Clinical trial results:
Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 years

Summary

EudraCT number	2008-006866-27
Trial protocol	Outside EU/EEA
Global end of trial date	16 February 2012

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	16 July 2015

Trial information

Trial identification

Sponsor protocol code	1160.88

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00844415
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 Pharma GmbH & Co. KG , +1 8002430127 , clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure , Boehringer Ingelheim Pharma GmbH & Co. KG , +1 8002430127 , clintriage.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)	EMEA-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	15 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2012
Global end of trial reached?	Yes
Global end of trial date	16 February 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate tolerability and safety of dabigatran etexilate capsules in adolescents. To explore preliminary pharmacokinetic and pharmacodynamic parameters in adolescents.

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	02 March 2009
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	Canada: 9
Worldwide total number of subjects	9
EEA total number of subjects	0

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)	9
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adolescent (12 to <18years) patients who successfully completed planned treatment with either low molecular weight heparins or oral anticoagulation for primary venous thrombotic event (VTE).

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 subject) met all strictly implemented inclusion/exclusion criteria. Subjects were not assigned to trial treatment if any one of the specific entry criteria were violated.

Period 1

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

Blinding implementation details:

Open-label study, only one investigational product used

Arms

Arm title	All patients

Arm description:

Dabigatran was administered twice daily for three consecutive days (total 6 doses). All patients received an initial oral dose of 1.71mg/kg of dabigatran (80 percent of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on thrombin time (TT) and clinical assessment, the dose was adjusted to the target dose of 2.14 mg/kg of dabigatran (100 percent of the adult dose adjusted for the patient's weight). Three patients received 75 mg dabigatran (first dose) followed by 100 mg twice daily (BID). Three patients took dabigatran 100 mg (first dose) followed by 125 mg BID. Two patients received a dose of 125 mg dabigatran followed by 150 mg BID. One patient received only a single dose of dabigatran (75 mg).

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

Dosage and administration details:

Dose 1: 50 mg capsule BID (100 mg daily)
Dose 2: 75 mg capsule BID (150 mg daily)
Dose 3: 2 X 50 mg capsules BID (200 mg daily)
Dose 4: 50 mg capsule & 75 mg capsule BID (250 mg daily)
Dose 5: 2 X 75 mg capsules BID (300 mg daily)
Maximum dose 150 mg BID

Number of subjects in period 1	All patients
Started	9
Pat. received 75 mg followed by 100 mg	3 [1]
Pat. received 100 mg followed by 125 mg	3 [2]

Pat. received 125 mg followed by 150 mg	2 [3]
Pat. received single dose 75 mg	1 [4]
Completed	8
Not completed	1
Consent withdrawn by subject	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Since the dose was adjusted by body weight, patients could receive different doses of dabigatran.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Since the dose was adjusted by body weight, patients could receive different doses of dabigatran.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Since the dose was adjusted by body weight, patients could receive different doses of dabigatran.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Since the dose was adjusted by body weight, patients could receive different doses of dabigatran.

Baseline characteristics

Reporting groups	
Reporting group title	All patients

Reporting group description:

Dabigatran was administered twice daily for three consecutive days (total 6 doses). All patients received an initial oral dose of 1.71mg/kg of dabigatran (80 percent of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on thrombin time (TT) and clinical assessment, the dose was adjusted to the target dose of 2.14 mg/kg of dabigatran (100 percent of the adult dose adjusted for the patient's weight). Three patients received 75 mg dabigatran (first dose) followed by 100 mg twice daily (BID). Three patients took dabigatran 100 mg (first dose) followed by 125 mg BID. Two patients received a dose of 125 mg dabigatran followed by 150 mg BID. One patient received only a single dose of dabigatran (75 mg).

Reporting group values	All patients	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			

Age Continuous | Units: years			
arithmetic mean	15.7		
standard deviation	± 1.3	-	
Gender, Male/Female Units: Participants			
Female	6	6	
Male	3	3	

End points

End points reporting groups

Reporting group title	All patients

Reporting group description:

Dabigatran was administered twice daily for three consecutive days (total 6 doses). All patients received an initial oral dose of 1.71mg/kg of dabigatran (80 percent of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on thrombin time (TT) and clinical assessment, the dose was adjusted to the target dose of 2.14 mg/kg of dabigatran (100 percent of the adult dose adjusted for the patient's weight). Three patients received 75 mg dabigatran (first dose) followed by 100 mg twice daily (BID). Three patients took dabigatran 100 mg (first dose) followed by 125 mg BID. Two patients received a dose of 125 mg dabigatran followed by 150 mg BID. One patient received only a single dose of dabigatran (75 mg).

Primary: Number of patients with adverse events

End point title	Number of patients with adverse events[1]

End point description:

Patients with treatment drug related adverse events (DRAEs) and serious adverse events (SAEs) are reported separately for on-treatment and post-treatment period. Events were considered „on-treatment" if occurring within 72 hours after last drug administration.

End point type	Primary

End point timeframe:

From Screening until 30 days after first drug administration (end of trial visit)

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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	9[2]			
Units: Participants				
DRAEs on-treatment	2			
SAEs on-treatment	0			
DRAEs post-treatment	0			
SAEs post-treatment	1			

Notes:

[2] - Treated Set (TS), all patients dispensed study medication that have taken at least one dose

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with bleeding events (major and minor)

End point title	Number of patients with bleeding events (major and minor)[3]

End point description:

Patients were carefully assessed for signs and symptoms of bleeding. Bleeding was to be classified as major or minor. Major bleeding had to satisfy one or more of the following criteria: Overt bleeding associated with a decrease in haemoglobin of at least 2 g/dL in 24 hours, Overt bleeding requiring a transfusion of red blood cells, Overt bleeding which was retroperitoneal, intracranial, intraocular, or intraarticular, any overt bleeding deemed by the attending physician to require discontinuation of study

medication. Minor bleeds were clinical bleeds that did not fulfill the criteria for major bleeds.

End point type	Primary

End point timeframe:

From Screening until 30 days after first drug administration (end of trial visit)

Notes:

[3] - 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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	9[4]			
Units: Participants	0			

Notes:

[4] - Treated Set (TS), all patients dispensed study medication that have taken at least one dose

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of free dabigatran

End point title	Plasma concentration of free dabigatran[5]

End point description:

Plasma concentration of free dabigatran measured at 72 hours after first dose

End point type	Primary

End point timeframe:

3 days

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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[6]			
Units: ng/ml				
geometric mean (geometric coefficient of variation)				
Patients with 75mg dose followed by 100mg (N=3)	28 (± 12.8)			
Patients with 100mg dose followed by 125mg (N=3)	41.6 (± 66.5)			

Notes:

[6] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Primary: Plasma concentration of total dabigatran

End point title	Plasma concentration of total dabigatran[7]

End point description:

Plasma concentration of total dabigatran measured at 72 hours after first dose

End point type	Primary

End point timeframe:

Day 3

Notes:

[7] - 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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[8]			
Units: ng/ml				
geometric mean (geometric coefficient of variation)				
Patients with 75mg dose followed by 100mg (N=3)	34.2 (± 3.56)			
Patients with 100mg dose followed by 125mg (N=3)	58.2 (± 48.7)			

Notes:

[8] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Primary: Thrombin time (TT) centrally measured

End point title	Thrombin time (TT) centrally measured[9]

End point description:

Measurement of TT was performed centrally by Hemoclot Thrombin Inhibitor clotting assay.

End point type	Primary

End point timeframe:

Day 3

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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[10]			
Units: seconds				
arithmetic mean (standard deviation)				
Patients with 75mg dose followed by 100mg (N=3)	36.9 (± 3.61)			
Patients with 100mg dose followed by 125mg (N=3)	37.4 (± 3.97)			

Notes:

[10] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Primary: TT locally measured

End point title	TT locally measured[11]

End point description:

Measurement of TT was performed locally by Hemoclot Thrombin Inhibitor clotting assay.

End point type	Primary

End point timeframe:

Day 3

Notes:

[11] - 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: According to the exploratory nature of this study only descriptive statistical methods were applied to all endpoints.

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[12]			
Units: seconds				
arithmetic mean (standard deviation)				
Patients with 75mg dose followed by 100mg (N=3)	33.5 (± 2.15)			
Patients with 100mg dose followed by 125mg (N=3)	36.8 (± 5.72)			

Notes:

[12] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Activated Partial Thromboplastin Time (aPTT) centrally measured at 72 hours after first dose

End point title	Activated Partial Thromboplastin Time (aPTT) centrally measured at 72 hours after first dose

End point description:

Measurement of aPTT was performed centrally using validated assays.

End point type	Secondary

End point timeframe:

Day 3

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[13]			
Units: seconds				
arithmetic mean (standard deviation)				
Patients with 75mg dose followed by 100mg (N=3)	38.6 (± 2.94)			

Patients with 100mg dose followed by 125mg (N=3)	47.4 (± 4.42)			

Notes:

[13] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Secondary: aPTT locally measured

End point title	aPTT locally measured

End point description:

Measurement of aPTT was performed locally using validated assays.

End point type	Secondary

End point timeframe:

Day 3

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[14]			
Units: seconds				
arithmetic mean (standard deviation)				
Patients with 75mg dose followed by 100mg (N=3)	29.9 (± 2.68)			
Patients with 100mg dose followed by 125mg (N=3)	33.6 (± 0.896)			

Notes:

[14] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Ecarin Clotting Time (ECT) centrally measured

End point title	Ecarin Clotting Time (ECT) centrally measured

End point description:

Measurement of ECT was performed centrally using validated assays. Descriptive statistics are only performed for the centrally measured ECT.

End point type	Secondary

End point timeframe:

Day 3

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	6[15]			
Units: seconds				
arithmetic mean (standard deviation)				
Patients with 75mg dose followed by 100mg (N=3)	43.3 (± 1.31)			
Patients with 100mg dose followed by 125mg (N=3)	49.6 (± 11.6)			

Notes:

[15] - Treated Set, all patients taking >= one dose. Statistics reported only for groups with > 2 patients

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with clinically relevant changes in any laboratory parameter, Electrocardiogram (ECG) or vital signs

End point title	Patients with clinically relevant changes in any laboratory parameter, Electrocardiogram (ECG) or vital signs

End point description:

Changes in any laboratory parameter, ECG or vital signs were judged clinically relevant by the investigator.

End point type	Secondary

End point timeframe:

Baseline and 3 days

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	9[16]			
Units: Participants	0			

Notes:

[16] - Treated Set (TS), all patients dispensed study medication that have taken at least one dose

Statistical analyses

No statistical analyses for this end point

Secondary: Occurences of clinical outcome

End point title	Occurences of clinical outcome

End point description:

Occurrences of clinical outcomes including recurrent venous thrombolic event (VTE), post thrombotic syndrome (PTS), pulmonary emboli (PEs), and total and VTE related mortality objectively assessed for example by ultrasound, venography or computed chromatography (CT) scan (based on the thrombus location). Number of patients with particular clinical outcome are reported.

End point type	Secondary

End point timeframe:

3 days

End point values	All patients			
Subject group type	Reporting group			
Number of subjects analysed	9[17]			
Units: Participants				
Patients with recurrent VTE	1			
Patients with PTS	0			
Patients with PE	0			
Patients with VTE related death	0			
Patients with other death	0			
Patients with other clinical outcome	0			

Notes:

[17] - Treated Set (TS), all patients dispensed study medication that have taken at least one dose

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 3 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1
Reporting groups	
Reporting group title	All patients

Reporting group description:

Dabigatran was administered twice daily for three consecutive days (total 6 doses). All patients received an initial oral dose of 1.71mg/kg of dabigatran (80 percent of the adult dose of 150 mg/70 kg adjusted for the patient's weight). Based on thrombin time (TT) and clinical assessment, the dose was adjusted to the target dose of 2.14 mg/kg of dabigatran (100 percent of the adult dose adjusted for the patient's weight). Three patients received 75 mg dabigatran (first dose) followed by 100 mg twice daily (BID). Three patients took dabigatran 100 mg (first dose) followed by 125 mg BID. Two patients received a dose of 125 mg dabigatran followed by 150 mg BID. One patient received only a single dose of dabigatran (75 mg).

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 9 (22.22%)		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Abdominal pain			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2009	Amendment 1 (06 March 2009) was implemented immediately as this amendment added verapamil to the list of restricted medications when new information became available concerning a potential interaction with dabigatran. There was also an administrative change to allow for analysis of screening/baseline TT and ECT.
29 September 2009	Amendment 2 (29 Sep 2009) was implemented to: 1.) Request parental consent / child assent for any left over plasma from local analyses and for an additional sample to be taken to be preserved for future research in coagulation studies performed by one of the Coordinating Investigators, Lesley Mitchell at the University of Alberta. This change to the protocol required Health Canada approval and REB approval prior to implementation. 2.) Provide clarification of some protocol requirements and to make administrative changes. These administrative changes to the protocol could be implemented without approval from Health Canada or institutional REBs.
19 February 2010	Amendment 3 (19Feb10), was implemented immediately when the results of two interaction study results became available. Total dabigatran concentrations were increased up to 2.5-fold by ketaconazole, a P-glycoprotein inhibitor. Rifampicin, a strong P-glycoprotein inducer, showed reductions in dabigatran concentrations by about 67%. A few minor administrative changes were also implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported