



Clinical trial results:

A Phase 3 Global, Open-Label, Randomized Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Hereditary Transthyretin-Mediated Amyloid Polyneuropathy

Summary

EudraCT number	2019-001698-10
Trial protocol	GB PT DE ES IT SE GR FR CY NL
Global end of trial date	12 July 2023

Results information

Result version number	v1 (current)
This version publication date	29 July 2024
First version publication date	29 July 2024

Trial information

Trial identification

Sponsor protocol code	ION-682884-CS3
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04136184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, 92010
Public contact	Global Regulatory Affairs, Ionis Pharmaceuticals, Inc., 1 760603-2346, globalregulatoryaffairs@ionis.com
Scientific contact	Global Regulatory Affairs, Ionis Pharmaceuticals, Inc., 1 760603-2346, globalregulatoryaffairs@ionis.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	12 July 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of eplontersen as compared to the historical control of the placebo cohort in the NEURO-TTR trial (NCT01737398/2012-001831-30), in subjects with hereditary transthyretin-mediated amyloidosis polyneuropathy (hATTR-PN).

Protection of trial subjects:

All subjects in this study were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Cyprus: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Portugal: 28
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Türkiye: 7
Country: Number of subjects enrolled	Argentina: 13
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Taiwan: 23
Worldwide total number of subjects	168
EEA total number of subjects	57

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)	116
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 46 investigative sites in 15 countries (Argentina, Australia, Brazil, Canada, Cyprus, France, Germany, Italy, New Zealand, Portugal, Spain, Sweden, Taiwan, Turkey, and the United States) from 11 December 2019 to 12 July 2023.

Pre-assignment

Screening details:

Subjects with a diagnosis of hATTR-PN were randomized in a 6:1 ratio to receive eplontersen (ION-682884) or inotersen respectively. The eplontersen arm of this study was compared to the placebo-cohort group from ISIS 420915-CS2 (NEURO-TTR) study (NCT01737398/ 2012-001831-30), which was used as an external control for efficacy analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Eplontersen

Arm description:

Subjects received eplontersen, 45 mg, SC, once every 4 weeks up to Week 81.

Arm type	Experimental
Investigational medicinal product name	Eplontersen
Investigational medicinal product code	
Other name	ION-682884, AKCEA-TTR-LRx, IONIS-TTR-LRx
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

45 mg eplontersen, Q4W administered by SC route

Arm title	Inotersen
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Arm description:

Subjects received inotersen, 300 milligrams (mg), subcutaneously (SC), once weekly up to Week 34. After Week 35 assessment, subjects received eplontersen, 45 mg, SC, once every 4 weeks starting from Week 37 up to Week 81.

Arm type	Active comparator
Investigational medicinal product name	Inotersen
Investigational medicinal product code	
Other name	Tegsedi®
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

300 mg inotersen, administered once weekly by SC route.

Number of subjects in period 1	Eplontersen	Inotersen
Started	144	24
Completed	22	1
Not completed	122	23
Lost to Follow Up	3	-
Voluntary Withdrawal (including enrolled OLE)	119	23

Baseline characteristics

Reporting groups

Reporting group title	Eplontersen
Reporting group description:	
Subjects received eplontersen, 45 mg, SC, once every 4 weeks up to Week 81.	
Reporting group title	Inotersen
Reporting group description:	
Subjects received inotersen, 300 milligrams (mg), subcutaneously (SC), once weekly up to Week 34. After Week 35 assessment, subjects received eplontersen, 45 mg, SC, once every 4 weeks starting from Week 37 up to Week 81.	

Reporting group values	Eplontersen	Inotersen	Total
Number of subjects	144	24	168
Age Categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	53.0 ± 15.0	51.1 ± 14.38	-
Gender categorical Units: Subjects			
Male	100	16	116
Female	44	8	52
Ethnicity Units: Subjects			
Hispanic or Latino	22	5	27
Not Hispanic or Latino	120	18	138
Unknown or Not Reported	2	1	3
Race Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	22	2	24
Black or African American	5	0	5
Native Hawaiian or Other Pacific Islander	0	0	0
White	112	19	131
Other	3	2	5
Multiple	1	0	1
Unknown or Not Reported	1	1	2
Serum Transthyretin (TTR) Concentration Units: grams per litre (g/L) arithmetic mean standard deviation	0.23 ± 0.075	0.22 ± 0.069	-
Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Total Score			

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 score indicates poorer quality of life. Number analysed is the number of

subjects with data available for analysis			
Units: scores on a scale			
arithmetic mean	0	40.05	
standard deviation	± 0	± 21.488	-
Modified Neuropathy Impairment Score Plus 7 (mNIS+7) Composite Score			
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 consists of 2 composite scores: the NIS composite score (maximum of 244 points) and the modified +7 composite score (maximum of 102.32 points). The mNIS+7 composite total score has a range of -22.32 to 346.32, and a higher score indicates lower function.			
Units: scores on a scale			
arithmetic mean	81.28	65.06	
standard deviation	± 43.401	± 33.515	-

Subject analysis sets

Subject analysis set title	External Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in the external placebo arm received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks of the NEURO-TTR study.	
Subject analysis set title	Eplontersen
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received eplontersen, 45 mg, SC, once every 4 weeks up to Week 81.	

Reporting group values	External Placebo	Eplontersen	
Number of subjects	60	137	
Age Categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Gender categorical			
Units: Subjects			
Male	0		
Female	0		
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	0	0	
Unknown or Not Reported			
Race			
Units: Subjects			
American Indian or Alaskan Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	0	0	

Other	0	0	
Multiple	0	0	
Unknown or Not Reported			
Serum Transthyretin (TTR) Concentration			
Units: grams per litre (g/L)			
arithmetic mean	0	0	
standard deviation	± 0	± 0	
Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Total Score			
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 score indicates poorer quality of life. Number analysed is the number of subjects with data available for analysis			
Units: scores on a scale			
arithmetic mean	0	44.09	
standard deviation	± 0	± 26.590	
Modified Neuropathy Impairment Score Plus 7 (mNIS+7) Composite Score			
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 consists of 2 composite scores: the NIS composite score (maximum of 244 points) and the modified +7 composite score (maximum of 102.32 points). The mNIS+7 composite total score has a range of -22.32 to 346.32, and a higher score indicates lower function.			
Units: scores on a scale			
arithmetic mean	0	0	
standard deviation	± 0	± 0	

End points

End points reporting groups

Reporting group title	Eplontersen
Reporting group description: Subjects received eplontersen, 45 mg, SC, once every 4 weeks up to Week 81.	
Reporting group title	Inotersen
Reporting group description: Subjects received inotersen, 300 milligrams (mg), subcutaneously (SC), once weekly up to Week 34. After Week 35 assessment, subjects received eplontersen, 45 mg, SC, once every 4 weeks starting from Week 37 up to Week 81.	
Subject analysis set title	External Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects in the external placebo arm received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks of the NEURO-TTR study.	
Subject analysis set title	Eplontersen
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects received eplontersen, 45 mg, SC, once every 4 weeks up to Week 81.	

Primary: Change from Baseline in Modified Neuropathy Impairment Score Plus 7 (mNIS+7) at Week 66

End point title	Change from Baseline in Modified Neuropathy Impairment Score Plus 7 (mNIS+7) at Week 66 ^[1]
End point description: mNIS+7 composite score is a measure of neurologic impairment evaluating muscle weakness, sensation, reflexes, nerve conduction, and autonomic function. mNIS+7 consists of 2 composite scores: NIS composite score (maximum of 244 points) & the modified +7 composite score (maximum of 102.32 points). mNIS+7 composite total score range= -22.32 to 346.32. Higher score =lower function. FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed = number of subjects with data available for analysis. Least square (LS) mean and standard error (SE) were analyzed using MMRM.	
End point type	Primary
End point timeframe: Baseline, Week 66	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	128	52		
Units: scores on a scale				
least squares mean (standard error)	25.0557 (± 2.3874)	25.0557 (± 2.3874)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 1E-8
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-24.7593
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.9552
upper limit	-18.5635

Primary: Change from Baseline in the Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Questionnaire at Week 66

End point title	Change from Baseline in the Norfolk Quality of Life Diabetic Neuropathy (QoL-DN) Questionnaire at Week 66 ^[2]
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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 138, and a higher score indicates poorer quality of life. FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed is the number of subjects with data available for analysis. LS mean and SE were analyzed using MMRM.

End point type	Primary
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End point timeframe:

Baseline, Week 66

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	128	52		
Units: scores on a scale				
least squares mean (standard error)	-5.4964 (± 2.2976)	14.2388 (± 2.3488)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 1E-8
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-19.7352
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.6301
upper limit	-13.8403

Primary: Percent Change from Baseline in Serum TTR Concentration at Week 65

End point title	Percent Change from Baseline in Serum TTR Concentration at Week 65 ^[3]
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End point description:

FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen and had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug and had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score.

End point type	Primary
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End point timeframe:

Baseline, Week 66

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	135	51		
Units: percentage				
least squares mean (standard error)	-81.65 (± 1.605)	-11.24 (± 1.910)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo

Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 1E-8
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-70.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.17
upper limit	-65.66

Primary: Percent Change from Baseline in Serum TTR Concentration at Week 35

End point title	Percent Change from Baseline in Serum TTR Concentration at Week 35 ^[4]
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End point description:

FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen and had a baseline and at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score.

End point type	Primary
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End point timeframe:

Baseline, Week 35

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	139	57		
Units: percentage				
least squares mean (standard error)	-81.14 (± 1.674)	-14.49 (± 1.966)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 1E-8
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-66.65

Confidence interval	
level	95 %
sides	2-sided
lower limit	-71.59
upper limit	-61.71

Primary: Change from Baseline in Modified Neuropathy Impairment Score Plus 7 (mNIS+7) at Week 35

End point title	Change from Baseline in Modified Neuropathy Impairment Score Plus 7 (mNIS+7) at Week 35 ^[5]
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End point description:

mNIS+7 composite score is a measure of neurologic impairment evaluating muscle weakness, sensation, reflexes, nerve conduction, and autonomic function. mNIS+7 consists of 2 composite scores: NIS composite score (maximum of 244 points) & the modified +7 composite score (maximum of 102.32 points). mNIS+7 composite total score range= -22.32 to 346.32. Higher score indicates lower function. FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed = number of subjects with data available for analysis. LS mean and SE were analyzed using MMRM.

End point type	Primary
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End point timeframe:

Baseline, Week 35

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	138	55		
Units: scores on a scale				
least squares mean (standard error)	0.6795 (± 1.9073)	10.0337 (± 1.8544)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00012203
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-9.3542

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8691
upper limit	-4.8394

Secondary: Change from Baseline in Neuropathy Symptom and Change (NSC) Score at Weeks 35 and 66

End point title	Change from Baseline in Neuropathy Symptom and Change (NSC) Score at Weeks 35 and 66 ^[6]
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End point description:

NSC score is a questionnaire composed of 38 questions divided into 5 domains: muscle weakness, sensory (hypo/loss of sensation), sensory (paresthesia, hyper sensation), autonomic (gastrointestinal & urinary incontinence), & autonomic (non-GI/non-urinary incontinence)]. Answers to questionnaire are yes/no and if yes, then degree of severity is graded as 1 (slight +), 2 (moderate ++) and 3 (severe +++). 0=no symptom. NSC total score is a sum of scores across all 5 domains. Total score= 0-114. Higher scores=more neuropathy symptoms. FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score.

End point type	Secondary
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End point timeframe:

Baseline, Week 35, Week 66

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	141	57		
Units: scores on a scale				
least squares mean (standard error)				
At Week 35	0.79 (± 0.867)	4.73 (± 0.870)		
At Week 66	-0.03 (± 0.955)	8.18 (± 0.962)		

Statistical analyses

Statistical analysis title	Week 66: External Placebo vs Eplontersen
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Statistical analysis description:

Week 66

Comparison groups	Eplontersen v External Placebo
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Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1E-8
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-8.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.65
upper limit	-5.76

Statistical analysis title	Week 35: External Placebo vs Eplontersen
Statistical analysis description: Week 35	
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00052447
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.08
upper limit	-1.8

Secondary: Change from Baseline in Norfolk QOL-DN at Week 35	
End point title	Change from Baseline in Norfolk QOL-DN at Week 35 ^[7]
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 138, and a higher score indicates poorer quality of life. FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed is the number of subjects with data available for analysis. LS mean and SE were analyzed using MMRM.	
End point type	Secondary
End point timeframe: Baseline, Week 35	
Notes:	

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	57		
Units: scores on a scale				
least squares mean (standard error)	-3.6306 (\pm 2.0678)	8.1896 (\pm 2.0730)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00001873
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-11.8202
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.8927
upper limit	-6.7477

Secondary: Change from baseline in Polyneuropathy Disability (PND) Score at Week 65

End point title	Change from baseline in Polyneuropathy Disability (PND) Score at Week 65 ^[8]
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End point description:

PND = 5-stage scoring system. PND score is defined as I=sensory disturbances in limbs without motor impairment; II=difficulty walking without need of a walking aid; IIIa=one stick or one crutch required for walking; IIIb=two sticks or two crutches needed; IV=wheelchair required or subject confined to bed. For analysis, no impairment is scored as 0, I is scored as 1, II as 2, IIIa as 3, IIIb as 4 & IV as 5. Lower scores = greater ambulatory function. FAS = all randomized subjects received at least 1 injection of ION-682884 or inotersen & who have a baseline and at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS included all randomized subjects who received at least 1 injection of study drug and who had a baseline and at least 1 post-baseline efficacy assessment for the mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
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End point timeframe:

Baseline, Week 35

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	134	51		
Units: scores on a scale				
least squares mean (standard error)	0.1 (± 0.07)	0.3 (± 0.07)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02407897
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0

Secondary: Change from Baseline in the Physical Component Summary (PCS) Score of the 36-Item Short Form Survey (SF-36) at Week 65

End point title	Change from Baseline in the Physical Component Summary (PCS) Score of the 36-Item Short Form Survey (SF-36) at Week 65 ^[9]
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End point description:

SF-36 comprises 36 items that yield 8 subscales & 2 summary measures (PCS & Mental component summary [MCS]). Multi-item subscales (35 items): physical function=10 items, role physical =4 items, bodily pain=2 items, general health=5 items, vitality=4 items, social functioning=2 items, role emotional =3 items & mental health=5 items. 8 subscales are scored from 0-100. Higher scores=better health. 8 subscales are aggregated into a PCS score (0-100). Higher scores=better health. FAS = all randomized subjects who received at least 1 injection of ION-682884/inotersen & have a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS=all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
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End point timeframe:

Baseline, Week 65

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	136	50		
Units: scores on a scale				
least squares mean (standard error)	0.851 (\pm 0.7913)	-4.455 (\pm 0.8338)		

Statistical analyses

Statistical analysis title	External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00000558
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	5.305
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.195
upper limit	7.416

Secondary: Change from Baseline in Modified Body Mass Index (mBMI) at Week 65

End point title	Change from Baseline in Modified Body Mass Index (mBMI) at Week 65 ^[10]
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End point description:

mBMI is defined as body mass index in kilograms per square meter (kg/m^2) multiplied by serum albumin in grams per liter (g/L). FAS was defined as all randomized subjects who received at least 1 injection of ION-682884/inotersen & have a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. For NEURO-TTR trial, FAS was defined as all randomized subjects who received at least 1 injection of study drug & had a baseline & at least 1 post-baseline efficacy assessment for mNIS+7 score or Norfolk QOL-DN questionnaire total score. Number analysed is the number of subjects with data available for analysis.

End point type	Secondary
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End point timeframe:

Baseline, Week 65

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint was planned to report data for External Placebo and Eplontersen arms only.

End point values	Eplontersen	External Placebo		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	130	49		
Units: kilogram(kg)/metre(m)^2*gram(g)/litre				
least squares mean (standard error)	-8.0655 (± 10.3786)	-90.7645 (± 10.9465)		

Statistical analyses

Statistical analysis title	Baseline External Placebo vs Eplontersen
Comparison groups	Eplontersen v External Placebo
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 2E-7
Method	MMRM
Parameter estimate	Difference in LS Mean
Point estimate	82.6991
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.6431
upper limit	110.7551

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 1 to Week 85

Adverse event reporting additional description:

Safety Set (SS) included all participants who were randomized and received at least 1 injection of eplontersen or inotersen.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Eplontersen
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Reporting group description:

Subjects received eplontersen, 45 mg, SC, Q4W up to Week 81.

Reporting group title	Eplontersen 45mg Week 37 - Week 85
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Reporting group description:

Subjects received 45 mg of eplontersen by SC route once every 4 weeks SC from Week 37 to Week 81.

Reporting group title	Inotersen (Prior to Switch)
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Reporting group description:

Subjects received 300 mg of inotersen by SC route once weekly from Week 1 through Week 34.

Serious adverse events	Eplontersen	Eplontersen 45mg Week 37 - Week 85	Inotersen (Prior to Switch)
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 144 (18.75%)	3 / 20 (15.00%)	3 / 24 (12.50%)
number of deaths (all causes)	4	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium test positive			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			

subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Burns third degree			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 144 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 144 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 144 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arrhythmia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 144 (0.69%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Syncope			
subjects affected / exposed	3 / 144 (2.08%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adverse drug reaction			
subjects affected / exposed	0 / 144 (0.00%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 144 (1.39%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 144 (3.47%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 15	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephroangiosclerosis			

subjects affected / exposed	0 / 144 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 144 (1.39%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 144 (1.39%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

COVID-19 pneumonia			
subjects affected / exposed	2 / 144 (1.39%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis chronic			
subjects affected / exposed	0 / 144 (0.00%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Eplontersen	Eplontersen 45mg Week 37 - Week 85	Inotersen (Prior to Switch)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 144 (90.97%)	18 / 20 (90.00%)	24 / 24 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 144 (3.47%)	2 / 20 (10.00%)	0 / 24 (0.00%)
occurrences (all)	5	2	0
Orthostatic hypotension			
subjects affected / exposed	6 / 144 (4.17%)	0 / 20 (0.00%)	0 / 24 (0.00%)
occurrences (all)	7	0	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	2 / 144 (1.39%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	2	1	0
Chills			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	5 / 24 (20.83%)
occurrences (all)	1	0	7
Pain			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	2 / 24 (8.33%)
occurrences (all)	1	0	2

Injection site swelling subjects affected / exposed occurrences (all)	0 / 144 (0.00%) 0	0 / 20 (0.00%) 0	3 / 24 (12.50%) 5
Injection site bruising subjects affected / exposed occurrences (all)	2 / 144 (1.39%) 3	0 / 20 (0.00%) 0	5 / 24 (20.83%) 18
Asthenia subjects affected / exposed occurrences (all)	4 / 144 (2.78%) 4	0 / 20 (0.00%) 0	0 / 24 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	4 / 144 (2.78%) 5	0 / 20 (0.00%) 0	7 / 24 (29.17%) 11
Injection site pruritus subjects affected / exposed occurrences (all)	3 / 144 (2.08%) 5	0 / 20 (0.00%) 0	1 / 24 (4.17%) 1
Injection site pain subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 8	0 / 20 (0.00%) 0	3 / 24 (12.50%) 5
Fatigue subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 9	2 / 20 (10.00%) 5	6 / 24 (25.00%) 9
Oedema peripheral subjects affected / exposed occurrences (all)	13 / 144 (9.03%) 14	2 / 20 (10.00%) 2	0 / 24 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 7	0 / 20 (0.00%) 0	8 / 24 (33.33%) 42
Immune system disorders Immunisation reaction subjects affected / exposed occurrences (all)	13 / 144 (9.03%) 19	0 / 20 (0.00%) 0	1 / 24 (4.17%) 4
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 8	0 / 20 (0.00%) 0	3 / 24 (12.50%) 3
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	4 / 144 (2.78%) 4	2 / 20 (10.00%) 2	0 / 24 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 5	2 / 20 (10.00%) 2	0 / 24 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	6 / 144 (4.17%) 6	1 / 20 (5.00%) 1	1 / 24 (4.17%) 1
Investigations			
Platelet count decreased subjects affected / exposed occurrences (all)	2 / 144 (1.39%) 2	0 / 20 (0.00%) 0	2 / 24 (8.33%) 2
Glomerular filtration rate Decreased subjects affected / exposed occurrences (all)	3 / 144 (2.08%) 3	2 / 20 (10.00%) 3	4 / 24 (16.67%) 5
Weight decreased subjects affected / exposed occurrences (all)	4 / 144 (2.78%) 4	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all)	9 / 144 (6.25%) 9	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 9	0 / 20 (0.00%) 0	2 / 24 (8.33%) 2
Injury, poisoning and procedural complications			
Thermal burn subjects affected / exposed occurrences (all)	6 / 144 (4.17%) 8	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	10 / 144 (6.94%) 13	2 / 20 (10.00%) 4	2 / 24 (8.33%) 2
Contusion subjects affected / exposed occurrences (all)	2 / 144 (1.39%) 3	0 / 20 (0.00%) 0	2 / 24 (8.33%) 2
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 144 (0.00%) 0	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	11 / 144 (7.64%) 12	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Neuralgia subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 7	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	4 / 144 (2.78%) 6	0 / 20 (0.00%) 0	1 / 24 (4.17%) 1
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 144 (0.69%) 1	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Syncope subjects affected / exposed occurrences (all)	5 / 144 (3.47%) 5	0 / 20 (0.00%) 0	0 / 24 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	9 / 144 (6.25%) 10	1 / 20 (5.00%) 1	5 / 24 (20.83%) 9
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	7 / 144 (4.86%) 8	0 / 20 (0.00%) 0	1 / 24 (4.17%) 2
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 144 (0.69%) 2	0 / 20 (0.00%) 0	4 / 24 (16.67%) 4
Eye disorders			
Vision blurred subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 11	0 / 20 (0.00%) 0	2 / 24 (8.33%) 2
Cataract subjects affected / exposed occurrences (all)	8 / 144 (5.56%) 8	1 / 20 (5.00%) 1	0 / 24 (0.00%) 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	28 / 144 (19.44%)	1 / 20 (5.00%)	1 / 24 (4.17%)
occurrences (all)	33	1	1
Vomiting			
subjects affected / exposed	11 / 144 (7.64%)	1 / 20 (5.00%)	4 / 24 (16.67%)
occurrences (all)	13	1	4
Nausea			
subjects affected / exposed	14 / 144 (9.72%)	0 / 20 (0.00%)	5 / 24 (20.83%)
occurrences (all)	19	0	6
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	6 / 144 (4.17%)	0 / 20 (0.00%)	2 / 24 (8.33%)
occurrences (all)	6	0	2
Rash			
subjects affected / exposed	7 / 144 (4.86%)	1 / 20 (5.00%)	2 / 24 (8.33%)
occurrences (all)	9	1	2
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	2 / 144 (1.39%)	2 / 20 (10.00%)	0 / 24 (0.00%)
occurrences (all)	2	2	0
Urinary retention			
subjects affected / exposed	6 / 144 (4.17%)	1 / 20 (5.00%)	0 / 24 (0.00%)
occurrences (all)	7	1	0
Proteinuria			
subjects affected / exposed	12 / 144 (8.33%)	1 / 20 (5.00%)	1 / 24 (4.17%)
occurrences (all)	14	1	1
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	7 / 144 (4.86%)	0 / 20 (0.00%)	5 / 24 (20.83%)
occurrences (all)	10	0	10
Pain in extremity			
subjects affected / exposed	9 / 144 (6.25%)	1 / 20 (5.00%)	3 / 24 (12.50%)
occurrences (all)	11	1	7
Back pain			
subjects affected / exposed	11 / 144 (7.64%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	12	0	1

Arthralgia			
subjects affected / exposed	10 / 144 (6.94%)	1 / 20 (5.00%)	4 / 24 (16.67%)
occurrences (all)	12	1	6
Muscle spasms			
subjects affected / exposed	6 / 144 (4.17%)	2 / 20 (10.00%)	1 / 24 (4.17%)
occurrences (all)	13	2	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	26 / 144 (18.06%)	4 / 20 (20.00%)	2 / 24 (8.33%)
occurrences (all)	50	11	4
COVID-19			
subjects affected / exposed	47 / 144 (32.64%)	5 / 20 (25.00%)	1 / 24 (4.17%)
occurrences (all)	49	5	1
Sinusitis			
subjects affected / exposed	0 / 144 (0.00%)	1 / 20 (5.00%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Influenza			
subjects affected / exposed	7 / 144 (4.86%)	1 / 20 (5.00%)	1 / 24 (4.17%)
occurrences (all)	8	1	3
Upper respiratory tract infection			
subjects affected / exposed	9 / 144 (6.25%)	0 / 20 (0.00%)	1 / 24 (4.17%)
occurrences (all)	11	0	1
Nasopharyngitis			
subjects affected / exposed	9 / 144 (6.25%)	0 / 20 (0.00%)	2 / 24 (8.33%)
occurrences (all)	12	0	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 144 (0.69%)	0 / 20 (0.00%)	5 / 24 (20.83%)
occurrences (all)	1	0	6
Vitamin A deficiency			
subjects affected / exposed	17 / 144 (11.81%)	2 / 20 (10.00%)	1 / 24 (4.17%)
occurrences (all)	17	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 August 2019	The main purpose of this amendment is to remove the collection of a whole blood sample (Section 6.1.3 Treatment Period) for whole genome sequencing.
18 September 2019	1. Additional exploratory efficacy assessments were added (5-Level EQ-5D [EQ-5D-5L] and Composite Autonomic Symptom Score-31 [COMPASS-31]). 2. Protocol was harmonised with the historical inotersen NEURO-TTR trial to support data comparison between the 2 trials better also with the Phase 3 ION-682884-CS2 ATTR .nd
29 January 2020	1. Two clinical outcome assessments were added to collect additional patient-reported outcomes data to assess the efficacy of ION-682884; 2. The international normalized ratio (INR) was added to the confirmatory tests in case of elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) (or 2 × Baseline value if the Baseline value was > ULN); 3. Adjustments to the schedule of sample collection for coagulation was done and collection of samples for additional biomarkers were added.
10 December 2020	In response to the COVID-19 pandemic, and in accordance with regulatory guidance worldwide, the main purpose of the protocol addendum was to enhance trial safety by minimizing patient and site personnel exposure to potentially SARS-CoV-2-infected individuals. Below measures were adopted: 1. Selected visits and procedures were conducted remotely (as “virtual visits”), 2. Selected time windows for certain visits and procedures had lengthened to provide increased scheduling flexibility. 3. The option for remote consent was added. 4. Additionally, the requirement for periodic ophthalmology assessments throughout the study was removed and selected eligibility criteria have been clarified.
12 August 2021	The purpose of this amendment was to update the frequency of safety monitoring of platelet count, eGFR and UPCR, per endorsement by the independent data and safety monitoring board (DSMB) and feedback from the US Food and Drug Administration (FDA) review division.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/37768671>