Clinical trial results:
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Multiple Doses of ISIS 416858 (IONIS-FXIRX an Antisense Inhibitor of Factor XI), Administered Subcutaneously to Patients with End-Stage Renal Disease on Hemodialysis

Summary

EudraCT number	2017-002165-21
Trial protocol	ES CZ AT NL BG BE GR LV
Global end of trial date	10 July 2019

Results information

Result version number	v1
This version publication date	26 July 2020
First version publication date	26 July 2020

Trial information

Trial identification

Sponsor protocol code	ISIS 416858-CS5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03358030
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, CA , 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	10 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial was to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ISIS 416858 (200, 250, and 300 milligrams (mg) once weekly) compared to placebo as assessed by factor XI (FXI) activity reduction in End-Stage Renal Disease on Hemodialysis (ESRD) subjects on hemodialysis.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form. Subjects were encouraged to complete the early termination study procedures and observations at the time of withdrawal.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 December 2017
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	Latvia: 4
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Czech Republic: 19
Country: Number of subjects enrolled	Greece: 33
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Russian Federation: 71
Worldwide total number of subjects	213
EEA total number of subjects	130

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)	127
From 65 to 84 years	84
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 10 countries (Latvia, Netherlands, Spain, Austria, Belgium, Bulgaria, Czech Republic, Greece, Canada and Russian Federation) from 26 December 2017 to 10 July 2019.

Pre-assignment

Screening details:

A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.

Pre-assignment period milestones

Number of subjects started	213
Number of subjects completed	210

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not receive study treatment: 3

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

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:

Subjects received placebo subcutaneously, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm title	Cohort A: ISIS 416858, 200 mg

Arm description:

Subjects received ISIS 416858, 200 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm type	Experimental
Investigational medicinal product name	ISIS 416858
Investigational medicinal product code	
Other name	IONIS-FXIRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ISIS 416858, 200 mg, subcutaneously, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm title	Cohort B: ISIS 416858, 250 mg

Arm description:

Subjects received ISIS 416858, 250 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm type	Experimental
Investigational medicinal product name	ISIS 416858
Investigational medicinal product code	
Other name	IONIS-FXIRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ISIS 416858, 250 mg, subcutaneously, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm title	Cohort C: ISIS 416858, 300 mg

Arm description:

Subjects received ISIS 416858, 300 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Arm type	Experimental
Investigational medicinal product name	ISIS 416858
Investigational medicinal product code	
Other name	IONIS-FXIRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received ISIS 416858, 300 mg, subcutaneously, once weekly from Week 1 (Day 1) through Week 26 of treatment period.

Number of subjects in period 1[1]	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg
Started	53	53	54
Safety Population	53	53	54
Per Protocol Population	49 [2]	45 [3]	43 [4]
Completed	50	52	46
Not completed	3	1	8
Unspecified	-	-	1
Adverse Event or SAE	2	-	6
Voluntary withdrawal	1	1	1

Number of subjects in period 1[1]	Cohort C: ISIS 416858, 300 mg

Started	50
Safety Population	50
Per Protocol Population	35 [5]
Completed	48
Not completed	2
Unspecified	-
Adverse Event or SAE	1
Voluntary withdrawal	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: A total of 213 subjects were enrolled and randomised in the study. Out of 213, 3 subjects did not receive the study drug and were not considered a part of the starting population.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort A: ISIS 416858, 200 mg
Reporting group description:	
Subjects received ISIS 416858, 200 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort B: ISIS 416858, 250 mg
Reporting group description:	
Subjects received ISIS 416858, 250 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort C: ISIS 416858, 300 mg
Reporting group description:	
Subjects received ISIS 416858, 300 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	

Reporting group values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg
Number of subjects	53	53	54
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	61	61	63
standard deviation	± 13	± 14	± 12
Gender categorical Units: Subjects			
Female	19	23	19
Male	34	30	35
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	6
Not Hispanic or Latino	52	53	48
Race Units: Subjects			
White	52	51	50

Black	0	0	3
Asian	1	1	0
Other Race	0	1	0
Multiple Race	0	0	1

Reporting group values	Cohort C: ISIS 416858, 300 mg	Total	
Number of subjects	50	210	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	58		
standard deviation	± 14	-	
Gender categorical Units: Subjects			
Female	20	81	
Male	30	129	
Ethnicity Units: Subjects			
Hispanic or Latino	5	12	
Not Hispanic or Latino	45	198	
Race Units: Subjects			
White	49	202	
Black	0	3	
Asian	1	3	
Other Race	0	1	
Multiple Race	0	1	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort A: ISIS 416858, 200 mg
Reporting group description:	
Subjects received ISIS 416858, 200 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort B: ISIS 416858, 250 mg
Reporting group description:	
Subjects received ISIS 416858, 250 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort C: ISIS 416858, 300 mg
Reporting group description:	
Subjects received ISIS 416858, 300 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	

Primary: Number of Subjects With Major Bleeding (MB) and Clinically Relevant Non-Major Bleeding (CRNMB)

End point title	Number of Subjects With Major Bleeding (MB) and Clinically Relevant Non-Major Bleeding (CRNMB)[1]
End point description:	
MB was defined as one of the following: Fatal bleeding; symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular if in a major joint, or pericardial, or intramuscular with compartment syndrome, clinically overt bleeding leading to transfusion of greater than or equal to (>=) 2 units of packed red blood cells or whole blood or a fall in hemoglobin of 20 grams per litre (g/L) (1.24 millimoles per litre [mmol/L]) or more within 24 hours. CRNMB was defined as overt bleeding not meeting the criteria for MB but that resulted, in either medical examination, intervention, or had clinical consequences for a subject. Safety population included all randomised subjects who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe:	
Up to Day 260	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis was performed for the combination of MB and CRNMB.

End point values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg	Cohort C: ISIS 416858, 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	54	50
Units: subjects	3	2	3	3

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline (PCFB) in Activated Partial Thromboplastin Time (aPTT)

End point title	Percent Change From Baseline (PCFB) in Activated Partial Thromboplastin Time (aPTT)

End point description:

PP population: All subjects, randomised without missing more than 2 doses during first 12 weeks or more than 5 doses over 26-week Treatment Period (TP) and not have any major protocol violations that would have affected interpretation/integrity of study results. Number analysed ("n") is the number of subjects with data available for analyses at the given time point.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1) up to Day 260

End point values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg	Cohort C: ISIS 416858, 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	45	43	35
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 49, 45, 43, 35)	30.1 (± 6.3)	28.0 (± 5.9)	30.1 (± 7.0)	30.1 (± 5.1)
PCFB at Day 5 (n= 48, 44, 43, 35)	-2.8 (± 23.1)	9.3 (± 41.5)	-2.8 (± 19.2)	0.7 (± 18.2)
PCFB at Day 12 (n= 47, 43, 42, 34)	1.4 (± 33.5)	9.4 (± 25.9)	0.8 (± 21.9)	3.6 (± 19.5)
PCFB at Day 15 (n= 49, 45, 42, 35)	3.8 (± 47.7)	7.5 (± 29.0)	12.5 (± 39.8)	12.5 (± 38.4)
PCFB at Day 22 (n= 48, 44, 43, 35)	-0.6 (± 25.6)	11.4 (± 38.1)	8.4 (± 30.4)	16.6 (± 32.0)
PCFB at Day 29 (n= 47, 45, 42, 35)	-1.9 (± 23.8)	11.0 (± 28.4)	11.4 (± 30.7)	18.8 (± 46.6)
PCFB at Day 36 (n= 47, 45, 42, 35)	-3.1 (± 17.8)	7.1 (± 18.2)	13.2 (± 35.5)	16.9 (± 21.0)
PCFB at Day 50 (n= 49, 44, 43, 33)	6.8 (± 46.9)	24.1 (± 53.4)	27.5 (± 42.4)	24.3 (± 34.3)
PCFB at Day 64 (n= 48, 44, 42,35)	6.0 (± 36.1)	20.3 (± 25.8)	29.9 (± 75.6)	40.5 (± 53.7)
PCFB at Day 78 (n= 46, 45, 42, 35)	6.6 (± 49.5)	27.9 (± 49.2)	27.9 (± 38.6)	42.9 (± 47.8)
PCFB at Day 92 (n= 47, 45, 42, 34)	9.5 (± 58.8)	19.1 (± 27.1)	52.5 (± 83.1)	42.1 (± 57.2)
PCFB at Day 106 (n= 49, 45, 42, 34)	10.9 (± 70.7)	38.9 (± 71.7)	28.5 (± 46.1)	44.8 (± 60.7)
PCFB at Day 120 (n= 45, 44, 42, 35)	2.6 (± 26.6)	28.5 (± 43.1)	22.5 (± 33.1)	41.4 (± 49.4)
PCFB at Day 134 (n= 49, 43, 43, 34)	-6.2 (± 16.0)	42.9 (± 86.6)	29.5 (± 49.8)	50.1 (± 98.1)
PCFB at Day 148 (n= 47, 45, 43, 34)	1.0 (± 25.8)	26.1 (± 28.7)	34.0 (± 53.5)	38.7 (± 61.5)
PCFB at Day 162 (n= 49, 44, 41, 33)	-1.6 (± 17.1)	27.6 (± 30.1)	31.6 (± 39.3)	33.3 (± 34.9)
PCFB at Day 176 (n= 47, 45, 42, 33)	3.7 (± 31.6)	28.8 (± 35.0)	36.3 (± 79.0)	32.3 (± 34.6)
PCFB at Day 190 (n= 44, 44, 42, 32)	-3.6 (± 12.5)	38.3 (± 92.9)	20.5 (± 31.6)	23.5 (± 20.2)
PCFB at Day 204 (n= 46, 44, 41, 33)	-0.4 (± 27.9)	17.4 (± 39.3)	13.3 (± 27.1)	16.9 (± 32.1)
PCFB at Day 218 (n= 47, 44, 41, 34)	-0.7 (± 26.4)	13.1 (± 25.8)	7.0 (± 24.6)	13.2 (± 30.3)
PCFB at Day 232 (n= 47, 43, 41, 33)	-0.7 (± 41.8)	8.6 (± 24.0)	16.8 (± 44.0)	3.1 (± 14.8)
PCFB at Day 246 (n= 46, 42, 38, 34)	-0.0 (± 44.2)	10.0 (± 26.9)	3.5 (± 25.2)	3.6 (± 20.6)
PCFB at Day 260 (n= 46, 41, 40, 34)	2.3 (± 50.7)	16.1 (± 54.4)	-2.9 (± 21.6)	3.6 (± 30.1)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Factor XI (FXI) Activity

End point title	Percent Change From Baseline in Factor XI (FXI) Activity

End point description:

PP population: All subjects, randomised without missing more than 2 doses during first 12 weeks or more than 5 doses over 26-week TP and not have any major protocol violations that would have affected interpretation/integrity of study results. "n" is the number of subjects with data available for analyses at the given time point.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1) up to Day 260

End point values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg	Cohort C: ISIS 416858, 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	45	43	35
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 49, 45, 43, 35)	0.99 (± 0.19)	1.00 (± 0.21)	1.05 (± 0.24)	1.03 (± 0.17)
PCFB at Day 5 (n= 48, 45, 43, 35)	-0.6 (± 14.4)	2.5 (± 24.6)	-0.0 (± 14.8)	-2.5 (± 18.3)
PCFB at Day 12 (n= 47, 43, 42, 34)	-1.9 (± 13.7)	-3.0 (± 17.3)	-8.8 (± 18.7)	-14.1 (± 16.1)
PCFB at Day 15 (n= 49, 45, 42, 35)	-0.6 (± 15.1)	-7.1 (± 16.2)	-14.0 (± 21.3)	-18.8 (± 17.3)
PCFB at Day 22 (n= 49, 44, 43, 35)	-3.7 (± 18.2)	-17.2 (± 16.2)	-22.7 (± 19.5)	-27.6 (± 19.3)
PCFB at Day 29 (n= 47, 45, 42, 35)	-3.3 (± 18.3)	-21.4 (± 16.9)	-31.5 (± 23.4)	-37.9 (± 18.5)
PCFB at Day 36 (n= 48, 45, 41, 35)	-6.0 (± 18.1)	-26.3 (± 18.4)	-37.3 (± 22.0)	-42.8 (± 17.9)
PCFB at Day 50 (n= 49, 45, 43, 34)	-3.2 (± 19.7)	-37.9 (± 22.2)	-48.1 (± 24.1)	-55.7 (± 20.6)
PCFB at Day 64 (n= 48, 44, 42,34)	-4.5 (± 20.2)	-41.8 (± 20.1)	-55.1 (± 24.0)	-61.7 (± 20.3)
PCFB at Day 78 (n= 46, 45, 42, 35)	-8.1 (± 19.6)	-44.6 (± 20.9)	-56.4 (± 23.9)	-64.2 (± 19.5)
PCFB at Day 92 (n= 46, 45, 43, 35)	-6.2 (± 16.0)	-45.0 (± 21.6)	-60.2 (± 21.8)	-66.0 (± 19.0)
PCFB at Day 106 (n= 49, 45, 43, 35)	-6.6 (± 19.2)	-49.4 (± 20.4)	-58.1 (± 22.2)	-67.8 (± 18.4)
PCFB at Day 120 (n= 46, 44, 43, 35)	-0.8 (± 23.0)	-47.8 (± 20.3)	-57.2 (± 28.1)	-66.9 (± 17.6)
PCFB at Day 134 (n= 49, 45, 43, 35)	-1.3 (± 18.1)	-50.0 (± 19.1)	-57.0 (± 28.0)	-67.7 (± 19.7)
PCFB at Day 148 (n= 49, 45, 43, 35)	-4.3 (± 23.6)	-50.4 (± 17.5)	-59.2 (± 24.0)	-65.5 (± 20.0)
PCFB at Day 162 (n= 49, 45, 43, 35)	-3.1 (± 22.8)	-48.9 (± 21.5)	-60.0 (± 23.4)	-64.1 (± 24.5)
PCFB at Day 176 (n= 48, 45, 42, 34)	-4.1 (± 23.6)	-49.9 (± 24.8)	-61.1 (± 21.2)	-64.3 (± 17.4)
PCFB at Day 190 (n= 44, 44, 42, 35)	-2.7 (± 17.8)	-45.4 (± 28.9)	-55.2 (± 22.2)	-60.9 (± 19.6)
PCFB at Day 204 (n= 47, 45, 41, 34)	-1.8 (± 25.0)	-36.9 (± 28.7)	-48.2 (± 24.3)	-52.2 (± 22.1)
PCFB at Day 218 (n= 48, 45, 42, 35)	-5.6 (± 17.8)	-29.3 (± 20.7)	-37.4 (± 22.8)	-41.8 (± 24.2)
PCFB at Day 232 (n= 47, 45, 41, 34)	-0.7 (± 18.6)	-19.5 (± 24.7)	-28.0 (± 21.2)	-29.6 (± 25.2)
PCFB at Day 246 (n= 46, 44, 37, 35)	-2.6 (± 21.0)	-13.6 (± 27.6)	-20.7 (± 18.4)	-22.3 (± 24.0)
PCFB at Day 260 (n= 46, 43, 40, 35)	-3.8 (± 21.3)	-11.1 (± 25.0)	-15.3 (± 19.5)	-16.0 (± 22.1)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Laboratory Abnormalities – Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST)

End point title	Number of Subjects With Laboratory Abnormalities – Alanine Transaminase (ALT) and Aspartate Aminotransferase (AST)

End point description:

Subjects were assessed based on pre-defined criteria in protocol for abnormality in ALT and AST values: Confirmed ALT (serum glutamic pyruvic transaminase [SGPT]); greater than (>) 3*Upper limit of normal range (ULN), >5*ULN and confirmed AST (serum glutamic-oxaloacetic transaminase [SGOT]); >3*ULN and >5*ULN. A confirmed value was based on a consecutive lab value within 7 days of the initial value. If that value was in the same or worse category the initial value was confirmed. If the consecutive value was in a better category then the initial value was confirmed using the consecutive value category. If there were multiple results on the same day, no matter from the same lab vendor or different lab vendors, then the worst value was used in the analysis. Abnormality in laboratory parameter was based on investigator's discretion. Safety population included all randomised subjects who received at least 1 dose of study drug.

End point type	Other pre-specified

End point timeframe:

Up to Day 260

End point values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg	Cohort C: ISIS 416858, 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	53	54	50
Units: subjects				
ALT: >3*ULN, Confirmed	0	0	1	0
ALT: >5*ULN, Confirmed	0	0	1	0
AST: >3*ULN, Confirmed	0	0	1	0
AST: >5*ULN, Confirmed	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percent Change From Baseline in Factor XI (FXI) Antigen Levels

End point title	Percent Change From Baseline in Factor XI (FXI) Antigen Levels

End point description:

PP population: All subjects, randomised without missing more than 2 doses during first 12 weeks or more than 5 doses over 26-week TP and not have any major protocol violations that would have affected interpretation/integrity of study results. "n" is the number of subjects with data available for analyses at the given time point.

End point type	Other pre-specified

End point timeframe:

Baseline (Day 1) up to Day 260

End point values	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg	Cohort C: ISIS 416858, 300 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	49	45	43	35
Units: percent change				
arithmetic mean (standard deviation)				
Baseline (n= 49, 45, 43, 35)	1.09 (± 0.23)	1.13 (± 0.26)	1.20 (± 0.31)	1.17 (± 0.26)
PCFB at Day 260 (n= 46, 43, 40, 35)	11.3 (± 27.0)	-3.4 (± 17.5)	-10.1 (± 21.8)	-13.9 (± 22.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Day 260	
Adverse event reporting additional description:	
Safety population included all randomised subjects who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort A: ISIS 416858, 200 mg
Reporting group description:	
Subjects received ISIS 416858, 200 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort B: ISIS 416858, 250 mg
Reporting group description:	
Subjects received ISIS 416858, 250 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	
Reporting group title	Cohort C: ISIS 416858, 300 mg
Reporting group description:	
Subjects received ISIS 416858, 300 mg, subcutaneously, within 2 hours post-dialysis, once weekly from Week 1 (Day 1) through Week 26 of treatment period.	

Serious adverse events	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 53 (18.87%)	6 / 53 (11.32%)	20 / 54 (37.04%)
number of deaths (all causes)	3	0	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Extremity necrosis			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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
Sudden death			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast disorders			

Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site complication			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial bypass thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula maturation failure			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Graft thrombosis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural hypotension			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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			
Angina unstable			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Bradycardia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Cardiovascular insufficiency			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral atrophy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Dizziness			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic intracranial hypertension			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	4 / 54 (7.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchitis viral			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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
Urinary tract infection			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	0 / 54 (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
Gangrene			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			

subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	1 / 54 (1.85%)
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			
Dehydration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	0 / 54 (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

Serious adverse events	Cohort C: ISIS 416858, 300 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 50 (26.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dry gangrene			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostatitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Arteriovenous fistula thrombosis				
subjects affected / exposed	3 / 50 (6.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site complication				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arterial bypass thrombosis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula maturation failure				

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site haematoma				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arteriovenous fistula site haemorrhage				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Graft thrombosis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Procedural hypotension				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina unstable				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiovascular insufficiency				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carpal tunnel syndrome				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral atrophy				

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Idiopathic intracranial hypertension			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis viral			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Placebo	Cohort A: ISIS 416858, 200 mg	Cohort B: ISIS 416858, 250 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 53 (47.17%)	27 / 53 (50.94%)	35 / 54 (64.81%)
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	7
Haemoglobin decreased			
subjects affected / exposed	0 / 53 (0.00%)	3 / 53 (5.66%)	2 / 54 (3.70%)
occurrences (all)	0	4	2
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	3 / 53 (5.66%)	3 / 53 (5.66%)	4 / 54 (7.41%)
occurrences (all)	3	3	7
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 53 (0.00%)	2 / 53 (3.77%)	3 / 54 (5.56%)
occurrences (all)	0	2	7
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	3 / 54 (5.56%)
occurrences (all)	1	2	5
Procedural hypotension			
subjects affected / exposed	0 / 53 (0.00%)	0 / 53 (0.00%)	5 / 54 (9.26%)
occurrences (all)	0	0	5
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 53 (5.66%)	2 / 53 (3.77%)	1 / 54 (1.85%)
occurrences (all)	3	2	1
Hypotension			
subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	3 / 54 (5.56%)
occurrences (all)	1	5	3
Nervous system disorders			
Headache			

subjects affected / exposed	4 / 53 (7.55%)	3 / 53 (5.66%)	2 / 54 (3.70%)
occurrences (all)	5	3	2
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	2 / 53 (3.77%)	12 / 53 (22.64%)	8 / 54 (14.81%)
occurrences (all)	2	24	47
Injection site erythema			
subjects affected / exposed	1 / 53 (1.89%)	6 / 53 (11.32%)	6 / 54 (11.11%)
occurrences (all)	1	23	12
Injection site pruritus			
subjects affected / exposed	2 / 53 (3.77%)	5 / 53 (9.43%)	6 / 54 (11.11%)
occurrences (all)	4	11	13
Injection site pain			
subjects affected / exposed	2 / 53 (3.77%)	4 / 53 (7.55%)	7 / 54 (12.96%)
occurrences (all)	2	4	10
Injection site bruising			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	3 / 54 (5.56%)
occurrences (all)	1	7	7
Pyrexia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Injection site discolouration			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	2 / 54 (3.70%)
occurrences (all)	0	9	3
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 53 (0.00%)	4 / 53 (7.55%)	6 / 54 (11.11%)
occurrences (all)	0	7	7
Anaemia			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	5 / 54 (9.26%)
occurrences (all)	1	1	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 53 (3.77%)	2 / 53 (3.77%)	4 / 54 (7.41%)
occurrences (all)	6	2	4
Vomiting			

subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	2 / 54 (3.70%)
occurrences (all)	6	6	2
Diarrhoea			
subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	0 / 54 (0.00%)
occurrences (all)	2	5	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 53 (5.66%)	2 / 53 (3.77%)	3 / 54 (5.56%)
occurrences (all)	3	2	4
Epistaxis			
subjects affected / exposed	1 / 53 (1.89%)	1 / 53 (1.89%)	2 / 54 (3.70%)
occurrences (all)	1	2	3
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 53 (5.66%)	2 / 53 (3.77%)	0 / 54 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 53 (1.89%)	4 / 53 (7.55%)	2 / 54 (3.70%)
occurrences (all)	1	5	2
Back pain			
subjects affected / exposed	0 / 53 (0.00%)	1 / 53 (1.89%)	4 / 54 (7.41%)
occurrences (all)	0	1	5
Pain in extremity			
subjects affected / exposed	1 / 53 (1.89%)	2 / 53 (3.77%)	3 / 54 (5.56%)
occurrences (all)	4	2	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 53 (7.55%)	2 / 53 (3.77%)	1 / 54 (1.85%)
occurrences (all)	5	3	2
Respiratory tract infection			
subjects affected / exposed	6 / 53 (11.32%)	1 / 53 (1.89%)	2 / 54 (3.70%)
occurrences (all)	7	1	4
Urinary tract infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 53 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1

Non-serious adverse events	Cohort C: ISIS 416858, 300 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 50 (78.00%)		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	7		
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Arteriovenous fistula site haematoma			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Procedural hypotension			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	8		
General disorders and administration site conditions			

Injection site haematoma subjects affected / exposed occurrences (all)	9 / 50 (18.00%) 26		
Injection site erythema subjects affected / exposed occurrences (all)	14 / 50 (28.00%) 39		
Injection site pruritus subjects affected / exposed occurrences (all)	11 / 50 (22.00%) 16		
Injection site pain subjects affected / exposed occurrences (all)	6 / 50 (12.00%) 9		
Injection site bruising subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 10		
Pyrexia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 5		
Injection site discolouration subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	7 / 50 (14.00%) 9		
Anaemia subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 50 (2.00%) 1		
Vomiting subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Diarrhoea			

subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	7		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	4		
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2018	The following changes were made in Amendment 1: 1. Clarified that subjects were encouraged to complete the entire treatment and post-treatment evaluation periods, even if study drug had been discontinued. 2. Added to exclusion criterion #3 to include FXI activity < 0.3 Units per millilitre (U/mL) at screening. 3. For subjects in the optional platelet function sub study, allowed aspirin or nonsteroidal anti-inflammatory drug (NSAID) use. 4. Extended the screening period for signing of the informed consent from 28 to 49 days. 5. Provided additional clarification on the expected completion of dialysis and study drug administration. 6. Clarified that subjects were also stratified based on their participation in either or both sub studies (PK and/or platelet sub study) as applicable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported