Clinical trial results:
An exploratory study to investigate the pharmacokinetics and effects of DABIgatran etexilate in patients with stable severe RENAL disease: DabiRenal

Summary

EudraCT number	2011-003081-32
Trial protocol	NL
Global end of trial date	20 December 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	17 April 2015

Trial information

Trial identification

Sponsor protocol code	1160.166

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01711853
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim Pharma GmbH & Co. KG
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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2013
Global end of trial reached?	Yes
Global end of trial date	20 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacokinetics and dynamics of dabigatran etexilate (75 mg twice daily) in patients with severe CKD (eGFR 15 - 30 ml/min).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were 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.
Based on the proven efficacy of dabigatran etexilate in NVAF patients, and the different safeguards and procedures implemented to protect patient safety, the benefit/risk ratio in this trial was considered as positive.

Background therapy:

No background therapy was given to the subjects

Evidence for comparator: -

Actual start date of recruitment	19 October 2012
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	Netherlands: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	2
From 65 to 84 years	16
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The screening visit (performed within a 9-day period before first trial drug administration) included documentation of patient information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, check of vital sign.

Period 1

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

Blinding implementation details:

This trial was performed open-label throughout. This seemed to be justified because the potential negative impact due to bias seemed to be low and did not outweigh practical considerations.

Arms

Arm title	Dabigatran 75 mg

Arm description:

Oral administration of 1 capsule of Dabigatran etexilate 75 mg twice daily

Arm type	Experimental
Investigational medicinal product name	Dabigatran 75 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral administration of 1 capsule of Dabigatran etexilate 75 mg twice daily

Number of subjects in period 1[1]	Dabigatran 75 mg
Started	16
Completed	16

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 patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Dabigatran 75 mg
Reporting group description:	
Oral administration of 1 capsule of Dabigatran etexilate 75 mg twice daily	

Reporting group values	Dabigatran 75 mg	Total	
Number of subjects	16	16	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	72.7		
standard deviation	± 7.6	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	13	13	

End points

End points reporting groups

Reporting group title	Dabigatran 75 mg

Reporting group description:

Oral administration of 1 capsule of Dabigatran etexilate 75 mg twice daily

Primary: Cmax,ss

End point title	Cmax,ss[1]

End point description:

Maximum concentration of Dabigatran etexilate in plasma at steady state was measured.
The samples for pharmacokinetics had to be taken from 30 min before drug administration up to 11 days after drug administration.

Pharmacokinetic set (PKS) which included all treated subjects that provided at least 1 observation for at least 1 primary pharmacokinetic endpoint without important protocol violations with respect to the evaluation of the pharmacokinetic endpoints and with predose values not greater than 5% of Cmax.

End point type	Primary

End point timeframe:

-0.5 hours (h), 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h, 23.5h, 47.5h, 71.5h, 95.5h, 119.5h, 155.5h, 167.5h, 168.5h, 169h, 170h, 171h, 172h, 174h, 176h, 179.5h, 180h, 192h, 216h, 240h

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: When the within group statistical analysis are provided, an error appears that the comparison groups are incomplete and that at least two comparison groups should be selected.Hence results for within group Statistical Analysis are not provided.

End point values	Dabigatran 75 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[2]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	207 (± 53.9)			

Notes:

[2] - Pharmacokinetic set (PKS)

Statistical analyses

No statistical analyses for this end point

Primary: AUCtau,ss

End point title	AUCtau,ss[3]

End point description:

Area under the plasma concentration-time curve of the total dabigatran at steady state over a uniform dosing interval tau was measured.

The samples for pharmacokinetics had to be taken from 30 min before drug administration up to 11 days after drug administration.

End point type	Primary

End point timeframe:

-0.5 hours (h), 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h, 23.5h, 47.5h, 71.5h, 95.5h, 119.5h, 155.5h, 167.5h, 168.5h, 169h, 170h, 171h, 172h, 174h, 176h, 179.5h, 180h, 192h, 216h, 240h

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: When the within group statistical analysis are provided, an error appears that the comparison groups are incomplete and that at least two comparison groups should be selected.Hence results for within group Statistical Analysis are not provided.

End point values	Dabigatran 75 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[4]			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	2140 (± 51.9)			

Notes:

[4] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first drug administration until 3 days after the last drug administration (Up to Day 11)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Dabigatran 75 mg
Reporting group description:	
Oral administration of 1 capsule of Dabigatran etexilate 75 mg twice daily	

Serious adverse events	Dabigatran 75 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (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 75 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)		
Injury, poisoning and procedural complications			
Nail injury			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2013	1] The maximum number of participating patients was increased from 15 to 20. 2] An additional aPTT measurement was added at 155:30 h planned time to better monitor patient safety and the total amount of blood taken from each patient was updated. At the same time the physical examination at 167:30 h planned time was removed, as a physical examination at screening only was considered sufficient. 3] Treatment non-compliance was more clearly defined and added as a reason for removal of individual patients from the trial. 4] At the end of the treatment period, patients previously on aspirin were allowed to re-start aspirin already at 192 h planned time (instead of 240 h), as this was not going to interfere with any of the pharmacokinetic or pharmacodynamic analyses. 5] It was clarified that patients were not allowed to eat for 1 h (instead of 2 h) before any of the blood samplings. 6] A definition of significant adverse events was added. 7] The allowed time between sampling and centrifugation was defined for samples taken at an external location. 8] An interim analysis was allowed during this trial, if needed. Another amendment was added on 30 January 2014 which stated that: Minor clarifications as well as additional creatinine measurements at 9 time points (-0:30 h, 23:30 h, 47:30 h,71:30 h, 95:30 h, 119:30 h, 115:30 h, 167:30 h, and 180:00 h planned time), in order to better monitor fluctuations in creatinine values due to the status of the patient’s renal impairment and analyse any effect of these fluctuations on pharmacokinetic parameters. Moreover, it was defined that plasma creatinine values were determined using a Roche Cobas analyser, so that the samples could be measured in the central laboratory. The above amendment is not provided as a separate amendment as we are getting an error as "global end of the trial date is before the protocol amendment date".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported