



## Clinical trial results:

### Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Have Acute Major Bleeding (ANNEXA-4).

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2015-001785-26    |
| Trial protocol           | NL GB BE DE FR    |
| Global end of trial date | 24 September 2020 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 13 November 2021 |
| First version publication date | 13 November 2021 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 14-505 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02329327 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Alexion Pharmaceuticals, Inc.  |
| Sponsor organisation address | 121 Seaport Boulevard, Boston, MA, United States, 02210  |
| Public contact               | European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 147100606, clinicaltrials.eu@alexion.com |
| Scientific contact           | European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 147100606, clinicaltrials.eu@alexion.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                       | 24 September 2020 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 September 2020 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the hemostatic efficacy of andexanet alfa (andexanet) in participants receiving a factor Xa (FXa) inhibitor (apixaban, rivaroxaban, edoxaban, enoxaparin) who were experiencing an acute major bleed. The safety of andexanet was also studied.

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 11 April 2015 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | Yes           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Belgium: 19        |
| Country: Number of subjects enrolled | United States: 205 |
| Country: Number of subjects enrolled | Japan: 19          |
| Country: Number of subjects enrolled | Canada: 7          |
| Country: Number of subjects enrolled | Germany: 179       |
| Country: Number of subjects enrolled | Spain: 5           |
| Country: Number of subjects enrolled | France: 8          |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | Netherlands: 12    |
| Worldwide total number of subjects   | 479                |
| EEA total number of subjects         | 223                |

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)                     | 47  |
| From 65 to 84 years                      | 306 |
| 85 years and over                        | 126 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Attempts were made to enroll participants on direct FXa inhibitors as well as those on indirect FXa inhibitors, and to limit the percentage of enrolled participants receiving indirect FXa inhibitors.

### Period 1

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

### Arms

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

Arm description:

Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Andexanet                                     |
| Investigational medicinal product code |   |
| Other name                             | ALXN2070, Andexanet Alfa, PRT064445, Ondexxya |
| Pharmaceutical forms                   | Solution for infusion                         |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

There were 2 possible dosing regimens: Low dose = 400 milligram (mg) bolus plus 4 mg/minute continuous infusion for 120 minutes; High dose = 800 mg bolus plus 8 mg/minute continuous infusion for 120 minutes.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Andexanet - Additional Participants |
|------------------|-------------------------------------|

Arm description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

|  |   |
|--|---|
| Arm type                               | Experimental                                  |
| Investigational medicinal product name | Andexanet                                     |
| Investigational medicinal product code |   |
| Other name                             | ALXN2070, Andexanet Alfa, PRT064445, Ondexxya |
| Pharmaceutical forms                   | Solution for infusion                         |
| Routes of administration               | Intravenous use                               |

Dosage and administration details:

There were 2 possible dosing regimens: Low dose = 400 mg bolus plus 4 mg/minute continuous infusion for 120 minutes; High dose = 800 mg bolus plus 8 mg/minute continuous infusion for 120 minutes.

| Number of subjects in period 1         | Andexanet          | Andexanet -<br>Additional<br>Participants |
|--|--------------------|---|
|  |                    |   |
| Started                                | 477                | 2   |
| Received At Least 1 Dose of Study Drug | 477                | 2   |
| Efficacy Population                    | 347 <sup>[1]</sup> | 2   |
| Death                                  | 3 <sup>[2]</sup>   | 0 <sup>[3]</sup>                          |
| Completed                              | 392                | 2   |
| Not completed                          | 85                 | 0   |
| Adverse event, serious fatal           | 78                 | -   |
| Consent withdrawn by subject           | 3                  | -   |
| Lost to follow-up                      | 4                  | -   |

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Notes:

[1] - 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: All participants who received at least 1 dose of study drug and who met protocol-specified criteria for bleeding and anti-fXa levels.

[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: These deaths occurred during the follow-up period.

[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: These deaths occurred during the follow-up period.

## Baseline characteristics

### Reporting groups

|                       |           |
|-----------------------|-----------|
| Reporting group title | Andexanet |
|-----------------------|-----------|

Reporting group description:

Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Andexanet - Additional Participants |
|-----------------------|-------------------------------------|

Reporting group description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

| Reporting group values  | Andexanet | Andexanet - Additional Participants | Total |
|---|-----------|-------------------------------------|-------|
| Number of subjects  | 477       | 2                                   | 479   |
| Age categorical   |           |                                     |       |
| Units: Subjects   |           |                                     |       |
| In utero  | 0         | 0                                   | 0     |
| Preterm newborn infants (gestational age < 37 wks)  | 0         | 0                                   | 0     |
| Newborns (0-27 days)  | 0         | 0                                   | 0     |
| Infants and toddlers (28 days-23 months)  | 0         | 0                                   | 0     |
| Children (2-11 years)   | 0         | 0                                   | 0     |
| Adolescents (12-17 years)   | 0         | 0                                   | 0     |
| Adults (18-64 years)  | 46        | 1                                   | 47    |
| From 65-84 years  | 305       | 1                                   | 306   |
| 85 years and over   | 126       | 0                                   | 126   |
| Age Continuous  |           |                                     |       |
| Units: years  |           |                                     |       |
| arithmetic mean   | 77.9      | 71.0                                | -     |
| standard deviation  | ± 10.66   | ± 11.31                             | -     |
| Sex: Female, Male   |           |                                     |       |
| Units: participants   |           |                                     |       |
| Female  | 218       | 1                                   | 219   |
| Male  | 259       | 1                                   | 260   |
| Ethnicity (NIH/OMB)   |           |                                     |       |
| Units: Subjects   |           |                                     |       |
| Hispanic or Latino  | 16        | 0                                   | 16    |
| Not Hispanic or Latino  | 449       | 2                                   | 451   |
| Unknown or Not Reported   | 12        | 0                                   | 12    |
| Race/Ethnicity, Customized  |           |                                     |       |
| Asian participants and American Indian or Alaska Native participants are reported as Other. |           |                                     |       |
| Units: Subjects   |           |                                     |       |
| White   | 414       | 0                                   | 414   |
| Black or African American   | 29        | 0                                   | 29    |
| Other   | 25        | 2                                   | 27    |
| Missing   | 9         | 0                                   | 9     |

|  |     |   |     |
|--|-----|---|-----|
| Region of Enrollment   |     |   |     |
| Units: Subjects  |     |   |     |
| North America  | 212 | 0 | 212 |
| Europe   | 248 | 0 | 248 |
| Japan  | 17  | 2 | 19  |
| FXa Inhibitor  |     |   |     |
| Units: Subjects  |     |   |     |
| Apixaban   | 245 | 0 | 245 |
| Rivaroxaban  | 174 | 2 | 176 |
| Edoxaban   | 36  | 0 | 36  |
| Enoxaparin   | 22  | 0 | 22  |
| Bleed Type   |     |   |     |
| Endpoint Adjudication Committee (EAC) determined if each participant met the bleeding entry criteria for inclusion in the Efficacy Population. |     |   |     |
| Units: Subjects  |     |   |     |
| Gastrointestinal   | 109 | 0 | 109 |
| Intracranial Hemorrhage  | 329 | 2 | 331 |
| Other  | 39  | 0 | 39  |

## End points

### End points reporting groups

|  |                                     |
|--|-------------------------------------|
| Reporting group title  | Andexanet                           |
| Reporting group description:<br>Participants received andexanet as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.  |                                     |
| Reporting group title  | Andexanet - Additional Participants |
| Reporting group description:<br>Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately. |                                     |
| Subject analysis set title   | FXa Inhibitor: Apixaban             |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitor apixaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.  |                                     |
| Subject analysis set title   | FXa Inhibitor: Rivaroxaban          |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitor rivaroxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.   |                                     |
| Subject analysis set title   | FXa Inhibitor: Edoxaban             |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitor edoxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.  |                                     |
| Subject analysis set title   | FXa Inhibitor: Enoxaparin           |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitor enoxaparin received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.  |                                     |
| Subject analysis set title   | Bleed Type: Gastrointestinal        |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants with gastrointestinal bleeding who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.   |                                     |
| Subject analysis set title   | Bleed Type: Intracranial Hemorrhage |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants with an intracranial hemorrhage who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.  |                                     |
| Subject analysis set title   | Bleed Type: Other                   |
| Subject analysis set type  | Sub-group analysis                  |
| Subject analysis set description:<br>Participants with other types of bleeding who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.   |                                     |
| Subject analysis set title   | Andexanet: Low Dose                 |



|  |   |
|--|---|
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitors received andexanet as an IV 400-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 480 mg (4 mg/minute) administered over ~120 minutes.   |   |
| Subject analysis set title   | Andexanet: High Dose  |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitors received andexanet as an IV 800-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 960 mg (8 mg/minute) administered over ~120 minutes.   |   |
| Subject analysis set title   | Overall   |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Participants who had recently received FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Does not include the 2 additional participants whose data were obtained and evaluated after the data cutoff date of 30-June-2020.   |   |
| Subject analysis set title   | FXa Inhibitor: Rivaroxaban - Additional Participants                              |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Two additional participants who had recently received FXa inhibitor rivaroxaban received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.  |   |
| Subject analysis set title   | Bleed Type: Intracranial Hemorrhage - Additional Participants                     |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>Two additional participants with an intracranial hemorrhage who had recently received an FXa inhibitor received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.   |   |
| Subject analysis set title   | Andexanet: Low Dose - Additional Participant                                      |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>One additional participant who had recently received FXa inhibitors received andexanet as an IV 400-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 480 mg (4 mg/minute) administered over ~120 minutes. Data from this participant were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.   |   |
| Subject analysis set title   | Andexanet: High Dose - Additional Participant                                     |
| Subject analysis set type  | Sub-group analysis  |
| Subject analysis set description:<br>One additional participant who had recently received FXa inhibitors received andexanet as an IV 800-mg bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion of 960 mg (8 mg/minute) administered over ~120 minutes. Data from this participant were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.   |   |
| <b>Primary: Percent Change From Baseline In Anti-fXa Activity By FXa Inhibitor</b>   |   |
| End point title  | Percent Change From Baseline In Anti-fXa Activity By FXa Inhibitor <sup>[1]</sup> |
| End point description:<br>Anti-fXa activity was measured to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Baseline was defined as the last value obtained prior to the start of the andexanet bolus. The change from baseline was calculated as the reduction in anti-fXa activity from baseline to the on-treatment nadir (that is, the minimum value between end of bolus and end of infusion). Percent reduction was calculated as the ratio between the maximum change from baseline and the baseline value, multiplied by 100. |   |
| End point type   | Primary   |

End point timeframe:

Baseline, 12 Hours (post infusion)

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: Quantitative statistical analysis (for example, a p-value) was not performed for this end point. Descriptive statistics are included (median and CI).

| End point values                 | FXa Inhibitor:<br>Apixaban | FXa Inhibitor:<br>Rivaroxaban | FXa Inhibitor:<br>Edoxaban | FXa Inhibitor:<br>Enoxaparin |
|----------------------------------|----------------------------|-------------------------------|----------------------------|------------------------------|
| Subject group type               | Subject analysis set       | Subject analysis set          | Subject analysis set       | Subject analysis set         |
| Number of subjects analysed      | 172                        | 130                           | 28                         | 17                           |
| Units: Percent Change            |                            |                               |                            |                              |
| median (confidence interval 95%) | -93.3 (-94.2 to -92.5)     | -94.1 (-95.1 to -93.0)        | -71.3 (-82.3 to -65.2)     | -75.41 (-79.17 to -66.67)    |

| End point values                 | FXa Inhibitor:<br>Rivaroxaban -<br>Additional<br>Participants |  |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Subject analysis set  |  |  |  |
| Number of subjects analysed      | 2   |  |  |  |
| Units: Percent Change            |   |  |  |  |
| median (confidence interval 95%) | -96.3 (-98.3 to -94.3)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Participants Achieving Hemostatic Efficacy

|                 |   |
|-----------------|---|
| End point title | Participants Achieving Hemostatic Efficacy <sup>[2]</sup> |
|-----------------|---|

End point description:

Hemostatic efficacy was achieved when the body had time to produce thrombin and a subsequent clot and was rated by the EAC as: excellent; good; poor/none; not evaluable due to non-administrative reasons; not evaluable due to administrative reasons. These ratings were based on pre-specified criteria that were included in the EAC Charter. The EAC was blinded to anti-fXa activity levels. Participant results were classified as either success or failure based on the hemostatic efficacy rating (success = excellent/good, failure = poor/none). Participants rated by the EAC as non-evaluable due to administrative reasons were excluded from the analysis of hemostatic efficacy.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

12 Hours (post infusion)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Quantitative statistical analysis (for example, a p-value) was not performed for this end point. Descriptive statistics are included (median and CI).

| End point values            | FXa Inhibitor:<br>Apixaban | FXa Inhibitor:<br>Rivaroxaban | FXa Inhibitor:<br>Edoxaban | FXa Inhibitor:<br>Enoxaparin |
|-----------------------------|----------------------------|-------------------------------|----------------------------|------------------------------|
| Subject group type          | Subject analysis set       | Subject analysis set          | Subject analysis set       | Subject analysis set         |
| Number of subjects analysed | 169                        | 127                           | 28                         | 16                           |
| Units: Percent Change       |                            |                               |                            |                              |
| Excellent/Good              | 134                        | 102                           | 22                         | 14                           |
| Poor/None                   | 35                         | 25                            | 6                          | 2                            |

| End point values            | Bleed Type:<br>Gastrointestinal | Bleed Type:<br>Intracranial<br>Hemorrhage | Bleed Type:<br>Other | Andexanet:<br>Low Dose |
|-----------------------------|---------------------------------|---|----------------------|------------------------|
| Subject group type          | Subject analysis set            | Subject analysis set                      | Subject analysis set | Subject analysis set   |
| Number of subjects analysed | 74                              | 244                                       | 22                   | 269                    |
| Units: Percent Change       |                                 |   |                      |                        |
| Excellent/Good              | 61                              | 193                                       | 18                   | 218                    |
| Poor/None                   | 13                              | 51  | 4                    | 51                     |

| End point values            | Andexanet:<br>High Dose | Overall              | FXa Inhibitor:<br>Rivaroxaban -<br>Additional<br>Participants | Bleed Type:<br>Intracranial<br>Hemorrhage -<br>Additional<br>Participants |
|-----------------------------|-------------------------|----------------------|---|---|
| Subject group type          | Subject analysis set    | Subject analysis set | Subject analysis set  | Subject analysis set  |
| Number of subjects analysed | 71                      | 240                  | 2   | 2   |
| Units: Percent Change       |                         |                      |   |   |
| Excellent/Good              | 54                      | 272                  | 2   | 2   |
| Poor/None                   | 17                      | 68                   | 0   | 0   |

| End point values            | Andexanet:<br>Low Dose -<br>Additional<br>Participant | Andexanet:<br>High Dose -<br>Additional<br>Participant |  |  |
|-----------------------------|---|--|--|--|
| Subject group type          | Subject analysis set                                  | Subject analysis set                                   |  |  |
| Number of subjects analysed | 1   | 1  |  |  |
| Units: Percent Change       |   |  |  |  |
| Excellent/Good              | 1   | 1  |  |  |
| Poor/None                   | 0   | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent Change From Baseline In Anti-fXa Activity By Hemostatic Efficacy

|  |  |
|--|--|
| End point title  | Percent Change From Baseline In Anti-fXa Activity By Hemostatic Efficacy |
| End point description:   |  |
| This outcome measure assessed the relationship between hemostatic efficacy and anti-fXa activity in participants receiving an FXa inhibitor who had acute major bleeding. Anti-fXa activity was measured to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Baseline was defined as the last value obtained prior to the start of the andexanet bolus. Hemostatic efficacy was achieved when the body had time to produce thrombin and a subsequent clot and was rated by the EAC as: excellent; good; poor/none; not evaluable due to non-administrative reasons; not evaluable due to administrative reasons. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, 12 Hours (post infusion)   |  |

| End point values                 | FXa Inhibitor: Apixaban | FXa Inhibitor: Rivaroxaban | FXa Inhibitor: Edoxaban | FXa Inhibitor: Enoxaparin |
|----------------------------------|-------------------------|----------------------------|-------------------------|---------------------------|
| Subject group type               | Subject analysis set    | Subject analysis set       | Subject analysis set    | Subject analysis set      |
| Number of subjects analysed      | 134                     | 102                        | 22                      | 14                        |
| Units: Percent Change            |                         |                            |                         |                           |
| median (confidence interval 95%) |                         |                            |                         |                           |
| Excellent/Good                   | -93.4 (-94.3 to -92.6)  | -94.6 (-95.2 to -93.5)     | -75.8 (-84.4 to -65.2)  | -75.20 (-77.08 to -65.91) |
| Poor/None                        | -93.3 (-95.3 to -90.6)  | -92.4 (-96.5 to -85.0)     | -65.2 (-85.3 to 3.0)    | -78.44 (-82.46 to -74.42) |

| End point values                 | FXa Inhibitor: Rivaroxaban - Additional Participants |  |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Subject analysis set                                 |  |  |  |
| Number of subjects analysed      | 2 <sup>[3]</sup>                                     |  |  |  |
| Units: Percent Change            |  |  |  |  |
| median (confidence interval 95%) |  |  |  |  |
| Excellent/Good                   | -96.3 (-98.3 to -94.3)                               |  |  |  |
| Poor/None                        | 999 (999 to 999)                                     |  |  |  |

Notes:

[3] - 999 = Not available due to 0 participants having a hemostatic efficacy of Poor/None.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Day 1 through Day 37.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Andexanet - Additional Participants |
|-----------------------|-------------------------------------|

Reporting group description:

Two additional participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. Data from these 2 participants were obtained and evaluated after the data cutoff date of 30-June-2020 and, as such, are presented separately.

|                       |           |
|-----------------------|-----------|
| Reporting group title | Andexanet |
|-----------------------|-----------|

Reporting group description:

Participants received andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes.

| Serious adverse events  | Andexanet - Additional Participants | Andexanet          |  |
|---|-------------------------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                                     |                    |  |
| subjects affected / exposed   | 0 / 2 (0.00%)                       | 200 / 477 (41.93%) |  |
| number of deaths (all causes)                                       | 0                                   | 81                 |  |
| number of deaths resulting from adverse events                      |                                     |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |                    |  |
| Anaplastic Astrocytoma  |                                     |                    |  |
| subjects affected / exposed   | 0 / 2 (0.00%)                       | 1 / 477 (0.21%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0              |  |
| Brain Neoplasm  |                                     |                    |  |
| subjects affected / exposed   | 0 / 2 (0.00%)                       | 1 / 477 (0.21%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0              |  |
| Gastrointestinal Stromal Tumour                                     |                                     |                    |  |
| subjects affected / exposed   | 0 / 2 (0.00%)                       | 1 / 477 (0.21%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0              |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| Bladder Cancer                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pancreatic Carcinoma                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Prostate Cancer Metastatic                      |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Lung Cancer Metastatic                          |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Vascular disorders                              |               |                 |  |
| Hypotension                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 4 / 477 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Deep Vein Thrombosis                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 5 / 477 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Arteriosclerosis                                |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypertension                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Aorto-Duodenal Fistula                          |               |                 |  |

|  |               |                 |  |
|--|---------------|-----------------|--|
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Haematoma  |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Haemorrhage  |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Iliac Artery Occlusion                               |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Shock Haemorrhagic                                   |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Surgical and medical procedures                      |               |                 |  |
| Tracheostomy   |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| Ventricular Drainage                                 |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |
| General disorders and administration site conditions |               |                 |  |
| Multi-Organ Failure                                  |               |                 |  |
| subjects affected / exposed                          | 0 / 2 (0.00%) | 5 / 477 (1.05%) |  |
| occurrences causally related to treatment / all      | 0 / 0         | 0 / 5           |  |
| deaths causally related to treatment / all           | 0 / 0         | 0 / 0           |  |

|   |               |                  |  |
|---|---------------|------------------|--|
| Death   |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1            |  |
| General Physical Health Deterioration           |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Sudden Cardiac Death                            |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1            |  |
| Gait Disturbance                                |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Sudden Death                                    |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 1            |  |
| Swelling  |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Social circumstances                            |               |                  |  |
| Social Stay Hospitalisation                     |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |               |                  |  |
| Respiratory Failure                             |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 12 / 477 (2.52%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |



|   |               |                 |  |
|---|---------------|-----------------|--|
| Pneumonia Aspiration                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 8 / 477 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pulmonary Embolism                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 8 / 477 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 4 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Acute Respiratory Failure                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypoxia   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Acute Pulmonary Oedema                          |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Respiratory Distress                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pulmonary Oedema                                |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Bronchial Secretion Retention                   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Pleural Effusion                                |               |                 |  |

|  |               |                 |  |
|--|---------------|-----------------|--|
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Chronic Obstructive Pulmonary Disease              |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Respiratory Arrest                                 |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Respiratory Acidosis                               |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Psychiatric disorders                              |               |                 |  |
| Mental Disorder Due To A General Medical Condition |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Mental Status Changes                              |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Investigations                                     |               |                 |  |
| Electrocardiogram QT Prolonged                     |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |
| Electroencephalogram Abnormal                      |               |                 |  |
| subjects affected / exposed                        | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all    | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all         | 0 / 0         | 0 / 0           |  |

|  |               |                 |  |
|--|---------------|-----------------|--|
| CSF Red Blood Cell Count Positive<br>subjects affected / exposed | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Troponin I Increased<br>subjects affected / exposed              | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 1 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Transaminases Increased<br>subjects affected / exposed           | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Liver Function Test Abnormal<br>subjects affected / exposed      | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications                |               |                 |  |
| Subdural Haematoma<br>subjects affected / exposed                | 0 / 2 (0.00%) | 8 / 477 (1.68%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 8           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Brain Herniation<br>subjects affected / exposed                  | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Lumbar Vertebral Fracture<br>subjects affected / exposed         | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Infusion Related Reaction<br>subjects affected / exposed         | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 1 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |

|  |               |                 |  |
|--|---------------|-----------------|--|
| Cervical Vertebral Fracture<br>subjects affected / exposed | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Cardiac disorders  |               |                 |  |
| Acute Myocardial Infarction<br>subjects affected / exposed | 0 / 2 (0.00%) | 5 / 477 (1.05%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 2 / 5           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Cardiac Failure<br>subjects affected / exposed             | 0 / 2 (0.00%) | 6 / 477 (1.26%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 1 / 6           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Cardiogenic Shock<br>subjects affected / exposed           | 0 / 2 (0.00%) | 4 / 477 (0.84%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 0 / 4           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Myocardial Infarction<br>subjects affected / exposed       | 0 / 2 (0.00%) | 5 / 477 (1.05%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 4 / 5           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Atrial Fibrillation<br>subjects affected / exposed         | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 0 / 3           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Cardiac Failure Congestive<br>subjects affected / exposed  | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 0 / 3           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Right Ventricular Failure<br>subjects affected / exposed   | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to<br>treatment / all         | 0 / 0         | 0 / 3           |  |
| deaths causally related to<br>treatment / all              | 0 / 0         | 0 / 0           |  |
| Cardiac Arrest   |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Bradycardia                                     |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Atrial Thrombosis                               |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Myocardial Ischaemia                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Atrial Flutter                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Atrioventricular Block Complete                 |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Atrioventricular Block                          |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cardiac Ventricular Thrombosis                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Coronary Artery Disease                         |               |                 |  |

|   |               |                  |  |
|---|---------------|------------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Cardio-Respiratory Arrest                       |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Sinus Node Dysfunction                          |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Nervous system disorders                        |               |                  |  |
| Ischaemic Stroke                                |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 10 / 477 (2.10%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 6 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Cerebral Haemorrhage                            |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 5 / 477 (1.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Haemorrhage Intracranial                        |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 7 / 477 (1.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Cerebrovascular Accident                        |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 8 / 477 (1.68%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 4 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Seizure   |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 5 / 477 (1.05%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Intraventricular Haemorrhage                    |               |                  |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Neurological Decompensation                     |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 4 / 477 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebral Infarction                             |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 5 / 477 (1.05%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Depressed Level Of Consciousness                |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebral Ischaemia                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Brain Oedema                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Transient Ischaemic Attack                      |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Intracranial Venous Sinus Thrombosis            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Syncope   |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Altered State Of Consciousness                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Basal Ganglia Haemorrhage                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Basilar Artery Thrombosis                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Carotid Artery Aneurysm                         |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Brain Compression                               |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebral Haematoma                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebellar Ischaemia                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebellar Infarction                           |               |                 |  |



|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Encephalopathy                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Embolic Stroke                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Cerebral Ventricle Dilatation                   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Haemorrhagic Stroke                             |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Epilepsy  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Facial Paresis                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Headache  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hydrocephalus                                   |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Peroneal Nerve Palsy                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Status Epilepticus                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Subarachnoid Haemorrhage                        |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Slow Response To Stimuli                        |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Blood and lymphatic system disorders            |               |                 |  |
| Heparin-Induced Thrombocytopenia                |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Haemorrhagic Anaemia                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Anaemia   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Lymphadenopathy                                 |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Ear and labyrinth disorders                     |               |                 |  |
| Deafness  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Vertigo   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Eye disorders                                   |               |                 |  |
| Diplopia  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Gastrointestinal disorders                      |               |                 |  |
| Gastrointestinal Haemorrhage                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Abdominal Pain                                  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Upper Gastrointestinal Haemorrhage              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Melaena   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| Diarrhoea                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Acute Abdomen                                   |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Constipation                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Rectal Haemorrhage                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Faecaloma                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Large Intestinal Haemorrhage                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Vomiting  |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hepatobiliary disorders                         |               |                 |  |
| Ischaemic Hepatitis                             |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Renal and urinary disorders                     |               |                 |  |

|   |               |                  |  |
|---|---------------|------------------|--|
| Acute Kidney Injury                             |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Renal Failure                                   |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Urinary Retention                               |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |               |                  |  |
| Musculoskeletal Pain                            |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Infections and infestations                     |               |                  |  |
| Pneumonia                                       |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 20 / 477 (4.19%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 21           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Urinary Tract Infection                         |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 3 / 477 (0.63%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Sepsis  |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 7 / 477 (1.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |
| Septic Shock                                    |               |                  |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 4 / 477 (0.84%)  |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0            |  |

|  |               |                 |  |
|--|---------------|-----------------|--|
| Lower Respiratory Tract Infection<br>subjects affected / exposed | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 2           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| CNS Ventriculitis<br>subjects affected / exposed                 | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Cellulitis<br>subjects affected / exposed                        | 0 / 2 (0.00%) | 2 / 477 (0.42%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 2           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Cystitis<br>subjects affected / exposed                          | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Eye Infection<br>subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Implant Site Infection<br>subjects affected / exposed            | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Respiratory Tract Infection<br>subjects affected / exposed       | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Serratia Bacteraemia<br>subjects affected / exposed              | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to<br>treatment / all               | 0 / 0         | 0 / 1           |  |
| deaths causally related to<br>treatment / all                    | 0 / 0         | 0 / 0           |  |
| Paronychia   |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Streptococcal Sepsis                            |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Tracheostomy Infection                          |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Subdural Empyema                                |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Staphylococcal Sepsis                           |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Urosepsis                                       |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Metabolism and nutrition disorders              |               |                 |  |
| Malnutrition                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hypokalaemia                                    |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Hyponatraemia                                   |               |                 |  |

|   |               |                 |  |
|---|---------------|-----------------|--|
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |
| Metabolic Syndrome                              |               |                 |  |
| subjects affected / exposed                     | 0 / 2 (0.00%) | 1 / 477 (0.21%) |  |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Andexanet -<br>Additional<br>Participants | Andexanet         |  |
|---|---|-------------------|--|
| Total subjects affected by non-serious adverse events |   |                   |  |
| subjects affected / exposed                           | 0 / 2 (0.00%)                             | 48 / 477 (10.06%) |  |
| Infections and infestations                           |   |                   |  |
| Urinary Tract Infection                               |   |                   |  |
| subjects affected / exposed                           | 0 / 2 (0.00%)                             | 48 / 477 (10.06%) |  |
| occurrences (all)                                     | 0   | 48                |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 30 January 2015 | <ul style="list-style-type: none"><li>• Modified the primary efficacy objective and primary efficacy end point to include changes in anti-fXa activity. The 2 primary efficacy end points were to be tested sequentially, with the proportion achieving hemostatic efficacy tested only if the change in anti-fXa activity was first demonstrated.</li><li>• Modified the secondary efficacy objective and secondary efficacy end point to assess the relationship between the 2 primary efficacy end points: to evaluate the relationship between change from baseline to the evaluation period in anti-fXa activity and effective hemostasis.</li><li>• Eliminated the original Study Day 1, 24-hour study data point and updated time points to Day 1, 8-hour and Day 1, 12-hour data points.</li><li>• Clarified the requirements, inclusion, and exclusion criteria regarding acute major bleeding.</li><li>• Changed the definition of history prior to Screening from 1 month to 2 weeks.</li><li>• Modified follow-up to include rescue therapy for participants with a poor or no response.</li><li>• Provided specific detail on the measurement of closed bleeds to document hemostatic control.</li><li>• Increased the number of sites allowed in North America and Europe from 60 to 120.</li></ul>  |
| 07 May 2015     | <ul style="list-style-type: none"><li>• Modified the duration of safety follow-up from 45 to 30 days to align follow-up period with standard clinical practice for intracranial hemorrhage recovery timelines.</li><li>• Clarified that (visible) bleeding must be overt to qualify for inclusion in this trial.</li><li>• Clarified that intracranial hemorrhage bleeds could be diagnosed and assessed with either computed tomography or magnetic resonance imaging.</li><li>• Included edoxaban as 1 of the FXa inhibitors that could qualify a participant for this trial. Also, clarified that the list of FXa inhibitors being studied in this study was restricted to apixaban, edoxaban, rivaroxaban, and enoxaparin.</li><li>• Clarified that participants who were scheduled for surgery to occur within the first 12 hours after receiving andexanet should not be enrolled in this study.</li><li>• Clarified the blood and blood-related products were allowed as well as the time frames allowed.</li><li>• Increased the size of allowable hematoma volume from 30 to 60 cubic centimetres to enable the participant population to be more representative of what might be expected in the clinical setting.</li><li>• Shortened and/or consolidated the restrictions around duration of prior exposure to medications to within 7 days of andexanet treatment, based on expected duration of effect.</li><li>• Provided specificity around rating of hemostatic efficacy for different subtypes of intracranial hemorrhage.</li></ul> |

|                  |  |
|------------------|--|
| 06 January 2017  | <ul style="list-style-type: none"> <li>Increased sample size from 250 participants to 350 participants.</li> <li>Enriched participant population for intracranial hemorrhage; ensured a minimum of 110 efficacy evaluable intracranial hemorrhage participants, including 50 participants at high risk for hematoma expansion.</li> <li>Added a requirement for a reasonable expectation that a participant would be treated with andexanet within 2 hours after a baseline scan (intracranial hemorrhage participants only).</li> <li>Excluded participants with visible, intra-articular, and musculoskeletal bleeding.</li> <li>Excluded participants for whom the Investigator believed that the hemoglobin would drop below 8 grams/deciliter after volume resuscitation.</li> <li>Changed threshold of efficacy evaluability for enoxaparin participants from 0.5 to 0.25 international units/milliliter (IU/mL).</li> <li>Added clinical criteria for re-bleeding and guidance for re-dosing of andexanet in the event of re-bleeding.</li> <li>Added re-bleeding, tissue factor pathway inhibitor (TFPI), antithrombin III, anti-IIa activity, Glasgow Coma Scale, Modified Rankin Score, and National Institutes of Health Stroke Scale as exploratory efficacy end points.</li> <li>Converted thrombin generation from a safety end point to an efficacy end point, and mortality from an efficacy end point to a safety end point.</li> <li>Added additional time points through 72 hours post-andexanet dosing for TFPI levels and thrombin generation.</li> <li>Updated andexanet dosing recommendations.</li> </ul>  |
| 02 July 2018     | <ul style="list-style-type: none"> <li>To establish lower anti-fXa activity threshold for participants taking edoxaban to reflect contemporary understanding of risks and benefits of edoxaban.</li> <li>Efficacy evaluable participants was re-defined as follows: All patients must have a central laboratory-determined anti-fXa activity <math>\geq 75</math> ng/mL for patients receiving apixaban and rivaroxaban, <math>\geq 40</math> ng/mL for patients receiving edoxaban, and <math>\geq 0.25</math> IU/mL for patients receiving enoxaparin. All other criteria stayed the same.</li> <li>Exclusion criterion #5 was updated as follows: The patient has a recent history (within 2 weeks) of a diagnosed TE as follows: Venous Thromboembolism (VTE; e.g., deep venous thrombosis, PE, cerebral venous thrombosis), MI (including an isolated troponin elevation), DIC, cerebral vascular accident, TIA, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening (see Protocol Amendment 5, Appendix E for DIC scoring algorithm).</li> <li>Clarified definition of re-bleeding to be consistent throughout protocol.</li> <li>Updated and clarified investigational product return and destruction.</li> </ul>   |
| 30 November 2018 | <ul style="list-style-type: none"> <li>Corrected an error in the Synopsis and updated for accuracy and to align with the protocol body.</li> <li>Clarified that adverse events and survival was to be followed through the study.</li> <li>Updated to simplify the description of the study periods related to safety monitoring.</li> <li>As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to participants who received their last dose of FXa inhibitor within 18 hours, if the timing is known. (If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible—following signing of the informed consent form [ICF] and completion of pretreatment procedures—but no later than 3 hours following signing of the ICF).</li> <li>Clarified exclusion criterion 4.2 to include language about the timing of additional surgery (12 hours after end of andexanet infusion).</li> <li>Updated the andexanet dosing to reflect accurate ranges of <math>&lt; 30</math> mg (low dose) and <math>\geq 30</math> mg (high dose) for andexanet dosing in participants receiving edoxaban.</li> <li>Added the Sponsor in Japan as Bristol-Myers Squibb K.K. in collaboration with Portola Pharmaceuticals, Inc.</li> <li>Eliminated or revised all sentences related to enoxaparin participants because the dose of enoxaparin allowed in the study was not approved in Japan.</li> <li>Modified andexanet dosing regimen for each FXa inhibitor.</li> <li>Revised sentences related to drug supply and accountability from managing by Portola Pharmaceuticals, Inc. to managing by Bristol-Myers Squibb K.K.</li> <li>Increased sample size to 500 participants to ensure adequate enrollment of various subgroups within the enrolled population.</li> </ul> |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported

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### **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/27573206>

<http://www.ncbi.nlm.nih.gov/pubmed/28009495>

<http://www.ncbi.nlm.nih.gov/pubmed/30730782>