Clinical trial results:
An Open Label, Non-Randomised, Phase II study to Determine if Dabigatran and its Metabolites are Detectable in Breast Milk Following Oral Administration to Non-Breastfeeding Mothers

Summary

EudraCT number	2014-004249-29
Trial protocol	GB
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	30 November 2017
First version publication date	30 November 2017

Trial information

Trial identification

Sponsor protocol code	DALMATION/7212

Additional study identifiers

ISRCTN number	ISRCTN87845776
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Regent Point, Newcastle upon Tyne, United Kingdom,
Public contact	Ms Jenn Walker, Newcastle University, +44 01912082520, jenn.walker@newcastle.ac.uk
Scientific contact	Dr Paul Ayuk, Newcastle upon Tyne Hospitals NHS Foundation Trust, +44 0191 2829325, paul.ayuk@nuth.nhs.uk

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	28 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine if dabigatran and its metabolites are detectable in breast milk following oral administration to non-breast feeding mothers.

Pregnancy and the post-partum period are recognised risk factors for venous thrombo-embolism (VTE). VTE is one of the most important causes of maternal mortality. Low molecular weight heparin (LMWH) is currently recommended for post-partum VTE prophylaxis. Dabigatran has approval for the prevention of VTE in patients who have undergone elective total hip or knee replacement surgery.

The study will therefore calculate the pharmacokinetics of dabigatran (Tmax, Cmax, t1/2, AUC) in maternal plasma and breast milk to explore the extent of dabigatran secretion into breast milk in women between 2 and 7 days after giving birth.

The study also aimed to develop an HPLC-MS assay to measure dabigatran concentrations in both plasma and breast milk following oral dosing of dabigatran.

Protection of trial subjects:

The trial involved an independent Trial Oversight (TOC) committee to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

The maternity unit at site is an accredited UNICEF baby friendly unit and the guidelines associated with this accreditation were followed.
Recruitment was also conducted in line with principles of Good Clinical Practice.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was an open label, non-randomised, single centre, phase 2 study approaching participants from post-natal wards and Midwifery-led Units. Participants were recruited to the study between February 2016 and December 2016.

Pre-assignment

Screening details:

Potential participants were identified through screening medical records to identify women who had made an informed decision not to feed their baby with breast milk. Women were approached a minimum of 48 hours after delivery and also those who initially breastfed but had since stopped but within 7 days of giving birth were also screened.

Pre-assignment period milestones

Number of subjects started	2
Number of subjects completed	2

Period 1

Period 1 title	Dabigatran (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dabigatran

Arm description: -

Arm type	IMP
Investigational medicinal product name	Dabigatran
Investigational medicinal product code	
Other name	Pradaxa
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

a single dose of two 110mg dabigatran etexilate capsules (total 220mg) within 7 days post partum

Number of subjects in period 1	Dabigatran
Started	2
Completed	2

Baseline characteristics

Reporting groups	
Reporting group title	Dabigatran
Reporting group description:	
A single dose of two 110mg dabigatran etexilate capsules (total 220mg).	

Reporting group values	Dabigatran	Total	
Number of subjects	2	2	
Age categorical			
Participant HR60 was 28 years of age at baseline. Participant HR61 was 36 years of age at baseline.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	2	2	
Male	0	0	
Height (metres)			
Participant HR60 was 171m Participant HR61 was 173m			
Units: Subjects			
N/A	2	2	
Weight at booking (kg)			
Participant HR60 = 67 kg Participant HR61 = 62 kg			
Units: Subjects			
N/A	2	2	
BMI at booking			
Participant HR60 BMI at booking = 22.9 Participant HR61 BMI at booking = 20.7			
Units: Subjects			
N/A	2	2	
Ethnicity			
1 = Caucasian			
Units: Subjects			
N/A	2	2	
Days post-partum			
Participant HR60 = 6 days post partum. Participant HR61 - 5 days post partum.			
Units: Subjects			

N/A	2	2	
Serum creatinine			
Participant HR60 Serum creatinine = 48µM Participant HR61 Serum creatinine = 54µM			
Units: Subjects			
N/A	2	2	
Serum Alanine Transaminase			
Participant HR60 Serum Alanine Transaminase= 23 IU Participant HR61 Serum Alanine Transaminase= 11 IU			
Units: Subjects			
N/A	2	2	

End points

End points reporting groups

Reporting group title	Dabigatran

Reporting group description: -

Primary: Dabigatran pharmacokinetics in plasma and breast milk

End point title	Dabigatran pharmacokinetics in plasma and breast milk[1]

End point description:

Dabigatran pharmacokinetic parameters in plasma and breast milk are presented. Dabigatran was detected in plasma 1h after dosing.

End point type	Primary

End point timeframe:

Time to Dabigatran detection in hours

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: Due to limited data descriptive statistics are presented.

End point values	Dabigatran			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
number (not applicable)				
Participant HR60 (plasma)	1			
Participant HR61 (plasma)	1			
Participant HR60 (breast milk)	3			
Participant HR61 (breast milk)	2			

Attachments (see zip file)	Dabigatran pharmacokinetics/Table 1 Dabigatran Dabigatran Concentrations/Figures 1 to 3 Dabigatran

Statistical analyses

No statistical analyses for this end point

Primary: Peak concentration of Dabigatran in plasma and breast milk (Cmax)

End point title	Peak concentration of Dabigatran in plasma and breast milk (Cmax)[2]

End point description:

Dabigatran pharmacokinetic parameters in plasma and breast milk are presented. Peak plasma dabigatran concentrations of 204.6 ng/ml in HR60 and 414.9 ng/ml in HR61 were reached between 2-3 hours following dabigatran administration.

End point type	Primary

End point timeframe:

Peak concentration of Dabigatran following administration of drug.

Notes:

[2] - 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: Due to limited data descriptive statistics are presented.

End point values	Dabigatran			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/ml				
number (not applicable)				
Participant HR60 (Plasma)	204.6			
Participant HR61 (Plasma)	414.9			
Participant HR60 (Breast Milk)	8.2			
Participant HR61 (Breast Milk)	52.6			

Statistical analyses

No statistical analyses for this end point

Primary: Tmax (hours) of Dabigatran concentration in plasma and breast milk

End point title	Tmax (hours) of Dabigatran concentration in plasma and breast milk[3]

End point description:

Dabigatran pharmacokinetic parameters in plasma and breast milk are presented. Peak plasma dabigatran concentrations of 204.6 ng/ml in HR60 and 414.9 ng/ml in HR61 were reached between 2-3 hours following dabigatran administration.

End point type	Primary

End point timeframe:

Tmax (hours) of dabigatran pharmacokinetics in plasma and breast milk

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: Due to limited data descriptive statistics are presented.

End point values	Dabigatran			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
number (not applicable)				
Participant HR60 (Plasma)	2			
Participant HR61 (Plasma)	3			
Participant HR60 (Breast Milk)	7			
Participant HR61 (Breast Milk)	7			

Statistical analyses

No statistical analyses for this end point

Primary: Observed Exposure to Dabigatran (AUC 0-t)

End point title	Observed Exposure to Dabigatran (AUC 0-t)[4]

End point description:

Dabigatran pharmacokinetic parameters in plasma and breast milk are presented.

End point type	Primary

End point timeframe:

Observed Exposure to Dabigatran (AUC 0-t)

Notes:

[4] - 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: Due to limited data descriptive statistics are presented.

End point values	Dabigatran			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ng/ml.h				
number (not applicable)				
Participant HR60 (Plasma)	752.7			
Participant HR61 (Plasma)	1523			
Participant HR60 (Breast Milk)	16			
Participant HR61 (Breast Milk)	171			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All non-serious AEs/ARs that occur during drug treatment will be recorded on the eCRF, in the patient medical notes and also sent to the Newcastle CTU Management team within 2 weeks.
All SAEs and SARs during drug treatment will be reported to Sponsor.

Assessment type	Systematic

Dictionary used

Dictionary name	As verbatim
Dictionary version	1

Reporting groups

Reporting group title	Dabigatran

Reporting group description: -

Serious adverse events	Dabigatran		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dabigatran		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (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: No adverse events were reported for this trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2016	Change made to the location within the Newcastle Hospitals NHS Foundation Trust of where IMP would be assembled. The amendment was requested by NuTHFT pharmacy for logistical reasons. The drug label was therefore updated to reflect the change in address and phone number, which was classified as a substantial amendment to the MHRA
25 February 2016	Update to study recruitment strategies. Participants could also be approached at the point of discharge and be able to return to hospital for the treatment visit. The participant information sheet(s) updated to confirm an antidote is available for dabigatran which reverses the effect of heavy bleeding. The protocol was also updated to clearly define the Reference Safety Information to be used for the Dalmation trial.
22 March 2016	Praxbind was made available for use at the Royal Victoria Infirmary (RVI) Newcastle, via approval from the Haematology department. The protocol and participant documents were updated to include this as part of substantial amendment 2 made to REC. In line with the updated, it was requested that the SmPC for Pradaxa 110mg hard capsules dated 2nd March 2016 was to be approved for use for the Dalmation study. Although the risk of bleeding is extremely small, the use of the Praxbind for participants in the Dalmation study had been agreed with the Chief Investigator, Sponsor, Trial Oversight Committee (8th March 2016) and Haematology Department at the RVI.
02 June 2016	Change to study recruitment strategy: allowing for Participant Identification Centres (PICs) to help screen, identify and refer potentially eligible women to Newcastle RVI for study participation. Change to last breast milk/blood sample collection time: allowing for the last sample to be collected at either the 8, 9 or 10 hour time point after administration of the drug.
07 July 2016	Study was temporarily suspended on 23/06/16.
16 August 2016	Request to re-start study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 June 2016	Study temporarily suspended due to serious breach. Susbtantial Amendment to restart the study was made on 16th August 2017. The study received MHRA approval to restart on 31/08/2016. Favourable ethical opinion was received on the 06/09/2016.	06 September 2016

Notes:

Limitations and caveats

None reported