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Title Page

Prospective Case Crossover Study to Assess Whether PDE5 Inhibitor Exposure in Men increase the Risk for the Development of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION)

[NAION]

Bayer study drug	BAY 38-9456/vardenfil/Levitra		
Study purpose:	Post Marketing Follow-up study		
Clinical study phase:	IV	**Date:**	20 March 2018
Study No.:	12912	**Version:**	1.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
CI	Confidence Interval
CSR	Clinical Study Report
ED	Erectile Dysfunction
LOS	Listing only set
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
NAION	Non-Arteritic Ischemic Optic Neuropathy
PDE5	Phosphodiesterase type 5
PPS	Per-protocol set
PT	Perferred Term
SAE	Serious adverse event
SOC	System Organ Class
SAP	Statistical Analysis Plan

1. Introduction

This SAP is based on the 12912 Integrated Protocol Version 4.0 02 MAR 2016. That protocol is an integrated protocol containing the modifications mandated in amendment 4.0.

This SAP refers to the final analysis to be completed after FDA released Bayer from this post-marketing commitment on 15 NOV 2017. The FDA concluded that Study 12912 is unlikely to provide value for further risk assessment of NAION associated with the class of PDE5 inhibitors indicated for the treatment of erectile dysfunction. Due to the limited number of patients valid for analysis (safety n=10 and Valid for NAION n=7) in this study an abbreviated set of tables and listing will be prepared.

2. Study Objectives

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

Because of the small sample size at termination of the study, the principal statistical analysis based on the valid for NAION analysis will not be performed. However, a summary of the frequency of PDE5 Inhibitor exposure during all 3 control and 1 risk periods will be provided for the valid for NAION analysis set, ie, the subset of subjects with unanimous NAION assessment (ie, “definite NAION” – 3 out of 3 experts confirm the diagnosis) and probable NAION assessment (2 of 3 experts confirm the diagnosis).

3. Study Design

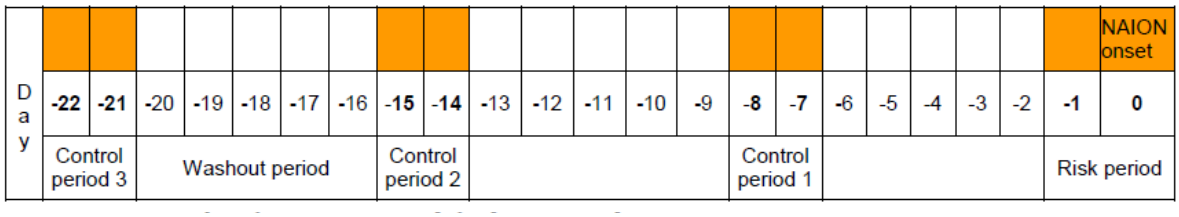
This is a case-crossover prospective field study, in which each subject will serve as his own control.Patients suffering from a suspected case of NAION are medically examined and interviewed for confirmation of suspected NAION and PDE5 Inhibitor use in the 28 days prior to onset of suspected NAION. Each subject will have 2 clinical visits. Visit 1 (Day 1) will include screening for NAION and other inclusion and exclusion criteria, enrollment, and conduct of a telephone interview for collection of data on PDE5 inhibitor use. Visit 2 (Day 90 +/- 30) will be a follow-up visit to document the persistence of vision loss.

In the case-crossover design of this study, the day of NAION onset and the day before (Days 0-1) are defined as the risk period* (Figure 3–1). Control periods are the same two days of the week in the preceding three weeks (Days 7-8, 14-15, 21-22).

Thus, there is one risk period, and 3 control periods 1 to 3 weeks prior to the risk period. These control periods will serve as artificial or ‘matched’ controls simulating a matched case-control study with the advantage of time invariant subject traits.

Study Design

Figure 3–1: Study Design



*Risk period: the 2 calendar days including the day of onset of suspected NAION symptoms and the preceding day (If the subject can specify onset only to within a 2-day window, then those 2 days constitute the risk period.)

Subjects to be screened must meet the following criteria:

- Preliminary diagnosis of NAION by an ophthalmologist

Note: "History of ED according to the subject" was removed in amendment 4. But no patients were enrolled under amendment 4.

- Use of a PDE5 inhibitor within the past year

The following times will be determined for this study:

- Date of onset of suspected NAION (must be within 45 days of initial presentation to the investigator)
- Date of initial presentation for medical evaluation in the study
- Date of NAION diagnosis as conducted by a study investigator
- Risk period: the 2 calendar days including the day of onset of suspected NAION symptoms and the preceding day (If the subject can specify onset only to within a 2-day window, then those 2 days constitute the risk period.)
- Last visit will be defined as the date of last contact with the subject

The final adjudication of NAION events will be done through an anonymous, independent assessment of medical records by an expert panel of 3 experts in neuroophthalmological diseases..

4. General Statistical Considerations

4.1 General Principles

The statistical tabulation and listing will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

4.2 Handling of Dropouts

A subject who withdraws is one who discontinues the study before visit 2 for any of the following reasons:

- At his/her own request
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- At the specific request of the sponsor

In all cases, the reason for withdrawal must be recorded in the Case Report Form (CRF) and in the subject's medical records.

There are no special instructions for handling dropouts in the TLF.

4.3 Handling of Missing Data

Subjects who fulfill all the criteria for NAION at Visit 1 who are subsequently lost to follow-up (no follow-up information available on visual status after 3 months) will be interpreted as definite NAION cases. Subjects not returning for Visit 2 will be contacted by telephone and questioned about their visual status. This information can be used for analysis instead of Visit 2 if supported by the Expert Panel.

The NAION onset date in main CRF (NAION history) pages are to be updated based on interview information. The updated NAION onset date should be used for all tables and listing except for NAION history listing where a footnote will explain that this date comes from NAION history but could have been updated in the Interview.

4.4 Interim Analyses and Data Monitoring

An interim analysis was initially scheduled to be performed after the inclusion of 100 confirmed NAION cases, however, no interim analysis was conducted as the trial was terminated early due to low enrollment. Furthermore, there was no data monitoring committee.

4.5 Data Rules

Unless otherwise specified baseline is Visit 1.

Enrolled is defined as all patients who signed the informed consent (including screen failures).

4.6 Blind Review

The final diagnosis of NAION will be made by an independent expert panel of 3 experts in neuro-ophthalmological diseases. A charter will be developed defining the review process by the expert panel. The expert panel will receive all information recorded on all cases in a blinded fashion. Experts will be blinded to the following information: The final adjudication of events will be done by the expert panel, with an anonymous, independent assessment from medical records by all 3 experts. In case of conflicting assessments, the experts are requested to discuss those cases in detail with the goal of finding agreement. Three categories of assessment are possible:

- Date of event
- PDE5 inhibitor use related to the event and during control periods or event period and history of use
- Presence of ED
- Concomitant medication
- Date and duration of concomitant diseases

The final adjudication of events will be done by the expert panel, with an anonymous, independent assessment from medical records by all 3 experts. In case of conflicting assessments, the experts are requested to discuss those cases in detail with the goal of finding agreement. Three categories of assessment are possible:

- Definite NAION – 3 experts confirm diagnosis (resulting in inclusion in the valid for NAION dataset)
- Probable NAION – 2 experts confirm diagnosis (resulting in inclusion in the valid for NAION dataset)
- Unlikely NAION – fewer than 2 experts confirm diagnosis (not included in the valid for NAION dataset)

5. Analysis Sets

Assignment of analysis sets

Valid for NAION analysis set

While no statistical analysis will be performed due the small sample, the frequency of exposure to PDE5 inhibitors at risk and control periods will be tabulated for the Valid for NAION analysis set (also known as the Per Protocol set), defined as the subset of subjects with a unanimous NAION assessment (ie, "definite NAION") and probable NAION assessment (2 of 3 experts confirmed the diagnosis). Subjects fulfilling all the criteria for NAION at Visit 1 who are subsequently lost to follow-up (no follow-up information available on visual status after 3 months) will be interpreted as definite NAION cases. Subjects not returning after 3 months for Visit 2 will be contacted by telephone and questioned about their visual status. This information can be used for analysis instead of Visit 2 if deemed appropriate by the expert panel.

Safety analysis set

All subjects who signed informed consent and who have any of the following collected at Visit 1 will be valid for safety: laboratory values, physical exam, any eye exams, or adverse events.

6. Statistical Methodology

Vardenafil project standards were used as appropriate (ie, Relative day, etc).

In the interview questionnaire, if there are any inconsistencies between the "Yes/no" questions (ie, Did you take a <PDE5 Inhibitor> on the day of or on the day before you noticed your eye problem; Did you take a PDE5-Inhibitor 7 or 8 days, 14 or 15 days or 21 or 22 before the day your eye problem started) and the subsequent dates associated with these question, then the dates will be used as the deciding factor as to whether the value falls within a certain risk or control period. If the patient says he doesn't remember we will not impute a date of exposure for that risk or control period.

In the interview questionnaire for PDE5 inhibitor used PRN, if a yes was given to question did you take a PDE5 Inhibitor 7 or 8 days, 14 or 15 days or 21 or 22 before the day your eye problem started, respectively but the only a partial date is given and the subject stated they took the PDE5 Inhibitor in the 28-day period before the eye problem started, then we impute the exposure partial dates as follows: the date of Day 0 during risk period and the date 7,14 and 21 days before the day NAION was started for the control periods.

In the interview questionnaire, if the concomitant medication page suggest PDE5 inhibitor use overlapped NAION onset but the interviewer failed to ask questions related to PRN use of the

PDE5 Inhibitor no assumptions about PDE5 Inhibitor exposure during the risk or any of the three control periods will be made. In this case PDE5 inhibitor exposure will be considered "Missing".

Due to the limited number of patients valid for analysis (safety n=10 and Valid for NAION n=7) in this study an abbreviated set of tables and listing will be prepared. No analysis will be done.

Demographics, subject disposition (overall, screening and end of study), subject validity and primary reason for exclusion and medical history will be tabulated. Continuous variables will be summarized by mean, SD, Median, Min and Max. Frequencies and percentages will be reported for categorical variables.

6.1 Population characteristics

Due to the limited number of patients valid for analysis (safety n=10 and Valid for NAION n=7) no subset analysis will be performed.

6.2 Efficacy

As this is a safety study, no assessment of efficacy will be made.

6.3 Pharmacokinetics/pharmacodynamics

N/A

6.4 Safety

Overall summary of number of subjects with adverse events, number of subjects with adverse events by primary SOC and PT after Visit 1, and frequency of exposure to PDE5 inhibitors at risk and control periods will be tabulated. A listing of serious AEs will also be provided. Laboratories (collected at baseline (Visit 1)) will be listed. Vital signs will also be listed. Frequencies and percentages will be reported for categorical variables.

Adverse conditions starting prior to informed consent will be captured as part of the medical history; adverse conditions reported after informed consent will be recorded as adverse events on the CRF. Accordingly, NAION starting before informed consent will be reported by the investigator and processed as a solicited postmarketing serious adverse event. Worsening of NAION after signing of informed consent will be recorded on the Adverse Event page of the CRF as a serious adverse event and reported. Concomitant diseases, pre-existing diseases, and laboratory data reported as medical history or reported as an adverse event will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1. Conditions that worsen or occur between Visit 1 and Visit 2, after the subjects had signed the informed consent form, will be recorded as adverse events on the CRF.

7. Document history and changes in the planned statistical analysis

No signed off SAPs before this SAP.

8. References

None