



Clinical trial results:

Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years

Summary

EudraCT number	2009-013618-29
Trial protocol	FR AT NL ES LT SK LV IT BE Outside EU/EEA
Global end of trial date	18 February 2016

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	1160.89
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01083732
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, +1 800 2430127, clintrriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 800 2430127, clintrriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000081-PIP01-07
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 February 2016
Global end of trial reached?	Yes
Global end of trial date	18 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives were:

- To provide paediatric PK/PD data
- To investigate the tolerability and safety of the dabigatran etexilate solution in children aged 1 to <12 years who had completed planned treatment with either low molecular weight heparins or oral anticoagulation for a venous thrombotic event (VTE)

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2011
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	Switzerland: 2
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Thailand: 4
Worldwide total number of subjects	18
EEA total number of subjects	5

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	6

months)	
Children (2-11 years)	12
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of 20 patients enrolled, 18 patients entered the trial.

Pre-assignment

Screening details:

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

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open label, non-randomised, uncontrolled, single arm study .

Arms

Are arms mutually exclusive?	Yes
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Arm title	Dabigatran etexilate (single dose, age group 1 to <2 years)
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Arm description:

The patients aged 1 to <2 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

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

Dosage and administration details:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose was adjusted based on age and weight and was equivalent to the adult dose of 150 mg dabigatran etexilate.

Arm title	Dabigatran etexilate (single dose, age group 2 to <12 years)
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Arm description:

The patients aged 2 to <12 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

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

Dosage and administration details:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose was adjusted based on age and weight and was equivalent to the adult dose of 150 mg dabigatran etexilate.

Arm title	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
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Arm description:

The patients aged 2 to <12 years were orally administered a multiple dose (3 days, twice daily) of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

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

Dosage and administration details:

The patients were orally administered multiple doses (3 days, twice daily) of dabigatran etexilate. The dose was adjusted based on age and weight. The first dose was chosen as 80% of the adult dose and the second up to the sixth dose were equivalent to the adult dose of 150 mg dabigatran etexilate.

Number of subjects in period 1	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
Started	6	9	3
Completed	6	9	3

Baseline characteristics

Reporting groups

Reporting group title	Dabigatran etexilate (single dose, age group 1 to <2 years)
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Reporting group description:

The patients aged 1 to <2 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Reporting group title	Dabigatran etexilate (single dose, age group 2 to <12 years)
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Reporting group description:

The patients aged 2 to <12 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Reporting group title	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
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Reporting group description:

The patients aged 2 to <12 years were orally administered a multiple dose (3 days, twice daily) of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Reporting group values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
Number of subjects	6	9	3
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS): This patient set included all subjects who were dispensed study medication and were documented to have taken at least 1 dose of trial medication.			
Units: years			
arithmetic mean	1	5.2	8.3
standard deviation	± 0	± 2.6	± 2.5
Gender, Male/Female			
Units: Participants			
Female	2	3	2
Male	4	6	1

Reporting group values	Total		
Number of subjects	18		
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS): This patient set included all subjects who were dispensed study medication and were documented to have taken at least 1 dose of trial medication.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	7		

Male	11		
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End points

End points reporting groups

Reporting group title	Dabigatran etexilate (single dose, age group 1 to <2 years)
Reporting group description: The patients aged 1 to <2 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)	
Reporting group title	Dabigatran etexilate (single dose, age group 2 to <12 years)
Reporting group description: The patients aged 2 to <12 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)	
Reporting group title	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
Reporting group description: The patients aged 2 to <12 years were orally administered a multiple dose (3 days, twice daily) of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)	
Subject analysis set title	Dabigatran etexilate (single dose, age group 1 to <12 years)
Subject analysis set type	Full analysis
Subject analysis set description: The patients aged 1 to <12 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)	

Primary: Plasma concentration of total dabigatran (SUM BIBR 953 ZW)

End point title	Plasma concentration of total dabigatran (SUM BIBR 953 ZW) ^[1]
End point description: Plasma concentration of total dabigatran (SUM BIBR 953 ZW). Pharmacokinetic set (PKS): This patient set included all treated patients who provided at least one pharmacokinetic/ pharmacodynamic (PK/PD) observation and had no important protocol violations (PVs) with respect to the statistical analysis of PK or PD endpoints. 99999 denotes the "missing value" or "not applicable". Missing values as time-points were not applicable for reporting results for respective dose groups.	
End point type	Primary
End point timeframe: At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate and at 2 h, 50 h, and 72 h after multiple dose administration of dabigatran etexilate.	

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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[2]	9 ^[3]	3 ^[4]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1h (N= 4, 9, 99999)	79.4 (± 45.6)	90.6 (± 48.8)	99999 (± 99999)	

2h (N=6, 9, 2)	129 (± 9.84)	114 (± 37.9)	26 (± 62.6)	
4h (N=6, 9, 99999)	91 (± 23)	87.7 (± 31.6)	99999 (± 99999)	
6h (N=6, 9, 99999)	62.9 (± 32.6)	56.2 (± 34.2)	99999 (± 99999)	
10h (N=6, 9, 99999)	34.8 (± 41.4)	28.2 (± 37)	99999 (± 99999)	
50h (N=99999, 99999, 2)	99999 (± 99999)	99999 (± 99999)	46 (± 64.7)	
72h (N=99999, 99999, 3)	99999 (± 99999)	99999 (± 99999)	11.9 (± 47.8)	

Notes:

[2] - PKS (evaluable cases)

[3] - PKS (evaluable cases)

[4] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of free dabigatran (BIBR 953 ZW).

End point title	Plasma concentration of free dabigatran (BIBR 953 ZW). ^[5]
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End point description:

Plasma concentration of free dabigatran (SUM BIBR 953 ZW).

99999 denotes the "missing value" or "not applicable".

Missing values as time-points were not applicable for reporting results for respective dose groups.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate and at 2 h, 50 h, and 72 h after multiple dose administration of dabigatran etexilate

Notes:

[5] - 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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[6]	9 ^[7]	3 ^[8]	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1h (N= 4, 9, 99999)	68.5 (± 43.8)	80 (± 43.9)	99999 (± 99999)	
2h (N=6, 9, 2)	101 (± 12.8)	98.5 (± 35.3)	23.4 (± 72.2)	
4h (N=6, 9, 99999)	75.3 (± 30.2)	74.5 (± 31.7)	99999 (± 99999)	
6h (N=6, 9, 99999)	51.6 (± 40)	48.4 (± 37.9)	99999 (± 99999)	
10h (N=6, 9, 99999)	28.1 (± 49.8)	23.7 (± 40.3)	99999 (± 99999)	
50h (N=99999, 99999, 2)	99999 (± 99999)	99999 (± 99999)	37.3 (± 60.7)	

72h (N=99999, 99999, 3)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	8.43 ($\pm$ 44)	
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Notes:

[6] - PKS (evaluable cases)

[7] - PKS (evaluable cases)

[8] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement of ECT (ecarin clotting time) at predose and 2 and 10 h after intake of study medication.

End point title	Central measurement of ECT (ecarin clotting time) at predose and 2 and 10 h after intake of study medication. ^{[9][10]}
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End point description:

Central measurement of ECT (ecarin clotting time) at predose and 2 and 10 h after intake of study medication. ECT was not planned to be measured in the multiple dose group. The Standard Deviation presented below is actually the % coefficient of variation.

End point type	Primary
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End point timeframe:

at predose and 2 and 10 h after intake of study medication.

Notes:

[9] - 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.

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

Justification: ECT was not planned to be measured in the multiple dose group

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[11]	9 ^[12]		
Units: seconds				
arithmetic mean (standard deviation)				
Ebase (N=6, 6)	36.9 ($\pm$ 7.49)	36.8 ($\pm$ 10.5)		
E2 (N=6, 7)	79.8 ($\pm$ 5.15)	73.6 ($\pm$ 22.1)		
E10 (N=5, 7)	49.7 ($\pm$ 5.36)	52.2 ($\pm$ 10.3)		

Notes:

[11] - PKS (evaluable cases)

[12] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Cmax (maximum measured concentration of total dabigatran in plasma)

End point title	Cmax (maximum measured concentration of total dabigatran in plasma) ^{[13][14]}
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End point description:

Cmax (maximum measured concentration of total dabigatran in plasma).

Cmax can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of Cmax.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate

Notes:

[13] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of Cmax.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[15]	9 ^[16]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	129 (± 9.84)	116 (± 38.6)		

Notes:

[15] - PKS

[16] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: tmax (time from dosing to maximum measured concentration of total dabigatran in plasma)

End point title	tmax (time from dosing to maximum measured concentration of total dabigatran in plasma) ^{[17][18]}
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End point description:

tmax (time from dosing to maximum measured concentration of total dabigatran in plasma)

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate.

Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of this parameter.

Notes:

[17] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of tmax.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[19]	9 ^[20]		
Units: hours				
median (full range (min-max))	1.99 (1.92 to 2.2)	2 (1.03 to 4.02)		

Notes:

[19] - PKS

[20] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tz (area under the concentration time curve of the total dabigatran in plasma over the time interval 0 up to the last quantifiable data point)

End point title	AUC0-tz (area under the concentration time curve of the total dabigatran in plasma over the time interval 0 up to the last quantifiable data point) ^{[21][22]}
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End point description:

AUC0-tz (area under the concentration time curve of the total dabigatran in plasma over the time interval 0 up to the last quantifiable data point).

Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of this parameter.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate

Notes:

[21] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of AUC0-tz.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[23]	9 ^[24]		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	715 (± 22.5)	658 (± 32.5)		

Notes:

[23] - PKS

[24] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Cmax (maximum measured concentration of free dabigatran in plasma)

End point title	Cmax (maximum measured concentration of free dabigatran in plasma) ^{[25][26]}
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End point description:

Cmax (maximum measured concentration of free dabigatran in plasma).

Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of this parameter.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate

Notes:

[25] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of Cmax.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[27]	9 ^[28]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	101 (± 12.8)	102 (± 36.9)		

Notes:

[27] - PKS

[28] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: tmax (time from dosing to maximum measured concentration of free dabigatran in plasma)

End point title	tmax (time from dosing to maximum measured concentration of free dabigatran in plasma) ^{[29][30]}
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End point description:

tmax (time from dosing to maximum measured concentration of free dabigatran in plasma).

Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of this parameter.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate

Notes:

[29] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of tmax.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[31]	9 ^[32]		
Units: hours				
median (full range (min-max))	1.99 (1.92 to 2.2)	2 (1.08 to 2.08)		

Notes:

[31] - PKS

[32] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-tz (area under the concentration time curve of the free dabigatran in plasma over the time interval 0 up to the last quantifiable data point)

End point title	AUC0-tz (area under the concentration time curve of the free dabigatran in plasma over the time interval 0 up to the last quantifiable data point) ^{[33][34]}
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End point description:

AUC0-tz (area under the concentration time curve of the free dabigatran in plasma over the time interval 0 up to the last quantifiable data point).

Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of this parameter.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate

Notes:

[33] - 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.

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

Justification: Endpoint can only be calculated for single dose patients. For multiple dose patients the time points do not allow calculation of AUC0-tz.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[35]	9 ^[36]		
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	581 (± 27.7)	566 (± 32.2)		

Notes:

[35] - PKS

[36] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of patients with incidence of any bleeding events (major, clinically relevant non-major (CRNM) and minor) during the treatment period.

End point title	Percentage of patients with incidence of any bleeding events (major, clinically relevant non-major (CRNM) and minor) during the treatment period. ^[37]
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End point description:

Major: Fatal bleeding, Clinically overt bleeding associated with decrease in haemoglobin of at least 2 g/dL in 24-h-period, bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system, bleeding that required surgical intervention in an operating suite. CRNM: Overt bleeding for which a blood product was administered & which was not directly attributable to the patient's underlying medical condition, bleeding that required medical or surgical intervention to restore haemostasis, other than in an operating suite. Minor: Any overt or macroscopic evidence of bleeding that did not fulfil the criteria for either major bleeding or CRNM bleeding. For multiple dosing, all events with an onset date after the date of first dose until the end of trial treatment including 3 days after the last treatment and for single dosing, all events with an onset during the 48-h-period after study medication intake were assigned to the on-treatment period.

End point type	Primary
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End point timeframe:

Up to 6 days

Notes:

[37] - 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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[38]	9 ^[39]	3 ^[40]	
Units: Percentage of participants				
number (not applicable)	0	0	0	

Notes:

[38] - TS

[39] - TS

[40] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of patients with any adverse events during the treatment period

End point title	Percentage of patients with any adverse events during the treatment period ^[41]
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End point description:

Percentage of patients with any adverse events during the treatment period. For patients with multiple dosing, all AEs with an onset date after the date of first dose until the end of trial treatment including 3 days after the last treatment were assigned to the on-treatment period. For patients with single dosing, all AEs with an onset during the 48-h-period after study medication intake were assigned to the on-treatment period.

End point type	Primary
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End point timeframe:

Up to 6 days

Notes:

[41] - 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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[42]	9 ^[43]	3 ^[44]	
Units: Percentage of participants				
number (not applicable)	0	0	33.3	

Notes:

[42] - TS

[43] - TS

[44] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement of aPTT (activated partial thromboplastin time) at predose and 2 and 10 h after intake of study medication

End point title	Central measurement of aPTT (activated partial thromboplastin time) at predose and 2 and 10 h after intake of study medication ^[45] ^[46]
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End point description:

Central measurement of aPTT (activated partial thromboplastin time) at predose and 2 and 10 h after intake of study medication.

For multiple dose patients only local measurements were planned.

The Standard Deviation presented below is actually the % coefficient of variation

End point type	Primary
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End point timeframe:

at predose and 2 and 10 h after intake of study medication

Notes:

[45] - 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.

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

Justification: For multiple dose patients central measurement of aPTT had not been planned.

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[47]	9 ^[48]		
Units: seconds				
arithmetic mean (standard deviation)				
Ebase (N=6, 7)	32.3 (± 24.6)	34.9 (± 24.5)		
E2 (N=6, 9)	47.5 (± 24.7)	77 (± 54.6)		
E10 (N=5, 8)	40.3 (± 19.6)	58.4 (± 40.6)		

Notes:

[47] - PKS (evaluable cases)

[48] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of unchanged dabigatran etexilate (BIBR 1048 BS)

End point title	Plasma concentration of unchanged dabigatran etexilate (BIBR 1048 BS) ^{[49][50]}
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End point description:

Plasma concentration of unchanged dabigatran etexilate (BIBR 1048 BS).

99999 denotes the "missing value";

For single dose group at 4h and 10h and multiple dose group at 2h, 50h and 72h values are missing as values were below the limit of quantification. Not calculated as reliable estimation can only be performed when at least 2/3 of the data are available and thus the gMean and gCV is not calculated according to internal rules.

For single dose group at 6h, all patients except one patient had values below the limit of quantification. Other values missing in the table are due to the time-points not applicable for the respective dose groups.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate and at 2 h, 50 h, and 72 h after multiple dose administration of dabigatran etexilate

Notes:

[49] - 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.

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

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	Dabigatran etexilate (single dose, age group 1 to <12 years)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[51]	15 ^[52]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1h (N=99999, 13)	99999 (± 99999)	3.82 (± 107)		

2h (N=2, 5)	99999 (± 99999)	3.23 (± 74.4)		
4h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
6h (N=99999, 1)	99999 (± 99999)	1.05 (± 99999)		
10h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
50h (N=2, 99999)	99999 (± 99999)	99999 (± 99999)		
72h (N=3, 99999)	99999 (± 99999)	99999 (± 99999)		

Notes:

[51] - PKS (evaluable cases)

[52] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of metabolite BIBR 951 BS

End point title	Plasma concentration of metabolite BIBR 951 BS ^[53] ^[54]
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End point description:

Plasma concentration of metabolite BIBR 951 BS.

99999 denotes the "missing value";

For single dose group at 6h and 10h and multiple dose group at 2h, 50h and 72h values are missing as values were below the limit of quantification. Not calculated as reliable estimation can only be performed when at least 2/3 of the data are available and thus the gMean and gCV is not calculated according to internal rules.

Other values missing in the table are due to the time-points not applicable for the respective dose groups.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate and at 2 h, 50 h, and 72 h after multiple dose administration of dabigatran etexilate

Notes:

[53] - 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.

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

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	Dabigatran etexilate (single dose, age group 1 to <12 years)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[55]	15 ^[56]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1h (N=99999, 13)	99999 (± 99999)	4.88 (± 82.2)		
2h (N=2, 15)	99999 (± 99999)	3.55 (± 83)		

4h (N=99999, 4)	99999 (± 99999)	1.71 (± 52.8)		
6h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
10h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
50h (N=2, 99999)	99999 (± 99999)	99999 (± 99999)		
72h (N=3, 99999)	99999 (± 99999)	99999 (± 99999)		

Notes:

[55] - PKS (evaluable cases)

[56] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of metabolite BIBR 1087 SE

End point title	Plasma concentration of metabolite BIBR 1087 SE ^[57] ^[58]
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End point description:

Plasma concentration of metabolite BIBR 1087 SE.

99999 denotes the "missing value";

For single dose group at 6h and 10h and multiple dose group at 2h, 50h and 72h values are missing as values were below the limit of quantification. Not calculated as reliable estimation can only be performed when at least 2/3 of the data are available and thus the gMean and gCV is not calculated according to internal rules.

For single dose group at 4h, all patients except one patient had values below the limit of quantification. Other values missing in the table are due to the time-points not applicable for the respective dose groups.

End point type	Primary
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End point timeframe:

At 1 hour (h), 2 h, 4 h, 6 h, and 10 h after single administration of dabigatran etexilate and at 2 h, 50 h, and 72 h after multiple dose administration of dabigatran etexilate

Notes:

[57] - 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.

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

Justification: Only those arms for which the comparisons are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	Dabigatran etexilate (single dose, age group 1 to <12 years)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3 ^[59]	15 ^[60]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
1h (N=99999, 12)	99999 (± 99999)	2.31 (± 54)		
2h (N=2, 8)	99999 (± 99999)	1.51 (± 38.5)		
4h (N=99999, 1)	99999 (± 99999)	1.18 (± 99999)		

6h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
10h (N=99999, 15)	99999 (± 99999)	99999 (± 99999)		
50h (N=2, 99999)	99999 (± 99999)	99999 (± 99999)		
72h (N=3, 99999)	99999 (± 99999)	99999 (± 99999)		

Notes:

[59] - PKS (evaluable cases)

[60] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Primary: Global assessment of tolerability of study medication- Taste assessment

End point title	Global assessment of tolerability of study medication- Taste assessment ^[61]
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End point description:

The investigator was to provide a global clinical assessment of tolerability including patient taste assessment. This assessment was based on 6-point scale (Very good, good, satisfactory, bad, very bad, missing).

The taste assessment was only provided when the patient was old enough to evaluate the taste.

End point type	Primary
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End point timeframe:

Day 1 (immediately after dosing)

Notes:

[61] - 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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[62]	9 ^[63]	3 ^[64]	
Units: Percentage of participants				
number (not applicable)				
Very Good	0	0	0	
Good	0	0	0	
Satisfactory	0	44.44	33.33	
Bad	0	0	66.67	
Very Bad	0	33.33	0	
Missing	100	22.22	0	

Notes:

[62] - TS

[63] - TS

[64] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement of dTT (diluted thrombin time) at predose and 2 and 10 h after intake of study medication

End point title	Central measurement of dTT (diluted thrombin time) at predose and 2 and 10 h after intake of study medication ^[65]
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End point description:

Central measurement of dTT (diluted thrombin time) at predose and 2 and 10 h after intake of study medication. 99999 denotes the "missing value"; Missing values as time-points were not applicable for the respective dose groups. The Standard Deviation presented below is actually the % coefficient of variation.

End point type	Primary
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End point timeframe:

at predose and 2 and 10 h after intake of study medication

Notes:

[65] - 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 (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[66]	9 ^[67]	3 ^[68]	
Units: seconds				
arithmetic mean (standard deviation)				
Ebase (N=6, 9, 2)	31.9 (± 4.67)	35.6 (± 10.1)	32.9 (± 4.73)	
E2 (N=6, 9, 2)	46.6 (± 6.02)	53.6 (± 18.4)	34.3 (± 1.24)	
E10 (N=6, 9, 99999)	35.5 (± 6.02)	39.7 (± 9.76)	99999 (± 99999)	

Notes:

[66] - PKS (evaluable cases)

[67] - PKS (evaluable cases)

[68] - PKS (evaluable cases)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with changes in laboratory and clinical parameters such as liver enzymes and physical examination

End point title	Percentage of patients with changes in laboratory and clinical parameters such as liver enzymes and physical examination
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End point description:

Percentage of patients with changes in laboratory and clinical parameters such as liver enzymes and physical examination.

Clinically Relevant Abnormalities for Laboratory Parameters were reported.

End point type	Secondary
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End point timeframe:

During the treatment period, Up to 6 days

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[69]	9 ^[70]	3 ^[71]	
Units: Percentage of participants				
number (not applicable)	0	0	0	

Notes:

[69] - TS

[70] - TS

[71] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of tolerability of study medication

End point title	Global assessment of tolerability of study medication
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End point description:

The investigator was to provide a global clinical assessment of tolerability of study medication by the patient. This assessment was based on 5-point scale (good, satisfactory, not satisfactory, bad, not assessable).

End point type	Secondary
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End point timeframe:

Day 1 (immediately after dosing)

End point values	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6 ^[72]	9 ^[73]	3 ^[74]	
Units: Percentage of participants				
number (not applicable)				
Good	33.33	11.11	100	
Satisfactory	16.67	22.22	0	
Not satisfactory	33.33	44.44	0	
Bad	0	22.22	0	
Not assessable	16.67	0	0	

Notes:

[72] - TS

[73] - TS

[74] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events (AEs) during the treatment period, up to 6 days.

Adverse event reporting additional description:

For patients with multiple dosing, all AEs with an onset date after the date of first dose until the end of trial treatment including 3 days after the last treatment and for patients with single dosing, all AEs with an onset during the 48-h-period after study medication intake were assigned to the on-treatment period.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Dabigatran etexilate (single dose, age group 1 to <2 years)
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Reporting group description:

The patients aged 1 to <2 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Reporting group title	Dabigatran etexilate (multiple dose, age group 2 to <12 years)
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Reporting group description:

The patients aged 2 to <12 years were orally administered a multiple dose (3 days, twice daily) of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Reporting group title	Dabigatran etexilate (single dose, age group 2 to <12 years)
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Reporting group description:

The patients aged 2 to <12 years were orally administered a single dose of dabigatran etexilate (Dabigatran etexilate oral liquid formulation (6.25 mg/mL) after reconstitution from dabigatran etexilate granules (167.5 mg) and solvent for oral liquid formulation)

Serious adverse events	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Dabigatran etexilate (single dose, age group 1 to <2 years)	Dabigatran etexilate (multiple dose, age group 2 to <12 years)	Dabigatran etexilate (single dose, age group 2 to <12 years)
Total subjects affected by non-serious adverse events			

subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 9 (0.00%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	0 / 9 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2010	Several P-glycoprotein inhibitors (amiodarone, cyclosporine, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, tacrolimus) and P-glycoprotein inducers (rifampicin, St.John's Wort, carbamazepin, phenytoin) were added as restricted concomitant medication. Other changes were of administrative nature.
14 July 2010	-The individual doses of the multiple dosing scheme were changed. No patients were treated in this trial before implementation of Global Amendment 2. Originally, the dosing was to increase from 50% of the target dose (Day 1) to 80% (Day 2) to 100% (Day 3). Based on data from other trial 1160.88 (NCT00844415), concerns were raised that patients may not have reached the full therapeutic dose by Day 3 when they received the 100% dose. Therefore, Global Amendment 2 changed the multiple dosing to 80% of the target dose for Dose 1 on Day 1, followed by 100% for all subsequent 5 doses - The exclusion criterion 3J was revised to correct the definition of uncontrolled hypertension - The planned target dose was corrected to 1.38 mg/kg - Other changes related to clarifications of wording
11 November 2010	In exclusion criterion 4, severe renal dysfunction was no longer defined as serum creatinine $\geq 200 \mu\text{M}$ but as eGFR $< 80 \text{ mL/min/1.73m}^2$ using the Schwartz formula; this reflects the more common definition in children. Other changes were of administrative nature or related to clarifications of wording.
28 March 2011	This amendment introduced the following changes: - The endpoint 'global assessment of tolerability to study medication (including taste assessment)' was changed to a secondary endpoint. The taste assessment was now to be done by the patient (if old enough). If patients withdrew early, the taste was also to be assessed - Wording was changed to reflect that the DMC first evaluated the older age group before recruitment of the younger age group started - Exclusion criterion 2 ('previous history of cerebral venous thromboembolism') was removed: children with a history of cerebral VTE would be at a low risk of bleeding once the clot had resolved. The greatest risk would be at the onset of the cerebral VTE and the start of standard therapy - Wording was changed for removal of individual patients. Patients with a minor bleeding event were no longer automatically removed from the study, but could continue in the study as per investigator judgement - Asparaginase was added as a restricted concomitant medication - Other changes were of administrative nature or related to clarifications of wording.
27 March 2012	This amendment introduced the following changes: - The dosing changed from multiple (3 days twice daily) to a single dose, as approved by the Paediatric Committee of the European Medicines Agency - The list of restricted medications was modified: ASA and ASA-containing over-the counter medications and oral corticosteroids were removed as restricted medication as their use in this single dose study had no impact on the PK of dabigatran, on coagulation tests measuring PD effects or on safety - Procedures for analysing/reporting drug-induced liver injury (DILI) event were added - Other changes were of administrative nature or related to clarifications of wording

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported