



## 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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| 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:

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**General information about the trial**

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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 (T<sub>max</sub>, C<sub>max</sub>, t<sub>1/2</sub>, 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:

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**Population of trial subjects**

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**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:

| <b>Subjects enrolled per age group</b>    |   |
|-------------------------------------------|---|
| 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

|                                        |               |
|----------------------------------------|---------------|
| <b>Arm title</b>                       | 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.<br>Participant HR61 was 36 years of age at baseline. |            |       |  |
| Units: Subjects                                                                                        |            |       |  |
| In utero                                                                                               | 0          | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                                                  | 0          | 0     |  |
| Newborns (0-27 days)                                                                                   | 0          | 0     |  |
| Infants and toddlers (28 days-23<br>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<br>Participant HR61 was 173m                                                 |            |       |  |
| Units: Subjects                                                                                        |            |       |  |
| N/A                                                                                                    | 2          | 2     |  |
| Weight at booking (kg)                                                                                 |            |       |  |
| Participant HR60 = 67 kg<br>Participant HR61 = 62 kg                                                   |            |       |  |
| Units: Subjects                                                                                        |            |       |  |
| N/A                                                                                                    | 2          | 2     |  |
| BMI at booking                                                                                         |            |       |  |
| Participant HR60 BMI at booking = 22.9<br>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.<br>Participant HR61 = 5 days post partum.                       |            |       |  |
| Units: Subjects                                                                                        |            |       |  |

|                                                                                                          |   |   |  |
|----------------------------------------------------------------------------------------------------------|---|---|--|
| N/A                                                                                                      | 2 | 2 |  |
| Serum creatinine                                                                                         |   |   |  |
| Participant HR60 Serum creatinine = 48µM<br>Participant HR61 Serum creatinine = 54µM                     |   |   |  |
| Units: Subjects                                                                                          |   |   |  |
| N/A                                                                                                      | 2 | 2 |  |
| Serum Alanine Transaminase                                                                               |   |   |  |
| Participant HR60 Serum Alanine Transaminase= 23 IU<br>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 <sup>[1]</sup> |
| End point description:<br>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:<br>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               |  |  |  |

|                                   |                                                                                                       |
|-----------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Dabigatran pharmacokinetics/Table 1 Dabigatran<br>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 (C<sub>max</sub>)

|                                                                                                                                                                                                                                                                   |                                                                                               |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                   | Peak concentration of Dabigatran in plasma and breast milk (C <sub>max</sub> ) <sup>[2]</sup> |
| End point description:<br>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:<br>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 <sup>[3]</sup> |
|-----------------|-----------------------------------------------------------------------------------|

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



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

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|                 |                                                          |
|-----------------|----------------------------------------------------------|
| End point title | Observed Exposure to Dabigatran (AUC 0-t) <sup>[4]</sup> |
|-----------------|----------------------------------------------------------|

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             |  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information<sup>[1]</sup>

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 | <p>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.</p> <p>The participant information sheet(s) updated to confirm an antidote is available for dabigatran which reverses the effect of heavy bleeding.</p> <p>The protocol was also updated to clearly define the Reference Safety Information to be used for the Dalmation trial.</p>                                                                                                                                                                                                                                        |
| 22 March 2016    | <p>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.</p> <p>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.</p> |
| 02 June 2016     | <p>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.</p> <p>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.</p>                                                                                                                                                                                                                                                                                              |
| 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. Substantial 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