldwide total number of subjects	135
EEA total number of subjects	37

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	72
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 135 subjects, of which 50 received placebo, and 85 received inotersen in the previous study ISIS 420915-CS2 (NCT01737398-CS2). Subjects enrolled into this study received inotersen. This study consisted of a 260-week Treatment Period, and 3-month Post-treatment Evaluation Period. Data is reported as per the previous(CS2) study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Previous Placebo-Inotersen 300 mg

Arm description:

Subjects received subcutaneous (SC) doses of 300 milligrams (mg) inotersen once weekly for up to 260 weeks. Subjects who received inotersen-matching placebo in the previous study- ISIS 420915-CS2 (NCT01737398) were included in this group.

Arm type	Experimental
Investigational medicinal product name	Inotersen
Investigational medicinal product code	
Other name	TEGSEDI, IONIS-TTR Rx, ISIS 420915
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inotersen 300 mg, SC

Arm title	Previous Inotersen-Inotersen 300 mg

Arm description:

Subjects received SC doses of 300 mg inotersen once weekly for up to 260 weeks. Subjects who received inotersen in the previous study- ISIS 420915-CS2 were included in this group.

Arm type	Experimental
Investigational medicinal product name	Inotersen
Investigational medicinal product code	
Other name	TEGSEDI, IONIS-TTR Rx, ISIS 420915
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inotersen 300 mg, SC

Number of subjects in period 1	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg
Started	50	85
Completed	9	9
Not completed	41	76
Voluntary Withdrawal	6	19
Investigator Judgment	1	4
Liver Transplant	1	-
Adverse Event or Serious Adverse Event (SAE)	5	14
Treatment With Commercial/Post-study Inotersen	27	39
Disease Progression	1	-

Baseline characteristics

Reporting groups

Reporting group title	Previous Placebo-Inotersen 300 mg
Reporting group description:	

Subjects received subcutaneous (SC) doses of 300 milligrams (mg) inotersen once weekly for up to 260 weeks. Subjects who received inotersen-matching placebo in the previous study- ISIS 420915-CS2 (NCT01737398) were included in this group.

Reporting group title	Previous Inotersen-Inotersen 300 mg
Reporting group description:	

Subjects received SC doses of 300 mg inotersen once weekly for up to 260 weeks. Subjects who received inotersen in the previous study- ISIS 420915-CS2 were included in this group.

Reporting group values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg	Total
Number of subjects	50	85	135
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	60.5	60.3	
standard deviation	± 14.62	± 11.86	-
Gender categorical			
Units: Subjects			
Female	15	26	41
Male	35	59	94
Ethnicity			
Units: Subjects			
Hispanic or Latino	6	12	18
Not Hispanic or Latino	44	73	117
Race			
Units: Subjects			
Asian	3	0	3
Black	0	1	1
White	44	81	125
White & Grayish-Brown	1	0	1
Other	2	3	5

End points

End points reporting groups

Reporting group title	Previous Placebo-Inotersen 300 mg
Reporting group description:	
Subjects received subcutaneous (SC) doses of 300 milligrams (mg) inotersen once weekly for up to 260 weeks. Subjects who received inotersen-matching placebo in the previous study- ISIS 420915-CS2 (NCT01737398) were included in this group.	
Reporting group title	Previous Inotersen-Inotersen 300 mg
Reporting group description:	
Subjects received SC doses of 300 mg inotersen once weekly for up to 260 weeks. Subjects who received inotersen in the previous study- ISIS 420915-CS2 were included in this group.	
Subject analysis set title	Previous Placebo-Inotersen 300 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received subcutaneous (SC) doses of 300 milligrams (mg) inotersen once weekly for up to 260 weeks. Subjects who received inotersen-matching placebo in the previous study- ISIS 420915-CS2 (NCT01737398) were included in this group.	
Subject analysis set title	Previous Inotersen-Inotersen 300 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received SC doses of 300 mg inotersen once weekly for up to 260 weeks. Participants who received inotersen in the previous study- ISIS 420915-CS2 were included in this group.	

Primary: Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Related to Study Drug

End point title	Percentage of Subjects With Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Related to Study Drug[1]

End point description:

An adverse event (AE) is any unfavorable and unintended sign (including a clinically-significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the study or use of investigational drug product, whether or not the AE is considered related to the investigational drug product. A TEAE is defined as an adverse event with an onset that occurs after receiving study drug. An SAE is any untoward medical occurrence that at any dose that results in death, is life threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, leads to a congenital anomaly/birth defect, or is an important medical event. TEAEs considered related to the study drug as assessed by the Investigator are reported. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)				
TEAEs	100	96.5		

Serious TEAEs	36.0	54.1		
TEAEs Related to Study Drug	82.0	69.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Change From Baseline in Vital Signs

End point title	Percentage of Subjects With Change From Baseline in Vital Signs[2]

End point description:

Vital signs included blood pressure, heart rate, respiratory rate, and temperature. Only categories with at least one subject with event are reported. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3. mmHg=millimeters of mercury.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)				
Systolic Blood Pressure:<90 mmHg	12.0	18.8		
Systolic Blood Pressure: >140 mmHg	32.0	41.2		
Systolic Blood Pressure: >160 mmHg	8.0	20.0		
Diastolic Blood Pressure: <50 mmHg	6.0	9.4		
Diastolic Blood Pressure: >90 mmHg	30.0	28.2		
Diastolic Blood Pressure: >100 mmHg	10.0	7.1		
Heart Rate: <60 beats per minute (bpm)	30.0	38.8		
Heart Rate: >100 bpm	16.0	9.4		
Temperature (°C): <36.0°C	46.0	55.3		
Respiratory Rate (breaths/minute): >20 breaths/min	24.0	21.2		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Change From Baseline in Weight

End point title	Percentage of Subjects With Change From Baseline in Weight[3]

End point description:

As prespecified in the protocol, percentage of participants with change from baseline in weight is reported in 2 categories, decrease of ≥7% from Baseline and increase of ≥7% from Baseline. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3. Number of subjects analysed are the number of subjects available for analyses.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	83		
Units: percentage of subjects				
number (not applicable)				
Weight (kg): Decrease of ≥7% From Baseline	30.0	47.1		
Weight (kg): Increase of ≥7% From Baseline	24.0	11.8		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Clinically Significant Change From Baseline in Laboratory Test Values

End point title	Percentage of Subjects With Clinically Significant Change From Baseline in Laboratory Test Values[4]

End point description:

Clinical laboratory tests included the analysis of chemistry, haematology, and urinalysis. Any value outside the normal range will be flagged for the attention of the investigator who will assess whether or not a flagged value is of clinical significance. Only those categories with at least one subject with event are reported. Normal range of creatinine clearance is 110 to 150 mL/min in males and 100 to 130 mL/min in females. Normal urine protein to creatinine (P/C) ratio= <0.2. Normal range for Alanine Aminotransferase (ALT) is 4 to 36 units per liter (U/L). Platelets normal range=140×10^9/L to 400×10^9/L. CCCL= confirmed creatinine clearance, ULN= upper limit of normal, ALT=alanine aminotransferase. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3. n= number analysed is the number of subjects with data available for analysis for the given category.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)				
CC CL by CKD-EPI <30 ml/min/1.73m^2 (n=50,83)	4.0	4.7		
Confirmed Urine P/C Ratio >5 × ULN (n=50,83)	8.0	10.6		
Confirmed ALT ≥3 x ULN (n=50,85)	4.0	4.7		
Confirmed Value of Platelets <75 × 10^9/L	12.0	12.9		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Change From Baseline in QT Interval Corrected Using Fridericia's Formula (QTcF) as Determined by Electrocardiogram (ECG)

End point title	Percentage of Subjects With Change From Baseline in QT Interval Corrected Using Fridericia's Formula (QTcF) as Determined by Electrocardiogram (ECG)[5]

End point description:

Normal QTcF at Baseline is defined as ≤450 milliseconds (ms) for males or ≤470 ms for females. Percentage of subjects with QT interval outside of normal range are reported. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

Notes:

[5] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)				
QTcF >450 ms	44.0	43.5		
QTcF >480 ms	20.0	23.5		
QTcF >500 ms	12.0	16.5		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Using Concomitant Medication for Nervous and Cardiovascular System Disorders

End point title	Percentage of Subjects Using Concomitant Medication for Nervous and Cardiovascular System Disorders[6]

End point description:

A concomitant therapy was any non-protocol-specified drug or substance (including over-the counter medications, herbal medications, and vitamin supplements) administered between signing of informed consent and the final post-treatment visit for treating nervous and cardiovascular system disorders. SS included all enrolled subjects who received at least 1 injection of inotersen in CS3.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

Notes:

[6] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)				
Nervous System Disorders	88.0	81.2		
Cardiovascular System Disorders	68.0	75.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Change From Baseline in Ophthalmic Examination as Assessed by Visual Acuity Changes

End point title	Percentage of Subjects With Change From Baseline in Ophthalmic Examination as Assessed by Visual Acuity Changes[7]

End point description:

SS included all enrolled subjects who received at least 1 injection of inotersen in CS3.

End point type	Primary

End point timeframe:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

Notes:

[7] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: percentage of subjects				
number (not applicable)	0.0	2.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants With Change From Baseline in Light Detection Ability Measured by Electroretinography

End point title	Percentage of Participants With Change From Baseline in Light Detection Ability Measured by Electroretinography[8]

End point description:

SS included all enrolled subjects who received at least 1 injection of inotersen in CS3. Number of subjects analysed are the number of subjects available for analyses at Baseline. n= number analysed is the number of participants with data available for analysis at the given time point. CFB=Change from Baseline.

End point type	Primary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

Notes:

[8] - 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: Only descriptive statistics was planned to be reported for this endpoint.

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	76		
Units: percentage of subjects				
number (not applicable)				
Subjects With Normal Baseline (n=39,76)	48.7	81.6		
Subjects With CFB at Week 78 (n=28,63)	25.0	12.7		
Subjects With CFB at Week 156 (n=16,33)	31.3	9.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Modified Neuropathy Impairment Score (mNIS)+7 Composite Score at Weeks 78 and 156

End point title	Change From Baseline in the Modified Neuropathy Impairment Score (mNIS)+7 Composite Score at Weeks 78 and 156

End point description:

The mNIS+7 composite score is a measure of neurologic impairment that evaluates muscle weakness, sensation, reflexes, nerve conduction, and autonomic function. The mNIS+7 Composite Score has a range of -22.32 to 346.32 and a higher mNIS+7 composite score indicates worsening disease. A positive change from Baseline indicates worsening of polyneuropathy impairments. Full Analysis Set (FAS) population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=31,66)	33.11 (± 28.915)	10.11 (± 18.204)		
Change From Baseline at Week 156 (n=21,35)	37.34 (± 29.030)	17.21 (± 27.307)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the mNIS+7 Composite Score at Week 78

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-17.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.12
upper limit	-9.56

Notes:

[9] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change From Baseline in the mNIS+7 Composite Score at Week 156

Comparison groups	Previous Inotersen-Inotersen 300 mg v Previous Placebo-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-20.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.27
upper limit	-8.95

Notes:

[10] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the mNIS +7 Component: Heart Rate to Deep Breathing Score at Weeks 78 and 156

End point title	Change From Baseline in the mNIS +7 Component: Heart Rate to Deep Breathing Score at Weeks 78 and 156

End point description:

Heart rate to deep breathing is a quantitative autonomic test using the CASE IV instrument that measures a patients change in heart rate after deep breathing. The maximum score of this component is 3.72 points. The Full Analysis Set (FAS) populations includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=35,72)	0.23 (± 0.977)	0.11 (± 0.761)		
Change From Baseline at Week 156 (n=22,39)	0.44 (± 1.099)	0.30 (± 0.504)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Heart Rate to Deep Breathing Score at Week 78

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.638 [11]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.2

Notes:

[11] - P-value=MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Heart Rate to Deep Breathing Score at Week 156

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.965 [12]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.29

Notes:

[12] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the mNIS +7 Component: Nerve Conduction Score at Weeks 78 and 156

End point title	Change From Baseline in the mNIS +7 Component: Nerve Conduction Score at Weeks 78 and 156

End point description:

The Nerve Conduction tests are quantitative tests that meassure the conduction attributes of preselected nerves. The maximum score of thsis component is 18.6 points. The Full Analysis Set (FAS) population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=32,68)	1.86 (± 2.313)	0.57 (± 1.361)		
Change From Baseline at Week 156 (n=21,36)	2.05 (± 2.351)	0.77 (± 1.724)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Nerve Conduction Score at Week 78

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [13]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	-0.5

Notes:

[13] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Nerve Conduction Score at Week 156

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067 [14]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	0.05

Notes:

[14] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the mNIS +7 Component: Heat-Pain Sensory Score at Weeks 78 and 156

End point title	Change From Baseline in the mNIS +7 Component: Heat-Pain Sensory Score at Weeks 78 and 156

End point description:

The Heat-Pain Sensory test uses the CASE IV instrument to perform standardized psychophysical measurement to determine pain sensory thresholds in response to heat. The maximum score of this component is 40 points. Full Analysis Set (FAS) included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=32,66)	2.60 (± 8.440)	2.45 (± 7.557)		
Change From Baseline at Week 156 (n=21,35)	2.90 (± 9.224)	3.40 (± 8.774)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Heat-Pain Sensory Score at Week 78

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.821 [15]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.67
upper limit	3.36

Notes:

[15] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change From Baseline in the mNIS +7 Component: Heat-Pain Sensory Score at Week 156

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293 [16]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.21
upper limit	1.9

Notes:

[16] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the mNIS +7 Component: Touch-Pressure Sensory Score at Weeks 78 and 156

End point title	Change From Baseline in the mNIS +7 Component: Touch-Pressure Sensory Score at Weeks 78 and 156

End point description:

The Touch-Pressure Sensory test uses the CASE IV instrument to perform standardized psychophysical measurement to determine pressure sensory thresholds in response to touch. The maximum score of this component is 40 points. The Full Analysis Set (FAS) population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=32,66)	1.00 (± 6.886)	-3.05 (± 8.878)		
Change From Baseline at Week 156 (n=21,35)	1.95 (± 6.866)	-2.34 (± 8.306)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change From Baseline in the mNIS +7 Component: Touch-Pressure Sensory Score at Week 78	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [17]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.53
upper limit	-0.03

Notes:

[17] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Change From Baseline in the mNIS +7 Component: Touch-Pressure Sensory Score at Week 156	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [18]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-3.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-0.13

Notes:

[18] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the Neuropathy Impairment (NIS) Composite Score at Week 52 of Years 4 and 5

End point title	Change From Baseline in the Neuropathy Impairment (NIS) Composite Score at Week 52 of Years 4 and 5

End point description:

The NIS score is a measure of neurologic impairment. The NIS Score has a range of 0 to 244 and a higher NIS score indicates lower function. A positive change from Baseline indicates worsening. FAS included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Week 52 of Years 4 and 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 52 of Year 4 (n=9,14)	35.78 (± 21.071)	18.32 (± 20.970)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	17.75 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the NIS Composite Score at Week 52 of Year 4

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [19]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-17.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.92
upper limit	-8.03

Notes:

[19] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the NIS Component: Cranial Nerves Score at Week 52 of Years 4 and 5

End point title	Change From Baseline in the NIS Component: Cranial Nerves Score at Week 52 of Years 4 and 5

End point description:

Cranial Nerve assessment involves testing 3rd and 6th nerves and facial, palate, and tongue weakness. The maximum score for this component is 40 points. The FAS population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Week 52 of Years 4 and 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 52 of Year 4 (n=9,14)	0.0 (± 0.0)	0.0 (± 0.0)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	0.0 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline in the NIS Component: Cranial Nerves Score Score at Week 52 of Year 4

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-

	Inotersen 300 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.941 [20]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.17

Notes:

[20] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the NIS Component: Muscle Weakness Score at Week 52 of Years 4 and 5

End point title	Change From Baseline in the NIS Component: Muscle Weakness Score at Week 52 of Years 4 and 5

End point description:

Muscle weakness involves testing 19 movements of muscles. The maximum score of this component is 152 points. The FAS population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Week 52 of Years 4 and 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 52 of Year 4 (n=9,14)	23.67 (± 16.712)	14.71 (± 19.479)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	13.75 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline in the NIS Component: Muscle Weakness Score at Week 52 of Years 4

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [21]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-9.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.97
upper limit	-2.16

Notes:

[21] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the NIS Component: Reflexes Score at Week 52 of Years 4 and 5

End point title	Change From Baseline in the NIS Component: Reflexes Score at Week 52 of Years 4 and 5
End point description:	

The Reflexes Score involves testing 5 reflexes to stimuli. The maximum score of this component is 20 points. The FAS population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary
End point timeframe:	

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Week 52 of Years 4 and 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 52 of Year 4 (n=9,14)	4.17 (± 3.553)	2.32 (± 1.957)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	4.00 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change from Baseline in the NIS Component: Reflexes Score at Week 52 of Years 4	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.356 [22]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.28
upper limit	1.18

Notes:

[22] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the NIS Component: Sensory Score at Week 52 of Years 4 and 5

End point title	Change From Baseline in the NIS Component: Sensory Score at Week 52 of Years 4 and 5

End point description:

The Sensory Score is based on testing an index finger and a big toe each to 4 stimuli. The maximum score of this component is 32 points. The FAS population includes all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Week 52 of Years 4 and 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	14		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 52 of Year 4 (n=9,14)	7.94 (± 5.288)	1.29 (± 3.662)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	0.00 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline in the NIS Component: Sensory Score at Week 52 of Years 4

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-

	Inotersen 300 mg
Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [23]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-5.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.58
upper limit	-2.19

Notes:

[23] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Questionnaire Total Score at Weeks 78 and 156

End point title	Change From Baseline in the Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Questionnaire Total Score at Weeks 78 and 156

End point description:

The Norfolk QoL-DN score is a measure of physical function/large fiber neuropathy, symptoms, activities of daily living, small fiber neuropathy, and autonomic neuropathy. The Norfolk QoL-DN total score has a range of -4 to 136, and a higher Norfolk QoL-DN score indicates poorer QoL. A positive change from Baseline indicates worsening in the QoL. The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156 and at the end of each subsequent treatment year (Week 52 of Years 4 and 5)

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=34,71)	15.22 (± 24.024)	3.76 (± 20.832)		
Change From Baseline at Week 156 (n=22,41)	14.94 (± 28.944)	5.98 (± 22.891)		
Change From Baseline at Week 52 of Year 4 (n=9,14)	6.22 (± 18.600)	2.36 (± 25.120)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	-1.00 (± 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change From Baseline in the Norfolk QOL-DN Questionnaire Total Score at Week 78

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [24]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-9.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.48
upper limit	-1.14

Notes:

[24] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Change From Baseline in the Norfolk QOL-DN Questionnaire Total Score at Week 156

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.107 [25]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.41
upper limit	1.62

Notes:

[25] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:	
Change From Baseline in the Norfolk QOL-DN Questionnaire Total Score at Week 52 of Year 4	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.669 [26]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.22
upper limit	9.77

Notes:

[26] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the Norfolk QoL-DN Physical Functioning/Large Fiber Neuropathy Domain Score

End point title	Change From Baseline in the Norfolk QoL-DN Physical Functioning/Large Fiber Neuropathy Domain Score

End point description:

The Norfolk QoL-DN physical functioning/large fiber neuropathy domain score is a sub-score of the total Norfolk QoL-DN Questionnaire. The Norfolk QoL-DN physical function/large fiber neuropathy domain score has a range of -4 to 56, and a higher Norfolk QoL-DN domain score indicates poorer quality of life (QoL). A positive change from Baseline indicates worsening in the QoL. The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156 and at Week 52 of Year 4

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	26		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=14,23)	11.21 (± 11.026)	3.61 (± 11.500)		
Change From Baseline at Week 156 (n=5,11)	12.60 (± 10.784)	-0.55 (± 8.042)		
Change From Baseline at Week 52 of Year 4 (n=2,4)	9.50 (± 9.192)	3.50 (± 7.047)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Change From Baseline in the Norfolk QOL-DN Change From CS2 Baseline in the Norfolk QOL-DN Questionnaire Total Score at Week 78	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.097
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.75
upper limit	1.15

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Change from Baseline in the Norfolk QoL-DN Physical Functioning/Large Fiber Neuropathy Domain Score at Week 156	
Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.081 [27]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-8.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.88
upper limit	1.11

Notes:

[27] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Change From Baseline in the Norfolk QOL-DN Physical Functioning/Large Fiber Neuropathy Domain Score at Week 52 of Year 4

Comparison groups	Previous Placebo-Inotersen 300 mg v Previous Inotersen-Inotersen 300 mg
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171 [28]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-11.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.89
upper limit	5.16

Notes:

[28] - P-value= MMRM with fixed categorical effects for treatment, time, treatment-by-time interaction, each of 3 randomization stratification factors, fixed covariates for parent study baseline value, baseline-by-time interaction.

Secondary: Change From Baseline in the Modified Body Mass Index (mBMI) at Weeks 78 and 156

End point title	Change From Baseline in the Modified Body Mass Index (mBMI) at Weeks 78 and 156

End point description:

BMI=weight (kg)/[height (m)^2]. The mBMI is the BMI multiplied by the serum albumin (g/L). The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: kg/m^2*g/L				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=35,71)	-166.27 (± 159.644)	-161.52 (± 134.779)		
Change From Baseline at Week 156 (n=21,39)	-191.68 (± 130.370)	-172.52 (± 131.602)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Body Mass Index (BMI) at Weeks 78 and 156

End point title	Change From Baseline in the Body Mass Index (BMI) at Weeks 78 and 156

End point description:

BMI=weight (kg)/[height (m)^2]. The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment f after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline, Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: kg/m^2				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=35,71)	-0.16 (± 2.617)	-0.44 (± 1.427)		
Change From Baseline at Week 156 (n=21,39)	-0.34 (± 1.908)	-0.66 (± 2.220)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Change From Baseline in the Polyneuropathy Disability (PND) Score

End point title	Percentage of Subjects With Change From Baseline in the Polyneuropathy Disability (PND) Score

End point description:

PND score=defined as I=sensory disturbances in limbs without motor impairment; II=difficulty walking without need of walking aid; III=one stick or one crutch required for walking; IV=two sticks or two crutches needed. V=wheelchair required or patient confined to bed. Change from Baseline: improved, not changed, worsened, and unknown. Percentage of subjects with changes from Baseline are presented category-wise in this outcome measure. Only categories with at least one subjects with event are reported. CFB=change from Baseline. The FAS population included all enrolled subjects who received at least 1 injection of post-baseline efficacy assessment after CS3 Study Day 1. 99999=data not available as no subjects were analysed during that time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 78 and 156 and at the end of each subsequent treatment year (Week 52 of each year)

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: percentage of subjects				
number (not applicable)				
CFB at Week 78: Improved (n=36,71)	5.6	11.3		
CFB at Week 78: Not Changed (n=36,71)	69.4	62.0		
CFB at Week 78: Worsened (n=36,71)	25.0	26.8		
CFB at Week 156: Improved (n=21,41)	4.8	7.3		
CFB at Week 156: Not Changed (n=21,41)	52.4	56.1		
CFB at Week 156: Worsened (n=21,41)	42.9	36.6		
CFB at Week 52 of Year 4: Improved (n=9,14)	11.1	14.3		
CFB at Week 52 of Year 4: Not Changed (n=9,14)	33.3	42.9		
CFB at Week 52 of Year 4: Worsened (n=9,14)	55.6	42.9		
CFB at Week 52 of Year 5: Not Changed (n=0,1)	99999	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram (ECHO) in the Cardiomyopathy-ECHO (CM-ECHO) Set

End point title	Percent Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram (ECHO) in the Cardiomyopathy-ECHO (CM-ECHO) Set

End point description:

GLS by ECHO is a measure of cardiac systolic function. The Cardiomyopathy-echocardiogram (CM-ECHO) Set included the subset of the 420915-CS2 Randomised Set that had a diagnosis of transthyretin (TTR) cardiomyopathy at study entry of the parent study, but were not in the ECHO Subgroup in the parent study, plus subjects who qualified to subjects in the ECHO Subgroup (whether consented or not). n= Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	59		
Units: percent change				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=18,32)	0.38 (± 3.178)	-0.74 (± 3.120)		
Change From Baseline at Week 156 (n=9,20)	1.46 (± 5.313)	0.07 (± 4.318)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in GLS by ECHO in the CS3 ECHO Subgroup

End point title	Percent Change From Baseline in GLS by ECHO in the CS3 ECHO Subgroup

End point description:

GLS by ECHO is a measure of cardiac systolic function. The Cardiomyopathy-echocardiogram (CM-ECHO) Set included the subset of the 420915-CS2 Randomised Set that had a diagnosis of transthyretin (TTR) cardiomyopathy at study entry of the parent study, but were not in the ECHO Subgroup in the parent study, plus subjects who qualified to subjects in the ECHO Subgroup (whether consented or not). n= Number analysed is the number of subjects with data available for analysis at the given time point.

End point type	Secondary

End point timeframe:

Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	36		
Units: percent change				
arithmetic mean (standard deviation)				
Percent Change From Baseline at Week 78 (n=12,18)	-6.93 (± 20.232)	8.99 (± 26.201)		
Percent Change From Baseline at Week 156 (n=5,12)	-2.79 (± 24.580)	11.46 (± 29.383)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Transthyretin (TTR) Level

End point title	Change From Baseline in Transthyretin (TTR) Level

End point description:

Measurement of transthyretin protein concentration in serum. The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: g/L				
arithmetic mean (standard deviation)				
Change From Baseline at Week 78 (n=36,72)	-0.1581 (± 0.05887)	-0.1555 (± 0.06751)		
Change From Baseline at Week 156 (n=25,43)	-0.1498 (± 0.06366)	-0.1692 (± 0.06025)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Retinol Binding Protein 4 (RBP4) Level

End point title	Change From Baseline in Retinol Binding Protein 4 (RBP4) Level

End point description:

Measurement of RBP4 protein concentration ins serum. The FAS population included all enrolled subjects who received at least 1 injection of inotersen in this study (CS3) and who had at least 1 efficacy assessment after CS3 Study Day 1.

End point type	Secondary

End point timeframe:

Baseline (Baseline is the Baseline of the Previous Study- Study CS2), Weeks 78 and 156, and at the end of each subsequent treatment year (Week 52 of Years 4 and 5)

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	81		
Units: micrograms per liter (µg/L)				
arithmetic mean (standard deviation)				

Change From Baseline at Week 78 (n=36,72)	-21073.1 (± 11038.53)	-19365.9 (± 10511.83)		
Change From Baseline at Week 156 (n=25,43)	-21489.4 (± 10670.52)	-22372.3 (± 10372.05)		
Change From Baseline at Week 52 of Year 4 (n=9,14)	-28307.1 (± 9539.75)	-24893.7 (± 5559.01)		
Change From Baseline at Week 52 of Year 5 (n=0,1)	99999 (± 99999)	-24444.0 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough: Trough Plasma Concentration of ISIS 420915

End point title	Ctrough: Trough Plasma Concentration of ISIS 420915

End point description:

CS3 Pharmacokinetic (PK) Set included all enrolled subjects who received at least 1 dose of inotersen in CS3 and who had at least 1 evaluable PK sample collected and analysed with reportable result in CS3. n= Number analysed is the number of subjects with data available for analyses at the given time point. 99999=Data was not estimable due to low number of subjects.

End point type	Secondary

End point timeframe:

Pre-dose on Days 1, 43, 85, 120, 176, 267, 358, 449, 540, 631, 722, 813, 904, 995, 1086, Days 1268, 1359 and 1450 of Year 4, Days 1632, 1723 and 1814 of Year 5

End point values	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	85		
Units: nanograms per milliliter (ng/ml)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=49,83)	99999 (± 99999)	34.1 (± 247)		
Day 43 (n=41,63)	22.9 (± 97.6)	74.0 (± 123)		
Day 85 (n=37,58)	28.6 (± 43.6)	83.0 (± 138)		
Day 120 (n=27,31)	31.5 (± 43.7)	81.9 (± 142)		
Day 176 (n=36,52)	38.0 (± 52.9)	80.0 (± 104)		
Day 267 (n=24,41)	47.3 (± 83.4)	98.2 (± 183)		
Day 358 (n=26,48)	56.2 (± 102)	110 (± 130)		
Day 449 (n=25,37)	71.1 (± 158)	130 (± 218)		
Day 540 (n=26,39)	78.7 (± 163)	111 (± 219)		
Day 631 (n=19,28)	83.8 (± 211)	141 (± 187)		
Day 722 (n=26,32)	97.6 (± 245)	101 (± 127)		
Day 813 (n=14,28)	98.0 (± 354)	150 (± 273)		
Day 904 (n=11,27)	91.4 (± 230)	116 (± 148)		
Day 995 (n=12,15)	147 (± 809)	134 (± 246)		
Day 1086 (n=13,27)	131 (± 340)	101 (± 159)		

Day 1268 of Year 4 (n=13,16)	167 (± 258)	102 (± 202)
Day 1359 of Year 4 (n=4,10)	432 (± 307)	157 (± 233)
Day 1450 of Year 4 (n=4,8)	55.0 (± 61.1)	83.0 (± 111)
Day 1632 of Year 5 (n=1,4)	37.4 (± 99999)	75.3 (± 26.9)
Day 1723 of Year 5 (n=1,0)	113 (± 99999)	99999 (± 99999)
Day 1814 of Year 5 (n=0,1)	99999 (± 99999)	62.1 (± 99999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 3 months post treatment period of 260 weeks (Up to approximately 272 weeks)

Adverse event reporting additional description:

SS included all enrolled participants who received at least 1 injection of inotersen in CS3.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Previous Placebo-Inotersen 300 mg

Reporting group description:

Subjects received subcutaneous (SC) doses of 300 milligrams (mg) inotersen once weekly for up to 260 weeks. Subjects who received inotersen-matching placebo in the previous study- ISIS 420915-CS2 (NCT01737398) were included in this group.

Reporting group title	Previous Inotersen-Inotersen 300 mg

Reporting group description:

Subjects received SC doses of 300 mg inotersen once weekly for up to 260 weeks. Subjects who received inotersen in the previous study- ISIS 420915-CS2 were included in this group.

Serious adverse events	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 50 (36.00%)	46 / 85 (54.12%)	
number of deaths (all causes)	2	15	
number of deaths resulting from adverse events	2	15	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangiocarcinoma			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			

subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vascular disorders				
Hypotension				
subjects affected / exposed	0 / 50 (0.00%)	3 / 85 (3.53%)		
occurrences causally related to treatment / all	0 / 0	0 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
Hypertension				
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 0	1 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Orthostatic hypotension				
subjects affected / exposed	1 / 50 (2.00%)	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 1	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Deep vein thrombosis				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Chills				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Generalised oedema				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		

Pyrexia				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Oedema peripheral				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Immune system disorders				
Anti-neutrophil cytoplasmic antibody positive vasculitis				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Amyloidosis				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
Reproductive system and breast disorders				
Ovarian mass				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Asphyxia				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Respiratory failure				

subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Hypoxia				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Injury, poisoning and procedural complications				
Subarachnoid haemorrhage				
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Facial bones fracture				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Fall				
subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Femur fracture				
subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Rib fracture				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		

Spleen contusion		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Femoral neck fracture		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hip fracture		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament sprain		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Toxicity to various agents		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Wrist fracture		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac disorders		
Cardiac failure congestive		
subjects affected / exposed	1 / 50 (2.00%)	4 / 85 (4.71%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Cardiac failure		
subjects affected / exposed	2 / 50 (4.00%)	3 / 85 (3.53%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1
Cardiac failure acute		

subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bradycardia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac tamponade			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			

subjects affected / exposed	1 / 50 (2.00%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	5 / 50 (10.00%)	8 / 85 (9.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal perforation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous floaters			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia, obstructive			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal hypomotility			
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Biliary cirrhosis primary			

subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Liver disorder				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Jaundice cholestatic				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Skin and subcutaneous tissue disorders				
Decubitus ulcer				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Haematuria				
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 0	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Calculus bladder				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nephrolithiasis				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urinary retention				

subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders

Lumbar spinal stenosis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations

Pneumonia			
subjects affected / exposed	4 / 50 (8.00%)	4 / 85 (4.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cellulitis			
subjects affected / exposed	0 / 50 (0.00%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	0 / 50 (0.00%)	3 / 85 (3.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis			
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)	2 / 85 (2.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Bacterial toxaemia		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bronchitis		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cellulitis streptococcal		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis infective		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Corona virus infection		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1
Endocarditis		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Gastroenteritis		
subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1
Influenza		

subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Localised infection		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Measles		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Osteomyelitis chronic		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumococcal sepsis		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumonia pseudomonal		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia viral		

subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Pyelonephritis acute				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Septic shock				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Skin infection				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Systemic infection				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Urosepsis				
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 0	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Appendicitis perforated				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Escherichia pyelonephritis				
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Orchitis				

subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
subjects affected / exposed	1 / 50 (2.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders		
Hyponatraemia		
subjects affected / exposed	0 / 50 (0.00%)	2 / 85 (2.35%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Dehydration		
subjects affected / exposed	1 / 50 (2.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fluid retention		
subjects affected / exposed	0 / 50 (0.00%)	1 / 85 (1.18%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malnutrition		
subjects affected / exposed	2 / 50 (4.00%)	0 / 85 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Previous Placebo-Inotersen 300 mg	Previous Inotersen-Inotersen 300 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	80 / 85 (94.12%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 50 (2.00%)	7 / 85 (8.24%)	
occurrences (all)	1	18	

Orthostatic hypotension		
subjects affected / exposed	3 / 50 (6.00%)	7 / 85 (8.24%)
occurrences (all)	4	8
Hypertension		
subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)
occurrences (all)	1	7
General disorders and administration site conditions		
Fatigue		
subjects affected / exposed	7 / 50 (14.00%)	20 / 85 (23.53%)
occurrences (all)	10	26
Chills		
subjects affected / exposed	7 / 50 (14.00%)	16 / 85 (18.82%)
occurrences (all)	7	29
Oedema peripheral		
subjects affected / exposed	8 / 50 (16.00%)	14 / 85 (16.47%)
occurrences (all)	9	19
Injection site erythema		
subjects affected / exposed	4 / 50 (8.00%)	12 / 85 (14.12%)
occurrences (all)	17	13
Injection site pain		
subjects affected / exposed	6 / 50 (12.00%)	12 / 85 (14.12%)
occurrences (all)	8	18
Pyrexia		
subjects affected / exposed	2 / 50 (4.00%)	11 / 85 (12.94%)
occurrences (all)	2	14
Asthenia		
subjects affected / exposed	4 / 50 (8.00%)	7 / 85 (8.24%)
occurrences (all)	4	8
Injection site pruritus		
subjects affected / exposed	3 / 50 (6.00%)	7 / 85 (8.24%)
occurrences (all)	3	7
Injection site rash		
subjects affected / exposed	4 / 50 (8.00%)	5 / 85 (5.88%)
occurrences (all)	5	6
Oedema		

subjects affected / exposed	2 / 50 (4.00%)	5 / 85 (5.88%)	
occurrences (all)	3	6	
Gait disturbance			
subjects affected / exposed	3 / 50 (6.00%)	4 / 85 (4.71%)	
occurrences (all)	3	4	
Injection site bruising			
subjects affected / exposed	4 / 50 (8.00%)	4 / 85 (4.71%)	
occurrences (all)	4	4	
Influenza like illness			
subjects affected / exposed	5 / 50 (10.00%)	3 / 85 (3.53%)	
occurrences (all)	6	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 50 (10.00%)	10 / 85 (11.76%)	
occurrences (all)	5	11	
Cough			
subjects affected / exposed	4 / 50 (8.00%)	8 / 85 (9.41%)	
occurrences (all)	4	9	
Epistaxis			
subjects affected / exposed	3 / 50 (6.00%)	2 / 85 (2.35%)	
occurrences (all)	3	2	
Pleural effusion			
subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)	
occurrences (all)	1	6	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 50 (0.00%)	6 / 85 (7.06%)	
occurrences (all)	0	6	
Depression			
subjects affected / exposed	3 / 50 (6.00%)	3 / 85 (3.53%)	
occurrences (all)	3	3	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 50 (8.00%)	7 / 85 (8.24%)	
occurrences (all)	4	7	
Platelet count decreased			

subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)	
occurrences (all)	1	6	
Glomerular filtration rate decreased			
subjects affected / exposed	4 / 50 (8.00%)	4 / 85 (4.71%)	
occurrences (all)	7	4	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 50 (22.00%)	17 / 85 (20.00%)	
occurrences (all)	17	25	
Wound			
subjects affected / exposed	3 / 50 (6.00%)	1 / 85 (1.18%)	
occurrences (all)	4	1	
Laceration			
subjects affected / exposed	3 / 50 (6.00%)	3 / 85 (3.53%)	
occurrences (all)	4	3	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 50 (8.00%)	5 / 85 (5.88%)	
occurrences (all)	5	6	

Nervous system disorders			
Syncope			
subjects affected / exposed	4 / 50 (8.00%)	7 / 85 (8.24%)	
occurrences (all)	7	16	
Headache			
subjects affected / exposed	7 / 50 (14.00%)	8 / 85 (9.41%)	
occurrences (all)	10	14	
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)	7 / 85 (8.24%)	
occurrences (all)	2	13	
Hypoaesthesia			
subjects affected / exposed	3 / 50 (6.00%)	6 / 85 (7.06%)	
occurrences (all)	3	10	
Paraesthesia			
subjects affected / exposed	4 / 50 (8.00%)	6 / 85 (7.06%)	
occurrences (all)	4	7	
Balance disorder			

subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)		
occurrences (all)	1	6		

Blood and lymphatic system disorders

Thrombocytopenia

subjects affected / exposed	22 / 50 (44.00%)	14 / 85 (16.47%)	
occurrences (all)	48	27	

Anaemia

subjects affected / exposed	5 / 50 (10.00%)	8 / 85 (9.41%)	
occurrences (all)	5	10	

Eye disorders

Cataract

subjects affected / exposed	3 / 50 (6.00%)	4 / 85 (4.71%)	
occurrences (all)	3	4	

Dry eye

subjects affected / exposed	3 / 50 (6.00%)	3 / 85 (3.53%)	
occurrences (all)	3	3	

Vision blurred

subjects affected / exposed	0 / 50 (0.00%)	5 / 85 (5.88%)	
occurrences (all)	0	6	

Gastrointestinal disorders

Nausea

subjects affected / exposed	7 / 50 (14.00%)	26 / 85 (30.59%)	
occurrences (all)	11	38	

Diarrhoea

subjects affected / exposed	12 / 50 (24.00%)	22 / 85 (25.88%)	
occurrences (all)	20	30	

Vomiting

subjects affected / exposed	6 / 50 (12.00%)	18 / 85 (21.18%)	
occurrences (all)	10	33	

Constipation

subjects affected / exposed	4 / 50 (8.00%)	12 / 85 (14.12%)	
occurrences (all)	5	12	

Abdominal pain

subjects affected / exposed	1 / 50 (2.00%)	8 / 85 (9.41%)	
occurrences (all)	1	9	

Dyspepsia

subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 50 (6.00%)	5 / 85 (5.88%)	
occurrences (all)	3	8	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 50 (8.00%)	3 / 85 (3.53%)	
occurrences (all)	4	5	
Urinary retention			
subjects affected / exposed	1 / 50 (2.00%)	4 / 85 (4.71%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 50 (2.00%)	10 / 85 (11.76%)	
occurrences (all)	1	11	
Arthralgia			
subjects affected / exposed	2 / 50 (4.00%)	8 / 85 (9.41%)	
occurrences (all)	2	10	
Back pain			
subjects affected / exposed	2 / 50 (4.00%)	7 / 85 (8.24%)	
occurrences (all)	2	9	
Pain in extremity			
subjects affected / exposed	3 / 50 (6.00%)	7 / 85 (8.24%)	
occurrences (all)	4	12	
Muscle atrophy			
subjects affected / exposed	2 / 50 (4.00%)	6 / 85 (7.06%)	
occurrences (all)	2	7	
Myalgia			
subjects affected / exposed	7 / 50 (14.00%)	5 / 85 (5.88%)	
occurrences (all)	10	7	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	12 / 50 (24.00%)	18 / 85 (21.18%)	
occurrences (all)	29	58	

Nasopharyngitis			
subjects affected / exposed	3 / 50 (6.00%)	7 / 85 (8.24%)	
occurrences (all)	3	8	
Bronchitis			
subjects affected / exposed	2 / 50 (4.00%)	5 / 85 (5.88%)	
occurrences (all)	2	7	
Upper respiratory tract infection			
subjects affected / exposed	2 / 50 (4.00%)	6 / 85 (7.06%)	
occurrences (all)	2	8	
Sinusitis			
subjects affected / exposed	2 / 50 (4.00%)	5 / 85 (5.88%)	
occurrences (all)	2	6	
Influenza			
subjects affected / exposed	4 / 50 (8.00%)	4 / 85 (4.71%)	
occurrences (all)	4	4	
Cellulitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 85 (0.00%)	
occurrences (all)	3	0	
Herpes zoster			
subjects affected / exposed	4 / 50 (8.00%)	3 / 85 (3.53%)	
occurrences (all)	4	3	
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	5 / 85 (5.88%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 50 (10.00%)	5 / 85 (5.88%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2015	The following changes were implemented based on Amendment 1: -Modified renal function monitoring rules and stopping rules to align with CS2. -Modified ocular monitoring and stopping rules to align with CS2. -Added GLS as a secondary efficacy endpoint. -Changed the definition of the analysis sets for ECHO endpoints to align with the definition used in CS2. -Modified the stopping rule for QTc prolongation to allow for clinical interpretation of the changes to the individual subject and the implementation of closer monitoring before permanently discontinuing study drug. -Added 4 additional visits at Weeks 15, 18, 23, and 29 to collect additional safety information. -Added additional urinalysis. -Added albumin-to-creatinine (Alb/C), ratio to urinalysis testing and required back-up retinol and urine samples to be collected.
10 August 2015	The following changes were implemented based on Amendment 2: -Extended the study duration to 3 years. -Removed language from the platelet stopping rule that mandated permanent treatment discontinuation after 2 dosing rechallenges to allow the Study Medical Monitor and investigator more discretion in determining the suitability of a subject for continued dosing and the need for any modification to treatment schedule or dose.
07 March 2016	The following changes were implemented based on Amendment 3: -Increased the frequency of safety lab monitoring (hematology and creatinine) to every 2-3 weeks. -Modified the platelet monitoring and stopping rules. -Updated the sample size in order to align with CS2 Amendment 7. -Modified renal monitoring rules. -Allowed use of tafamidis after 18 months at discretion of Study Medical Monitor. -Updated statistical considerations for the efficacy endpoints.
13 May 2016	The following changes were implemented based on Amendment 4: -Increased the frequency of platelet monitoring from every 2-3 weeks to every week throughout the treatment period and for a minimum of 6 weeks after the last dose of study drug. -Modified the platelet monitoring rule.
22 February 2017	The following changes were implemented based on Amendment 5: -Increased the treatment period to 5 years if inotersen is not commercially available at the end of 3 years of treatment. -Updated visit information based on extension to treatment period. -Added alternative reasons for withdrawal, including if inotersen became commercially available or was rejected by the regulatory authority in the local country.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported