PASS Information

Title	Observational Study Description H6D-MC-LVHQ(b) A Prospective Case-Crossover Study to Evaluate the Possible Association between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION)
Version identifier of the final study report	1.0
Date of last version of the final study report	N/A
EU PAS register number	ENCEPP/SDPP/13266
Active substances	Tadalafil: G04BE08 Sildenafil: G04BE03 Vardenafil: G04BE09
Medicinal products	Tadalafil: Cialis® Sildenafil: Viagra® Vardenafil: Levitra®
Product reference	MA number: EU/1/02/237/001-010
Procedure number	N/A
Marketing authorisation holder	Eli Lilly and Company
Joint PASS	No
Research question and objectives	The purpose of this study was to evaluate whether there is a possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult men. The primary objective of this study was to evaluate the rate ratio for the potential association between the intermittent use of PDE5 inhibitors and the development of acute NAION over a 30-day period, using a person-time approach and defining exposure on the basis of effect period. Secondary analyses were to evaluate the rate ratio for the potential association between the intermittent use of PDE5 inhibitors and the development of acute NAION over the 12 months before the index date of onset (using a person-time analysis and defining exposure on the basis of effect period) and over the 42 days before the index date of onset (using a matched-interval analysis and defining exposure on the basis of effect period).
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Approval Date: 25-May-2016 GMT

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1. Abstract

Protocol H6D-MC-LVHQ(b): A Prospective Case-Crossover Study to Evaluate the Possible Association between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischaemic Optic Neuropathy (NAION).

Keywords: case-crossover study; erectile dysfunction; nonarteritic anterior ischaemic optic neuropathy (NAION); phosphodiesterase type 5 (PDE5) inhibitors

Rationale and Background

Acute nonarteritic anterior ischaemic optic neuropathy (NAION) is a rare disease characterised by a sudden and painless unilateral vision loss, with optic disc oedema, in the absence of arteritis. It typically occurs in people over 50 years of age. The aetiology is unknown but it is believed to be ischaemic in origin. Suspected risk factors include diabetes, hypertension, atherosclerosis, hyperlipidaemia, ischaemic heart disease, and prothrombotic tendencies, presence of small cup-to-disk ratio, history of anterior chamber surgical procedures, and use of angiotensin-converting enzyme inhibitors, amitriptyline, and PDE5 inhibitors.

Research Question and Objectives

This observational, multicentre, case-crossover study design evaluated the possible association between PDE5 inhibitor use and the risk of acute NAION in adult men using a person-time analysis. The primary objective evaluated the rate ratio (RR) for NAION occurring in association with exposure to PDE5 inhibitors, defined by using the number of days of exposure to PDE5 inhibitors within 30 days before the onset of NAION.

Setting, Subjects, and Study Size

Adult men visiting 1 of 41 participating ophthalmology and neuro-ophthalmology centres in the United States and presenting with symptoms consistent with NAION, within 45 days of onset, were considered. Adult men with physician-diagnosed NAION were evaluated for eligibility. Study participation was limited to the day that the patient first presented with symptoms.

Between 05 May 2010 and 15 December 2015, 344 adult men with suspected NAION met the inclusion and exclusion criteria, provided informed consent, and had a known date of symptom onset. Of these, 279 were confirmed as having NAION on the basis of adjudication committee decision.

Variables and Data Sources

Subjects with physician-diagnosed NAION completed a structured questionnaire to document PDE5 inhibitor use and other risk factors for the period up to 1 year before onset of suspected NAION, and clinical examinations were performed. Exposure was defined on the basis of the PDE5 inhibitor effect period, which was 5 times the half-life of the PDE5 inhibitor (4 days for tadalafil and 1 day for sildenafil and vardenafil). An independent adjudication committee, blinded to subject PDE5 inhibitor use, confirmed the NAION diagnosis for each physician-diagnosed case on the basis of committee majority decision.

Results

Of the 279 subjects with adjudication-confirmed NAION, 22 were intermittent users of PDE5 inhibitors with nonchronic exposure within the 30 days before the index date of onset (IDO) of NAION. The Mantel-Haenszel RR for the risk of NAION associated with PDE5 inhibitor exposure within 1 to 5 half-lives of NAION onset was 2.27 (95% confidence interval [CI]: 0.99, 5.20). Sensitivity analyses modifying the exposure definition and imputing missing exposure information were conducted. The RRs for these analyses ranged from 2.55 to 2.84 and were statistically significant. A secondary analysis using the person-time method was conducted to evaluate the association between the risk of NAION and PDE5 inhibitor use in the 12 months before IDO. The RR for PDE5 inhibitor exposure within 1 to 5 half-lives of NAION onset was 3.52 (95% CI: 1.59, 7.79). Therefore the person-time analyses are suggestive of an association between PDE5 inhibitor exposure and NAION.

In addition, a secondary matched-interval analysis was conducted using 4-day hazard and control periods. The hazard ratio was 1.64 (95% CI: 0.60, 4.51). Seven sensitivity analyses, varying the durations and numbers of control periods, resulted in hazard ratio estimates ranging from 1.09 to 2.23 and were not statistically significant. Findings from the matched-interval analysis do not support an association between PDE5 inhibitor exposure and NAION.

Discussion

The primary analysis was not statistically significant; however, the results of both the main (primary and secondary) and sensitivity person-time analyses are suggestive of an increased risk of NAION occurring in association with PDE5 inhibitor exposure. The matched-interval analyses were also not statistically significant, although the statistical power of the matched-interval analyses was limited. Campbell et al. (2015) used a similar case-crossover study design, although it used different assumptions, and reported an increased risk of NAION occurring within 5 half-lives of PDE5 inhibitor dosing. Patients and their health care providers should continue to weigh the risks and benefits of PDE5 inhibitors, including the potential for NAION, before prescribing PDE5 inhibitors.

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2. List of Abbreviations

Term	Definition
12-month analysis set	all subjects with adjudication-confirmed NAION who are nonchronic users of PDE5 inhibitors within 12 months before the onset of NAION (also referred to as a 'secondary analysis set')
30-day analysis set	all subjects with adjudication-confirmed NAION who are nonchronic users of PDE5 inhibitors within 30 days before the onset of NAION (also referred to as 'primary analysis set')
42-day analysis set	all subjects with adjudication-confirmed NAION who are nonchronic users of PDE5 inhibitors within 42 days before the onset of NAION (also referred to as a 'secondary analysis set')
adjudication-confirmed	physician-diagnosed NAION that has been confirmed by the adjudication committee per the New Data Standards criteria (ie, the list of criteria used by the adjudication committee to confirm a diagnosis of NAION in a physician-diagnosed case)
analysis population	all subjects with adjudication committee-confirmed NAION who are intermittent (not chronic) users of PDE5 inhibitors
ATC	Anatomical Therapeutic Chemical
chronic user	a subject who has had continuous daily dosing with 1 or more PDE5 inhibitors during a specified analysis period before the date of onset of NAION
chronic exposure	continuous daily exposure, defined on the basis of the assumed effect period (approximately 5 half-lives) after administration of each dose, to 1 or more PDE5 inhibitors
CI	confidence interval
control period	study time before the hazard period
CRF	case report form
effect period	the time between the minimum and maximum induction times in the population. In this study, the minimum induction time for any PDE5 inhibitor was taken to be zero, and the maximum induction time was taken to be approximately 5 half-lives, so the effect period is 5 half-lives of whichever PDE5 inhibitor was used.
enrolled set	subjects with suspected NAION who signed informed consent
exposed case	For the primary analysis, a subject was considered to be a PDE5 inhibitor–exposed case if his reported exposure (defined on the basis of the effect period of his PDE5 inhibitor) extended into the hazard period for that PDE5 inhibitor.

FDA	Food and Drug Administration
hazard period	The period of potential harm from the factor under study. In this study, the hazard period is the period of time immediately before the onset of NAION, which was 4 days for tadalafil users and 1 day for sildenafil or vardenafil users.
IDO	index date of onset; defined as the day when the patient first experienced the abrupt loss of vision in one eye. Because no time of IDO was collected, the time of IDO was imputed conservatively as 00:01 (24-hour clock), and the IDO was not counted as part of the hazard period for any analysis method.
induction time	the time between cause and effect in an individual: minimally, the smallest delay of risk exposure before effect; maximally, the time after which the effects are hypothesised to no longer exist
intermittent user	a nonchronic user (ie, a subject who has used 1 or more PDE5 inhibitors during specified analysis period before the onset of NAION and is not a chronic user)
MedDRA	Medical Dictionary for Regulatory Activities
NAION	nonarteritic anterior ischaemic optic neuropathy
nonchronic user	a subject who has used 1 or more PDE5 inhibitors during a specified analysis period before the onset of NAION and who is not a chronic user (ie, an intermittent user)
nonuser	a subject who has had no exposure to any PDE5 inhibitor during a specified analysis period before the onset of NAION
OR	odds ratio
PDE5 inhibitor	phosphodiesterase type 5 inhibitor
PDE6	phosphodiesterase type 6
physician-diagnosed	diagnosed by the investigator on the basis of examinations and diagnostic test(s) as per normal clinical practice at the participating site; upon diagnosis, data collection forms are submitted and the subject with physician-diagnosed suspected NAION becomes part of the study population
primary analysis set	30-day analysis set
PT	preferred term
RR	rate ratio
SAP	statistical analysis plan
SD	standard deviation

secondary analysis sets	42-day analysis set and 12-month analysis set
SOC	system organ class
study set	all subjects with physician-diagnosed NAION with a known date of symptom onset who met the inclusion and exclusion criteria and signed informed consent
suspected NAION	NAION that is considered highly probable on the basis of initial assessment of patient presenting with unilateral vision symptoms by the investigator; patients meeting the eligibility criteria are invited to participate in the study
TrialEASTM	an INC Research system that manages external adjudication data
unexposed case	for the primary analysis, a case of NAION in a subject in the specified analysis set who did not have exposure to a PDE5 inhibitor extending into the hazard period for the PDE5 inhibitor used
WHO-DD	World Health Organization Drug Dictionary

3. Investigators

Principal investigators for this study are listed below. A listing of investigators can be provided on request. A listing of clinical sites that participated in this study is included in Annex 2.

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5. Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data collection	First subject, first visit: 19 April 2010	First subject, first visit: 05 May 2010	
End of data collection	05 January 2016	19 February 2016	Data collection was extended because of sample size revision.
Final report of study results	18 May 2016	26 May 2016	

6. Rationale and Background

6.1. Background

6.1.1. PDE5 Inhibitor Use in the United States

Phosphodiesterase type 5 (PDE5) inhibitors approved in the United States, including tadalafil (Cialis®), sildenafil (Viagra® and Revatio®), vardenafil hydrochloride (Levitra®), and avanafil (Stendra®), are indicated for on-demand use for the treatment of erectile dysfunction. In addition, chronic use of tadalafil and sildenafil are approved for specific indications; tadalafil (Cialis) is approved for once-a-day dosing (2.5 mg and 5 mg) for the treatment of erectile dysfunction, and sildenafil (Revatio) is approved for 3 times-a-day dosing (20 mg) for the treatment of pulmonary arterial hypertension. Tadalafil was approved for once-daily use for the treatment of pulmonary arterial hypertension (Adcirca®; US approval 22 May 2009). Patients using Revatio or Adcirca were not included in the analysis because they have daily (not intermittent) dosing.

Since this study was initiated in 2010, tadalafil has also been approved for once-a-day dosing for treatment of benign prostatic hyperplasia and erectile dysfunction/benign prostatic hyperplasia (Cialis US approval 10 June 2011). In 2012, after this study started, avanafil (Stendra) was approved for on-demand use for the treatment of erectile dysfunction; however, no subjects in this study reported using avanafil.

PDE5 is the predominant cyclic guanosine monophosphate metabolizing phosphodiesterase in cavernosal tissue and in penile arteries. In addition to PDE5, the above-noted drugs also have different degrees of effects on phosphodiesterase type 6 (PDE6), which is expressed only in the retina and plays a critical role in signal transduction of vision. Inhibition of this enzyme can induce visual disturbances. Selectivity for PDE6 differs among the drugs. Tadalafil has less potential than vardenafil and sildenafil to inhibit PDE6. Specifically, inhibition of PDE6 requires 780-fold, 15-fold, and 7-fold higher concentrations of tadalafil, sildenafil, and vardenafil, respectively, than is required to produce the same magnitude of inhibition of PDE5 (Bischoff 2004).

6.1.2. Nonarteritic Anterior Ischaemic Optic Neuropathy

Nonarteritic anterior ischaemic optic neuropathy (NAION) is characterised by a sudden and painless loss of vision in one eye, usually with optic disc oedema, in the absence of arteritis. Although the precise cause of NAION is unclear, it appears to be associated with a subclinical reduction of blood flow to the optic nerve head, resulting in hypoxia and subtle oedema of axonal tissue that accumulates over time. When combined with a crowded optic nerve outlet, vascular occlusion and infarction of the nerve tissue occurs, resulting in NAION symptom onset (Peeler and Cestari 2016). Clinical features of NAION include a sudden, painless, monocular vision loss, often described as a ‘shadow’ or ‘cloud’ over the vision (Peeler and Cestari 2016). Only 8% to 12% of patients with NAION report pain with vision loss, and this can help distinguish NAION from other optic neuropathies (Peeler and Cestari 2016).

Many patients with NAION (estimates range from 40% to 73%) report symptom onset upon awakening, and it has been suggested that nocturnal hypotension may be a precipitating event (Peeler and Cestari 2016; Hayreh 2009). An assessment of 20 case reports of NAION occurring in temporal relationship to PDE5 inhibitor use found that most cases had a rapid onset ranging from 30 minutes to overnight (upon awakening), with the exception of one case that developed 7 days after the use of tadalafil (Carter 2007). Rizzo and Lessell (1991) reported an average time to maximum visual loss of 4.7 days. In contrast with arteritic anterior ischaemic optic neuropathy, patients with NAION may not realise they have NAION: it can go unrecognised because the initial vision loss may be painless and typically involves only one eye. The other eye often can compensate for the loss of vision.

NAION is a rare disease that typically occurs in people over 50 years of age, but it can also occur in younger individuals (Preechawat et al. 2007). The incidence of NAION is 2.5 to 11.8 cases per 100,000 in men aged 50 years and older (Johnson and Arnold 1994; Hattenhauer et al. 1997). In men aged 50 and older, the annual incidence rate is higher in white people (2.8 per 100,000) than in black and Hispanic people (approximately 0.3 per 100,000) (Johnson and Arnold 1994). Tobacco use has been suggested as a risk factor for NAION; however, this remains controversial (Biousse and Newman 2015; Hayreh 2009). Other risk factors for NAION besides increasing age and Caucasian race include diabetes, hypertension, coronary artery disease, atherosclerosis, ischaemic heart disease, hyperlipidaemia, hyperhomocystinaemia, and prothrombotic tendencies (Salomon et al. 1999; Weger et al. 2001; Hayreh 2009; Kerr et al. 2009; Hayreh 2011; Lee et al. 2011; Papageorgiou et al. 2012; Chen et al. 2013; Peeler and Cestari 2016; Zotz et al. 2016). Nocturnal arterial hypotension is a risk factor for NAION, and medications such as angiotensin-converting enzyme inhibitors and amitriptyline, particularly when taken at bedtime, may increase the degree of nocturnal arterial hypotension and thereby increase the risk of NAION (Hayreh 2000). Individuals with small cup-to-disc ratios, crowding of axons at the nerve heads, and histories of anterior chamber surgery are also thought to be at increased risk for NAION (Reddy 1995; McCulley et al. 2003; Peeler and Cestari 2016). In a retrospective matched-cohort study, Chang et al. (2016) found an incidence of NAION in patients with end-stage renal disease that was 3 times higher than the incidence in controls. Wu et al. (2015) conducted a meta-analysis to evaluate the association of obstructive sleep apnoea and NAION and found that obstructive sleep apnoea was a strong independent risk factor for NAION. The first reports describing cases of NAION occurring in temporal association with use of PDE5 inhibitors were in the postmarketing setting (Boshier et al. 2002; Pomeranz et al. 2002; Boshier et al. 2004). There were no reported NAION events in placebo-controlled clinical trials of tadalafil for erectile dysfunction, benign prostatic hyperplasia, and pulmonary arterial hypertension. One case of NAION was identified in a postmarketing study of 16,129 men prescribed tadalafil for erectile dysfunction (Hazell et al. 2009). NAION is very rarely reported in postmarketing reports for tadalafil-treated patients (less than 1 instance in 10,000 patients).

Men with erectile dysfunction have many of the comorbidities that are risk factors for NAION, including hypertension, cardiovascular disease, hyperlipidaemia, and diabetes, therefore it is difficult to evaluate whether an individual reported case of NAION is related to the use of PDE5

inhibitors or to underlying risk factors. For these reasons, a causal association cannot be determined on the basis of reviews of individual case reports.

6.1.3. Summary of Existing Literature

The existing literature includes numerous case reports of NAION occurring in temporal association with PDE5 inhibitor use in addition to multiple review and opinion publications. The limitations of case reports have been mentioned above, and the following summary focuses on the literature that presents observational data.

McGwin et al. (2006) published results of a small case-control study investigating the association between PDE5 inhibitor use and NAION that reported statistically significant increases in risk, as measured by odds ratios (ORs); however, this manuscript was subsequently retracted in 2011 (McGwin et al. 2011); the use of flawed and biased methodology in this study was highlighted by Sobel and Cappelleri (2006).

Since Study H6D-MC-LVHQ (Study LVHQ) was initiated in 2010, results from other observational studies have been published. Nathoo et al. (2015) conducted analyses using routinely collected health insurance claims data and reported no association between PDE5 inhibitor use and NAION; however, the diagnosis of NAION was not confirmed, and the temporality of the association was subject to assumptions regarding the timing of use of PDE5 inhibitors, which may incur misclassification bias.

The case-crossover study sponsored by Pfizer at the request of the US Food and Drug Administration (NCT00759174) was conducted to assess the association between recent intermittent PDE5 inhibitor use and the risk of acute NAION (Campbell et al. 2015). The results of this study suggested an increased risk of NAION within 5 half-lives of PDE5 inhibitor use (OR = 2.15; 95% confidence interval [CI]: 1.06, 4.34) when PDE5 inhibitor exposure in the day before NAION onset is compared with exposure in the 29 preceding days. Campbell et al. (2015) estimated, on the basis of weekly use and assuming an annual baseline risk of 11.8 cases per 100,000 men aged 50 years and older, that approximately 3 additional cases of NAION would occur annually in this population. As in Study LVHQ, subjects enrolled in the Pfizer study included users of tadalafil, sildenafil, and vardenafil, and the results are considered applicable to the entire class of PDE5 inhibitors. The case-crossover study design was chosen because it is a method suitable for intermittent drug exposure with a transient effect (ie, on-demand use of PDE5 inhibitors to treat erectile dysfunction) and an acute outcome such as NAION.

6.1.4. Risk Management

Tadalafil labelling provides detailed warnings as well as guidance to physicians and patients regarding the risk of NAION in tadalafil users. Lilly has undertaken to conduct Study LVHQ to further investigate the possible association between NAION onset and PDE5 inhibitor exposure. Labelling has been updated to reflect the results of the recently completed Pfizer observational study (NCT00759174; Campbell et al. 2015).

6.1.5. Contribution of Study LVHQ

Study LVHQ (NCT01131104) is another prospective case-crossover study to be completed that has evaluated the association between PDE5 inhibitor exposure and the risk of acute NAION.

Results from Campbell et al. (2015) suggest that recent PDE5 inhibitor use is associated with an increased risk of NAION. However, this single observational study does not definitively establish a causal association between NAION and PDE5 inhibitors. In addition, there are differences in the assumptions, methods, and statistical analyses used by Campbell et al. (2015) and those used in Study LVHQ. Therefore, Study LVHQ will add meaningful data to the body of evidence related to and will contribute to the understanding of the potential association between PDE5 inhibitors and NAION.

6.2. Rationale

Labelling changes were made after reports of the initial cases of NAION occurring in temporal association with use of PDE5 inhibitors. The European Medicines Agency and the FDA requested additions to the summary of product characteristics and the US package insert for all PDE5 inhibitors in 2005 and 2006, respectively. These additions included a class warning and a precaution about the occurrence of NAION in temporal association with the use of PDE5 inhibitors and the addition of NAION as an undesirable effect. The European Medicines Agency also added a class contraindication for use of PDE5 inhibitors in patients with loss of vision in one eye due to NAION.

In December 2005, Lilly received correspondence from the FDA requesting the conduct of an observational study to evaluate whether the use of a PDE5 inhibitor, such as tadalafil, is an independent risk factor for NAION. Initially, a case-control study was requested, but after extensive discussions between Lilly and the FDA regarding use of different data sources and methodology, a prospective case-crossover study protocol was agreed upon, and Study LVHQ commenced in May 2010. Pfizer (the sponsor of sildenafil) and Bayer (the sponsor of vardenafil) were also requested to conduct similar studies (NCT00759174 and NCT00867815, respectively). The Pfizer study results were uploaded to www.clinicaltrials.gov in August 2013. The estimated completion date for the Bayer-sponsored study is February 2018.

7. Research Question and Objectives

The purpose of this noninterventional, case-crossover, observational study was to evaluate whether there is a possible association between the use of PDE5 inhibitors and the risk of acute NAION in adult men.

The primary objective of this study was to evaluate the rate ratio (RR) for the potential association between the intermittent use of PDE5 inhibitors and the development of acute NAION over a 30-day period by using a person-time approach and defining exposure on the basis of effect period.

Secondary analyses conducted as part of this study were as follows:

- Evaluate the RR for the potential association between the intermittent use of PDE5 inhibitors and the development of acute NAION over the 12 months before the index date of onset (IDO) by using a person-time analysis and defining exposure on the basis of effect period.
- Evaluate the RR for the potential association between the intermittent use of PDE5 inhibitors and the development of acute NAION over the 42 days before the IDO by using a matched-interval analysis and defining exposure on the basis of effect period.

8. Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	07-May-2010 (a)	Section 3.5	Amendment	Retrospective data collection was expanded from 30 days to 42 days to accommodate the matched-interval analysis, which used a 4-day hazard period preceded by 4 weekly 4-day control periods. To capture exposure to PDE5 inhibitors in all 4 of the control periods, additional retrospective data collection beyond the 30 days was needed.
2	06-Jun-2014 (b)	Section 4	Amendment	Section 4.1 was modified to retain the original sample size justification in Section 4.1.1 and to add Section 4.1.2. Section 4.1.2 included a description of (1) an administrative analysis of sample size assumptions performed when study enrolment neared the projected sample size of 125 adjudication-confirmed NAION subjects, and (2) plans for extended enrolment to achieve approximately 80% power to detect an odds ratio of 3 in the primary analysis.

9. Research Methods

9.1. Study Design

9.1.1. Description of Study Design

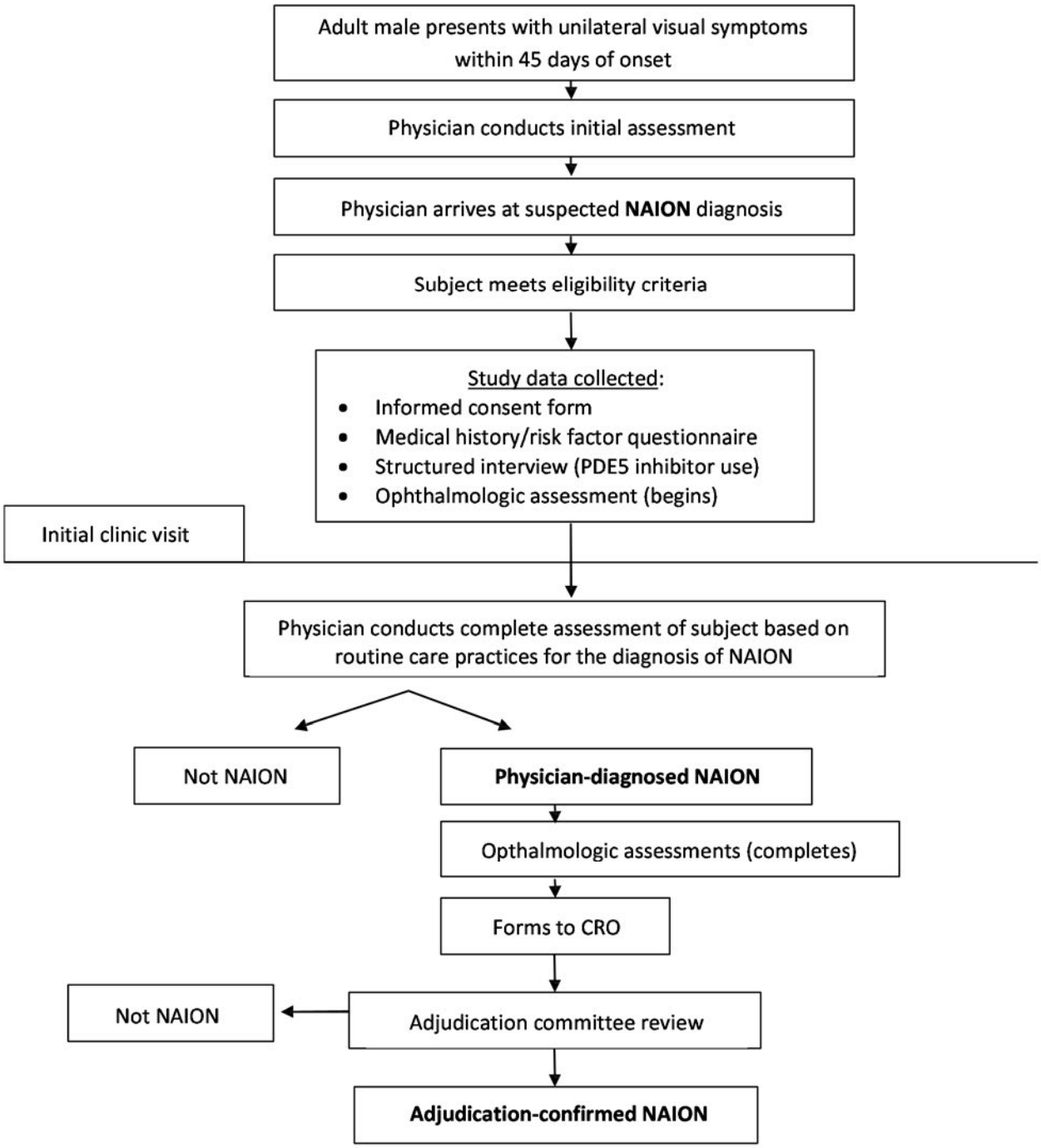
Study LVHQ was an observational, prospective, case-crossover study. All treatment and diagnostic decisions were solely at the discretion of the physician and the subject. Treatment for NAION and other conditions was prescribed in accordance with standard of care. There was no attempt to influence the prescribing patterns of any individual investigator, and the study sponsor provided no medications.

Figure LVHQ.9.1 depicts the procedure for subject enrolment and confirmation of NAION. Participating ophthalmology and neuro-ophthalmology centres were asked to identify all subjects with suspected NAION among all adult male subjects with unilateral visual symptoms who visited the centre within 45 days of the initial occurrence of visual loss and were diagnosed with NAION by a physician. A suspected case was defined as NAION that was considered highly probable on the basis of the initial assessment of the subject presenting with unilateral vision symptoms. All subjects with suspected NAION were further evaluated for study eligibility. Subjects who met the study inclusion and exclusion criteria were invited to participate in the study and were enrolled after giving signed informed consent.

The study included only one study visit for each subject; a subject was enrolled and completed the study on the day on which he first presented to the investigator with symptoms consistent with acute NAION. During the study visit, the investigator evaluated and treated the subject in accordance with the standard of care. In addition, the investigator conducted a structured interview for each subject to collect historical data on PDE5 inhibitor use, NAION risk factors, medication use, and medical/surgical history. These exposures and data were captured for the 42 days before NAION symptom onset and in less detail for the preceding 12 months.

The diagnosis of NAION by the investigator was based on examinations and diagnostic tests per standard clinical practice at the participating site. Results from the clinical examinations related to NAION were documented for study purposes, including case adjudication. Although a subject may have needed additional visits to the clinic office for his condition, the additional visits were not required for the study and involved no data collection or study activities.

Information from physician-diagnosed NAION was evaluated by an independent adjudication committee before it confirmed the diagnosis of NAION for study purposes. During the adjudication process, members of the committee independently reviewed the clinical examination data for each physician-diagnosed NAION case, excluding all information related to PDE5 inhibitor use. Subjects were designated as having adjudication-confirmed NAION cases if they met the criteria in the predetermined data standards (Section 9.3.3) according to the committee majority.



Abbreviations: CRO = contract research organization; NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Figure LVHQ.9.1. Procedure for subject enrolment and confirmation of NAION.

9.1.2. Rationale for Study Design

The case-crossover study design, developed by Maclure (1991), is an epidemiological method appropriate when the exposure to the drug being studied is intermittent, the effect on risk is

immediate and transient, and the outcome is abrupt. The key features of this design are that the study involves cases only and each case serves as its own control. The case-crossover study design is based exclusively on case series to evaluate within-subject comparisons of drug exposure over time, comparing the drug exposure under study just before the event (during the hazard period) with that at other time points in the subject's history (the control period) to estimate the risk association between exposure and outcome.

This study, by design, investigated the possible association of the risk of acute NAION associated with the transient effect of intermittent use of PDE5 inhibitors. The continuous or chronic use of PDE5 inhibitors cannot be evaluated in this case-crossover study design, and subjects who had NAION but had not used a PDE5 inhibitor in the period preceding NAION onset were excluded from the analyses because concordant exposure or nonexposure in hazard and control periods adds no new information about the within-patient PDE5 inhibitor exposure risk. To evaluate the association between PDE5 inhibitor use and NAION, 2 statistical methods for a case-crossover study (as described by Maclure [1991]) were used: the person-time method and the matched-interval method.

In the person-time method, relative risk was expressed as a Mantel-Haenszel RR. For the matched-interval analysis, risk was expressed as a hazard ratio from a conditional logistic regression model. In this study, the primary analysis and associated sensitivity analysis was conducted with the person-time approach and focused on the exposures occurring during the 30 days before NAION onset. The person-time analysis examining the 12 months before NAION onset was used in a secondary analysis and sensitivity analyses. The matched-interval approach was also used to address secondary and sensitivity analyses. Further details are provided in Section 9.9.4.2.2.

To ensure that enrolled subjects had a recent and acute onset of NAION, only subjects who experienced abrupt visual changes in one eye and visited a neuro-ophthalmologist within 45 days of the initial occurrence of visual loss were eligible for the study.

9.1.3. Study Endpoints

The primary endpoint for each subject in the population is the number of days of exposure to PDE5 inhibitors within 30 days before the onset of NAION.

The secondary endpoints include the following:

- the number of days of subject exposure to PDE5 inhibitors within 12 months (365 days) immediately before the onset of NAION, where exposure is defined on the basis of the PDE5 inhibitor effect periods
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 4-day control periods within 42 days immediately before the onset of NAION, where exposure is defined on the basis of the PDE5 inhibitor effect period

Other endpoints included alternative definitions of the primary and secondary endpoints and/or alternative control period definitions. These other endpoints were used for sensitivity analyses and included the following:

- the number of days of subject exposure to PDE5 inhibitors, defined using the recorded number of days of dosing with PDE5 inhibitors within 30 days before the onset of NAION
- the number of days of subject exposure to PDE5 inhibitors, defined using the PDE5 inhibitor effect period and assuming that subjects with unknown PDE5 inhibitor type but known dates of PDE5 inhibitor dosing were exposed to tadalafil (Cialis) during the hazard period
- the number of days of subject exposure to PDE5 inhibitors, defined using the PDE5 inhibitor effect period and assuming that subjects with unknown PDE5 inhibitor type but known dates of PDE5 inhibitor dosing were exposed to sildenafil (Viagra, Revatio) during the hazard period
- the number of days of subject exposure to PDE5 inhibitors, where exposure is defined using the recorded number of days of dosing with PDE5 inhibitors within 12 months (365 days) immediately before the onset of NAION
- the number of days of subject exposure to PDE5 inhibitors, defined on the basis of the number of days of subject exposure to PDE5 inhibitors within 12 months (365 days) immediately before the onset of NAION, where exposure is defined on the basis of the PDE5 inhibitor effect periods and missing monthly exposure is imputed as the subject's monthly average for subjects who reported the number of doses of PDE5 inhibitor used for ≥50% of the expected 12-month data
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 4-day matched-interval control periods within 42 days immediately before the onset of NAION, where exposure status is defined on the basis of recorded dosing with a PDE5 inhibitor
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 1-day matched-interval control periods within 42 days immediately before the onset of NAION, where exposure status is defined on the basis of recorded dosing with a PDE5 inhibitor
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 2-day matched-interval control periods within 42 days immediately before the onset of NAION, where exposure status is defined on the basis of recorded dosing with a PDE5 inhibitor
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 3-day matched-interval control periods within 42 days immediately before the onset of NAION, where exposure status is defined on the basis of recorded dosing with a PDE5 inhibitor
- subject exposure status (exposed or not exposed) during a hazard period and a series of preceding 7-day (1 week) matched-interval control periods within 42 days immediately before the onset of NAION, where exposure status is defined on the basis of recorded dosing with a PDE5 inhibitor

9.2. Setting

This observational study was conducted in the United States at 41 investigative sites specialising in ophthalmology and neuro-ophthalmology. The first subject was enrolled on 05 May 2010, and the last subject was enrolled on 15 December 2015.

9.3. Subjects

Subjects who met the study inclusion and exclusion criteria were invited to participate in the study. Subjects were enrolled upon their signing informed consent.

9.3.1. Inclusion and Exclusion Criteria

Subjects were eligible to participate in the study only if they met all of the following criteria:

1. were adult male subjects, at least 18 years of age, willing to participate in the study
2. experienced abrupt visual loss (defined as visual loss typically occurring during less than a 1-day period or visual loss noted upon awakening) in one eye and presented to an ophthalmologist within 45 days of onset of NAION symptoms for an initial visit that resulted in a diagnosis of suspected NAION by the investigator

Subjects were excluded from the study if they met any of the following criteria:

1. had previous history of NAION
2. had previous history of arteritis (anywhere in the body) or clinical or diagnostic testing evidence of temporal arteritis
3. had history of glaucoma in either one eye or both eyes
4. had history of multiple sclerosis or diagnostic testing evidence of optic neuritis
5. had dementia or other reasons for memory impairment in the opinion of the investigator
6. had participated in other nonobservational studies within 3 months before NAION onset

9.3.2. Case Ascertainment

Case ascertainment was conducted through an independent adjudication committee. Clinical information, including results from examinations and diagnostic tests conducted in accordance with routine care, was collected for all subjects with suspected NAION and, for subjects with physician-diagnosed NAION, was sent to the adjudication committee members for review. The adjudication committee was composed of 3 neuro-ophthalmologists who used consistent and agreed-upon data standards (Section 9.3.3), defined in the committee charter, to assess each suspected case on the basis of the clinical information provided by the investigator.

9.3.3. Adjudication Process and Confirmation of NAION

The essential aspects of unbiased endpoint adjudication included blinding of PDE5 inhibitor use, anonymisation of records, and documentation. Blinding and anonymisation was performed at the site and ensured by INC Research.

After identification of a physician-diagnosed case of NAION, the investigator provided INC Research with a deidentified packet of case-specific information. All references to subject name

and PDE5 inhibitor use were removed from the items in the packet. The packet was then sent to INC Research, where a quality control check was performed to ensure compliance.

After the quality control check, all components of the packet were uploaded in PDF format (documents) and JPEG or bitmap format (images) to TrialEAS™, an electronic adjudication system. All members of the adjudication committee were then notified by email informing them that a case was awaiting adjudication. This email prompted the adjudicators to log in to the TrialEAS system and navigate to the case that was available for review.

The adjudication committee reviewed all clinical information collected on the NAION ophthalmologic assessment form and the medical history and risk factor questionnaire. The adjudicator was allowed to request additional case-specific information as needed, although this was limited to readily available information in the subject's medical record. Additional subject visits for the purpose of collecting this information were not permitted.

Each adjudicator independently reviewed the case-specific information, decided on a diagnosis regarding the presence or absence of NAION for study purposes, and documented the decision on the adjudication form. The adjudication form allowed for 3 options: 'Yes' (Confirm NAION), 'No' (Not NAION), or 'unable to adjudicate'. If 'unable to adjudicate' was selected, the adjudicator was asked to indicate whether this inability was related to insufficient information provided by the investigator or some other reason. If the inability was related to some other reason, the adjudicator was asked to describe the reason on the adjudication form.

All individual decisions by adjudicators and the final decision of the committee were recorded via TrialEAS and maintained in the database. Only the adjudicators' responses to the question 'Can you confirm the presence of NAION in the subject?' were considered for comparison among adjudicators. A subject was deemed to have adjudication-confirmed NAION on the basis of majority decision, with at least 2 of the 3 adjudicators confirming NAION. An outcome of 'unable to adjudicate' or 'No' was considered an unconfirmed diagnosis of NAION. In the event that the decision of the adjudication committee was at variance with the diagnosis of the investigator, the decision of the adjudication committee was deemed final.

Confirming the presence of NAION required a review of the subject's medical history, risk factors, and results from various laboratory and ophthalmologic assessments combined with an evaluation of exclusion of other possible causes of the subject's symptoms.

A combination of the following criteria elements were considered before confirmation of NAION:

- subjects with history of painless loss of vision in one eye; vision loss should be acute and may be static or progressive over 2 weeks
- appropriate subject age
- characteristic defect in reactions of the pupil
- loss of visual acuity
- pale swelling of the optic nerve head
- characteristic visual field defect

- optic disc swelling in the affected eye and a disc at risk in the unaffected eye
- relative afferent pupillary defect in the affected eye

All of these findings must have been supported by absence of any indication of conditions such as central retinal artery occlusion, embolism to the ocular circulation, and giant cell arteritis and by absence of indication of systemic and/or regional vasculitis. Atypical cases received appropriate evaluation, imaging, and follow-up as part of the standard of care.

9.3.4. Ethical Conduct

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and applicable laws and regulations of the United States. Because this was an observational study that did not impose any form of intervention, subjects provided authorisation for the use and disclosure of their personal health information. This authorisation covered the collection and release of data regarding treatment and its outcomes for the entire period of the study. The confidential nature of the subject information was maintained.

9.4. Variables

To address the study's objective, data related to outcomes, exposures, and potential confounders or effect modifiers were collected. On the basis of subject recall, detailed information on exposure to PDE5 inhibitors was collected for each day on which a PDE5 inhibitor was taken for the following 2 distinct time periods: 42 days and 12 months before the IDO. Subjects were asked to recall specific days on which PDE5 inhibitors were taken, which PDE5 inhibitor was taken (tadalafil, sildenafil, or vardenafil), and dosing information. Exposure (effect period) was quantified in days as 5 times the half-life of the specific PDE5 inhibitor, which for tadalafil included the dosing day and the next 3 days, and for sildenafil and vardenafil included only the dosing day (Section 9.9.4.1).

During the study visit, information about concomitant medications, medical history, and risk factors was collected separately for the 42 days and 12 months before IDO.

For the 42 days before IDO, the following information was collected on case report forms (CRFs):

- medications taken on demand within the 42 days before IDO
- PDE5 inhibitors taken within the 42 days before IDO
- other medications associated with a condition for which the subject was taking PDE5 inhibitors, taken on demand within the 42 days before IDO
- medical conditions with a diagnosis or onset within the 42 days before IDO
- medical procedures occurring or present within the 42 days before IDO
- medical procedures occurring or present within the 42 days before IDO and associated with a condition for which the subject was taking PDE5 inhibitors

For the 12 months before IDO, the following information was collected on CRFs:

- medications taken within 12 months before IDO, including supplements and on-demand medications not previously captured on the 42-day CRF but excluding PDE5 inhibitors
- medical conditions occurring or present within the 12 months before IDO
- history of using tobacco, alcohol, or recreational drug use in the 12 months before IDO (excluding PDE5 inhibitors), including quantity, frequency, and dates
- use of PDE5 inhibitors within the 12 months before IDO (not previously captured on the 42-day CRF)
- medical conditions associated with a condition for which the subject was taking PDE5 inhibitors and with a diagnosis or onset within the 12 months before IDO (not previously captured in the 42-day CRF)
- medical procedures occurring or present within the 42 days before IDO that were associated with a condition for which the subject was taking PDE5 inhibitors

9.5. Data Sources

In this study, data sources are described in Table LVHQ.9.1.

Table LVHQ.9.1. Description of Data Collection Instruments

Case Report Form	Data Collected
Eligibility assessment form	• inclusion and exclusion criteria, informed consent date
Medical history and risk factor questionnaire *Note: This form excluded all data related to PDE5 inhibitor use so that the adjudication committee members could review it without learning of exposure.*	• demographics, baseline disease status, lifestyle factors • medications taken on demand within 42 days before IDO, excluding PDE5 inhibitors • all medications taken within 12 months before IDO excluding PDE5 inhibitors • medical conditions with diagnosis or onset within 42 days before IDO excluding conditions related to PDE5 inhibitors • medical conditions with diagnosis or onset within 12 months before IDO excluding conditions related to PDE5 inhibitors • medical procedures occurring within the 42 days before IDO excluding conditions related to PDE5 inhibitors
Other medications of interest[a]	• medications used for conditions that are associated with PDE5 inhibitors • collected separately for the 42 days and 12 months before IDO
Expanded medical history and procedures associated with PDE5 inhibitor use[a]	• medical conditions that are associated with the use of PDE5 inhibitors with diagnosis or onset within o 42 days before IDO o 12 months before IDO • medical procedures that are associated with the use of PDE5 inhibitors occurring within 42 days before IDO
PDE5 inhibitor medications	• detailed information on PDE5 inhibitor use within o 42 days before IDO, quantified with start and stop dates o 12 months before IDO, quantified by number of days per month
NAION form	• completed by each adjudicator after a subject was diagnosed by a physician as having NAION and all CRF data were clean
Patient status form	• status: completed or withdrawn

Abbreviations: CRF = case report form; IDO = index date of onset; PDE5 = phosphodiesterase type 5; NAION = nonarteric anterior ischaemic optic neuropathy.

[a] Medications associated with PDE5 inhibitor use were classified as such according to the investigator's discretion and were collected on CRFs separate from the medical history and risk factor questionnaire.

A structured interview was used to collect information about PDE5 inhibitor use. At the beginning of the interview, after identifying the IDO, subjects were asked to provide their average use of PDE5 inhibitors over the past year. Then the interview delved into a detailed calendar-based discussion of PDE5 inhibitor use day by day for the 42 days before IDO. To the extent possible, specific dates recalled by the subject were recorded for the entire 12-month period before the IDO. To aid in recall, a 12-month calendar beginning with the IDO and tailored during the interview with anchors such as subject-specific dates and events (eg, holidays, weekends, vacation days). Other medications, lifestyle factors, and medical history were also captured at this time. All study personnel interviewing subjects received training on appropriate administration of the questionnaire and conduct of the structured interview.

9.6. Bias

Bias is defined as any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth (Last 2001). Bias can result in an overestimation or an underestimation of the true value. When bias results in an overestimation of the true value, it can be falsely interpreted as a causal relationship (ie, biases the estimate away from the null hypothesis). Conversely, when bias results in an underestimation of the true value, it can be falsely interpreted that there is no causal relationship, (ie, biases the estimate toward the null hypothesis). There are 3 major types of bias seen in epidemiologic studies: selection bias, information (or misclassification) bias, and confounding.

9.6.1. Selection Bias

Selection bias is a distortion of evidence resulting from the way data, particularly data that are or are not selected to be in the study, are collected. In the case-crossover design, cases serve as their own controls, which is one of the strengths of the design. Therefore, this study did not incur selection bias as a result of inappropriate selection of controls from the population that produces cases; however, biased case selection was possible.

Selection bias can also occur if cases are inappropriately selected, as would be true for misdiagnosed cases of NAION. In this study, the adjudication of cases before inclusion in the primary and secondary analysis sets minimised the potential for selection bias by ensuring, to the extent possible, that all enrolled subjects with NAION (cases) were consistently diagnosed as NAION for study purposes (Section 9.3.3).

Inappropriate selection of control periods can introduce bias in case-crossover studies (Sorock et al. 2001). In the control periods, subjects should have opportunity for exposure equal to that in the hazard period, and circumstances around these hazard and control periods should be otherwise similar. Appropriate control periods should have the same accuracy in exposure measurement as the hazard period, and exposure information should be captured using the same method for both hazard and control periods. In interview-based data collection, interviewers may collect the exposure information in a way that is consistent with hypotheses; this would result in differences in exposure accuracy in the control period (Maclure 1991). In this study, several methods were used to increase the accuracy and consistency in the collection of historical exposure data. Interviewers were trained on proper interviewing techniques, and a structured interview approach was used. Information on concomitant medications, medical history, and risk factors was collected during the study visit separately for the 42 days and 12 months before IDO. PDE5 inhibitor use was captured on a day-by-day basis for the 42-day history and as a monthly count for the 12-month history.

9.6.2. Recall Bias

In a case-control study, information bias occurs when study data are collected differently from subjects with the disease (cases) and from subjects without the disease (controls). Recall bias is one type of information bias, which represents a major threat to the internal validity and credibility of studies using self-reported data (Basso et al. 1997). Recall bias occurs when cases

are more likely to recall events that led up to the onset of disease than are controls who do not have the disease. Interview bias occurs when the interviewer's knowledge or assumptions about the subject's exposures or outcomes inadvertently affects the manner in which the interview is conducted. If the interviewer approach influences the subject's responses, bias has been introduced.

In this study, subjects were required to recall the use of PDE5 inhibitors day by day in the 42 days before IDO and monthly for the 12 months before IDO. In addition, all study data, including PDE5 inhibitor use and NAION risk factors, were collected via a structured interview (Section 9.5).

The structured questionnaire was designed to minimise the potential for recall bias. Before administering the structured questionnaire, all study personnel interviewing subjects received training on appropriate administration of the questionnaire and conduct of the structured interview.

In addition, several different approaches to defining exposure were used in the primary, secondary, and multiple sensitivity analyses to assess the potential effect of information bias.

9.6.2.1. Confounding

NAION is believed to be a multifactorial disease (Hayreh 2005) that shares a number of risk factors with erectile dysfunction. Potential risk factors for NAION reported from literature are summarised in Protocol H6D-MC-LVHQ(b) (Appendices 1 and 2). Most NAION risk factors are chronic diseases or conditions, such as diabetes mellitus, cardiovascular disease, hypertension, atherosclerosis, cerebrovascular disease, hyperlipidaemia, and hyperhomocystinemia. Therefore, as chronic conditions, they are generally constant within an individual, particularly over a short period of time such as the 42-day period evaluated in this study. Although aging is a time-dependent risk factor, in this study, because of the short study period (12 months before IDO at maximum for the person-time method), age was treated as a time-invariant risk factor. The case-crossover study accounts for these time-invariant risk factors. Given the nature of the case-crossover study design, the primary analysis was planned to control only time-variant risk factors and not for time-invariant risk factors. However, it is possible that subjects' conditions and use of medications, even for the chronic diseases, may have varied over the study duration, which may have resulted in changes in the list of time-variant confounders.

NAION risk factors that may have occurred sporadically within the 42-day period, such as acute myocardial infarction, stroke, haemorrhage, and surgery (including anterior segment, cardiac, and other general surgery) as well as a number of medications that have been associated with NAION (Section 6.1.2) and may have been taken by subjects sporadically were evaluated. These were considered as time-variant risk factors. These time-variant risk factors could differ between case and control periods, so they were evaluated in descriptive analyses and were planned for use in the multivariate statistical models in the secondary matched-interval analysis. Subjects were asked during the interview to describe the conditions of diseases and to report any significant changes or medical events and the use of on-demand medications over the study

period. The descriptive analyses of these risk factors indicated that none of them were present in any of the primary and secondary analysis sets, therefore controlling for these factors in a multivariate analysis was not necessary or feasible.

9.7. Study Size

There is no direct sample size calculation for person-time analysis in a case-crossover design. A reasonable method to estimate sample size is to apply the matched case-control formula (Dupont 1988), which treats the control period as a large matching ratio. Although the term 'control' in the matched case-control scenario refers to a subject, the term 'control' refers to a single control period within subject in the case-crossover design. The mathematics is comparable. Statistical methods and models for case-crossover and matched case-control designs make use of the intermittent users only. The inclusion of a particular subject's data in specific analyses may vary depending on the hazard and control period definitions that are applied and the analysis method used.

9.7.1. Original Sample Size Calculation

When this study was designed, the results from sample size calculations suggested that 125 subjects with adjudication-confirmed NAION who were not chronic users of PDE5 inhibitors would be needed. The assumptions used for calculating the original sample size for this study were:

- α = 5% (2-sided test based on matched case-control method)
- power = 80%
- exposure prevalence in a control period of 10%
- 7 control periods for each case
- correlation of control periods to the case period of 0.6
- OR under the alternative hypothesis of 3
- case is a subject with adjudication-confirmed NAION and who is not a chronic user of PDE5 inhibitors

On the basis of these assumptions and by using PASS2008 software (Hintze 2008), it was estimated that an enrolled sample size of 125 subjects who were not chronic users of PDE5 inhibitors and had adjudication-confirmed NAION were required to provide 80% power to detect a true OR of 3.0. The initial prevalence estimation of the PDE5 inhibitor use in the control period was determined from claims data, and the initial correlation coefficient was based on data from a simulation study.

As the number of subjects with adjudication-confirmed NAION enrolled in Study LVHQ neared the target sample size of 125, the study's statistical team at INC Research estimated that the observed PDE5 inhibitor exposure rate in the 30-day control period was substantially lower than the protocol-assumed 10% exposure rate, which could reduce the overall power of primary objective to less than the desired 80%. This estimate was based on observation of study data from all enrolled subjects (n = 107) from the beginning of the study to 06 November 2013.

Subsequently, the team examined the observed exposure prevalence in the 30-day control period, estimates of the correlation coefficient based on patterns of reported PDE5 inhibitor use, and the effect of these factors on the statistical power based on the initial sample size estimate. The group concluded that the initial sample size was insufficient and enrolment of additional subjects was needed (statistical analysis plan [SAP], version 2.0, Appendix 21.4).

9.7.2. Revised Sample Size Calculation

The first revision of the sample size calculation in January 2014 involved a rigorous process that included external consultants and the use of 3 different evaluation methods. Two of the methods were based on the number of exposed control windows relative to the number of available control windows. The third method was based on the number of exposed days relative to available days. Additional detail is found in the SAP, version 2.0 (Appendix 21.4).

In summary, the estimated prevalence, correlation coefficient, and sample size were determined on the basis of the study data available as of January 2014, which included 10 intermittent PDE5 inhibitor users. Note that 1 subject reported taking at least 1 dose of PDE5 inhibitor during the hazard and all control periods, resulting in an effect on the calculations. Hence, the estimates were calculated with and without data from that subject.

In the revised estimates, the prevalence of PDE5 inhibitor used in the 30-day control period ranged from 2.2% to 3.6% depending on which methods were used. When the 1 subject with exposure in all periods was excluded, prevalence rates decreased (corresponding range 1.3% to 2.7%).

Summary statistics for the estimated correlation coefficients using all 3 methods, based on all 10 subjects, were as follows: mean 0.41, standard deviation (SD) 0.16, and range 0.22 to 0.56. When the 1 subject with exposure in all periods was excluded, the mean correlation coefficient was 0.21; the SD was 0.22, and the range was –0.03 to 0.45.

The sample size was reestimated using methods per the approved protocol, and the analyses were performed in PASS2008 software (Hintze 2008). On the basis of a PDE5 inhibitor prevalence rate of 1.5% in the control period and a correlation coefficient of 0.4, it was estimated that an enrolled sample size of 443 subjects with adjudication-confirmed NAION who were intermittent users of PDE5 inhibitors was required to provide 80% power to detect a true OR of 3.0. Given the small number of enrolled patients, it was decided that the estimated correlation and prevalence would be recalculated on the basis of data obtained after 200 subjects with adjudication-confirmed NAION were enrolled. This was communicated to the FDA, and the protocol was amended to include an increased sample size.

In February 2015, the prevalence and correlation coefficient were reevaluated by using data from the 200 enrolled subjects with adjudication-confirmed NAION who were intermittent PDE5 inhibitor users enrolled until the previous month. The estimates for prevalence and the correlation coefficient were 1.7% and 0.31, respectively.

Additionally, the original software used to calculate sample size was found to be in error. By using a revised version of PS software (and verifying all calculations independently via code

developed in R), an estimated sample size of 248 adjudication-confirmed NAION subjects was obtained on the basis of these revised parameter estimates, 2-sided type I error of 5%, 80% power, and an underlying OR of 3. The enrolment target was revised to 260 subjects (adjudication-confirmed NAION, intermittent users) to account for continuous-use subjects whose data were excluded from the parameter reestimation. This was communicated to the FDA.

9.7.3. Sample Size Comment Regarding Secondary Analyses

As discussed above, the method used to determine the appropriate sample size for this study is an application of the matched case-control formula for determining sample size (Dupont 1988), which treats the control period as a large matching ratio. There are a number of ways this could be applied depending on the study design, analysis methods to be used, exposure periods, and assumptions regarding exposure time. Ultimately, the method chosen to arrive at the sample size was that which most closely matched the person-time primary analysis method (Method 3; SAP, version 2.0, Appendix 21.4). The study sample size was not calculated to provide statistical power for the secondary analyses; in particular, the secondary analysis with 4 matched control periods would have required a different calculation and was likely to be underpowered.

For this secondary analysis, there were matched sets of hazard period intervals and 4 matched control intervals per case. If the same approach as above was used, new estimates of correlation and prevalence would be derived to match this secondary analysis approach. Given the structure of the analysis, it was expected that the correlation coefficient for exposure between matched hazard period and control period intervals in this analysis would be higher than the same correlation seen in the subjects included in the primary analysis (because correlations in the primary analysis would be between the same days of the week and would be 4-day blocks—either exposed or unexposed). A higher correlation coefficient would have meant that the statistical power to detect an association between PDE5 inhibitor exposure and NAION would have been lower in this analysis. Therefore, the possibility of failing to reject the null hypothesis when it is false was increased.

9.8. Data Transformation

Raw data collected on paper CRFs and via electronic CRFs at some study sites were held in TrialBase, an electronic data collection system. External data sources included adjudication data that was collected and transmitted directly to the INC Research biostatistics team from the INC TrialEAS adjudication system. Excluding sample size calculations, all analyses were conducted with SAS, version 9.3.

Creation and validation of the clinical database and management of data were conducted in accordance with 21 CFR Part 11 and Guidance for Industry on Computerized Systems Used in Clinical Trials. All coding of medical history and concomitant medications was performed electronically at INC Research.

Data were coded to the most appropriate terminology available in the dictionary. Clarification needed to code a verbatim term present in the clinical database generated a manual query, which

was sent to the site for resolution. Medical history events were coded by system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA), version 18.1. Medications were coded according to the Anatomical Therapeutic Chemical (ATC) Level 4 term and PT according to the World Health Organization Drug Dictionary (WHO-DD), version September 2015. MedDRA and WHO-DD were updated annually for use in this study. Updated dictionaries that were received were uploaded and compared with previous dictionaries and previously coded data. If implementing the new dictionary resulted in changes to previously coded data, the affected terms were recoded.

9.9. Statistical Methods

9.9.1. Definitions

9.9.1.1. Hazard Period

In this study, the hazard period in the person-time analysis was the period immediately preceding the NAION onset. Depending on the type of PDE5 inhibitor reported as used, the subject's hazard period may have been 4 days (tadalafil) or 1 day (sildenafil or vardenafil).

The hazard period in the matched-interval method consisted of a fixed period of days immediately before the NAION event.

9.9.1.2. Control Period

Control period may be explained loosely as study time before the hazard period.

Control period in the person-time analysis was calculated as the total time in an analysis period minus the hazard period (period immediately preceding NAION onset). The 2 analysis periods for the person-time analyses are 30 days before IDO and 12 months before IDO.

Control periods in the matched case-control method each consisted of a fixed period of days occurring before the hazard period and matched to the hazard period by the day of the week.

9.9.1.3. Effect Period

The effect period is the time between the minimum and maximum induction times in the population. In this study, by assuming that the PDE5 inhibitor's effect was instantaneous and the use of PDE5 inhibitors had a minimum induction time of zero, the effect (hazard) period would equal the maximum induction time of PDE5 inhibitors, which approximates 5 times the half-life of PDE5 inhibitors.

Because the half-life for tadalafil is approximately 17.5 hours, a 4-day window (ie, 5 times the half-life of 17.5 hours equals 87.5 hours or 3.6 days) constituted the effect period for subjects who used tadalafil, which included the dosing day and the next 3 days. A 1-day window was defined as the effect period for subjects who used sildenafil and vardenafil, corresponding to a half-life of 3 to 4 hours multiplied by 5 (ie, 5 times the half-life of 4 hours equals 20 hours or 1 day), which included only the dosing day.

9.9.1.4. Exposed and Unexposed Days

Exposed days are defined on the basis of the effect period of the PDE5 inhibitor; unexposed days are the remainder of the study period under analysis.

9.9.2. Analysis Sets

In addition to an analysis set used to address the primary objective (30-day analysis set), 2 other analysis sets (42-day analysis set and 12-month analysis set) were used for secondary and sensitivity analyses. In addition, 30-day, 42-day, and 12-month modified analysis sets were created to evaluate the effect of missing data related to PDE5 inhibitor use in sensitivity analyses.

The study analysis populations (sets) were as follows:

- enrolled set: subjects who signed informed consent and met inclusion and exclusion criteria. Unless specified otherwise, the enrolled set was used for subject listings and for summaries of subject status.
- study set: enrolled subjects who met inclusion/exclusion criteria and had physician-diagnosed NAION with a known date of onset. The study set was used to describe study population characteristics in analysis tables.
- adjudication-confirmed NAION set: subjects in the study set confirmed by the adjudication committee to have NAION. The adjudication-confirmed NAION set included subjects who were chronic users, intermittent (nonchronic) users, and nonusers of PDE5 inhibitors. These were defined by the protocol as follows:
    - A chronic user was a subject who reported continuous daily dosing with 1 or more PDE5 inhibitors during the specified analysis period (ie, 30 days, 42 days, or 12 months) before the IDO of NAION.
    - An intermittent (nonchronic) user was a subject who reported taking a dose of 1 or more PDE5 inhibitors during the specified analysis period (ie, 30 days, 42 days, or 12 months) before the IDO of NAION and who was not a chronic user.
    - A nonuser was a subject who had not reported use of any PDE5 inhibitor within the specified analysis period (ie, 30 days, 42 days, or 12 months) before the IDO of NAION.
- 30-day analysis set: subjects with adjudication-confirmed NAION who were intermittent users of PDE5 inhibitor medications during the 30 days before IDO, provided dosing dates of PDE5 inhibitor use and complete dates of IDO, and knew which PDE5 inhibitor medication(s) had been used. The 30-day analysis set was used to perform the primary analysis (a 30-day person-time analysis) and some related sensitivity analyses.
- 42-day analysis set: subjects with adjudication-confirmed NAION who were intermittent users of PDE5 inhibitor medications during the 42 days before IDO, provided dosing dates of PDE5 inhibitor use and complete dates of IDO, and knew which PDE5 inhibitor medication(s) had been used. This set was used to conduct the secondary matched-interval analysis and related sensitivity analyses.

- 12-month analysis set: subjects with adjudication-confirmed NAION who were intermittent users of PDE5 inhibitor medications during the 12 months before IDO, and provided complete dates of IDO and the number of doses taken per month for all 12 months before IDO. This set was used to conduct the secondary person-time analysis and related sensitivity analyses.
- 30-day modified analysis set: subjects in the 30-day analysis set plus subjects who were intermittent users of PDE5 inhibitor medications during the 30 days before IDO, provided dosing dates of PDE5 inhibitor use and complete dates of IDO, and did not recall which PDE5 inhibitor medication(s) had been used. This set was used for sensitivity analyses.
- 42-day modified analysis set: subjects in the 42-day analysis set plus subjects who were intermittent users of PDE5 inhibitor medications during the 42 days before IDO, provided dosing dates of PDE5 inhibitor use and complete dates of IDO, and did not recall which PDE5 inhibitor medication(s) had been used. This set was used for sensitivity analyses.
- 12-month modified analysis set: subjects in the 12-month analysis set plus subjects who were intermittent users of PDE5 inhibitor medications during the 12 months before IDO, provided complete dates of IDO, and provided information regarding PDE5 inhibitor use per month for at least 50% of the 12-month period. This set was used for sensitivity analyses.

Only those subjects who had NAION diagnoses confirmed by the independent adjudication committee were eligible for analysis. Only subjects with intermittent PDE5 inhibitor use were included in the case-crossover analyses.

No subjects received medication or any other form of therapy under this protocol; therefore, no analyses of general safety were conducted and a safety set was not defined.

Specific rules for imputing the missing data for these subjects are described in the SAP, version 2.0 (Sections 8, 9, and 10 [in the context of each planned analysis])

9.9.3. NAION Risk Factors

Several medications, medical conditions, and medical events have been associated with NAION and are listed in Protocol H6D-MC-LVHQ(b) (Appendix 1). The SAP planned that time-variant NAION risk factors reported in the 42 days before IDO would be controlled for in a multivariate analysis. To identify these risk factors, the study's clinical database was searched for the following terms:

- medical history (by PT; coded according to MedDRA, version 18.1): acute myocardial infarction, stroke, haemorrhage, and surgery (including anterior segment, cardiac, and other general surgery). A complete list of all searched PTs is available in the SAP, version 2.0 (Section 21.1).
- medications of interest (by medication category; coded according to WHO-DD, version September 2015): phentermine, interferon-α, sumatriptan, beta-blocker eye drops, and

nasal decongestants. A complete list of all searched preferred names is available in the SAP, version 2.0 (Section 21.2).

9.9.4. Main Summary Measures

Measures used to summarise study data included descriptive statistics, case-crossover person-time analysis, and conditional logistic regression analysis. Continuous variables were summarised using the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables were summarised using number of observations (n), frequency, and percentages of subjects.

Demographic and baseline information was summarised for the adjudication-confirmed 30-day analysis set, 42-day analysis set, 12-month analysis set, and each 42-day PDE5 inhibitor use category (42-day intermittent [nonchronic] users, 42-day chronic users, and 42-day nonusers). Continuous variables were summarised with the following descriptive statistics: n, mean, median, SD, minimum, and maximum. For categorical data, frequencies and percentages were provided.

9.9.4.1. Exposure to PDE5 Inhibitors

Detailed information on exposure to PDE5 inhibitors was collected for 2 distinct time periods: 42 days before the IDO (in units of dates) and 12 months before the IDO (in units of days per month). Exposure data also included the specific PDE5 inhibitor taken (tadalafil, sildenafil, or vardenafil) and dosing information.

The duration of exposure to an individual PDE5 inhibitor was defined on the basis of its effect period (Section 9.9.1.3). Dosing day, defined as the actual day that the PDE5 inhibitor was ingested (without taking the effect period into consideration), was also used to quantify exposure for sensitivity analyses.

The effect periods for this analysis, defined as exposure to PDE5 inhibitors in person-time, were estimated on the basis of subject recollection of PDE5 inhibitor use in the 30-day period immediately before the NAION event. Although daily medication use was collected for 42 days before IDO, the primary analysis only used exposure in the 30 days before IDO.

9.9.4.2. Measure of Risk Estimates

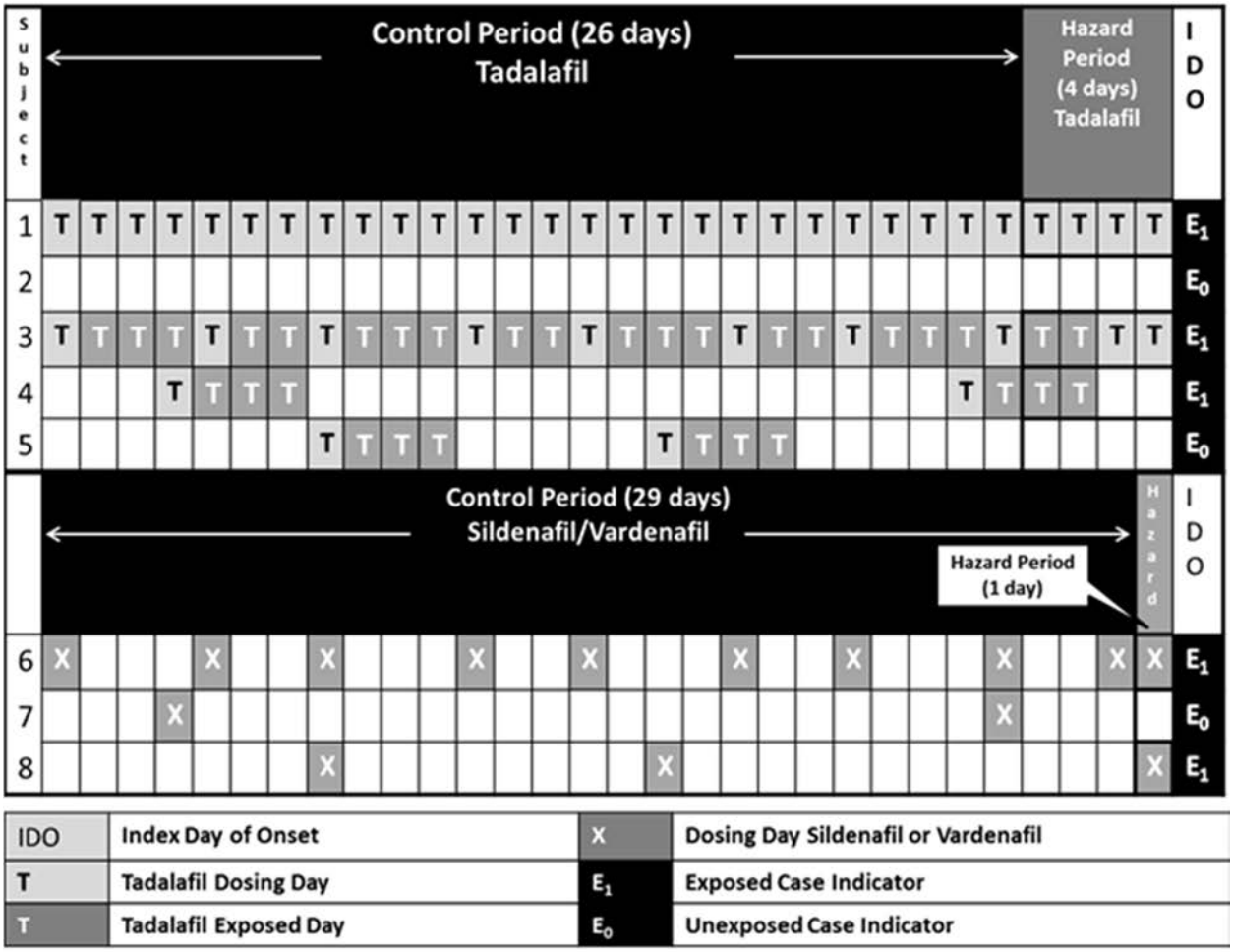
To examine risk, the exposure to PDE5 inhibitors in the hazard period (ie, the period of time immediately before the onset of NAION) was compared with the exposure in the control period. The exposure in the control period was estimated using 2 different approaches: (1) person-time method and (2) matched-interval method (PDE5 inhibitor exposure in the hazard period and time-matched control periods before the onset of NAION). In this study, the person-time method was designated the primary approach to quantifying exposure to PDE5 inhibitors.

9.9.4.2.1. Person-Time Method

Exposure to PDE5 inhibitors in person-time was estimated on the basis of the frequency of PDE5 inhibitor use that subjects recalled in the 30-day period and the 1-year period before the IDO.

For the 30-day period, the study compared PDE5 inhibitor exposure in the 30 days before IDO by exposed case definition (ie, exposure immediately before the IDO within the hazard period). The person-time exposed to PDE5 inhibitors during the 30-day period before the IDO was calculated by multiplying the reported frequency of PDE5 inhibitor use by the duration of PDE5 inhibitor effect period of 5 half-lives (ie, 4-day exposure duration for tadalafil and 1-day exposure duration for sildenafil and vardenafil). Unexposed person-time was then calculated by subtracting the exposed person-time from the total number of days in the 30-day period.

Figure LVHQ.9.2 is provided for illustration. Because of the different hazard periods for tadalafil and sildenafil/vardenafil, the scenarios are different for subjects depending on which PDE5 inhibitor they reported taking. Hypothetical Subjects 1 and 2 shown in Figure LVHQ.9.2 will not contribute to the analysis on the basis of chronic use and no use, respectively. Subject 3 is a nonchronic user, and therefore will be included in the 30-day analysis set but on the basis of chronic exposure to tadalafil (4-day exposure periods for each dose) will not contribute to the primary analysis because there is no discordance in exposure between hazard and control periods. He will contribute to the associated sensitivity analysis for dosing days where he will be counted as exposed in the hazard period. Subject 4 will contribute 8 exposed days to the person-time (2 tadalafil doses) and will be classified as an exposed case because he is exposed within the 4-day hazard period for tadalafil before NAION onset (IDO). Subject 5 will contribute 8 exposed days of person-time (2 tadalafil doses) and will be classified as an unexposed case because he was unexposed within the 4-day hazard period for tadalafil before NAION onset (IDO). Subjects 6 to 8 reported either sildenafil or vardenafil use; therefore, their dosing days are also their exposure days, and a 1-day hazard period is applied. Subject 6 will contribute 10 days of exposed person-time, and Subjects 7 and 8 will contribute 2 and 3 days of exposed person-time, respectively. Subjects 6 and 8 will be classified as exposed cases on the basis of each reporting taking a dose of either sildenafil or vardenafil on the day before NAION onset (IDO).



Abbreviations: IDO = index date of onset; PDE5 = phosphodiesterase type 5.

Figure LVHQ.9.2. Exposure to PDE5 inhibitors in 8 hypothetical subjects receiving tadalafil (top) and sildenafil/vardenafil (bottom).

The Mantel-Haenszel RR was calculated by the following equation (simplified from the protocol because the total days of follow-up are the same for all subjects) for *i* subjects with intermittent PDE5 inhibitor exposure:

$$RR_{MH} = \frac{\sum_i (Exposed\ case\ indicator\ X\ Total\ person\ time\ unexposed\ for\ exposed\ cases)}{\sum_i (Unexposed\ case\ indicator\ X\ Total\ person\ time\ exposed\ for\ unexposed\ cases)}$$

For analyses evaluating exposure over a 12-month period, the amount of PDE5 inhibitor–exposed person-time was estimated using the same method described for the 30-day period. Unexposed person-time was then calculated by subtracting the exposed person-time in days from the total number of days in the 12-month period.

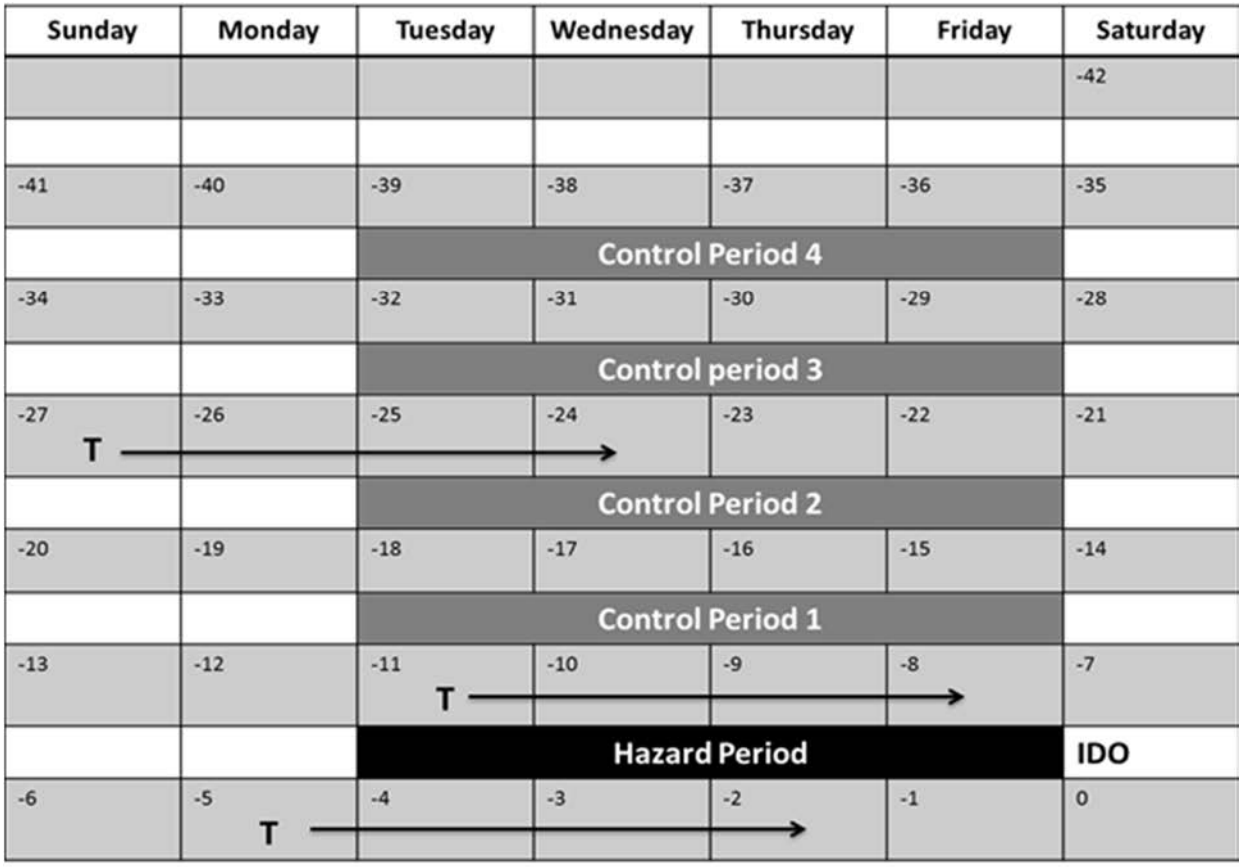
9.9.4.2.2. Matched-Interval Method

In the matched-interval method approach, the IDO was used to identify 1 hazard period and 4 control periods, defined by intervals representing effect time in the 4 weeks preceding IDO; the intervals are matched on the day of the week of the IDO.

Figure LVHQ.9.3 is provided for illustration. For example, if a subject develops NAION on a Saturday, the day of symptom onset (Saturday) is identified as the IDO (Day 0), and the 4-day period before the IDO is defined as the hazard period, corresponding to Days –1 through –4 (Tuesday to Friday). In the week before the IDO, the 4-day period spanning Tuesday (Day –11) through Friday (Day –8) is defined as the first control period. This pattern repeats to establish the second, third, and fourth control periods, which consistently cover Tuesday through Friday of each preceding week.

If the subject took a PDE5 inhibitor during the control period, it is considered an exposed control period. If the subject took a PDE5 inhibitor before the control period but exposure (5 half-lives) continued into the control period, it is also considered an exposed control period.

When exposure is classified on the basis of the effect period (5 half-lives), a subject who reports taking a dose of tadalafil (T) on Days –5, –11, and –27 would be classified as exposed in the hazard period, control period 1, and control period 3, respectively.



Abbreviations: IDO = index date of onset; PDE5 = phosphodiesterase type 5; T = date on which the hypothetical subject ingested a dose of tadalafil.

Figure LVHQ.9.3. Exposure of PDE5 inhibitors in the matched-interval control periods before index date of onset, with an example for a hypothetical subject who reported taking tadalafil.

It is believed that little is to be gained from going beyond 4 control periods matched to each case in a case-control study. This rule of thumb also applies to the case-crossover study design. A study by Mittleman et al. (1995) suggested that the CIs of relative risk were reduced by up to 35% when control periods were increased from 1 to 4 and were reduced by up to 40% when control periods were increased from 4 to 100. Therefore, in this case-crossover study, for the matched-interval approach, 4 control periods were selected and matched to a hazard period.

9.9.5. Main Statistical Methods

9.9.5.1. Primary Endpoint Analysis

In the primary analysis, the 30-day person-time method based on PDE5 inhibitor effect period was used. The analysis was conducted with the 30-day analysis set and by using Maclure's (1991) case-crossover analysis method described previously (Section 9.1.2). The key statistic for the primary analysis is the Mantel-Haenszel RR for exposure to PDE5 inhibitors within 30 days

before the onset of NAION, with exposure defined on the basis of the PDE5 inhibitor effect period (Section 9.9.1.3; SAP, version 2.0 [Section 10.1.1.1]).

The formal statistical hypotheses are:

H_0: The RR is not different from 1.0; NAION is not associated with exposure to PDE5 inhibitors.

H_A: The RR is different from 1.0; NAION is associated with exposure to PDE5 inhibitors.

The null hypothesis H_0 would be rejected if the 2-sided 95% CI did not include a value of 1.0. An RR with the lower 95% confidence limit >1.0 may suggest a higher risk of NAION with the use of PDE5 inhibitors. An RR with the upper confidence limit <1 may suggest a lower risk of NAION with the use of PDE5 inhibitors. If the 95% CI for the RR included 1.0, then the study would be interpreted as failing to establish an association between the use of PDE5 inhibitors and the occurrence of NAION.

9.9.5.2. Secondary Endpoint Analyses

9.9.5.2.1. 12-Month Person-Time Method

The number of days of exposure to PDE5 inhibitors within 12 months (365 days) immediately before the onset of NAION was evaluated in a secondary analysis. Exposure was defined on the basis of the PDE5 inhibitor effect period, and subjects in the 12-month analysis set were included. The 12-month person-time analysis used the same statistical methods as the 30-day person-time analysis.

PDE5 inhibitor exposure was estimated for each month before IDO. The exposed time during the month of IDO was calculated from the reported dosing dates that were collected for the 30 days before IDO. If less than 4 days of data were available from the month of IDO, the preceding month was used from the 42-day data. In other months, the exposed time was calculated as the number of recorded dose administrations multiplied by the appropriate duration of exposure for the drug that was taken.

Dosing dates were not collected on the 12-month CRF, for which subjects were asked to recall the drug, dose, units, route, indication, and number of days per month that a PDE5 inhibitor was taken. For calculation purposes in the database, it was assumed that all periods of exposure in a month occurred sequentially, starting from the day of the month that is closest to the IDO and counting backwards. Also, it was assumed that there were no multiple exposures on a single day, unless specifically documented otherwise. No imputed dates were used to assign exposure to a hazard period. Unexposed person-time was calculated by subtracting the exposed person-time in days from the 365 days.

9.9.5.2.2. Matched-Interval Analysis

In a secondary analysis, a matched-interval approach evaluated the association between PDE5 inhibitor exposure in the 42 days before IDO and acute NAION. Exposure was based on the

PDE5 inhibitor effect periods and was evaluated using a 4-day hazard period and a series of 4 preceding 4-day control intervals.

The analysis was conducted in the 42-day analysis set and used 4-day hazard and control periods selected from the 42 days immediately before the IDO.

Conditional logistic regression was used to investigate the relationship between the occurrence of NAION and PDE5 exposure. The occurrence of NAION was predicted by a discrete logistic model that included period (1 = hazard, 2 = control 1, 3 = control 2, etc) as the dependent variable, an indicator for the occurrence of the NAION event in each period as a censoring variable, and exposure to PDE5 inhibitors as a single independent risk factor. Because subjects served as their own matched controls, the model was conditioned on subject.

For the matched-interval method, the null hypothesis was rejected (and statistical significance declared) if the lower 95% confidence limit of the adjusted hazard ratio exceeded 1 or the upper confidence limit was less than 1. An adjusted hazard ratio with the lower 95% confidence limit >1.0 may be suggestive of an increased risk of NAION with the use of PDE5 inhibitors. An adjusted hazard ratio with the upper confidence limit <1.0 may be suggestive of a decreased risk of NAION with the use of PDE5 inhibitors. If the 95% CI for the adjusted hazard ratio included 1.0, then the study would be interpreted as failing to establish an association between the use of PDE5 inhibitors and the occurrence of NAION.

To examine the effect of time-variant risk factors, the study team planned to include covariates representing potential confounders in the matched-interval models. The specific dichotomous time-variant confounding risk factors (covariates) of interest were as follows:

- myocardial infarction, transient ischaemic attach or ischaemic stroke, haemorrhagic stroke (yes/no)
- haemorrhage (yes/no)
- any use of phentermine, interferon-α, sumatriptan, beta-blocker eye drops, or nasal decongestants (yes/no)

Indicator variables for the above risk factors were based on the coded medical history (according to MedDRA, version 18.1) and concomitant medications (according to WHO-DD, version September 2015) for the 42 days before IDO. If there was an occurrence of a risk factor in a specific hazard or control period, then the indicator flag was assigned 1 for that period; if not, the indicator flag was assigned 0 for that period. However, the multivariate analysis was not conducted because none of the subjects in the analysis populations had any of the reported risk factors.

9.9.6. Missing Values

Subjects who enrolled and provided data on PDE5 inhibitor use were assumed to have completed the study if their cases were adjudicated, even if their end-of-study status was missing. Subjects who were not adjudicated and failed to meet subject inclusion/exclusion criteria were classified as early terminations due to failure to meet inclusion/exclusion criteria if their end-of-study

status was missing. Any missing end-of-study date was imputed as the latter of the subject's visit date or their date of informed consent.

Subjects who had partial or missing IDOs were excluded from all analyses, and the IDOs were not imputed.

The exposure of subjects who reported dosing dates but were unsure of which PDE5 inhibitor had been taken during the 30 days before IDO were imputed in 2 ways as follows: (1) assuming tadalafil was taken and (2) assuming sildenafil was taken. Both of these approaches were included in the sensitivity analyses.

Subjects who did not report the dosing dates or who reported incomplete dosing dates during the 30 days before the IDO were excluded from the 30-day analysis.

For both the 30-day and the 12-month recall periods, in situations where the subject was not aware of or failed to recall which PDE5 inhibitor was taken, a 4-day window was assigned as the exposure duration to estimate the person-time exposure.

Missing, uncertain, unknown exposure data during the 12-month analysis period was imputed for subjects who recorded at least half (≥50%) of the expected PDE5 inhibitor medication data (ie, PDE5 inhibitor use information was provided for at least 6 of 12 months). Each missing month was imputed as that subject's average monthly use, calculated from the months that were recorded.

All 12-month data were assumed to have no overlapping doses. It was also assumed that any reported or imputed exposure occurred during the portion of the month that was closest to the IDO.

9.9.7. Sensitivity Analyses

9.9.7.1. Sensitivity Analysis for the Person-Time Analysis (Primary Objective)

Three separate sensitivity analyses were conducted to evaluate the robustness of the primary analysis:

- ***Sensitivity Analysis 1.*** 30-day person-time method based on PDE5 inhibitor–reported dosing days. For this sensitivity analysis, the 30-day person-time method based on the reported dosing days of the PDE5 inhibitor was used. This differed from the primary analysis in that this analysis used reported dates of PDE5 inhibitor dosing instead of the effect period. The key statistic for this sensitivity analysis was the Mantel-Haenszel RR based on the reported dates of actual dosing with a PDE5 inhibitor. This analysis was conducted in the 30-day analysis set. The statistical methods used for the primary analysis were also used in this sensitivity analysis.
- ***Sensitivity Analysis 2.*** 30-day person-time method with exposure based on PDE5 inhibitor effect period and unknown PDE5 inhibitor medications imputed as tadalafil. This sensitivity analysis was identical to the primary analysis with the following 2 exceptions: (1) Unknown PDE5 inhibitor medications were imputed as tadalafil (ie, subjects who reported dosing dates but were unsure of which PDE5 inhibitor had been

taken during the 30 days before IDO were assumed to have ingested tadalafil). Subjects who did not report the dosing dates or reported incomplete dosing dates were not used in these analyses. (2) The analysis was conducted in the 30-day modified analysis set.

- ***Sensitivity Analysis 3.*** 30-day person-time method with exposure based on PDE5 inhibitor effect period and unknown PDE5 inhibitor medications imputed as sildenafil. This sensitivity analysis is identical to sensitivity analysis 2 above with one exception: unknown PDE5 inhibitor medications were imputed as sildenafil.

9.9.7.2. Sensitivity Analysis for Number of Days of PDE5 Inhibitor Exposure within 12 Months before the Index Date of Onset (Secondary Analysis)

Sensitivity analyses evaluating the 12-month person-time analysis based on PDE5 inhibitor effect periods (Section 9.9.5.2.1) involved 2 approaches:

- ***Sensitivity Analysis 1.*** 12-month person-time method with exposure based on PDE5 inhibitor–reported dosing days. For this sensitivity analysis, the 12-month person-time method based on the reported dosing days of the PDE5 inhibitor was used. This differed from the 12-month person-time secondary analysis in that this analysis used reported dates of PDE5 inhibitor dosing instead the effect period. The key statistic for this sensitivity analysis was the Mantel-Haenszel RR based on the reported dates of actual dosing with a PDE5 inhibitor. This analysis was conducted in the 12-month analysis set. The statistical methods used for the primary analysis were also used in this sensitivity analysis.
- ***Sensitivity Analysis 2.*** 12-month person-time method with exposure based on PDE5 inhibitor–reported effect period and unknown monthly frequency of use imputed as the subject's monthly average. For subjects who recorded exposure data for at least 50% of the expected months, the subject's monthly average was used to impute any missing months. Subjects who recorded exposure data for less than 50% of the expected months were excluded from this analysis. The 12-month modified analysis set was used for this analysis.

9.9.7.3. Sensitivity Analysis for the Matched-Interval Method (Secondary Analysis)

9.9.7.3.1. Varying Exposure Intervals

Different exposure intervals were evaluated as a sensitivity analysis for the secondary objective analysis using matched intervals: 1-day, 2-day, 3-day, and 7-day windows were used to define the exposure window for the hazard period and control period.

- ***Sensitivity Analysis 1.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and 1-day controls. This analysis was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 1 day.
- ***Sensitivity Analysis 2.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and 2-day controls (analysis set). This analysis was conducted in

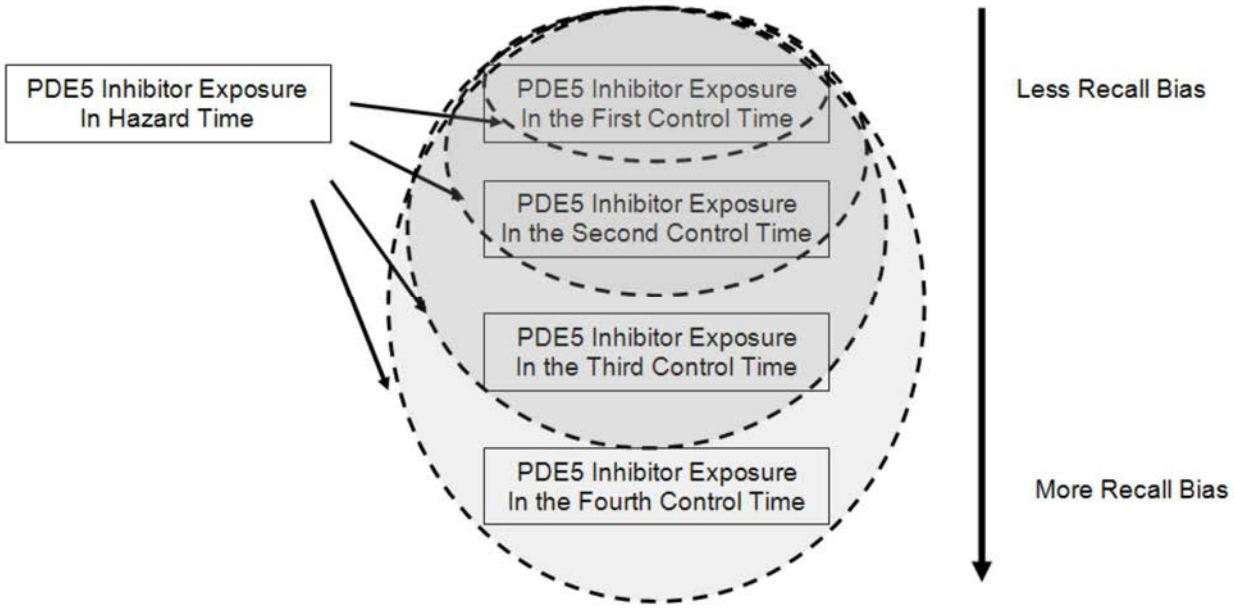
the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 2 days.

- ***Sensitivity Analysis 3.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and 3-day controls (analysis set). This analysis was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 3 days.
- ***Sensitivity Analysis 4.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and 7-day controls (Analysis Set). This analysis was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 7 days. No data were excluded when 7-day control periods are used, so this analysis was expected to give a result that had the most similarity to the primary analysis method.

9.9.7.3.2. Varying Control Periods

Different controls periods were evaluated to evaluate to the effect of recall bias for the matched-interval analysis. The magnitude of the recall bias is likely to vary across different exposure periods. That is, the further back the subjects are required to recall, the more recall bias will occur. Therefore, the information obtained in the first control period might be more reliable than the information from the second, third, and fourth control periods. In the sensitivity analysis, the OR was estimated for 3 scenarios: using the exposure from the first control period only, both the first and the second control periods, and the first 3 control periods. The effect of recall bias on the robustness of the findings was evaluated (Figure LVHQ.9.4). Additional details of the 3 scenarios varying control periods are provided below.

- ***Sensitivity Analysis 5***. Matched-interval analysis using exposure based on PDE5 inhibitor effect period and the first 4-day control period (analysis set). This analysis of subject exposure status within 42 days before NAION was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 4 days. Only the 1 control period closest to the NAION IDO was used.
- ***Sensitivity Analysis 6.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and the first two 4-day control periods (analysis set). This analysis of subject exposure status within 42 days before NAION was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 4 days. Only the 2 control periods closest to the NAION IDO were used.
- ***Sensitivity Analysis 7.*** Matched-interval analysis using exposure based on PDE5 inhibitor effect period and the first three 4-day control periods (analysis set). This analysis of subject exposure status within 42 days before NAION was conducted in the 42-day analysis set, using the methods described in the SAP, version 2.0 (Section 10.2.1.1), with the duration of each control period set to 4 days. Only the 3 control periods closest to the NAION IDO were used.



Abbreviation: PDE5 = phosphodiesterase type 5.

Figure LVHQ.9.4. Sensitivity analysis given the selection of different control periods as comparison groups for matched-interval method.

9.9.8. Amendments to the Statistical Analysis Plan

The statistical analyses for this study included the following unforeseen changes or deviations:

- The definition of the analysis set was changed from 'adjudication-confirmed NAION cases who are not chronic users of PDE5 inhibitors' to 'adjudication-confirmed NAION cases who are nonchronic users of PDE5 inhibitors' for consistency with data that can be used in the primary analysis. (Note that in this report, 'nonchronic' users are referred to as 'intermittent' users.)
- The single protocol-specified analysis set based on the 42-day PDE5 inhibitor user categories has been replaced with 3 analysis populations:
  - the 30-day analysis set,
  - the 42-day analysis set (original), and
  - the 12-month analysis set.
- The single protocol-specified modified analysis set has likewise been replaced with:
  - the 30-day modified analysis set,
  - the 42-day modified analysis set (original), and
  - the 12-month modified analysis set.
- Conditional logistic regression model parameters were deemed statistically significant assuming a 2-sided α level of 0.05 on the basis of the Wald test for individual parameters.

In the statistical analysis tables 24 through 31 for the matched-interval method, the predictors (eg, acute myocardial infarction, stroke, etc) were dropped from the originally planned model

because no subjects in the corresponding analysis sets had such risk factors within 42 days of IDO.

The SAP was also updated to reflect the increase in sample size and the plan to re-estimate sample size (described in Section 9.7.2).

9.10. Quality Control

Quality control methods related to data collection included data validation checks, 100% critical data quality control checks, noncritical data quality control checks, and the use of electronic CRF Completion Guidelines. Details are available in the Data Management Plan.

Quality control methods related to biostatistics and statistical programming are described in INC Research Standard Operating Procedure 03.009.03. These quality control procedures were performed for all SAS programs and output. Quality control was defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency, and commenting and by review of the produced output.

Other INC Research standard operating procedures, which apply to activities related to statistical analysis for this study, are as follows:

- SOP 03.007, Development of a Statistical Analysis Plan
- SOP 03.010, Development of SAS® Programs
- SOP 03.009, Quality Control of SAS® Programming
- SOP 03.013, Development and Production of Mapped and Analysis Datasets

All tables and listings were produced with the SAS system, version 9.3. Statistical programming for derived data sets, listings, and tables was verified by independent double programming in SAS, with electronic comparison of the results. Tables were visually examined for adherence to the study requirements, internal consistency, and consistency of results across tables.

Case ascertainment was conducted through an independent adjudication committee. Clinical information for all suspected cases was collected for subsequent review and evaluated by the adjudication committee. The committee used prespecified, consistent, and agreed-upon data standards, as defined in the committee charter, to assess each suspected case on the basis of the clinical information provided by the investigator. The committee was permitted to request additional subject-specific information; however, this was limited to information readily available in the subject's medical record and excluded information on PDE5 inhibitor use. Additional study visits to collect this information were not permitted (Section 9.3.3).

10. Results

10.1. Participants

Numbers of subjects in each of the analysis sets are presented in Table LVHQ.10.2. Definitions for each of the analysis sets are provided in Section 9.9.2.

Between 05 May 2010 and 15 December 2015 (Listing 1), a total of 345 subjects met the inclusion and exclusion criteria, signed informed consent, and were enrolled in the study (the enrolled set).

One subject in the enrolled set (Subject [redacted]) had no information on IDO, resulting in 344 subjects in the study set.

Of the 344 subjects in the study set, 279 (81.1%) were confirmed as having NAION on the basis of adjudication committee decision and composed the adjudication-confirmed NAION set.

Table LVHQ.10.2. Summary of Enrolment and Analysis Sets (Enrolled Subjects)

Population	Number of Subjects
Enrolled set	345
Study set	344
Adjudication-confirmed NAION set	279
30-day analysis set	24
42-day analysis set	28
12-month analysis set	26
30-day modified analysis set	25
42-day modified analysis set	29
12-month modified analysis set	32

Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy.
Analysis sets are defined in Section 9.9.2.
Source: Table 1.

A summary of subject status is presented in Table LVHQ.10.3.

Of the 344 subjects in the study set, 332 (96.5%) completed the study, and 12 (3.5%) discontinued participation before completing the study. The following reasons for discontinuation were provided: 3 were based on subjects' decisions, 4 were based on physicians' decisions, and the reasons for 5 were unknown ('information not available'). Although each subject participated in the study for only 1 day, study activities such as the assembling of assessments for adjudication and adjudication committee review may have occurred at the site after the study visit; therefore, subjects may have discontinued participation beyond the 1 study visit day.

Of the 279 subjects in the adjudication-confirmed NAION set, 276 (98.9%) completed the study and 3 (1.1%) discontinued early. Reasons for early discontinuation were reported on the CRF as 'unknown'; these 3 subjects (Subjects [redacted], and [redacted]) were among the aforementioned 12 discontinuations in the study set.

Table LVHQ.10.3. Summary of Subject Status (Enrolled Subjects)

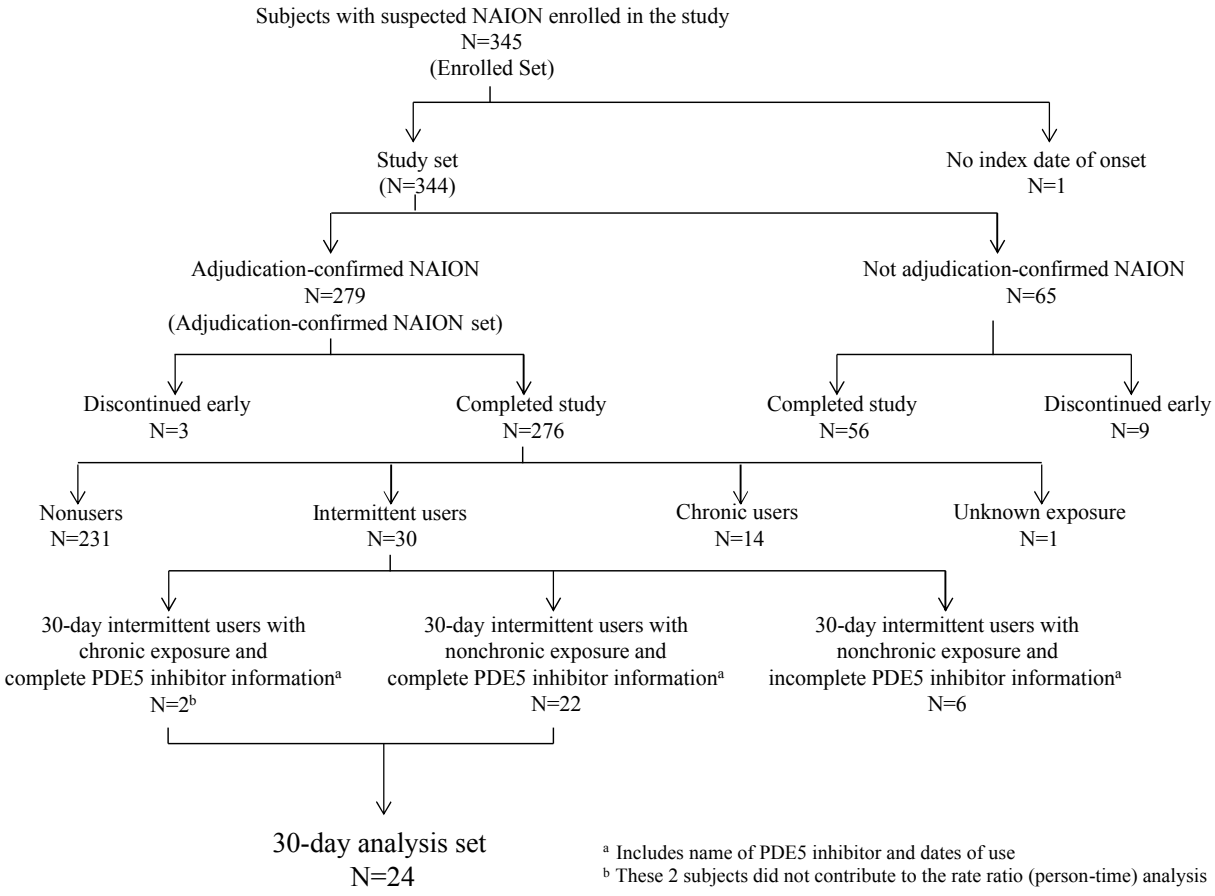
	Study Set (N = 344) n (%)	Adjudication-Confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
Subjects who completed the study	332 (96.5%)	276 (98.9%)	24 (100.0%)	28 (100.0%)	26 (100.0%)
Subjects who discontinued the study	12 (3.5%)	3 (1.1%)	0	0	0
Reason for discontinuation:					
Patient decision	3 (0.9%)	0	0	0	0
Physician decision	4 (1.2%)	0	0	0	0
Sponsor decision	0	0	0	0	0
Information not available	5 (1.5%)	3 (1.1%)	0	0	0

Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy.
Note: Percentages are calculated with the denominator defined as the number of subjects in the population.
Source: Table 2.

A summary of subject status with respect to the 30-day analysis set is presented in Figure LVHQ.10.5.

During the 30 days before IDO, 30 of the 276 subjects with adjudication-confirmed NAION who completed the study were intermittent (nonchronic) users, 231 were nonusers, 14 were chronic users, and 1 subject had unknown exposure.

Of the 30 intermittent users, 6 subjects did not have complete PDE5 inhibitor information (ie, the names of PDE5 inhibitor(s) used and/or dates of use were unknown) and were therefore not included in the 30-day analysis set. The remaining 24 intermittent users had complete PDE5 inhibitor information and were included in the 30-day analysis set; of these, 2 subjects had chronic exposure (defined on the basis of the effect period of the PDE5 inhibitor) during the 30 days before IDO and were not included in the RR (person-time) analyses. The remaining 22 subjects had nonchronic exposure during the 30 days before IDO and were included in the RR (person-time) analyses.



Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

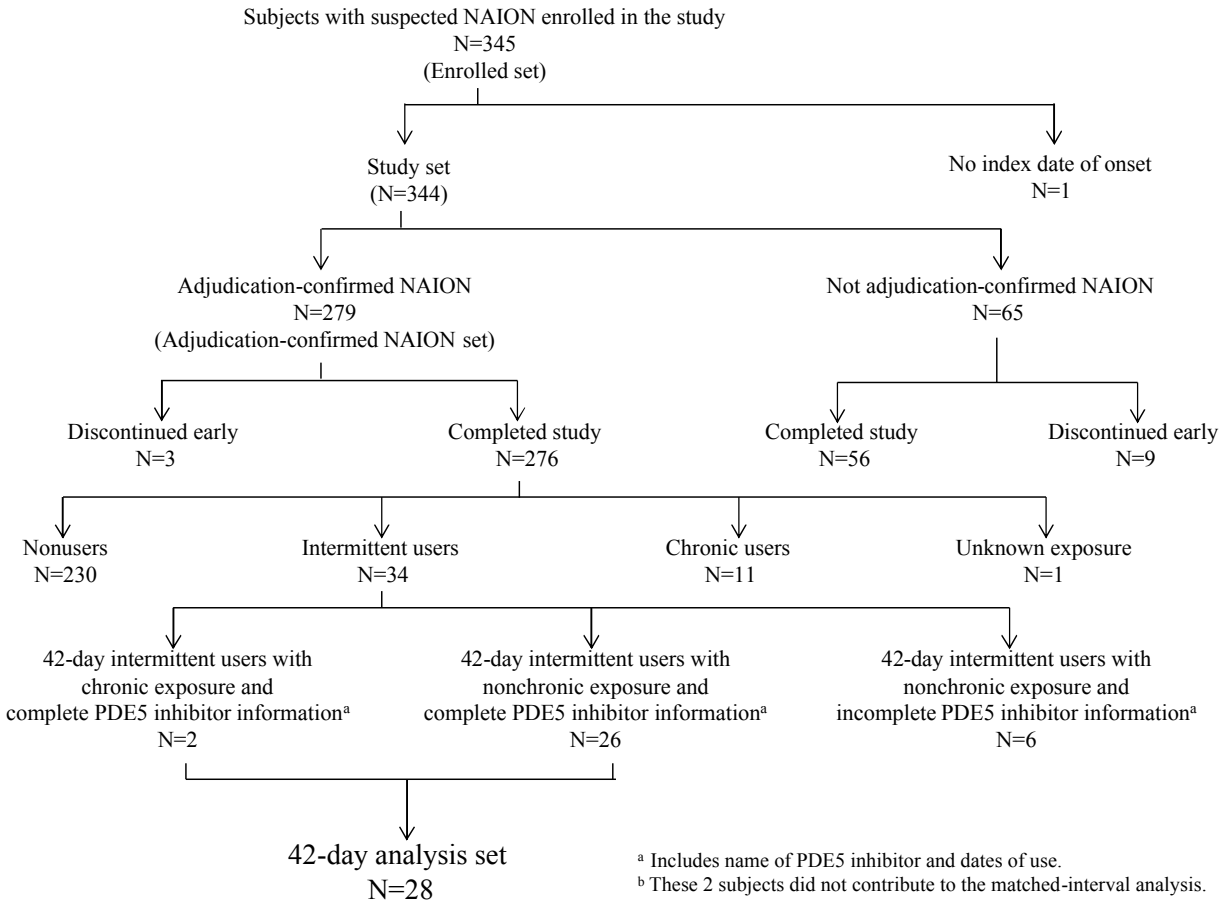
Figure LVHQ.10.5. Selection of the 30-day analysis set.

A summary of subject status with respect to the 42-day analysis set is presented in Figure LVHQ.10.6.

During the 42 days before IDO, 34 of the 276 subjects with adjudication-confirmed NAION who completed the study were intermittent (nonchronic) users, 230 were nonusers, 11 were chronic users, and 1 subject had unknown exposure.

Of the 34 intermittent users, 6 subjects did not have complete PDE5 inhibitor information (ie, the names of PDE5 inhibitor(s) used and/or dates of use were unknown) and were therefore not included in the 42-day analysis set. The remaining 28 intermittent users had complete PDE5 inhibitor information and were included in the 42-day analysis set; of these, 2 subjects had chronic exposure (defined on the basis of the effect period of the PDE5 inhibitor) during the 42 days before IDO and did not contribute to the analyses. The remaining 26 subjects had nonchronic exposure during the 42 days before IDO and were suitable for inclusion analyses.

The 4 additional subjects in the 42-day analysis set compared with the 30-day analysis set reported taking PDE5 inhibitors between Day 31 and Day 42 before IDO but did not take any PDE5 inhibitors during the 30 days preceding their IDO. These subjects were classified as nonusers in the 30-day analysis set and intermittent users in the 42-day analysis set.



Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Figure LVHQ.10.6. Selection of the 42-day analysis set.

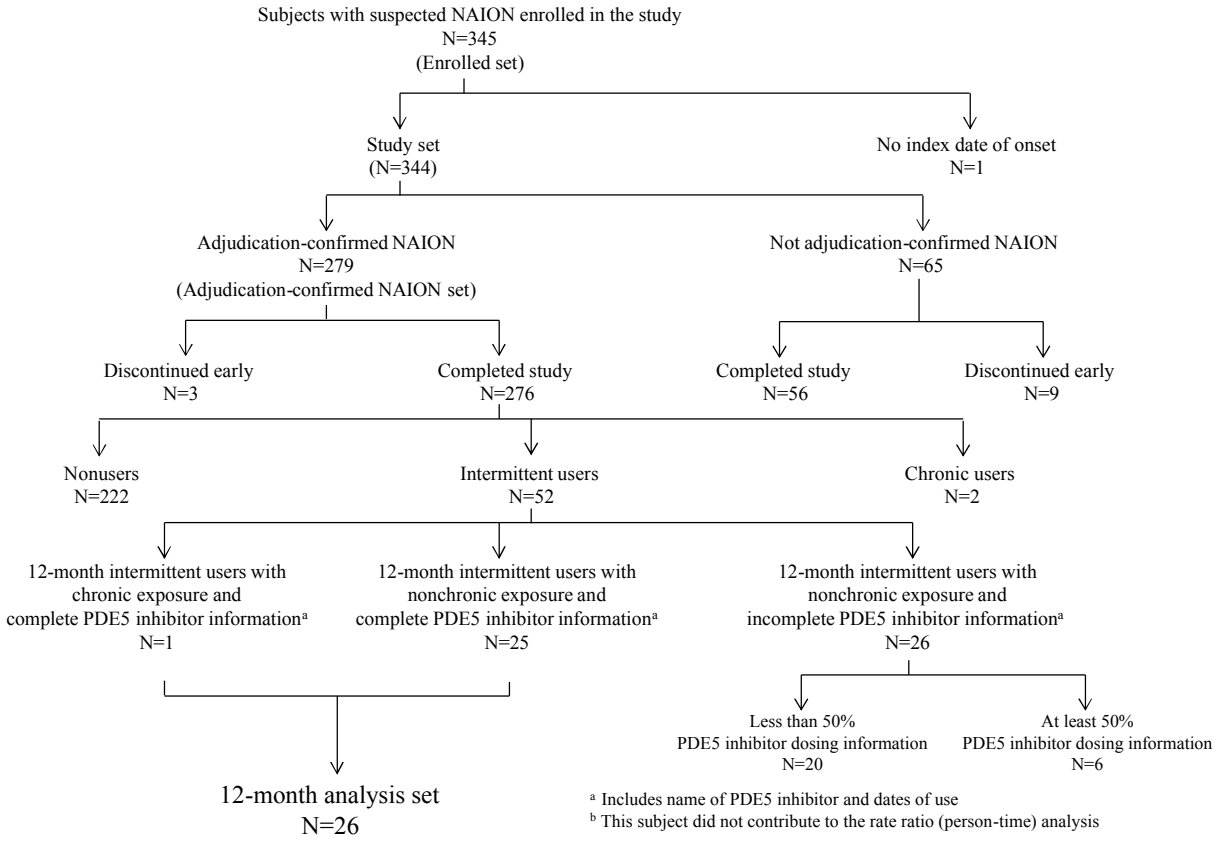
A summary of subject status with respect to the 12-month analysis set is presented in Figure LVHQ.10.7.

During the 12 months before IDO, 52 of the 276 subjects with adjudication-confirmed NAION who completed the study were intermittent (nonchronic) users, 222 were nonusers, and 2 were chronic users.

Of the 52 intermittent users, 26 subjects did not have complete PDE5 inhibitor information (ie, the names of PDE5 inhibitor(s) used and/or dates of use were unknown), of which 20 subjects

had less than 50% PDE5 inhibitor dosing information and 6 subjects had at least 50% PDE5 inhibitor dosing information. These 26 subjects with incomplete PDE5 inhibitor information were not included in the 12-month analysis set. The remaining 26 intermittent users had complete PDE5 inhibitor information and were included in the 12-month analysis set; of these, 1 subject had chronic exposure during the 12 months before IDO and was not included in the RR (person-time) analyses. The remaining 25 subjects in the 12-month analysis set had nonchronic exposure during the 12 months before IDO and were included in the RR (person-time) analyses.

In the 12-month analysis, exposure was captured monthly as the number of days per month. In the 30-day and 42-day analysis sets, exposure to PDE5 inhibitors was captured daily. Therefore, the 2 more subjects in the 42-day analysis set than in the 12-month analysis set (28 and 26 subjects, respectively) suggest that at least 2 subjects reported their individual PDE5 inhibitor use differently on the day-by-day recall for the 42 days before IDO and the 12 months before IDO.



Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Figure LVHQ.10.7. Selection of the 12-month analysis set.

Fourteen subjects are included in all 3 of the primary and secondary analysis sets. All 24 of the subjects in the 30-day analysis set were also in the 42-day analysis set. Ten subjects are in the 12-month analysis set but not in the 30-day or 42-day analysis sets (Listing 1). This overlap is evident when noting the similarities in demographic and baseline summaries, particularly between the 30-Day and 42-day analysis sets.

10.2. Descriptive Data

10.2.1. Demographics

A summary of demographic and baseline (at IDO) characteristics for the adjudication-confirmed NAION set and the primary and secondary analysis sets is presented in Table LVHQ.10.4.

Subjects participating in this study and included in the adjudication-confirmed NAION set were predominantly Caucasian (95.7%, n = 267), approximately 61 years of age (mean = 61.5; range = 36 to 95), and not Hispanic or Latino (95.0%, n = 265).

Among the 24 subjects in the 30-day analysis set, the mean age was 61.8 years (SD = 8.27, median = 60 years, range = 49-81 years); the majority (95.7%, n = 23) were Caucasian; all (100%) were not Hispanic or Latino. The mean height and weight values were 177.4 cm (SD = 7.44) and 88.72 kg (SD = 15.73), respectively. These demographics of the 42-day and 12-month analysis sets were similar to those of the 30-day analysis set. (Note: 1 subject in both the adjudication-confirmed NAION set and the 12-month analysis set was erroneously recorded with a height of 363 cm, thereby affecting the mean heights recorded for these 2 analysis sets.)

In the 30-day analysis set, 50.0% (n = 12) of subjects were employed full time, 4.2% (n = 1) were employed part time, and 45.8% (n = 11) was unemployed. This was similar across analysis sets with the exception of the 12-month analysis set, of which 69.2% (n = 18) were employed full-time. The option of 'retired' was not included on the CRF; because of the age distribution among subjects, it is likely that many of the unemployed subjects were retired.

Among subjects in the 30-day analysis set, the highest level of education reported was high school (25.0%, n = 6), college (45.8%, n = 11), postgraduate school (25.0%, n = 6), or vocational training (4.2%, n = 1). This was similar for the 42-day analysis set, but in the 12-month analysis set, a higher percentage had completed postgraduate school (38.5%, n = 10) with a subsequently lower percentage of subjects reporting college as their highest level of education (34.6%, n = 9).

Table LVHQ.10.4 Summary of Baseline and Demographic Information

	Adjudication-Confirmed NAION Set (N = 279)	30-Day Analysis Set (N = 24)	42-Day Analysis Set (N = 28)	12-Month Analysis Set (N = 26)
Age (years)[a]				
Mean	61.5	61.8	61.6	61.3
SD	10.70	8.27	8.58	10.46
Median	61.0	60.0	60.0	58.0
Min, max	36, 95	49, 81	49, 81	42, 84
Race				
Caucasian	267 (95.7%)	23 (95.8%)	27 (96.4%)	26 (100.0%)
Black	2 (0.7%)	0	0	0
Asian	2 (0.7%)	0	0	0
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0	0	0
Multiple	2 (0.7%)	1 (4.2%)	1 (3.6%)	0
Not provided	5 (1.8%)	0	0	0
Ethnicity				
Hispanic or Latino	11 (3.9%)	0	0	0
Not Hispanic or Latino	265 (95.0%)	24 (100.0%)	28 (100.0%)	26 (100.0%)
Not provided	3 (1.1%)	0	0	0
Height (cm)				
Mean	177.2[b]	177.4	176.8	184.6[b]
SD	13.45	7.44	7.23	37.11
Median	177.8	176.5	175.3	176.5
Min	155	165	165	168
Max	363[b]	203	203	363[b]
Weight (kg)				
Mean	91.90	88.72	88.42	89.06
SD	20.534	15.733	15.599	14.944
Median	88.45	83.01	83.01	88.45
Min	59.0	67.1	66.7	66.2
Max	262.6	117.9	117.9	117.9
Employment status				
Full time	159 (57.0%)	12 (50.0%)	16 (57.1%)	18 (69.2%)
Part time	20 (7.2%)	1 (4.2%)	1 (3.6%)	0
Unemployed	100 (35.8%)	11 (45.8%)	11 (39.3%)	8 (30.8%)
Highest level of education				
Elementary school	3 (1.1%)	0	0	0
Middle school	6 (2.2%)	0	0	0
High school	83 (29.7%)	6 (25.0%)	6 (21.4%)	6 (23.1%)
College	112 (40.1%)	11 (45.8%)	13 (46.4%)	9 (34.6%)
Postgraduate school	63 (22.6%)	6 (25.0%)	8 (28.6%)	10 (38.5%)
Vocational training	11 (3.9%)	1 (4.2%)	1 (3.6%)	1 (3.8%)
No formal education	0	0	0	0

Summary of Baseline and Demographic Information

Abbreviations: max = maximum; min = minimum; NAION = nonarteritic anterior ischaemic optic neuropathy; SD = standard deviation.

Note: The denominator of each percentage is the number of subjects in the population.

[a] Age is calculated at date of informed consent from year of birth.

[b] One subject in both the Adjudication-Confirmed NAION Set and the 12-Month Analysis Set was erroneously recorded with a height of 363 cm, thereby affecting the mean heights recorded for these 2 analysis sets.

Source: Table 3.

10.2.2. Lifestyle Factors

Lifestyle and behaviour factors are shown in Table LVHQ.10.5. In general, subjects in the adjudication-confirmed NAION set and the primary and secondary analysis sets were predominantly nonsmokers; around 60% consumed alcohol, and very few used recreational or illicit drugs.

Table LVHQ.10.5. Summary of Lifestyle Factors

	Adjudication-confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
Tobacco use				
Yes	47 (16.8)	3 (12.5)	4 (14.3)	6 (23.1)
No	232 (83.2)	21 (87.5)	24 (85.7)	20 (76.9)
Unknown	0	0	0	0
Alcohol consumption				
Yes	174 (62.4)	15 (62.5)	16 (57.1)	17 (65.4)
No	102 (36.6)	9 (37.5)	12 (42.9)	9 (34.6)
Unknown	3 (1.1)	0	0	0
Recreational/illicit drug use				
Yes	17 (6.1)	1 (4.2)	1 (3.6)	2 (7.7)
No	262 (93.9)	23 (95.8)	27 (96.4)	24 (92.3)
Unknown	0	0	0	0

Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy.

Source: Table 13.

10.2.3. Baseline Vision Loss Symptoms

A summary of baseline vision loss symptoms is presented in Table LVHQ.10.6.

For most of the 279 subjects included in the adjudication-confirmed NAION set, the onset of vision loss was rapid (acute) (85.3%, n = 238), with slow (chronic) onset for 10.4% (n = 29) of subjects, and unknown or information not available for the remaining 4.3% (n = 12) of subjects. The majority of subjects (72.4%, n = 202) in the adjudication-confirmed NAION set reported stable vision since IDO, with the remainder reporting vision loss progressively declining for a

period less than 1 week after IDO (17.9%, n = 50) or progressively declining for a period greater than a week since IDO (9.7%, n = 27).

In the 30-day analysis set, a majority (79.2%, n = 1) of subjects reported rapid (acute) onset of vision loss, 8.3% (n = 2) of subjects reported slow (chronic) onset of vision loss, and the rate of onset of vision loss was unknown for the remaining 12.5% (n = 3) of subjects. Vision loss data were similar for the 28 subjects in the 42-day analysis sets; however, the 12-month analysis set had a slightly higher percentage of subjects (19.2%, n = 5) with slow (chronic) loss and a corresponding reduction in percentage of subjects (73.1%, n = 19) with rapid (acute) onset.

Since the IDO, progression of vision loss for the 30-day analysis set was stable for 62.5% (n = 15) of subjects, progressively declining for a period less than 1 week after IDO for 33.3% (n = 8) of subjects, and progressively declining for a period greater than 1 week since IDO for 4.2% (n = 1) of subjects. This was similar for the 42-day and 12-month analysis sets. Vision loss was described as 'painless' for nearly all subjects in these analysis sets (95.8% to 96.4%).

Table LVHQ.10.6. Summary of Baseline Vision Loss Symptoms

	Adjudication-Confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
Onset of vision loss				
Rapid (acute)	238 (85.3%)	19 (79.2%)	22 (78.6%)	19 (73.1%)
Slow (chronic)	29 (10.4%)	2 (8.3%)	3 (10.7%)	5 (19.2%)
Unknown	11 (3.9%)	3 (12.5%)	3 (10.7%)	2 (7.7%)
Information not available	1 (0.4%)	0	0	0
Progression of vision loss since IDO				
Stable	202 (72.4%)	15 (62.5%)	17 (60.7%)	16 (61.5%)
Progressively declining < 1 week	50 (17.9%)	8 (33.3%)	10 (35.7%)	10 (38.5%)
Progressively declining after 1 week	27 (9.7%)	1 (4.2%)	1 (3.6%)	0
Pain associated with vision loss				
Painful	16 (5.7%)	1 (4.2%)	1 (3.6%)	1 (3.8%)
Painless	263 (94.3%)	23 (95.8%)	27 (96.4%)	25 (96.2%)

Abbreviations: IDO = index date of onset; NAION = nonarteritic anterior ischaemic optic neuropathy.
Note: The denominator of each percentage is the number of subjects in the population.
Source: Table 4.

10.2.4. PDE5 Inhibitor Exposure

A summary of PDE5 inhibitor use within 42 days and 12 months before IDO is presented for the adjudication-confirmed NAION set and the primary and secondary analysis sets in Table LVHQ.10.7.

The use of PDE5 inhibitors was captured by subject recall on 2 separate CRFs. On the 42-day CRF, subjects were queried to recall PDE5 inhibitors on a day-by-day basis for the 42 days before IDO; this CRF was used for determining PDE5 inhibitor exposure of subjects in the 30-day and 42-day analysis sets. On the 12-month CRF, exposure was captured monthly as the number of days per month on a month-by-month basis; this CRF was used in combination with the 42-day CRF for determining PDE5 inhibitor exposure for the 12-month secondary analyses.

Among the 279 subjects in the adjudication-confirmed NAION, PDE5 inhibitor use was reported by 16.1% (n = 45) in the 42 days before IDO and 19.4% (n = 54) in the 12 months before IDO.

By definition, subjects included in the primary and secondary analysis sets were intermittent users of PDE5 inhibitors. All (100%) of the subjects in each of the 30-day analysis set (n = 24) and the 42-day analysis set (n = 28) and 92.3% (n = 24) of subjects in the 12-month analysis set took a PDE5 inhibitor in the 42 days before IDO. All (100%) of subjects in each of the 3 primary and secondary data sets reported taking a PDE5 inhibitor within 12 months before IDO.

Subjects may have taken >1 PDE5 inhibitor product during the study recall periods. Tadalafil was the most frequently used PDE5 inhibitor among subjects in this study. Approximately 50% of subjects in the primary and secondary analysis sets reported using tadalafil in the 42 days before IDO. On average, sildenafil was used by 44% and vardenafil by 10%. A similar distribution was seen in the 12 months before IDO for tadalafil and vardenafil; however, sildenafil users increased to around 50%. Five subjects reported taking an unspecified PDE5 inhibitor.

In the 42 days before IDO, the mean numbers of dosing days per subject ranged from 7.7 to 15.8 for subjects in the primary and secondary analysis sets, and the mean number of exposure days ranged from 12.0 to 19.5. These compared with 22.2 days in the adjudication-confirmed NAION set. (Note: the adjudication-confirmed NAION set also included chronic PDE5 inhibitor users [N = 14] and nonusers [N = 231]). The mean number of exposure days for tadalafil is generally higher than the mean for the other PDE5 inhibitors, and this is likely to be because tadalafil has a longer half-life than those of sildenafil and vardenafil (Section 9.9.4.1; Section 9.9.1.3).

Subjects in the primary and secondary analysis sets reported PDE5 inhibitor exposure in approximately 10 out of 12 months, with around 3 to 4 doses per month. Tadalafil users reported slightly more dosing days per month compared with sildenafil users.

Table LVHQ.10.7. PDE5 Inhibitor Exposure

	Adjudication-Confirmed NAION Set (N = 279)	30-Day Analysis Set (N = 24)	42-Day Analysis Set (N = 28)	12-Month Analysis Set (N = 26)
42 days before IDO				
Used a PDE5 inhibitor, n (%)[a]	45 (16.1)[b]	24 (100)	28 (100)	24 (92.3)
Used Cialis, n	25	13	15	13
Used Viagra, n	19	10	12	12
Used Levitra, n	6	2	3	3
Used unknown, n	1	0	0	0
Number of dosing days per subject (mean)[c]				
Any PDE5 inhibitor	19.7	7.7	10.1	15.8
Cialis	19.2	7.2	8.3	13.2
Viagra	17.8	5.7	10.3	15.0
Levitra	12.0	17.0	11.7	11.3
Unknown	1.0	--	--	--
Exposure days per subject (mean)[d]				
Any PDE5 inhibitor	22.2	12.0	14.0	19.5
Cialis	23.6	15.2	15.5	19.9
Viagra	17.8	5.7	10.3	15.0
Levitra	12.0	17.0	11.7	11.3
Unknown	4.0	--	--	--
12 months before IDO				
Used a PDE5 inhibitor, n (%)[a]	54 (19.4)[b]	24 (100)	28 (100)	26 (100)
Used Cialis, n	27	13	15	13
Used Viagra, n	28	12	14	15
Used Levitra, n	8	2	3	3
Used unknown, n	10	5	5	0
Months of exposure per subject (mean)				
Any PDE5 inhibitor	9.8	10.0	9.9	11.6
Cialis	7.8	8.6	8.1	10.0
Viagra	7.5	7.3	7.4	10.3
Levitra	7.5	6.5	8.0	11.7
Unknown	7.6	6.6	6.6	
Doses per subject per month (mean)				
Any PDE5 inhibitor	5.8	3.1	3.4	4.4
Cialis	5.2	3.0	2.9	3.6
Viagra	4.7	1.8	2.4	3.8
Levitra	2.6	2.2	2.8	3.4
Unknown	2.5	2.2	2.2	

Abbreviations: IDO = index date of onset; NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

[a] Number and percentage of subjects in the indicated population that reported using the medication.

[b] Includes also chronic users of PDE5 inhibitors, in addition to the intermittent (nonchronic) users included in the 30-day, 42-day, and 12-month analysis sets.

[c] Dosing days = number of unique days in which a subject reported ingesting a PDE5 inhibitor.

PDE5 Inhibitor Exposure

[d] Exposure days = total number of days exposed to a PDE5 inhibitor, defined on the basis of the reported date of dosing and the assumed effect period (approximately 5 half-lives) of the PDE5 inhibitor used.

Sources: Table 14, Table 15.

10.2.5. Medical History

Summaries of the most frequently reported (by > 10% of subjects in an analysis set) medical conditions in the adjudication-confirmed NAION set and the 30-day, 42-day, and 12-month analysis sets for the 42 days and 12 months before IDO are presented in Table LVHQ.10.8 and Table LVHQ.10.9, respectively.

Among the 279 subjects with adjudication-confirmed NAION, 44.8% (n = 125) reported 1 or more events in their medical or surgical history occurring within 42 days before IDO, with a similar percentage reported by subjects in the 30-day, 42-day, and 12-month analysis sets (37.5%, n = 9; 42.9%, n = 12; and 42.3%, n = 11; respectively).

The most frequently reported (by ≥10% of subjects) SOCs for subjects in the above-noted analysis sets were, in order of descending frequency for the 30-day analysis set, reproductive system and breast disorders (16.7%, n = 4), gastrointestinal disorders (12.5%, n = 3), investigations (8.3%, n = 2), metabolism and nutrition disorders (8.3%, n = 2), and vascular disorders (4.2%, n = 1). Higher percentages of subjects in the 42-day and 12-month analysis sets than in the 30-day analysis set reported events within the SOCs of investigations (14.3% and 15.4%, respectively) and vascular disorders (10.7% and 11.5%, respectively), as well as metabolism and nutrition events for the 42-day analysis set (14.3%), representing 2 additional subjects per SOC.

For each of the 30-day, 42-day, and 12-month analysis sets, the reported events (by PT) within each of the frequently reported SOCs were mostly similar and included the following: reproductive system and breast disorders (erectile dysfunction and prostatic disorders); gastrointestinal disorders (celiac disease, dyspepsia, and gastroesophageal reflux disease); investigations (blood cholesterol increased, blood testosterone decreased, and blood triglycerides decreased); metabolism and nutrition disorders (diabetes mellitus, gout, and hyperlipidaemia); and vascular disorders (hypertension). Events that were reported by >1 subject in any of these 3 analysis sets included erectile dysfunction (3, 5, and 6 subjects in the 30-day, 42-day, and 12-month analysis sets, respectively); blood cholesterol increased (3 subjects in each of the 42-day and 12-month analysis sets); and diabetes mellitus and hypertension (each with 3 subjects in the 42-day analysis set).

When recording medical history events, investigators were requested to identify events they considered to be related to PDE5 inhibitors; these events were collected separately, were classified as related to PDE5 inhibitors according to the investigator's discretion, and were not queried, corrected, or reconciled. Medical history events that occurred within 42 days of IDO and were determined by the investigator to be related to PDE5 inhibitors were reported by 4.3% (n = 12) of subjects in the adjudication-confirmed NAION set and by 20.8% (n = 5), 25.0%

(n = 7), and 29.4% (n = 10) of subjects in the 30-day, 42-day, and 12-month analysis sets, respectively. Erectile dysfunction was the most frequently reported event determined by the investigator to be related to PDE5 inhibitors and was reported by 12.5% (n = 3), 17.9% (n = 5), and 23.1% (n = 6) subjects in the 30-day, 42-day, and 12-month analysis sets, respectively. Two additional events included postprocedural complications (1 subject in each of the 4 above-noted analysis sets) and radical prostatectomy (1 subject in each of the 30-day and 42-day analysis sets) (Table 10).

Table LVHQ.10.8. Most Frequently Reported (by >10% of Subjects in an Analysis Set) Medical Conditions within 42 days before Index Date of Onset

System Organ Class Preferred Term	Adjudication-Confirmed NAION Set (N = 279)[a] n (%)	30-Day Analysis Set (N = 24)[b] n (%)	42-Day Analysis Set (N = 28)[b] n (%)	12-Month Analysis Set (N = 26)[b] n (%)
Any medical/surgical events	**125 (44.8)**	**9 (37.5)**	**12 (42.9)**	**11 (42.3)**
Reproductive system and breast disorders	**18 (6.5)**	**4 (16.7)**	**6 (21.4)**	**7 (26.9)**
Erectile dysfunction	10 (3.6)	3 (12.5)	5 (17.9)	6 (23.1)
Prostatic disorder	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Gastrointestinal disorders	**19 (6.8)**	**3 (12.5)**	**3 (10.7)**	**2 (7.7)**
Coeliac disease	1 (0.4)	1 (4.2)	1 (3.6)	0
Dyspepsia	3 (1.1)	1 (4.2)	1 (3.6)	1 (3.8)
Gastrooesophageal reflux disease	10 (3.6)	1 (4.2)	1 (3.6)	1 (3.8)
Investigations	**27 (9.7)**	**2 (8.3)**	**4 (14.3)**	**4 (15.4)**
Blood cholesterol increased	17 (6.1)	1 (4.2)	3 (10.7)	3 (11.5)
Blood testosterone decreased	4 (1.4)	1 (4.2)	1 (3.6)	1 (3.8)
Blood triglycerides increased	2 (0.7)	0	1 (3.6)	1 (3.8)
Metabolism and nutrition disorders	**42 (15.1)**	**2 (8.3)**	**4 (14.3)**	**2 (7.7)**
Diabetes mellitus	14 (5.0)	1 (4.2)	3 (10.7)	1 (3.8)
Gout	7 (2.5)	1 (4.2)	1 (3.6)	1 (3.8)
Hypercholesterolaemia	13 (4.7)	0	0	1 (3.8)
Hyperlipidaemia	8 (2.9)	1 (4.2)	1 (3.6)	0
Vascular disorders	**48 (17.2)**	**1 (4.2)**	**3 (10.7)**	**3 (11.5)**
Hypertension	47 (16.8)	1 (4.2)	3 (10.7)	3 (11.5)

Abbreviations: NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Notes: Medical history was coded using the *Medical Dictionary for Regulatory Activities* (version 18.1). Only medical history events (by preferred term) in the listed system organ class and reported by subjects in the 30-day, 42-day, or 12-month analysis sets are included in this table. The denominator of each percentage is the number of subjects in the population. A subject was counted only once in the numerator for each system organ class and once in the numerator for each preferred term. Table is sorted in descending frequency of system organ classes for the 30-day analysis set.

[a] Includes PDE5 inhibitor users and nonusers.

[b] Includes PDE5 inhibitor users only.

Source: Table 9.

A summary of the most frequently reported (by >10% of subjects in an analysis set) medical conditions in the adjudication-confirmed NAION set and the 30-day, 42-day, and 12-month analysis sets for the 12 months before IDO is presented in Table LVHQ.10.11.

Among the 279 subjects with adjudication-confirmed NAION, 68.1% (n = 190) reported 1 or more conditions in their medical or surgical history within 12 months before IDO, with similar results for the 30-day (75.0%, n = 18), 42-day (71.4%, n = 20), and 12-month analysis sets (73.1%, n = 19).

The most frequently reported SOC was metabolism and nutrition disorders, with events in this group reported by 58.3% (n = 14), 53.6% (n = 15), and 42.3% (n = 11) of subjects in the 30-day, 42-day, and 12-month analysis sets, respectively. System organ classes that were reported by 20% to 40% of subjects in any of the 3 above-noted analysis sets included respiratory, thoracic, and mediastinal disorders; vascular disorders; and investigations (12-month analysis set only).

The most frequently reported medical history events (by PT) were, in order of descending frequency by the 30-day analysis set, hypercholesterolaemia (37.5%, n = 9); hypertension (16.7%, n = 4); and diabetes mellitus, asthma, arthritis, erectile dysfunction, and hypersensitivity (each with 12.5%, n = 3). Results were generally similar for the 42-day and 12-month analysis sets, except that slightly higher percentages of subjects in these groups reported erectile dysfunction (14.3%, n = 4; and 19.2%, n = 5; respectively), and a higher percentage of subjects in the 12-month group (15.4%, n = 4) reported gastroesophageal reflux disease than subjects in the 30-day and 42-day analysis sets (8.3%, n = 2; and 7.1%, n = 2; respectively).

Of interest is that the number of subjects who self-reported erectile dysfunction occurring within the 12 months before IDO (4 and 5 subjects in the 42-day and 12-month analysis sets, respectively) was discrepant with the number of subjects in these analysis sets who reported erectile dysfunction occurring within the 42 days before IDO (5 and 6 subjects, respectively).

When recording medical history events, investigators were requested to identify events they considered to be related to PDE5 inhibitors. Reported medical history events that occurred within 12 months before IDO and were determined by the investigator to be associated with PDE5 inhibitor use were reported by 6.8% (n = 19) of subjects in the adjudication-confirmed NAION set (Table 12). Among subjects in the 30-day, 42-day, and 12-month analysis sets, 12.5% (n = 3), 14.3% (n = 4), and 19.2% (n = 5) of subjects, respectively, reported events that occurred within 12 months before IDO and were determined by the investigator to be associated with PDE5 inhibitor use. For these 3 analysis sets, these events were all in the SOC of reproductive system and breast disorders, and all with the PT of erectile dysfunction (Table 12).

Table LVHQ.10.9. Most Frequently Reported (by >10% of Subjects in an Analysis Set) Medical Conditions within 12 Months before Index Date of Onset

System Organ Class Preferred Term	Adjudication-Confirmed NAION Set (N = 279)[a] n (%)	30-Day Analysis Set (N = 24)[b] n (%)	42-Day Analysis Set (N = 28)[b] n (%)	12-Month Analysis Set (N = 26)[b] n (%)
Any medical/surgical events	**190 (68.1)**	**18 (75.0)**	**20 (71.4)**	**19 (73.1)**
Metabolism and nutrition disorders	**88 (31.5)**	**14 (58.3)**	**15 (53.6)**	**11 (42.3)**
Decreased appetite	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Diabetes mellitus	26 (9.3)	3 (12.5)	3 (10.7)	3 (11.5)
Hypercholesterolaemia	46 (16.5)	9 (37.5)	10 (35.7)	7 (26.9)
Hyperlipidaemia	13 (4.7)	2 (8.3)	2 (7.1)	1 (3.8)
Type 2 diabetes mellitus	12 (4.3)	2 (8.3)	2 (7.1)	1 (3.8)
Vitamin D deficiency	3 (1.1)	2 (8.3)	2 (7.1)	2 (7.7)
Respiratory, thoracic, mediastinal disorders	**37 (13.3)**	**6 (25.0)**	**6 (21.4)**	**7 (26.9)**
Asthma	9 (3.2)	3 (12.5)	3 (10.7)	3 (11.5)
Asthma exercise induced	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Chronic obstructive pulmonary disease	4 (1.4)	0	0	1 (3.8)
Pleural effusion	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Pulmonary embolism	2 (0.7)	0	0	1 (3.8)
Sleep apnoea syndrome	15 (5.4)	2 (8.3)	2 (7.1)	1 (3.8)
Vascular disorders	**90 (32.3)**	**5 (20.8)**	**6 (21.4)**	**6 (23.1)**
Aortic aneurysm	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Blood pressure fluctuation	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Hypertension	86 (30.8)	4 (16.7)	5 (17.9)	5 (19.2)
Musculoskeletal/connective tissue disorders	**47 (16.8)**	**4 (16.7)**	**4 (14.3)**	**3 (11.5)**
Arthritis	17 (6.1)	3 (12.5)	3 (10.7)	1 (3.8)
Back pain	9 (3.2)	1 (4.2)	1 (3.6)	1 (3.8)
Exostosis	1 (0.4)	0	0	1 (3.8)
Intervertebral disc protrusion	3 (1.1)	0	0	1 (3.8)
Tendonitis	1 (0.4)	0	0	1 (3.8)
Nervous system disorders	**29 (10.4)**	**4 (16.7)**	**4 (14.3)**	**3 (11.5)**
Headache	8 (2.9)	1 (4.2)	1 (3.6)	1 (3.8)
Hypogeusia	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Migraine	4 (1.4)	2 (8.3)	2 (7.1)	1 (3.8)
Reproductive system and breast disorders	**36 (12.9)**	**4 (16.7)**	**5 (17.9)**	**6 (23.1)**
Benign prostatic hyperplasia	14 (5.0)	0	0	1 (3.8)
Erectile dysfunction	15 (5.4)	3 (12.5)	4 (14.3)	5 (19.2)
Prostatomegaly	6 (2.2)	1 (4.2)	1 (3.6)	0
Gastrointestinal disorders	**48 (17.2)**	**3 (12.5)**	**3 (10.7)**	**5 (19.2)**
Barrett's oesophagus	3 (1.1)	1 (4.2)	1 (3.6)	1 (3.8)
Constipation	4 (1.4)	1 (4.2)	1 (3.6)	1 (3.8)
Gastrooesophageal reflux disease	37 (13.3)	2 (8.3)	2 (7.1)	4 (15.4)

Most Frequently Reported (by >10% of Subjects in an Analysis Set) Medical Conditions within 12 Months before Index Date of Onset

System Organ Class Preferred Term	Adjudication-Confirmed NAION Set (N = 279)[a] n (%)	30-Day Analysis Set (N = 24)[b] n (%)	42-Day Analysis Set (N = 28)[b] n (%)	12-Month Analysis Set (N = 26)[b] n (%)
Immune system disorders	**25 (9.0)**	**3 (12.5)**	**3 (10.7)**	**3 (11.5)**
Hypersensitivity	4 (1.4)	3 (12.5)	3 (10.7)	2 (7.7)
Seasonal allergy	13 (4.7)	0	0	1 (3.8)
Psychiatric disorders	**48 (17.2)**	**3 (12.5)**	**4 (14.3)**	**5 (19.2)**
Alcoholism	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Anxiety	14 (5.0)	1 (4.2)	1 (3.6)	1 (3.8)
Depression	23 (8.2)	1 (4.2)	1 (3.6)	1 (3.8)
Drug dependence	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Insomnia	13 (4.7)	0	1 (3.6)	2 (7.7)
Sleep disorder	2 (0.7)	1 (4.2)	1 (3.6)	1 (3.8)
Renal and urinary disorders	**12 (4.3)**	**3 (12.5)**	**3 (10.7)**	**2 (7.7)**
Calculus urinary	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Dysuria	2 (0.7)	1 (4.2)	1 (3.6)	0
Micturition urgency	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Cardiac disorders	**25 (9.0)**	**2 (8.3)**	**3 (10.7)**	**5 (19.2)**
Arrhythmia	3 (1.1)	0	1 (3.6)	1 (3.8)
Atrial fibrillation	9 (3.2)	2 (8.3)	2 (7.1)	3 (11.5)
Cardiac disorder	4 (1.4)	0	0	1 (3.8)
Injury, poisoning, and procedural complications	**10 (3.6)**	**2 (8.3)**	**3 (10.7)**	**2 (7.7)**
Brachial plexus injury	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Ligament rupture	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Meniscus injury	4 (1.4)	0	1 (3.6)	0
Tendon rupture	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Investigations	**35 (12.5)**	**2 (8.3)**	**3 (10.7)**	**6 (23.1)**
Blood cholesterol increased	24 (8.6)	0	0	3 (11.5)
Blood testosterone decreased	7 (2.5)	2 (8.3)	3 (10.7)	3 (11.5)
Intraocular pressure increased	1 (0.4)	0	1 (3.6)	1 (3.8)
Urine output decreased	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Weight decreased	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Notes: Medical history was coded using MedDRA (version 18.1). Only medical history events (by preferred term) in the listed system organ class and reported by subjects in the 30-Day, 42-Day, or 12-Month Analysis Sets are included in this table. The denominator of each percentage is the number of subjects in the population. A subject was counted only once in the numerator for each system organ class and once in the numerator for each preferred term. Medical history reported in the 42-day analysis set from different case report forms than used for reporting medications for the 12-month analysis set.

[a] Includes PDE5 inhibitor users and nonusers.

[b] Includes PDE5 inhibitor users only.

Source: Table 11.

10.2.6. Concomitant Medications

Summaries of the most frequently reported (by >10% of subjects in an analysis set) on-demand medications taken within 42 days before IDO and within 12 months before IDO are presented for the adjudication-confirmed NAION set and the 30-day, 42-day, and 12-month analysis sets in Table LVHQ.10.10 (42 days before IDO) and Table LVHQ.10.11 (12 months before IDO).

In the adjudication-confirmed NAION set, 43.4% (n = 121) of subjects reported having taken at least 1 medication during the 42 days before IDO; the percentage increased to 93.5% (n = 261) for the 12 months before IDO (Table LVHQ.10.10). The percentage of subjects who reported having taken at least 1 medication in the 42 days before IDO was similar among the 30-day (50.0%, n = 12), 42-day (46.4%, n = 13), and 12-month (50.0%, n = 13) analysis sets. All subjects (100%) in the 30-day and 42-day analysis sets and 92.3% (n = 24) of subjects in the 12-month analysis set reported taking at least 1 medication within 12 months before IDO.

When recording concomitant medications and medications used within the specified periods (42 days or 12 months) before IDO, investigators were requested to identify medications they considered to be related to conditions associated with PDE5 inhibitor use. These medications were collected separately and were classified as associated with conditions related to PDE5 inhibitors according to the investigator's discretion. There were no medications reported by subjects to be taken within 42 days before IDO and determined by the investigator to be related to conditions associated with PDE5 inhibitor use for the 30-day, 42-day, and 12-month analysis sets (Table 6).

Table LVHQ.10.10. Frequently Reported (>10% of Subjects in an Analysis Set) On-Demand Medications Taken within 42 Days before Index Date of Onset

ATC Level 4 Term Preferred Term (ATC Level 5 Term)	Adjudication-Confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
At least 1 on-demand medication 42 days before IDO	**121 (43.4)**	**12 (50.0)**	**13 (46.4)**	**13 (50.0)**
Propionic acid derivatives	**45 (16.1)**	**5 (20.8)**	**5 (17.9)**	**5 (19.2)**
Ibuprofen	32 (11.5)	5 (20.8)	5 (17.9)	5 (19.2)
HMG CoA reductase inhibitors[a]	**12 (4.3)**	**2 (8.3)**	**3 (10.7)**	**2 (7.7)**
Atorvastatin	6 (2.2)	2 (8.3)	3 (10.7)	2 (7.7)
Anilides	**18 (6.5)**	**1 (4.2)**	**1 (3.6)**	**2 (7.7)**
Paracetamol	11 (3.9)	1 (4.2)	1 (3.6)	2 (7.7)
Platelet aggregation inhibitors excluding heparin	**19 (6.8)**	**1 (4.2)**	**2 (7.1)**	**3 (11.5)**
Acetylsalicylic acid	18 (6.5)	1 (4.2)	2 (7.1)	3 (11.5)
Clopidogrel bisulfate	2 (0.7)	0	0	1 (3.8)
Prasugrel hydrochloride	1 (0.4)	0	0	1 (3.8)

Abbreviations: ATC = Anatomical Therapeutic Chemical; HMG CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; NAION = nonarteritic anterior ischaemic optic neuropathy; WHO = World Health Organization.

Notes: Only medications in the listed ATC Level 4 terms that were reported taken by >10% of subjects in either the adjudication-confirmed NAION set or the 30-day, 42-day, or 12-month analysis sets are included in this table. Medications are coded using WHO Drug Dictionary, version September 2015. Data are sorted in order of decreasing frequency by the 30-day analysis set. The denominator of each percentage is the number of subjects in the population. A subject was counted only once in the numerator for each ATC class and once in the numerator for each preferred term.

[a] These drugs were not on demand and were erroneously reported on the 42-day case report form.

Source: Table 5.

The most frequently reported medications taken within 12 months before IDO were mostly similar across the 30-day, 42-day, and 12-month analysis sets, with some differences in the 12-month analysis set (Table LVHQ.10.11).

During the 12 months before IDO, only 1 subject (Subject [redacted], who was included in each of the 30-day, 42-day, and 12-month analysis sets) reported taking a medication that was determined by the investigator to be related to conditions associated with PDE5 inhibitor use. For this subject, the investigator designated 11 medications as related to conditions associated with PDE5 inhibitor use), including metoprolol succinate, metoprolol tartrate, testosterone gel, losartan potassium, amiodarone, prednisone, rosuvastatin, ibuprofen, aspirin, and furosemide (Table 8).

Table LVHQ.10.11. Frequently Reported (>10% of Subjects in an Analysis Set) Medications Taken within 12 Months before Index Date of Onset

ATC Level 4 Term Preferred Term (ATC Level 5 Term)	Adjudication-Confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
At least 1 medication 12 months before IDO	**261 (93.5)**	**24 (100.0)**	**28 (100.0)**	**24 (92.3)**
HMG CoA reductase inhibitors	**107 (38.4)**	**10 (41.7)**	**13 (46.4)**	**13 (50.0)**
Atorvastatin	18 (6.5)	3 (12.5)	4 (14.3)	2 (7.7)
Atorvastatin calcium	28 (10.0)	1 (4.2)	2 (7.1)	5 (19.2)
Pravastatin	13 (4.7)	1 (4.2)	1 (3.6)	1 (3.8)
Pravastatin sodium	4 (1.4)	1 (4.2)	1 (3.6)	0
Rosuvastatin calcium	15 (5.4)	3 (12.5)	3 (10.7)	2 (7.7)
Simvastatin	24 (8.6)	1 (4.2)	2 (7.1)	3 (11.5)
Caduet[a]	3 (1.1)	0	0	1 (3.8)
Multivitamins, plain	**44 (15.8)**	**8 (33.3)**	**9 (32.1)**	**5 (19.2)**
Vitamins NOS	44 (15.8)	8 (33.3)	9 (32.1)	5 (19.2)
Other lipid modifying agents	**48 (17.2)**	**8 (33.3)**	**8 (28.6)**	**3 (11.5)**
Fish oil	39 (14.0)	7 (29.2)	7 (25.0)	2 (7.7)
ω-3-acid ethyl ester	4 (1.4)	1 (4.2)	1 (3.6)	1 (3.8)
Platelet aggregation inhibitors excluding heparin	**110 (39.4)**	**8 (33.3)**	**10 (35.7)**	**10 (38.5)**
Acetylsalicylic acid	105 (37.6)	8 (33.3)	10 (35.7)	10 (38.5)
Clopidogrel bisulfate	12 (4.3)	0	0	1 (3.8)
Prasugrel hydrochloride	3 (1.1)	0	0	1 (3.8)
Propionic acid derivatives	**48 (17.2)**	**6 (25.0)**	**6 (21.4)**	**5 (19.2)**
Ibuprofen	33 (11.8)	6 (25.0)	6 (21.4)	5 (19.2)
Vitamin D and analogues	**34 (12.2)**	**5 (20.8)**	**5 (17.9)**	**5 (19.2)**
Vitamin D NOS	20 (7.2)	5 (20.8)	5 (17.9)	5 (19.2)
3-oxoandrosten (4) derivatives	**16 (5.7)**	**4 (16.7)**	**5 (17.9)**	**5 (19.2)**
Testosterone	11 (3.9)	4 (16.7)	5 (17.9)	5 (19.2)
Proton pump inhibitors	**64 (22.9)**	**4 (16.7)**	**4 (14.3)**	**6 (23.1)**
Omeprazole	47 (16.8)	3 (12.5)	3 (10.7)	4 (15.4)
Pantoprazole	4 (1.4%)	1 (4.2)	1 (3.6)	1 (3.8)
Anilides	**25 (9.0)**	**4 (16.7)**	**4 (14.3)**	**3 (11.5)**
Paracetamol	16 (5.7)	3 (12.5)	3 (10.7)	2 (7.7)
Thomapyrin N	3 (1.1)	1 (4.2)	1 (3.6)	1 (3.8)
Beta blocking agents, selective	**41 (14.7)**	**4 (16.7)**	**4 (14.3)**	**4 (15.4)**
Metoprolol	16 (5.7)	2 (8.3)	2 (7.1)	2 (7.7)
Metoprolol succinate	4 (1.4)	1 (4.2)	1 (3.6)	1 (3.8)
Metoprolol tartrate	5 (1.8)	2 (8.3)	2 (7.1)	1 (3.8)

Frequently Reported (>10% of Subjects in an Analysis Set) Medications Taken within 12 Months before Index Date of Onset

ATC Level 4 Term Preferred Term (ATC Level 5 Term)	Adjudication-Confirmed NAION Set (N = 279) n (%)	30-Day Analysis Set (N = 24) n (%)	42-Day Analysis Set (N = 28) n (%)	12-Month Analysis Set (N = 26) n (%)
ACE inhibitors, plain	**49 (17.6)**	**3 (12.5)**	**5 (17.9)**	**2 (7.7)**
Lisinopril	34 (12.2)	2 (8.3)	3 (10.7)	1 (3.8)
Ramipril	5 (1.8)	1 (4.2)	2 (7.1)	1 (3.8)
Adrenergics in combination with corticosteroids	**12 (4.3)**	**3 (12.5)**	**3 (10.7)**	**4 (15.4)**
Fluticasone propionate with salmeterol	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Seretide[b]	9 (3.2)	2 (8.3)	2 (7.1)	2 (7.7)
Alpha-adrenoreceptor antagonists	**30 (10.8)**	**3 (12.5)**	**3 (10.7)**	**2 (7.7)**
Doxazosin	4 (1.4)	1 (4.2)	1 (3.6)	0
Tamsulosin	8 (2.9)	1 (4.2)	1 (3.6)	1 (3.8)
Tamsulosin hydrochloride	8 (2.9)	1 (4.2)	1 (3.6)	1 (3.8)
Biguanides	**39 (14.0)**	**3 (12.5)**	**5 (17.9)**	**3 (11.5)**
Metformin	36 (12.9)	3 (12.5)	5 (17.9)	2 (7.7)
Metformin hydrochloride	3 (1.1)	0	0	1 (3.8)
Glucocorticoids	**9 (3.2)**	**3 (12.5)**	**3 (10.7)**	**3 (11.5)**
Fluticasone propionate	1 (0.4)	1 (4.2)	1 (3.6)	0
Prednisone	5 (1.8)	2 (8.3)	2 (7.1)	2 (7.7)
Insulins and analogues for injection, long-acting	**10 (3.6)**	**3 (12.5)**	**3 (10.7)**	**2 (7.7)**
Insulin glargine	9 (3.2)	3 (12.5)	3 (10.7)	2 (7.7)
Other anti-inflammatory and antirheumatic agents	**16 (5.7)**	**3 (12.5)**	**3 (10.7)**	**1 (3.8)**
Chondroitin with glucosamine	8 (2.9)	2 (8.3)	2 (7.1)	1 (3.8)
Nabumetone	1 (0.4)	1 (4.2)	1 (3.6)	0
Salicylic acid and derivatives	**10 (3.6)**	**3 (12.5)**	**3 (10.7)**	**2 (7.7)**
Acetylsalicylic acid	8 (2.9)	3 (12.5)	3 (10.7)	2 (7.7)
Anacin[c]	2 (0.7)	1 (4.2)	1 (3.6)	0
Fibrates	**11 (3.9)**	**2 (8.3)**	**3 (10.7)**	**3 (11.5)**
Fenofibrate	7 (2.5)	2 (8.3)	3 (10.7)	2 (7.7)
Gemfibrozil	3 (1.1)	0	0	1 (3.8)
Sulfonylureas	**18 (6.5)**	**2 (8.3)**	**3 (10.7)**	**2 (7.7)**
Glipizide	9 (3.2)	2 (8.3)	3 (10.7)	2 (7.7)
Unknown	**28 (10.0)**	**2 (8.3)**	**2 (7.1)**	**4 (15.4)**
All other therapeutic products	3 (1.1)	1 (4.2)	1 (3.6)	1 (3.8)
Fibre, dietary	1 (0.4)	1 (4.2)	1 (3.6)	1 (3.8)
Selective serotonin reuptake inhibitors	**29 (10.4)**	**1 (4.2)**	**1 (3.6)**	**1 (3.8)**
Escitalopram oxalate	3 (1.1)	1 (4.2)	1 (3.6)	1 (3.8)
Angiotensin II antagonists, plain	**28 (10.0)**	**1 (4.2)**	**1 (3.6)**	**2 (7.7)**
Losartan potassium	7 (2.5)	1 (4.2)	1 (3.6)	2 (7.7)
Dihydropyridine derivatives	**29 (10.4)**	**0**	**1 (3.6)**	**2 (7.7)**
Amlodipine besilate	12 (4.3)	0	1 (3.6)	1 (3.8)

Frequently Reported (>10% of Subjects in an Analysis Set) Medications Taken within 12 Months before Index Date of Onset

Abbreviations: ATC = Anatomical Therapeutic Chemical; HMG CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; NAION = nonarteritic anterior ischaemic optic neuropathy; NOS = not otherwise specified; WHO = World Health Organization.

Notes: Only medications in the listed ATC Level 4 terms that were reported taken by >10% of subjects in either the adjudication-confirmed NAION set, or the 30-day, 42-day, or 12-month analysis sets are included in this table. Medications are coded using WHO Drug Dictionary version September 2015. Data are sorted in order of decreasing frequency for the 30-day analysis set. The denominator of each percentage is the number of subjects in the population. A subject was counted only once in the numerator for each ATC class and once in the numerator for each preferred term.

[a] Amlodipine besylate/atorvastatin calcium.

[b] Fluticasone propionate/salmeterol xinafoate.

[c] Acetylsalicylic acid/caffeine.

Source: Table 7.

10.2.7. NAION Risk Factors

Several medications, medical conditions, and medical events have been associated with NAION and are listed in Protocol H6D-MC-LVHQ(b) (Appendix 1) (Section 9.9.3). None of the risk factors were present in the 30-day, 42-day, and 12-month analysis sets, and low numbers were seen in the adjudication-confirmed NAION set.

10.3. Outcome Data

In this case-crossover design, the primary outcome of interest is adjudication-confirmed NAION. Subjects were included in 1 or more of the 30-day, 42-day, and 12-month analysis sets if they had adjudication-confirmed NAION and exposure in the appropriate time periods (in addition to meeting the other condition of the analysis sets). The adjudication-confirmed NAION set was the basis from which the analysis sets were drawn, and this set included all subjects with adjudication-confirmed NAION with or without PDE5 inhibitor use.

10.4. Main Results

10.4.1. Primary Analysis

Table LVHQ.10.12 presents results of the primary analysis and 3 sensitivity analyses evaluating the risk of NAION associated with PDE5 inhibitor use in the 30-day analysis set.

The primary analysis for this study evaluated the risk of NAION associated with PDE5 inhibitor exposure in the 30 days before IDO, specifically comparing PDE5 inhibitor exposure in the 30 days before IDO by exposed case definition (ie, exposure immediately before IDO within the hazard period). Exposure was quantified in days as 5 times the PDE5 inhibitor half-life, using the person-time method, and the 30-day analysis set was used for this analysis. The Mantel-Haenszel RR for exposure to PDE5 inhibitors for exposed cases relative to nonexposed cases was 2.27 (95% CI: 0.99, 5.20), which was not indicative of a statistically significant difference.

The primary analysis included all 24 subjects, all with adjudication-confirmed NAION, in the 30-day analysis set. Of the 24, 11 subjects were exposed to a PDE5 inhibitor during the hazard period, and 13 subjects had no PDE5 inhibitor exposure in the hazard period. The 11 subjects who were exposed during the hazard period ('exposed cases') contributed 153 person-days of exposure and 177 unexposed person-days to the analysis. Two of the 11 exposed cases were intermittent users but were chronically exposed (on the basis of 5 PDE5 inhibitor half-lives), resulting in concordance between the hazard and all control periods. Because only discordant exposure can contribute to the person-time analysis, these 2 subjects were among the 153 person-days of exposure, but they did not contribute person-time to the analysis and did not affect the analytical results. The 13 cases in subjects who were not exposed during the hazard period ('unexposed cases') contributed 78 person-days of exposure and 312 unexposed person-days to the analysis.

Three sensitivity analyses that modified the exposure definition and analysis populations were conducted. In the first sensitivity analysis, PDE5 inhibitor exposure was defined on the basis of reported dosing days in the 30-day analysis set. An exposed case for this sensitivity analysis was classified on the basis of reported PDE5 inhibitor use (dosing day) in the hazard period. Because these were intermittent users and exposure was defined on the basis of the dosing day only, all 24 subjects were discordant pairs and contributed to the analysis. The Mantel-Haenszel RR was 2.84 (95% CI: 1.34, 6.04).

The 30-day modified analysis set was used in the second and third sensitivity analyses to account for unknown medication type, and a statistically significant increase in risk was seen in both. When the unknown medication was imputed as tadalafil, the Mantel-Haenszel RR was 2.55 (95% CI: 1.14, 5.73). When the unknown medication was imputed as sildenafil, the Mantel-Haenszel RR was 2.59 (95% CI: 1.17, 5.73). The 30-day modified analysis set included only 1 additional subject: this was a subject who switched from sildenafil to vardenafil and could not remember which one he had taken on 1 of the dosing days (and was thus excluded from the primary analysis). Had the patient remembered which of the 2 drugs had been taken, the primary analysis results would be the same as seen in this sensitivity analysis.

Although the primary analysis results did not reach statistical significance, the 3 sensitivity analyses did suggest a potential increase in the risk of NAION associated with PDE5 inhibitor exposure in hazard period before IDO. In summary, the person-time analyses conducted in the 30 days before NAION onset suggested that there may be an increased risk of NAION associated with PDE5 inhibitor exposure in the hazard period immediately preceding NAION onset.

Table LVHQ.10.12. Primary Analysis and 3 Sensitivity Analyses Evaluating the Risk of NAION Associated with PDE5 Inhibitor Use in the 30 Days before Index Date of Onset

	Unexposed Cases	Exposed Cases	Total	Rate Ratio (95% CI)
Primary analysis[a]				
NAION events	13	11	24	
Person-days exposed	78	153	231	
Person-days unexposed	312	177	489	2.27 (0.99, 5.20)
Sensitivity analysis 1[b]				
NAION events	15	9	24	
Person-days exposed	70	71	141	
Person-days unexposed	380	199	579	2.84 (1.34, 6.04)[c]
Sensitivity analysis 2[d]				
NAION events	13	12	25	
Person-days exposed	78	161	239	
Person-days unexposed	312	199	511	2.55 (1.14, 5.73)[c]
Sensitivity analysis 3[e]				
NAION events	13	12	25	
Person-days exposed	78	158	236	
Person-days unexposed	312	202	514	2.59 (1.17, 5.73)[c]

Abbreviations: CI = confidence interval; NAION = nonarteritic anterior optic neuropathy; PDE5 = phosphodiesterase type 5.

Note: Subjects representing concordant pairs do not contribute to the rate ratio (person-time) analyses.

[a] Exposure based on effect period; 30-day analysis set.

[b] Exposure based on dosing days; 30-day analysis set.

[c] Statistically significant.

[d] Exposure based on effect period, unknown PDE5 inhibitor imputed as tadalafil; 30-day modified analysis set.

[e] Exposure based on effect period, unknown PDE5 inhibitor imputed as sildenafil; 30-day modified analysis set.

Sources: Table 17, Table 18, Table 19, Table 20.

10.4.2. Secondary Analyses

10.4.2.1. Person-Time Analysis, 12 Months before the Index Date of Onset

Table LVHQ.10.13 presents results from a secondary analysis and 2 sensitivity analyses evaluating the risk of NAION associated with PDE5 inhibitor use in the 12 months before IDO. For all 3 of the analyses, the Mantel-Haenszel RR suggested a statistically significant increased risk.

A secondary analysis was conducted evaluating the risk of NAION associated with PDE5 inhibitor exposure in the 12 months before IDO, specifically comparing PDE5 inhibitor exposure in the 12 months before IDO by exposed-case definition (ie, exposure immediately before the IDO within the hazard period). Exposure was classified on the basis of the PDE5 inhibitor effect period, using the person-time method. The 12-month analysis set was used for this analysis and

associated sensitivity analyses, and the same statistical methods as the 30-day person-time analysis (primary analysis). The Mantel-Haenszel RR for exposure to PDE5 inhibitors for exposed cases relative to unexposed cases was 3.52 (95% CI: 1.59, 7.79), and this was statistically significant. One of the 13 exposed cases was a concordant pair and did not contribute to the analysis.

Two person-time sensitivity analyses were conducted and both suggest a statistically significant increase in the risk of NAION associated PDE5 inhibitor exposure (Table LVHQ.10.13). First, exposure was defined on the basis of PDE5 inhibitor dosing days in the 12 months before IDO (Mantel-Haenszel RR: 7.07 [95% CI: 2.79, 17.94]). Secondly, using the 12-month modified analysis set, missing data on PDE5 inhibitor frequency was imputed as average monthly use and exposure was defined on the basis of effect period (Mantel-Haenszel RR: 3.73 [95% CI: 1.75, 7.95]).

Overall, secondary analyses using the person-time 12-month method were consistent with the overall conclusion from the primary analysis (and associated sensitivity analyses) and revealed a statistically significant association between PDE5 inhibitor exposure and NAION.

Table LVHQ.10.13. Secondary Analysis and 2 Sensitivity Analyses Evaluating the Risk of NAION Associated with PDE5 Inhibitor Use in the 12 Months before Index Date of Onset

	Unexposed Cases	Exposed Cases	Total	Rate Ratio (95% CI)
Secondary analysis[a]				
NAION events	13	13	26	
Person-days exposed	891	1613	2504	
Person-days unexposed	3855	3134	6989	3.52 (1.59, 7.79)
Sensitivity analysis 1[b]				
NAION events	14	12	26	
Person-days exposed	496	874	1370	
Person-days unexposed	4615	3508	8123	7.07 (2.79, 17.94)
Sensitivity analysis 2[c]				
NAION events	16	16	32	
Person-days exposed	1035	1978	3013	
Person-days unexposed	4806	3865	8671	3.73 (1.75, 7.95)

Abbreviations: CI = confidence interval; NAION = nonarteritic anterior ischaemic optic neuropathy; PDE5 = phosphodiesterase type 5.

Note: Subjects representing concordant pairs do not contribute to the rate ratio (person-time) analyses.

[a] Exposure based on effect period; 12-month analysis set.

[b] Exposure based on dosing days; 12-month analysis set.

[c] Exposure based on effect period with missing PDE5 inhibitor imputed as subject's monthly average; 12-month modified analysis set.

Sources: Table 21 (note that this table should be headed 'Secondary Analysis' and not, as it is incorrectly headed, 'Sensitivity Analysis'), Table 22, Table 23.

10.4.2.2. Matched-Interval Analysis

A secondary analysis, using the matched-interval method and 4-day hazard and control periods, was conducted to evaluate the risk of NAION associated with PDE5 inhibitor use in the 42-day analysis set (Table LVHQ.10.14). The hazard ratio estimate was 1.64 (95% CI: 0.60, 4.51). These results are not suggestive of an association between PDE5 inhibitor exposure and NAION.

Of the 28 subjects in the 42-day analysis set, 15 (53.6%) were exposed to PDE5 inhibitors during the hazard period. Fourteen (50%) of the 28 subjects were exposed in control interval 1; 15 (53.6%) in control interval 2; 11 (39.3%) in control interval 3; and 11 (39.3%) in control interval 4. Six subjects were concordant pairs because they had exposure in all 4 control periods and the hazard period (exposure days had at least 1 day overlapping with each of all 4 controls periods and the hazard period).

It was intended that this model would control for time-varying factors (Section 9.9.4.2.2); however, there were no subjects with these risk factors in the 42-day analysis set.

Seven sensitivity analyses were conducted in the 42-day analysis set (Section 9.9.7.3), which modified the duration of the hazard and control periods and the number of control periods included in the model (Table LVHQ.10.14).

In the 3 sensitivity analyses with modified control period lengths, results similar to the secondary analysis (4-day control periods) were seen. Using 1-, 2-, 3-, and 7-day control periods, the hazard ratio estimates ranged from 1.22 to 2.23 and were not statistically significant. Similarly, in the 4 sensitivity analyses using varied control periods, the hazard ratio estimates ranged from 1.09 to 1.42, and none were statistically significant.

In summary, the results from the secondary analyses using the matched-interval are not suggestive of an association between PDE5 inhibitors and NAION.

Table LVHQ.10.14. Secondary Analysis and 7 Sensitivity Analyses Using a Matched-Interval Approach and Exposure Based on Effect Period in the 42-Day Analysis Set

	Hazard Ratio Estimate	95% Confidence Interval	Wald p-Value
Secondary analysis			
4-day hazard and control periods	1.64	0.60, 4.51	0.33
Sensitivity analyses			
Varying duration of control periods			
1-day hazard and control periods	1.22	0.31, 4.77	0.78
2-day hazard and control periods	1.71	0.46, 6.33	0.42
3-day hazard and control periods	1.70	0.56, 5.16	0.35
7-day hazard and control periods	2.23	0.85, 5.86	0.10
Varying number of control periods			
1st 4-day control period	1.17	0.39, 3.47	0.78
1st and 2nd 4-day control period	1.09	0.40, 2.98	0.86
1st, 2nd, and 3rd 4-day control period	1.42	0.51, 3.99	0.50

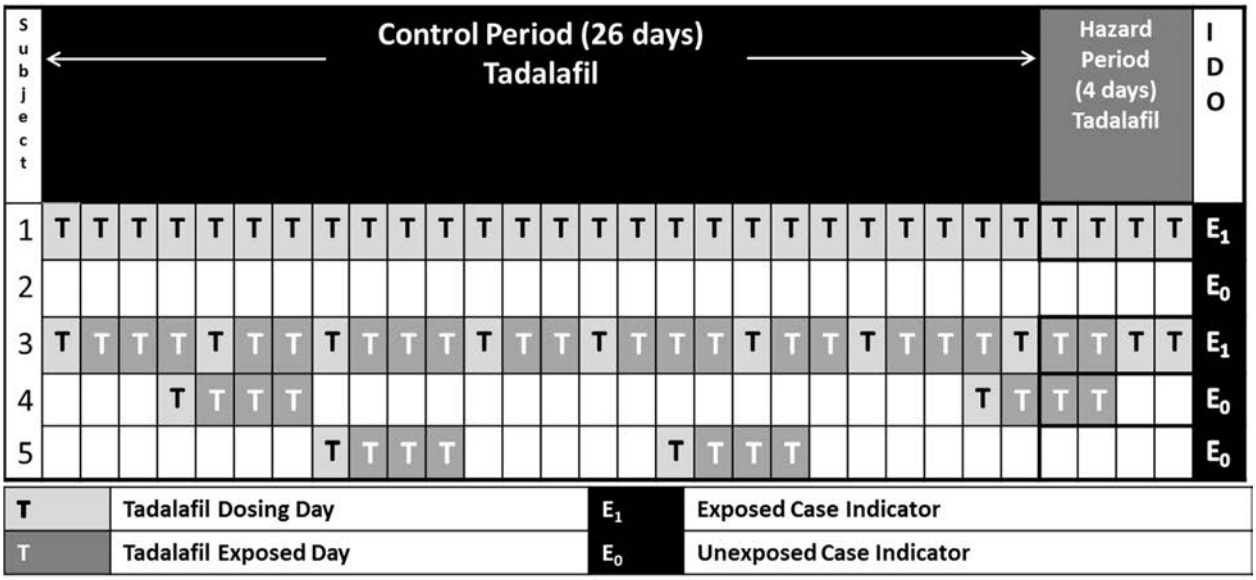
Note: Subjects representing concordant pairs do not contribute to the hazard ratio estimate in the matched-interval analyses.

Sources: Table 24, Table 25, Table 26, Table 27, Table 28, Table 29, Table 30, Table 31.

10.5. Other Analyses

The primary analysis conducted used a conservative estimate of an exposed case, particularly for tadalafil users, as illustrated in Figure LVHQ.9.2. A direct comparison of the results of Study LVHQ with Campbell et al. (2015) was not possible because the definition applied in the primary analysis by Campbell et al. (2015) compared PDE5 inhibitor exposure in the day before NAION onset with exposure in the 29 preceding days (all PDE5 inhibitor exposed cases had reported taking a PDE5 inhibitor within 5 half-lives of NAION onset). Therefore, to enable a better comparison of the results of Study LVHQ with those of the Pfizer-sponsored study (Campbell et al. 2015), a post-hoc analysis was conducted to evaluate the risk of NAION associated with PDE5 inhibitor *use* (dosing day) reported in the hazard period as opposed to PDE5 inhibitor *exposure* occurring in the hazard period.

This modification to the primary analysis affects the definition of an exposed case for tadalafil users. To illustrate, Subject 4 in Figure LVHQ.10.8 (modified from Figure LVHQ.9.2) would be classified as an exposed case in the primary analysis on the basis of tadalafil *exposure* extending into in the hazard period; however, in the post-hoc analysis he would be classified as an unexposed case because of his tadalafil *use* occurring outside the hazard period.



Abbreviations: IDO = index date of onset.

Figure LVHQ.10.8. Illustration of case indicators for hypothetical subjects, 4 of whom were tadalafil users in the post-hoc analyses.

Post-hoc analyses of the primary analysis and 2 sensitivity analyses in the 30-day analysis set and the secondary analysis and sensitivity analysis of the 12-month analysis set were conducted.

The post-hoc analysis of the primary analysis included all 24 subjects in the 30-day analysis set; of the 24 subjects, 9 used a PDE5 inhibitor during the hazard period and 15 reported no PDE5 inhibitor use in the hazard period. The Mantel-Haenszel RR for use of PDE5 inhibitors during the hazard period relative to the control period was increased (1.41; 95% CI: 0.60, 3.31), although it was not a statistically significant result. The results of the 2 sensitivity analyses in the 30-day modified analysis set that imputed the unknown medication as tadalafil and then sildenafil/vardenafil were also not statistically significant.

A post-hoc analysis of the secondary analysis of the 12-month analysis set and the associated sensitivity analyses was conducted. The Mantel-Haenszel RR for use of PDE5 inhibitors during the hazard period relative to control period was 2.85 (95% CI: 1.31, 6.20), and this was statistically significant, although lower than the original secondary analysis (RR = 3.52, 95% CI: 1.59, 7.79). These post-hoc analyses using the 12-month analysis set were suggestive of an association between PDE5 inhibitor use and NAION onset, and these results were statistically significant.

Overall, the post-hoc analyses results showed an attenuation of this association compared with the protocol-designated analyses.

10.6. Adverse Events/Adverse Reactions

This study was an observational case-crossover study specifically intended to evaluate the possible association between the use of PDE5 inhibitors (sildenafil, tadalafil, and vardenafil) and the risk of acute NAION. This study was not intended to evaluate the general safety profile of

PDE5 inhibitors, thus only adverse events pertaining to NAION were collected and analysed because this was the primary objective of the study. Subjects with adjudication-confirmed NAION and PDE5 inhibitor exposure were reported to the manufacturers of each of the PDE5 inhibitors. If investigators participating in this study suspected any adverse drug reactions that were not related to NAION or product complaints with PDE5 inhibitors, they were instructed to report these to the FDA and/or to the appropriate compound manufacturer as they would in normal practice, taking into account applicable local laws, regulations, and practices.

No analysis of the general safety profile of PDE5 inhibitors was conducted for this study.

11. Discussion

11.1. Key Results

This study included subjects who had taken tadalafil, sildenafil, or vardenafil; therefore the results are considered applicable to the entire class of PDE5 inhibitors. The primary (person-time) analysis suggested an increased risk of NAION associated with PDE5 inhibitor exposure within 5 half-lives before IDO; however, the results were not statistically significant. Although the lower bound of the CI was very close to 1.0, this analysis failed to conclusively establish an association between the use of PDE5 inhibitors and the occurrence of NAION. A series of 3 sensitivity analyses was conducted, and the results were statistically significant, suggesting a potential increase in the risk of NAION associated with PDE5 inhibitor exposure.

Results from the person-time analysis evaluating PDE5 inhibitor exposure in the 12 months before IDO suggest an increased risk of NAION associated with exposure to PDE5 inhibitors (within 5 half-lives before IDO). Two sensitivity analyses were conducted and were also suggestive of an increased risk. The results of all 3 of these analyses were statistically significant.

The results of the matched-interval analyses do not suggest that there is an association between PDE5 inhibitor exposure and NAION. However, their relatively lower statistical power to detect such association compared with the power of the primary analysis needs to be taken into account. In this study, sample size was calculated for the primary person-time analysis. In the matched-interval analysis, concordance of exposure in the hazard and control periods was greater; therefore the statistical power of this analysis is reduced. Seven sensitivity analyses were conducted, and none of the results were statistically significant.

In summary, results of the primary analysis were not statistically significant; however, the results of both the main (primary and secondary) and sensitivity person-time analyses are suggestive of an increased risk of NAION occurring in association with PDE5 inhibitor exposure. The results from the secondary analysis using the matched-interval approach do not suggest an association between PDE5 inhibitor exposure and NAION. In addition, the results of post-hoc person-time analyses were attenuated when the exposed case was defined on the basis of PDE5 inhibitor use rather than exposure in the hazard period.

11.2. Limitations

Although the case-crossover study design has several advantages over other designs, it is subject to limitations. In this study, limitations involved inherent issues in case-crossover methods; the low incidence of NAION, which affected study duration, sample size, and power; and potential sources of bias.

11.2.1. Case-Crossover Design

The case crossover is best applied when the exposure under study is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt. Because of the assumptions of the case-crossover design, the results of this analysis are not applicable to daily users of PDE5

inhibitors for erectile dysfunction/benign prostatic hyperplasia or pulmonary arterial hypertension. The results are also subject to the assumptions that 5 half-lives of the PDE5 inhibitor is the relevant effect period and that the hazard and control periods are appropriately selected.

In the protocol-specified analyses, a conservative approach was taken to defining an exposed case; exposure was defined as 5 half-lives of the PDE5 inhibitor (after the dosing day). Therefore, a tadalafil user would be considered an 'exposed case' even if the dosing day was up to 3 days before the hazard period (or 7 days before IDO). When the definition of an exposed case is based on dosing day (day of use) occurring in the hazard period, this hypothetical subject would be considered an 'unexposed case'. This latter definition of an exposed case was used in sensitivity analysis 1 of the primary analysis and the post-hoc analysis; for illustration see Figure LVHQ.10.8.

The limitations of selecting the assumptions in a case-crossover study are thus highlighted. The study findings were subject to change based on the method of ascertaining an exposed case, as illustrated from the post-hoc analysis (ie, an exposed case in which the subject reported using a PDE5 inhibitor in the hazard period). In the post-hoc analyses the association was attenuated. Hence it could be argued that the resulting estimate of relative risk within the primary analysis using the more conservative approach of defining an exposed case would likely overestimate the actual risk.

11.2.2. Study Duration

This study took over 5 years to complete. During this time, prescribing patterns and use of PDE5 inhibitors changed, in part because of the approval of new indications for once-daily use. In this study, daily users of PDE5 inhibitors were enrolled; however, with the case-crossover methods used, they did not contribute data in the analyses, and this is a limitation of the study design.

NAION is a rarely occurring disease with an estimated annual incidence of 2.5 to 11.8 cases per 100,000 in men aged 50 and older (Johnson and Arnold 1994; Hattenhauer et al. 1997). Therefore the prospective enrolment and adjudication of subjects with NAION was challenging and took a substantial amount of time and resources. Coincident with this study, 2 similar studies were also recruiting men with NAION in the United States (NCT00759174 and NCT00867815); consequently, this study took longer than expected to complete. It must also be acknowledged that this study population may be similar to that of the other 2 studies because some of the same sites were used to enrol patients.

The prevalence of PDE5 inhibitor use in men who were later diagnosed with NAION was found to be quite low. Since 2006, the US package insert for all PDE5 inhibitors has included warning and precaution statements to prescribers and patients regarding the use of PDE5 inhibitors and the risk of NAION. As a result, prescribers have been aware of this risk and may have avoided prescribing PDE5 inhibitors to patients at risk for NAION; however, this cannot be verified. Only 16.1% (n = 45) of subjects with adjudication-confirmed NAION were PDE5 inhibitor users (of which 15 were chronic users) in the 30 days preceding IDO. Therefore the enrolment rate of

subjects with adjudication-confirmed NAION who contributed to the analysis was very low and had implications on the sample size and the time taken to complete the study.

11.2.3. Sample Size and Power

The absence of a precise method to evaluate sample size for this study design is a limitation and posed challenges. During the study, the initial assumptions regarding sample size were evaluated, leading to a determination that the original sample size requirements were too low and that enrolment needed to be extended. The sample size was reestimated to reflect what was observed in the subjects enrolled at that time, specifically, the PDE5 inhibitor exposure prevalence and correlation coefficient; details are provided in Section 9.7.

In the original sample size calculation, the assumption regarding the prevalence of PDE5 inhibitor use was not upheld mainly because of challenges discussed above—chronic use of PDE5 inhibitors and low prescribing rates in the population. Assumptions about the correlation coefficient were based on the degree of concordance in the hazard and control periods, and this was similarly difficult to predict. The method chosen to arrive at the revised sample size was that which most closely matched the person-time primary analysis method. However, this method resulted in inadequate power for the secondary matched-interval analyses—a limitation in this study.

11.2.4. Potential Sources of Bias

11.2.4.1. Selection Bias

Biased selection of cases may have been introduced if subjects with recent exposure to PDE5 inhibitors were more willing to participate in the study than subjects with NAION who decided not to participate (Maclure 1991). This may have occurred if subjects were aware of the potential association between NAION and PDE5 inhibitor use because of the warning and precaution in the label. Conversely, subjects may have been less willing to participate if they were uncomfortable discussing PDE5 inhibitor use. These aspects of selection bias are difficult to evaluate.

Selection of control periods may be a source of bias in a case-crossover study design (Sorock et al. 2001). Therefore this study used 2 different analytic methods, namely the person-time analysis and the matched-interval analysis. In addition, numerous sensitivity analyses were conducted for the primary and secondary analyses. In the matched-interval analysis, sensitivity analyses evaluated modifications in the duration of the control intervals and the number of control intervals included in the model. To the extent possible, the bias potentially introduced by inappropriate control selection was examined in sensitivity analyses.

11.2.4.2. Recall Bias

Recall bias may be particularly problematic for the recall of transient exposures (Redelmeier and Tibshirani 1997) and irregular exposures (Gmel and Daeppen 2007). Unlike a traditional case-control study in which recall bias can be substantial, all subjects in this study experienced

the event of NAION and exposure to PDE5 inhibitors, potentially diminishing recall bias within the analysis data sets.

In this study, exposure information about PDE5 inhibitor use and exposure to potential time-varying confounding variables was based exclusively on subject recall for the 42 days and 12 months before IDO. Day-by-day recall was limited to 42 days before IDO to account for decreasing accuracy of recall over time. Recall in the 12 months before IDO was poorer, requiring more imputations of missing data. In addition, multiple sensitivity analyses were conducted in the secondary (matched-interval) analysis to evaluate the effect of recall bias by varying control periods.

Some examples of poor recall were present in the study set. At least 2 subjects reported their PDE5 inhibitor use differently when reporting on the day-by-day recall for the 42 days before IDO and the 12 months before IDO. When identifying the 30-day analysis set for the primary analysis, 6 subjects had incomplete information about PDE5 inhibitor use (either missing date[s] or unknown PDE5 inhibitor used) and could not be included in the primary analysis. Only 1 of these 6 subjects was eligible for inclusion in sensitivity analyses because this subject could recall the date of PDE5 inhibitor use but not the particular PDE5 inhibitor product that was used (he had switched medications). The unknown medication was imputed as sildenafil and as tadalafil in 2 separate sensitivity analyses, and this moved the point estimates to statistical significance. Thus, in a study of this size, poor recall of exposure data from a single subject is a limitation and an additional subject in the analysis can influence the interpretation of the results.

This study may also have been subject to underreporting or failing to report prescribed medication or medical history by the subject. This is seen in the discrepancy between self-reported erectile dysfunction that occurred within 42 days and within 12 months before IDO among subjects who were intermittent users of PDE5 inhibitors (Section 10.2.5). This underreporting may be because of the sensitivity of reporting the condition in a face-to-face interview. This discrepancy did not affect the primary or secondary analyses; however, the degree of underreporting of other conditions is unknown.

11.2.4.3. Confounding

By design, time-invariant confounders are controlled for in the case-crossover study. While chronic conditions are generally time invariant, the severity and treatment could have varied over the study duration. This was addressed by collecting information about changes in chronic conditions and long-term medication use to evaluate the assumptions of time-invariant confounders (Section 9.6.2.1). An additional objective of matched-interval analyses was to adjust for time-varying confounders, occurring in the 42-day period before IDO, in a conditional logistic regression model. Because no time-varying confounders were identified in the enrolled and eligible subjects in the 42 days before IDO, the multivariate analyses were not conducted. Other factors related to lifestyle which may be time-varying, such as alcohol use, were not captured during the 42-day period for use in analyses.

11.3. Interpretation

11.3.1. Interpretation of Key Results

This study evaluated the risk of NAION associated with PDE5 inhibitor exposure using a case-crossover design. The primary analysis suggested that an association, perhaps as much as a doubling of risk (RR = 2.27, 95% CI: 0.99, 5.20), may exist. The finding of an increased risk cannot be conclusively determined because the results are not statistically significant. However the lower limit of the 95% CI is slightly under 1.0, and 3 sensitivity analyses resulted in a statistically significantly increased risk. To further evaluate the association between PDE5 inhibitor exposure and NAION, 2 secondary objectives were evaluated. First, a 12-month person-time analysis and 2 sensitivity analyses were conducted, and all indicated a statistically significant increase in risk. Second, matched-interval analyses were conducted, and the results were inconsistent with the person-time analyses; a statistically significant increase in risk was not seen.

One of the reasons for conducting the matched-interval analysis was to control for time-variant risk factors associated with NAION. None of the risk factors were present in the analysis sets; therefore these multivariate analyses were not feasible. A different interpretation was required for the matched-interval model; a statistically significantly increased risk was not observed, and this was replicated in several sensitivity analyses. However, the statistical power for the matched-interval analyses, compared with the person-time analyses, was limited.

The post-hoc analysis was consistent with the protocol-specified primary person-time analyses; results of both were not statistically significant but suggested an increased risk of NAION. The point estimates in the secondary 12-month person-time analyses were attenuated. The exposure definition differed between the 2 approaches. The approach used in the protocol-specified analyses defined an exposed case on the basis of the product's exposure extending into the hazard period, and the post-hoc analysis defined an exposed case on the basis of PDE5 inhibitor use (dosing day) occurring in the hazard period. This difference in exposure definition may have classified more subjects as exposed in the protocol-specified analyses potentially overestimating the association.

11.3.2. Strengths of the Study Design

Several elements of this study were included to address the potential for bias. By design, time-invariant confounders are controlled for in the case-crossover study. All subjects with physician-diagnosed NAION were reviewed and adjudicated by experts blinded to PDE5 inhibitor use, and only subjects with adjudication-confirmed NAION were eligible for inclusion in the analysis sets. A thorough structured interview was used to ascertain exact dates on which subjects used PDE5 inhibitors to improve the accuracy of exposure data in the hazard and control periods. Multiple analytical methods for quantifying control windows were used to support the primary analysis. Finally, study data were monitored for time-varying confounders so that they could be adequately addressed in the analysis.

11.3.3. Findings in the Context of Similar Studies

The person-time analyses in this study were suggestive of an association between exposure to PDE5 inhibitors and acute NAION onset. Overall, this result is consistent with the findings from Campbell et al. (2015); however, the methods in this study and Campbell et al. differed. Different exposure effect periods were used by Campbell et al. (2015) (5 days for tadalafil and 2 days for sildenafil/vardenafil) and in Study LVHQ (which used 4 days and 1 day, respectively). The hazard period (immediately before IDO) used in Study LVHQ differed (4 days and 1 day for tadalafil and sildenafil/vardenafil respectively) from the 1-day hazard period in the Campbell et al. (2015) study (ie, exposure was based on dosing day only). The statistical analyses methods were also different.

The results reported by Campbell et al. (2015) suggest an increased risk of NAION within 5 half-lives of PDE5 inhibitor *use* (OR = 2.15, 95% CI: 1.06, 4.34), defined as PDE5 inhibitor exposure on the day before NAION onset with the 29 preceding days (Campbell et al. 2015). Study LVHQ found an increased risk of NAION when exposed cases were defined on the basis of PDE5 inhibitor *exposure* (5 half-lives after reported dose) occurring within the hazard period. The post-hoc analysis conducted as part of Study LVHQ applied a definition of an exposed case more similar to that in the Campbell et al. (2015) study (the post-hoc analysis defined exposure on the basis of dosing day occurring in the hazard period). An attenuation of the RR was seen in the post-hoc analysis relative to the RR in the protocol-designated analyses. Findings from the post-hoc analysis must be interpreted with caution because the results were not statistically different from the protocol-designated analyses, and the post-hoc analysis probably had less statistical power.

Nathoo et al. (2015) found no association between PDE5 inhibitor use and NAION; however, that group conducted its analyses using routinely collected health insurance claims data, in which the diagnosis of NAION was not confirmed and the temporality of the association was subject to assumptions regarding exposure to PDE5 inhibitors.

11.3.4. Public Health Impact

NAION is a rarely occurring event; however, it appears that the combination of NAION and PDE5 inhibitor use is rarer. In the 345 subjects with physician-diagnosed NAION, 279 (80.9%) cases were adjudication-confirmed NAION, and only 16.1% (n = 45) of the patients with these cases were PDE5 inhibitor users. Prescribers have been informed of the risk of NAION associated with PDE5 inhibitor use since 2006 because of changes in product labelling. Therefore it is expected that the prescribing of PDE5 inhibitors to patients at increased risk for NAION may have decreased since 2006.

Campbell et al. (2015) estimated the absolute risk of NAION associated with intermittent PDE5 inhibitor use. Assuming once-per-week dosing, they estimated that use of a PDE5 inhibitor added 3 cases per 100,000 men aged 50 years or older per year. The risk of NAION related to daily use was not evaluated by Campbell et al. (2015) or in Study LVHQ.

It is anticipated that the evolving evidence will result in a thorough evaluation of underlying NAION risk factors before prescribing PDE5 inhibitors. The results of this study, the study published by Campbell et al. (2015), and the ongoing Bayer-sponsored study (estimated to be completed in February 2018) will provide further data to inform discussions between patients and their prescribers to reduce the risk of NAION.

11.4. Generalisability

The design of this case-crossover study, as already mentioned, limits its generalisability to the risk of NAION in subjects who use PDE5 inhibitors on an intermittent basis; it does not provide information on this risk in subjects who use these medicines continuously.

This study was conducted in 41 specialist sites in the United States. Geography and the selection of sites affect generalisability. Because subjects enrolled in this study were enrolled from specialist health care facilities in the United States, the enrolled subjects may not be reflective of all patients with NAION. However, with only 20 to 30 subjects included in the analyses, the effect of the selection bias on the results is unknown. Therefore, the study population may not be representative of individuals outside the United States and those with limited access to specialised health care.

Subjects participating in this study were reflective of the epidemiology of NAION; they were predominantly white, had a mean age of approximately 61 years, and were not Hispanic or Latino. In the primary analysis population, 23 of the 24 subjects were white (1 was of more than 1 race, and none were reported as black or Hispanic or Latino) and the 24 subjects in this population had a mean age of 61.8 years. The demographic characteristics of the primary analysis population were not markedly different from the demographics of the 279 subjects with adjudication-confirmed NAION from which the analysis population was drawn (95.7% Caucasian, 0.7% black, and 3.9% Hispanic or Latino). The demographic characteristics of the analysis populations may limit the generalisability of the results to younger men or to black or Hispanic or Latino men in the United States.

Other risk factors for NAION besides increasing age and Caucasian race include diabetes, hypertension, and hyperlipidaemia. These chronic diseases were observed in the 279 subjects with adjudication-confirmed NAION and in the subjects included in the analysis sets. Although the numbers were small, this suggested that the study population and the reference population had similar comorbidities.

12. Other Information

Not applicable.

13. Conclusion

The results of this study should be interpreted in the context of existing information on NAION. Overall, this study suggests an increased risk of NAION associated with PDE5 inhibitor exposure. The increased risk was demonstrated when using person-time analyses over a 30-day and 12-month period before onset of acute NAION. Although the primary analysis was not statistically significant, all secondary and sensitivity analyses suggested a statistically significantly increased risk for NAION related to PDE5 inhibitor exposure. The overall conclusions of this study are consistent with those of Campbell et al. (2015), although the assumptions and study design were different, and Study LVHQ took a more conservative approach to classifying an exposed case.

The clinical implications of this study are consistent with the tadalafil prescribing information (Cialis prescribing information 2015). Physicians should advise patients to stop using PDE5 inhibitors and seek medical attention in the event of a sudden loss of vision in one or both eyes. Physicians should consider whether their patients with underlying NAION risk factors could be adversely affected by use of PDE5 inhibitors. Individuals who have already experienced NAION are at increased risk of NAION recurrence. Therefore, PDE5 inhibitors should be used with caution in these patients and only when the anticipated benefits outweigh the risks. Individuals with 'crowded' optic discs are also considered at greater risk than the general population for NAION; however, evidence is insufficient to support screening of prospective users of PDE5 inhibitors, including Cialis, for this uncommon condition.

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Annex 1. List of Standalone Documents

The following documents can be provided on request:

Number	Document Reference No	Date	Title
1.	Not applicable	06 June 2014	Observational Study Description H6D-MC-LVHQ(b): A Prospective Case-Crossover Study to Evaluate the Possible Association Between the Use of PDE5 Inhibitors and the Risk of Acute Nonarteritic Anterior Ischemic Option Neuropathy (NAION)
2.	Not applicable	09 November 2014	Statistical Analysis Plan, Version 2.0

Annex 2. Additional Information

Adjudication Committee Members:

Member	Specialty	Address
[redacted], MD	Neuro-ophthalmology	Department of Neurology and Ophthalmology Michigan State University 138 Service Road, Suite A-217 East Lansing, MI 48824
[redacted], MD	Neuro-ophthalmology	University of Pennsylvania School of Medicine D603 Richards Building 3700 Hamilton Walk Philadelphia, PA 19104-6075
[redacted], MD	Neuro-ophthalmology	27450 Schoenherr Road Warren, MI 48088

Participating Sites:

Address Type	Site Name	Site Address
Clinic	Neuro-Ophthalmic Services	3535 West 13 Mile Road, Suite 606 Royal Oak, MI 48073
Clinic	North Bay Eye Associates, Inc.	104 Lynch Creek Way, Suite 12 Petaluma, CA 94954
Clinic	Black Hills Regional Eye Institute	2800 3rd Street Rapid City, SD 57701
Clinic	JFK Medical Center New Jersey Neurosciences Institute	65 James Street Edison, NJ 08818
Academic/University	Albert Einstein College of Medicine Montefiore Medical Center Moses Research Tower	111 East 210th Street Centennial Building, 3rd Floor Bronx, NY 10467
Academic/University	Clinical Research Center of Wheaton Eye Clinic	2015 North Main Street Wheaton, IL 60187
Clinic	Pacific Eye Associates	2100 Webster Street, Suite 214 San Francisco, CA 94115
Clinic	E.K. Harkness Eye Institute	635 West 165th Street, Suite 304 New York, NY 10032
Clinic	Medical Center Ophthalmology Associates	9157 Huebner Road San Antonio, TX 78240
Clinic	Retina Consultants	3531 Mary Ader Avenue, Building D Charleston, SC 29414
Clinic	Chattanooga Eye Institute	5715 Cornelson Road, Building 6600 Chattanooga, TN 37421
Clinic	Eye Surgical and Medical Associates, Inc.	5021 West Noble Avenue, Suite A Visalia, CA 93327
Clinic	Michigan Neuro-Ophthalmology	27450 Schoenher Road, Suite 500 Warren, MI 48088

Address Type	Site Name	Site Address
Clinic	Sarasota Retina Institute	3400 Bee Ridge Road, Suite 200 Sarasota, FL 34239
Clinic	Northshore Eye and Vision Center	2050 Pfingston Road, Suite 280 Glenview, IL 60026
Clinic	Great Lakes Eye Institute	2393 Schust Road Sagina, MI, 48603
Clinic	Bethesda Neurology, LLC	7830 Old Georgetown Road, Suite C-20 Bethesda, MD 20814
Academic/University	University of Illinois at Chicago Department of Ophthalmology and Visual Sciences	1855 W. Taylor Street, M/C 648 Chicago, IL 60612
Clinic	Midwest Eye Institute	200 West 103rd Street, Suite 1000 Indianapolis, IN 46290
Clinic	Paducah Retinal Center	1900 Broadway, Suite 2 Paducah, KY 42001
Academic/University	University of Utah Health Sciences Center Moran Eye Center	65 Mario Capecchi Drive Salt Lake City, UT 84132
Clinic	Florida Retina Consultants	2202 Lakeland Hills Boulevard Lakeland, FL 33805
Clinic	Longwood Medical Eye Center	330 Brookline Avenue, Shapiro 5 Boston, MA 02215
Clinic	The Methodist Hospital Research Institute	6565 Fannin Street Houston, TX 77030
Academic/University	UW Medical Center	Box 359608 325 9th Avenue Seattle, WA 98104
Academic/University	University of Kentucky Department of Neurology Kentucky Clinic	740 South Limestone Street, Suite L445 Lexington, KY 40535
Academic/University	University of Florida	219 Grinter Hall Gainesville, FL 32611
Academic/University	University of Pennsylvania Scheie Eye Institute	51 North 39th Street Philadelphia, PA 19104
Clinic	Swedish Neuroscience Research	550 16th Avenue, Suite 303 Seattle, WA 98122
Academic/University	University of Miami	900 NW 17th Street Miami, FL 33180
Clinic	USF Eye Institute	13127 USF Magnolia Drive Tampa, FL 33612
Academic/University	Ohio State University Department of Ophthalmology	915 Olentangy River Road, Suite 5000 Columbus, OH 43210
Academic/University	University of Minnesota Department of Ophthalmology and Visual Neuroscience	420 Delaware Street, SE, MMC 493 Minneapolis, MN 55455
Academic/University	Saint Louis University	1465 South Grand Boulevard St Louis, MO 63104
Clinic	Neuro-Ophthalmology of Texas	2501 West Holcombe Boulevard, Suite G Houston, TX 77030

Address Type	Site Name	Site Address
Clinic	Allegheny Ophthalmic and Orbital Associates	420 East North Avenue, Suite 116 Pittsburgh, PA 15212
Clinic	Family Eye Care	2110 Harris Pike Lancaster, PA 17601
Academic/University	Stony Brook University	33 Research Way, Suite 13 East Setauket, NY 11733
Clinic	The Eye Care Group	1201 West Main Street New Haven, CT 06708
Academic/University	Massachusetts Eye and Ear Infirmary	243 Charles Street Boston, MA 02114
Academic/University	University of Alabama at Birmingham	1720 2nd Avenue South, EFH 601 Birmingham, AL 35295