NOVARTIS

Clinical Development

Non-Interventional Study Protocol

CRFB002F2401

A 36 month observational study to describe the long-term efficacy and safety of ranibizumab 0.5 mg treatment in patients with visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Protocol version identifier	00 (Original Protocol)
Date	08 Dec 2014
EU PAS register number	Study not registered
Active substance	Ranibizumab
Medicinal product	Lucentis®
Product reference	EMEA/H/C/000715
Procedure number	EMEA/H/C/000715/II/0034

Marketing authorization holder(s)	Novartis Europharm limited
Joint PASS	No
Research questions and objectives	Primary objective is to describe the long-term efficacy of ranibizumab for the treatment of visual impairment due to CNV secondary to PM as assessed by the change in best corrected visual acuity (BVCA) from study entry throughout a 36 month observational period.
Countries of study	Not determined yet
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[redacted]

QPPV or delegate Signature Date

Marketing authorization holder(s)

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2 List of abbreviations

AE	Adverse Event
AMD	Age-Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CNV	Choroidal Neovascularization
CPO	Country Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
GCP	Good Clinical Practices
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
PI	Principal Investigator
PT	Preferred Term
REB	Research Ethics Board
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
vPDT	Verteporfin (Visudyne) Photodynamic Therapy
WHO	World Health Organization

3 Responsible parties

Table 3-1 Main responsible parties

Role	Person
Main protocol author	[redacted], PhD [redacted] Novartis Pharma AG Novartis Campus 4002 Basel
Principal investigator (PI)	Prof. Dr. [redacted]
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4 Abstract

Title	A 36 month observational study to describe the long-term efficacy and safety of ranibizumab 0.5 mg treatment, in patients with visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM).
Version and Date	00 (original protocol), 08 Dec 2014
Name and affiliation of main author	[redacted], MD Novartis Pharma AG
Rationale and background	Following the approval of the indication for the treatment of visual impairment due to CNV secondary to PM for Lucentis (ranibizumab) on 04 July 2013, the European Medicines Agency (EMA) requested, as a post-approval measure, that the MAH perform a 300 patient, 36 month observational study to obtain long-term efficacy and safety data.
Research question and objectives	This observational study is to describe the long-term efficacy and safety of ranibizumab, in patients with visual impairment due to CNV secondary to PM. This study is a voluntary PASS.
Study design	This is a 36-month, 300-patient observational study to describe the long-term efficacy and safety of ranibizumab, in patients treated according to local regulations and standards of clinical practice.
Population	The study is to enroll 300 patients with visual impairment due to CNV secondary to PM. Patients with previous or concomitant treatment with verteporfin-PDT or previous laser are eligible for enrollment. Enrolled patients should not have received treatment with a systemic VEGF inhibitor for 90 days prior to enrollment, or an ocular VEGF inhibitor for 30 days prior to enrollment.
Objectives	Primary objective: To describe the long-term efficacy of ranibizumab as it is used in routine clinical practice for the treatment of visual impairment due to CNV secondary to PM. This will be determined by assessing the change in best corrected visual acuity (BCVA) from study entry throughout a 36 month observational period, in the primary eye designated for treatment. Secondary objectives: To describe the ocular and systemic safety of ranibizumab 0.5 mg. To describe the categorized change in BCVA over time, from study entry to month 36. Categorized change will be evaluated by an increase of ≥ 5, ≥ 10, or ≥ 15 letters or a decrease of ≥ 5, ≥ 10, or ≥ 15 letters from baseline. To evaluate efficacy by lesion subtype (subfoveal, juxtafoveal, and extrafoveal lesions). While limited data may be available, the following secondary endpoints will also be explored: Visual acuity outcomes in patients previously treated with vPDT or laser treatment. Visual acuity outcomes and safety in patients receiving combined treatment of vPDT and ranibizumab during the 36 month observational

	period The risk of late reactivation of CNV throughout the 36 Month study duration. In the event that the patient's second eye requires treatment with ranibizumab for CNV due to PM during the course of the study, the following efficacy objective will be explored for the second eye: BCVA change from time of first treatment to end of study
Variables	Patient characteristics will be collected at the study entry visit, in particular demographic data (e.g. date of birth, gender, race/ethnicity), relevant non-ocular medical and surgical history, current medical conditions, concomitant medications, ocular medical and surgical history including previous treatment for myopic CNV, and ocular characteristics.
Data sources	Patients will be recruited from selected investigator sites. Initiation of the participating sites will be performed by Novartis and/or a designated CRO. The clinical site will be provided access to an Electronic Data Capture (EDC) system that has been fully validated and conforms to 21 CFR Part 11 requirements. Sites enrolling patients in this study will record data on electronic Case Report/Record Form (eCRFs) provided by Novartis (or designee) which will capture, check, and store the data.
Study size	The study is to enroll 300 patients with visual impairment due to CNV secondary to PM, from EU as well as non-EU countries.
Data analysis	The primary efficacy objective of this study will be assessed by the change in best corrected visual acuity (BVCA) from study entry throughout the 36 month observational period in the primary eye designated for treatment. Baseline characteristics of the enrolled patients will be summarized descriptively. The number of ranibizumab treatments by patient and by primary treated eye will be summarized. Incidence rates of ocular and non-ocular adverse events will be evaluated.
Milestones	Start of data collection (FPFV) Q2 2015 End of data collection (DBL) Q4 2019 Study progress reports annually Registration in the EU PAS register: Q2 2015 Final report of study results (published CSR) Q2 2020

5 Amendments and updates

None

6 Milestones

Table 6-1 Study milestones

Milestone	Planned date
Start of data collection (FPFV)	Q2 2015
End of data collection (DBL)	Q4 2019
Study progress reports**	Annually*
Registration in the EU PAS register>	Q2 2015
Final report of study results (published CSR)	Q2-2020

*Study status will be reviewed annually and provided in the PSURs. **Status progress reports will include only an update on recruitment and list of changes required to the protocol if any.

7 Rationale and background

7.1 Background

Pathologic myopia (PM) is characterized by abnormal and progressive lengthening of the eyeball, usually to an axial length greater than 26mm with concomitant degenerative changes in the posterior segment of the eye. Such degenerative changes can include: posterior staphyloma, chorioretinal atrophy, Bruch's membrane (lacquer) cracks, subretinal hemorrhage, retinal detachment, and choroidal neovascularization (CNV) (Miller et al 2001, Neelam et al 2012).

It is estimated that CNV develops in 4-11% of eyes with PM (Avila et al 1984). CNV secondary to PM is associated with a poor prognosis, with a high proportion of patients experiencing a loss in visual acuity in the absence of treatment (Ng et al 2012). In addition, PM is one of the leading causes of choroidal neovascularization (CNV) in individuals younger than 50 years (Cohen et al 1996). The resulting loss of vision has a deleterious effect on productivity, financial status, career expectations, and quality of life individuals with CNV secondary to PM (Miller et al 1996).

Prior to the development of anti-VEGF therapies for retinal disease involving CNV, thermal laser photocoagulation and photodynamic therapy were used to treat CNV secondary to PM, with verteporfin (Visudyne) Photodynamic Therapy (vPDT) the only approved treatment for subfoveal CNV in patients with PM.

Further understanding of the pathological aspects associated with PM has led to the development of more effective treatments, using VEGF inhibition.

On 04 July 2013, Lucentis (ranibizumab), which was already marketed in the European Union for neovascular AMD, visual impairment due to diabetic macular edema (DME) and macular edema secondary to retinal vein occlusion (RVO), became the first intravitreal anti-VEGF

therapy to receive approval for the treatment of visual impairment due CNV secondary to PM. The approval was based upon the clinical study RADIANCE (RFB002F2301) which demonstrated a mean average change in visual acuity from baseline through Month 3 of +10.5 letters in ranibizumab-treated patients.

7.2 Purpose and Rationale

Following the approval of the indication for the treatment of visual impairment due to CNV secondary to PM for Lucentis (ranibizumab) on 04 July 2013, the European Medicines Agency (EMA) requested, as a post-approval measure, that the MAH perform a 300 patient, 36 month observational study with the aim to obtain:

- Data on long-term (i.e. beyond one year of treatment) efficacy (primary objective)
- Data on long-term safety (secondary objective)
- Data in patients previously treated with verteporfin-PDT (or laser treatment)
- Data in patients receiving combined treatment with vPDT and ranibizumab during the 36 month observational period
- Additional efficacy data in subjects with extrafoveal lesions
- Data to evaluate whether there is a risk of late reactivation of CNV during the 36 month observational period

This study has been classified as a voluntary PASS.

8 Research question and objectives

The objective of this observational study is to describe the long-term efficacy and safety of ranibizumab, when administered according to local regulations and standards of clinical practice, for the treatment of patients with visual impairment due to CNV secondary to PM.

Primary Objective

The primary objective of the study is to describe the long-term efficacy of ranibizumab as used in routine clinical practice, for the treatment of visual impairment due to CNV secondary to PM.

This will be determined by assessing the change in best corrected visual acuity (BVCA) from study entry throughout a 36 month observational period in the primary eye designated for treatment.

Secondary Objectives

The secondary objectives of the study are defined as follows:

- To describe the ocular and systemic safety of ranibizumab 0.5 mg
- To describe the categorized change in BCVA over time, from study entry up to 36 months. Categorized change will be evaluated by an increase of ≥ 5, ≥ 10, or ≥ 15 letters or a decrease of ≥ 5, ≥ 10, or ≥ 15 letters from baseline
- To evaluate efficacy of 0.5 mg ranibizumab by lesion subtype (subfoveal, juxtafoveal, and extrafoveal lesions)

While limited data may be available, the following secondary endpoints will also be explored:

- To describe visual acuity outcomes in patients previously treated with vPDT or laser treatment
- To describe visual acuity outcomes and safety in patients receiving combined treatment of vPDT and ranibizumab during the 36 month observational period
- To evaluate the risk of CNV reactivation of throughout the 36 Month study duration

The secondary efficacy objectives above will pertain to the primary eye designated for treatment.

In the event that the patient's second eye (the secondtreated eye) requires treatment for CNV due to PM with ranibizumab during the course of the study, the following efficacy objective will be explored:

- BCVA change from time of first treatment to end of study

9 Research methods

9.1 Study design

This is an observational, non-interventional, multicenter, open label study to describe the long-term efficacy (primary objective) and safety (secondary objective) of ranibizumab 0.5 mg treatment in patients with visual impairment due to CNV secondary to PM, over a period of 36 months.

Patients treated according to local routine clinical practice will be enrolled in the study upon signing an Informed Consent.

The study entry visit will be used to assess eligibility and to collect baseline characteristics and is considered Day 1 of the 36 month observation period.

Since this is an observational study, patient visits after study entry (baseline) should be performed as per the study investigator's discretion and in line with local regulations and standards of clinical practice for the treatment of visual impairment due to CNV secondary to PM with ranibizumab. Patients are allowed to be treated with vPDT during the study investigator's discretion. After study entry, a minimum of one visit per year is required.

All visits should be documented in the CRF. The CRF should be completed after every visit.

The study will use data collected at study entry (baseline characteristics) and at subsequent visits.

In order to evaluate the long-term efficacy of ranibizumab, the BCVA will be measured at each visit and BCVA changes from study entry throughout the 36 month observational period in the primary eye designated for treatment will be assessed. At the time of study entry, patients will be categorized according to their treatment history with respect to prior anti-VEGF treatment. If the number of patients treated previously with vPDT or laser allows, further subgroup analysis will be conducted.

9.2 Setting

300 male or female patients will be entered into the study and will be observed for a period of 36 months.

Selection criteria:

- The patient must be willing and able to sign an Informed Consent.
- The patient must be diagnosed with visual impairment due to CNV secondary to PM and be intended to be treated with ranibizumab.
- The patient must be ≥ 18 years old (adults per local regulations).
- The patient must not have been treated with a systemic VEGF inhibitor for 90 days prior to enrollment.
- The patient must not have been treated with an ocular VEGF inhibitor for 30 days prior to enrollment, or intravitreal/subTenons steroids for 90 days prior to enrollment.

Pregnant women should not be included except if, in the opinion of the investigator, the expected benefit outweighs the potential risk to the fetus (please see Section 11 for further information). Women of childbearing potential must use an effective method of contraception. Breast-feeding is not recommended during the use of Lucentis.

The patient may have received previous treatment with vPDT or laser for the treatment of myopic CNV.

Further eligibility for treatment may be determined by the locally approved prescribing information for ranibizumab, as applicable.

9.3 Variables

9.3.1 Baseline characteristics

Patient characteristics will be collected at the study entry visit:

- Demographic data (e.g. date of birth, gender, race/ethnicity)
- Relevant ocular and non-ocular medical and surgical history
- Current medical and ocular conditions
- Concomitant medications
- Previous treatment for myopic CNV (with anti-VEGF, intravitreal/subTenons steroids, vPDT or laser)
- Ocular characteristics of both eyes, including BCVA

At subsequent visits throughout the observation period, the following information will be updated:

- New systemic and ocular medical and surgical patient information
- Change in concomitant medications, including treatment with vPDT or laser

9.3.2 Exposure

Information regarding ranibizumab administration including date and reason for dosing during the study will be collected on the Dosage Administration Record of the eCRF/EDC for both eyes.

9.3.3 Visual acuity

Effectiveness of ranibizumab treatment will be described by BCVA assessment at study entry and all subsequent visits. BCVA will be measured according to the method used by the treating investigator in the course of routine care and recorded in the eCRF. However, for consistency and analyses, it is recommended that the same method of assessment be used throughout the study wherever possible. Use of the ETDRS-like chart (starting at 4 meter distance) is preferred.

Measuring the BCVA for both eyes at baseline and all subsequent visits is recommended.

9.3.4 Ophthalmic examination

An ophthalmic examination performed as per routine clinical practice must be done by the treating investigator, including measurement of BCVA, IOP, and dilated fundus examination and diagnostic measures such as Fluorescein Angiography (FA) and Optical Coherence Tomography (OCT) as deemed necessary. At each visit, assessment of mCNV lesion activity should be documented in the eCRF, including lesion reactivation. It is recommended that the ophthalmic exam is done in both eyes at baseline and all subsequent visits. An ophthalmic examination must be performed and documented in the eCRF for the second- eye if diagnosed with CNV secondary to PM.

9.3.5 Adverse Events

Both AEs and SAEs must be collected in the electronic data capture system (EDC) on an ongoing basis (see Section 11 for further information) and should be entered into the electronic case report form (eCRF) after each visit.

9.4 Data sources

Patients will be recruited from selected investigator sites. Initiation of the participating sites will be performed by Novartis and/or a designated CRO. Before study initiation, a Novartis representative (or designee) will review the protocol and eCRF with the physicians and their staff.

Sites enrolling patients in this study will record data on eCRFs provided by Novartis (or designee) which will capture, check, and store the data. Data sources are linked by means of a unique patient identifier, i.e. a combination of site number and patient number. The site number is assigned by Novartis to the investigative site.

In case of outsourcing of data management (whether partial or total outsourcing), the CROs will follow their own internal SOPs that have been reviewed and approved by Novartis. Data will be transferred to Novartis as per contractual agreement.

9.4.1 Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedures, or a visit schedule. Patients will be treated according to routine medical practice in terms of visit frequency (with the exception of one visit mandatory per year) and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete if possible at every patient visit the appropriate eCRF/EDC.

A recommended data collection schedule is described below.

Investigators are strongly encouraged to ensure that data are collected for each participating patient at least at Months 6, 18, 30 and 36 in order to ensure the availability of data for the main analyses. Therefore whenever possible and appropriate, routine medical care visits following baseline should be scheduled around Months 6, 18, 30 and 36.

Table 9-1 Data collection

Phase	**Baseline** (Study Entry)	**Each clinical follow-up after enrollment** (At least once per year until 36 months)	**Study Discontinuation/ Completion**
Demographics	x		
Relevant systemic medical and surgical history and medical conditions at baseline visit	x		
Ocular medical and surgical history and ocular conditions at baseline visit	x		
Inclusion/Exclusion criteria	x		
Information & Informed consent	x		
Prior and concomitant medications (ocular and systemic)	x[b,c]	x[c]	x[c]
Ophthalmic examination	x	x	x

Best Corrected Visual Acuity	x	x	x
Adverse events	x	x	x
Ranibizumab treatment given	x[a]	x[a]	

x[a]: Treatment as needed.

x[b]: Only prior medications taken in the last 4 months (120 days) before study entry should be recorded.

x[c]: Prior or concomitant vPDT treatment should also be captured.

Patients who successfully complete the follow-up for the planned 36 months (+/- 1 month) and provide information on his/her current disease status at Month 36 during the study visit will be considered as having completed the study. The study will be considered completed when the last patient has completed the study.

A patient may discontinue participation at any time during the study. For patients who discontinue prematurely, the reason for discontinuation should be determined.

When a patient discontinues prematurely during the study, all efforts must be made to measure BCVA and perform the ophthalmic examination, as well as assess adverse events.

A patient should not be considered lost to follow-up until his/her Month 36 visit would have occurred. For patients whose status is unclear because they fail to appear for visits without stating an intention to withdraw, 'due diligence' would include contacting the patient, his/her family or family physician as agreed in the informed consent at minimum at Month 12 and Month 24, and Month 36. The steps taken to contact the patient (e.g. date of telephone calls, registered letters, etc.) must be documented in the source documents.

The clinical site will be provided access to an EDC system that has been fully validated and conforms to 21 CFR Part 11 requirements. Designated investigator site staff will be trained on the EDC system. Investigator site staff will not be given access to the EDC system until they have been trained.

Designated investigational staff will enter the data required by the protocol into the eCRFs using their computer. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigational staff. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRF. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

9.5 Study size

It is planned to enroll 300 patients into the study as requested by the EMA.

9.6 Data management

A Novartis representative and/or a designated CRO will review the eCRFs entered by investigational site personnel for completeness and accuracy, following standard operating procedures.

Subsequently, the entered data will be systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Errors or omissions will be entered on Data Query Forms, and sent to the investigational site using an electronic data query system for resolution. Designated investigator site staff will be required to respond to the query and make any necessary changes to the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Data Management staff, who in turn will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

9.7 Data analysis

All analyses will be performed by Novartis or a designated CRO.

Descriptive analyses will include n, mean, standard deviation, median, first quartile, third quartile and ranges for continuous variables and frequencies and percentages for categorical variables. Summaries will be presented together with estimates and corresponding 95% confidence intervals (CI) as appropriate. The presentation of these summaries will consider the treatment status of the primary treated eye (prior to study entry) with respect to ranibizumab and other ocular treatments (e.g. other anti VEGF treatment or vPDT). Complete analytical specifications will be fully detailed in the statistical analysis plan (SAP).

9.7.1 Analysis sets

The **enrolled set** will include all patients having signed the Informed Consent, who have at a minimum a study entry assessment.

The **safety set** will include all patients who provide Informed Consent to collect information and who were treated with at least one dose of ranibizumab during this study, and had at least one safety assessment after the first treatment. Of note, the statement that a patient had no AE also constitutes a safety assessment.

All efficacy analyses will be carried out on the enrolled set, while all safety analyses will be conducted within the safety set.

The primary treated eye will be the first treated eye with ranibizumab during the study (note that patients may be treated in both eyes). If both eyes are treated for the first time within the study with ranibizumab on the same day, the eye with an earlier date of diagnosis will be considered as the primary treated eye.

If both eyes have the same diagnosis and treatment date, one of the two eyes will be chosen randomly as the primary treated eye.

If the second eye also requires treatment during the study with ranibizumab for CNV due to PM then it will be considered as the second-treated eye; If the second eye does not require ranibizumab treatment for CNV due to PM throughout the whole 3 years of observation, then this untreated second eye is designated as the fellow eye. Therefore, the term "fellow eye" always refers to the non-ranibizumab-treated eye of a patient in the safety set.

All patient demographics, medical history, ocular history and characteristics, prior treatments, and other baseline characteristics will be presented using standard descriptive statistics.

The number of ranibizumab injections administered and the average time interval (in weeks) between consecutive injections will be summarized for the primary treated eye, the secondary-treated eye and for both treated eyes. The reasons for treatment/termination will also be summarized. Visit frequency will be characterized.

The efficacy analyses will focus on the primary treated eye. The primary efficacy variable will be the mean change in best corrected visual acuity (BCVA) from baseline throughout Month 36 for the primary treated eye set. Details on describing the time-course of BCVA will be given in the statistical analysis plan considering the frequency and amount of captured data during the study (e.g. describing changes on a yearly basis). In completion to the analysis related to the change in BCVA, the categorized change in VA will be evaluated on a yearly basis (if the amount of data allow):

- Proportion of patients with a gain in VA of ≥ 5, ≥ 10 or ≥ 15 letters
- Proportion of patients with a loss in VA of ≥ 5, ≥ 10 or ≥ 15 letters

The analysis of efficacy of the primary treated eye data will be presented by treatment history, i.e. there will be the following subgroups for (primary) naïve eyes and pre-treated eyes:

- Subgroup 1: (primary) naïve eye
- Subgroup 2: pre-treated eye: ranibizumab, other anti-VEGF or intravitreal/subTenons steroid for mCNV
- Subgroup 3: pre-treated eye: vPDT, laser

Furthermore, a subgroup analysis of the change in BCVA will be evaluated based on baseline lesion subtype categories (subfoveal, juxtafoveal, and extrafoveal lesions).

The risk of late reactivation of CNV will be assessed through a time to event analysis, considering the time to reactivation of CNV as event time (if these data are recorded for a sufficient number of patients).

If there are a sufficient number of patients who receive combination treatment (ranibizumab, vPDT) further efficacy analyses may be conducted.

In the event that the patient's second eye (the secondary-treated eye) requires treatment with ranibizumab during the course of the study, the following efficacy objective will be explored:

- BCVA change from time of first treatment to end of study

For the safety analysis the incidence rates of non-ocular ranibizumab treatment-emergent adverse events by patient, as well as ocular treatment-emergent adverse events (for the primary treated eye, secondary treated eye, and fellow eye) will be summarized.

An adverse event will be considered as treatment-emergent if it starts on or after first treatment with ranibizumab during the study. Treatment-emergent adverse events will be summarized by presenting the number and percentage of patients experiencing adverse events by system organ class, preferred term and severity of adverse events.

Treatment-emergent adverse events related to identified and potential RMP risks will be summarized.

In addition, a separate analysis of incidences of adverse events in patients receiving injections of ranibizumab in both eyes (within one-month period) will be performed.

For those patients who withdraw from the study, the analyses will include all data collected up to 30 days after study discontinuation unless explicitly stated otherwise and as collected in the clinical database. AEs and SAEs collected after the database lock will not be included in the analysis.

All adverse events will be listed.

Analysis of complete data as well as additional analyses to evaluate the impact of missing data on the validity of conclusions will be conducted. The analysis of adverse events will be based on observed data.

Further details on how missing data will be handled will be outlined in the SAP.

9.8 Quality control

9.8.1 Data quality assurance

Novartis Data Management or designated CRO will assure database quality by reviewing the data entered into the eCRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

9.8.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records or eSource if available) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file. The physician must also keep the original Informed Consent form signed by the patient (a signed copy is given to the patient).The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries. No information in source documents about the identity of the patients will be disclosed.

9.8.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study. The Novartis data management / designated CRO will assure compliance monitoring.

9.9 Limitations of the research methods

The study size of 300 patients is in accord with the recommendation by the EMA and reasonable given that CNV secondary to PM is not a common disease. However, the number of subjects or the number observations (as a result of infrequent study visits) may be too low to conduct some of the analyses.

10 Protection of human subjects

By signing the protocol, the investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

In this observational study, patients will be followed according to routine medical practice and as per the study investigator's discretion for the treatment of visual impairment due to CNV secondary to PM with ranibizumab. They will not be exposed to additional risk by participating in the study.

During the study, the field monitor will visit the site regularly to check the completeness of patient records, the adherence to the protocol and to Good Clinical Practice. The investigator is required to give access to all relevant data and records to CRO monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Novartis monitoring standards require full verification for the presence of Informed Consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

10.1 Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

10.2 Informed Consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis or designee will provide to treating physicians or other involved medical professionals in a separate document a proposed Informed Consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

11 Management and reporting of adverse events/adverse reactions

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – must be collected and recorded in the study database, irrespective of causal association. All AEs, including SAEs occurring in association with exposure to the Novartis drug of interest, also have to be recorded in the Novartis safety database.

Adverse Drug Reactions (ADRs) occurring in association with exposure to Novartis drug other than the Novartis drug of interest, can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or Novartis DS&E as a spontaneous report.

All adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

11.1 Adverse event reporting

An adverse event is any untoward medical occurrence in a patient administered ranibizumab that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of ranibizumab, whether or not related to the medicinal product.

The drug of interest is ranibizumab. In addition, verteporfin-PDT (Visudyne) may be used by the investigator concomitantly and patients will also be monitored for adverse events related to either Visudyne or the PDT procedure.

A determination should be made by the investigator whether worsening of the underlying condition is due to natural disease progression or lack of drug efficacy. Lack of effectiveness would be considered an adverse event.

Any AE occurring from the time of Informed Consent signature until study completion must be reported in the CRF. All adverse events will be collected and reported in the clinical and safety database, irrespective of suspected causal association and according to the processes described below.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

All adverse events must be recorded on the Adverse Events case report/case record form (CRF) with the following information:

1. the severity grade (mild, moderate, severe)
2. the site (right eye, left eye, both eyes, or non-ocular)
3. the relationship to ranibizumab, and / or the ocular injection (suspected/not suspected)
4. the duration of the adverse event (start and end dates or if continuing at final exam)
5. whether it constitutes a serious adverse event (SAE)

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during lactation or breast-feeding,
- Lack of effectiveness (as determined by the investigator)
- Overdose (the administration of a single dose greater than that specified in the product information, i.e. > 0.5 mg into one eye, or more frequent administration than specified in the product information), based on the clinical judgment of the investigator
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors
- Off-label use
- Withdrawal or rebound symptoms

Any action taken due to an adverse event should be recorded on the Adverse Event CRF. Some examples are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to ranibizumab and / or the ocular injection, the interventions required to treat it, and the outcome.

Information about adverse effects already known about the medicinal product can be found in the product information. This information will be included in the patient Informed Consent and should be discussed with the patient during the study as needed.

Information on all AEs is included in the individual patient eCRFs which must be updated and committed in the study database on a periodic basis but not later than once a month.

Based on requirements in the new EMA GVP guidelines for non-interventional studies, adverse events, irrespective of causality, are transferred to Novartis Safety on a periodic basis for inclusion in the Novartis Safety Database. Novartis will review all AE reports received and make a company assessment of seriousness. Novartis may need to reach out to Investigators for additional information on AEs submitted as non-serious, including further information to support the non-serious assessment of the reported AE.

11.2 Serious adverse event reporting

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, *unless* hospitalization is for:
    - Routing treatment or monitoring of the studied indication, not associated with any deterioration in condition. This would include when the patient is hospitalized either pre or post-injection for routine monitoring, as per local custom.
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a serious adverse event and not resulting in hospital admission
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Involves transmission of an infectious agent via medicinal product

As per the Lucentis Risk Management Plan (RMP) certain ocular events that are reported as serious are followed up using a targeted checklist sent by Novartis to investigators. Events requiring such additional follow up are identified based upon SAEs submitted to Novartis. There are no non-serious AEs of special interest requiring expedited reporting to Novartis.

To ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of the drug of interest taken or last visit whichever is later) must be reported to Novartis/designated CRO within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period should only be reported to Novartis/designated CRO if the treating physician or other involved health care professional suspects a causal relationship to the drug of interest.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the treating physician or other involved health care professional receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The treating physician or other involved health care professional must assess the relationship to the drug of interest, complete the SAE Report Form and send the completed, signed form by fax or email (with a PDF signed by the investigator) within 24 hours to the local Novartis Drug Safety Department. The telephone, telefax number and email address of the contact persons in the local Novartis Safety department, specific to the site, are listed in the healthcare professional folder provided to each site. The original copy of the SAE Report Form and the fax confirmation or email read receipt must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the product information, a local Novartis Safety Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

11.3 Pregnancy and Breast-feeding

Women of childbearing potential should use effective contraception during treatment. Ranibizumab should not be used during a pregnancy unless the expected benefit outweighs the potential risk to the fetus. In case of pregnancy during the study, the treating physician, in conjunction with the patient or other necessary consultants, will decide the appropriate measure which reflects the best interest of the patient.

For ranibizumab, no clinical data on exposed pregnancies are available. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/fetal development. The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo/fetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus.

To ensure patient safety, any occurrence of a pregnancy in a patient on the drug of interest must be reported to Novartis/designated CRO within 24 hours of learning of its occurrence. Any SAE experienced during pregnancy must also be reported within 24 hours. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pregnancy Form and reported by the treating physician or other involved health care professional to the local Novartis Safety Department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug of interest should be reported.

It is unknown whether Lucentis is excreted in human milk. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis.

12 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

The final manuscript for this non-interventional PASS study will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

13 References

Avila MP, Weiter JJ, Jalkh AE et al. Natural history of choroidal neovascularization in degenerative myopia. Ophthalmology 1984; 91:1573–81.

Cohen SY, Laroche A, Leguen Y et al. Etiology of choroidal neovascularization in young patients. Ophthalmology 1996; 103(8):1241-4.

Miller DG, Singerman LJ. Natural history of choroidal neovascularization in high myopia. Curr Opin Ophthalmol 2001; 12(3): 222-4.

Miller DG, Singerman LJ. Vision loss in younger patients: a review of choroidal neovascularization. Optom Vis Sci 2006; 83(5):316-25.

Neelam K, Cheung CMG, Ohno-Matsui K et al. Choroidal neovascularization in pathological myopia. Progress in Retinal and Eye Research 2012; 31:495-525.

Ng DS, Kwok AKH, Chan CW. Anti-vascular endothelial growth factor for myopic choroidal neovascularization. Clinical and Experimental Ophthalmology 2012; 40: e98–e110.

Annex 1 – List of stand-alone documents

None

Annex 2 – ENCePP checklist for study protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A 36 month observational study to describe the long-term efficacy and safety of ranibizumab 0.5 mg treatment in patients with visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Study reference number:
RFB002F2401

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☒	☐	☐	10
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

No interim study reports will be issued as this is a 36-month study to evaluate long-term efficacy and safety of ranibizumab without interim database lock/analysis

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	11-12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

The study has no formal hypothesis but is designed as an observational study to answer specific questions raised by the EMA as outlined in Section 7.2 page 13

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11-12
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

This is a single arm study with no comparbale arms, therfore no measures of effect are described

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☐	☒	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	13
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	13

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☒	☐	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Exposure is defined by the number of injections administed by the Investigator.

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	14, 18-19
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

Further details on endpoint definition and analysis will be provided in the statistical analysis plan referenced in section 9.7.

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☒	☐	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☐	18-19

Comments:

Treatment history and lesion type may be effect modifiers, this information is collected and sub-analyses will be performed.

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	14
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	14
8.1.3 Covariates?	☐	☒	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	14
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☐	14
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☐	☒	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	17
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	17
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	17
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	14

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	

Comments:
Sample size is based on the recommendation from EMA.

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	18-19
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	18-19

Comments:
Details on efficacy analysis will be provided in the statistical analysis plan referenced in section 9.7

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	17
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	19
11.3 Are methods of quality assurance described?	☒	☐	☐	19

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:
Reference is made in the protocol to standard operating procedures.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☒ ☒	☐ ☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	21
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	20

Comments:
The protocol has not been submitted to Ethics Committees yet.

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	10

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: 04/11/2014

Signature: [redacted]