Clinical trial results:
Evaluation of Edoxaban in Anticoagulant Naïve Patients with Non-Valvular Atrial Fibrillation (NVAF) and high Creatinine Clearance

Summary

EudraCT number	2016-001795-30
Trial protocol	LV CZ EE LT SK DK HU ES BE PL HR
Global end of trial date	09 October 2018

Results information

Result version number	v1 (current)
This version publication date	25 October 2019
First version publication date	25 October 2019

Trial information

Trial identification

Sponsor protocol code	DU176b-C-E314

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02964949
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	26 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the exposure (based on average concentration at steady state (Cav), minimum concentration in plasma (Cmin), and anti-factor Xa [anti-FXa]) of edoxaban 75 mg once daily (QD) dose to edoxaban 60 mg QD dose in NVAF anticoagulant-naïve patients with CHADS2 score of ≥ 2 and CrCL > 100 mL/min (as calculated by the Cockcroft-Gault formula) treated for up to 12 months.

Protection of trial subjects:

This study was conducted in compliance with the protocol, the ethical principles derived from the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Slovakia: 49
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 91
Country: Number of subjects enrolled	Czech Republic: 36
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Hungary: 43
Country: Number of subjects enrolled	Latvia: 41
Country: Number of subjects enrolled	Lithuania: 29
Country: Number of subjects enrolled	Russian Federation: 53
Country: Number of subjects enrolled	Serbia: 27
Country: Number of subjects enrolled	Ukraine: 170
Worldwide total number of subjects	607
EEA total number of subjects	357

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)	396
From 65 to 84 years	211
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 607 subjects who met the inclusion and none of the exclusion criteria were randomized; 606 subjects received the study drug.

Pre-assignment

Screening details:

Subjects were recruited after verification of inclusion and exclusion criteria including a diagnosis of non-valvular atrial fibrillation (NVAF) and anticoagulant-naive, and creatinine clearance (CrCL) >100 mL/min (calculated by Cockcroft-Gault formula).

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a randomized, double-blind study. Blinding was applied to all personnel related to the study (subjects, investigators, and Sponsor).

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban 75 mg

Arm description:

Subjects received Edoxaban 60 mg and Edoxaban 15 mg orally, once daily at the same time (preferably morning) up to 12 months.

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

Dosage and administration details:

One 60 mg active tablet and one 15 mg active tablet taken orally once every day

Arm title	Edoxaban 60 mg

Arm description:

Subjects received Edoxaban 60 mg and placebo 15 mg orally, once daily at the same time (preferably morning) up to 12 months.

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

Dosage and administration details:

One 60 mg active tablet and one 15 mg placebo tablet taken orally once every day

Number of subjects in period 1	Edoxaban 75 mg	Edoxaban 60 mg
Started	304	303
Completed	297	299
Not completed	7	4
Consent withdrawn by subject	-	1
Death	7	3

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban 75 mg
Reporting group description:	
Subjects received Edoxaban 60 mg and Edoxaban 15 mg orally, once daily at the same time (preferably morning) up to 12 months.	
Reporting group title	Edoxaban 60 mg
Reporting group description:	
Subjects received Edoxaban 60 mg and placebo 15 mg orally, once daily at the same time (preferably morning) up to 12 months.	

Reporting group values	Edoxaban 75 mg	Edoxaban 60 mg	Total
Number of subjects	304	303	607
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	201	195	396
From 65-84 years	103	108	211
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	60.4	60.9	
standard deviation	± 8.39	± 8.06	-
Gender categorical Units: Subjects			
Female	82	88	170
Male	222	215	437

End points

End points reporting groups

Reporting group title	Edoxaban 75 mg
Reporting group description:	
Subjects received Edoxaban 60 mg and Edoxaban 15 mg orally, once daily at the same time (preferably morning) up to 12 months.	
Reporting group title	Edoxaban 60 mg
Reporting group description:	
Subjects received Edoxaban 60 mg and placebo 15 mg orally, once daily at the same time (preferably morning) up to 12 months.	

Primary: Analysis of Pharmacokinetic Parameter: Average Concentration of Edoxaban (Cav)

End point title	Analysis of Pharmacokinetic Parameter: Average Concentration of Edoxaban (Cav)
End point description:	
Cav is the average concentration of Edoxaban in plasma.	
End point type	Primary
End point timeframe:	
Days 30, 90, and 360 post-dose and at steady state (SS)	

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	298		
Units: Mean concentration				
arithmetic mean (standard deviation)				
Day 30 (n=297, 297)	93.25 (± 16.18)	75.09 (± 13.38)		
Day 90 (n=288, 295)	94.18 (± 17.42)	75.81 (± 14.49)		
Day 360 (n=279, 286)	94.72 (± 18.03)	76.60 (± 15.10)		
Steady state (n=297, 298)	93.24 (± 16.21)	74.84 (± 13.33)		

Statistical analyses

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg)-D30
Statistical analysis description:	
This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (Day 30).	
Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg

Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	1.28

Notes:

[1] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg)-D90

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=288) and Edoxaban 60 mg (n=295) (Day 90).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	1.28

Notes:

[2] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60mg)-D360

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=279) and Edoxaban 60 mg (n=286) (Day 360).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.28

Notes:

[3] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60mg)-SS

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (steady state [SS]).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	1.28

Notes:

[4] - Ratio of means

Primary: Analysis of Pharmacokinetic Parameter: Maximum Concentration of Edoxaban (Cmax)

End point title	Analysis of Pharmacokinetic Parameter: Maximum Concentration of Edoxaban (Cmax)

End point description:

Cmax is the maximum concentration of Edoxaban in plasma.

End point type	Primary

End point timeframe:

Days 30, 90, and 360 post-dose and at steady state (SS)

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	298		
Units: Mean concentration				
arithmetic mean (standard deviation)				
Day 30 (n=297, 297)	268.70 (± 62.59)	216.42 (± 51.67)		
Day 90 (n=288, 295)	266.99 (± 72.41)	215.97 (± 62.76)		
Day 360 (n=279, 286)	273.65 (± 65.66)	219.63 (± 53.36)		

Steady state (n=297, 298)	268.72 (± 62.36)	214.43 (± 51.09)		

Statistical analyses

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg)-D30

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (Day 30).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.29

Notes:

[5] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg)-D90

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=288) and Edoxaban 60 mg (n=295) (Day 90).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.3

Notes:

[6] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60mg)-D360

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=279) and Edoxaban

60 mg (n=286) (Day 360).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1.3

Notes:

[7] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60 mg)-SS

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (steady state [SS]).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.21
upper limit	1.3

Notes:

[8] - Ratio of means

Primary: Analysis of Pharmacokinetic Parameter: Minimum Concentration of Exdoxaban (Cmin)

End point title	Analysis of Pharmacokinetic Parameter: Minimum Concentration of Exdoxaban (Cmin)

End point description:

Cmin is the minimum concentration of Edoxaban in plasma.

End point type	Primary

End point timeframe:

Days 30, 90, and 360 post-dose and at steady state (SS)

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	298		
Units: Mean concentration				
arithmetic mean (standard deviation)				
Day 30 (n=297, 297)	22.40 (± 6.48)	18.31 (± 5.33)		
Day 90 (n=288, 295)	22.79 (± 5.52)	18.44 (± 4.52)		
Day 360 (n=279, 286)	22.92 (± 7.77)	18.70 (± 6.19)		
Steady state (n=297, 298)	22.52 (± 6.49)	18.18 (± 5.20)		

Statistical analyses

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg)-D30

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (Day 30).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.29

Notes:

[9] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75 mg/Edoxaban 60 mg-D90

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=288) and Edoxaban 60 mg (n=295) (Day 90).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.19
upper limit	1.29

Notes:

[10] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60mg)-D360

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg (n=279) and Edoxaban 60 mg (n=286) (Day 360).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.16
upper limit	1.3

Notes:

[11] - Ratio of means

Statistical analysis title	Ratio of Means (Edoxaban 75mg/Edoxaban 60 mg)-SS

Statistical analysis description:

This statistical analysis assesses the ratio of means between Edoxaban 75 mg and Edoxaban 60 mg (steady state [SS]).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	595
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.0001
Method	Based on log-transformed values
Parameter estimate	Ratio of means
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	1.3

Notes:

[12] - Ratio of means

Primary: Analysis of Pharmacodynamics: Mean Exposure of Edoxaban Using Anti-Factor Xa Assay

End point title	Analysis of Pharmacodynamics: Mean Exposure of Edoxaban Using Anti-Factor Xa Assay

End point description:

The exposure of Edoxaban 75 mg was compared with Edoxaban 60 mg using a pharmacodynamic marker, anti-FXa.

End point type	Primary

End point timeframe:

Day 0 (baseline) and at Days 30, 90, and 360 (at pre-dose [SS], 1-2 hours post-dose, and 4-8 hours post-dose)

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	292	291		
Units: Mean concentration				
arithmetic mean (standard deviation)				
Day 0 (n=292, 291)	11.02 (± 37.18)	12.54 (± 41.83)		
Day 30 pre-dose (n=284, 284)	33.44 (± 58.22)	28.02 (± 58.12)		
Day 30, 1-2 h post-dose (n=291, 280)	233.37 (± 121.92)	201.24 (± 109.48)		
Day 30, 4-8 h post-dose (n=292, 280)	190.84 (± 73.36)	161.38 (± 63.46)		
Day 90 pre-dose (n=273, 281)	33.42 (± 59.23)	23.10 (± 47.12)		
Day 90, 1-2 h post-dose (n=280, 281)	229.32 (± 119.89)	179.69 (± 107.48)		
Day 90, 4-8 h post-dose (n=277, 283)	183.90 (± 78.65)	156.73 (± 67.12)		
Day 360 pre-dose (n=269, 276)	35.87 (± 59.23)	26.01 (± 55.48)		
Day 360, 1-2 h post-dose (n=269, 277)	214.73 (± 126.44)	181.13 (± 111.22)		
Day 360, 4-8 h post-dose (n=267, 279)	183.75 (± 94.73)	147.23 (± 76.63)		

Statistical analyses

Statistical analysis title	Difference of least square means (Day 30 pre-dose)
Statistical analysis description:	
This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=284) and Edoxaban 60 mg (n=284) (Day 30 pre-dose).	
Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.2644
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	5.464
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.14
upper limit	15.07

Notes:

[13] - Difference in least square means

Statistical analysis title	Difference of least square means (Day 30, 1-2 h)
Statistical analysis description:	
This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=291) and Edoxaban 60 mg (n=280) (Day 30, 1-2 h post-dose).	
Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	32.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.14
upper limit	51.39

Notes:

[14] - Difference in least square means

Statistical analysis title	Difference of least square means (Day 30, 4-8 h)
Statistical analysis description:	
This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=292) and Edoxaban 60 mg (n=280) (Day 30, 4-8 h post-dose).	
Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	29.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.49
upper limit	41.08

Notes:

[15] - Difference in least square means

Statistical analysis title	Difference of least square means (Day 90 pre-dose)
Statistical analysis description:	
This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=273) and Edoxaban 60 mg (n=281) (Day 90 pre-dose).	
Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg

Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0228
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	10.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.45
upper limit	19.31

Notes:

[16] - Difference in least square means

Statistical analysis title	Difference of least square means (Day 90, 1-2 h)

Statistical analysis description:

This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=280) and Edoxaban 60 mg (n=281) (Day 90, 1-2 h post-dose).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	49.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	31.11
upper limit	68.88

Notes:

[17] - Difference in least square means

Statistical analysis title	Difference of least square means; Day 360 pre-dose

Statistical analysis description:

This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=269) and Edoxaban 60 mg (n=276) (Day 360 pre-dose).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.0478
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	9.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	19.45

Notes:

[18] - Difference in least square means

Statistical analysis title	Difference of least square means; Day 360, 1-2 h

Statistical analysis description:

This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=269) and Edoxaban 60 mg (n=277) (Day 360, 1-2 h post-dose).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.0011
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	33.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.54
upper limit	53.6

Notes:

[19] - Difference in least square means

Statistical analysis title	Difference of least square means; Day 360, 4-8 h

Statistical analysis description:

This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=267) and Edoxaban 60 mg (n=279) (Day 360, 4-8 h post-dose).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	36.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	22.41
upper limit	51.32

Notes:

[20] - Difference in least square means

Statistical analysis title	Difference of least square means (Day 90, 4-8 h)

Statistical analysis description:

This statistical analysis reports the difference in the least square means between Edoxaban 75 mg (n=277) and Edoxaban 60 mg (n=283) (Day 90, 4-8 h post-dose).

Comparison groups	Edoxaban 75 mg v Edoxaban 60 mg
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Difference of least square means
Point estimate	27.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.27
upper limit	39.5

Notes:

[21] - Difference in least square means

Secondary: Number of Subjects With Adjudicated Composite Endpoint: Composite of Stroke, Transient Ischemic Attack, and Systemic Embolic Events (On-Treatment Period)

End point title	Number of Subjects With Adjudicated Composite Endpoint: Composite of Stroke, Transient Ischemic Attack, and Systemic Embolic Events (On-Treatment Period)

End point description:

The composite endpoint included stroke, transient ischemic attack (TIA), and systemic embolic events (SEE).

End point type	Secondary

End point timeframe:

Within 360 days post-dose

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	303		
Units: number of subjects				
number (not applicable)				
First of stroke, TIA, and SEE	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of Adjudicated Composite Endpoint: Composite of Stroke, Transient Ischemic Attack, Systemic Embolic Events, Myocardial Infarction, Cardiovascular Death, and Major Bleeding (On-Treatment Period)

End point title	Analysis of Adjudicated Composite Endpoint: Composite of

	Stroke, Transient Ischemic Attack, Systemic Embolic Events, Myocardial Infarction, Cardiovascular Death, and Major Bleeding (On-Treatment Period)

End point description:

The composite endpoint included Stroke, Transient Ischemic Attack (TIA), Systemic Embolic Events (SEE), Myocardial Infarction (MI), Cardiovascular Death, and Major Bleeding events.

End point type	Secondary

End point timeframe:

Within 360 days post-dose

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	303		
Units: Number of subjects				
number (not applicable)				
First stroke, TIA, SEE, MI, death, and bleeding	8	5		
First adjudicated stroke	3	2		
First adjudicated TIA	0	0		
First adjudicated SEE	0	0		
First adjudicated MI	0	0		
First adjudicated death	5	1		
First adjudicated major bleeding	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis of Adjudicated Bleeding Events: Major Bleeding and/or Clinically Relevant Non-Major Bleeding (On-Treatment Period)

End point title	Analysis of Adjudicated Bleeding Events: Major Bleeding and/or Clinically Relevant Non-Major Bleeding (On-Treatment Period)

End point description:

Adjudicated bleeding events (major bleeding and clinically relevant non-major [CRNM] bleeding events) were assessed.

End point type	Secondary

End point timeframe:

Within 360 days post-dose

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	303		
Units: Number of subjects				
number (not applicable)				
Major bleeding or CRNM bleeding	10	11		
First adjudicated major bleeding	3	2		
First adjudicated CRNM bleeding	7	9		
All bleeding	20	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adjudicated Composite Endpoint: Composite of Ischemic Stroke, Transient Ischemic Attack, and Systemic Embolic Events (On-Treatment Period)

End point title	Number of Subjects With Adjudicated Composite Endpoint: Composite of Ischemic Stroke, Transient Ischemic Attack, and Systemic Embolic Events (On-Treatment Period)

End point description:

The composite endpoint included ischemic stroke, transient ischemic attack (TIA), and systemic embolic events (SEE).

End point type	Secondary

End point timeframe:

Within 360 days post-dose

End point values	Edoxaban 75 mg	Edoxaban 60 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	303		
Units: Number of subjects				
number (not applicable)				
First of ischemic stroke, TIA, and SEE	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected and reported from the time of signing the informed consent form to the end of study assessment and follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Edoxaban 75 mg

Reporting group description:

Subjects received Edoxaban 60 mg and Edoxaban 15 mg orally, once daily at the same time (preferably morning) up to 12 months.

Reporting group title	Edoxaban 60 mg

Reporting group description:

Subjects received Edoxaban 60 mg and placebo 15 mg orally, once daily at the same time (preferably morning) up to 12 months.

Serious adverse events	Edoxaban 75 mg	Edoxaban 60 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 303 (14.52%)	33 / 303 (10.89%)	
number of deaths (all causes)	7	3	
number of deaths resulting from adverse events	5	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 303 (0.66%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Prostatic specific antigen increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal haematoma			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
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	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 303 (0.33%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	10 / 303 (3.30%)	8 / 303 (2.64%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 303 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 303 (1.32%)	6 / 303 (1.98%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure acute			

subjects affected / exposed	0 / 303 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 303 (0.33%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinoatrial block			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 303 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemorrhagic anaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Gastritis erosive			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 303 (0.66%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 303 (0.33%)	
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			
Muscle mass			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 303 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rheumatoid arthritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (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	2 / 303 (0.66%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Edoxaban 75 mg	Edoxaban 60 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 303 (43.56%)	115 / 303 (37.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 303 (2.64%)	8 / 303 (2.64%)	
occurrences (all)	8	8	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 303 (1.65%)	1 / 303 (0.33%)	
occurrences (all)	5	1	
Oedema peripheral			
subjects affected / exposed	1 / 303 (0.33%)	3 / 303 (0.99%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 303 (0.66%)	3 / 303 (0.99%)	
occurrences (all)	2	3	
Epistaxis			
subjects affected / exposed	3 / 303 (0.99%)	2 / 303 (0.66%)	
occurrences (all)	3	2	
Investigations			
Blood pressure increased			
subjects affected / exposed	3 / 303 (0.99%)	2 / 303 (0.66%)	
occurrences (all)	3	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	14 / 303 (4.62%)	12 / 303 (3.96%)	
occurrences (all)	14	12	
Cardiac failure			
subjects affected / exposed	5 / 303 (1.65%)	7 / 303 (2.31%)	
occurrences (all)	5	7	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 303 (1.98%)	7 / 303 (2.31%)	
occurrences (all)	6	7	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 303 (0.00%)	3 / 303 (0.99%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 303 (0.00%)	3 / 303 (0.99%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Anal haemorrhage			
subjects affected / exposed	3 / 303 (0.99%)	0 / 303 (0.00%)	
occurrences (all)	3	0	
Diarrhea			
subjects affected / exposed	4 / 303 (1.32%)	2 / 303 (0.66%)	
occurrences (all)	4	2	
Gingival bleeding			
subjects affected / exposed	0 / 303 (0.00%)	3 / 303 (0.99%)	
occurrences (all)	0	3	
Haemorrhoids			
subjects affected / exposed	4 / 303 (1.32%)	1 / 303 (0.33%)	
occurrences (all)	4	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	3 / 303 (0.99%)	
occurrences (all)	0	3	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	4 / 303 (1.32%)	4 / 303 (1.32%)	
occurrences (all)	4	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 303 (0.99%)	2 / 303 (0.66%)	
occurrences (all)	3	2	
Back pain			
subjects affected / exposed	5 / 303 (1.65%)	0 / 303 (0.00%)	
occurrences (all)	5	0	
Osteoarthritis			

subjects affected / exposed	3 / 303 (0.99%)	2 / 303 (0.66%)	
occurrences (all)	3	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 303 (2.31%)	4 / 303 (1.32%)	
occurrences (all)	7	4	
Influenza			
subjects affected / exposed	6 / 303 (1.98%)	5 / 303 (1.65%)	
occurrences (all)	6	5	
Nasopharyngitis			
subjects affected / exposed	4 / 303 (1.32%)	4 / 303 (1.32%)	
occurrences (all)	4	4	
Pneumonia			
subjects affected / exposed	3 / 303 (0.99%)	2 / 303 (0.66%)	
occurrences (all)	3	2	
Respiratory tract infection viral			
subjects affected / exposed	6 / 303 (1.98%)	1 / 303 (0.33%)	
occurrences (all)	6	1	
Upper respiratory tract infection			
subjects affected / exposed	6 / 303 (1.98%)	3 / 303 (0.99%)	
occurrences (all)	6	3	
Urinary tract infection			
subjects affected / exposed	3 / 303 (0.99%)	1 / 303 (0.33%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 303 (1.32%)	1 / 303 (0.33%)	
occurrences (all)	4	1	
Hyperuricaemia			
subjects affected / exposed	2 / 303 (0.66%)	3 / 303 (0.99%)	
occurrences (all)	2	3	
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 303 (0.99%)	3 / 303 (0.99%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	Clarified inclusion and exclusion criteria, updated the list of participating countries, updated screening, randomization, and baseline procedures, clarified adverse event collection and reporting procedures, confirmed appropriate reporting procedures for prior and concomitant medications, updated the PK/PD procedures, and modified study period and bleeding definitions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported