



Clinical trial results:

RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period

Summary

EudraCT number	2015-004412-38
Trial protocol	PT NL ES DE IT
Global end of trial date	27 June 2018

Results information

Result version number	v1 (current)
This version publication date	23 June 2019
First version publication date	23 June 2019

Trial information

Trial identification

Sponsor protocol code	1160.248
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	08 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2018
Global end of trial reached?	Yes
Global end of trial date	27 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the net clinical benefit of the treatment arms, as measured by the composite of venous thrombotic event (VTE) (recurring cerebral venous thrombosis [CVT]; deep vein thrombosis [DVT] of any limb, pulmonary embolism [PE], or splanchnic vein thrombosis) or major bleeding events (MBEs) according to ISTH (International Society on Thrombosis and Haemostasis) criteria, after up to 24 weeks. Secondary objectives included a comparison of additional efficacy and safety parameters. A substudy at selected trial centres looked at the development of dural fistulas during the 24-week treatment period following the qualifying CVT.

Protection of trial subjects:

Only participants that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All participants were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all participants was adhered to throughout the trial conduct. Rescue medication was allowed for all participants as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 December 2016
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	Germany: 13
Country: Number of subjects enrolled	India: 20
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Portugal: 22
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Spain: 4
Worldwide total number of subjects	123
EEA total number of subjects	81

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)	110
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This is a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE [prospective, randomised, open-label, blinded endpoint] design), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period.

Pre-assignment

Screening details:

All participants were screened for eligibility to participate in the trial. Participants attended specialist sites which would then ensure that they (all participants) met all inclusion/exclusion criteria. Participants were not to be randomised to trial treatment if any one of the specific entry criteria were not met.

Period 1

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

Blinding implementation details:

This was a randomised, open-label, exploratory trial with blinded endpoint adjudication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabigatran etexilate

Arm description:

Participants were orally treated with Dabigatran etexilate 150 milligram (mg) capsule twice daily for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Dabigatran etexilate
Investigational medicinal product code	
Other name	Pradaxa®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were orally treated with Dabigatran etexilate 150 milligram (mg) capsule twice daily for 24 weeks.

Arm title	Warfarin
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Arm description:

Participants were orally treated with Warfarin 1 mg/3 mg/5 mg tablet, as needed to maintain a target international normalised ratio (INR) of 2.0 - 3.0, once daily for 24 weeks.

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

Dosage and administration details:

Participants were orally treated with Warfarin 1 mg/3 mg/5 mg tablet, as needed to maintain a target international normalised ratio (INR) of 2.0 - 3.0, once daily for 24 weeks.

Number of subjects in period 1^[1]	Dabigatran etexilate	Warfarin
Started	60	60
Completed	59	58
Not completed	1	2
Adverse event, non-fatal	1	-
Lost to follow-up	-	1
Reason not listed	-	1

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: The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups

Reporting group title	Dabigatran etexilate
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Reporting group description:

Participants were orally treated with Dabigatran etexilate 150 milligram (mg) capsule twice daily for 24 weeks.

Reporting group title	Warfarin
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Reporting group description:

Participants were orally treated with Warfarin 1 mg/3 mg/5 mg tablet, as needed to maintain a target international normalised ratio (INR) of 2.0 - 3.0, once daily for 24 weeks.

Reporting group values	Dabigatran etexilate	Warfarin	Total
Number of subjects	60	60	120
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS): The set includes patients who received at least one dose of study medication and were analysed according to the treatment they received.			
Units: years			
arithmetic mean	44.4	46.0	
standard deviation	± 14.06	± 13.64	-
Sex: Female, Male			
TS			
Units: Subjects			
Female	33	33	66
Male	27	27	54
Race (NIH/OMB)			
TS			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	12	7	19
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	45	49	94
More than one race	0	0	0
Unknown or Not Reported	3	4	7
Ethnicity (NIH/OMB)			
TS			
Units: Subjects			
Hispanic or Latino	4	11	15
Not Hispanic or Latino	52	43	95
Unknown or Not Reported	4	6	10

End points

End points reporting groups

Reporting group title	Dabigatran etexilate
Reporting group description: Participants were orally treated with Dabigatran etexilate 150 milligram (mg) capsule twice daily for 24 weeks.	
Reporting group title	Warfarin
Reporting group description: Participants were orally treated with Warfarin 1 mg/3 mg/5 mg tablet, as needed to maintain a target international normalised ratio (INR) of 2.0 - 3.0, once daily for 24 weeks.	

Primary: Percentage of participants with composite of Venous Thrombotic Event (VTE) or major bleeding event (MBE) according to International Society on Thrombosis and Haemostasis (ISTH) criteria in full observation period

End point title	Percentage of participants with composite of Venous Thrombotic Event (VTE) or major bleeding event (MBE) according to International Society on Thrombosis and Haemostasis (ISTH) criteria in full observation period ^[1]
End point description: Composite of the percentage of participants with MBE according to ISTH criteria and VTE (recurring cerebral venous thrombosis (CVT); deep venous thrombosis (DVT) of any limb, pulmonary embolism (PE), splanchnic vein thrombosis) in full observation period. All components were adjudicated in a blinded manner. Major bleeds were defined according to the ISTH definition of a major bleed, as follows: -Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or - Bleeding associated with a reduction in haemoglobin of at least 2 grams/decilitre (1.24 millimole/Litre) within 24 h, or leading to transfusion of 2 or more units of blood or packed cells and/or -Fatal bleed.	
End point type	Primary
End point timeframe: From first administration of trial medication until 6 days after last administration of trial medication, up to 25 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[2]	60 ^[3]		
Units: Percentage of participants				
number (confidence interval 95%)	1.7 (0.0 to 8.9)	3.3 (0.4 to 11.5)		

Notes:

[2] - Full analysis set (FAS)

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with recurring cerebral venous and dural sinus thrombosis; DVT of any limb, PE or splanchnic vein thrombosis in full

observation period

End point title	Percentage of participants with recurring cerebral venous and dural sinus thrombosis; DVT of any limb, PE or splanchnic vein thrombosis in full observation period
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End point description:

VTE criteria: -New neurological signs/symptoms or worsening of previous signs/symptoms with new CVT on neuroimaging. -DVT of any limb was documented by: Abnormal compression ultrasonography; An intraluminal filling defect on venography; At autopsy -Splanchnic vein thrombosis: The presence of endoluminal material/absence of flow in the extrahepatic portal veins/mesenteric veins as shown by duplex-Doppler ultrasound/contrast-enhanced CT scan/MRI. -PE was documented by: An intraluminal filling defect in segmental/more proximal branches on spiral CT scan; An intraluminal filling defect/an extension of an existing defect/a sudden cut-off of vessels >2.5 mm in diameter on the pulmonary angiogram; Perfusion defect of at least 75% of a segment with a local normal ventilation result on ventilation/perfusion lung scan; Inconclusive spiral CT, pulmonary angiography/lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasonography/venography; At autopsy.

End point type	Secondary
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End point timeframe:

From first administration of trial medication until 6 days after last administration of trial medication, up to 25 weeks.

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[4]	60 ^[5]		
Units: Percentage of participants				
number (confidence interval 95%)				
Recurring CVT	0.0 (0.0 to 6.0)	0.0 (0.0 to 6.0)		
DVT of any limb	0.0 (0.0 to 6.0)	0.0 (0.0 to 6.0)		
PE	0.0 (0.0 to 6.0)	0.0 (0.0 to 6.0)		
Splanchnic vein thrombosis	0.0 (0.0 to 6.0)	0.0 (0.0 to 6.0)		

Notes:

[4] - FAS

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses at week 24

End point title	Cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses at week 24
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End point description:

Cerebral venous recanalisation was assessed by imaging and was adjudicated. Occlusion of cerebral veins and sinuses was scored as: 1 = full occlusion; 0 = no occlusion/partial occlusion. This score was applied using the below conventions: Superior sagittal, straight, cavernous sinuses, left and right jugular veins each scored individually as either 0 or 1; Right lateral transverse and sigmoid sinus were scored together, Left lateral transverse and sigmoid sinus were scored together, Superior petrous sinus and inferior petrous sinus were scored together, these were scored together as 0 = neither was fully occluded and 1 = at least 1 of them was fully occluded; Deep venous system, Superficial cortical veins, Cerebellar veins were scored as systems with conventions as 0 = none was fully occluded and 1 = at least 1 was fully occluded. For each patient a total score was calculated at baseline and at EOT and the recanalisation score was calculated as EOT - baseline total scores.

End point type	Secondary
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End point timeframe:
Baseline and week 24

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55 ^[6]	52 ^[7]		
Units: Units on scale				
arithmetic mean (standard deviation)	-0.8 (± 0.78)	-1.0 (± 0.92)		

Notes:

[6] - FAS - Patients with missing/not analysable MRI scan at EOT are excluded from the analysis

[7] - FAS - Patients with missing/not analysable MRI scan at EOT are excluded from the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major bleeding according to ISTH criteria in full observation period

End point title	Percentage of participants with major bleeding according to ISTH criteria in full observation period
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End point description:

Major bleeds were defined according to the ISTH definition of a major bleed, as follows: -Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or -Bleeding associated with a reduction in haemoglobin of at least 2 grams/decilLitre (1.24 millimole/Litre) within 24 h, or leading to transfusion of 2 or more units of blood or packed cells and/or -Fatal bleed

End point type	Secondary
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End point timeframe:

From first administration of trial medication until 6 days after last administration of trial medication, up to 25 weeks.

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[8]	60 ^[9]		
Units: Percentage of participants				
number (confidence interval 95%)	1.7 (0.0 to 8.9)	3.3 (0.4 to 11.5)		

Notes:

[8] - TS

[9] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Composite endpoint of percentage of participants with new Intracranial haemorrhage or worsening of the haemorrhagic component of a previous lesion after up to 24 weeks

End point title	Composite endpoint of percentage of participants with new Intracranial haemorrhage or worsening of the haemorrhagic component of a previous lesion after up to 24 weeks
End point description: Intracranial haemorrhage (ICH) comprised the subtypes of intracerebral bleeds, subdural bleeds, epidural bleeds and subarachnoid bleeds that were recorded.	
End point type	Secondary
End point timeframe: From first administration of trial medication until end of treatment visit, up to 24 weeks.	

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56 ^[10]	53 ^[11]		
Units: Percentage of participants				
number (confidence interval 95%)	1.8 (0.0 to 9.6)	3.8 (0.5 to 13.0)		

Notes:

[10] - TS - Patients with missing/not analysable MRI scan at baseline or EOT are excluded from the analysis

[11] - TS - Patients with missing/not analysable MRI scan at baseline or EOT are excluded from the analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinically relevant non-major bleeding events in full observation period

End point title	Percentage of participants with clinically relevant non-major bleeding events in full observation period
End point description: A clinically relevant non-major bleeding event (CRNMBE) was a clinically overt bleed that did not meet the criteria for a major bleed but prompted a clinical response, in that it led to at least 1 of the following: A hospital admission (i.e. overnight stay in the hospital) for bleeding / A physician guided medical or surgical treatment for bleeding / A physician guided change, interruption or discontinuation of trial medication.	
End point type	Secondary
End point timeframe: From first administration of trial medication until 6 days after last administration of trial medication, up to 25 weeks.	

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[12]	60 ^[13]		
Units: Percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 6.0)	1.7 (0.0 to 8.9)		

Notes:

[12] - TS

[13] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with major bleeding according to ISTH criteria or CRNMBEs after up to 24 weeks

End point title	Percentage of participants with major bleeding according to ISTH criteria or CRNMBEs after up to 24 weeks
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End point description:

Percentage of participants with major bleeding according to ISTH criteria or CRNMBEs after up to 24 weeks.

End point type	Secondary
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End point timeframe:

From first administration of trial medication until end of treatment visit, up to 24 weeks.

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[14]	60 ^[15]		
Units: Percentage of participants				
number (confidence interval 95%)	1.7 (0.0 to 8.9)	5.0 (1.0 to 13.9)		

Notes:

[14] - TS

[15] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with any bleeding event after up to 24 weeks

End point title	Percentage of participants with any bleeding event after up to 24 weeks
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End point description:

Percentage of participants with any bleeding event after up to 24 weeks where any bleeding event is the sum of all major and non-major bleeding events.

End point type	Secondary
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End point timeframe:

From first administration of trial medication until end of treatment visit, up to 24 weeks.

End point values	Dabigatran etexilate	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60 ^[16]	60 ^[17]		
Units: Percentage of participants				
number (confidence interval 95%)	20.0 (10.8 to 32.3)	20.0 (10.8 to 32.3)		

Notes:

[16] - TS

[17] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of trial medication until 6 days after last administration of trial medication, up to 25 weeks.

Adverse event reporting additional description:

TS

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Warfarin
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Reporting group description:

Participants were orally treated with Warfarin 1 mg/3 mg/5 mg tablet, as needed to maintain a target international normalised ratio (INR) of 2.0 - 3.0, once daily for 24 weeks.

Reporting group title	Dabigatran etexilate
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Reporting group description:

Participants were orally treated with Dabigatran etexilate 150 milligram (mg) capsule twice daily for 24 weeks.

Serious adverse events	Warfarin	Dabigatran etexilate	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 60 (10.00%)	8 / 60 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningioma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio fluctuation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			

subjects affected / exposed	2 / 60 (3.33%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (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	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial venous sinus thrombosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Evans syndrome			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal necrosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haematoma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			

subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe fever with thrombocytopenia syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Warfarin	Dabigatran etexilate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 60 (28.33%)	21 / 60 (35.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 60 (13.33%)	10 / 60 (16.67%)	
occurrences (all)	9	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 60 (3.33%)	4 / 60 (6.67%)	
occurrences (all)	2	4	
Dyspepsia			
subjects affected / exposed	0 / 60 (0.00%)	4 / 60 (6.67%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 60 (0.00%)	5 / 60 (8.33%)	
occurrences (all)	0	5	
Psychiatric disorders			
Depression			

subjects affected / exposed	4 / 60 (6.67%)	2 / 60 (3.33%)	
occurrences (all)	4	2	
Insomnia			
subjects affected / exposed	4 / 60 (6.67%)	0 / 60 (0.00%)	
occurrences (all)	4	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2017	The number of planned patients was changed from a total of 180 to 120 (and from 90 to 60 patients planned in each treatment arm). The anticipated drop-out rate was changed from 15-20% to 10%, resulting in an estimated 108 evaluable patients (54 per treatment arm). It was clarified that all women of childbearing potential (WOCBP) should perform a pregnancy test every 4 weeks. A list of acceptable contraception methods was added and tubal ligation was removed from the list of procedures to render a woman not of childbearing potential. It was also specified that WOCBP should use effective methods of birth control from the moment of signing informed consent for the trial until completion of the follow-up visit (Visit 6). It was clarified that the primary objective did not require 24 weeks of treatment. The set up of the adjudication committee (AC) was performed by BI and not by a third party. A caution statement was added regarding treatment with warfarin in patients with known protein C or protein S deficiency. The requirements for confirmation of DVT, PE and splanchnic vein thrombosis were changed to require images and/or reports (instead of both) to be provided to the AC. An additional patient population, Screened Set (SCR), was defined, i.e. All patients who signed informed consent and completed at least some screening procedures. The list of documents and images that would be made available for adjudication purposes was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Full analysis set (FAS): All patients randomised were analysed in the treatment group to which they were randomised regardless of whether they took study medication. This followed the intent-to-treat principle.

Notes: