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
Arm title	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.

Arm title	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.

Number of subjects in period 1	Clopidogrel	Edoxaban
Started	102	101
Completed	96	89
Not completed	6	12
Physician decision	1	-
Consent withdrawn by subject	3	5
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:	
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.	

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

End point title	Percentage of Subjects with Re-stenosis/re-occlusion
End point description:	
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:	
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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

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	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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 (± 1.159)	0.9 (± 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:

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:

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 (± 0.265)	0.67 (± 0.279)		
Month 1 (n= 93, 93)	0.97 (± 0.188)	0.93 (± 0.189)		
Change from Month 1 to Month 3 (n= 88, 84)	-0.05 (± 0.16)	-0.03 (± 0.148)		
Change from Month 1 to Month 6 (n= 83, 73)	-0.06 (± 0.213)	-0.03 (± 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:

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

End point values	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): Stage2(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):Stage6(Ulceration or gangrene)	0	0		

Statistical analyses

No statistical analyses for this end point

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 yocardial 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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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[1]

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 stud 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

	Generation lag time

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

End point values	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 %

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

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

Nasal congestion			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Drug dependence			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Mental status changes			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Investigations			
Blood cholesterol increased			
subjects affected / exposed	3 / 100 (3.00%)	0 / 101 (0.00%)	
occurrences (all)	3	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 100 (1.00%)	2 / 101 (1.98%)	
occurrences (all)	1	2	
Blood pressure increased			
subjects affected / exposed	0 / 100 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	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			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Pedal pulse decreased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Weight decreased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
White blood cell count increased			
subjects affected / exposed	1 / 100 (1.00%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Avulsion fracture			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Confusion postoperative			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Excoriation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Contusion			
subjects affected / exposed	2 / 100 (2.00%)	4 / 101 (3.96%)	
occurrences (all)	2	7	
Eye injury			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	2 / 100 (2.00%)	0 / 101 (0.00%)	
occurrences (all)	2	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	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	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 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	6 / 100 (6.00%)	4 / 101 (3.96%)	
occurrences (all)	6	5	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Dermal cyst			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Diabetic foot			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	0 / 100 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	3	
Hyperhidrosis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	2 / 100 (2.00%)	0 / 101 (0.00%)	
occurrences (all)	2	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			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 100 (4.00%)	1 / 101 (0.99%)	
occurrences (all)	4	2	
Arthralgia			
subjects affected / exposed	6 / 100 (6.00%)	2 / 101 (1.98%)	
occurrences (all)	6	2	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Costochondritis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Flank pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Gouty arthritis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Joint swelling			
subjects affected / exposed	2 / 100 (2.00%)	2 / 101 (1.98%)	
occurrences (all)	2	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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported