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 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 Units: years			
arithmetic mean	62.3		
standard deviation	± 11.1	-	
Gender Categorical Units: Subjects			
Female	0	0	
Male	10	10	
Race (NIH/OMB) 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 occurrences (all)	1 / 10 (10.00%) 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. - 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. - 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). - Eligibility criteria and data recording related to PDE5 inhibitor use were changed. - 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: