



## 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          | v2 (current)  |
| This version publication date  | 05 January 2023   |
| First version publication date | 26 July 2020  |
| Version creation reason        | <ul style="list-style-type: none"><li>New data added to full data set</li><li>New data added to full data set</li></ul> |

#### 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, Carer, Subject |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | 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.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | 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.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | 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.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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 <sup>[2]</sup> | 45 <sup>[3]</sup>             | 43 <sup>[4]</sup>             |
| Completed   | 50                | 52                            | 46                            |
| Not completed                                       | 3                 | 1                             | 8                             |
| Unspecified   | -                 | -                             | 1                             |
| Adverse Event or SAE                                | 2                 | -                             | 6                             |
| Voluntary withdrawal                                | 1                 | 1                             | 1                             |

|   |                               |
|---|-------------------------------|
| <b>Number of subjects in period 1<sup>[1]</sup></b> | Cohort C: ISIS 416858, 300 mg |
|---|-------------------------------|

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

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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 |

| <b>Reporting group values</b>                         | Cohort C: ISIS<br>416858, 300 mg | Total |  |
|---|----------------------------------|-------|--|
| Number of subjects                                    | 50                               | 210   |  |
| Age categorical<br>Units: Subjects                    |                                  |       |  |
| In utero  |                                  | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) |                                  | 0     |  |
| Newborns (0-27 days)                                  |                                  | 0     |  |
| Infants and toddlers (28 days-23<br>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<br>Units: years                        |                                  |       |  |
| arithmetic mean                                       | 58                               |       |  |
| standard deviation                                    | ± 14                             | -     |  |
| Gender categorical<br>Units: Subjects                 |                                  |       |  |
| Female  | 20                               | 81    |  |
| Male  | 30                               | 129   |  |
| Ethnicity<br>Units: Subjects                          |                                  |       |  |
| Hispanic or Latino                                    | 5                                | 12    |  |
| Not Hispanic or Latino                                | 45                               | 198   |  |
| Race<br>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:<br>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:<br>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:<br>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:<br>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) <sup>[1]</sup> |
| End point description:<br>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 ( $\geq$ ) 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:<br>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

**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 did 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**

**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 Related to Platelet Count**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Laboratory Abnormalities Related to Platelet Count |
|-----------------|--|

End point description:

Subjects were assessed based on pre-defined criteria in the protocol for platelet count abnormality: 100 - less than (<)140, 75 - <100, 50 - <75, 25 - <50 and < 25 thousands per cubic millimetre (K/mm<sup>3</sup>) 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              |                 |                               |                               |                               |
| 100 - <140 K/mm <sup>3</sup> | 9               | 21                            | 20                            | 21                            |
| 75 - <100 K/mm <sup>3</sup>  | 2               | 2                             | 6                             | 7                             |
| 50 - <75 K/mm <sup>3</sup>   | 0               | 0                             | 4                             | 0                             |
| 25 - <50 K/mm <sup>3</sup>   | 0               | 0                             | 1                             | 1                             |
| < 25 K/mm <sup>3</sup>       | 0               | 0                             | 1                             | 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: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

|  |   |
|--|---|
| End point title  | Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) |
| End point description:   |   |
| 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             | 33              | 37                            | 46                            | 44                            |

### Statistical analyses

No statistical analyses for this end point

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

|   |   |
|---|---|
| End point title   | Percent Change From Baseline (BL) 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 did 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

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

### Statistical analyses

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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<br>subjects affected / exposed   | 1 / 53 (1.89%) | 0 / 53 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to<br>treatment / all              | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Prostatitis<br>subjects affected / exposed                      | 0 / 53 (0.00%) | 0 / 53 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Respiratory, thoracic and mediastinal<br>disorders              |                |                |                |
| Respiratory failure<br>subjects affected / exposed              | 1 / 53 (1.89%) | 0 / 53 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to<br>treatment / all              | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 1          | 0 / 0          | 0 / 0          |
| Chronic obstructive pulmonary<br>disease                        |                |                |                |
| subjects affected / exposed                                     | 0 / 53 (0.00%) | 0 / 53 (0.00%) | 0 / 54 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Haemoptysis<br>subjects affected / exposed                      | 0 / 53 (0.00%) | 1 / 53 (1.89%) | 0 / 54 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Psychiatric disorders   |                |                |                |
| Confusional state<br>subjects affected / exposed                | 0 / 53 (0.00%) | 0 / 53 (0.00%) | 1 / 54 (1.85%) |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural<br>complications               |                |                |                |
| Arteriovenous fistula thrombosis<br>subjects affected / exposed | 1 / 53 (1.89%) | 0 / 53 (0.00%) | 2 / 54 (3.70%) |
| occurrences causally related to<br>treatment / all              | 0 / 1          | 0 / 0          | 0 / 3          |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0          | 0 / 0          |
| Arteriovenous fistula site<br>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<br>Pneumonia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 53 (1.89%)<br>0 / 1<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 4 / 54 (7.41%)<br>0 / 4<br>0 / 1 |
| Bronchitis viral<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                         | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 53 (1.89%)<br>0 / 1<br>0 / 0 | 0 / 54 (0.00%)<br>0 / 0<br>0 / 0 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                  | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 54 (0.00%)<br>0 / 0<br>0 / 0 |
| Appendicitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                             | 1 / 53 (1.89%)<br>0 / 1<br>0 / 1 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 54 (0.00%)<br>0 / 0<br>0 / 0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                               | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 54 (1.85%)<br>0 / 1<br>0 / 0 |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                               | 1 / 53 (1.89%)<br>0 / 1<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 54 (0.00%)<br>0 / 0<br>0 / 0 |
| Gangrene<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 54 (1.85%)<br>0 / 1<br>0 / 0 |
| Osteomyelitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                            | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 0 / 53 (0.00%)<br>0 / 0<br>0 / 0 | 1 / 54 (1.85%)<br>0 / 1<br>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          |

|   |                                  |  |  |
|---|----------------------------------|--|--|
| <b>Serious adverse events</b>                                       | Cohort C: ISIS<br>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 %

| <b>Non-serious adverse events</b>                     | Placebo          | Cohort A: ISIS<br>416858, 200 mg | Cohort B: ISIS<br>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<br>occurrences (all)                                  | 4 / 53 (7.55%)<br>5 | 3 / 53 (5.66%)<br>3    | 2 / 54 (3.70%)<br>2   |
| General disorders and administration<br>site conditions                           |                     |                        |                       |
| Injection site haematoma<br>subjects affected / exposed<br>occurrences (all)      | 2 / 53 (3.77%)<br>2 | 12 / 53 (22.64%)<br>24 | 8 / 54 (14.81%)<br>47 |
| Injection site erythema<br>subjects affected / exposed<br>occurrences (all)       | 1 / 53 (1.89%)<br>1 | 6 / 53 (11.32%)<br>23  | 6 / 54 (11.11%)<br>12 |
| Injection site pruritus<br>subjects affected / exposed<br>occurrences (all)       | 2 / 53 (3.77%)<br>4 | 5 / 53 (9.43%)<br>11   | 6 / 54 (11.11%)<br>13 |
| Injection site pain<br>subjects affected / exposed<br>occurrences (all)           | 2 / 53 (3.77%)<br>2 | 4 / 53 (7.55%)<br>4    | 7 / 54 (12.96%)<br>10 |
| Injection site bruising<br>subjects affected / exposed<br>occurrences (all)       | 1 / 53 (1.89%)<br>1 | 2 / 53 (3.77%)<br>7    | 3 / 54 (5.56%)<br>7   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 53 (1.89%)<br>1 | 0 / 53 (0.00%)<br>0    | 1 / 54 (1.85%)<br>1   |
| Injection site discolouration<br>subjects affected / exposed<br>occurrences (all) | 0 / 53 (0.00%)<br>0 | 1 / 53 (1.89%)<br>9    | 2 / 54 (3.70%)<br>3   |
| Blood and lymphatic system disorders  |                     |                        |                       |
| Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 53 (0.00%)<br>0 | 4 / 53 (7.55%)<br>7    | 6 / 54 (11.11%)<br>7  |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 53 (1.89%)<br>1 | 1 / 53 (1.89%)<br>1    | 5 / 54 (9.26%)<br>5   |
| Gastrointestinal disorders  |                     |                        |                       |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 53 (3.77%)<br>6 | 2 / 53 (3.77%)<br>2    | 4 / 54 (7.41%)<br>4   |
| Vomiting  |                     |                        |                       |



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

|  |                                  |  |  |
|--|----------------------------------|--|--|
| <b>Non-serious adverse events</b>                        | Cohort C: ISIS<br>416858, 300 mg |  |  |
| Total subjects affected by non-serious<br>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<br>complications        |                                  |  |  |
| Arteriovenous fistula site<br>complication               |                                  |  |  |
| subjects affected / exposed                              | 6 / 50 (12.00%)                  |  |  |
| occurrences (all)  | 7                                |  |  |
| Arteriovenous fistula site<br>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<br>site conditions  |                                  |  |  |

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported