



## Clinical trial results:

### A Randomized, Open-Label, Parallel-Group, Multi-Center Study of Adding Edoxaban or Clopidogrel to Aspirin to Maintain Patency in Subjects With Peripheral Arterial Disease Following Femoropopliteal Endovascular Intervention - Edoxaban in Peripheral Arterial Disease (ePAD)

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-003009-88   |
| Trial protocol           | DE BE NL AT      |
| Global end of trial date | 03 December 2014 |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1             |
| This version publication date  | 18 August 2016 |
| First version publication date | 18 August 2016 |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | DU176b-E-U210 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01802775 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Daiichi Sankyo Pharma Development   |
| Sponsor organisation address | 399 THORNALL STREET, Edison, New Jersey, United States, 08837                               |
| Public contact               | Clinical Trial Information, Daiichi Sankyo Development Ltd, +44 1753482800, info@dsd-eu.com |
| Scientific contact           | Clinical Trial Information, Daiichi Sankyo Development Ltd, +44 1753482800, info@dsd-eu.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 03 December 2014 |
| Is this the analysis of the primary completion data? | No               |

|                                  |                  |
|----------------------------------|------------------|
| Global end of trial reached?     | Yes              |
| Global end of trial date         | 03 December 2014 |
| Was the trial ended prematurely? | No               |

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate clinically relevant bleeding (that is, major or clinically relevant non-major bleeding) occurring during treatment or within 3 days of interrupting or stopping study drug and to evaluate re-stenosis/re-occlusion at the treated segment(s) measured at 1, 3 and 6 months after randomization using color coded duplex ultrasonography scanning (DUS).

Protection of trial subjects:

The safety assessments included clinical laboratory tests, Physical examination, vital signs and ECG variables. Adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 06 February 2013 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 3 Months         |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 89 |
| Country: Number of subjects enrolled | Switzerland: 25   |
| Country: Number of subjects enrolled | Israel: 12        |
| Country: Number of subjects enrolled | Netherlands: 13   |
| Country: Number of subjects enrolled | Austria: 28       |
| Country: Number of subjects enrolled | Belgium: 15       |
| Country: Number of subjects enrolled | Germany: 21       |
| Worldwide total number of subjects   | 203               |
| EEA total number of subjects         | 77                |

Notes:

### Subjects enrolled per age group

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

|  |     |
|--|-----|
| Infants and toddlers (28 days-23 months) | 0   |
| Children (2-11 years)                    | 0   |
| Adolescents (12-17 years)                | 0   |
| Adults (18-64 years)                     | 63  |
| From 65 to 84 years                      | 133 |
| 85 years and over                        | 7   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 275 subjects were screened, of these 203 subjects were randomized into the study, with 101 subjects in the edoxaban group and 102 subjects in the clopidogrel group.

### Period 1

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

### Arms

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

Arm description:

Subjects administered with a loading dose of clopidogrel 300 milligram (mg) (four 75-mg tablets) as first dose within 4 hours of hemostasis followed by 75 mg once daily (QD) (one 75 mg tablet) orally for a total of approximately 3 months on a background of aspirin 100 mg enteric coated tablets QD.

|  |                   |
|--|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Clopidogrel       |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Tablet            |
| Routes of administration               | Oral use          |

Dosage and administration details:

Subjects administered with a loading dose of clopidogrel 300 milligram (mg) (four 75-mg tablets) as first dose within 4 hours of hemostasis followed by 75 mg once daily (QD) (one 75 mg tablet) orally for a total of approximately 3 months.

|  |          |
|--|----------|
| Investigational medicinal product name | Aspirin  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects administered with aspirin 100 mg enteric coated tablets QD orally as background treatment along with Clopidogrel for 3 months.

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

Arm description:

Subjects administered with edoxaban 60 mg once daily (two 30 mg tablets) for approximately 3 months starting with the first dose given within 4 hours of hemostasis on a background of aspirin 100 mg tablets QD.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Aspirin      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Subjects administered with aspirin 100 mg enteric coated tablets QD orally as background treatment

along with Edoxaban for 3 months.

|  |          |
|--|----------|
| Investigational medicinal product name | Edoxaban |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects administered with edoxaban 60 mg once daily (two 30 mg tablets) for approximately 3 months.

| <b>Number of subjects in period 1</b> | Clopidogrel | Edoxaban |
|---------------------------------------|-------------|----------|
| Started                               | 102         | 101      |
| Completed                             | 96          | 89       |
| Not completed                         | 6           | 12       |
| Consent withdrawn by subject          | 3           | 5        |
| Physician decision                    | 1           | -        |
| Adverse event, non-fatal              | 1           | 1        |
| Death                                 | -           | 3        |
| Other                                 | -           | 1        |
| Lost to follow-up                     | 1           | 2        |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Clopidogrel |
|-----------------------|-------------|

Reporting group description:

Subjects administered with a loading dose of clopidogrel 300 milligram (mg) (four 75-mg tablets) as first dose within 4 hours of hemostasis followed by 75 mg once daily (QD) (one 75 mg tablet) orally for a total of approximately 3 months on a background of aspirin 100 mg enteric coated tablets QD.

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

Reporting group description:

Subjects administered with edoxaban 60 mg once daily (two 30 mg tablets) for approximately 3 months starting with the first dose given within 4 hours of hemostasis on a background of aspirin 100 mg tablets QD.

| Reporting group values | Clopidogrel | Edoxaban | Total |
|------------------------|-------------|----------|-------|
| Number of subjects     | 102         | 101      | 203   |
| Age categorical        |             |          |       |
| Units: Subjects        |             |          |       |
| Adults (18-64 years)   | 33          | 30       | 63    |
| From 65-84 years       | 68          | 65       | 133   |
| 85 years and over      | 1           | 6        | 7     |
| Age continuous         |             |          |       |
| Units: years           |             |          |       |
| arithmetic mean        | 66.7        | 68       |       |
| standard deviation     | ± 8.55      | ± 10.36  | -     |
| Gender categorical     |             |          |       |
| Units: Subjects        |             |          |       |
| Female                 | 24          | 34       | 58    |
| Male                   | 78          | 67       | 145   |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Clopidogrel |
| Reporting group description:<br>Subjects administered with a loading dose of clopidogrel 300 milligram (mg) (four 75-mg tablets) as first dose within 4 hours of hemostasis followed by 75 mg once daily (QD) (one 75 mg tablet) orally for a total of approximately 3 months on a background of aspirin 100 mg enteric coated tablets QD. |             |
| Reporting group title  | Edoxaban    |
| Reporting group description:<br>Subjects administered with edoxaban 60 mg once daily (two 30 mg tablets) for approximately 3 months starting with the first dose given within 4 hours of hemostasis on a background of aspirin 100 mg tablets QD.  |             |

### Primary: Percentage of Subjects with Re-stenosis/re-occlusion

|   |  |
|---|--|
| End point title   | Percentage of Subjects with Re-stenosis/re-occlusion |
| End point description:<br>Percentage of subjects with re-stenosis/re-occlusion, defined as Duplex ultrasonography scanning (DUS) Peak systolic velocity ratio (PSVR) greater than or equal to 2.4, at the treated segment(s) at 1, 3, and 6 months, as read at VasCore. Modified Intent-to-Treat (mITT) Set 2 population included all randomized subjects who received at least 1 dose of the study drug and had at least 1 post-dose duplex scanning. Here 'n' indicates the number of subjects analysed at specific time point. |  |
| End point type  | Primary  |
| End point timeframe:<br>Months 1, 3 and 6   |  |

| End point values              | Clopidogrel     | Edoxaban        |  |  |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type            | Reporting group | Reporting group |  |  |
| Number of subjects analysed   | 99              | 96              |  |  |
| Units: percentage of subjects |                 |                 |  |  |
| number (not applicable)       |                 |                 |  |  |
| Month 1 (n = 88, 90)          | 5.7             | 10              |  |  |
| Month 3 (n = 94, 93)          | 13.8            | 23.7            |  |  |
| Month 6 (n = 95, 94)          | 34.7            | 30.9            |  |  |

### Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Statistical analyses_Month 1 |
| Comparison groups          | Edoxaban v Clopidogrel       |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 195                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | 4.3                  |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -3.5                 |
| upper limit                             | 12.2                 |

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Statistical analyses_Month 3 |
| Comparison groups                       | Edoxaban v Clopidogrel       |
| Number of subjects included in analysis | 195                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| Parameter estimate                      | Risk difference (RD)         |
| Point estimate                          | 9.8                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -1.3                         |
| upper limit                             | 20.9                         |

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Statistical analyses_Month 6 |
| Comparison groups                       | Edoxaban v Clopidogrel       |
| Number of subjects included in analysis | 195                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| Parameter estimate                      | Risk difference (RD)         |
| Point estimate                          | -3.9                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -17.3                        |
| upper limit                             | 9.5                          |

**Primary: Percentage of subjects with Adjudicated Bleeding Events in the On-Treatment Period Based on International Society of Thrombosis and Haemostasis (ISTH)**

|                 |  |
|-----------------|--|
| End point title | Percentage of subjects with Adjudicated Bleeding Events in the On-Treatment Period Based on International Society of Thrombosis and Haemostasis (ISTH) |
|-----------------|--|

End point description:

Clinically relevant bleeding Major or Clinically relevant non-major (CRNM) Bleeding, Major Bleeding, Life-



threatening Bleeding, CRNM Bleeding, Minor Bleeding and Any Bleeding was assessed. Safety Analysis Set population included all subjects who received at least 1 dose of study drug.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| up to 3 months       |         |

| End point values                                    | Clopidogrel         | Edoxaban          |  |  |
|---|---------------------|-------------------|--|--|
| Subject group type                                  | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed                         | 101                 | 100               |  |  |
| Units: percentage of subjects                       |                     |                   |  |  |
| number (confidence interval 95%)                    |                     |                   |  |  |
| Including Access Site Bleeding (IASB): Any Bleeding | 27.7 (19.3 to 37.5) | 30 (21.2 to 40)   |  |  |
| IASB: Major or CRNM Bleeding                        | 7.9 (3.5 to 15)     | 11 (5.6 to 18.8)  |  |  |
| IASB : Major Bleeding                               | 5 (1.6 to 11.2)     | 1 (0 to 5.4)      |  |  |
| IASB : Life-threatening Bleeding                    | 2 (0.2 to 7)        | 1 (0 to 5.4)      |  |  |
| IASB : CRNM Bleeding                                | 4 (1.1 to 9.8)      | 10 (4.9 to 17.6)  |  |  |
| IASB : Minor Bleeding                               | 20.8 (13.4 to 30)   | 20 (12.7 to 29.2) |  |  |
| Excluding Access Site Bleeding (EASB) Any Bleeding  | 22.8 (15 to 32.2)   | 25 (16.9 to 34.7) |  |  |
| EASB : Major or CRNM Bleeding                       | 5.9 (2.2 to 12.5)   | 6 (2.2 to 12.6)   |  |  |
| EASB : Major Bleeding                               | 4 (1.1 to 9.8)      | 1 (0 to 5.4)      |  |  |
| EASB : Life-threatening Bleeding                    | 2 (0.2 to 7)        | 1 (0 to 5.4)      |  |  |
| EASB : CRNM Bleeding                                | 3 (0.6 to 8.4)      | 5 (1.6 to 11.3)   |  |  |
| EASB : Minor Bleeding                               | 17.8 (10.9 to 26.7) | 19 (11.8 to 28.1) |  |  |

## Statistical analyses

|   |  |
|---|--|
| Statistical analysis title  | Statistical analyses_ IASB: Major or CRNM Bleeding |
| Statistical analysis description:   |  |
| Statistical analysis was compared for Including Access Site Bleeding (IASB) Major or Clinically relevant non-major (CRNM) Bleeding. |  |
| Comparison groups   | Edoxaban v Clopidogrel                             |
| Number of subjects included in analysis   | 201  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | superiority  |
| Parameter estimate  | Risk difference (RD)                               |
| Point estimate  | 3.1  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | -5   |
| upper limit   | 11.2   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical analyses_IASB: Major Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                    |
| Number of subjects included in analysis | 201                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | superiority                               |
| Parameter estimate                      | Risk difference (RD)                      |
| Point estimate                          | -4  |
| Confidence interval                     |   |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -8.6                                      |
| upper limit                             | 0.7                                       |

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | SA_IASB: Life-threatening Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel             |
| Number of subjects included in analysis | 201                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| Parameter estimate                      | Risk difference (RD)               |
| Point estimate                          | -1                                 |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -4.3                               |
| upper limit                             | 2.4                                |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_IASB: CRNM Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                   |
| Number of subjects included in analysis | 201                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| Parameter estimate                      | Risk difference (RD)                     |
| Point estimate                          | 6  |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1                                       |
| upper limit                             | 13                                       |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Statistical analyses_IASB: Minor Bleeding |
|-----------------------------------|---|

|   |                        |
|---|------------------------|
| Comparison groups                       | Edoxaban v Clopidogrel |
| Number of subjects included in analysis | 201                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| Parameter estimate                      | Risk difference (RD)   |
| Point estimate                          | -0.8                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -11.9                  |
| upper limit                             | 10.3                   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical analyses_IASB: Any Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                  |
| Number of subjects included in analysis | 201                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| Parameter estimate                      | Risk difference (RD)                    |
| Point estimate                          | 2.3                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -10.2                                   |
| upper limit                             | 14.8                                    |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ EASB: Major or CRNM Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                             |
| Number of subjects included in analysis | 201  |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | superiority  |
| Parameter estimate                      | Risk difference (RD)                               |
| Point estimate                          | 0.1  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -6.5   |
| upper limit                             | 6.6  |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Statistical analyses_EASB: Major Bleeding |
| Comparison groups                 | Edoxaban v Clopidogrel                    |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 201                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | -3                   |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -7.2                 |
| upper limit                             | 1.3                  |

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | SA_EASB: Life-threatening Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel             |
| Number of subjects included in analysis | 201                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| Parameter estimate                      | Risk difference (RD)               |
| Point estimate                          | -1                                 |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -4.3                               |
| upper limit                             | 2.4                                |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_EASB: CRNM Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                   |
| Number of subjects included in analysis | 201                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| Parameter estimate                      | Risk difference (RD)                     |
| Point estimate                          | 2  |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.4                                     |
| upper limit                             | 7.4                                      |

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Statistical analyses_EASB: Minor Bleeding |
| Comparison groups                 | Edoxaban v Clopidogrel                    |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 201                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | 1.2                  |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -9.5                 |
| upper limit                             | 11.9                 |

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Statistical analyses_EASB: Any Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                  |
| Number of subjects included in analysis | 201                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | superiority                             |
| Parameter estimate                      | Risk difference (RD)                    |
| Point estimate                          | 2.2                                     |
| Confidence interval                     |   |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -9.6                                    |
| upper limit                             | 14                                      |

### **Primary: Percentage of Subjects with Adjudicated Bleeding Events in the On-Treatment Period Based on Thrombolysis in Myocardial Infarction (TIMI)**

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with Adjudicated Bleeding Events in the On-Treatment Period Based on Thrombolysis in Myocardial Infarction (TIMI) |
|-----------------|--|

End point description:

Clinically relevant bleeding Major or Clinically relevant non-major (CRNM) Bleeding, Major Bleeding, Life-threatening Bleeding, CRNM Bleeding, Minor Bleeding and Any Bleeding was assessed. Safety Analysis Set population included all subjects who received at least 1 dose of study drug.

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

End point timeframe:

Up to 3 months

|   |                   |                 |  |  |
|---|-------------------|-----------------|--|--|
| <b>End point values</b>                           | Clopidogrel       | Edoxaban        |  |  |
| Subject group type                                | Reporting group   | Reporting group |  |  |
| Number of subjects analysed                       | 101               | 100             |  |  |
| Units: percentage of subjects                     |                   |                 |  |  |
| number (confidence interval 95%)                  |                   |                 |  |  |
| Including Access Site Bleeding(IASB):Any Bleeding | 8.9 (4.2 to 16.2) | 5 (1.6 to 11.3) |  |  |
| IASB : Major Bleeding                             | 2 (0.2 to 7)      | 0 (0 to 0)      |  |  |

|  |                   |                |  |  |
|--|-------------------|----------------|--|--|
| IASB : Life-threatening Bleeding                   | 2 (0.2 to 7)      | 0 (0 to 0)     |  |  |
| IASB : Minor Bleeding                              | 2 (0.2 to 7)      | 3 (0.6 to 8.5) |  |  |
| IASB : Minimal Bleeding                            | 5 (1.6 to 11.2)   | 2 (0.2 to 7)   |  |  |
| Excluding Access Site Bleeding (EASB):Any Bleeding | 6.9 (2.8 to 13.8) | 2 (0.2 to 7)   |  |  |
| EASB : Major Bleeding                              | 2 (0.2 to 7)      | 0 (0 to 0)     |  |  |
| EASB : Life-threatening Bleeding                   | 2 (0.2 to 7)      | 0 (0 to 0)     |  |  |
| EASB : Minor Bleeding                              | 1 (0 to 5.4)      | 2 (0.2 to 7)   |  |  |
| EASB : Minimal Bleeding                            | 4 (1.1 to 9.8)    | 0 (0 to 0)     |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ IASB: Major Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                     |
| Number of subjects included in analysis | 201  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| Parameter estimate                      | Risk difference (RD)                       |
| Point estimate                          | -2   |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -4.7                                       |
| upper limit                             | 0.7  |

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | SA_ IASB:Life-threatening Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel             |
| Number of subjects included in analysis | 201                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority                        |
| Parameter estimate                      | Risk difference (RD)               |
| Point estimate                          | -2                                 |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | -4.7                               |
| upper limit                             | 0.7                                |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical analyses_ IASB: Minor Bleeding |
| Comparison groups                 | Edoxaban v Clopidogrel                     |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 201                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | 1                    |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -3.3                 |
| upper limit                             | 5.3                  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ IASB: Minimal Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                       |
| Number of subjects included in analysis | 201  |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | superiority                                  |
| Parameter estimate                      | Risk difference (RD)                         |
| Point estimate                          | -3   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided                                      |
| lower limit                             | -8   |
| upper limit                             | 2.1  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ IASB: Any Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                   |
| Number of subjects included in analysis | 201                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| Parameter estimate                      | Risk difference (RD)                     |
| Point estimate                          | -3.9                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -10.9                                    |
| upper limit                             | 3.1                                      |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical analyses_ EASB: Major Bleeding |
| Comparison groups                 | Edoxaban v Clopidogrel                     |

|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 201                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | -2                   |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -4.7                 |
| upper limit                             | 0.7                  |

|   |                                  |
|---|----------------------------------|
| <b>Statistical analysis title</b>       | SA_ EASB: Life-threatening Bleed |
| Comparison groups                       | Edoxaban v Clopidogrel           |
| Number of subjects included in analysis | 201                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| Parameter estimate                      | Risk difference (RD)             |
| Point estimate                          | -2                               |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -4.7                             |
| upper limit                             | 0.7                              |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ EASB: Minor Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                     |
| Number of subjects included in analysis | 201  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| Parameter estimate                      | Risk difference (RD)                       |
| Point estimate                          | 1  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -2.3                                       |
| upper limit                             | 4.4  |

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical analyses_ EASB: Minimal Bleeding |
| Comparison groups                 | Edoxaban v Clopidogrel                       |



|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 201                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| Parameter estimate                      | Risk difference (RD) |
| Point estimate                          | -4                   |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | -7.8                 |
| upper limit                             | -0.2                 |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Statistical analyses_ EASB: Any Bleeding |
| Comparison groups                       | Edoxaban v Clopidogrel                   |
| Number of subjects included in analysis | 201                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| Parameter estimate                      | Risk difference (RD)                     |
| Point estimate                          | -4.9                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -10.6                                    |
| upper limit                             | 0.7                                      |

### Secondary: Change in Peak Systolic Velocity Ratio (PSVR) in the Treated Segment(s) at 3 and 6 Months Compared to 1 Month

|                        |  |
|------------------------|--|
| End point title        | Change in Peak Systolic Velocity Ratio (PSVR) in the Treated Segment(s) at 3 and 6 Months Compared to 1 Month  |
| End point description: | Change in Peak Systolic Velocity Ratio was evaluated. Modified Intent-to-Treat Set 1 population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point. |
| End point type         | Secondary  |
| End point timeframe:   | Month 1, 3 and 6   |

| End point values                           | Clopidogrel     | Edoxaban        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                         | Reporting group | Reporting group |  |  |
| Number of subjects analysed                | 101             | 100             |  |  |
| Units: ratio                               |                 |                 |  |  |
| arithmetic mean (standard deviation)       |                 |                 |  |  |
| Month 1 (n= 72, 65)                        | 1.47 (± 0.721)  | 1.61 (± 1.175)  |  |  |
| Change from Month 1 to Month 3 (n= 59, 50) | 0.23 (± 0.683)  | 0.36 (± 1.074)  |  |  |

|  |                     |                   |  |  |
|--|---------------------|-------------------|--|--|
| Change from Month 1 to Month 6 (n= 49, 42) | 0.81 ( $\pm$ 1.159) | 0.9 ( $\pm$ 1.37) |  |  |
|--|---------------------|-------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Ankle-brachial index (ABI) at 3 and 6 months compared to 1 month

|  |  |
|--|--|
| End point title  | Change in Ankle-brachial index (ABI) at 3 and 6 months compared to 1 month |
| End point description:<br>Ratio between the systolic pressure measured at the ankle and the systolic pressure measured in the arm as follows: Ankle: The systolic pressure will be measured in the index limb at the arteria dorsalis pedis and/or the arteria tibialis posterior. If both pressures are measured, the highest pressures will be used for the ABI calculation. Brachial: The systolic pressure will be measured in both arms, and the highest of both pressures will be used for the ABI calculation. Here 'n' indicates the number of subjects analysed at specific time point. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline, Month 1, 3 and 6   |  |

| End point values                           | Clopidogrel          | Edoxaban             |  |  |
|--|----------------------|----------------------|--|--|
| Subject group type                         | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed                | 101                  | 100                  |  |  |
| Units: ratio                               |                      |                      |  |  |
| arithmetic mean (standard deviation)       |                      |                      |  |  |
| Baseline (n= 100, 93)                      | 0.69 ( $\pm$ 0.265)  | 0.67 ( $\pm$ 0.279)  |  |  |
| Month 1 (n= 93, 93)                        | 0.97 ( $\pm$ 0.188)  | 0.93 ( $\pm$ 0.189)  |  |  |
| Change from Month 1 to Month 3 (n= 88, 84) | -0.05 ( $\pm$ 0.16)  | -0.03 ( $\pm$ 0.148) |  |  |
| Change from Month 1 to Month 6 (n= 83, 73) | -0.06 ( $\pm$ 0.213) | -0.03 ( $\pm$ 0.32)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects in Rutherford stage at 1, 3, and 6 months

|  |  |
|--|--|
| End point title  | Number of Subjects in Rutherford stage at 1, 3, and 6 months |
| End point description:<br>Modified Intent-to-Treat Set 1 population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point. |  |
| End point type   | Secondary  |

End point timeframe:

Months 1, 3 and 6

| <b>End point values</b>                               | Clopidogrel     | Edoxaban        |  |  |
|---|-----------------|-----------------|--|--|
| Subject group type                                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed                           | 101             | 100             |  |  |
| Units: subjects                                       |                 |                 |  |  |
| number (not applicable)                               |                 |                 |  |  |
| Month 1 (n=95, 97): Stage 0 (Asymptomatic)            | 59              | 51              |  |  |
| Month 1 (n=95, 97): Stage 1 (Mild Claudication)       | 24              | 23              |  |  |
| Month 1 (n=95, 97): Stage 2 (Moderate Claudication)   | 6               | 10              |  |  |
| Month 1 (n=95, 97): Stage 3 (Severe Claudication)     | 1               | 7               |  |  |
| Month 1 (n=95, 97): Stage 4 (Ischemic rest pain)      | 1               | 3               |  |  |
| Month 1 (n=95, 97): Stage 5 (Minor tissue loss)       | 4               | 3               |  |  |
| Month 1 (n=95, 97): Stage 6 (Ulceration or gangrene)  | 0               | 0               |  |  |
| Month 3 (n= 92, 88): Stage 0 (Asymptomatic)           | 62              | 55              |  |  |
| Month 3 (n= 92, 88): Stage 1 (Mild Claudication)      | 14              | 16              |  |  |
| Month 3 (n= 92, 88): Stage 2 (Moderate Claudication)  | 11              | 9               |  |  |
| Month 3 (n= 92, 88): Stage 3 (Severe Claudication)    | 2               | 5               |  |  |
| Month 3 (n= 92, 88): Stage 4 (Ischemic rest pain)     | 0               | 1               |  |  |
| Month 3 (n= 92, 88): Stage 5 (Minor tissue loss)      | 2               | 2               |  |  |
| Month 3 (n= 92, 88): Stage 6 (Ulceration or gangrene) | 1               | 0               |  |  |
| Month 6 (n= 85, 78): Stage 0 (Asymptomatic)           | 48              | 40              |  |  |
| Month 6 (n= 85, 78): Stage 1 (Mild Claudication)      | 19              | 14              |  |  |
| Month 6 (n= 85, 78): Stage 2 (Moderate Claudication)  | 10              | 13              |  |  |
| Month 6 (n= 85, 78): Stage 3 (Severe Claudication)    | 6               | 10              |  |  |
| Month 6 (n= 85, 78): Stage 4 (Ischemic rest pain)     | 1               | 1               |  |  |
| Month 6 (n= 85, 78): Stage 5 (Minor tissue loss)      | 1               | 0               |  |  |
| Month 6 (n= 85, 78): Stage 6 (Ulceration or gangrene) | 0               | 0               |  |  |

## Statistical analyses

**Secondary: Number of Subjects with Targeted Clinical Events Adjudicated by Clinical Events Committee**

|  |   |
|--|---|
| End point title  | Number of Subjects with Targeted Clinical Events Adjudicated by Clinical Events Committee |
| End point description:   |   |
| Targeted Clinical Events included Symptomatic Acute Thrombosis Event, Target Lesion Revascularization Event, Amputation, Major adverse cardiovascular events (MACEs) - Non-Fatal myocardial Infarction (MI), Non-Fatal Stroke, CV-Death and Systemic Embolism Event. Modified Intent-to-Treat Set 1 population included all subjects who received at least 1 dose of study drug. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Up to 6 months   |   |

| End point values                                 | Clopidogrel     | Edoxaban        |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                               | Reporting group | Reporting group |  |  |
| Number of subjects analysed                      | 101             | 100             |  |  |
| Units: subjects                                  |                 |                 |  |  |
| number (not applicable)                          |                 |                 |  |  |
| Symptomatic Acute Thrombosis Event               | 5               | 7               |  |  |
| Target Lesion Revascularization Event            | 10              | 11              |  |  |
| Amputation                                       | 4               | 1               |  |  |
| MACEs - Non-Fatal MI, Non-Fatal Stroke, CV-Death | 1               | 3               |  |  |
| Systemic Embolism Event : Fatal                  | 0               | 0               |  |  |
| Systemic Embolism Event : Non-fatal              | 0               | 0               |  |  |
| Myocardial Infarction (MI) event                 | 1               | 2               |  |  |
| Death  | 0               | 3               |  |  |

**Statistical analyses**

|   |   |
|---|---|
| Statistical analysis title              | Statistical analyses_Symptomatic Acute Thrombosis |
| Comparison groups                       | Edoxaban v Clopidogrel                            |
| Number of subjects included in analysis | 201   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | superiority                                       |
| Parameter estimate                      | Relative Risk                                     |
| Point estimate                          | 1.41  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.46  |
| upper limit                             | 4.31  |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | SA_Target Lesion Revascularization Event |
| Comparison groups                       | Edoxaban v Clopidogrel                   |
| Number of subjects included in analysis | 201                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| Parameter estimate                      | Relative Risk                            |
| Point estimate                          | 1.11                                     |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 0.49                                     |
| upper limit                             | 2.5                                      |

|   |                        |
|---|------------------------|
| <b>Statistical analysis title</b>       | SA_Amputation          |
| Comparison groups                       | Edoxaban v Clopidogrel |
| Number of subjects included in analysis | 201                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| Parameter estimate                      | Relative Risk          |
| Point estimate                          | 0.25                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.03                   |
| upper limit                             | 2.22                   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | SA_Major Adverse Cardiovascular Events |
| Comparison groups                       | Edoxaban v Clopidogrel                 |
| Number of subjects included in analysis | 201                                    |
| Analysis specification                  | Pre-specified                          |
| Analysis type                           | superiority                            |
| Parameter estimate                      | Relative Risk                          |
| Point estimate                          | 3.03                                   |
| Confidence interval                     |  |
| level                                   | 95 %                                   |
| sides                                   | 2-sided                                |
| lower limit                             | 0.32                                   |
| upper limit                             | 28.64                                  |

---

**Secondary: Number of Subjects with All-Cause Mortality Events During the Overall Study Period Adjudicated by Clinical Events Committee**

|                 |   |
|-----------------|---|
| End point title | Number of Subjects with All-Cause Mortality Events During the Overall Study Period Adjudicated by Clinical Events Committee |
|-----------------|---|

End point description:

Mortality was evaluated. Modified Intent-to-Treat Set 1 population included all subjects who received at least 1 dose of study drug.

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

End point timeframe:

up to 7 weeks after last dose administration

| End point values            | Clopidogrel     | Edoxaban        |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 101             | 100             |  |  |
| Units: subjects             |                 |                 |  |  |
| number (not applicable)     | 0               | 3               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma concentrations of edoxaban (DU-176) and its metabolite D21-2393

|                 |   |
|-----------------|---|
| End point title | Plasma concentrations of edoxaban (DU-176) and its metabolite D21-2393 <sup>[1]</sup> |
|-----------------|---|

End point description:

Safety Analysis Set population included all subjects who received at least 1 dose of edoxaban. Here 'n' indicates the number of subjects analysed at specific time point.

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

End point timeframe:

Day 30 and Day 90

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Plasma concentration for Clopidogrel was not evaluated.

| End point values                     | Edoxaban             |  |  |  |
|--------------------------------------|----------------------|--|--|--|
| Subject group type                   | Reporting group      |  |  |  |
| Number of subjects analysed          | 100                  |  |  |  |
| Units: nanogram per milliliter       |                      |  |  |  |
| arithmetic mean (standard deviation) |                      |  |  |  |
| DU-176, Day 30 (n= 81)               | 132.066 (± 110.056)  |  |  |  |
| DU-176, Day 90 (n= 76)               | 129.053 (± 105.7143) |  |  |  |
| D21-2393, Day 30 (n= 81)             | 12.3681 (± 15.45542) |  |  |  |
| D21-2393, Day 90 (n=75)              | 11.2873 (± 11.63869) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Day 1 to Day 90 in anti-Factor Xa low-molecular-weight heparin (LMWH)

|                 |   |
|-----------------|---|
| End point title | Change From Day 1 to Day 90 in anti-Factor Xa low-molecular-weight heparin (LMWH) |
|-----------------|---|

End point description:

Change in anti-Factor Xa was assessed as a part of Pharmacodynamic analysis. Safety Analysis Set population included all subjects who received at least 1 dose of edoxaban. Here, 99999 indicates data was not evaluated at specific time point.

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

End point timeframe:

Day 1, 30 and 90

| End point values                          | Clopidogrel      | Edoxaban         |  |  |
|---|------------------|------------------|--|--|
| Subject group type                        | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed               | 101              | 100              |  |  |
| Units: International units per millilitre |                  |                  |  |  |
| arithmetic mean (standard deviation)      |                  |                  |  |  |
| Day 1 (n= 61, 60)                         | 0.912 (± 0.8447) | 0.803 (± 0.5937) |  |  |
| Day 30 (n= 0, 86)                         | 99999 (± 99999)  | 1.323 (± 1.0705) |  |  |
| Day 90 (n= 0, 72)                         | 99999 (± 99999)  | 1.351 (± 1.0105) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: DDimer

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: DDimer |
|-----------------|--|

End point description:

Safety Analysis Set population included all subjects who received at least 1 dose of study drug. Units for Change From Day 1 to Day 90 in DDimer is milligram per litre (mg/L fibrinogen-equivalent units(FEU)).

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

End point timeframe:

Day 1, 30 and 90

| End point values                        | Clopidogrel      | Edoxaban         |  |  |
|---|------------------|------------------|--|--|
| Subject group type                      | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed             | 101              | 100              |  |  |
| Units: milligram per litre (mg/L (FEU)) |                  |                  |  |  |
| arithmetic mean (standard deviation)    |                  |                  |  |  |
| Day 1 (n=95, 90)                        | 1.149 (± 1.3628) | 1.283 (± 1.7241) |  |  |
| Day 30 (n= 86, 93)                      | 1.022 (± 1.358)  | 0.837 (± 1.8743) |  |  |
| Day 90 (n= 84, 85)                      | 0.912 (± 1.0351) | 0.932 (± 2.5883) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Factor Xa

|  |   |
|--|---|
| End point title  | Pharmacokinetic or Pharmacodynamic Parameter: Factor Xa |
| End point description:   |   |
| Change in Factor Xa was assessed as a part of Pharmacodynamic analysis. Safety Analysis Set population included all subjects who received at least 1 dose of study drug. |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Days 1, 30 and 90  |   |

| End point values                     | Clopidogrel       | Edoxaban          |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 101               | 100               |  |  |
| Units: percentage                    |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Day 1 (n= 95, 92)                    | 102.5 (± 21.989)  | 101.24 (± 17.665) |  |  |
| Day 30 (n= 86, 94)                   | 116.25 (± 25.404) | 73.09 (± 28.79)   |  |  |
| Day 90 (n= 85, 88)                   | 114.7 (± 23.752)  | 75.47 (± 29.86)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic or Pharmacodynamic Parameter: hs-C-Reactive Protein

|   |   |
|---|---|
| End point title   | Pharmacokinetic or Pharmacodynamic Parameter: hs-C-Reactive Protein |
| End point description:  |   |
| Change in hs-C-Reactive Protein was assessed as a part of Pharmacodynamic analysis. Safety Analysis |   |



Set population included all subjects who received at least 1 dose of study drug. 'n' indicates number of subjects evaluated at specific time point.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Day 1, 30 and 90     |           |

| End point values                     | Clopidogrel     | Edoxaban        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 101             | 100             |  |  |
| Units: milligram per litre           |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 1 (n= 99, 99)                    | 6.34 (± 10.75)  | 4.75 (± 7.88)   |  |  |
| Day 30 (n= 95, 96)                   | 5.3 (± 6.602)   | 5.67 (± 8.254)  |  |  |
| Day 90 (n= 92, 88)                   | 5.73 (± 13.127) | 4.74 (± 8.657)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: International Normalized Ratio

|   |  |
|---|--|
| End point title   | Pharmacokinetic or Pharmacodynamic Parameter: International Normalized Ratio |
| End point description:  |  |
| Change in International Normalized Ratio was evaluated as a part of Pharmacodynamic analysis. Safety Analysis Set population included all subjects who received at least 1 dose of study drug. 'n' indicates number of subjects evaluated at specific time point. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Day 1, 30 and 90  |  |

| End point values                     | Clopidogrel     | Edoxaban        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 101             | 100             |  |  |
| Units: ratio                         |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 1 (n= 95, 91)                    | 1.22 (± 0.482)  | 1.18 (± 0.548)  |  |  |
| Day 30 (n= 87, 89)                   | 1 (± 0.229)     | 1.37 (± 0.367)  |  |  |
| Day 90 (n= 85, 85)                   | 0.99 (± 0.185)  | 1.37 (± 0.512)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: P-Selectin

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: P-Selectin |
|-----------------|--|

End point description:

P-Selectin was evaluated as a part of Pharmacodynamic parameters. Safety Analysis Set population included all subjects who received at least 1 dose of study drug. 'n' indicates number of subjects evaluated at specific time point.

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

End point timeframe:

Day 1, 30 and 90

| End point values                     | Clopidogrel      | Edoxaban         |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 101              | 100              |  |  |
| Units: nanogram per millilitre       |                  |                  |  |  |
| arithmetic mean (standard deviation) |                  |                  |  |  |
| Day 1 (n= 101, 95)                   | 43.16 (± 20.96)  | 45.4 (± 28.921)  |  |  |
| Day 30 (n= 93, 93)                   | 41.19 (± 18.989) | 43.48 (± 22.403) |  |  |
| Day 90 (n= 87, 89)                   | 41.91 (± 30.932) | 43.45 (± 24.406) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Partial Thromboplastin Time

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: Partial Thromboplastin Time |
|-----------------|---|

End point description:

Safety Analysis Set population included all subjects who received at least 1 dose of study drug. 'n' indicates number of subjects evaluated at specific time point.

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

End point timeframe:

Day 1, 30 and 90

| End point values                     | Clopidogrel     | Edoxaban         |  |  |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type                   | Reporting group | Reporting group  |  |  |
| Number of subjects analysed          | 101             | 100              |  |  |
| Units: seconds                       |                 |                  |  |  |
| arithmetic mean (standard deviation) |                 |                  |  |  |
| Day 1 (n= 77, 80)                    | 45.35 (± 37.66) | 46.24 (± 33.985) |  |  |
| Day 30 (n= 85, 93)                   | 24.98 (± 2.341) | 29.51 (± 9.181)  |  |  |
| Day 90 (n= 85, 86)                   | 25.13 (± 2.209) | 28.2 (± 5.767)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Thrombin area under curve

|   |   |
|---|---|
| End point title   | Pharmacokinetic or Pharmacodynamic Parameter: Thrombin area under curve |
| End point description:  |   |
| Safety Analysis Set population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point. |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Day 1, 30 and 90  |   |

| End point values                     | Clopidogrel          | Edoxaban             |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 101                  | 100                  |  |  |
| Units: nM*minute                     |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Day 1 (n= 95, 93)                    | 1443.25 (± 1870.763) | 1719.53 (± 2008.222) |  |  |
| Day 30 (n= 86, 91)                   | 4253.18 (± 791.133)  | 3536.43 (± 1191.284) |  |  |
| Day 90 (n= 83, 87)                   | 4260.99 (± 861.846)  | 3576.43 (± 981.259)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Thrombin Generation lag time

|                 |  |
|-----------------|--|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: Thrombin |
|-----------------|--|

End point description:

Safety Analysis Set population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point.

End point type Secondary

End point timeframe:

Day 1, 30 and 90

| End point values                     | Clopidogrel      | Edoxaban        |  |  |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type                   | Reporting group  | Reporting group |  |  |
| Number of subjects analysed          | 101              | 100             |  |  |
| Units: minute                        |                  |                 |  |  |
| arithmetic mean (standard deviation) |                  |                 |  |  |
| Day 1 (n= 95, 93)                    | 11.81 (± 17.218) | 9.59 (± 14.157) |  |  |
| Day 30 (n= 86, 91)                   | 11.04 (± 2.786)  | 15.53 (± 6.389) |  |  |
| Day 90 (n= 83, 87)                   | 11.03 (± 2.392)  | 16.62 (± 9.242) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Thrombin

End point title Pharmacokinetic or Pharmacodynamic Parameter: Thrombin

End point description:

Safety Analysis Set population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point.

End point type Secondary

End point timeframe:

Day 1, 30 and 90

| End point values                     | Clopidogrel        | Edoxaban           |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 101                | 100                |  |  |
| Units: nM                            |                    |                    |  |  |
| arithmetic mean (standard deviation) |                    |                    |  |  |
| Day 1 (n= 95, 93)                    | 178.07 (± 237.533) | 204.97 (± 248.189) |  |  |
| Day 30 (n= 86, 91)                   | 494.87 (± 123.986) | 357.59 (± 187.161) |  |  |
| Day 90 (n= 83, 87)                   | 509.97 (± 129.717) | 346.45 (± 168.209) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Thrombin time to peak

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: Thrombin time to peak |
|-----------------|---|

End point description:

Change in Thrombin time to peak was evaluated as a part of Pharmacodynamic analysis. Safety Analysis Set 1 population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point.

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

End point timeframe:

Day 1, 30 and 90

| End point values                     | Clopidogrel     | Edoxaban        |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 101             | 100             |  |  |
| Units: minute                        |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Day 1 (n= 95, 93)                    | 7.15 (± 9.314)  | 7.96 (± 9.304)  |  |  |
| Day 30 (n= 86, 91)                   | 15.73 (± 3.921) | 21.49 (± 9.436) |  |  |
| Day 90 (n= 83, 87)                   | 15.48 (± 3.041) | 22 (± 8.707)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic or Pharmacodynamic Parameter: Thrombin velocity index

|                 |   |
|-----------------|---|
| End point title | Pharmacokinetic or Pharmacodynamic Parameter: Thrombin velocity index |
|-----------------|---|

End point description:

Change in Thrombin velocity index was evaluated as a part of Pharmacodynamic analysis. Safety Analysis Set population included all subjects who received at least 1 dose of the study drug. Here 'n' indicates the number of subjects analysed at specific time point.

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

End point timeframe:

Day 1, 30 and 90

---

|                                      |                   |                  |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| <b>End point values</b>              | Clopidogrel       | Edoxaban         |  |  |
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 101               | 100              |  |  |
| Units: nM/min                        |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Day 1 (n= 95, 93)                    | 49.49 (± 72.482)  | 53.97 (± 71.745) |  |  |
| Day 30 (n= 86, 91)                   | 130.1 (± 68.48)   | 84.14 (± 65.21)  |  |  |
| Day 90 (n= 83, 87)                   | 132.03 (± 70.044) | 77.91 (± 64.268) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the signing of informed consent form up to end of the study (6 months)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Subjects administered with edoxaban 60 milligram (mg) once daily (QD) (two 30 mg tablets) for approximately 3 months on a background of aspirin 100 mg tablets QD.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Clopidogrel |
|-----------------------|-------------|

Reporting group description:

Subjects administered with a loading dose of clopidogrel 300 milligram (mg) (our 75-mg tablets) as first dose within 4 hours of hemostasis followed by 75 mg once daily (QD) (one 75 mg tablet) orally for a total of approximately 3 months on a background of aspirin 100 mg QD.

| Serious adverse events  | Edoxaban          | Clopidogrel       |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 31 / 100 (31.00%) | 30 / 101 (29.70%) |  |
| number of deaths (all causes)                                       | 3                 | 0                 |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Lung neoplasm malignant   |                   |                   |  |
| subjects affected / exposed   | 0 / 100 (0.00%)   | 1 / 101 (0.99%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Pancreatic carcinoma metastatic                                     |                   |                   |  |
| subjects affected / exposed   | 1 / 100 (1.00%)   | 0 / 101 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Vascular disorders  |                   |                   |  |
| Femoral artery occlusion  |                   |                   |  |
| subjects affected / exposed   | 2 / 100 (2.00%)   | 0 / 101 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             |  |
| Haemorrhage   |                   |                   |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Hypertension   |                 |                 |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Intermittent claudication                            |                 |                 |  |
| subjects affected / exposed                          | 2 / 100 (2.00%) | 4 / 101 (3.96%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease                |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 3 / 101 (2.97%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral artery stenosis                           |                 |                 |  |
| subjects affected / exposed                          | 2 / 100 (2.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral artery thrombosis                         |                 |                 |  |
| subjects affected / exposed                          | 3 / 100 (3.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all      | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral embolism                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                                 |                 |                 |  |
| subjects affected / exposed                          | 1 / 100 (1.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Chest pain   |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 100 (2.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrosis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| 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 |                 |                 |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Alcohol Abuse                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (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  |                 |                 |  |
| Arterial restenosis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral artery restenosis                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 100 (3.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haematoma                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post procedural haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular pseudoaneurysm                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 100 (4.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound   |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 100 (2.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 100 (2.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Carotid artery stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhagic stroke                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Iron deficiency anaemia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Intestinal Ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Skin Ulcer                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Haematuria                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure acute                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| 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 |                 |                 |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Compartment syndrome                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Clostridium colitis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gangrene  |                 |                 |  |
| subjects affected / exposed                     | 2 / 100 (2.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Infected skin ulcer                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Fluid Overload                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| 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: 0 %

| <b>Non-serious adverse events</b>                     | Edoxaban          | Clopidogrel       |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 77 / 100 (77.00%) | 75 / 101 (74.26%) |  |
| Vascular disorders                                    |                   |                   |  |
| Aortic dilatation                                     |                   |                   |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Haematoma   |                   |                   |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)   | 1 / 101 (0.99%)   |  |
| occurrences (all)                                     | 0                 | 1                 |  |
| Femoral artery occlusion                              |                   |                   |  |
| subjects affected / exposed                           | 0 / 100 (0.00%)   | 2 / 101 (1.98%)   |  |
| occurrences (all)                                     | 0                 | 2                 |  |
| Hypertension  |                   |                   |  |

|                                       |                 |                 |  |
|---------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed           | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                     | 1               | 3               |  |
| Hypertensive crisis                   |                 |                 |  |
| subjects affected / exposed           | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                     | 1               | 0               |  |
| Intermittent claudication             |                 |                 |  |
| subjects affected / exposed           | 2 / 100 (2.00%) | 4 / 101 (3.96%) |  |
| occurrences (all)                     | 2               | 5               |  |
| Hypotension                           |                 |                 |  |
| subjects affected / exposed           | 0 / 100 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences (all)                     | 0               | 2               |  |
| Peripheral artery stenosis            |                 |                 |  |
| subjects affected / exposed           | 3 / 100 (3.00%) | 4 / 101 (3.96%) |  |
| occurrences (all)                     | 3               | 4               |  |
| Peripheral arterial occlusive disease |                 |                 |  |
| subjects affected / exposed           | 0 / 100 (0.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)                     | 0               | 3               |  |
| Peripheral artery thrombosis          |                 |                 |  |
| subjects affected / exposed           | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                     | 1               | 0               |  |
| Peripheral coldness                   |                 |                 |  |
| subjects affected / exposed           | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                     | 1               | 0               |  |
| Raynaud's phenomenon                  |                 |                 |  |
| subjects affected / exposed           | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                     | 0               | 1               |  |
| Varicose vein                         |                 |                 |  |
| subjects affected / exposed           | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                     | 1               | 0               |  |
| Venous insufficiency                  |                 |                 |  |
| subjects affected / exposed           | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                     | 0               | 1               |  |
| Surgical and medical procedures       |                 |                 |  |
| Toe amputation                        |                 |                 |  |
| subjects affected / exposed           | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                     | 0               | 1               |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Tooth extraction<br>subjects affected / exposed<br>occurrences (all)       | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| General disorders and administration site conditions                       |                      |                      |  |
| Calcinosis<br>subjects affected / exposed<br>occurrences (all)             | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)               | 0 / 100 (0.00%)<br>0 | 2 / 101 (1.98%)<br>2 |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)             | 0 / 100 (0.00%)<br>0 | 2 / 101 (1.98%)<br>2 |  |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)       | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Chills<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                | 4 / 100 (4.00%)<br>5 | 1 / 101 (0.99%)<br>1 |  |
| Malaise<br>subjects affected / exposed<br>occurrences (all)                | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Necrosis<br>subjects affected / exposed<br>occurrences (all)               | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Non-cardiac chest pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)      | 4 / 100 (4.00%)<br>4 | 1 / 101 (0.99%)<br>1 |  |
| Oedema   |                      |                      |  |



|  |                       |                       |  |
|--|-----------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 100 (1.00%)<br>2  | 0 / 101 (0.00%)<br>0  |  |
| Pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 100 (1.00%)<br>1  | 1 / 101 (0.99%)<br>1  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1  | 1 / 101 (0.99%)<br>1  |  |
| Immune system disorders<br>Hypersensitivity<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1  | 1 / 101 (0.99%)<br>1  |  |
| Reproductive system and breast disorders<br>Vaginal Haemorrhage<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 100 (0.00%)<br>0  | 1 / 101 (0.99%)<br>1  |  |
| Respiratory, thoracic and mediastinal disorders<br>Chronic obstructive pulmonary disease<br>subjects affected / exposed<br>occurrences (all) | 2 / 100 (2.00%)<br>2  | 0 / 101 (0.00%)<br>0  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 100 (2.00%)<br>2  | 0 / 101 (0.00%)<br>0  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1  | 2 / 101 (1.98%)<br>2  |  |
| Emphysema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1  | 0 / 101 (0.00%)<br>0  |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)  | 7 / 100 (7.00%)<br>12 | 7 / 101 (6.93%)<br>15 |  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 100 (1.00%)<br>1  | 0 / 101 (0.00%)<br>0  |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Psychiatric disorders  |                      |                      |  |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Drug dependence<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Mental status changes<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Investigations   |                      |                      |  |
| Blood cholesterol increased<br>subjects affected / exposed<br>occurrences (all)            | 3 / 100 (3.00%)<br>3 | 0 / 101 (0.00%)<br>0 |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 2 / 101 (1.98%)<br>2 |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 100 (0.00%)<br>0 | 2 / 101 (1.98%)<br>2 |  |
| Blood testosterone decreased   |                      |                      |  |

|   |                 |                 |
|---|-----------------|-----------------|
| subjects affected / exposed                 | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                           | 0               | 1               |
| Blood thyroid stimulating hormone increased |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 1               | 0               |
| Blood triglycerides increased               |                 |                 |
| subjects affected / exposed                 | 3 / 100 (3.00%) | 1 / 101 (0.99%) |
| occurrences (all)                           | 3               | 1               |
| Blood uric acid increased                   |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 1               | 0               |
| Carotid bruit                               |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 1 / 101 (0.99%) |
| occurrences (all)                           | 1               | 1               |
| Creatinine renal clearance decreased        |                 |                 |
| subjects affected / exposed                 | 6 / 100 (6.00%) | 3 / 101 (2.97%) |
| occurrences (all)                           | 6               | 3               |
| Creatinine renal clearance increased        |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 1               | 0               |
| Glycosylated haemoglobin increased          |                 |                 |
| subjects affected / exposed                 | 2 / 100 (2.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 2               | 0               |
| Eosinophil count increased                  |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 1               | 0               |
| Haemoglobin decreased                       |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 1 / 101 (0.99%) |
| occurrences (all)                           | 1               | 1               |
| Low density lipoprotein increased           |                 |                 |
| subjects affected / exposed                 | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                           | 1               | 0               |
| Lymphocyte percentage increased             |                 |                 |
| subjects affected / exposed                 | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                           | 0               | 1               |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Neutrophil percentage increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Pedal pulse decreased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 1 / 101 (0.99%)<br>1 |  |
| Injury, poisoning and procedural complications                                       |                      |                      |  |
| Arterial restenosis<br>subjects affected / exposed<br>occurrences (all)              | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Avulsion fracture<br>subjects affected / exposed<br>occurrences (all)                | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Confusion postoperative<br>subjects affected / exposed<br>occurrences (all)          | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Excoriation<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 100 (2.00%)<br>2 | 4 / 101 (3.96%)<br>7 |  |
| Eye injury<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 100 (2.00%)<br>2 | 0 / 101 (0.00%)<br>0 |  |
| Foot fracture  |                      |                      |  |

|                              |                 |                 |
|------------------------------|-----------------|-----------------|
| subjects affected / exposed  | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Fractured coccyx             |                 |                 |
| subjects affected / exposed  | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)            | 0               | 1               |
| Incision site haemorrhage    |                 |                 |
| subjects affected / exposed  | 3 / 100 (3.00%) | 0 / 101 (0.00%) |
| occurrences (all)            | 3               | 0               |
| Limb injury                  |                 |                 |
| subjects affected / exposed  | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Peripheral artery restenosis |                 |                 |
| subjects affected / exposed  | 2 / 100 (2.00%) | 2 / 101 (1.98%) |
| occurrences (all)            | 2               | 2               |
| Overdose                     |                 |                 |
| subjects affected / exposed  | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Post procedural haematoma    |                 |                 |
| subjects affected / exposed  | 6 / 100 (6.00%) | 3 / 101 (2.97%) |
| occurrences (all)            | 6               | 3               |
| Post procedural complication |                 |                 |
| subjects affected / exposed  | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)            | 0               | 1               |
| Post procedural haemorrhage  |                 |                 |
| subjects affected / exposed  | 1 / 100 (1.00%) | 2 / 101 (1.98%) |
| occurrences (all)            | 1               | 2               |
| Post procedural swelling     |                 |                 |
| subjects affected / exposed  | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)            | 1               | 0               |
| Procedural pain              |                 |                 |
| subjects affected / exposed  | 2 / 100 (2.00%) | 3 / 101 (2.97%) |
| occurrences (all)            | 2               | 3               |
| Scratch                      |                 |                 |
| subjects affected / exposed  | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)            | 0               | 1               |
| Scrotal haematoma            |                 |                 |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Spinal compression fracture |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Traumatic haematoma         |                 |                 |  |
| subjects affected / exposed | 4 / 100 (4.00%) | 4 / 101 (3.96%) |  |
| occurrences (all)           | 4               | 4               |  |
| Subcutaneous haematoma      |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Vascular pseudoaneurysm     |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences (all)           | 0               | 2               |  |
| Wound                       |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 1               | 3               |  |
| Wound secretion             |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Cardiac disorders           |                 |                 |  |
| Angina pectoris             |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Atrial fibrillation         |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Bradycardia                 |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Coronary artery stenosis    |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Sinus tachycardia           |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |

|                                      |                 |                 |  |
|--------------------------------------|-----------------|-----------------|--|
| Nervous system disorders             |                 |                 |  |
| Amputation stump pain                |                 |                 |  |
| subjects affected / exposed          | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Convulsion                           |                 |                 |  |
| subjects affected / exposed          | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                    | 0               | 1               |  |
| Dizziness                            |                 |                 |  |
| subjects affected / exposed          | 5 / 100 (5.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                    | 5               | 1               |  |
| Headache                             |                 |                 |  |
| subjects affected / exposed          | 5 / 100 (5.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                    | 5               | 0               |  |
| Hypoaesthesia                        |                 |                 |  |
| subjects affected / exposed          | 2 / 100 (2.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                    | 2               | 0               |  |
| Migraine                             |                 |                 |  |
| subjects affected / exposed          | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Loss of consciousness                |                 |                 |  |
| subjects affected / exposed          | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                    | 1               | 0               |  |
| Paraesthesia                         |                 |                 |  |
| subjects affected / exposed          | 3 / 100 (3.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                    | 3               | 1               |  |
| Neuropathy peripheral                |                 |                 |  |
| subjects affected / exposed          | 0 / 100 (0.00%) | 2 / 101 (1.98%) |  |
| occurrences (all)                    | 0               | 2               |  |
| Sciatica                             |                 |                 |  |
| subjects affected / exposed          | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                    | 1               | 1               |  |
| Tremor                               |                 |                 |  |
| subjects affected / exposed          | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                    | 0               | 1               |  |
| Blood and lymphatic system disorders |                 |                 |  |

|                                 |                 |                 |  |
|---------------------------------|-----------------|-----------------|--|
| Anaemia                         |                 |                 |  |
| subjects affected / exposed     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 0               | 1               |  |
| Leukocytosis                    |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)               | 1               | 0               |  |
| Iron deficiency anaemia         |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)               | 1               | 0               |  |
| Thrombocytosis                  |                 |                 |  |
| subjects affected / exposed     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 0               | 1               |  |
| Normochromic Normocytic Anaemia |                 |                 |  |
| subjects affected / exposed     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 0               | 1               |  |
| Ear and labyrinth disorders     |                 |                 |  |
| Vertigo                         |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 1               | 1               |  |
| Eye disorders                   |                 |                 |  |
| Blepharitis                     |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)               | 1               | 0               |  |
| Conjunctival haemorrhage        |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 1               | 1               |  |
| Cataract                        |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)               | 1               | 0               |  |
| Ocular hyperaemia               |                 |                 |  |
| subjects affected / exposed     | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)               | 1               | 0               |  |
| Retinal tear                    |                 |                 |  |
| subjects affected / exposed     | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)               | 0               | 1               |  |
| Vision blurred                  |                 |                 |  |



|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Gastrointestinal disorders                       |                      |                      |  |
| Abdominal discomfort                             |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                    |  |
| Abdominal pain                                   |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 2 / 101 (1.98%)      |  |
| occurrences (all)                                | 1                    | 3                    |  |
| Abdominal distension                             |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Abdominal pain upper                             |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Constipation                                     |                      |                      |  |
| subjects affected / exposed                      | 2 / 100 (2.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                    |  |
| Dental caries                                    |                      |                      |  |
| subjects affected / exposed                      | 2 / 100 (2.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 2                    | 0                    |  |
| Diarrhoea  |                      |                      |  |
| subjects affected / exposed                      | 4 / 100 (4.00%)      | 2 / 101 (1.98%)      |  |
| occurrences (all)                                | 4                    | 2                    |  |
| Flatulence                                       |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Dyspepsia  |                      |                      |  |
| subjects affected / exposed                      | 0 / 100 (0.00%)      | 1 / 101 (0.99%)      |  |
| occurrences (all)                                | 0                    | 1                    |  |
| Gastrointestinal angiodysplasia<br>haemorrhagic  |                      |                      |  |
| subjects affected / exposed                      | 1 / 100 (1.00%)      | 0 / 101 (0.00%)      |  |
| occurrences (all)                                | 1                    | 0                    |  |
| Gastritis alcoholic                              |                      |                      |  |

|                                  |                 |                 |
|----------------------------------|-----------------|-----------------|
| subjects affected / exposed      | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Gastrooesophageal reflux disease |                 |                 |
| subjects affected / exposed      | 0 / 100 (0.00%) | 2 / 101 (1.98%) |
| occurrences (all)                | 0               | 2               |
| Haematemesis                     |                 |                 |
| subjects affected / exposed      | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 0               | 1               |
| Gingival bleeding                |                 |                 |
| subjects affected / exposed      | 3 / 100 (3.00%) | 0 / 101 (0.00%) |
| occurrences (all)                | 3               | 0               |
| Haematochezia                    |                 |                 |
| subjects affected / exposed      | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Haemorrhoidal haemorrhage        |                 |                 |
| subjects affected / exposed      | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Hiatus hernia                    |                 |                 |
| subjects affected / exposed      | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 0               | 1               |
| Pancreatitis                     |                 |                 |
| subjects affected / exposed      | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)                | 1               | 0               |
| Stomatitis                       |                 |                 |
| subjects affected / exposed      | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 0               | 1               |
| Rectal haemorrhage               |                 |                 |
| subjects affected / exposed      | 1 / 100 (1.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 1               | 2               |
| Tooth loss                       |                 |                 |
| subjects affected / exposed      | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 0               | 1               |
| Vomiting                         |                 |                 |
| subjects affected / exposed      | 2 / 100 (2.00%) | 1 / 101 (0.99%) |
| occurrences (all)                | 3               | 1               |
| Nausea                           |                 |                 |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all) | 6 / 100 (6.00%)<br>6 | 4 / 101 (3.96%)<br>5 |  |
| Hepatobiliary disorders                          |                      |                      |  |
| Hepatic cirrhosis                                |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Skin and subcutaneous tissue disorders           |                      |                      |  |
| Alopecia   |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Dermal cyst                                      |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Dermatitis                                       |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Dermatitis contact                               |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Diabetic foot                                    |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Eczema   |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Ecchymosis                                       |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 2 / 101 (1.98%)<br>3 |  |
| Hyperhidrosis                                    |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Erythema   |                      |                      |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 100 (2.00%)<br>2 | 0 / 101 (0.00%)<br>0 |  |
| Increased tendency to bruise                     |                      |                      |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Ingrowing nail              |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Neurodermatitis             |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Night sweats                |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Rash                        |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 2 / 101 (1.98%) |  |
| occurrences (all)           | 1               | 2               |  |
| Pruritus generalised        |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Skin fissures               |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Scab                        |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Skin ulcer                  |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)           | 1               | 5               |  |
| Renal and urinary disorders |                 |                 |  |
| Chromaturia                 |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Nephrolithiasis             |                 |                 |  |
| subjects affected / exposed | 2 / 100 (2.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 2               | 0               |  |
| Haematuria                  |                 |                 |  |
| subjects affected / exposed | 4 / 100 (4.00%) | 4 / 101 (3.96%) |  |
| occurrences (all)           | 5               | 4               |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Renal failure acute<br>subjects affected / exposed<br>occurrences (all)             | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Renal impairment<br>subjects affected / exposed<br>occurrences (all)                | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Musculoskeletal and connective tissue disorders                                     |                      |                      |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                       | 4 / 100 (4.00%)<br>4 | 1 / 101 (0.99%)<br>2 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                      | 6 / 100 (6.00%)<br>6 | 2 / 101 (1.98%)<br>2 |  |
| Chondrocalcinosis pyrophosphate<br>subjects affected / exposed<br>occurrences (all) | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Costochondritis<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 100 (0.00%)<br>0 | 1 / 101 (0.99%)<br>1 |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Gouty arthritis<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Groin pain<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 100 (1.00%)<br>1 | 0 / 101 (0.00%)<br>0 |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)                  | 2 / 100 (2.00%)<br>2 | 2 / 101 (1.98%)<br>2 |  |
| Muscle spasms   |                      |                      |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 100 (3.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 3               | 1               |  |
| Musculoskeletal discomfort  |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |
| Musculoskeletal chest pain  |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Musculoskeletal pain        |                 |                 |  |
| subjects affected / exposed | 2 / 100 (2.00%) | 2 / 101 (1.98%) |  |
| occurrences (all)           | 2               | 2               |  |
| Pain in extremity           |                 |                 |  |
| subjects affected / exposed | 9 / 100 (9.00%) | 7 / 101 (6.93%) |  |
| occurrences (all)           | 9               | 8               |  |
| Myalgia                     |                 |                 |  |
| subjects affected / exposed | 3 / 100 (3.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)           | 3               | 0               |  |
| Sensation of heaviness      |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Infections and infestations |                 |                 |  |
| Bronchitis                  |                 |                 |  |
| subjects affected / exposed | 1 / 100 (1.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)           | 1               | 3               |  |
| Cellulitis                  |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Gangrene                    |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Cystitis                    |                 |                 |  |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 0               | 1               |  |
| Gastroenteritis viral       |                 |                 |  |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)           | 2               | 1               |  |

|                                    |                 |                 |  |
|------------------------------------|-----------------|-----------------|--|
| Herpes zoster                      |                 |                 |  |
| subjects affected / exposed        | 1 / 100 (1.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                  | 1               | 1               |  |
| Localised infection                |                 |                 |  |
| subjects affected / exposed        | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Nasopharyngitis                    |                 |                 |  |
| subjects affected / exposed        | 4 / 100 (4.00%) | 5 / 101 (4.95%) |  |
| occurrences (all)                  | 4               | 6               |  |
| Osteomyelitis                      |                 |                 |  |
| subjects affected / exposed        | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Pharyngitis streptococcal          |                 |                 |  |
| subjects affected / exposed        | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Respiratory tract infection viral  |                 |                 |  |
| subjects affected / exposed        | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Upper respiratory tract infection  |                 |                 |  |
| subjects affected / exposed        | 2 / 100 (2.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)                  | 3               | 4               |  |
| Urinary tract infection            |                 |                 |  |
| subjects affected / exposed        | 4 / 100 (4.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)                  | 4               | 3               |  |
| Vulvovaginal mycotic infection     |                 |                 |  |
| subjects affected / exposed        | 0 / 100 (0.00%) | 1 / 101 (0.99%) |  |
| occurrences (all)                  | 0               | 1               |  |
| Metabolism and nutrition disorders |                 |                 |  |
| Decreased appetite                 |                 |                 |  |
| subjects affected / exposed        | 1 / 100 (1.00%) | 0 / 101 (0.00%) |  |
| occurrences (all)                  | 1               | 0               |  |
| Gout                               |                 |                 |  |
| subjects affected / exposed        | 1 / 100 (1.00%) | 3 / 101 (2.97%) |  |
| occurrences (all)                  | 1               | 3               |  |
| Hyperglycaemia                     |                 |                 |  |

|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Hyperlipidaemia             |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Hyperkalaemia               |                 |                 |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hypoglycaemia               |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Hypokalaemia                |                 |                 |
| subjects affected / exposed | 2 / 100 (2.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 2               | 1               |
| Hyponatraemia               |                 |                 |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Hypomagnesaemia             |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Obesity                     |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Multi-vitamin deficiency    |                 |                 |
| subjects affected / exposed | 1 / 100 (1.00%) | 0 / 101 (0.00%) |
| occurrences (all)           | 1               | 0               |
| Type 2 diabetes mellitus    |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |
| Vitamin D deficiency        |                 |                 |
| subjects affected / exposed | 0 / 100 (0.00%) | 1 / 101 (0.99%) |
| occurrences (all)           | 0               | 1               |



## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported