Clinical trial results:
A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy

Summary

EudraCT number	2012-001831-30
Trial protocol	GB PT DE IT ES BG
Global end of trial date	07 November 2017

Results information

Result version number	v1 (current)
This version publication date	24 July 2019
First version publication date	24 July 2019

Trial information

Trial identification

Sponsor protocol code	ISIS420915-CS2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01737398
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	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@ionisph.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Pharmaceuticals, Inc., +1 800-679-4747, patients@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 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of ISIS 420915 as compared to placebo, given for 65 weeks, as measured by the change from baseline in the modified neuropathy impairment score +7 (mNIS+7) and in the norfolk quality of life-diabetic neuropathy (Norfolk QOL-DN) questionnaire total score, in subjects with familial amyloid polyneuropathy (FAP).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 82
Country: Number of subjects enrolled	Brazil: 22
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	172
EEA total number of subjects	60

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)	98
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects randomized: 113 inotersen and 60 placebo; received study treatment: 112 inotersen and 60 placebo. One subject in the inotersen group was ineligible, but was randomized in error. This study consisted of a 65-week Treatment Period, 1-week End of Treatment (EOT) Period, and a 6-month Post-treatment Evaluation Period.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Inotersen

Arm description:

Subjects received 3 subcutaneous (SC) doses of 300 milligrams (mg) inotersen during Week 1, followed by once-weekly SC administration for 64 weeks.

Arm type	Experimental
Investigational medicinal product name	Inotersen
Investigational medicinal product code	
Other name	ISIS 420915
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inotersen administered as subcutaneous (SC) injection, 300 mg in Week 1 followed by once-weekly SC injection for 64 weeks.

Arm title	Placebo

Arm description:

Subjects received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo administered as SC injection in Week 1 followed by once-weekly SC injection for 64 weeks.

Number of subjects in period 1	Inotersen	Placebo
Started	112	60
Completed	87	52
Not completed	25	8
Consent withdrawn by subject	2	3
Stopping Rule Met	2	1
Liver Transplant	1	-
Sponsor Decision	2	-
Adverse Event or Serious Adverse Event (SAE)	16	1
Disease Progression	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Inotersen
Reporting group description:	
Subjects received 3 subcutaneous (SC) doses of 300 milligrams (mg) inotersen during Week 1, followed by once-weekly SC administration for 64 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks.	

Reporting group values	Inotersen	Placebo	Total
Number of subjects	112	60	172
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	59.0	59.5	
standard deviation	± 12.53	± 14.05	-
Gender categorical Units: Subjects			
Female	35	19	54
Male	77	41	118
Ethnicity Units: Subjects			
Hispanic or Latino	17	7	24
Not Hispanic or Latino	95	53	148
Race Units: Subjects			
Asian	1	3	4
Black	3	1	4
White	105	53	158
White & Grayish-Brown	0	1	1
Other	3	2	5
Subjects diagnosed with Familial Amyloid Cardiomyopathy Units: Subjects			
Yes	45	22	67
No	67	38	105

End points

End points reporting groups

Reporting group title	Inotersen
Reporting group description:	
Subjects received 3 subcutaneous (SC) doses of 300 milligrams (mg) inotersen during Week 1, followed by once-weekly SC administration for 64 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks.	
Subject analysis set title	Inotersen 300 mg IM Positive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 3 SC doses of 300 mg inotersen during Week 1, followed by once-weekly SC administration for 64 weeks, and had a positive immunogenicity (IM) status.	
Subject analysis set title	Inotersen 300 mg IM Negative
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects received 3 SC doses of 300 mg inotersen during Week 1, followed by once-weekly SC administration for 64 weeks, and had a negative IM status.	

Primary: Change From Baseline in the Modified Neuropathy Impairment Score (mNIS) +7 Composite Score at Week 66

End point title	Change From Baseline in the Modified Neuropathy Impairment Score (mNIS) +7 Composite Score at Week 66
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 lower function. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.	
End point type	Primary
End point timeframe:	
Baseline and Week 66	

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	52		
Units: score on a Scale				
arithmetic mean (standard deviation)	4.16 (± 15.672)	23.89 (± 24.190)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Inotersen v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0 [1]
Method	MMRM
Parameter estimate	Least Square Mean Difference
Point estimate	-19.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.43
upper limit	-13.03

Notes:

[1] - P-value was calculated using mixed effects model with repeated measures (MMRM).

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

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. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Primary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	52		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.08 (± 18.967)	10.77 (± 21.134)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Inotersen v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	MMRM
Parameter estimate	Least Square Mean Difference
Point estimate	-11.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.29
upper limit	-5.06

Secondary: Change From Baseline in the Norfolk QoL-DN Questionnaire Symptoms Domain Score at Week 66

End point title	Change From Baseline in the Norfolk QoL-DN Questionnaire Symptoms Domain Score at Week 66

End point description:

The Norfolk QoL-DN symptoms score is a sub-score of the total Norfolk QoL-DN questionnaire. The Norfolk QoL-DN symptoms domain score has a range of 0-32, and a higher Norfolk QoL-DN score indicates poorer QoL. This endpoint only measured subjects with Stage 1 hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) in full analysis set. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	33		
Units: score on a scale				
arithmetic mean (standard deviation)	-1.40 (± 4.763)	1.18 (± 5.270)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Norfolk QoL-DN Questionnaire Physical Functioning/Large Fiber Neuropathy Domain Score at Week 66

End point title	Change From Baseline in the Norfolk QoL-DN Questionnaire Physical Functioning/Large Fiber Neuropathy Domain Score at Week 66

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 QoL. This

endpoints only measured subjects who had Stage 2 hATTR-PN in full analysis set. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	19		
Units: score on a scale				
arithmetic mean (standard deviation)	1.05 (± 11.924)	8.74 (± 9.689)		

Statistical analyses

No statistical analyses for this end point

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

End point description:

The mBMI is the BMI multiplied by the serum albumin g/L. The full analysis set included all randomized subject who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	49		
Units: kilogram(kg)/metre(m)^2*gram(g)/litre				
arithmetic mean (standard deviation)	-73.32 (± 96.311)	-85.21 (± 91.259)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Body Mass Index (BMI) at Week 65

End point title	Change From Baseline In Body Mass Index (BMI) at Week 65

End point description:

The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	49		
Units: kg/m^2				
arithmetic mean (standard deviation)	-0.24 (± 1.521)	-0.87 (± 1.202)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Neuropathy Impairment Score (NIS) at Week 66

End point title	Change From Baseline in Neuropathy Impairment Score (NIS) at Week 66

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. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	52		
Units: score on a scale				
arithmetic mean (standard deviation)	4.47 (± 10.329)	17.29 (± 16.986)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Modified +7 at Week 66

End point title	Change From Baseline in Modified +7 at Week 66

End point description:

The Modified +7 score is a version of the NIS score that is a measure of neurologic impairment. The Modified +7 Score has a range of -22.32 to 102.32 and a higher NIS score indicates lower function. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	52		
Units: score on a scale				
arithmetic mean (standard deviation)	-0.31 (± 11.134)	6.60 (± 12.770)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in NIS+7 at Week 66

End point title	Change From Baseline in NIS+7 at Week 66

End point description:

The NIS+7 score is a version of the NIS score that is a measure of neurologic impairment. The NIS+7 Score has a range of -26.04 to 270.04 and a higher NIS score indicates lower function. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 66

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	52		
Units: score on a scale				
arithmetic mean (standard deviation)	5.10 (± 10.709)	19.00 (± 16.824)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram (ECHO) at Week 65 in the CM-ECHO Set

End point title	Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram (ECHO) at Week 65 in the CM-ECHO Set

End point description:

GLS by ECHO is a measure of cardiac systolic function. The CM-ECHO set included the subset of the randomized set who had a diagnosis of transthyretin (TTR) cardiomyopathy at study entry but are not in the ECHO subgroup, plus subjects who qualified to participate in the ECHO subgroup (whether consented or not). Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	25		
Units: percent change				
arithmetic mean (standard deviation)	0.69 (± 3.134)	0.46 (± 2.702)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram ECHO at Week 65 in the ECHO Subgroup

End point title	Change From Baseline in Global Longitudinal Strain (GLS) by Echocardiogram ECHO at Week 65 in the ECHO Subgroup

End point description:

GLS by ECHO is a measure of cardiac systolic function. The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	16		
Units: percent change				
arithmetic mean (standard deviation)	0.25 (± 3.163)	1.05 (± 2.745)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Transthyretin (TTR) Level at Week 65

End point title	Change From Baseline in Transthyretin (TTR) Level at Week 65

End point description:

The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	51		
Units: g/L				
arithmetic mean (standard deviation)	-0.1570 (± 0.0619)	-0.0146 (± 0.0402)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Retinol Binding Protein 4 (RBP4) Level at Week 65

End point title	Change From Baseline in Retinol Binding Protein 4 (RBP4) Level at Week 65

End point description:

The full analysis set included all randomized subjects who received at least 1 injection of study drug (inotersen or placebo) 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. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Baseline and Week 65

End point values	Inotersen	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	51		
Units: microgram (ug)/L				
arithmetic mean (standard deviation)	-21725.9 (± 9884.04)	-1768.7 (± 8027.78)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Measured Plasma Concentration (Cmax) Of Inotersen At Week 65

End point title	Maximum Measured Plasma Concentration (Cmax) Of Inotersen At Week 65

End point description:

The pharmacokinetic (PK) Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: micrograms per millilitre (ug/mL)				
arithmetic mean (standard deviation)	11.1 (± 4.80)	6.76 (± 1.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time To The Maximum Plasma Concentration (Tmax) Of Inotersen At Week 65

End point title	Time To The Maximum Plasma Concentration (Tmax) Of Inotersen At Week 65

End point description:

The PK Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: hour (hr)				
arithmetic mean (standard deviation)	3.48 (± 0.684)	4.14 (± 1.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Plasma Concentration-time Curve From 0 To 24 Hours (AUC[0-24hr]) Of Inotersen At Week 65

End point title	Area Under The Plasma Concentration-time Curve From 0 To 24 Hours (AUC[0-24hr]) Of Inotersen At Week 65

End point description:

The PK Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: microgram hours (ug*hr) per/mL				
arithmetic mean (standard deviation)	92.4 (± 77.3)	93.1 (± 30.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Plasma Concentration-time Curve From 0 To 168 Hours (AUC[0-168hr]) Of Inotersen At Week 65

End point title	Area Under The Plasma Concentration-time Curve From 0 To 168 Hours (AUC[0-168hr]) Of Inotersen At Week 65

End point description:

The PK Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: ug*hr/mL				
arithmetic mean (standard deviation)	103 (± 88.2)	98.9 (± 33.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Clearance From 0 To 24 Hours (CL[0-24hr]/F) Of Inotersen At Week 65

End point title	Plasma Clearance From 0 To 24 Hours (CL[0-24hr]/F) Of Inotersen At Week 65

End point description:

The PK Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	5		
Units: L/hr				
arithmetic mean (standard deviation)	6.14 (± 5.92)	3.57 (± 1.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Inotersen Plasma Clearance At Steady State (CLss/F) At Week 65

End point title	Inotersen Plasma Clearance At Steady State (CLss/F) At Week 65

End point description:

The PK Set was defined as all randomized subjects who received at least 1 dose of active study drug (inotersen) and had at least 1 evaluable PK sample collected and analysed with a reportable result. Subjects analysed is the number of subjects with evaluable data at the given time-point.

End point type	Secondary

End point timeframe:

Week 65

End point values	Inotersen 300 mg IM Positive	Inotersen 300 mg IM Negative		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	3	4		
Units: L/hr				
arithmetic mean (standard deviation)	5.46 (± 5.13)	3.33 (± 1.21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 1 to Week 91

Adverse event reporting additional description:

Adverse events that first occurred or worsened after the first dose of study drug (inotersen or placebo), including serious adverse events, were summarized for each treatment group. Analysis is based on data collected while study treatment was administered and during follow-up until the day of the subject's last contact date within the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Inotersen

Reporting group description:

Subjects received 3 SC doses of 300 mg inotersen during Week 1, followed by once-weekly SC administration for 64 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects received 3 SC doses of placebo during Week 1, followed by once-weekly SC administration for 64 weeks.

Serious adverse events	Inotersen	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 112 (32.14%)	13 / 60 (21.67%)	
number of deaths (all causes)	5	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 112 (0.00%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			

subjects affected / exposed	0 / 112 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 112 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 112 (0.89%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiopathy			
subjects affected / exposed	0 / 112 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	4 / 112 (3.57%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 112 (1.79%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			

subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (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			
Dementia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuritis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (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	0 / 112 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (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	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mesenteric arterial occlusion			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			

subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 112 (0.89%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 112 (1.79%)	2 / 60 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 112 (0.89%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			

subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 112 (0.89%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 112 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 112 (2.68%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cachexia			

subjects affected / exposed	2 / 112 (1.79%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	Inotersen	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 112 (98.21%)	60 / 60 (100.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 112 (5.36%)	2 / 60 (3.33%)	
occurrences (all)	8	4	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	35 / 112 (31.25%)	0 / 60 (0.00%)	
occurrences (all)	117	0	
Injection site pain			
subjects affected / exposed	23 / 112 (20.54%)	4 / 60 (6.67%)	
occurrences (all)	47	7	
Fatigue			
subjects affected / exposed	28 / 112 (25.00%)	12 / 60 (20.00%)	
occurrences (all)	43	14	
Chills			
subjects affected / exposed	20 / 112 (17.86%)	2 / 60 (3.33%)	
occurrences (all)	40	3	
Pyrexia			
subjects affected / exposed	22 / 112 (19.64%)	5 / 60 (8.33%)	
occurrences (all)	32	6	
Oedema peripheral			

subjects affected / exposed	21 / 112 (18.75%)	6 / 60 (10.00%)	
occurrences (all)	23	6	
Asthenia			
subjects affected / exposed	14 / 112 (12.50%)	8 / 60 (13.33%)	
occurrences (all)	17	11	
Injection site pruritus			
subjects affected / exposed	13 / 112 (11.61%)	0 / 60 (0.00%)	
occurrences (all)	16	0	
Influenza like illness			
subjects affected / exposed	9 / 112 (8.04%)	2 / 60 (3.33%)	
occurrences (all)	10	2	
Injection site bruising			
subjects affected / exposed	8 / 112 (7.14%)	2 / 60 (3.33%)	
occurrences (all)	8	2	
Peripheral swelling			
subjects affected / exposed	7 / 112 (6.25%)	0 / 60 (0.00%)	
occurrences (all)	7	0	
Injection site reaction			
subjects affected / exposed	6 / 112 (5.36%)	0 / 60 (0.00%)	
occurrences (all)	7	0	
Gait disturbance			
subjects affected / exposed	6 / 112 (5.36%)	5 / 60 (8.33%)	
occurrences (all)	6	5	
Injection site swelling			
subjects affected / exposed	6 / 112 (5.36%)	0 / 60 (0.00%)	
occurrences (all)	6	0	
Pain			
subjects affected / exposed	2 / 112 (1.79%)	5 / 60 (8.33%)	
occurrences (all)	2	6	
Oedema			
subjects affected / exposed	1 / 112 (0.89%)	3 / 60 (5.00%)	
occurrences (all)	1	4	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 112 (0.89%)	4 / 60 (6.67%)	
occurrences (all)	1	4	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	10 / 112 (8.93%)	2 / 60 (3.33%)	
occurrences (all)	13	2	
Cough			
subjects affected / exposed	10 / 112 (8.93%)	8 / 60 (13.33%)	
occurrences (all)	11	8	
Oropharyngeal pain			
subjects affected / exposed	6 / 112 (5.36%)	2 / 60 (3.33%)	
occurrences (all)	6	2	
Dyspnoea exertional			
subjects affected / exposed	2 / 112 (1.79%)	3 / 60 (5.00%)	
occurrences (all)	2	3	
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 112 (6.25%)	4 / 60 (6.67%)	
occurrences (all)	7	5	
Insomnia			
subjects affected / exposed	6 / 112 (5.36%)	3 / 60 (5.00%)	
occurrences (all)	6	3	
Anxiety			
subjects affected / exposed	1 / 112 (0.89%)	4 / 60 (6.67%)	
occurrences (all)	1	5	
Investigations			
Platelet count decreased			
subjects affected / exposed	12 / 112 (10.71%)	0 / 60 (0.00%)	
occurrences (all)	14	0	
Glomerular filtration rate decreased			
subjects affected / exposed	6 / 112 (5.36%)	2 / 60 (3.33%)	
occurrences (all)	7	2	
Weight decreased			
subjects affected / exposed	4 / 112 (3.57%)	5 / 60 (8.33%)	
occurrences (all)	5	7	
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	19 / 112 (16.96%)	13 / 60 (21.67%)	
occurrences (all)	26	16	
Contusion			
subjects affected / exposed	9 / 112 (8.04%)	1 / 60 (1.67%)	
occurrences (all)	11	1	
Thermal burn			
subjects affected / exposed	6 / 112 (5.36%)	6 / 60 (10.00%)	
occurrences (all)	6	6	
Ligament sprain			
subjects affected / exposed	1 / 112 (0.89%)	3 / 60 (5.00%)	
occurrences (all)	2	5	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 112 (5.36%)	1 / 60 (1.67%)	
occurrences (all)	6	1	
Nervous system disorders			
Headache			
subjects affected / exposed	26 / 112 (23.21%)	7 / 60 (11.67%)	
occurrences (all)	34	10	
Paraesthesia			
subjects affected / exposed	11 / 112 (9.82%)	2 / 60 (3.33%)	
occurrences (all)	21	3	
Dizziness			
subjects affected / exposed	14 / 112 (12.50%)	7 / 60 (11.67%)	
occurrences (all)	17	7	
Syncope			
subjects affected / exposed	9 / 112 (8.04%)	2 / 60 (3.33%)	
occurrences (all)	16	2	
Hypoaesthesia			
subjects affected / exposed	10 / 112 (8.93%)	6 / 60 (10.00%)	
occurrences (all)	11	7	
Presyncope			
subjects affected / exposed	6 / 112 (5.36%)	0 / 60 (0.00%)	
occurrences (all)	10	0	
Neuralgia			

subjects affected / exposed	3 / 112 (2.68%)	8 / 60 (13.33%)	
occurrences (all)	3	8	
Neuropathy peripheral			
subjects affected / exposed	2 / 112 (1.79%)	4 / 60 (6.67%)	
occurrences (all)	3	5	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	14 / 112 (12.50%)	1 / 60 (1.67%)	
occurrences (all)	19	2	
Anaemia			
subjects affected / exposed	15 / 112 (13.39%)	2 / 60 (3.33%)	
occurrences (all)	16	2	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	2 / 112 (1.79%)	3 / 60 (5.00%)	
occurrences (all)	3	3	
Blepharitis			
subjects affected / exposed	2 / 112 (1.79%)	4 / 60 (6.67%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	35 / 112 (31.25%)	7 / 60 (11.67%)	
occurrences (all)	44	9	
Diarrhoea			
subjects affected / exposed	27 / 112 (24.11%)	12 / 60 (20.00%)	
occurrences (all)	29	16	
Vomiting			
subjects affected / exposed	17 / 112 (15.18%)	2 / 60 (3.33%)	
occurrences (all)	21	2	
Constipation			
subjects affected / exposed	15 / 112 (13.39%)	6 / 60 (10.00%)	
occurrences (all)	16	7	
Abdominal pain			
subjects affected / exposed	6 / 112 (5.36%)	4 / 60 (6.67%)	
occurrences (all)	6	5	
Dry mouth			

subjects affected / exposed	6 / 112 (5.36%)	1 / 60 (1.67%)	
occurrences (all)	6	1	
Dysphagia			
subjects affected / exposed	2 / 112 (1.79%)	3 / 60 (5.00%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	5 / 112 (4.46%)	4 / 60 (6.67%)	
occurrences (all)	7	4	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	7 / 112 (6.25%)	2 / 60 (3.33%)	
occurrences (all)	9	3	
Haematuria			
subjects affected / exposed	5 / 112 (4.46%)	5 / 60 (8.33%)	
occurrences (all)	5	7	
Dysuria			
subjects affected / exposed	2 / 112 (1.79%)	4 / 60 (6.67%)	
occurrences (all)	2	4	
Urinary retention			
subjects affected / exposed	2 / 112 (1.79%)	3 / 60 (5.00%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	17 / 112 (15.18%)	6 / 60 (10.00%)	
occurrences (all)	25	7	
Arthralgia			
subjects affected / exposed	13 / 112 (11.61%)	5 / 60 (8.33%)	
occurrences (all)	20	9	
Muscle spasms			
subjects affected / exposed	11 / 112 (9.82%)	4 / 60 (6.67%)	
occurrences (all)	13	5	
Pain in extremity			
subjects affected / exposed	10 / 112 (8.93%)	8 / 60 (13.33%)	
occurrences (all)	12	11	
Muscular weakness			

subjects affected / exposed	11 / 112 (9.82%)	6 / 60 (10.00%)	
occurrences (all)	11	7	
Back pain			
subjects affected / exposed	10 / 112 (8.93%)	5 / 60 (8.33%)	
occurrences (all)	11	5	
Musculoskeletal pain			
subjects affected / exposed	6 / 112 (5.36%)	1 / 60 (1.67%)	
occurrences (all)	6	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	21 / 112 (18.75%)	11 / 60 (18.33%)	
occurrences (all)	46	13	
Nasopharyngitis			
subjects affected / exposed	9 / 112 (8.04%)	6 / 60 (10.00%)	
occurrences (all)	9	7	
Upper respiratory tract infection			
subjects affected / exposed	7 / 112 (6.25%)	3 / 60 (5.00%)	
occurrences (all)	8	4	
Influenza			
subjects affected / exposed	4 / 112 (3.57%)	3 / 60 (5.00%)	
occurrences (all)	4	3	
Rhinitis			
subjects affected / exposed	0 / 112 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	4	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 112 (9.82%)	0 / 60 (0.00%)	
occurrences (all)	14	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported