Clinical trial results:
open-label, single dose, tolerability, Pharmacokinetic/Pharmacodynamics and safety study of dabigatran etexilate given at the end of standard anticoagulant therapy in children aged less than 1 year old.

Summary

EudraCT number	2014-001259-22
Trial protocol	AT IT FR Outside EU/EEA
Global end of trial date	09 February 2016

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016

Trial information

Trial identification

Sponsor protocol code	1160.105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02223260
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, 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)	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	22 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2016
Global end of trial reached?	Yes
Global end of trial date	09 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to investigate the safety and tolerability of dabigatran etexilate solution in children aged less than 1 year, to demonstrate comparable PK/PD relationship to older children and adults and to confirm dabigatran etexilate dosing algorithm for children aged less than 1 year.

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 subjects as required. An independent DMC was implemented to monitor safety and tolerability on an ongoing basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Russian Federation: 6
Worldwide total number of subjects	10
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1
Infants and toddlers (28 days-23 months)	9
Children (2-11 years)	0
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:

Before inclusion into the trial, all patients had to complete the planned treatment with either Low molecular weight heparin(LMWH),Unfractionated heparin(UFH), or oral anticoagulation for Venous thrombotic event (VTE) prior to intake of the single dose of study medication.

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 strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment 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	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an Open-label, multicentre, non-randomised, uncontrolled, single-arm, single dose study.

Arms

Arm title	Dabigatran etexilate

Arm description:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose were adjusted based on an age and weight (equivalent to a 150 mg dose in adults). In case the patient could not take the full dose at once, the assigned dose could have been given as divided doses.

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 were adjusted based on an age and weight (equivalent to a 150 mg dose in adults).

Number of subjects in period 1[1]	Dabigatran etexilate
Started	8
Completed	8

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: Baseline characteristics are based on the 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

Reporting group description:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose were adjusted based on an age and weight (equivalent to a 150 mg dose in adults). In case the patient could not take the full dose at once, the assigned dose could have been given as divided doses.

Reporting group values	Dabigatran etexilate	Total	
Number of subjects	8	8	
Age categorical Units: Subjects			

Age Continuous			
Treated set (TS): the treated set included 8 patients who were dispensed study medication and were documented to have taken at least 1 dose of trial medication.			
Units: months			
arithmetic mean	2.912		
standard deviation	± 1.694	-	
Gender, Male/Female Units: Participants			
Female	5	5	
Male	3	3	

End points

End points reporting groups

Reporting group title	Dabigatran etexilate

Reporting group description:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose were adjusted based on an age and weight (equivalent to a 150 mg dose in adults). In case the patient could not take the full dose at once, the assigned dose could have been given as divided doses.

Primary: Plasma concentrations of total dabigatran at 2h and 12 h (+/-2h) post administration of dabigatran etexilate

End point title	Plasma concentrations of total dabigatran at 2h and 12 h (+/-2h) post administration of dabigatran etexilate[1]

End point description:

Plasma concentrations of total dabigatran at 2h and 12 h (+/-2h) post administration of dabigatran etexilate.

Pharmacokinetic set (PKS): This patient set included all treated patients who provided at least 1 PK/PD observation and had no important protocol violations(PV's) with respect to statistical analysis of PK or PD (Pharmacodynamic) endpoints.

End point type	Primary

End point timeframe:

2 hours (h) and 12h after drug administration on day 1

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			
Subject group type	Reporting group			
Number of subjects analysed	8[2]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
2h	120 (± 62.1)			
12h	60.4 (± 30)			

Notes:

[2] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean aPTT coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean aPTT coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.[3]

End point description:

Central measurement: The mean aPTT (activated partial thromboplastin time) coagulation time at 2 h and 12 h (±2 h) post administration of dabigatran etexilate. Standard deviation is actually the Coefficient of Variation.

End point type	Primary

End point timeframe:

2 h and 12 h after dosing on day 1

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

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[4]			
Units: second				
arithmetic mean (standard deviation)				
E2	78.9 (± 26.7)			
E12	62.8 (± 27.7)			

Notes:

[4] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean of ECT coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean of ECT coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.[5]

End point description:

Central measurement: The mean of Ecarin Clotting Time (ECT) coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate. Standard deviation is actually the Coefficient of Variation.

End point type	Primary

End point timeframe:

2 h and 12 h after dosing on day 1

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			
Subject group type	Reporting group			
Number of subjects analysed	8[6]			
Units: second				
arithmetic mean (standard deviation)				
E2	101 (± 44.3)			
E12	66.9 (± 23.5)			

Notes:

[6] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean of diluted thrombin time (dTT) coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean of diluted thrombin time (dTT) coagulation time at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.[7]

End point description:

Central measurement: The mean of dTT (AntiFactor IIa activity) coagulation time at 2 h and 12h (+/-2h) post administration
of dabigatran etexilate. Standard deviation is actually the Coefficient of Variation.

End point type	Primary

End point timeframe:

2 h and 12 h after dosing on day 1

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

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[8]			
Units: second				
arithmetic mean (standard deviation)				
E2	48.7 (± 24)			
E12	38.6 (± 8.12)			

Notes:

[8] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean aPTT ratio at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean aPTT ratio at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.[9]

End point description:

Central measurement: The mean aPTT (activated partial thromboplastin time) ratio at 2 h and 12 h (±2 h) post administration of dabigatran etexilate. Standard deviation is actually the Coefficient of Variation.

aPTT ratio= aPTT (post dose)/aPTT (baseline). The mean of aPTT ratio is presented.

End point type	Primary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h and 12 h after dosing on day 1

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.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[10]			
Units: ratio				
arithmetic mean (standard deviation)				
ER2	1.86 (± 19.5)			
ER12	1.47 (± 17.7)			

Notes:

[10] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean ECT ratio at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean ECT ratio at 2 h and 12h (+/-2h) post administration of dabigatran etexilate.[11]

End point description:

Central measurement: The mean Ecarin Clotting Time (ECT) ratio at 2 h and 12h (+/-2h) post administration of dabigatran etexilate. Standard deviation is actually the Coefficient of Variation.

ECT ratio= ECT(Post dose)/ECT(baseline), The mean of ECT ratio is presented.

End point type	Primary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h, and 12 h after dosing on day 1

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

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[12]			
Units: Ratio				
arithmetic mean (standard deviation)				
ER2	2.42 (± 34.2)			
ER12	1.63 (± 13.8)			

Notes:

[12] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Central measurement: The mean of dTT ratio at 2h and 12h (+/-2h) post administration of dabigatran etexilate.

End point title	Central measurement: The mean of dTT ratio at 2h and 12h (+/-2h) post administration of dabigatran etexilate.[13]

End point description:

Central measurement: The mean of dTT (AntiFactor IIa activity) ratio at 2 h and 12 h (±2 h) post administration of dabigatran

etexilate. Standard deviation is actually the Coefficient of Variation.

dTT ratio= dTT(post dose)/dTT(baseline). The mean of dTT ratio is presented.

End point type	Primary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h, and 12 h after dosing on day 1

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.

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[14]			
Units: ratio				
arithmetic mean (standard deviation)				
ER2	1.59 (± 25.4)			
ER12	1.26 (± 5.67)			

Notes:

[14] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters aPTT values.

End point title	PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters aPTT values.

End point description:

Linear regression models were used for modeling the relationship between total dabigatran plasma concentration and coagulation parameters aPTT values. For our simple regression model, R-squared is equal to the square of Pearson's coefficient of correlation. The R-squared can be between 0 and 1. R-squared =1 means a perfect fit.

End point type	Secondary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h, and 12 h after dosing on day 1

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[15]			
Units: R-Square				
number (not applicable)	0.752			

Notes:

[15] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters ECT values.

End point title	PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters ECT values.

End point description:

Linear regression models were used for modeling the relationship between total dabigatran plasma concentration and coagulation parameters ECT values. For our simple regression model, R-squared is equal to the square of Pearson's coefficient of correlation. The R-squared can be between 0 and 1. R-squared =1 means a perfect fit.

End point type	Secondary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h, and 12 h after dosing on day 1

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[16]			
Units: R-Square				
number (not applicable)	0.858			

Notes:

[16] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters dTT values.

End point title	PK-PD relationship: Relationship between total dabigatran plasma concentration and coagulation parameters dTT values.

End point description:

Linear regression models were used for modeling the relationship between total dabigatran plasma concentration and coagulation parameters dTT (AntiFactor IIa activity) ratio. For our simple regression model, R-squared is equal to the square of Pearson's coefficient of correlation. The R-squared can be between 0 and 1. R-squared =1 means a perfect fit.

End point type	Secondary

End point timeframe:

baseline (0.5 h before intake of study medication), 2 h, and 12 h after dosing on day 1

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[17]			
Units: R-Square				
number (not applicable)	0.92			

Notes:
[17] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of all bleeding events (major, CRNM and minor) during the treatment period.

End point title	Incidence of all bleeding events (major, CRNM and minor) during the treatment period.

End point description:

Percentage of patients with Incidence of all bleeding events(major, clinically relevant non-major (CRNM) & minor) during the treatment period (including the residual effect period).Bleeding events were classified as follow: Major bleeding: 1) Fatal bleeding 2) Clinically overt bleeding associated with decrease in haemoglobin of at least 2 g/dL (20 g/L) in 24-h-period 3) Bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system 4) Bleeding that required surgical intervention in an operating suite. CRNM bleeding: 1) Overt bleeding for which a blood product was administered & which was not directly attributable to the patient's underlying medical condition 2) Bleeding that required medical or surgical intervention to restore haemostasis, other than in an operating suite. Minor bleeding defined as any overt or macroscopic evidence of bleeding that did not fulfil the criteria for either major bleeding or CRNM bleeding.

End point type	Secondary

End point timeframe:

Within two days after the administration of trial medication, up to 3 days

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[18]			
Units: Percentage of participants				
number (not applicable)	0			

Notes:
[18] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of all AEs during the treatment period

End point title	Incidence of all AEs during the treatment period

End point description:

Percentage of patients with all adverse events during the treatment period (including REP).

End point type	Secondary

End point timeframe:

Within two days after the administration of trial medication, up to 3 days

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[19]			
Units: percentage of participants				
number (not applicable)	0			

Notes:

[19] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Global assessment of acceptability and tolerability of study medication

End point title	Global assessment of acceptability and tolerability of study medication

End point description:

The investigator was to provide a global clinical assessment of tolerability and acceptability 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

End point timeframe:

Day 1 (immediately after dosing)

End point values	Dabigatran etexilate			
Subject group type	Reporting group			
Number of subjects analysed	8[20]			
Units: percentage of participants				
number (not applicable)				
Good	75			
Satisfactory	12.5			
Not satisfactory	0			
Bad	12.5			
Not assessable	0			

Notes:

[20] - Treated set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Within two days after the administration of trial medication, up to 3 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	dabigatran etexilate

Reporting group description:

The patients were orally administered a single dose of liquid formulation of dabigatran etexilate. The dose were adjusted based on an age and weight (equivalent to a 150 mg dose in adults). In case the patient could not take the full dose at once, the assigned dose could have been given as divided doses.

Serious adverse events	dabigatran etexilate		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (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	dabigatran etexilate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: In this study no non-serious adverse events data documented, thus no non-serious adverse events are reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported