# Clinical trial results:
# Prospective Case Crossover Study to Assess Whether PDE5 Inhibitor Exposure in Men Increases the Risk for the Development of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)

## Summary

| | |
|---|---|
| EudraCT number | 2010-023586-22 |
| Trial protocol | DE |
| Global end of trial date | 28 March 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 17 March 2019 |
| First version publication date | 17 March 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BAY38-9456/12912 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00867815 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Bayer AG |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany, |
| Public contact | Therapeutic area head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact | Therapeutic area head, Bayer AG, clinical-trials-contact@bayer.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 | 28 March 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 28 March 2018 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to have been to determine whether the use of PDE5 inhibitors (vardenafil, sildenafil, tadalafil or avanafil) increases the risk for the development of NAION.

Protection of trial subjects:

The primary objective of this study was to have been to determine whether the use of PDE5 inhibitors (vardenafil, sildenafil, tadalafil or avanafil) increases the risk for the development of NAION.

Background therapy:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 13 July 2009 |
| 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 States: 10 |
| Worldwide total number of subjects | 10 |
| EEA total number of subjects | 0 |

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) | 5 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study started on 13 JUL 2009 (FPFV) and the date of last visit was 29 DEC 2017 (LPLV).

### Pre-assignment

Screening details:

There were 10 screening failures. The primary reasons for screen failure are protocol violation (8 participants) and consent withdrawn (2 participants)

### Period 1

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

### Arms

| | |
|---|---|
| **Arm title** | PDE5 inhibitor Use & Risk of NAION |

Arm description:

Participants were assessed at 2 visits. Visit 1 (Day 1) included screening, confirmation of the diagnosis of NAION, enrollment, and collection of data on PDE5 inhibitor and other concomitant medication use. Visit 2 (Day 90+/-30) was a follow-up visit to document the persistence of vision loss and confirm the diagnosis of NAION. No interventional treatment was administered in the context of this study.

| | |
|---|---|
| Arm type | No interventional treatment |
| Investigational medicinal product name | No interventional treatment |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

No interventional treatment was administered in this study.

| **Number of subjects in period 1** | PDE5 inhibitor Use & Risk of NAION |
|---|---|
| Started | 10 |
| Completed | 9 |
| Not completed | 1 |
| Lost to follow-up | 1 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Study |
|---|---|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---|---|---|
| Number of subjects | 10 | 10 | |
| Age Categorical<br>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) | 5 | 5 | |
| From 65-84 years | 5 | 5 | |
| 85 years and over | 0 | 0 | |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 62.3 | | |
| standard deviation | ± 11.1 | - | |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 10 | 10 | |
| Race (NIH/OMB)<br>Units: Subjects | | | |
| White | 10 | 10 | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| More than one race | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | PDE5 inhibitor Use & Risk of NAION |

Reporting group description:

Participants were assessed at 2 visits. Visit 1 (Day 1) included screening, confirmation of the diagnosis of NAION, enrollment, and collection of data on PDE5 inhibitor and other concomitant medication use. Visit 2 (Day 90+/-30) was a follow-up visit to document the persistence of vision loss and confirm the diagnosis of NAION. No interventional treatment was administered in the context of this study.

### Primary: Number of participants with confirmed diagnosis of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)

| | |
|---|---|
| End point title | Number of participants with confirmed diagnosis of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)[1] |

End point description:

The study population consisted of adult men, first diagnosed with NAION which started within 45 days before study start and took PDE5 inhibitors (vardenafil, sildenafil, tadalafil or avanafil) in the 1 year prior to enrollment.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Up to 45 days prior to study enrollment

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: In November 2017, FDA reviewed and approved the sponsor's request to terminate the study, concluding that study 12912 was unlikely to provide value for further risk assessment of NAION associated with the class of PDE5 inhibitors indicated for the treatment of erectile dysfunction. Because of the small sample size at termination of the study, the principal statistical analyses based on the valid for NAION analysis were not performed.

| End point values | PDE5 inhibitor Use & Risk of NAION | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: subjects | 10 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with most frequent medical history findings by primary system organ class at Visit 1

| | |
|---|---|
| End point title | Number of participants with most frequent medical history findings by primary system organ class at Visit 1 |

End point description:

The safety population includes participants who signed informed consent and who had any of the following collected at Visit 1 for safety: laboratory values, physical exam, any eye exams, or adverse events.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Day 1

| End point values | PDE5 inhibitor Use & Risk of NAION | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: subjects | | | | |
| Metabolism and nutrition disorders | 7 | | | |
| Eye disorders | 6 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with any adverse events reported at Visit 2

| End point title | Number of participants with any adverse events reported at Visit 2 |
|---|---|

End point description:

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject and can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally occurring during the trial.

| End point type | Secondary |
|---|---|

End point timeframe:

From informed consent signed up to Visit 2 (Day 90+/-30)

| End point values | PDE5 inhibitor Use & Risk of NAION | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 10 | | | |
| Units: subjects | 3 | | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From inform consent signed up to approximately 3 months after first diagnosis of NAION.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | PDE5 inhibitor Use & Risk of NAION |

Reporting group description:

Participants were assessed at 2 visits. Visit 1 (Day 1) included screening, confirmation of the diagnosis of NAION, enrollment, and collection of data on PDE5 inhibitor and other concomitant medication use. Visit 2 (Day 90+/-30) was a follow-up visit to document the persistence of vision loss and confirm the diagnosis of NAION. No interventional treatment was administered in the context of this study.

| Serious adverse events | PDE5 inhibitor Use & Risk of NAION | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Eye disorders | | | |
| Optic ischaemic neuropathy | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | PDE5 inhibitor Use & Risk of NAION | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| Eye disorders | | | |
| Eye irritation | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Ocular discomfort | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all) | 1 / 10 (10.00%)<br>1 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 01 February 2011 | - The time interval from suspected onset of NAION until initial presentation to the investigator was extended from 4 weeks to 45 days in order to have the possibility of including more patients in the study within this extended time period.<br>- The inclusion criteria number 1b was modified to state the circumstances under which patients without Relative Afferent Papillary Defect (RAPD) could be admitted into the study.<br>- The medical exclusion criteria number 2d was modified to state the circumstances under which patients with an ESR above 40 mm/hr could be included in the study. |
| 02 March 2016 | - Erectile dysfunction as an inclusion criterion was removed (but the information on erectile dysfunction is collected).<br>- Eligibility criteria and data recording related to PDE5 inhibitor use were changed.<br>- Correlation coefficient for exposure was removed from the list of sample size parameters to be analyzed during interim analysis, because the analyst will be blinded to the timing of PDE5 inhibitor exposure in the risk period. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

- Study was prematurely terminated, no statistical analysis was performed due to small sample of population.
- There was no treatment administered in this study, product information is entered with the mere purpose to erase validation error.

Notes: