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Official Title:	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)
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Bayer
CLINICAL STUDY PROTOCOL

Title:	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) *(Note: Erectile Dysfunction was removed in amendment 4)*
Test Drugs:	Non-investigational drugs: vardenafil (e.g. Levitra®), sildenafil (e.g. Viagra®), tadalafil (e.g. Cialis®), avanafil (e.g. Stendra/Spedra®) *(Note: Avanafil was added in amendment 4)*
Sponsor's Name and Address:	Bayer HealthCare AG, D-51368 Leverkusen
Sponsor's Telephone Number:	PPD (Study Manager) (Medical Expert) *(Note: Telephone numbers were changed in amendment 4)*
Study Number/Version/Date:	12912 / Integrated Protocol Version 4.0 / 02 MAR 2016 This document is an integrated protocol containing the modifications mandated in amendment 4.0 Supersedes: Version 3.0 / 01 Feb 2011
Development Phase:	Phase IV EudraCT number: 2010-023586-22 *(Note: This number was included as described in amendment 2)*

The undersigned confirm that they agree to conduct the study under the conditions *...ote: The names of the signatories were changed in amendment 4)*

PPD

8 Mar 2016
Date

8 Mar 2016
Date

4 March 2016
Date

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Additional Signatures

Name:	PPD	Signature:	PPD
Function:	Coordinating Investigator	Date:	16 March 2016
Address:	PPD		
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Name:	PPD	Signature:	PPD
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Glossary and Abbreviations *(Note: Some abbreviations were added or removed in amendment 4)*

AE	adverse event
AION	arteritic anterior ischemic optic neuropathy
CBC	complete blood count
CCDS	Company Core Data Sheet
CI	confidence interval
CRF	Case Report Form (electronic)
CRP	C-reactive protein
EC	Ethics Committee
ECG	electrocardiogram
ED	erectile dysfunction
eg, e.g.	*exempli gratia*, for example
EOS	end of the study
ESR	erythrocyte sedimentation rate
EU	European Union
GCP	Good Clinical Practice
GMS	Global Medical Standards
GPRD	General Practice Research Database
HR	hazard ratio
IB	Investigator Brochure
ID	identification
ie, i.e.	*id est*, that is
IOP	intraocular pressure
IP	Investigational Product
IRB	Institutional Review Board
LPLV	last patient last visit
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter *hydrargyrum*, millimeter of mercury
MS	multiple sclerosis
NAION	non-arteritic anterior ischemic optic neuropathy
OR	odds ratio
PASS	Power Analysis and Sample Size
PDE5	phosphodiesterase type 5
PRN	*pro re nata*, as needed
RAPD	relative afferent pupillary defect
RBC	red blood cells
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
US	United States of America
vs.	*versus*, compared with, as opposed to
WBC	white blood cells
WHOART	World Health Organization Adverse Reactions Terminology
ϕ	phi-coefficient, correlation coefficient to express the degree of

1. INTRODUCTION

Erectile dysfunction (ED) has been noted to be a common disorder in adult men. According to one estimate, it affects 17% of men in the United States (US) (more than 16 million men, age range 20-79 years).[1] *Note: Reference to the IB was removed in amendment 4.* According to the Men's Attitudes to Life Events and Sexuality (MALES) study, ED affects 16% of men in Europe, North America, and South America, with rates varying markedly from one country to another.[2-5] The incidence of ED increases with increasing age. Co-morbidities that contribute to ED include diabetes, cardiovascular disease, hypertension, dyslipidemia, and depression.[2] Other factors associated with an increased risk of ED include smoking and high dietary intake of cholesterol and unsaturated fats.[6]

Currently, several phosphodiesterase type 5 (PDE5) inhibitors are available for the treatment of ED. *Note: The sentence was modified in amendment 4.*The number of men seeking medical consultation for the condition is highly variable.[1,6] In the US population, it is estimated that approximately 27% of men with ED will take a PDE5 inhibitor.[7]

Non-arteritic anterior ischemic optic neuropathy (NAION) is a form of acute optic neuropathy that affects an estimated 5700 patients a year in the US[8], generally over age 50. It affects men and women equally, with onset of clinical manifestations occurring on average at 60 years of age. Clinical manifestations include acute unilateral loss of visual field with acuity variably affected associated with a swollen optic nerve.[9,10] Risk factors for NAION include small cup to disc ratio of the optic nerve head, diabetes, hypertension, hypercholesterolemia, and smoking.[11]

The diagnosis of NAION involves differentiation from arteritic ischemic optic neuropathy from temporal arteritis or other forms of arteritis, demylinating optic neuritis, or other inflammatory optic neuropathies, eg, sarcoid or syphilis, compressive or infiltrative optic neuropathy, and post-papilledema optic atrophy on the basis of setting, clinical course, physical examination findings, and laboratory test results. Sometimes NAION must be distinguished from branch or central retinal

artery occlusion if the patient is seen late after the visual loss. There is no specific laboratory test definitive for NAION.

The epidemiology of NAION is not well described in the literature. By one estimate, the age- and sex-adjusted incidence of NAION is 10.2 cases per 100,000 patients per year in people aged 50 and older.[8] Another, earlier study that used surveys of referring physicians, estimated the mean annual incidence as 2.30 cases per 100,000 population for subjects aged 50 and older.[12]

Several case reports have been published in the last few years on a potential association between the use of the PDE5 inhibitor sildenafil, used for the treatment of ED, and the development of NAION.[13-16] Similar reports have also been published for tadalafil, another PDE5 inhibitor.[11,17-19] Subsequently, a pooled analysis of data on sildenafil, collected from 103 clinical trials involving more than 13,000 men and observational studies generating more than 35,000 person-years found an estimated incidence rate of 2.8 cases of NAION per 100,000 person-years of sildenafil use.[20] This rate in men using PDE5 inhibitors was deemed to be similar to that expected in the general US population, where estimates range from 2.5 to 11.8 per 100,000 men over the age of 50. Most recently, a small case-control study of 38 cases of NAION and 38 matched controls determined an odds ratio (OR) of NAION associated with sildenafil or tadalafil of 1.81 (95% confidence interval [CI]: 0.51 - 6.37). However, the OR was 10.7 (95% CI: 1.3 – 95.8) among subjects with a history of myocardial infarction and 6.9 (95% CI: 0.8 – 63.6) among those with a history of hypertension.[21]

As a result of these reports, precautionary statements have been added to the product labeling of all PDE5 inhibitors.[22-24] (See Appendix 10.2). Individuals with a history of NAION are advised not to use these products, and those individuals who are using a PDE5 inhibitor and experience the loss of vision are advised to stop their medication and see their physician.

To further address this matter, Bayer sponsored a pilot study by 3 independent medical experts to explore the feasibility of conducting a retrospective epidemiology

study by using the General Practice Research Database (GPRD) in the United Kingdom to provide a more recent incidence rate estimate of NAION.

A case validation algorithm for establishing a diagnosis of NAION was used by independent medical experts. The GPRD pilot study found an incidence rate of 6.9 cases of NAION per 100,000 person-years for men and 4.8 cases per 100,000 person-years for women. However, the data available were significantly deficient for diagnosis of NAION. Contributing to the difficulties identified in the pilot study is the difficulty in establishing a diagnosis of NAION retrospectively, even by medical experts.

Other methodological difficulties in performing an epidemiologic study include a multitude of confounding factors, the as-needed (PRN) use of PDE5 inhibitors, potential selection bias, and the large sample size required. Thus, the results of almost any epidemiology database study would be difficult to interpret.

Because the study herein described is to provide information on a possible association between a rare medical condition (NAION) and a relatively uncommon drug exposure (PDE5 inhibitors), a prospective field study has been chosen. A prospective approach will optimize the potential to assess timing of exposure to PDE5 inhibitors and provide a more reliable means of diagnosing NAION. Different study designs, in particular a case-crossover design and a case-control design, were assessed. The following difficulties with a prospective case-control design are described below:

- Selection bias: Subjects without the outcome of interest would be asked to give consent to participate in a study involving questionnaires dealing with ED and PDE5 inhibitor use. It is not clear that subjects who self-select for participation as controls in such a study would be comparable to the cases. It is also not clear whether a sufficient number of control subjects could be identified.
- Confounding: Though controls could be matched to cases with respect to ED, and multiple control subjects could be matched to the cases, the prospective

case-control design does not permit matching on the wide range of covariates (risk factors) that may be associated with NAION. Imbalances between cases and controls could be addressed only in the analysis by logistic regression, which, in the case of major imbalances, cannot reliably protect against confounding.

- Diagnostic bias: It is possible that the likelihood of a diagnosis of NAION may itself depend upon exposure history, given the knowledge of reports suggesting a possible association between NAION and the use of PDE5 inhibitors became wide-spread among health care providers and consumers in 2005.

The following difficulties with a prospective case-crossover design are described below:

- Recall bias: Subjects are asked to recall the exposure just prior to onset of the event as well as exposure at some earlier time. Of necessity, the time period for which the subject is questioned about earlier exposure is more remote from the event, and the subject's ability to recall and accurately report the details of exposure for the more remote time period is less reliable than his ability to report a recent exposure, especially an exposure just prior to the onset of symptoms of changes in vision.
- Diagnostic bias: Subjects experiencing symptoms may be more likely to seek medical care and to receive a diagnosis of NAION if the symptoms develop shortly after the use of a PDE5 inhibitor.

The case-crossover design provides some advantages over a case-control design. Since it would be difficult to find a comparable control population balanced with the NAION population with respect to multiple confounding factors, a case-crossover design is preferable. In a case-crossover study, each case serves as its own control. A relative strength of this design is that it controls for known and unknown covariates (provided that these do not change with time), reducing the likelihood of confounding on this basis. The problem of recall bias and diagnostic bias remain.

The case-crossover design examines PDE5 inhibitor exposure at the time of NAION onset compared with prior time points for the same subject. The study design calls for a narrow exposure window that is consistent for each subject and each assessment period. This is in contrast to a case-control design, in which the lack of a narrow exposure window could result in enhancement of the effects of other underlying, confounding disease states.

Based on this assessment, a case-crossover design was chosen for this study.

The case-crossover study to be conducted under this protocol will examine only subjects with a NAION event. A 3-person, blinded expert panel will confirm the diagnosis of NAION. To enhance the capacity of the study to detect a safety signal between NAION and the use of PDE5 inhibitors, it will focus on a narrow exposure window (a 2-day time frame for NAION onset) that will prevent dilution of the time span from ingestion of PDE5 inhibitor to the onset of NAION and it will include control periods in the proceeding months.[25]

2. STUDY OBJECTIVE(S)

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. *Note: The text was changed in amendment 4.*

3. INVESTIGATOR(S) AND OTHER STUDY PARTICIPANTS

Coordinating Principal Investigator responsible for signing the Study Report:

Name:	PPD
Title:	PPD
Address:	PPD United States
Telephone:	PPD
Fax:	PPD

The sponsor will set up an independent expert panel of 3 experts in neuro-ophthalmological diseases. *Note: This text was modified as described in amendment 2.*

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments and/or institutions, as well as information on members of additional study committees, will be found in the study files of the sponsor and on site if requested. This information will include contact details for serious adverse event reporting.

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

This will be a case-crossover prospective field study, in which each subject will serve as his own control.

The primary study variable is the relative risk (as measured by the hazard ratio [HR]) of NAION, contrasting PDE5 inhibitor exposure in the risk period with PDE5 inhibitor exposure during the control periods for each NAION case.

Suspicion of NAION (event onset prior to the signing of informed consent for this study) will be reported by the investigator. These events will be processed as solicited post-marketing adverse events (please refer to Section 7.4.1).

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.

- 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) *Note: The time point of onset was changed in amendment 2.*
- 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.)

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. Visits and procedures are described in Section 4.6.3, and in the Study Flow Chart (Appendix 10.1).

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 neuro-ophthalmological diseases. *Note: This text was modified as described in amendment 2.*

About 300 subjects will be enrolled in at least 60 sites globally. *Note: The information on number of centers and country scope was changed in amendment 2.*

In the case-crossover design of this study, the day of NAION onset and the day before (Days 0-1) are defined as risk period (Figure 4–1). Control periods are the same two days of the week in the preceding three weeks (Days 7-8, 14-15, 21-22). The relative risk (as measured by the HR) contrasts PDE5 inhibitor exposure in the risk period with PDE5 inhibitor exposure in the control periods of each NAION case.

Figure 4–1: Study Design

																						NAION onset
Day	**-22**	**-21**	-20	-19	-18	-17	-16	**-15**	**-14**	-13	-12	-11	-10	-9	**-8**	**-7**	-6	-5	-4	-3	-2	**-1**	**0**
	Control period 3		Washout period					Control period 2							Control period 1							Risk period	

Note: This figure was modified in amendment 2.

The 2-day control periods were chosen taking into account the terminal half-lives of PDE5 inhibitor drug products, ie approximately 4 hours for vardenafil, sildenafil and avanafil, and 17.5 hours for tadalafil. *Note: This text was changed as described in amendment 4.*

An interim evaluation will be done after 100 confirmed NAION cases have been collected. The purpose of the interim evaluation is to determine whether the parameter settings for the sample size calculation are adequate and the 10% inaccuracy rate for diagnosis of potential NAION cases is appropriate.

The primary outcome will be determined after last patient last visit (LPLV); the end of the study (EOS) will be the date when the expert panel has provided their final assessments and the clean data base is available.

4.2 Selection of Study Population

The study population will consist of adult men, first diagnosed with NAION which started within 45 days before study start, and who took PDE5 inhibitors in the 1 year prior to enrollment in the study. *Note: The time point for first diagnosis was changed in amendment 2. ED was removed and "1 year prior to NAION onset" was replaced by "1 year prior to enrollment in the study" in amendment 4.*

4.2.1 Inclusion Criteria

To be enrolled in the study, subjects must meet all of the following criteria:

1. NAION onset within 45 days before entry to the study defined as including all of the following: *Note: The time point of onset was changed in amendment 2.*
   a) Visual field defect consistent with optic neuropathy

b) Relative Afferent Pupillary Defect (RAPD)-Subjects without RAPD may be included in the study if: 1) optic neuropathy was present in the non-study eye, preventing an RAPD in the study eye, or 2) an RAPD could not be measured because the subject had a non-study prosthetic eye or postsurgical pupils. *Note: The modification of this inclusion criterion is described under amendment 2.*

c) Optic disc edema. Subjects without optic disc edema may be included in the study if optic disc edema was documented by another qualified physician after the onset of NAION and before entry into the study. *Note: The modification of this inclusion criterion is described under amendment 2.*

2. NAION onset definable by the subject within a 2 calendar day window. (If the subject specifies an exact day of onset, the risk period will include that day and the preceding day.)

   Note: Criterion 3 "Men with a history of ED at least 1 year prior to enrollment" was removed in amendment 4.

4. Men who have taken at least 1 dose of PDE5 inhibitor(s) at any time in the 1 year prior to enrollment in the study *Note: This criterion was modified in amendment 4.*

5. Age 40 years or older

6. Ability to complete a phone interview and recall history adequately

7. Documented, signed and dated written Informed Consent

4.2.2 Exclusion Criteria

Medical

1. History of multiple sclerosis (MS) or suggestive for MS (probable or possible MS) or optic neuritis (or any of the following symptoms or signs suggestive of these diagnoses)

   a) Pain on motion of the globe within 3 days of loss of vision
   b) Marked recovery of field loss and vision
   c) Marked delays on visual evoked potential

2. Evidence of temporal arteritis, as indicated by any of the following findings:

   a) Positive temporal artery biopsy
   b) Jaw claudication or temporal tenderness
   c) Polymyalgia rheumatica
   d) High ESR (>40 mm/h) platelets (>400 x 10^9 L), and/or CRP (>10 mg/dL). Subjects with an ESR above 40 mm/hr are allowed to be included if 1) the elevated sedimentation rate could be attributed to some other cause and/or 2) the subject had no other symptoms or indications of temporal arteritis or if temporal arteritis has been excluded by appropriate diagnostic methods. *Note: The modification of this exclusion criterion is described under amendment 2.*
   e) Large cup in fellow eye with a >50% cup to disc ratio

3. History of vasculitis or collagen vascular disease (eg, systemic lupus erythematosus, polyarteritis nodosa), or any other inflammatory disease associated with arteritic anterior ischemic optic neuropathy (AION) or disc swelling

4. Evidence of elevated intracranial pressure

   Note: Criterion 5 "Use of PDE5 inhibitors from other than a sample or prescription" was removed in amendment 4.

6. Daily dosing of PDE5 inhibitor for benign prostatic hyperplasia and/or pulmonary arterial hypertension *Note: This criterion was added in amendment 4.*

Opthalmological

1. Any of the following orbital signs

   a) Proptosis or resistance to retropulsion which may be associated with Graves eye disease or Graves-related exophthalmos
   b) Arterialized conjunctival vessels
   c) Choroidal folds
   d) Orbital mass

2. Ocular inflammation that may be associated with any of the following conditions:
    a) Iritis or vitritis
    b) Evidence of active sarcoidosis
    c) Evidence of active syphilis
3. Acute glaucoma or intraocular pressure (IOP) ≥30 mmHg
4. Retinal vein occlusion
5. Previous history of NAION
6. Retinal detachment
7. Uveitis
8. Lens opacities (which prevent an adequate examination)
9. Use of any drugs known to affect the optic nerve or retina that cannot be excluded

4.3 Removal of Subjects from Study

A subject who withdraws is one who discontinues in a clinical study for any reason.

Subjects may be withdrawn from the study for the following reasons:

- At their 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.

4.4 Premature Termination of Study/Closure of Center

The sponsor has the right to close this study, and the investigator/sponsor has the right to close a center, at any time, although this should occur only after consultation between involved parties. The Ethics Committee (EC)/Institutional Review Board (IRB) must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

4.5 Treatments

4.5.1 Treatments to be Administered

No interventional treatment will be administered in the context of this study. Only the subject's history of PDE5 inhibitor use will be assessed and recorded as specified in Section 4.5.6.

Subjects must not take PDE5 inhibitors while participating in the study, ie between Visit 1 and Visit 2. Subjects will continue with their usual medical therapies, including any treatment for NAION.

4.5.2 Method of Assigning Subjects to Treatment Groups

Not applicable.

4.5.3 Selection of Doses in the Study

Not applicable.

4.5.4 Selection and Timing of Dose for Each Subject

Not applicable.

4.5.5 Blinding

Not applicable.

4.5.6 Prior and Concomitant Therapy

All medications taken by the subjects prior to signing informed consent (including during the event and historical control period) are to be documented as medication history. Within the first 2 months before Visit 1, PDE5 inhibitors use and/or any intermittent use of additional medications will be recorded according to the subject's best recollection on the CRF. The source of PDE5 inhibitors should be recorded (documented source, i.e. sample or prescription vs. non-documented, i.e. other source). *Note: This sentence was added in amendment 4.* All medications used at study entry will be recorded.

All medications taken by the subjects during the study (from Visit 1 to Visit 2) are termed concomitant medication. All concomitant medications must be documented on the CRF (name, start and stop date and daily dose) throughout the study duration.

Concomitant medications also have to be recorded in the subject's medical records.

4.5.7 Treatment Compliance

Not applicable.

4.6 Study Variables

4.6.1 Efficacy Variable

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

4.6.2 Safety Variables

The primary study variable is the relative risk (as measured by the HR) of NAION, contrasting PDE5 inhibitor exposure in the risk period with PDE5 inhibitor exposure during the control periods for each NAION case.

Any additional safety information provided by the subject will be collected through the medical history taken at Visit 1 and any adverse events reported at Visit 2.

4.6.3 Assessment Periods

Subjects will be assessed at 2 visits, as summarized in the Study Flow Chart (Appendix 10.1). Visit 1 (Day 1) will include screening, confirmation of the diagnosis of NAION (with date and time of onset), enrollment, and collection of data on PDE5 inhibitor and other concomitant medication use. Visit 2 (Day 90) will be a follow-up visit to document the persistence of vision loss and confirm the diagnosis of NAION.

4.6.3.1 Visit 1 (Day 1)

Subjects with possible NAION will be assessed at clinical eye centers including referrals from the surrounding community. Subjects will be enrolled in the trial, if they fulfill the inclusion criteria and if none of the exclusion criteria apply.

Informed consent will be obtained from each subject before any study-related assessment is done, ie, before screening of inclusion / exclusion criteria.

Clinical and laboratory examinations will be made initially according to the standards usually applied at each investigational site. Procedures must include the following:

- Suspicion of NAION (event onset prior to the signing of informed consent for this study) will be reported by the investigator. These events will be processed as solicited post-marketing adverse events (please refer to Section 7.4.1).

- Obtain informed consent
- Enrollment
- Complete detailed medical history and surgical measures (including dental interventions)
- Complete medication history, including medications taken on an intermittent basis (including herbal/naturopathic medications and vitamins)
- History of erectile dysfunction as reported by the subject
- Examination of visual acuity
- Examination of formal visual field
- Ophthalmic examination, including pupil evaluation, slit lamp examination, applanation tonometry, fundus examination under dilated condition, with description of retinal vessel caliber and cup-to-disc ratio
- If applicable, ophthalmic examination documentation from another qualified physician to document the presence of optic disc edema after the onset of NAION symptoms before entry into the study. *Note: This text was added as described amendment 2.*
- Physical examination including weight, height, and vital signs
- Fundus photography
- Report any adverse event that starts after signing informed consent

Laboratory tests will include the following:

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Complete blood count (CBC) with platelet count

After preliminary confirmation of the suspected diagnosis of NAION, subjects will be interviewed by telephone to assess their history of PDE5 inhibitor use (tadalafil, sildenafil, vardenafil or avanafil) and other relevant conditions, including new conditions and concomitant medications and changes in existing conditions or concomitant medications during the 4 weeks before the onset of visual symptoms and including the day of NAION onset. *Note: Trade names were replaced by generic names, and avanafil was added in amendment 4.* This interview should take place on the enrollment day.

A subject will be enrolled in the study if the preliminary diagnosis of NAION is made (final diagnosis will be made after Visit 2) and the phone interview on the history of PDE5 inhibitor use and other concomitant therapies has been completed.

Subject exposure to PDE5 inhibitor will be assessed during the 2-day event window and 3 control periods (Figure 4–1), as follows:

- Risk period: 2 consecutive calendar days, including the day of onset of NAION (Each subject must be able to specify the time of onset to within the 2-day window. If the subject specifies the exact day of onset, the risk period will include that day and the proceeding day). Must be no more than 45 days before entry to the study, ie the day of onset of NAION must be within 45 days of the Visit 1. *Note: The extension of the time points before onset of symptoms is described amendment 2.*
- Control periods: 2 consecutive calendar days corresponding to the same days of the week as in the event window, for 1, 2, and 3 weeks preceding the event onset (designated Week -1, Week -2, and Week -3).

4.6.3.2 Visit 2 (Day 90 ± 30)

Approximately 3 months after first diagnosis, the subject will be examined again to document the persistence of vision loss and the conversion of the disc edema to optic atrophy.

At this second visit, clinical examinations to support the persistence of vision loss can be performed, if required. Procedures will include the following:

- Examination of formal visual acuity
- Examination of visual field
- Ophthalmic examination including pupil evaluation, slit lamp examination, applanation tonometry, and fundus examination under dilated condition with description of retinal vessel caliber and cup to disc ratio
- Physical examination including weight and vital signs
- Fundus photography
- Collection of adverse events and concomitant medications

4.6.3.3 Expert Panel

The final diagnosis of NAION will be made by an independent expert panel of 3 experts in neuro-ophthalmological diseases. *Note: This text was modified as described in amendment 2.*

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:

- Date of event
- PDE5 inhibitor use related to the event and during control periods or event period and history of use

- Presence of ED *Note: This text was modified as described in amendment 4.*
- 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
- Probable NAION – 2 experts confirm diagnosis
- Unlikely NAION – fewer than 2 experts confirm diagnosis

4.6.4 Observations and Measurements

The principal variables to be assessed are the following:

- Occurrence of NAION
- Use of PDE5 inhibitor on specified days
- Source of PDE5 inhibitor *Note: This text was added in amendment 4.*

Other observations and measurements will include the following:

- General medical history and current medications, focusing on prior 4 weeks
- Diagnosis of erectile dysfunction
- Examination of visual acuity
- Examination of formal visual fields
- Ophthalmic examination, including pupil evaluation, slit lamp examination, applanation tonometry, and fundus examination under dilated condition with description of retinal vessel caliber and cup to disc ratio
- Physical examination

- Fundus photography
- Laboratory values: ESR, CRP, and CBC with platelets
- Adverse events reported at Visit 2

4.6.5 Drug Concentration Measurements

Not applicable.

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP, and legal aspects. This will include on-site checking of the CRF for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

4.8 Documentation

Entries made in the CRF must be either verifiable against source documents or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification given by the sponsor for destruction.

5. ETHICAL AND LEGAL ASPECTS

5.1 Ethics Committee (EC) or Institutional Review Board (IRB)

Documented approval from appropriate ECs/IRBs will be obtained for all participating centers/countries prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to the sponsor. The EC/IRBs must supply to the sponsor, upon request, a list of the EC/IRBs members involved in the vote and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations.

5.2 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives. Additionally, this study is designed to ensure that good pharmacoepidemiology practices are met.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior EC/IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and if appropriate the proposed protocol amendment should be submitted to the EC/IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/ authorizations/ notifications, where required, must be in place and fully documented prior to study start.

5.4 Subject Information and Consent

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the EC/IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the EC/IRB together with the approved subject information/Informed Consent Forms must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

5.5 Insurance

All subjects participating in the study have insurance coverage by the sponsor, which is in line with applicable laws and/or regulations.

5.6 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (eg, pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, EC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical and Analytical Plans

In the case-crossover design of this study, the day of NAION onset and the day before are defined as the risk period. Control periods are the same 2 days of the week in the preceding 3 weeks. The relative risk (as measured by the HR), contrasts PDE5 inhibitor exposure in the risk period with PDE5 inhibitor exposure in the control periods for each NAION case. In this sense the case-crossover design is a matched case-control study in which each subject serves as his own control.

Primary statistical analysis will investigate whether use of PDE5 inhibitors increases the risk for the occurrence of NAION.

6.1.1 Populations for Analysis

Valid for NAION analysis set

The principal statistical analysis will be based on the valid for NAION analysis set, ie, the subset of subjects with a unanimous NAION assessment (ie, "definite NAION") and probable NAION assessment (2 of 3 experts confirm 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.

Safety analysis set

All subjects who sign 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.

6.1.2 Derived Data and Data Sets

None planned.

6.1.3 Demography, Medical History, Concomitant Medication

Demographic variables, medical history, ED history, and findings will be tabulated overall and by stratum. *Note: the text was modified in amendment 4.* Sample size, mean values, standard deviations, minimum, median, and maximum values will be calculated for quantitative variables. Frequencies and percentages will be reported for binary variables.

6.1.4 Efficacy Analysis

Not applicable. Determination of sample size is based on the primary safety variable.

6.1.5 Safety Analysis

6.1.5.1 Risk Contribution of PDE5 Inhibitor Exposure to NAION

The primary analysis will be conducted using a conditional logistic regression model (Proc PHREG; SAS™ Institute). The dependent variable (outcome) distinguishes between "case" and "control" phase. The predictor will be "exposed" or "not exposed" to PDE5 inhibitor. According to the case-crossover design, subject (patient) will be the stratum variable. Association of PDE5 inhibitor exposure and NAION will be concluded if the lower limit of the 90% confidence interval of the HR of an increased risk under PDE5 inhibitors exceeds 1.0.

As a secondary analysis, time-variant covariates, as the intermediate (non-regular) ingestion of other medications, treatments, or critical external events, as well as their interaction, will be included in the logistic model to test the independence from confounding factors. The final model will be selected via backward elimination.

If a significant HR indicating an increased risk with PDE5 inhibitors is found, stratified analyses will be conducted on an exploratory basis, including those subjects constituting subsamples with comparable time-invariant medical conditions (eg, diabetes, hypertension, hyperlipidemia, cardiovascular disease, and cup to disc ratio).

Sensitivity Analysis *Note: The text was modified as described in amendment 4.*

Depending on sample composition, the primary analysis will be repeated by:

1. Subjects with ED taking a PDE5 inhibitor versus subjects without ED taking a PDE5 inhibitor, to assess the impact of ED on primary analysis,

2. Source of PDE5 inhibitor (patients who always used a documented source of PDE5 inhibitor, that is, sample or prescription, versus those with at least one non-documented source of PDE5 inhibitor), to assess the impact of source of PDE5 inhibitor.

3. Age (eg, 40 – 49 years and ≥ 50 years),

It is known that the study may not be adequately powered in these subgroups and that these results should only be considered as descriptive.

6.1.5.2 Adverse Events

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 post-marketing serious adverse event. Please refer to Section 7.4.1 for investigator reporting requirements. 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 according to guidelines in Section 7.4.2 for investigator reporting requirements.

Concomitant diseases, pre-existing diseases, and laboratory data reported as medical history or reported as an adverse event will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). 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.

6.1.5.3 Laboratory Data

Baseline laboratory data (Visit 1) will be summarized as means, standard deviations, minimum, median, and maximum values, per stratum (Global Medical Standards [GMS]) provided they are quantitative variables. *Note: "Strata" was replaced by "stratum" in amendment 4.*

6.1.5.4 Vital Signs

Vital signs data (systolic/diastolic blood pressure and heart rate) will be tabulated as means, standard deviations, minimum, median, and maximum values per visit and stratum (GMS).

6.1.5.5 ECG Data

Not applicable

6.1.5.6 Other Safety Data

Ophthalmic data will be summarized as means, standard deviations, minimum, median, and maximum values per visit and stratum (GMS) provided they are quantitative variables. Qualitative variables will be tabulated as frequencies and percentages.

6.1.6 Interim Analysis

After inclusion of 100 confirmed NAION cases, an interim evaluation will be done by an analyst who will be blinded to the use of PDE5 inhibitor exposure in the risk period, to determine whether the parameter settings for the sample size calculation are adequate (that is, the 1-day prevalence of PDE5 inhibitor use in the control period) and to determine whether the 10% inaccuracy rate for diagnosis of potential NAION cases is appropriate. *Note: This text was modified as described in amendment 4.* This is a technical interim analysis that is not scheduled for deciding on potential early termination. If necessary, the study will be extended but not significantly reduced with regard to the number of cases estimated in this protocol.

6.1.7 Blind Review

Not applicable.

Each case will be assessed by an independent panel of 3 experts in neuro-ophthalmological diseases to confirm the diagnosis of NAION (please refer to Section 4.6.3.3). *Note: This text was modified as described in amendment 2.*

6.1.8 Handling of Dropouts and Missing Data

Subjects who do not complete Visit 2 will still be evaluated by the expert panel and may contribute to the analysis, if this is supported by the Expert Panel.

6.2 Determination of Sample Size

In the case-crossover design in this study the day of NAION onset and the day before (Days 0-1) are defined as the risk period. Control periods are the same 2 days of the week in the preceding 3 weeks (Days 7-8, 14-15, 21-22). The relative risk (as measured by the HR) contrasts PDE5 inhibitor exposure in the risk period with PDE5 inhibitor exposure in the control periods of each NAION case.[26-28]

According to the US Government Census for 2000[29], the prevalence of ED is estimated to be about 17.21% (N=16,104,421; age range: 20-79 years) in all adult male US citizens. It is also expected that about 71% of all diseased subjects will ask for medical consultation (N=11,434,139), and a final set of 27% of the total will take PDE5 inhibitors (N=3,087,218).An internal analysis on the average use of PDE5 inhibitors, neglecting the type of PDE5 inhibitor treatment (ie, vardenafil, sildenafil, tadalafil), estimated an average annual prescription rate of 3.71. The average overall prescription number in all ED subjects within the target age range is then calculated as N= 11,359,884 prescriptions per calendar year. This estimation is based on 5 tablets per blister pack and prescription. The average prevalence of PDE5 inhibitor use in the ED population estimated for a 1-day risk was then calculated as 0.00965625.[1]

The sample size estimation is based on the assumptions of a matched case-control design, which are also applicable to case-crossover designs.[30, 31]

According to the proposal of Dupont[32] for retrospective matched case-control study and using the statistics programs PS[33] and Power Analysis and Sample Size

(PASS)[34] the study will require 258 confirmed NAION cases with ED to detect an increased risk of 3.0 (OR) under exposure with PDE5 inhibitors and considering 3 within-control periods per NAION case, a type 1 error rate of 5% (1-sided), a power of 80%, a correlation coefficient for exposure of 0.2, and a 1-day prevalence of PDE5 inhibitor use in ED patients of 0.0097 (2 days: 0.0194). The correlation coefficient was calculated based on the PDE5 inhibitor drug prevalence in the risk- and control period.[32] Although the calculation supported the view of independence, it was recommended to use tentatively ϕ=0.2.

Summarizing, the study is designed to test the superiority hypothesis that ED subjects exposed to any PDE5 inhibitor will have an increased risk (λ) of suffering from NAION. Thus the null hypothesis is:

$$H_0 : \lambda = 1$$

The alternative hypothesis is:

$$H_1 : \lambda > 1$$

The alternative hypothesis will be accepted if the 1-sided lower 95% confidence interval of the estimated HR does not include 1.

Assuming an accuracy of 90% for the NAION diagnosis that includes definite and probable cases, the number of potential NAION cases with ED to be included in this study is increased from 258 to 284. This corresponds to an inter-rater reliability of approximately 0.9.

7. ADVERSE EVENTS

7.1 Warnings/Precautions

Not applicable.

7.2 Adverse Event Monitoring

Subjects will be monitored for adverse events. Adverse events should be assessed in terms of their seriousness and severity.

7.3 Adverse Event Definitions

7.3.1 Adverse Event

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.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice.
- An adverse event occurring from an overdose whether accidental or intentional.
- An adverse event occurring from drug abuse.
- An adverse event occurring from drug withdrawal.
- An adverse event where there is a reasonable possibility that the event occurred purely as a result of the subject participation in the study (eg, adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event.

7.3.2 Serious Adverse Event

A serious adverse event is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It

does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as "serious", unless at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours.

  OR

- The admission is pre-planned (ie, elective or scheduled surgery arranged prior to the start of the study).

  OR

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of "medically important" and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the World Health Organization Adverse Reaction Terminology (WHOART) – Critical Terms List. These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

7.3.3 Unexpected Adverse Event

Expectedness of adverse events and serious adverse events will be assessed on the basis of the Investigator Brochure (IB)/Company Core Data Sheet (CCDS).

Worsening of NAION during the study is to be recorded in the CRF as serious adverse event and the procedures for serious adverse event reporting should be followed (see Section 7.4).

7.3.4 Relationship of Adverse Event to Investigational Product

No investigational product will be administered during the course of this study**;** therefore, no assessment of causal relationship to the investigational product is applicable.

Sponsor's Fulfillment of Pharmacovigilance Reporting Requirements

As this study is non-interventional and observational, some definitions and processes need to be outlined and explained. As a prerequisite for the special conditions a few agreements have been made beforehand.

- All events dealing with NAION and /or the suspicion of NAION with the use of PDE5 inhibitors are considered 'serious'. The Bayer HealthCare Global Pharmacovigilance system requires cases to be assessed as associated by either the investigator or by Bayer HealthCare to trigger distribution for expedited reporting to health authorities, depending upon local reporting requirements. Therefore, Bayer HealthCare will assess the serious NAION (suspected or confirmed) cases as associated to the PDE5 inhibitor. This includes screen failures.

- Although no investigational product will be administered during the course of this study, for pharmacovigilance reporting purposes PDE5 inhibitors are considered the 'Investigational Product' (IP). This is reasonable from a medical point of view concerning the issue and questioning of this study and is to ensure that all events concerning NAION will be processed and handled in the context of PDE5 inhibitor use. Furthermore, a 'suspect drug' is a 'minimum requirement' for defining a case internally within the Bayer HealthCare Global Pharmacovigilance system.
- Definitions and wording are taken from the EU Directive 2001/20 and the respective document '*Detailed guidance on the collection, verification, and*

presentation of adverse reaction reports arising from clinical trials on medicinal products for human use (April 2006, revision 2)'as Bayer HealthCare is an EU-based pharmaceutical company. This shall not be in conflict with fulfilment of reporting requirements to all concerned authorities, boards and committees. Bayer HealthCare will follow a very conservative strategy of reporting to ensure maximum possible transparency in terms of safety-relevant information.

Events/case reports will be processed as follows:

Suspected NAION Prior to the Signing of the Informed Consent

Enrolment of an individual into the study is linked to three main conditions: male person, prior intake of PDE5 inhibitor and the suspicion of NAION. *Note: This text was modified as described in amendment 4.* Consequently, every subject enrolled in this study will have had suspicion of NAION and will have taken at least 1 dose of PDE5 inhibitor prior to suspicion of NAION (although the PDE5 inhibitor may have been taken as much as 1 year before the suspicion of NAION). These adverse events will therefore be processed as solicited post-marketing adverse events. As Bayer HealthCare is actively looking for such case reports they are considered 'solicited' and will be assessed as 'serious' and associated to the PDE5 inhibitor (as noted above) to allow for distribution for expedited reporting. They will be reported expeditedly to all parties involved (please refer to Section 7.4.1). This includes screen failures with NAION and/or the suspicion of NAION with a history of PDE5 inhibitor use.

If there is follow-up information on the course of NAION at any time after enrolment this will trigger a follow-up report of the 'solicited' post-marketing adverse event report. From a medical and procedural point of view it is reasonable not to consider this a new serious adverse event (SAE) or suspected unexpected serious adverse reaction (SUSAR), as no new exposure to a PDE5 inhibitor took place. This does not refer to a worsening of NAION which is considered a new SAE and should be reported according to the procedures in Section 7.4.2. The condition of "worsening" is based on the investigator's clinical judgment.

Adverse Events/SAEs Occurring After the Signing of the Informed Consent

Use of PDE5 inhibitors during the study is not allowed. However, if a subject reports side-effects after PDE5 inhibitor intake during the study**,** they will be processed as adverse event or SAE.

7.3.5 Severity of the Adverse Event

The following classification should be used:

The severity of adverse events should be graded as follows:

- Mild: usually transient in nature and generally not interfering with normal activities.
- Moderate: sufficiently discomforting to interfere with normal activities.
- Severe: prevents normal activities.

7.3.6 Adverse Event Documentation

All adverse events occurring after the subject has signed the informed consent must be fully recorded in the subject's CRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, eg, causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, action taken and outcome.

7.4 Reporting of Serious Adverse Events

Serious adverse events, including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A Serious Adverse Event Form must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file. Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

When required, and according to local law and regulations, serious adverse events must be reported to the EC/IRB and Regulatory Authorities.

7.4.1 Reporting of Suspected NAION Cases prior to Informed Consent

Suspicion of NAION (event onset prior to the signing of informed consent for this study) in subjects who have a history of taking a PDE5 inhibitor will be reported by the investigator within 24 hours of investigator's awareness. The suspected NAION events are to be recorded on the CRF on the history page only (NOT on the Adverse Event CRF page) and on the solicited post-marketing adverse event form. These reports will be processed by Bayer HealthCare as solicited post-marketing reports.

Subject with suspicion of NAION but not qualifying or not consenting for enrolment will be recorded on standard "subject pre-screening failure log".

7.4.2 Reporting of Worsening Cases of NAION

The investigator is to complete and submit the Serious Adverse Event Form within 24 hours of investigator's awareness of the event (see Section 7.4 above for further details). The condition of "worsening" is based on the investigator's clinical judgment.

In addition, after signing of informed consent, any cases of worsening of NAION will be recorded on the Adverse Event Form of the CRF and will be assessed as serious.

8. USE OF DATA AND PUBLICATION

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the sponsor prior to release and obtain written consent of the sponsor on the intended publication. The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the sponsor 30 days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly, and approval will not be withheld

unreasonably. In case of a difference of opinion between the sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution which satisfies both parties.

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10. APPENDICES

10.1 Study Flow Chart

Procedures and assessments	**Visit 1** Day 1	**Visit 2** Day 90 ± 30
Report suspected NAION cases as a solicited post-marketing cases	X	
Obtain Informed Consent	X	
Enrollment	X	
Medical history (including NAION history)	X	
ED history	X	
Medication history (including during the risk and control periods)	X	
PDE5 inhibitor use history	X	
Concomitant medications	X	
Physical examination (including weight, height [a] and vital signs)	X	X
Examination of visual acuity	X	X
Examination of visual fields	X	X
Ophthalmic examination including pupil evaluation, slit lamp examination, applanation tonometry, fundus examination under dilated condition with description of retinal vessel caliber and cup to disc ratio	X	X
Fundus photography	X	X
Adverse events starting after signing informed consent	X	X
Laboratory tests (ESR, CRP, CBC)	X	
Phone interview	X	

a Height only at Visit 1
Abbreviations:
ED: erectile dysfunction, PDE5: phosphodiesterase type 5, NAION: non-arteritic anterior ischemic optic neuropathy
ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CBC: complete blood count

10.2 Package Inserts for PDE5 Inhibitors

Note: The following text was added to this section in amendment 2. Generic names were added in the following sections headings in amendment 4.

10.2.1 Package insert for sildenafil (e.g. Viagra®)

US package insert accessed on 6 Oct 2010 from the following web site:

http://media.pfizer.com/files/products/uspi_viagra.pdf

EU SmPC accessed on 6 Oct 2010 from the following web site:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000202/WC500049830.pdf

10.2.2 Package insert for tadalafil (e.g. Cialis®)

US package insert accessed on 6 Oct 2010 from the following web site:

http://pi.lilly.com/us/cialis-pi.pdf

EU SmPC accessed on 6 Oct 2010 from the following web site:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000436/WC500026318.pdf

10.2.3 Package insert for vardenafil (e.g. Levitra®)

US package insert accessed on 26 Oct 2015 from the following web site:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021400s017lbl.pdf

Note: the URL to US package was changed in amendment 4.

EU SmPC accessed on 6 Oct 2010 from the following web site:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000475/WC500039992.pdf

10.2.4 Package insert for avanafil (e.g. Stendra® / Spedra®)

Note: this section was added in amendment 4.

US package insert accessed on 9 Oct 2015 from the following website:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202276s013lbl.pdf

EU SmPC accessed on 9 Oct 2015 from the following website:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002581/WC500145206.pdf

10.3 Laboratory Parameters

Complete blood count (CBC)

- Hemoglobin
- Hematocrit
- RBC
- MCV
- MCHC
- WBC
- Neutrophils
- Bands
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets
- Cell morphology

Erythrocyte sedimentation rate (ESR)

C-reactive protein (CRP)

10.4 12912 NAION Interview

Date:_____ Time:_____

Subject number:_____

Date of Birth:_____
DD/MMM/YYYY

Instructions how to complete the interview (for the interviewer): ***will be italics throughout and will not be read aloud to patient***

The intent of this phone interview is to help the subject remember the dates and time when he took his medications. In particular, please ask detailed question about the medications, medical/surgical/dental interventions and alcohol consumption taken in the 4 weeks before the eye problem date of onset. Determine which medications to ask about by reviewing the start dates from the Con Med page and only asking about those that were being taken from the "Date of suspected NAION Onset" and back 4 weeks.

A call/fax will be received from the site indicating that a patient is being seen for the Bayer study and that data will be available for review.

When contact is received from site, verify with the Study Coordinator the following:

- *Subject Number / and Date of Birth*
- *Site contact call back number*

Upon contact, ensure the site has provided the information via edc or fax if necessary:

- *Medical History page (including the date of suspected NAION onset)*
- *Previous Medication page*
- *Demography page*
- *Previous or concomitant sexually enhancing medication page*

If any of the above cannot be provided, call cannot take place at that time.
Contingency plans:

- *Site can re-fax medical history/concomitant medication list but interviewer needs time to review prior to speaking with patient*

Note: Questions and text in the interview marked as ***W*** *are considered as supporting questions and answers to these questions should not be recorded in the CRF pages. The answers to questions and text marked as* ***Q*** *should be recorded in the CRF pages.*

Introductory statement:

Thank you for agreeing to participate in this research study. You have been seen in the eye specialist's office because of your eye problem and had all or will have all of the necessary diagnostic assessments done. As a final part of this assessment, I would like to find out which medications you were taking at the time when you experienced your eye problem. I will ask you a few questions about these medications as well as any medical visits that happened during that time, including dental or specialist visits. In addition, I will ask you about alcohol consumption.

W: Do you have any questions for me at this time regarding this interview? If you have any questions regarding the study or your condition, please direct these to your study doctor.

☐ Yes ☐ No

(Allow time for questions.)

W: Can we continue with the interview?

☐ Yes ☐ No

If "yes" start the interview.

If "No": ***W:*** I understand that you are not ready to complete the interview at this time. It is important that we review your medications as soon as possible. Do you think that you could take time tonight *(preferably)* or tomorrow to speak with me?"

> *If "Yes" confirm time:* **W:** Here is the number where I can be reached (give number). When you call, please be sure to have the calendar page given to you by the study staff with you as we will be referring to it during the call.
>
> **W:** Do I have your permission to call you if we do not hear from you as expected?
>
> **W:** What is the number where can I reach you?
>
> **W:** Is it acceptable to leave a message regarding the Bayer study on this line's voicemail?

If "No", continue to encourage the subject to call up to 3 days in future. If the interview cannot be scheduled within 45 days of NAION onset, thank caller and direct him to Study Coordinator. Note: The time of onset was changed in amendment 2.

Note: for the purpose of the interview scheduling, the interviewer should use the "date of NAION onset" obtained by the investigator.

*Note: Please ensure that the interview is scheduled within 48 days of NAION onset (45 days plus 3 days for scheduling the interview**)**. Note: The time of onset was changed in amendment 2.*

Start of the interview:

Review NAION onset date on medical history CRF page provided by study coordinator.
*If onset date was narrowed to **1 day** proceed to question **Onset 1***
*If NAION onset date was narrowed to **2 days** proceed to question **Onset 2***

> **Q: *Onset 1:*** You have reported an eye problem which started on [date (see date of onset *NAION History EDC screen)*].Is it correct? ☐ Yes ☐ No

If "Yes, go to section A.

*If "No", write down the new date of Suspected NAION onset as reported by the patient and use that date to count back the weeks that medication will need to be reviewed for**.***

> **Q**: New onset 1: What is the new onset date?
> _____(enter date)

Now clarify with the patient the reason for the onset date change:

> ***Q:*** You are saying that your eye problem began on [date just given] and not on [date given to investigator]. Can you please confirm this change and give a reason? (*enter free text)*
> _____ (enter reason)

Go to section A.

> **Q: *Onset 2***:You have reported an eye problem which started on either of these 2 days[date(see date of onset *NAION History EDC screen)*].
> Is it correct? ☐ Yes ☐ No

If "Yes", go to section A.
*If "No"write down the new date of Suspected NAION onset as reported by the patient and use that date to count back the weeks that medication will need to be reviewed for**.***

> **Q:** New onset 2: What is the new onset date?
> _____(enter date)

Now clarify with the patient the reason for the onset date change:

> ***Q:*** You are saying that your eye problem began on [date just given] and not on [date given to investigator]. Can you please confirm this change and give a reason? (*enter free text)*

_____ (enter reason)

Go to section A.

IMPORTANT: If the suspected NAION onset date has been narrowed down to 2 days , for the purpose of collecting the data, the date of suspected NAION onset is considered as the latter of the two days.

If during the phone interview the patient reported a different date of suspected NAION onset than what was reported to the investigator, request the patient update the calendar under direction of interviewer (the calendar should include the date of suspected NAION onset and the time period covering 4 weeks prior to NAION onset).

A. Previous medications (Duplicate page as needed)

Begin by asking about a drug from the received list that is expected to be taken daily. Once all questions are asked for that drug, ask about PDE5 inhibitors, (i.e. tadalafil, vardenafil, sildenafil or avanafil). Note: trade names were replaced by generic in amendment 4. Then ask about cardiovascular drugs, then etc. based on prioritization list provided by Bayer.

I will now begin asking you questions about the medications your doctor has recorded.

- *If beginning of interview:* I'd like to begin with [drug name-*drug 1 on Previous Medication page*].

OR

- *If subsequent drugs:* Now I'll be asking you about [drug name-*drug 2, etc. on Previous Medication page*].

A1. Q**:** Do you take this drug every day? ☐ Yes ☐ No

If "Yes", continue interview using Questions for Medications Taken Daily. Ask questions B for EACH drug.
If "No", continue interview using Questions for Medications Taken PRN. Ask questions C for EACH drug.

B. Questions for Medications Taken Daily (Duplicate page as needed)

Q: (enter the drug name here)_____

Q: (total daily dose)_____

B1. **Q:** Did you start this medication before, on or after you first noticed the eye problem?
☐ before ☐ on ☐ after

*If the start date is **before** the day of suspected NAION onset, ask the question B2*
*If the start date is **on** the day of suspected NAION onset, ask the question B3*
*If the start date is **after** the suspected NAION onset (do not enter this drug into the phone interview page), go to section A ands ask about the next medication on the Previous Medication page*

B2: **Q:** I see that you have started your medication before the day you first noticed the eye problem. Can you please provide the date you started this medication.

Start date (if within 28 days of eye problem onset)_____
or ☐ started more than 28 days before eye problem onset

Go to question B4

B3: **Q:** I see that you started your medication on the day you first notice the eye problem. On that day, did you take the medication before or after you first noticed the eye problem?
☐ before ☐ after

If "before" go to question B4
If "after" (do not enter this drug into the phone interview page).Go to section A and ask about the next drug.

B4: Did you stop this medication before, on or after you first noticed the eye problem?
☐ before ☐ on ☐ after/continuing

*If the stop date is **before** the day of suspected NAION onset, ask the question B5*
*If the stop date is **on** the day of suspected NAION onset, ask the question B6*
*If the stop date is **after**/*continuing *the suspected NAION onset, go to question A and ask about the next medication on the conmed page.*

B5: **Q:** I see that you stopped your medication **before** the day you first noticed the eye problem. Can you please provide the date when you stopped this medication?
Stop date_____

Go to section A and ask about the next medication on the Previous Medication page

B6: **Q:** I see that you stopped your medication **on the day** you first notice the eye problem. On that day, did you stop the medication before or after the you first noticed the eye problem?
☐ before ☐ after

Go to section A and ask about the next medication on the Previous Medication page

.

C: Questions for Medications Taken PRN (Duplicate page as needed)

Q: (enter the drug name here)_____

Q: (total daily dose)_____

W: Please look carefully at calendar to help you to remember better and take your time.

C1: **Q:** Looking at the calendar, in the 28 days prior to first noticing the eye problem
were there any days that you took this medication?

☐ Yes ☐ No ☐ Don't remember

If "Yes", continue interview with question C2.
Note: If the answer is "No" or "Don't remember", go to C3.a

C2. **Q**: Can you please tell me which days you took this drug?
*enter days*_____

C3. **Q:** You have reported that you took medication on [repeat days reported in C2]? Are there any other days that you took this drug?

☐ Yes ☐ No ☐ Don't remember

If "Yes", return to C2.

If patient answers "No" or "Don't remember" make additional efforts to help him to recall using the calendar and asking questions from C3.a through C3.d.

W: Please look carefully at calendar to help you to remember better and take your time

C3.a Q: Looking at the calendar did you take this drug on the day **of** or on the day **before** you noticed your eye problem started? This would be (state date from calendar- Day 0 & -Day 1.

Allow some time for patient to think, if necessary

☐ Yes ☐ No ☐ Don't remember

If Yes, please enter the date and go to C3.b.
*(enter date)*_____
If No or Don't remember, go to the C3.b

C3.b Q: Looking at the calendar did you take this drug seven or eight days before the day your eye problem started? This would be (*state date from calendar- Day 7 & -Day 8)*

Allow some time for patient to think, if necessary

☐ Yes ☐ No ☐ Don't remember

If Yes, please enter the date and go to C3.c.
*(enter date)*_____
If No or Don't remember, go to the C3.c

C3.c Q: Looking at the calendar did you take this drug fourteen or fifteen days before the day your eye problem started? This would be (*state date from calendar- Day 14 & -Day 15)*

Allow some time for patient to think, if necessary

☐ Yes ☐ No ☐ Don't remember

If Yes, please enter the date and go to C3.d.
*(enter date)*_____
If No or Don't remember, go to the C3.d

C3.d Q: Looking at the calendar did you take this drug twenty-one or twenty-two days before the day your eye problem started? This would be (*state date from calendar- Day 21 & -Day 22)*

Allow some time for patient to think, if necessary

☐ Yes ☐ No ☐ Don't remember

If Yes, please enter the date and see the notes below.
*(enter date)*_____
If No or Don't remember , see the notes below.

Note: If the answer is "Don't remember" for all the questions from C1 through C3d, ***and the medication is PDE5 inhibitor****, please complete the interview, but the patient will be considered a Screen Failure.*

If this medication was taken on the same day as the suspected NAION onset ask patient:

C4. **Q:** I see you took this medication on the day you first noticed the eye problem. On that day did you take this medication before or after you first noticed the eye problem?
☐ before ☐ after ☐ I don't know.

Continue asking the Daily or PRN questions for all drugs listed on the received list. Please communicate to the investigator the names of all medications which were not reported to the investigator initially.

After all drugs listed have been discussed:

D. Homeopathic treatments, vitamins etc.

D1. **W:**Looking at the calendar, in the 28 days prior to first noticing the eye problem were there any drugs, prescription, over the counter or other types (including homeopathic treatments or vitamins) that you took during that time that we have not talked about? ☐ Yes ☐ No ☐ Don't remember

If "Yes", continue interview with question A.

Review Medical History for past 4 weeks. Ask question E1 for each procedure from the "Date of Onset" and back 4 weeks.

E. Questions for medications during procedures/surgical/dental etc. (Duplicate page as needed)

E1. W: Looking at the calendar, in the 28 days prior to first noticing the eye problem were there any days that you had any medical/dental procedure (e.g. surgeries, tooth extractions, cavities being filled, etc.)?
☐ Yes ☐ No ☐ Don't remember

If "Yes", continue interview with question E2.
If "No", continue interview with question F.

E2. Q: Can you please tell me which days you had this procedure?
*(Enter procedure)*_____
*(enter days)*_____

E3. Q: You have reported that you had a procedure on [repeat days reported in E2]? Are there any other days that you had any procedures? *(if "Yes", enter procedure and enter days)*
(*enter procedure)*_____
*(enter days)*_____

If any procedure occurred on the same day as the suspected NAION onset, ask the patient question E4 for each procedure reported in E2 and E3:

E4. Q: I see you had this procedure on the day you first noticed the eye problem. On that day, did you have this procedure before or after you first noticed the eye problem?
☐ before ☐ after ☐ I don't know.

E5. W: During your procedure on the [date], did your medical professional give you any type of medication, including anaesthesia that we have not discussed?
☐ Yes ☐ No ☐ Don't remember

If "No", continue interview with question F.
If "Yes", will need to ask Questions for Medications Taken PRN for each drug.

F Alcohol consumption

F1: **Q:** Looking at the calendar, in the 28 days prior to first noticing the eye problem did you consume alcoholic beverages daily or occasionally?
☐ daily ☐ occasionally ☐ none at all

If used daily go to F2.
If occasional use go to F9
If "none at all" go to G

F2. **Q:** Did you start taking the alcohol beverage on a daily basis before, on or after you first noticed the eye problem?
☐ before ☐ on ☐ after

*If the start date is **before** the day of suspected NAION onset, ask the question F3*
*If the start date is **on** the day of suspected NAION onset, ask the question F4*
*If the start date is **after** the suspected NAION onset, go to question G.*

F3: **Q:** I see that you have started taking alcoholic beverages before the day you first noticed the eye problem. Can you please provide the date you started drinking alcoholic beverages
Start date_____
or ☐ started more than 28 days before eye problem onset

Level of consumption :
How many drinks per day did you drink?_____
(Answer will be entered by interviewer in one of three categories: 1-2 drinks =mild, 3-4 drinks = moderate,5+ drinks =heavy

Go to question F5

F4: **Q:** I see that you started drinking alcoholic beverages on a daily basis on the day you first notice the eye problem . On that day, did you drink alcoholic beverages before or after you first noticed the eye problem?
☐ before ☐ after

Go to question F5

F5: **Q:** Did you stop drinking alcoholic beverages on a daily basis before, on or after you first noticed the eye problem?
☐ before ☐ on ☐ after

*If the stop date is **before** the day of suspected NAION onset, ask the question F6*

*If the stop date is **on** the day of suspected NAION onset, ask the question F7*
*If the stop date is **after** the suspected NAION onset, please check the check box under question **F8** and then go to question .*

F6: **Q:** I see that you stopped drinking alcoholic beverages on a daily basis **before** the day you first noticed the eye problem. Can you please provide the date when you stopped drinking alcoholic beverages?
Stop date_____

Go to question G.

F7: **Q:** I see that you stopped drinking alcoholic beverages on a daily basis **on the day** you first notice the eye problem. On that day, did you stop drinking alcoholic beverages before or after you first noticed the eye problem?
☐ before ☐ after

Go to question G.

F8: **Q:** Check box below:
☐ stopped after eye problem onset

Go to question G.

F9: **Q:** Looking at the calendar, in the 28 days prior to first noticing the eye problem
were there any individual days that you consumed alcoholic beverages?
☐ Yes ☐ No ☐ Don't remember

If "Yes", continue interview with question F10.
If "No", continue interview with question G

F10. **Q:** Can you please tell me which days you consumed alcoholic beverages?
*enter days*_____

Level of consumption :
How many drinks per day did you drink?_____
(Answer will be entered by interviewer in one of three categories: 1-2 drinks =mild, 3-4 drinks = moderate,5+ drinks =heavy

F11. **Q:** You have reported that you consumed alcohol on [repeat days reported in F10]? Are there any other individual days that you consumed alcoholic beverages?
☐ Yes ☐ No ☐ Don't remember **(Duplicate page as needed)**

If "Yes", please return to F10.
If "No" or "Don't remember" please go to section G.

If alcohol was consumed on the same day as the suspected NAION onset ask patient:

F12. **Q:** I see you consumed alcohol on the day you first noticed the eye problem. On that day, did you consume alcohol before or after you first noticed the eye problem?
☐ before ☐ after ☐ I don't know.

Go to section G

G. Other

G1: **W:** Looking at the calendar, are there any drugs/dr/dentist/other medical appointments that we did not discuss? ☐ Yes ☐ No ☐ Don't remember

If "No", continue interview with Conclusion.
If "Yes", will need to go back to appropriate section.

H. Conclusion

I'd like to thank you for your participation in this study and taking the time to speak with me today. If you have any questions regarding our conversation or the medications discussed, please speak with your study staff or eye doctor before leaving the office today.

10.5 Instruction on How to Perform Perimetry

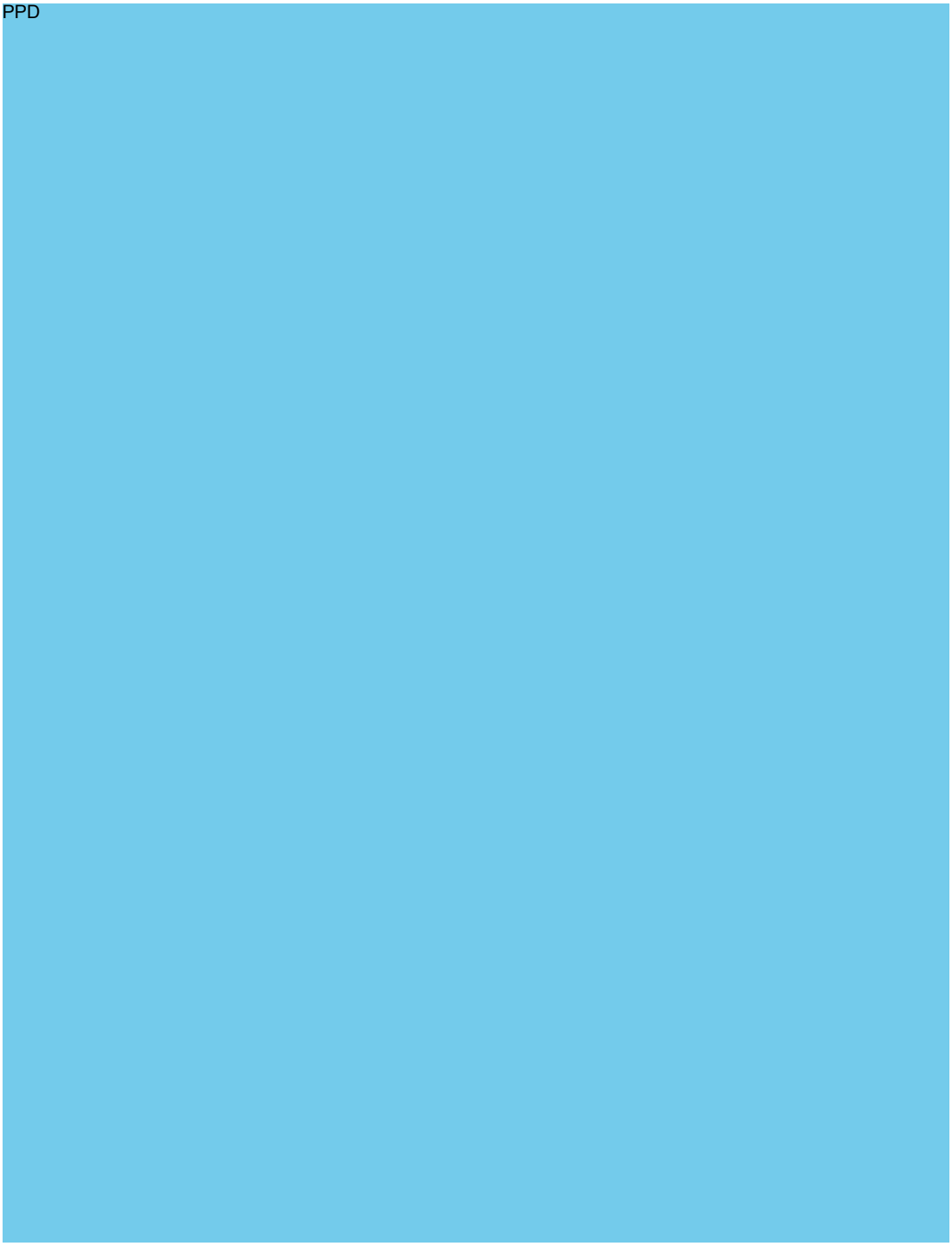
In this study, Humphrey's Field Analyzer and Octopus perimeters will be used for the visual field assessments. *Note: Octopus perimetry was added in amendment 2*. The perimetry should be performed by a trained and experienced staff.

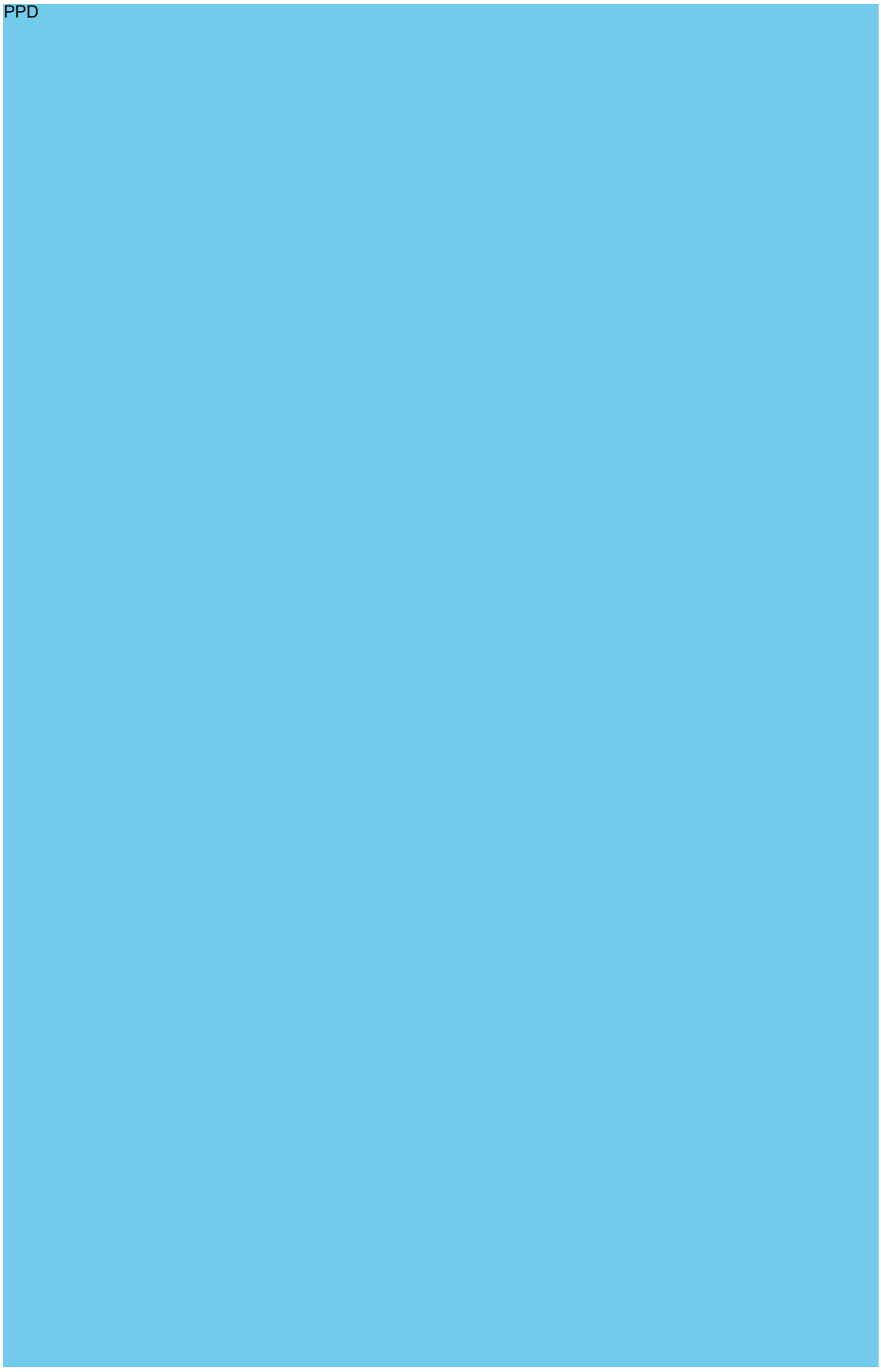
Copies of all perimetry printouts must be signed and dated by the investigator (or his/her delegate) and kept in the Investigator's Study File for source data verification. The printouts must be marked with study code, patient number, as well as date of measurement.

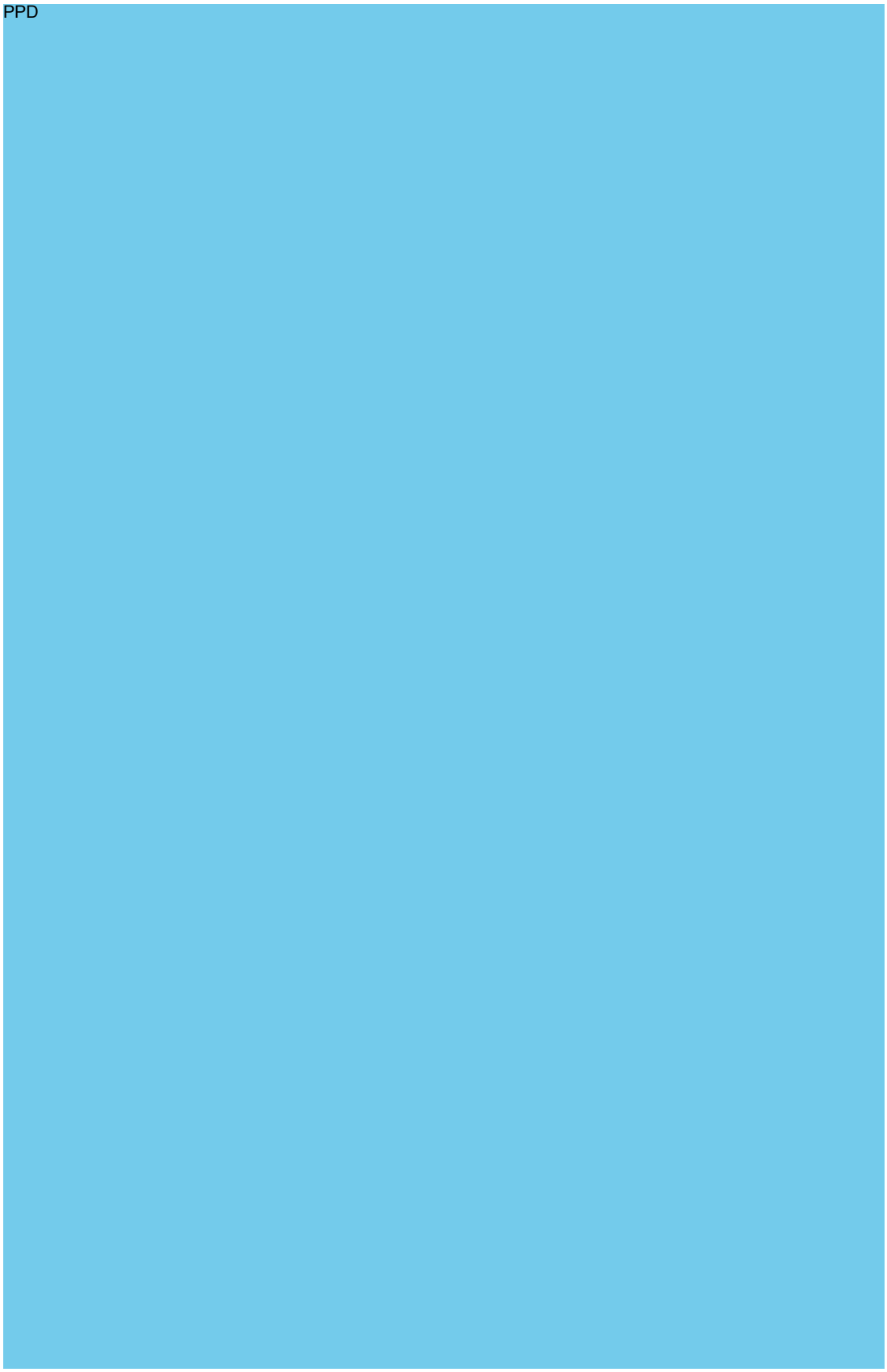
In order to standardize how the perimetry testing will be performed in this study, technicians at each site will be provided with an instruction manual.

10.6 Sample Narrative to Expert Panel

The sample narrative below is to illustrate how partial blinding of the Expert Panel should be ensured.




PPD


PPD


PPD