



Clinical trial results:

An Open-label, Randomised, Parallel-group, Multicentre, Observational Trial to Evaluate Safety and Efficacy of Edoxaban Tosylate in Children From 38 Weeks Gestational Age to Less Than 18 Years of Age With Cardiac Diseases At Risk of Thromboembolic Events

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2017-000475-90 |
| Trial protocol | GB HU DE ES AT FR PL HR IT |
| Global end of trial date | 03 December 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 18 June 2022 |
| First version publication date | 18 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | DU176b-C-U313 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03395639 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Daiichi Sankyo, Inc. |
| Sponsor organisation address | 211 Mount Airy Rd., Basking Ridge, United States, 07920 |
| Public contact | Clinical Trial Information Contact, Daiichi Sankyo Inc, +1 908-992-6400, CTRinfo@dsi.com |
| Scientific contact | Clinical Trial Information Contact, Daiichi Sankyo Inc, +1 908-992-6400, CTRinfo@dsi.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000788-PIP02-11 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 December 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 December 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the safety of edoxaban with the SOC in pediatric subjects with cardiac diseases at risk of thromboembolic complications who need primary or secondary anticoagulant prophylaxis with regard to the combination of major and clinically relevant non-major (CRNM) bleedings per International Society on Thrombosis and Haemostasis [ISTH] definition occurring on treatment (ie, during treatment or within 3 days of completing, interrupting or stopping study treatment during the first 3-month treatment period).

Protection of trial subjects:

The study protocol, amendments (if any), the informed consent form(s) (ICFs), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 15 February 2018 |
| 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 | Spain: 1 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Austria: 15 |
| Country: Number of subjects enrolled | Hungary: 7 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Egypt: 37 |
| Country: Number of subjects enrolled | India: 4 |
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Lebanon: 7 |
| Country: Number of subjects enrolled | United States: 34 |
| Country: Number of subjects enrolled | France: 18 |
| Country: Number of subjects enrolled | Croatia: 1 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Russian Federation: 3 |
| Country: Number of subjects enrolled | Turkey: 10 |

| | |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Ukraine: 6 |
| Worldwide total number of subjects | 168 |
| EEA total number of subjects | 52 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 16 |
| Children (2-11 years) | 108 |
| Adolescents (12-17 years) | 44 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 168 participants who met all inclusion criteria and no exclusion criteria were randomized to treatment; 167 participants received treatment and were included in the modified Intent to Treat and Safety Populations.

Pre-assignment

Screening details:

All subjects at the Screening Visit were assessed for international normalized ratio (INR) and activated partial thromboplastin time (aPTT) and evaluated at the local laboratory.

Period 1

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

Blinding implementation details:

Open label

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Edoxaban |

Arm description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Edoxaban |
| Investigational medicinal product code | |
| Other name | Lixiana, Savaysa |
| Pharmaceutical forms | Granules for oral suspension, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets (15- and/or 30-mg strength) or granules for oral suspension (60 mg, 6 mg/mL) were administered orally once a day, at the same time every day, with or without food. Tablets were to be swallowed with a glass of water.

| | |
|------------------|------------------------|
| Arm title | Standard of Care (SOC) |
|------------------|------------------------|

Arm description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Standard of Care (SOC) |
| Investigational medicinal product code | |
| Other name | Warfarin/heparin, Vitamin K antagonist |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Standard of care (SOC) was administered according to the clinical site's SOC treatment regimen.

| Number of subjects in period 1 | Edoxaban | Standard of Care (SOC) |
|--|----------|------------------------|
| Started | 110 | 58 |
| Completed | 106 | 55 |
| Not completed | 4 | 3 |
| Consent withdrawn by subject | 2 | 2 |
| Participant discontinued at Principal Investigator | - | 1 |
| Adverse event, non-fatal | 1 | - |
| Did not receive study drug | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Edoxaban |
|-----------------------|----------|

Reporting group description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

| | |
|-----------------------|------------------------|
| Reporting group title | Standard of Care (SOC) |
|-----------------------|------------------------|

Reporting group description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

| Reporting group values | Edoxaban | Standard of Care (SOC) | Total |
|--|----------|------------------------|-------|
| Number of subjects | 110 | 58 | 168 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 8 | 8 | 16 |
| Children (2-11 years) | 74 | 34 | 108 |
| Adolescents (12-17 years) | 28 | 16 | 44 |
| 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 | 7.7 | 7.3 | |
| standard deviation | ± 4.8 | ± 5.1 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 38 | 21 | 59 |
| Male | 72 | 37 | 109 |

End points

End points reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Edoxaban |
|-----------------------|----------|

Reporting group description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

| | |
|-----------------------|------------------------|
| Reporting group title | Standard of Care (SOC) |
|-----------------------|------------------------|

Reporting group description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | Edoxaban (Extension Period) |
|----------------------------|-----------------------------|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

Primary: Number of Participants With Adjudicated Bleeding Events Within the Main Treatment Period

| | |
|-----------------|--|
| End point title | Number of Participants With Adjudicated Bleeding Events Within the Main Treatment Period |
|-----------------|--|

End point description:

Adjudicated bleeding events included major and clinically-relevant non-major (CRNM) bleeding events per International Society on Thrombosis and Haemostasis (ISTH) definition occurring within the main treatment period. Based on modified ISTH recommendations, major bleeding is defined as a composite (ie, any) of the following: fatal bleeding; and/or symptomatic bleeding in a critical area or organ; and/or bleeding causing a decrease in hemoglobin level of >2 g/dL, or leading to transfusion of the equivalent of ≥2 units of whole blood or red cells. A CRNM bleed is an acute or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following: a hospital admission for bleeding, or a physician guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy. Minor bleeding is any other overt bleeding event that does not meet criteria for either major or CRNM bleeding

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

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

| End point values | Edoxaban | Standard of Care (SOC) | | |
|-------------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 58 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Major or CRNM bleeding events | 1 | 1 | | |
| Major bleeding events | 0 | 0 | | |

| | | | | |
|--|---|---|--|--|
| All bleeding events (Major, CRNM, minor) | 4 | 2 | | |
|--|---|---|--|--|

Statistical analyses

| | |
|---|------------------------------------|
| Statistical analysis title | Edoxaban vs Standard of Care (SOC) |
| Comparison groups | Edoxaban v Standard of Care (SOC) |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| Parameter estimate | Annualized rate difference |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.18 |
| upper limit | 0.12 |

Notes:

[1] - Difference in adjudicated major or CRNM bleeding rates were assessed.

| | |
|---|------------------------------------|
| Statistical analysis title | Edoxaban vs Standard of Care (SOC) |
| Comparison groups | Edoxaban v Standard of Care (SOC) |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Annualized rate difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |

Notes:

[2] - Difference in adjudicated major bleeding rates were assessed.

| | |
|---|------------------------------------|
| Statistical analysis title | Edoxaban vs Standard of Care (SOC) |
| Comparison groups | Edoxaban v Standard of Care (SOC) |
| Number of subjects included in analysis | 167 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| Parameter estimate | Annualized rate difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.24 |
| upper limit | 0.25 |

Notes:

[3] - Difference in all adjudicated bleeding (major, CRNM, minor) rates were assessed.

Secondary: Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways Within the Main Treatment Period

| | |
|-----------------|---|
| End point title | Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways Within the Main Treatment Period |
|-----------------|---|

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

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

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

| End point values | Edoxaban | Standard of Care (SOC) | | |
|--|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 58 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Thromboembolic event, Any Event | 0 | 1 | | |
| Deep vein thrombosis | 0 | 1 | | |
| Pulmonary embolism | 0 | 1 | | |
| Stroke | 0 | 0 | | |
| Systemic embolic event | 0 | 0 | | |
| Intracardiac thrombus | 0 | 0 | | |
| Myocardial infarction | 0 | 0 | | |
| Asymptomatic intracardiac thrombus-cardiac imaging | 0 | 0 | | |
| Death as a result of TE | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Thromboembolic Event Within the Main Treatment Period

| | |
|-----------------|--|
| End point title | Number of Participants Who Died as a Result of Thromboembolic Event Within the Main Treatment Period |
|-----------------|--|

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

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

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study

treatment was discontinued, whichever was earlier

| End point values | Edoxaban | Standard of Care (SOC) | | |
|-----------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 58 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Died as a result of TE | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) Within the Main Treatment Period

| | |
|-----------------|---|
| End point title | Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) Within the Main Treatment Period |
|-----------------|---|

End point description:

Death due to any cause (all-cause mortality) was assessed.

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

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

| End point values | Edoxaban | Standard of Care (SOC) | | |
|-----------------------------|-----------------|------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 58 | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| All-cause mortality | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Bleeding Events During the Extension Period

| | |
|-----------------|---|
| End point title | Number of Participants With Adjudicated Bleeding Events During the Extension Period |
|-----------------|---|

End point description:

Adjudicated bleeding events included major and clinically-relevant non-major (CRNM) bleeding events

per International Society on Thrombosis and Haemostasis (ISTH) definition occurring within the main treatment period. Based on modified ISTH recommendations, major bleeding is defined as a composite (ie, any) of the following: fatal bleeding; and/or symptomatic bleeding in a critical area or organ; and/or bleeding causing a decrease in hemoglobin level of >2 g/dL, or leading to transfusion of the equivalent of ≥ 2 units of whole blood or red cells. A CRNM bleed is an acute or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following: a hospital admission for bleeding, or a physician guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy. Minor bleeding is any other overt bleeding event that does not meet criteria for either major or CRNM bl

| | |
|-------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| End of Month 3 up to Month 13 | |

| End point values | Edoxaban (Extension Period) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 144 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Major or CRNM bleeding events | 1 | | | |
| Major bleeding events | 1 | | | |
| All bleeding events (Major, CRNM, minor) | 4 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways During the Extension Period

| | |
|-------------------------------|--|
| End point title | Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways During the Extension Period |
| End point description: | |
| | Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI). |
| End point type | Secondary |
| End point timeframe: | |
| End of Month 3 up to Month 13 | |

| End point values | Edoxaban (Extension Period) | | | |
|--|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 144 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| Thromboembolic event, Any Event | 4 | | | |
| Deep vein thrombosis | 0 | | | |
| Pulmonary embolism | 0 | | | |
| Stroke | 2 | | | |
| Systemic embolic event | 0 | | | |
| Intracardiac thrombus | 0 | | | |
| Myocardial infarction | 2 | | | |
| Asymptomatic intracardiac thrombus- cardiac imaging | 0 | | | |
| Death as a result of TE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Thromboembolic Event During the Extension Period

| | |
|--|--|
| End point title | Number of Participants Who Died as a Result of Thromboembolic Event During the Extension Period |
| End point description: Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI). | |
| End point type | Secondary |
| End point timeframe: End of Month 3 up to Month 13 | |

| End point values | Edoxaban (Extension Period) | | | |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 144 | | | |
| Units: participant | | | | |
| number (not applicable) | | | | |
| Died as a result of TE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) During the Extension Period

| | |
|-----------------|--|
| End point title | Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) During the Extension Period |
|-----------------|--|

End point description:

Death due to any cause (all-cause mortality) was assessed.

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

End point timeframe:

End of Month 3 up to Month 13

| End point values | Edoxaban (Extension Period) | | | |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 144 | | | |
| Units: participants | | | | |
| number (not applicable) | | | | |
| All-cause mortality | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the time of signing the informed consent form up to 30 days after the last dose of study drug, up to 13 months.

Adverse event reporting additional description:

Adverse events (AEs) were defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Edoxaban |
|-----------------------|----------|

Reporting group description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

| | |
|-----------------------|------------------------|
| Reporting group title | Standard of Care (SOC) |
|-----------------------|------------------------|

Reporting group description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

| Serious adverse events | Edoxaban | Standard of Care (SOC) | |
|--|-------------------|------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 109 (21.10%) | 3 / 58 (5.17%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Pyrexia | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery stenosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (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 / 109 (0.00%) | 1 / 58 (1.72%) | |
| 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 | 2 / 109 (1.83%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Pulmonary arterial pressure increased | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Skin laceration | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue injury | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Traumatic liver injury | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Coarctation of the aorta | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 109 (1.83%) | 1 / 58 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Coronary artery thrombosis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebellar infarction | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|-----------------|----------------|--|
| Haemolysis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune thrombocytopenia | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucous stools | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 1 / 58 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Petechiae | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess limb | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 109 (0.92%) | 0 / 58 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 109 (0.00%) | 1 / 58 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Edoxaban | Standard of Care (SOC) | |
|---|-------------------|------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 48 / 109 (44.04%) | 12 / 58 (20.69%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 109 (11.93%) | 2 / 58 (3.45%) | |
| occurrences (all) | 19 | 2 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 17 / 109 (15.60%) | 1 / 58 (1.72%) | |
| occurrences (all) | 19 | 1 | |
| Gastrointestinal disorders | | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 109 (6.42%) | 1 / 58 (1.72%) | |
| occurrences (all) | 11 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 14 / 109 (12.84%) | 2 / 58 (3.45%) | |
| occurrences (all) | 18 | 2 | |
| Epistaxis | | | |

| | | | |
|---|-----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 8 / 109 (7.34%) 14 | 2 / 58 (3.45%) 2 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 8 / 109 (7.34%) 10 | 1 / 58 (1.72%) 1 | |
| Infections and infestations | | | |
| Influenza subjects affected / exposed occurrences (all) | 6 / 109 (5.50%) 6 | 0 / 58 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 8 / 109 (7.34%) 8 | 3 / 58 (5.17%) 3 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 9 / 109 (8.26%) 16 | 2 / 58 (3.45%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 16 October 2017 | Risk/Benefit section was added, eligibility criteria were updated, drug formulation and administration procedures were clarified, study assessment procedures were clarified, and vendors were updated. |
| 27 March 2018 | Timeframe for primary/secondary objectives was updated and the secondary objectives, primary/secondary endpoints, statistical analysis, drug administration, and study design were revised |
| 03 June 2019 | Drug administration and study procedures were clarified and eligibility criteria were updated. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported