



Clinical trial results:

An exploratory study to investigate the pharmacokinetics and effects of DABlgatran 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: C_{max,ss}

| | |
|-----------------|------------------------------------|
| End point title | C _{max,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 C_{max}.

| | |
|----------------|---------|
| 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: AUC_{tau,ss}

| | |
|-----------------|--------------------------------------|
| End point title | AUC _{tau,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 | <p>1] The maximum number of participating patients was increased from 15 to 20.</p> <p>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.</p> <p>3] Treatment non-compliance was more clearly defined and added as a reason for removal of individual patients from the trial.</p> <p>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.</p> <p>5] It was clarified that patients were not allowed to eat for 1 h (instead of 2 h) before any of the blood samplings.</p> <p>6] A definition of significant adverse events was added.</p> <p>7] The allowed time between sampling and centrifugation was defined for samples taken at an external location.</p> <p>8] An interim analysis was allowed during this trial, if needed.</p> <p>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.</p> <p>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.</p> <p>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".</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported