Clinical trial results:
An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention

Summary

EudraCT number	2014-002004-24
Trial protocol	NO BG AT BE DK NL PL PT ES CZ DE SE SK GB
Global end of trial date	03 December 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	CV185-316

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Global end of trial reached?	Yes
Global end of trial date	03 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The dual primary objectives of this study were: 1) To determine if apixaban is noninferior to Vitamin K Antagonist (VKA) (INR target range 2.0-3.0) on the combined endpoint of International Society on Thrombosis and Haemostasis (ISTH) major and clinically relevant non-major bleeding in patients with nonvalvular atrial fibrillation (NVAF) who develop acute coronary syndrome (ACS) and/or undergo percutaneous coronary intervention (PCI) with planned concomitant P2Y12 inhibitor therapy. 2) To determine if anticoagulant plus single antiplatelet therapy with a P2Y12 inhibitor is superior to anticoagulant plus dual antiplatelet therapy with a P2Y12 inhibitor and aspirin on the combined outcome of ISTH major and clinically relevant non-major bleeding in patients with NVAF who develop ACS and/or undergo PCI with concomitant anticoagulant therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 287
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 39
Country: Number of subjects enrolled	Brazil: 323
Country: Number of subjects enrolled	Bulgaria: 154
Country: Number of subjects enrolled	Canada: 198
Country: Number of subjects enrolled	Colombia: 9
Country: Number of subjects enrolled	Croatia: 100
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Denmark: 40
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Germany: 324
Country: Number of subjects enrolled	Hungary: 95
Country: Number of subjects enrolled	India: 24

Country: Number of subjects enrolled	Israel: 104
Country: Number of subjects enrolled	Korea, Republic of: 107
Country: Number of subjects enrolled	Mexico: 92
Country: Number of subjects enrolled	Netherlands: 19
Country: Number of subjects enrolled	Norway: 27
Country: Number of subjects enrolled	Peru: 21
Country: Number of subjects enrolled	Poland: 339
Country: Number of subjects enrolled	Portugal: 71
Country: Number of subjects enrolled	Romania: 64
Country: Number of subjects enrolled	Russian Federation: 767
Country: Number of subjects enrolled	Serbia: 138
Country: Number of subjects enrolled	Slovakia: 198
Country: Number of subjects enrolled	Spain: 67
Country: Number of subjects enrolled	Sweden: 53
Country: Number of subjects enrolled	Switzerland: 9
Country: Number of subjects enrolled	Ukraine: 333
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	United States: 520
Worldwide total number of subjects	4683
EEA total number of subjects	1732

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)	1285
From 65 to 84 years	3208
85 years and over	190

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

4683 participants enrolled, 4614 randomized. Reasons not randomized: 2 adverse event; 1 request to stop therapy; 12 withdrew consent; 1 lost to follow-up; 1 poor/non-compliance; 35 no longer met criteria; 2 admin reasons by Sponsor; 10 lack of IP at site; 1 IWRS down; 2 physician recommended; 1 leaving the country; 1 pharmacogenetic sample positive

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	Apixaban with Acetylsalicylic acid film coated tablet

Arm description:

5 mg or 2.5 mg Apixaban tablets orally twice per day with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Arm type	Experimental
Investigational medicinal product name	Acetylsalicylic acid = Aspirin; Apixaban = BMS-562247
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Acetylsalicylic acid, 81 mg; Apixaban, 5 mg or 2.5 mg

Arm title	Apixaban with Placebo matching Acetylsalicylic acid

Arm description:

5 mg or 2.5 mg Apixaban tablets orally twice per day with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Arm type	Experimental
Investigational medicinal product name	Placebo matching Acetylsalicylic acid = placebo matching Aspirin; Apixaban = BMS-562247
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching Acetylsalicylic acid, 0 mg; Apixaban, 5 mg or 2.5 mg

Arm title	Vitamin K Antagonist (VKA) with Acetylsalicylic acid

Arm description:

VKA tablets orally once daily with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Arm type	Experimental

Investigational medicinal product name	Acetylsalicylic acid = Aspirin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Acetylsalicylic acid, 81 mg; VKA, 5 mg or 1 mg

Arm title	VKA with Placebo matching Acetylsalicylic acid

Arm description:

VKA tablets orally once daily with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Arm type	Experimental
Investigational medicinal product name	Placebo matching Acetylsalicylic acid = placebo matching Aspirin; VKA = Warfarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching Acetylsalicylic acid, 0 mg; VKA, 5 mg or 1 mg

Number of subjects in period 1[1]	Apixaban with Acetylsalicylic acid film coated tablet	Apixaban with Placebo matching Acetylsalicylic acid	Vitamin K Antagonist (VKA) with Acetylsalicylic acid
Started	1153	1153	1154
Completed	1087	1091	1069
Not completed	66	62	85
Adverse event, serious fatal	39	41	35
Randomized in error	2	-	-
Poor/Non-Compliance	-	1	3
Stroke and stroke rehabilitation	-	-	1
Participant withdrew consent	14	12	30
Participant wanted home visits	1	-	-
Participant in jail	-	-	1
State regulations prevent participation	-	-	1
Coagulation values cannot be set	-	-	1
Participant no longer meets criteria	2	-	-
Participant request to stop therapy	4	3	8
Poor treatment monitoring	-	-	1
Adverse event, non-fatal	-	1	1
Investigator decision	-	-	1
Site closure; participant won't transfer	-	-	-
Lost to follow-up	3	3	2

Participant doesn't answer phone	1	-	-
No study drug on site	-	1	-

Number of subjects in period 1[1]	VKA with Placebo matching Acetylsalicylic acid
Started	1154
Completed	1071
Not completed	83
Adverse event, serious fatal	42
Randomized in error	-
Poor/Non-Compliance	4
Stroke and stroke rehabilitation	-
Participant withdrew consent	21
Participant wanted home visits	-
Participant in jail	-
State regulations prevent participation	-
Coagulation values cannot be set	-
Participant no longer meets criteria	1
Participant request to stop therapy	6
Poor treatment monitoring	-
Adverse event, non-fatal	2
Investigator decision	1
Site closure; participant won't transfer	1
Lost to follow-up	5
Participant doesn't answer phone	-
No study drug on site	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 4683 participants enrolled in the study, however, only 4614 were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	Apixaban with Acetylsalicylic acid film coated tablet
Reporting group description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	Apixaban with Placebo matching Acetylsalicylic acid
Reporting group description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	Vitamin K Antagonist (VKA) with Acetylsalicylic acid
Reporting group description:	
VKA tablets orally once daily with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	VKA with Placebo matching Acetylsalicylic acid
Reporting group description:	
VKA tablets orally once daily with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	

Reporting group values	Apixaban with Acetylsalicylic acid film coated tablet	Apixaban with Placebo matching Acetylsalicylic acid	Vitamin K Antagonist (VKA) with Acetylsalicylic acid
Number of subjects	1153	1153	1154
Age, Customized			
Units: Subjects			
< 65 years old	308	333	311
65-80 years old	664	660	662
>=80	181	160	181
Age Continuous			
Units: Years			
arithmetic mean	70.2	69.3	70.0
standard deviation	± 9.12	± 9.32	± 9.09
Sex: Female, Male			
Units: Subjects			
Female	357	313	339
Male	796	840	815
Race/Ethnicity, Customized			
Table is for category of Race.			
Units: Subjects			
White	1039	1058	1043
Black/African American	17	12	12
Asian	35	35	39
American Indian/Alaska Native	4	6	2
Native Hawaiian/Other Pacific Islander	0	0	0
Other	47	29	38
Not Reported	11	13	20
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino (US only)	2	10	7

Not Hispanic or Latino (US only)	114	123	120
Unknown or Not Reported	1037	1020	1027

Reporting group values	VKA with Placebo matching Acetylsalicylic acid	Total	
Number of subjects	1154	4614	
Age, Customized Units: Subjects			
< 65 years old	315	1267	
65-80 years old	657	2643	
>=80	182	704	
Age Continuous Units: Years			
arithmetic mean	70.0		
standard deviation	± 9.13	-	
Sex: Female, Male Units: Subjects			
Female	328	1337	
Male	826	3277	
Race/Ethnicity, Customized			
Table is for category of Race.			
Units: Subjects			
White	1044	4184	
Black/African American	18	59	
Asian	31	140	
American Indian/Alaska Native	4	16	
Native Hawaiian/Other Pacific Islander	1	1	
Other	43	157	
Not Reported	13	57	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino (US only)	5	24	
Not Hispanic or Latino (US only)	126	483	
Unknown or Not Reported	1023	4107	

Subject analysis sets

Subject analysis set title	Apixaban (treated)
Subject analysis set type	Full analysis
Subject analysis set description: 5 mg or 2.5 mg Apixaban tablets orally twice per day (all treated participants)	
Subject analysis set title	Vitamin K Antagonist (treated)
Subject analysis set type	Full analysis
Subject analysis set description: VKA tablets orally once daily (all treated participants)	
Subject analysis set title	Acetylsalicylic acid (aspirin) film coated tablet (treated)
Subject analysis set type	Full analysis
Subject analysis set description: 81 mg Acetylsalicylic acid film coated tablet orally once daily (all treated participants)	

Subject analysis set title	Placebo matching aspirin film coated tablet (treated)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo matching Acetylsalicylic acid film coated tablet orally once daily (all treated participants)	
Subject analysis set title	Apixaban (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day [all randomized (RND) participants]	
Subject analysis set title	Vitamin K Antagonist (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
VKA tablets orally once daily (all randomized participants)	
Subject analysis set title	Acetylsalicylic acid film coated tablet (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
81 mg Acetylsalicylic acid film coated tablet orally once daily (all randomized participants)	
Subject analysis set title	Placebo matching aspirin film coated tablet (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo matching Acetylsalicylic acid film coated tablet orally once daily (all randomized participants)	

Reporting group values	Apixaban (treated)	Vitamin K Antagonist (treated)	Acetylsalicylic acid (aspirin) film coated tablet (treated)
Number of subjects	2290	2259	2277
Age, Customized Units: Subjects			
< 65 years old 65-80 years old >=80			
Age Continuous Units: Years arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: Subjects			
Female Male			
Race/Ethnicity, Customized			
Table is for category of Race.			
Units: Subjects			
White Black/African American Asian American Indian/Alaska Native Native Hawaiian/Other Pacific Islander Other Not Reported			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino (US only) Not Hispanic or Latino (US only)			

Unknown or Not Reported			

Reporting group values	Placebo matching aspirin film coated tablet (treated)	Apixaban (randomized)	Vitamin K Antagonist (randomized)
Number of subjects	2279	2306	2308
Age, Customized Units: Subjects			
< 65 years old		641	626
65-80 years old		1324	1319
>=80		341	363
Age Continuous Units: Years			
arithmetic mean		69.8	70.0
standard deviation	±	± 9.23	± 9.11
Sex: Female, Male Units: Subjects			
Female		670	667
Male		1636	1641
Race/Ethnicity, Customized			
Table is for category of Race.			
Units: Subjects			
White		2097	2087
Black/African American		29	30
Asian		70	70
American Indian/Alaska Native		10	6
Native Hawaiian/Other Pacific Islander		0	1
Other		76	81
Not Reported		24	33
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino (US only)		12	12
Not Hispanic or Latino (US only)		237	246
Unknown or Not Reported		2057	2050

Reporting group values	Acetylsalicylic acid film coated tablet (randomized)	Placebo matching aspirin film coated tablet (randomized)	
Number of subjects	2307	2307	
Age, Customized Units: Subjects			
< 65 years old	619	648	
65-80 years old	1326	1317	
>=80	362	342	
Age Continuous Units: Years			
arithmetic mean	70.1	69.6	
standard deviation	± 9.10	± 9.23	

Sex: Female, Male Units: Subjects			
Female	696	641	
Male	1611	1666	
Race/Ethnicity, Customized			
Table is for category of Race.			
Units: Subjects			
White	2082	2102	
Black/African American	29	30	
Asian	74	66	
American Indian/Alaska Native	6	10	
Native Hawaiian/Other Pacific Islander	0	1	
Other	85	72	
Not Reported	31	26	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino (US only)	9	15	
Not Hispanic or Latino (US only)	234	249	
Unknown or Not Reported	2064	2043	

End points

End points reporting groups

Reporting group title	Apixaban with Acetylsalicylic acid film coated tablet
Reporting group description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	Apixaban with Placebo matching Acetylsalicylic acid
Reporting group description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	Vitamin K Antagonist (VKA) with Acetylsalicylic acid
Reporting group description:	
VKA tablets orally once daily with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Reporting group title	VKA with Placebo matching Acetylsalicylic acid
Reporting group description:	
VKA tablets orally once daily with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy	
Subject analysis set title	Apixaban (treated)
Subject analysis set type	Full analysis
Subject analysis set description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day (all treated participants)	
Subject analysis set title	Vitamin K Antagonist (treated)
Subject analysis set type	Full analysis
Subject analysis set description:	
VKA tablets orally once daily (all treated participants)	
Subject analysis set title	Acetylsalicylic acid (aspirin) film coated tablet (treated)
Subject analysis set type	Full analysis
Subject analysis set description:	
81 mg Acetylsalicylic acid film coated tablet orally once daily (all treated participants)	
Subject analysis set title	Placebo matching aspirin film coated tablet (treated)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo matching Acetylsalicylic acid film coated tablet orally once daily (all treated participants)	
Subject analysis set title	Apixaban (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
5 mg or 2.5 mg Apixaban tablets orally twice per day [all randomized (RND) participants]	
Subject analysis set title	Vitamin K Antagonist (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
VKA tablets orally once daily (all randomized participants)	
Subject analysis set title	Acetylsalicylic acid film coated tablet (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
81 mg Acetylsalicylic acid film coated tablet orally once daily (all randomized participants)	
Subject analysis set title	Placebo matching aspirin film coated tablet (randomized)
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo matching Acetylsalicylic acid film coated tablet orally once daily (all randomized participants)	

Primary: The rate of International Society on Thrombosis and Haemostasis (ISTH) major or Clinically Relevant Non-Major (CRNM) bleeding with Apixaban versus Vitamin K Antagonist (VKA) during the treatment period

End point title	The rate of International Society on Thrombosis and Haemostasis (ISTH) major or Clinically Relevant Non-Major (CRNM) bleeding with Apixaban versus Vitamin K Antagonist (VKA) during the treatment period

End point description:

Time to first ISTH major or CRNM bleeding during the 6-month period of treatment with Apixaban or VKA. N is the number of participants treated with Apixaban or VKA. n is the number of participants treated with Apixaban or VKA with major or CRNM bleeding in each treatment group during the 6-month period of treatment. Event rates are calculated based on the number of participants with major or CRNM bleeding divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Primary

End point timeframe:

Approximately 6 months

End point values	Apixaban (treated)	Vitamin K Antagonist (treated)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	332		
Units: Percentage per year				
number (not applicable)	24.66	35.79		

Statistical analyses

Statistical analysis title	ISTH major or CRNM bleeding with Apixaban vs. VKA

Statistical analysis description:

Separate hierarchical testing was performed for apixaban vs VKA: 1) Non-inferiority for the primary endpoint.

Comparison groups	Apixaban (treated) v Vitamin K Antagonist (treated)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	1-sided p-value for NI test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.82

Statistical analysis title	ISTH major or CRNM bleeding with Apixaban vs. VKA

Statistical analysis description:

Separate hierarchical testing was performed for apixaban vs VKA: 2) Superiority for the primary endpoint

Comparison groups	Apixaban (treated) v Vitamin K Antagonist (treated)
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	2-sided p-value for superiority test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.82

Primary: The rate of ISTH major or CRNM bleeding with aspirin versus no aspirin during the treatment period

End point title	The rate of ISTH major or CRNM bleeding with aspirin versus no aspirin during the treatment period

End point description:

Time to first ISTH major or CRNM bleeding during the treatment period of 6 months with aspirin or placebo. N is the number of participants with aspirin or placebo. n is the number of participants treated with aspirin or placebo with major or CRNM bleeding in each treatment group during the 6-month period of treatment. Event rates are calculated based on the number of participants with event of interest divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Primary

End point timeframe:

Approximately 6 months

End point values	Acetylsalicylic acid (aspirin) film coated tablet (treated)	Placebo matching aspirin film coated tablet (treated)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	367	204		
Units: Percentage per year				
number (not applicable)	40.51	21.03		

Statistical analyses

Statistical analysis title	ISTH major or CRNM bleeding with ASA vs no ASA

Statistical analysis description:

Separate hierarchical testing was performed for aspirin vs placebo: 2) Superiority for the primary

endpoint.

Comparison groups	Acetylsalicylic acid (aspirin) film coated tablet (treated) v Placebo matching aspirin film coated tablet (treated)
Number of subjects included in analysis	571
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	2-sided p-value for superiority test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	2.23

Secondary: Superiority on ISTH major or CRNM bleeding for Apixaban versus VKA

End point title	Superiority on ISTH major or CRNM bleeding for Apixaban versus VKA

End point description:

Time to first occurrence during the time the participants were treated with Apixaban or VKA. N is the number of participants treated with Apixaban or VKA. n is the number of participants treated with Apixaban or VKA with major or CRNM bleeding in each treatment group during the 6-month period of treatment. Event rates are calculated based on the number of participants with event of interest divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Secondary

End point timeframe:

Approximately 6 months

End point values	Apixaban (treated)	Vitamin K Antagonist (treated)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	241	332		
Units: Percentage per year				
number (not applicable)	24.66	35.79		

Statistical analyses

Statistical analysis title	ISTH major or CRNM bleeding with Apixaban vs. VKA

Statistical analysis description:

Separate hierarchical testing was performed for apixaban vs VKA: 2) Superiority for the primary endpoint.

Comparison groups	Apixaban (treated) v Vitamin K Antagonist (treated)

Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	2-sided p-value for superiority test

Secondary: The rate of all-cause death or all-cause rehospitalization with apixaban versus VKA

End point title	The rate of all-cause death or all-cause rehospitalization with apixaban versus VKA

End point description:

Time to first occurrence during the 6-month treatment period with Apixaban or VKA. N is the number of participants treated with Apixaban or VKA. n is the number of participants treated with Apixaban or VKA with death or ischemic events in each treatment group during the during the 6-month period of treatment. Event rates are calculated based on the number of participants with death or ischemic events divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Secondary

End point timeframe:

Approximately 6 months

End point values	Apixaban (randomized)	Vitamin K Antagonist (randomized)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	541	632		
Units: Percentage per year				
number (not applicable)	57.24	69.19		

Statistical analyses

Statistical analysis title	Death or rehospitalization with Apixaban vs VKA

Statistical analysis description:

Separate hierarchical testing was performed for apixaban vs VKA: 3) Superiority for all-cause death and all-cause rehospitalization.

Comparison groups	Apixaban (randomized) v Vitamin K Antagonist (randomized)
Number of subjects included in analysis	1173
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0033
Method	2-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	0.94

Secondary: The rate of all-cause death or all-cause rehospitalization with aspirn versus no aspirin

End point title	The rate of all-cause death or all-cause rehospitalization with aspirn versus no aspirin

End point description:

Time to first death or ischenic event during the 6-month treatment period with aspirin or placebo. N is the number of participants treated with aspirin or placebo. n is the number of participants treated with aspirin or placebo with death or ischemic events in each treatment group during the 6-month treatment period. Event rates are calculated based on the number of participants with death or ischemic events divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Secondary

End point timeframe:

Approximately 6 months

End point values	Acetylsalicylic acid film coated tablet (randomized)	Placebo matching aspirin film coated tablet (randomized)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	604	569		
Units: Percentage per year				
number (not applicable)	65.72	60.56		

Statistical analyses

Statistical analysis title	Death or rehospitalization with ASA vs no ASA

Statistical analysis description:

Separate hierarchical testing was performed for aspirin vs placebo: 3) Superiority for all-cause death and all-cause rehospitalization.

Comparison groups	Acetylsalicylic acid film coated tablet (randomized) v Placebo matching aspirin film coated tablet (randomized)
Number of subjects included in analysis	1173
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2219
Method	2-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.96
upper limit	1.2

Secondary: The rate of the composite endpoint of death or ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) with Apixaban versus VKA

End point title	The rate of the composite endpoint of death or ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) with Apixaban versus VKA

End point description:

Time to first all-cause death or all-cause hospitalization during the during the 6-month treatment period with Apixaban or VKA. N is the number of participants treated with Apixaban or VKA. n is the number of participants treated with Apixaban or VKA with all-cause death or all-cause hospitalization in each treatment group during the 6-month period of treatment. Event rates are calculated based on the number of participants with all-cause death or all-cause hospitalization divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Secondary

End point timeframe:

Approximately 6 months

End point values	Apixaban (randomized)	Vitamin K Antagonist (randomized)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	170	182		
Units: Percentage per year				
number (not applicable)	15.85	17.17		

Statistical analyses

Statistical analysis title	Rate of death or ischemic events (Apixaban vs VKA)

Statistical analysis description:

Separate hierarchical testing was performed for apixaban vs VKA: 4) Superiority for all-cause death and ischemic events.

Comparison groups	Apixaban (randomized) v Vitamin K Antagonist (randomized)
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.437
Method	2-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.13

Secondary: The composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) with aspirin versus no aspirin

End point title	The composite endpoints of death and ischemic events (stroke, myocardial infarction, stent thrombosis, urgent revascularization) with aspirin versus no aspirin

End point description:

Time to first all-cause death or all-cause hospitalization during the 6-month period of treatment with aspirin or placebo. N is the number of participants treated with aspirin or placebo. n is the number of participants treated with aspirin or placebo with all-cause death or all-cause hospitalization in each treatment group during the 6-month period of treatment. Event rates are calculated based on the number of participants with all-cause death or all-cause hospitalization divided by the sum of the number of days from the first dose of study drug to the event date or censoring date and expressed as percentage per year.

End point type	Secondary

End point timeframe:

Approximately 6 months

End point values	Acetylsalicylic acid film coated tablet (randomized)	Placebo matching aspirin film coated tablet (randomized)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	163	189		
Units: Percentage per year				
number (not applicable)	15.28	17.73		

Statistical analyses

Statistical analysis title	Rate of death or ischemic events (ASA vs no ASA)

Statistical analysis description:

Separate hierarchical testing was performed for aspirin vs placebo: 4) Superiority for all-cause death and ischemic events.

Comparison groups	Acetylsalicylic acid film coated tablet (randomized) v Placebo matching aspirin film coated tablet (randomized)

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1742
Method	2-sided p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.07

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events (AEs) with onset on or after the first dose of study medication through 2 days (for nonserious AE) or 30 days (for serious AE) after the last dose of study medication. Study Start: June 2014; Study Completion: Nov 2018(approx 54 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	APIXABAN AND ASA

Reporting group description:

5 mg or 2.5 mg Apixaban tablets orally twice per day with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Reporting group title	APIXABAN AND PLACEBO

Reporting group description:

5 mg or 2.5 mg Apixaban tablets orally twice per day with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Reporting group title	VITAMIN K ANTAGONIST AND ASA

Reporting group description:

VKA tablets orally once daily with 81 mg Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Reporting group title	VITAMIN K ANTAGONIST AND PLACEBO

Reporting group description:

VKA tablets orally once daily with placebo matching Acetylsalicylic acid film coated tablet orally once daily with concomitant P2Y12 inhibitor therapy

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There are no non-serious AEs to report considering the 5% threshold for reporting of non-serious AEs

Serious adverse events	APIXABAN AND ASA	APIXABAN AND PLACEBO	VITAMIN K ANTAGONIST AND ASA
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 1145 (4.63%)	50 / 1143 (4.37%)	52 / 1123 (4.63%)
number of deaths (all causes)	42	45	38
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lip squamous cell carcinoma			

subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm malignant			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer stage iv			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemorrhage			

subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cardiac death			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Death			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multimorbidity			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	2 / 1145 (0.17%)	2 / 1143 (0.17%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 1
Sudden death			
subjects affected / exposed	5 / 1145 (0.44%)	3 / 1143 (0.26%)	2 / 1123 (0.18%)
occurrences causally related to treatment / all	1 / 5	0 / 3	0 / 2
deaths causally related to treatment / all	1 / 5	0 / 3	0 / 2
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary hypertension			

subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain herniation			

subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Overdose			
subjects affected / exposed	2 / 1145 (0.17%)	0 / 1143 (0.00%)	5 / 1123 (0.45%)
occurrences causally related to treatment / all	1 / 2	0 / 0	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute myocardial infarction			
subjects affected / exposed	3 / 1145 (0.26%)	1 / 1143 (0.09%)	6 / 1123 (0.53%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 6
Angina pectoris			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Angina unstable			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	2 / 1145 (0.17%)	3 / 1143 (0.26%)	3 / 1123 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 3
Cardiac failure			
subjects affected / exposed	1 / 1145 (0.09%)	9 / 1143 (0.79%)	5 / 1123 (0.45%)
occurrences causally related to treatment / all	0 / 2	0 / 9	1 / 5
deaths causally related to treatment / all	0 / 1	0 / 8	0 / 4
Cardiac failure acute			
subjects affected / exposed	1 / 1145 (0.09%)	2 / 1143 (0.17%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardio-Respiratory arrest			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiogenic shock			
subjects affected / exposed	2 / 1145 (0.17%)	2 / 1143 (0.17%)	2 / 1123 (0.18%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 2
Cardiomyopathy			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiovascular disorder			

subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery disease			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Myocardial infarction			
subjects affected / exposed	4 / 1145 (0.35%)	5 / 1143 (0.44%)	5 / 1123 (0.45%)
occurrences causally related to treatment / all	0 / 4	1 / 5	0 / 5
deaths causally related to treatment / all	0 / 4	1 / 5	0 / 5
Myocardial ischaemia			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			

subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	3 / 1123 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Loss of consciousness			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	2 / 1123 (0.18%)
occurrences causally related to treatment / all	1 / 1	1 / 1	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Intestinal ischaemia			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Melaena			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Rectal haemorrhage			

subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Liver injury			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal failure			
subjects affected / exposed	0 / 1145 (0.00%)	2 / 1143 (0.17%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Meningoencephalitis bacterial			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 1145 (0.09%)	1 / 1143 (0.09%)	2 / 1123 (0.18%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1

Pneumonia bacterial			
subjects affected / exposed	0 / 1145 (0.00%)	1 / 1143 (0.09%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 1145 (0.09%)	2 / 1143 (0.17%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Septic shock			
subjects affected / exposed	3 / 1145 (0.26%)	1 / 1143 (0.09%)	1 / 1123 (0.09%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 1
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 1145 (0.09%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	VITAMIN K ANTAGONIST AND PLACEBO		
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 1126 (4.80%)		
number of deaths (all causes)	41		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lip squamous cell carcinoma			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	2 / 1126 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Malignant neoplasm progression				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neoplasm malignant				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal cancer stage iv				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic aneurysm				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				

subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shock				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Shock haemorrhagic				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
General disorders and administration site conditions				
Cardiac death				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Death				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multimorbidity				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sudden cardiac death				

subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sudden death				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				

subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	4 / 1126 (0.36%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Brain herniation			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Overdose			

subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Acute myocardial infarction				
subjects affected / exposed	2 / 1126 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Angina pectoris				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina unstable				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial flutter				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	3 / 1126 (0.27%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Cardiac failure				

subjects affected / exposed	4 / 1126 (0.36%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 4		
Cardiac failure acute			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure chronic			
subjects affected / exposed	3 / 1126 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Cardiac failure congestive			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-Respiratory arrest			
subjects affected / exposed	2 / 1126 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiogenic shock			
subjects affected / exposed	2 / 1126 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Cardiomyopathy			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiovascular disorder			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			

subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	2 / 1126 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Myocardial ischaemia				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Brain injury				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	2 / 1126 (0.18%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Cerebral infarction				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic stroke			
subjects affected / exposed	2 / 1126 (0.18%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Ischaemic stroke			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Loss of consciousness			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Status epilepticus			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic anaemia			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			

subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Intestinal ischaemia				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mesenteric artery thrombosis				
subjects affected / exposed	0 / 1126 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 1126 (0.09%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatotoxicity				

subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver injury			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Meningoencephalitis bacterial			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1126 (0.09%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	3 / 1126 (0.27%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Septic shock			
subjects affected / exposed	2 / 1126 (0.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 1126 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	APIXABAN AND ASA	APIXABAN AND PLACEBO	VITAMIN K ANTAGONIST AND ASA
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1145 (0.00%)	0 / 1143 (0.00%)	0 / 1123 (0.00%)

Non-serious adverse events	VITAMIN K ANTAGONIST AND PLACEBO		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 1126 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2016	The purpose of this amendment is to clarify language for the targeted SAE reporting, add language referencing stopping guidance in the DMC charter, and correct omissions from the original protocol. In the inclusion section, wording was changed to accommodate countries where age of adulthood is not 18 years of age. The target population was clarified to address NSTEMI with cardiac biomarkers to distinguish from unstable angina. Study was originally meant to allow patients who had balloon angioplasty, either with or without a stent being placed. Removing the word "with a stent" allows balloon angioplasty without stent. Additional language on unstable angina entry also added for clarification of the population. In addition, other revisions and/or clarifications are listed below within the synopsis and the protocol body. 1. Addition of word "and" after ACS in multiple places to clarify the population. 2. Replaced word antiplatelet with anticoagulant in hypothesis 3. In study figure 3.1.1 clarified exclusion box for CABG 4. Corrected exclusion criteria typo for serum creatinine from 133 micromol/L to 221 micromol/L 5. Deleted duplicate text for WOCBP who are breastfeeding. 6. Deleted Aspirin Placebo from Adverse drug reactions. 7. Added additional subcriteria under "other criteria". 8. Clarified Prohibited/restricted treatments paragraph 9. Corrected greater than and less than signs 10. Asterisk added for Visits 1-3 in Short Term Procedure Outline 11. Clarified SAE reporting 12. Added paragraph to DMC 13. Clarified wording for Drug Study Records. 14. Added 2 abbreviation to terms table 15. Corrected any typographical errors. Removing the version number from of the Investigator Brochure
28 April 2016	The purpose of amendment 02 is to clarify the hypothesis, objectives and patient population in regard to patients who have non-valvular atrial fibrillation and acute coronary syndrome and/or PCI by adding the word "and" in front of "PCI" throughout the protocol, editing the study schematic, as well as to add clarifying language to the targeted SAE reporting section. Table 4-1 was updated to include BMS study medication that will be supplied in some countries where local sourcing is not an option. In addition sections 4.3, 4.8, 4.9, and 9.2.2 were updated based on the mandatory language in the revised protocol model document.
11 October 2017	The purpose of Amendment 05 is to reword inconsistent language in the current protocol to clarify the patient eligibility criteria, add an efficacy composite endpoint of all-cause death/all-cause re-hospitalization and to correct typographical errors. In addition, Amendment 05 lists some of the data not specified in the protocol but included in the electronic case report form; this data is planned for potential secondary publications. Medical Monitor Address Change
21 August 2018	Amendment 07 - (1) Describes the use of hierarchical statistical testing to analyze the data for apixaban vs VKA and aspirin vs aspirin placebo; (2) Notes the change in the Medical Monitor and his contact information. Change in Medical Monitor Contact information. Date corrected on title page of protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported