



## Clinical trial results:

### A RANDOMIZED, OPEN-LABEL, ACTIVE CONTROLLED, SAFETY AND DESCRIPTIVE EFFICACY STUDY IN PEDIATRIC SUBJECTS REQUIRING ANTICOAGULATION FOR THE TREATMENT OF A VENOUS THROMBOEMBOLIC EVENT

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2014-002606-20                      |
| Trial protocol           | DE Outside EU/EEA AT GB ES PT IT FR |
| Global end of trial date | 30 April 2024                       |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 25 October 2024 |
| First version publication date | 25 October 2024 |

#### Trial information

##### Trial identification

|                       |                    |
|-----------------------|--------------------|
| Sponsor protocol code | CV185-325/B0661037 |
|-----------------------|--------------------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT02464969     |
| WHO universal trial number (UTN)   | U1111-1160-6336 |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Bristol-Myers Squibb  |
| Sponsor organisation address | Chaussee de la Hulpe 185, Brussels, Belgium, 1170   |
| Public contact               | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact           | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com              |

Notes:

#### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-000185-PIP02-12 |
| 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? | Yes                 |

Notes:

## Results analysis stage

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 30 April 2024 |
| Is this the analysis of the primary completion data? | No            |

|                                  |               |
|----------------------------------|---------------|
| Global end of trial reached?     | Yes           |
| Global end of trial date         | 30 April 2024 |
| Was the trial ended prematurely? | No            |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 22 November 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 | Australia: 1           |
| Country: Number of subjects enrolled | Canada: 14             |
| Country: Number of subjects enrolled | Germany: 4             |
| Country: Number of subjects enrolled | France: 3              |
| Country: Number of subjects enrolled | Spain: 6               |
| Country: Number of subjects enrolled | Austria: 1             |
| Country: Number of subjects enrolled | Türkiye: 1             |
| Country: Number of subjects enrolled | Russian Federation: 24 |
| Country: Number of subjects enrolled | Ukraine: 7             |
| Country: Number of subjects enrolled | United Kingdom: 7      |
| Country: Number of subjects enrolled | United States: 161     |
| Worldwide total number of subjects   | 229                    |
| EEA total number of subjects         | 14                     |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 16 |

|  |     |
|--|-----|
| Infants and toddlers (28 days-23 months) | 32  |
| Children (2-11 years)                    | 44  |
| Adolescents (12-17 years)                | 137 |
| Adults (18-64 years)                     | 0   |
| From 65 to 84 years                      | 0   |
| 85 years and over                        | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled in 11 countries.

### Pre-assignment

Screening details:

Of the 243 participants screened for entry into the study, 229 participants were randomized to treatment, and 14 participants did not fulfill all eligibility criteria at screening

### Period 1

|                              |                              |
|------------------------------|------------------------------|
| Period 1 title               | Main Phase (Day 1 to Day 84) |
| Is this the baseline period? | Yes                          |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Not blinded                  |

### Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | Participants receiving Apixaban |

Arm description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|  |   |
|--|---|
| Arm type                               | Experimental                                |
| Investigational medicinal product name | Apixaban                                    |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Dispersible tablet, Chewable tablet, Tablet |
| Routes of administration               | Oral use                                    |

Dosage and administration details:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Participants treated with Standard of Care |
|------------------|--|

Arm description:

Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|   |                                     |
|---|-------------------------------------|
| Investigational medicinal product name                      | Vitamin K antagonist                |
| Investigational medicinal product code                      |                                     |
| Other name  |                                     |
| Pharmaceutical forms  | Tablet                              |
| Routes of administration                                    | Oral use                            |
| Dosage and administration details:                          |                                     |
| Standard of care per local prescribing practices/guidelines |                                     |
| Investigational medicinal product name                      | Unfractionated heparin (UFH)        |
| Investigational medicinal product code                      |                                     |
| Other name  |                                     |
| Pharmaceutical forms  | Injection                           |
| Routes of administration                                    | Intravenous use                     |
| Dosage and administration details:                          |                                     |
| Standard of care per local prescribing practices/guidelines |                                     |
| Investigational medicinal product name                      | Low molecular weight heparin (LMWH) |
| Investigational medicinal product code                      |                                     |
| Other name  |                                     |
| Pharmaceutical forms  | Injection                           |
| Routes of administration                                    | Subcutaneous use                    |
| Dosage and administration details:                          |                                     |
| Standard of care per local prescribing practices/guidelines |                                     |

| Number of subjects in period 1       | Participants receiving Apixaban | Participants treated with Standard of Care |
|--------------------------------------|---------------------------------|--|
|                                      |                                 |  |
| Started                              | 155                             | 74   |
| Completed                            | 138                             | 65   |
| Not completed                        | 17                              | 9  |
| Adverse event, serious fatal         | 1                               | 1  |
| Consent withdrawn by subject         | 1                               | -  |
| Adverse event, non-fatal             | 7                               | -  |
| Other Reasons                        | 4                               | 2  |
| Withdrawal by Parent/Guardian        | -                               | 4  |
| Lost to follow-up                    | 3                               | -  |
| No Longer Meets Eligibility Criteria | -                               | 1  |
| Entrance Criteria                    | 1                               | 1  |

## Period 2

|                              |                                     |
|------------------------------|-------------------------------------|
| Period 2 title               | Extension Phase (Day 85 to Day 168) |
| Is this the baseline period? | No                                  |
| Allocation method            | Not applicable                      |
| Blinding used                | Not blinded                         |

## Arms

|  |   |
|--|---|
| <b>Arm title</b>   | Participants receiving Apixaban             |
| Arm description:   |   |
| Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter. |   |
| Arm type   | Experimental                                |
| Investigational medicinal product name   | Apixaban                                    |
| Investigational medicinal product code   |   |
| Other name   |   |
| Pharmaceutical forms   | Dispersible tablet, Chewable tablet, Tablet |
| Routes of administration   | Oral use                                    |

### Dosage and administration details:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Participants receiving Apixaban |
|---|---------------------------------|
| Started   | 53                              |
| Completed   | 50                              |
| Not completed                                       | 3                               |
| Adverse event, non-fatal                            | 1                               |
| Other Reasons                                       | 1                               |
| Withdrawal by Parent/Guardian                       | 1                               |

### Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only participants randomized to the apixaban treatment group who subsequently completed the Main Phase of the study on assigned therapy, and then consented to continue their participation, were enrolled in the Extension Phase of the study. Therefore, of the original 155 randomized to apixaban treatment in the Main Phase of the study (152 of them treated), only 53 continued participation into the Extension Phase.

## Baseline characteristics

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Participants receiving Apixaban |
|-----------------------|---------------------------------|

Reporting group description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                       |  |
|-----------------------|--|
| Reporting group title | Participants treated with Standard of Care |
|-----------------------|--|

Reporting group description:

Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

| Reporting group values                             | Participants receiving Apixaban | Participants treated with Standard of Care | Total |
|--|---------------------------------|--|-------|
| Number of subjects                                 | 155                             | 74   | 229   |
| Age categorical                                    |                                 |  |       |
| Units: Subjects                                    |                                 |  |       |
| In utero   | 0                               | 0  | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                               | 0  | 0     |
| Newborns (0-27 days)                               | 12                              | 4  | 16    |
| Infants and toddlers (28 days-23 months)           | 22                              | 10   | 32    |
| Children (2-11 years)                              | 30                              | 14   | 44    |
| Adolescents (12-17 years)                          | 91                              | 46   | 137   |
| Adults (18-64 years)                               | 0                               | 0  | 0     |
| From 65-84 years                                   | 0                               | 0  | 0     |
| 85 years and over                                  | 0                               | 0  | 0     |
| Age Continuous                                     |                                 |  |       |
| Units: years                                       |                                 |  |       |
| arithmetic mean                                    | 11.10                           | 11.68                                      |       |
| standard deviation                                 | $\pm 6.51$                      | $\pm 6.02$                                 | -     |
| Sex: Female, Male                                  |                                 |  |       |
| Units: participants                                |                                 |  |       |
| Female   | 85                              | 43   | 128   |
| Male   | 70                              | 31   | 101   |
| Race/Ethnicity, Customized                         |                                 |  |       |
| Units: Subjects                                    |                                 |  |       |
| White  | 120                             | 55   | 175   |
| Black  | 22                              | 9  | 31    |
| Asian  | 5                               | 4  | 9     |
| American Indian or Alaska Native                   | 1                               | 0  | 1     |
| Other  | 6                               | 5  | 11    |

|                         |     |    |     |
|-------------------------|-----|----|-----|
| Multiracial             | 1   | 1  | 2   |
| Ethnicity (NIH/OMB)     |     |    |     |
| Units: Subjects         |     |    |     |
| Hispanic or Latino      | 12  | 13 | 25  |
| Not Hispanic or Latino  | 143 | 61 | 204 |
| Unknown or Not Reported | 0   | 0  | 0   |



## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Participants receiving Apixaban            |
| Reporting group description:  |  |
| Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.   |  |
| Reporting group title   | Participants treated with Standard of Care |
| Reporting group description:  |  |
| Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.   |  |
| Reporting group title   | Participants receiving Apixaban            |
| Reporting group description:  |  |
| Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.   |  |
| Subject analysis set title  | Participants between age 12 to < 18 years  |
| Subject analysis set type   | Sub-group analysis                         |
| Subject analysis set description:   |  |
| Participants between age 12 to < 18 years were dosed on a body weight tiered regimen. Subjects $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter. |  |
| Subject analysis set title  | Participants between age 2 - < 12 years    |
| Subject analysis set type   | Sub-group analysis                         |
| Subject analysis set description:   |  |
| Participants between age 2 - < 12 years were dosed on a body weight tiered regimen. Subjects $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.   |  |
| Subject analysis set title  | Participants with age 28 days - < 2 years  |
| Subject analysis set type   | Sub-group analysis                         |

#### Subject analysis set description:

Participants with age 28 days - < 2 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants in age group-Birth - $\leq 27$ days |
| Subject analysis set type  | Sub-group analysis                               |

#### Subject analysis set description:

Participants in age group-Birth -  $\leq 27$  days were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants between age 12 to < 18 years |
| Subject analysis set type  | Sub-group analysis                        |

#### Subject analysis set description:

Participants between age 12 to < 18 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants between age 2 - < 12 years |
| Subject analysis set type  | Sub-group analysis                      |

#### Subject analysis set description:

Participants between age 2 - < 12 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                            |   |
|----------------------------|---|
| Subject analysis set title | Participants with age 28 days - < 2 years |
| Subject analysis set type  | Sub-group analysis                        |

#### Subject analysis set description:

Participants with age 28 days - < 2 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

|                            |  |
|----------------------------|--|
| Subject analysis set title | Participants in age group-Birth - $\leq 27$ days |
|----------------------------|--|

|                           |                    |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

#### Subject analysis set description:

Participants in age group-Birth - ≤ 27 days were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

### Primary: Percentage of Participants with Composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding (Safety Population)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding (Safety Population) <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding includes: (i) fatal bleeding; (ii) clinically overt bleeding with a decrease in Hgb of at least 20 g/L (2 g/dL) in 24 hours; (iii) retroperitoneal, pulmonary, intracranial, or central nervous system bleeding; and (iv) bleeding requiring surgical intervention in an operating suite (including interventional radiology). Clinically relevant non-major bleeding includes: (i) overt bleeding requiring a blood product not attributable to the participant's underlying condition; and (ii) bleeding requiring medical or surgical intervention to restore hemostasis, other than in an operating suite.

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

#### End point timeframe:

From first dose (Day 1) up to 114 days

#### 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: Study CV185325 was designed as a descriptive efficacy and safety study and so was not powered for any endpoints. As such, formal statistical analyses were not included in the protocol.

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 152                             | 73   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (confidence interval 95%)  | 1.3 (0.1 to 5.0)                | 1.4 (0.0 to 8.1)                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Primary: Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE) and VTE-Related Mortality

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE) and VTE-Related Mortality <sup>[2]</sup> |
|-----------------|--|

#### End point description:

Recurrent VTE, defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to deep vein thrombosis (DVT), pulmonary embolism (PE) and paradoxical embolism.

95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8.

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

End point timeframe:

From first dose (Day 1) up to 114 days

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: Study CV185325 was designed as a descriptive efficacy and safety study and so was not powered for any endpoints. As such, formal statistical analyses were not included in the protocol.

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (confidence interval 95%)  | 2.6 (0.8 to 6.7)                | 2.7 (0.2 to 9.9)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with VTE-related Mortality

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with VTE-related Mortality |
|-----------------|---|

End point description:

Participants were assessed for death due to VTE. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose (Day 1) up to 114 days

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (not applicable)           | 0                               | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants who Died

|  |                                     |
|--|-------------------------------------|
| End point title  | Percentage of Participants who Died |
| End point description:<br>95% CI was calculated using the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8. |                                     |
| End point type   | Secondary                           |
| End point timeframe:<br>From first dose (Day 1) up to 114 days   |                                     |

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (confidence interval 95%)  | 1.3 (0.1 to 4.9)                | 1.4 (0.0 to 8.0)                           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Index VTE Status

|  |  |
|--|--|
| End point title  | Number of Participants with Index VTE Status |
| End point description:<br>Index VTE status was defined as the last image obtained during the Main treatment phase for each participant's comparison to baseline imaging. Index VTE status was classified as Recurrence-contiguous; Recurrence-new; Unchanged; Regression; Resolution; Indeterminate/Nondiagnostic. Participants could have multiple concomitant index events such as presence of DVT and PE at baseline. Regression was defined as (ie, unequivocal decrease [ $>50\%$ ] of the total volume/mass of the thrombus compared to the index event). The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8. Participants with a negative or Non-Diagnostic Index Event were excluded. |  |
| End point type   | Secondary                                    |
| End point timeframe:<br>From first dose (Day 1) up to 91 days  |  |

| End point values            | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------|---------------------------------|--|--|--|
| Subject group type          | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed | 128                             | 65   |  |  |
| Units: participants         |                                 |  |  |  |
| Recurrence-contiguous       | 2                               | 0  |  |  |
| Recurrence-new              | 0                               | 0  |  |  |
| Unchanged                   | 8                               | 6  |  |  |
| Regression                  | 25                              | 11   |  |  |
| Resolution                  | 77                              | 36   |  |  |

|                             |    |   |  |  |
|-----------------------------|----|---|--|--|
| Indeterminate/Nondiagnostic | 15 | 7 |  |  |
| Missing Follow-up Imaging   | 5  | 8 |  |  |
| Imaging not completed       | 6  | 1 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE) |
|-----------------|---|

End point description:

Recurrent VTE, defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to deep vein thrombosis (DVT), pulmonary embolism (PE) and paradoxical embolism. 95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose (Day 1) up to 114 days

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (confidence interval 95%)  | 2.6 (0.8 to 6.7)                | 2.7 (0.2 to 9.9)                           |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Stroke

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Stroke |
|-----------------|--|

End point description:

Participants were assessed for incidence of stroke. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose (Day 1) up to 114 days

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants | 0                               | 0  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with New Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE)

|                 |  |
|-----------------|--|
| End point title | Number of Participants with New Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE) |
|-----------------|--|

End point description:

Participants were assessed for incidence of Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE). The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From first dose (Day 1) up to 114 days

| End point values                    | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-------------------------------------|---------------------------------|--|--|--|
| Subject group type                  | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed         | 155                             | 74   |  |  |
| Units: participants                 |                                 |  |  |  |
| New Symptomatic or Asymptomatic DVT | 1                               | 1  |  |  |
| New Symptomatic or Asymptomatic PE  | 0                               | 0  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants with Clinically Relevant Non-Major (CRNM) Bleeding, Major Bleeding and Minor Bleeding

|                 |  |
|-----------------|--|
| End point title | Number of Participants with Clinically Relevant Non-Major (CRNM) Bleeding, Major Bleeding and Minor Bleeding |
|-----------------|--|

End point description:

Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding includes: (i) fatal bleeding; (ii) clinically overt bleeding with a decrease in Hgb of at least 20 g/L (2 g/dL) in 24 hours; (iii)

retroperitoneal, pulmonary, intracranial, or central nervous system bleeding; and (iv) bleeding requiring surgical intervention in an operating suite (including interventional radiology). Clinically relevant non-major bleeding includes: (i) overt bleeding requiring a blood product not attributable to the participant's underlying condition; and (ii) bleeding requiring medical or surgical intervention to restore hemostasis, other than in an operating suite. Minor bleeding was defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding.

|  |           |
|--|-----------|
| End point type                         | Secondary |
| End point timeframe:                   |           |
| From first dose (Day 1) up to 114 days |           |

| End point values                       | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|--|---------------------------------|--|--|--|
| Subject group type                     | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed            | 152                             | 73   |  |  |
| Units: participants                    |                                 |  |  |  |
| Major Bleeding                         | 0                               | 0  |  |  |
| Clinically Relevant Non-major Bleeding | 2                               | 1  |  |  |
| Minor Bleeding                         | 54                              | 21   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with Other Symptomatic and Asymptomatic Venous Thromboembolism (VTE)

|  |   |
|--|---|
| End point title  | Percentage of Participants with Other Symptomatic and Asymptomatic Venous Thromboembolism (VTE) |
| End point description:   |   |
| Other VTE included events such as cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis. If VTE event type was blank, it was included in the Other VTE. 95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From first dose (Day 1) up to 114 days   |   |

| End point values                  | Participants receiving Apixaban | Participants treated with Standard of Care |  |  |
|-----------------------------------|---------------------------------|--|--|--|
| Subject group type                | Reporting group                 | Reporting group                            |  |  |
| Number of subjects analysed       | 155                             | 74   |  |  |
| Units: percentage of participants |                                 |  |  |  |
| number (confidence interval 95%)  | 1.9 (0.4 to 5.8)                | 1.4 (0.0 to 8.0)                           |  |  |



## Statistical analyses

No statistical analyses for this end point

### Secondary: Blood Concentration of Apixaban (ng/mL)

|                 |   |
|-----------------|---|
| End point title | Blood Concentration of Apixaban (ng/mL) |
|-----------------|---|

End point description:

Blood samples were collected to assess the apixaban concentration at specified timepoints. Day 1 PK concentrations were only collected for participants in the Birth to  $\leq 27$  days arm. The lower limit of quantification (LLOQ) is 1.0 ng/mL for plasma samples, and 0.5 ng/mL for dried blood samples. 99999 stands for Not applicable as no participants were analyzed for those arms at that specific timepoint. The PK analysis population is defined as all participants randomized to and treated with apixaban who have at least 1 concentration of apixaban. Participants with sample size of quantifiable values ( $\geq$  LLOQ) at the specified timepoints were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3 hour (H), 12 H, 24 H at Day 3; pre and post dose at Day 14 and Day 42

| End point values                       | Participants between age 12 to < 18 years | Participants between age 2 - < 12 years | Participants with age 28 days - < 2 years | Participants in age group- Birth - $\leq 27$ days |
|--|---|---|---|---|
| Subject group type                     | Subject analysis set                      | Subject analysis set                    | Subject analysis set                      | Subject analysis set                              |
| Number of subjects analysed            | 64  | 22                                      | 15  | 11  |
| Units: nanogram per millilitre (ng/mL) |   |   |   |   |
| arithmetic mean (standard deviation)   |   |   |   |   |
| Hour 3 at Day 1 (n=0,0,0,11)           | 99999 ( $\pm$ 99999)                      | 99999 ( $\pm$ 99999)                    | 99999 ( $\pm$ 99999)                      | 30.7 ( $\pm$ 12.9)                                |
| Hour 12 at Day 1 (n=0,0,0,10)          | 99999 ( $\pm$ 99999)                      | 99999 ( $\pm$ 99999)                    | 99999 ( $\pm$ 99999)                      | 13.9 ( $\pm$ 5.70)                                |
| Hour 24 at Day 1 (n=0,0,0,11)          | 99999 ( $\pm$ 99999)                      | 99999 ( $\pm$ 99999)                    | 99999 ( $\pm$ 99999)                      | 23.3 ( $\pm$ 10.1)                                |
| Pre-dose at Day 14 (n=64,22,15,7)      | 61.1 ( $\pm$ 53.7)                        | 72.7 ( $\pm$ 42.5)                      | 56.4 ( $\pm$ 65.6)                        | 48.3 ( $\pm$ 23.0)                                |
| Post-dose at Day 14 (n=61,21,14,6)     | 152 ( $\pm$ 80.2)                         | 189 ( $\pm$ 61.0)                       | 203 ( $\pm$ 118)                          | 119 ( $\pm$ 45.7)                                 |
| Pre-dose at Day 42 (n=24,5,3,2)        | 54.5 ( $\pm$ 33.7)                        | 67.9 ( $\pm$ 33.8)                      | 123 ( $\pm$ 123)                          | 50.2 ( $\pm$ 34.1)                                |
| Post-Dose at Day 42 (n=27,7,4,3)       | 151 ( $\pm$ 79.1)                         | 212 ( $\pm$ 89.8)                       | 143 ( $\pm$ 88.0)                         | 109 ( $\pm$ 56.0)                                 |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentration of Plasma Anti-Factor Xa (ng/mL)

|                 |  |
|-----------------|--|
| End point title | Concentration of Plasma Anti-Factor Xa (ng/mL) |
|-----------------|--|

---

**End point description:**

Blood samples were collected to assess the Anti-Factor Xa concentration at specified timepoints. Day 1 PK concentrations were only collected for participants in the Birth to ≤27 days arm. The lower limit of quantification (LLOQ) is 35.0 ng/mL. 99999 stands for Not applicable where participants analyzed is 0 and 999999 also stands for not applicable where only 1 participant was analyzed and SD could not be analyzed. The PK analysis population is defined as all participants randomized to and treated with apixaban who have at least 1 concentration of apixaban. Participants with sample size of quantifiable values (≥ LLOQ) at the specified timepoints were analyzed.

---

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

---

**End point timeframe:**

Pre and post dose at Day 14 and Day 42

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| End point values                       | Participants between age 12 to < 18 years | Participants between age 2 - < 12 years | Participants with age 28 days - < 2 years | Participants in age group- Birth - ≤ 27 days |
|--|---|---|---|--|
| Subject group type                     | Subject analysis set                      | Subject analysis set                    | Subject analysis set                      | Subject analysis set                         |
| Number of subjects analysed            | 60  | 20                                      | 13  | 3  |
| Units: nanogram per millilitre (ng/mL) |   |   |   |  |
| arithmetic mean (standard deviation)   |   |   |   |  |
| Pre-dose at Day 14(n=51,18,10,3)       | 72.7 (± 60.4)                             | 82.7 (± 41.3)                           | 74.7 (± 69.7)                             | 48.0 (± 1.00)                                |
| Post-dose at Day 14(n=60,20,13,3)      | 147 (± 83.5)                              | 202 (± 75.8)                            | 190 (± 105)                               | 127 (± 4.04)                                 |
| Pre-dose at Day 42(n=20,4,2,0)         | 63.9 (± 27.4)                             | 75.3 (± 31.0)                           | 53.5 (± 13.4)                             | 99999 (± 99999)                              |
| Post-Dose at Day 42(n=27,7,5,1)        | 153 (± 84.9)                              | 220 (± 98.4)                            | 156 (± 92.2)                              | 101 (± 999999)                               |

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**Statistical analyses**

No statistical analyses for this end point

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## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Non-SAEs were collected from first dose Day 1 up to end of treatment visit (Day 168) plus 35 days i.e., up to 203 days. SAEs were collected from Screening (Day -7) to end of treatment visit (Day 168) plus 35 days i.e., up to 210 days.

Adverse event reporting additional description:

SAEs and Non SAEs were collected for safety population who received at least one dose of study drug.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Participants treated with Standard of Care |
|-----------------------|--|

Reporting group description:

Participants were treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Participants receiving Apixaban |
|-----------------------|---------------------------------|

Reporting group description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects  $\geq 35$ kg received 10mg twice daily (BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; <9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates  $\geq 2.6$ kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis, participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

| Serious adverse events  | Participants treated with Standard of Care | Participants receiving Apixaban |  |
|---|--|---------------------------------|--|
| Total subjects affected by serious adverse events                   |  |                                 |  |
| subjects affected / exposed   | 17 / 73 (23.29%)                           | 40 / 152 (26.32%)               |  |
| number of deaths (all causes)                                       | 1  | 2                               |  |
| number of deaths resulting from adverse events                      | 0  | 0                               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                                 |  |
| Embryonal rhabdomyosarcoma  |  |                                 |  |
| subjects affected / exposed   | 0 / 73 (0.00%)                             | 1 / 152 (0.66%)                 |  |
| occurrences causally related to treatment / all                     | 0 / 0                                      | 0 / 2                           |  |
| deaths causally related to treatment / all                          | 0 / 0                                      | 0 / 0                           |  |
| Vascular disorders  |  |                                 |  |
| Post thrombotic syndrome  |  |                                 |  |

|  |                |                 |  |
|--|----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Axillary vein thrombosis                             |                |                 |  |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Subclavian vein thrombosis                           |                |                 |  |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Superficial vein thrombosis                          |                |                 |  |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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 |                |                 |  |
| Death  |                |                 |  |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Chest pain   |                |                 |  |
| subjects affected / exposed                          | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Mucosal inflammation                                 |                |                 |  |
| subjects affected / exposed                          | 0 / 73 (0.00%) | 2 / 152 (1.32%) |  |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Pyrexia  |                |                 |  |
| subjects affected / exposed                          | 1 / 73 (1.37%) | 4 / 152 (2.63%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           |  |
| Peripheral swelling                                  |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Non-cardiac chest pain                          |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Multiple organ dysfunction syndrome             |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Immune system disorders                         |                |                 |  |
| Transplant rejection                            |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Reproductive system and breast disorders        |                |                 |  |
| Heavy menstrual bleeding                        |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pulmonary embolism                              |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumomediastinum                               |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute chest syndrome                            |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Acute respiratory distress syndrome             |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Dyspnoea  |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hyperventilation                                |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Psychiatric disorders                           |                |                 |  |
| Depression                                      |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Munchausen's syndrome                           |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Selective eating disorder                       |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Product issues                                  |                |                 |  |
| Device malfunction                              |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Investigations                                  |                |                 |  |
| Alanine aminotransferase increased              |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 3 / 152 (1.97%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Blood urea increased                            |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Medical observation                             |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Weight increased                                |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                |                 |  |
| Gun shot wound                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Incisional hernia                               |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| Lower limb fracture                             |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Shunt thrombosis                                |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Suture rupture                                  |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiac disorders                               |                |                 |  |
| Cardiac arrest                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cardiogenic shock                               |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nervous system disorders                        |                |                 |  |
| Complex regional pain syndrome                  |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Headache  |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |



|   |                |                 |  |
|---|----------------|-----------------|--|
| Hypoxic-ischaemic encephalopathy<br>subjects affected / exposed | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1          | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Intracranial pressure increased<br>subjects affected / exposed  | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Seizure<br>subjects affected / exposed                          | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1          | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Cerebral venous sinus thrombosis<br>subjects affected / exposed | 0 / 73 (0.00%) | 2 / 152 (1.32%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 1 / 2           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Thoracic outlet syndrome<br>subjects affected / exposed         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Transient ischaemic attack<br>subjects affected / exposed       | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 1          | 0 / 0           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Blood and lymphatic system disorders                            |                |                 |  |
| Thrombocytopenia<br>subjects affected / exposed                 | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 2           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Cold type haemolytic anaemia<br>subjects affected / exposed     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to<br>treatment / all              | 0 / 0          | 0 / 1           |  |
| deaths causally related to<br>treatment / all                   | 0 / 0          | 0 / 0           |  |
| Febrile neutropenia   |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 73 (2.74%) | 3 / 152 (1.97%) |  |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Myelosuppression                                |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Neutropenia                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pancytopenia                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sickle cell anaemia with crisis                 |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 2 / 152 (1.32%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Eye disorders                                   |                |                 |  |
| Eye movement disorder                           |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrointestinal disorders                      |                |                 |  |
| Gastrointestinal pain                           |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Colitis   |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Abdominal pain                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Gastrooesophageal reflux disease                |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Stomatitis                                      |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Small intestinal obstruction                    |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Oesophagitis                                    |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Ileus paralytic                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haematochezia                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 2 / 152 (1.32%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Haematemesis                                    |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Hepatobiliary disorders                         |                |                 |  |
| Drug-induced liver injury                       |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Nephrotic syndrome                              |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Polyuria  |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| 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 |                |                 |  |
| Connective tissue disorder                      |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Cytarabine syndrome                             |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infections and infestations                     |                |                 |  |
| Cellulitis                                      |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Atypical pneumonia                                  |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Device related bacteraemia                          |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Varicella   |                |                 |  |
| subjects affected / exposed                         | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Escherichia urinary tract infection                 |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Gastroenteritis rotavirus                           |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Infective pulmonary exacerbation of cystic fibrosis |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Meningitis bacterial                                |                |                 |  |
| subjects affected / exposed                         | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0           |  |
| Mycoplasma infection                                |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Osteomyelitis                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Urinary tract infection bacterial               |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Upper respiratory tract infection               |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Toxic shock syndrome                            |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Sepsis  |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Rhinovirus infection                            |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pyomyositis                                     |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pseudomonal bacteraemia                         |                |                 |  |

|   |                |                 |  |
|---|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Pneumonia viral                                 |                |                 |  |
| subjects affected / exposed                     | 0 / 73 (0.00%) | 1 / 152 (0.66%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Escherichia pyelonephritis                      |                |                 |  |
| subjects affected / exposed                     | 1 / 73 (1.37%) | 0 / 152 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Participants treated with Standard of Care | Participants receiving Apixaban |  |
|---|--|---------------------------------|--|
| Total subjects affected by non-serious adverse events |  |                                 |  |
| subjects affected / exposed                           | 59 / 73 (80.82%)                           | 132 / 152 (86.84%)              |  |
| Injury, poisoning and procedural complications        |  |                                 |  |
| Contusion   |  |                                 |  |
| subjects affected / exposed                           | 10 / 73 (13.70%)                           | 14 / 152 (9.21%)                |  |
| occurrences (all)                                     | 10   | 14                              |  |
| Nervous system disorders                              |  |                                 |  |
| Headache  |  |                                 |  |
| subjects affected / exposed                           | 10 / 73 (13.70%)                           | 27 / 152 (17.76%)               |  |
| occurrences (all)                                     | 13   | 43                              |  |
| Blood and lymphatic system disorders                  |  |                                 |  |
| Thrombocytopenia                                      |  |                                 |  |
| subjects affected / exposed                           | 4 / 73 (5.48%)                             | 5 / 152 (3.29%)                 |  |
| occurrences (all)                                     | 24   | 17                              |  |
| Leukopenia  |  |                                 |  |
| subjects affected / exposed                           | 4 / 73 (5.48%)                             | 3 / 152 (1.97%)                 |  |
| occurrences (all)                                     | 23   | 7                               |  |
| Anaemia   |  |                                 |  |

|   |                       |                       |  |
|---|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 8 / 73 (10.96%)<br>42 | 5 / 152 (3.29%)<br>14 |  |
| General disorders and administration<br>site conditions |                       |                       |  |
| Fatigue   |                       |                       |  |
| subjects affected / exposed                             | 4 / 73 (5.48%)        | 5 / 152 (3.29%)       |  |
| occurrences (all)                                       | 4                     | 6                     |  |
| Injection site bruising                                 |                       |                       |  |
| subjects affected / exposed                             | 12 / 73 (16.44%)      | 1 / 152 (0.66%)       |  |
| occurrences (all)                                       | 13                    | 1                     |  |
| Injection site haemorrhage                              |                       |                       |  |
| subjects affected / exposed                             | 4 / 73 (5.48%)        | 0 / 152 (0.00%)       |  |
| occurrences (all)                                       | 4                     | 0                     |  |
| Non-cardiac chest pain                                  |                       |                       |  |
| subjects affected / exposed                             | 5 / 73 (6.85%)        | 12 / 152 (7.89%)      |  |
| occurrences (all)                                       | 6                     | 16                    |  |
| Pyrexia   |                       |                       |  |
| subjects affected / exposed                             | 7 / 73 (9.59%)        | 11 / 152 (7.24%)      |  |
| occurrences (all)                                       | 9                     | 20                    |  |
| Gastrointestinal disorders                              |                       |                       |  |
| Abdominal pain  |                       |                       |  |
| subjects affected / exposed                             | 5 / 73 (6.85%)        | 11 / 152 (7.24%)      |  |
| occurrences (all)                                       | 7                     | 15                    |  |
| Abdominal discomfort                                    |                       |                       |  |
| subjects affected / exposed                             | 4 / 73 (5.48%)        | 0 / 152 (0.00%)       |  |
| occurrences (all)                                       | 5                     | 0                     |  |
| Vomiting  |                       |                       |  |
| subjects affected / exposed                             | 4 / 73 (5.48%)        | 22 / 152 (14.47%)     |  |
| occurrences (all)                                       | 4                     | 31                    |  |
| Nausea  |                       |                       |  |
| subjects affected / exposed                             | 5 / 73 (6.85%)        | 12 / 152 (7.89%)      |  |
| occurrences (all)                                       | 6                     | 15                    |  |
| Diarrhoea   |                       |                       |  |
| subjects affected / exposed                             | 6 / 73 (8.22%)        | 15 / 152 (9.87%)      |  |
| occurrences (all)                                       | 6                     | 19                    |  |
| Constipation  |                       |                       |  |



|  |   |   |  |
|--|---|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 73 (4.11%)</p> <p>3</p> <p>4 / 73 (5.48%)</p> <p>4</p>   | <p>10 / 152 (6.58%)</p> <p>12</p> <p>8 / 152 (5.26%)</p> <p>9</p>   |  |
| <p>Reproductive system and breast disorders</p> <p>Heavy menstrual bleeding</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>3 / 73 (4.11%)</p> <p>5</p>  | <p>16 / 152 (10.53%)</p> <p>20</p>  |  |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Nasal congestion</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Epistaxis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 73 (2.74%)</p> <p>2</p> <p>14 / 73 (19.18%)</p> <p>15</p> <p>6 / 73 (8.22%)</p> <p>7</p> <p>1 / 73 (1.37%)</p> <p>1</p> <p>6 / 73 (8.22%)</p> <p>6</p> | <p>10 / 152 (6.58%)</p> <p>13</p> <p>27 / 152 (17.76%)</p> <p>51</p> <p>9 / 152 (5.92%)</p> <p>9</p> <p>12 / 152 (7.89%)</p> <p>16</p> <p>9 / 152 (5.92%)</p> <p>10</p> |  |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pain in extremity</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>2 / 73 (2.74%)</p> <p>2</p> <p>3 / 73 (4.11%)</p> <p>3</p> <p>6 / 73 (8.22%)</p> <p>6</p>  | <p>8 / 152 (5.26%)</p> <p>11</p> <p>11 / 152 (7.24%)</p> <p>24</p> <p>15 / 152 (9.87%)</p> <p>25</p>  |  |

|  |                     |                        |  |
|--|---------------------|------------------------|--|
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 73 (2.74%)<br>2 | 11 / 152 (7.24%)<br>11 |  |
| Metabolism and nutrition disorders<br>Hypokalaemia<br>subjects affected / exposed<br>occurrences (all)               | 4 / 73 (5.48%)<br>5 | 3 / 152 (1.97%)<br>3   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 20 July 2015    | The protocol amendments include several key updates. Firstly, the eligibility criteria were refined to specify that participants must be children aged 12 to <18 years at the time of consent, with a note that an approved amended protocol will be implemented before enrolling each subsequent age group. In Section 2.2, the examples of Index VTE status were corrected from "progression, regression, or resolution" to "unchanged, regression, or resolution." Section 7.1 was updated to include targeted physical examinations for evidence of bleeding at Day 14, Day 42, and Day 84 (End of Treatment, EOT) visits, as well as when clinically indicated. Additionally, visits on Days 28 and 63 were added, which can be conducted either by telephone or on-site. Lastly, the statement regarding radiologic images was revised to include "Day 84 (EOT)" and "if not medically necessary," now reading: "Radiologic images that require sedation or radiation at the Day 42 or Day 84 (EOT) visits are not required and may be omitted, if not medically necessary." These updates ensure clarity and compliance with the amended guidelines.   |
| 01 March 2017   | The protocol amendments include several significant updates. Appendix 2 was added to provide the dose selection rationale for Amendment 3, detailing eliquis (apixaban) dose recommendations for subjects aged 2 to 18 years, both those who are $\geq 35$ kg and those who are <35 kg. Section 12, which covers the background and rationale for dose selection, was updated to include the revised eliquis (apixaban) doses for Age Groups 1 and 2 in Table 1. The follow-up period was changed from "30 $\pm$ 5 days post End of Treatment" to "35 $\pm$ 5 days post End of Treatment" to comply with current Pfizer and BMS SOPs. Inclusion criterion 1 was updated to allow for the enrollment of children aged 2 to 18 years at the time of consent, covering both age groups 1 and 2. Inclusion criterion 6 was corrected to ensure consistency across the protocol, requiring contraception use for at least 33 days (5 half-lives plus 30 days) after the last dose of the assigned treatment for women of childbearing potential. Additional instructions were added for subjects on eliquis (apixaban) treatment who required the medication beyond Day 84. Section 9.1 on Sample Size Determination was updated to specify that the study team, in conjunction with regulators, will evaluate exposure duration, imaging results, and other trial aspects to determine if the data from the subjects are sufficient to address the study objectives. Throughout the trial, the sponsor will monitor the number of subjects who do not complete 12 weeks of eliquis (apixaban) treatment and will determine if additional subjects need to be recruited to supplement the safety database. These updates ensure the protocol remains clear, consistent, and compliant with current guidelines. |
| 30 October 2017 | Appendix 3 was added to provide the dose selection rationale for Amendment 4, detailing dose recommendations for subjects aged $\geq 3$ months and weighing $\geq 6$ kg. The Schedule of Activities in Section 6.4 was updated to include a 6-week or 12-week Extension Phase for subjects continuing on eliquis (apixaban). A footnote "p" was added to clarify that sites should continue the mg/kg dosing regimen for subjects randomized and dosed using the eliquis (apixaban) oral solution when Protocol Amendment 3 was effective, as depicted in Table 1. Section 12, covering the background and rationale for dose selection, was updated to reflect both the mg/kg dosing under Protocol Amendment 3 for subjects already dosed and the fixed-dose body weight-tiered regimen for subjects randomized or switched to the 0.5 mg tablet under Protocol Amendment 4. Inclusion criterion 1 was updated to allow the enrollment of children aged 3 months to 18 years with a minimum weight of 6 kg at the time of consent. Inclusion criterion 6 was updated per the Portugal Competent Authority's request to include abstinence from heterosexual intercourse as acceptable contraception for women of childbearing potential. Neonates were defined throughout the protocol as $\geq 34$ weeks gestational or $\geq 37$ weeks post-conceptual but not more than 27 days of age.  |

|                   |   |
|-------------------|---|
| 31 August 2018    | The protocol amendments include adding language in Section 5 to specify that only Vitamin K Antagonist formulations are to be administered to pediatric subjects in Germany, per local regulations. Section 7.2 and Table 4 were added to provide an overview and summary of the maximum potential blood volume collected in pediatric subjects during the study, based on a regulatory request.  |
| 06 September 2019 | The protocol amendments include several key updates. Appendix 4 was added to provide the dose selection rationale for Amendment 6, detailing dose recommendations for age group 3 subjects aged $\geq 28$ days to 2 years and weighing $\geq 4$ kg. The Schedule of Activities was updated to allow SOC administration up to 14 days prior to randomization and to permit local labs to replace central labs to minimize blood volume collected in younger subjects. Section 12 was updated with PK data to inform updated dosing. Section 3 added the definition of the index event and specified that midpoint imaging for subjects aged 2 years is only required at the investigator's discretion, but an EOT image should be collected. Inclusion criterion 1 was updated to allow enrollment of children aged 28 days to 18 years with a minimum weight of 4 kg. Inclusion criterion 3 was updated to include children aged 2 years with the intent to treat for 6 to 12 weeks. Exclusion criterion 1 was updated to extend the unacceptable length of time for anticoagulation treatment for the index VTE prior to randomization from 7 to 14 days. Additional inclusion and exclusion criteria were added for safety and program consistency, including criteria for oral, nasogastric, or gastric feeding tolerance, exclusion of subjects using aggressive lifesaving therapies, and exclusion of subjects with certain medical conditions. Section 5 was updated to include a 0.1 mg eliquis (apixaban) formulation and limit SOC to heparin (UFH or LMWH) for subjects aged 2 years. Section 7.6 was added to include details on the adjudication of safety and efficacy endpoints. Section 8.5 was added to define medication errors for eliquis (apixaban). Section 9.1 updated the sample size determination from 150 to 250 with rationale. These updates ensure the protocol remains clear, consistent, and compliant with current guidelines. |
| 12 February 2020  | Appendix 5 was added to provide the dose selection rationale for Age Group 4 ( $\leq 27$ days of age) in Amendment 7, including dose recommendations for neonates. Section 12.4 updated Table 2 to include starting doses for neonates in both PK and post-PK cohorts and explained dosing adjustments when a subject reaches 28 days or older. Section 2.2 clarified that endpoints would include "other thrombotic events" as a component of the primary endpoint, given the prevalence of catheter-related thrombosis in neonates. This change was reflected throughout the protocol for consistency, and other thrombotic events were also added as a secondary endpoint. The description of PE was updated to include both symptomatic and asymptomatic cases. Inclusion criterion 1 was updated to define neonates and clarify that neonates could be enrolled if they achieved a minimum weight of 2.6 kg, with relevant updates made elsewhere in the protocol. Inclusion criterion 2 was updated to include central venous catheter-related thrombosis as an example of index VTE. Exclusion criterion 1 was updated to describe pretreatment SOC requirements for both PK and post-PK cohorts. Exclusion criterion 12 was updated to include allergies to other ingredients in the eliquis (apixaban) formulation or hypersensitivity to any components of the comparators. Section 6.2.4 added language for physical examination, allowing the investigator to contact the study sponsor to discuss a possible change in dosing regimen if there is a 20% change in weight for subjects aged 2 years or older. Section 6.4 clarified that the Extension Phase is only applicable to subjects in age groups 1 through 3.  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption   | Restart date |
|---------------|--|--------------|
| 23 March 2020 | Recruitment in the trial was temporarily paused for 3 weeks at all sites due to the impact of COVID-19 pandemic. | 04 May 2020  |

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Notes:

## **Limitations and caveats**

None reported