NOVARTIS

Clinical Development

Ranibizumab; Lucentis®

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A Phase IV, prospective, open-label, uncontrolled, European **S**tudy in patients with neovascular **A**ge-related macular degeneration (nAMD), evaluating the efficacy and safety of switching **F**rom intravitreal **A**flibercept to **R**an**I**bizumab 0.5mg: the SAFARI study

RAP Module 3 – Detailed Statistical Methodology

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List of abbreviations

AE	Adverse event
AMD	Age-related Macular Degeneration
[redacted]	[redacted]
AREAATRS	Area size of atrophy (total area)
AREACNVS	Area of macular CNV lesion
AREALEKS	Area of leakage
AREATOTS	Area of total lesion (including CNV, blood, scar)
BCVA	Best-corrected visual acuity
BMI	Body mass index
CI	Confidence interval
CNV	Choroidal neovascularization
CRF	Case Report Form
CSR	Clinical Study Report
CSRT	Central subfield retinal thickness
CSRV	Central subfield retinal volume
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
IOP	Intraocular pressure
IRC	Intra-retinal cysts
IVT	Intravitreal
MedDRA	Medication Dictionary for Regulatory Activities
nAMD	Neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
OD	Occulus Dexter
ORT	Outer Retinal Tubulations
OS	Occulus Sinister
PD	Protocol deviation
PED	Pigment epithelial detachment
PT	Preferred Term
PPS	Per Protocol Set

PRN	Pro re nata/administer as required
PTF	Primary treatment failure
RAP	Report and Analysis Plan
RETFL	Intraretinal fluid
RETIRC	Intraretinal fluid (at least some intraretinal fluid of cystoid origin)
RETSF	Intraretinal/subretinal Fluid within the Central Subfield (diameter 1000 microns)
RPE	Retinal Pigment Epithelium
SAE	Serious adverse event
SAF	Safety Set
SF	Subretinal fluid
SOC	System Organ Class
[redacted]	[redacted]
SRT	Subfoveal retinal thickness
STR	Suboptimal treatment response
SUBCENT	Change of Subretinal Fluid within the Central Subfield
TEAE	Treatment-emergent adverse event
VEGF	Vascular endothelial growth factor
WHODrug	World Health Organization Drug dictionary

1 Statistical methods planned in the protocol and determination of sample size

This document is based on protocol version 02 dated 11 May 2016 and annotated Case Report Form (CRF) version 05 dated 05Aug2014. All comments documented in the CRF will be listed.

Data will be analyzed by [redacted] according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the clinical study report (CSR). Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR.

Following are the changes from the protocol planned analysis:

- [redacted]
- SF volume and IRC volume were mentioned in the protocol as secondary efficacy variables. Due to technical limitations, there is no robust way in the reading center to assess these two parameters. CSRT thickness and subfoveal retinal thickness will be used to assess SF volume, and maximum height of intra-retinal cysts (IRC) will be used to assess IRC volume.
- 'Intra-retinal cystoid changes' was listed as a variable in the secondary objectives section. This is being assessed by presence of intraretinal fluid and whether some of the intraretinal fluid is of cystoid origin.
- [redacted]

This is a phase IV, unmasked, uncontrolled, single arm, and multicenter study in patients diagnosed with visual impairment due to nAMD who have been treated with aflibercept and where either no treatment response has been achieved or where there is suboptimal treatment response. The study will enroll 150 patients in 30 ophthalmology centers in Western European countries. Patients will be enrolled according to 2 subgroups: primary treatment failure subgroup (maximum of 30 patients) or suboptimal response subgroup.

The study includes 8 study visits over a minimum of 6 months. All patients with nAMD and eligible to enter the study will receive 3 monthly intravitreal (IVT) ranibizumab 0.5mg injections followed thereafter by monthly IVT injections of ranibizumab 0.5mg on a pro re nata/administer as required (PRN) basis. There will be 3 periods in this study: Screening period from Day -70 to Day 0, Monthly Treatment period from Baseline (Day 1) to Day 60, and PRN Treatment period from Day 61 to Day 180.

All assessments will be performed according to the assessment schedule (see Table 6-1 and Table 6-2 in Section 6 of the protocol).

The purpose of this study is to determine, in patients with nAMD treated with aflibercept and where there is evidence of persistent or increasing disease activity, whether switching treatment to ranibizumab 0.5mg reduces disease activity over a 6 month period as assessed by a variety of measures.

2 Statistical and analytical plans

For all patients only one eye will be considered as the study eye, but efficacy and safety parameters will be recorded for both eyes. Data presentations will distinguish study and fellow eye values.

Summary statistics for continuous variables will include n (the number of non-missing observations), mean, standard deviation, minimum, median, maximum, and, where appropriate, 95% confidence interval (CI).

Summary statistics for categorical variables will include frequencies and percentages, and, where appropriate, 95% CI.

Unless otherwise specified, all statistical tests will be two-sided and use the 0.05 level of significance.

All data will be listed by patient, and where applicable, by eye, for all screened patients.

Baseline will be defined as the last available non-missing value collected prior to the start of treatment in the study eye. The protocol deviation review at the end of the study will identify any patients where the gap between the prior reading and the start of the study is too wide, i.e. > 3 days.

For patients with screening assessments who do not enter the treatment period, data will only be listed. For patients who do not enter the treatment period due to a study eye specific exclusion criterion, descriptive statistics as described above will be provided.

2.1 Patients and treatments

2.1.1 Analysis sets

Assignment of patients to analysis sets will be agreed between the study statistician and the Sponsor prior to database lock, once all study data are available and verified. All efficacy analyses will be performed on the study eye. For visual acuity tests, the results for the fellow eye (non-study eye) will also be summarized for reference.

Full Analysis Set (FAS): The FAS consists of all patients who received at least one application of study treatment in the study eye, have baseline and have at least one post-baseline assessment for CSRT. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned. No data will be excluded from the FAS analyses because of protocol deviations.

Per Protocol Set (PPS): The PPS consists of all patients in the FAS who followed the assigned treatment and completed the study without clinically significant protocol deviations.

Safety Set (SAF): The SAF consists of all patients who received at least one application of study treatment in the study eye and had at least one post-baseline safety assessment.

All efficacy evaluations will be carried out on the Full Analysis Set and all safety evaluations will be carried out on the Safety Set. For sensitivity purposes, the primary analysis will be repeated using the Per Protocol Set. Any major discrepancies in the results across analyses will be investigated as necessary.

In addition, 2 subgroups of patients are defined:

- Group 1. Primary treatment failure (PTF)
- Group 2. Suboptimal treatment response (STR)

2.1.2 Disposition of patients

The following patient disposition details will be summarized by subgroups and overall, and will include the number and percentage of patients:

- screened
- treated at V2
- included in the each study population (FAS, PPS, SAF)
- who completed the study
- who prematurely withdrew, including a breakdown of the primary reasons for withdrawal

All screened patients will be listed indicating their eligibility to each analysis set and reasons for exclusion from the analysis sets as appropriate.

Eligibility details, individual reasons for withdrawal and protocol deviations details will be listed separately.

2.1.3 Protocol deviations

Protocol deviations (PDs) are collected as per the latest version of the VAP Module 3 - Protocol Deviations (see Appendix 2). This document gives a full list of possible PDs, including whether they are programmatically or manually derived, as well as Severity/Analysis classification codes to be assigned to each PD. Rules for patient classification in the analysis sets based on PDs are as follows:

Protocol deviations and impact on analysis

Code	VAP de-code	Impact on analyses
0	Exclude from all efficacy analysis (including ITT)	Exclude patient completely from the FAS and Per-Protocol Sets.
1	Exclude from Per-Protocol analysis	Exclude patient completely from Per-Protocol Set.
2	Exclude from data analysis from this date	Data from this date/visit onwards excluded from per protocol analyses (patient not excluded from population).

49	Report relevant protocol deviation – include in all analyses	Include in all analysis

A protocol deviation meeting will be organized. The criteria and determination of clinically relevant protocol deviations and patient specific identification of data to be excluded from the PPS following this meeting will be databased and finalized prior to database lock.

All protocol deviations will be listed. All responses to the screening and baseline log will also be listed.

2.1.4 Demographic and baseline characteristics

The following demographic and baseline characteristics, collected at screening, will be summarized by subgroup and overall for the FAS: age, sex, height, weight, body mass index (BMI), predominant race, and ethnicity. All demographic and baseline characteristics will be listed.

Descriptive statistics of the baseline value for the following continuous efficacy endpoints will be provided by subgroup and overall for the FAS, including a count of the number of missing readings/records:

- From optical coherence tomography (OCT):
    - Central subfield retinal thickness (CSRT) (*GRADE*: CSRTTHK)
    - Subfoveal Retinal Thickness (SRT) *(GRADE:* SUBFOVTK)
    - Central Subfield Retinal Volume (CSRV) (*GRADE:* CSRVVOL)
    - Subfoveal Choroidal Thickness (*GRADE*: SUBCHTK)
    - Maximum height of IRC (*GRADE*: IRCHEIGH)
    - Maximum height of pigment epithelial detachments (PED) (*GRADE*: PEDHEIGH)
    - Maximum diameter of PED (*GRADE*: PEDDIAM)
- From visual acuity: best-corrected visual acuity (BCVA) for study eye and fellow eye separately

Categorical summaries (Number and %) of the baseline results for the following efficacy endpoints will be provided by subgroup and overall for the FAS, including a count of the number of missing readings/records:

- From OCT:
    - OCT quality (OS – Oculus sinister or left eye (GRADE: OCQUALOS) and OD oculus dexter or right eye (*GRADE*: OCQUALOD))
    - Acceptability of OCT submission (*GRADE*: OCTSUB)
    - Presence of intraretinal fluid *(GRADE*: RETFL)
    - Presence of subretinal fluid (*GRADE*: RETFLSF)

  - Presence of intraretinal fluid (at least some intraretinal fluid of cystoid origin) *(GRADE*: RETIRC)
  - Presence of intraretinal/subretinal fluid within the central subfield (diameter 1000 microns) (*GRADE:* RETSF)
  - Presence of PED (*GRADE*: PEDDET)
  - Presence of central retinal pigment epithelium (RPE) atrophy (*GRADE*: RPEATRO)
  - Presence of macular geographic atrophy (*GRADE*: MACARO)
  - Presence of outer retinal tubulations (ORT) (*GRADE*: ORTTUB)
  - Presence of vitreomacular traction (*GRADE*: VITTRAC)
  - Presence of dry retina. Dry retina is defined as eye without intraretinal fluid (RETFL from derived.grade) AND eye without subretinal fluid (RETFLSF from derived.grade) AND eye without intraretinal cysts (RETIRC from derived.grade)
  - Development of RPE rip (*GRADE*: RPETIP)
  - Is there atrophy outside the active choroidal neovascularization (CNV) lesion? (*GRADE*: ATROCNV)
  - CNV subtype (study eye) (*GRADE*: CNVTYPE)
  - Area of macular CNV lesion (standardized) (*GRADE*: AREACNVS)
  - Area of leakage (standardized) (*GRADE*: AREALEKS)
  - Area of total lesion (including CNV, blood, scar) (*GRADE*: AREATOTS)
  - Area size of atrophy (total area) (GRADE: AREAATRS)

- From Indocyanine Angiography (ICG):
  - Presence of intraretinal/subretinal or sub-RPE hemorrhage (study eye) (*GRADE*: PRESHEM)
- From General Image Grading:
  - Does the hemorrhage include the fovea (study eye) (*GRADE*: HEMFOV)
  - Presence of active leakage in the sense of a neovascular membrane (study eye) (*GRADE*: LEAKNEO)

Age is calculated in years as (year of drug administration - year of birth)

BMI is calculated as (weight (kg) / [height (cm)/100]^2))

All demographic and baseline characteristics details, including derived variables, will be listed.

Age-related macular degeneration diagnosis details, pregnancy test details, historical retinal images details will be listed separately.

2.1.5 Medical history

Relevant medical history (ocular and non-ocular) and current medical conditions will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher.

Prior to database lock, a complete list of medical history events, as recorded on the eCRF, will be provided by [redacted] to Novartis in an Excel spreadsheet. Novartis will review the individual medical history events and classify them as ocular or non-ocular.

The number and percentage of patients with ocular (in study eye and fellow eye) medical histories will be tabulated by system organ class (SOC) and preferred term (PT), by subgroup and overall for the FAS. SOCs will be ordered in decreasing frequency of the total number of patients with ocular medical histories and conditions reported in each SOC and PTs will be ordered within a SOC in decreasing frequency of the total number of patients with ocular medical histories and conditions.

The same table will be provided for ocular current medical conditions, non-ocular medical histories and non-ocular current medical conditions.

All relevant medical history (ocular and non-ocular) and current medical conditions details will be listed.

2.1.6 Prior and concomitant medications

Prior and concomitant medications will be coded according to the World Health Organization Drug dictionary (WHODrug) (Standard) version of September 2015 or higher.

Prior medications are defined as those for which the end date is prior to the date of first dose of study treatment.

Concomitant medications are defined as those which are indicated as 'Ongoing' on the date of first dose of study treatment, or those which start on or after the date of first dose of study treatment, or those which start prior to date of first dose of study treatment and have an end date after the first dose of study treatment.

If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of patients who took any prior medications and the number and percentage of patients who took any concomitant medications will be presented separately by medication class and standardized medication names sorted alphabetically, by subgroup and overall for the SAF.

All prior and concomitant medications will be listed by reported name, medication class, standardized medication name, indication, dose, dose unit, frequency, route of administration, start date and end date or 'ongoing' flag.

2.1.7 Treatment exposure

Treatment exposure to ranibizumab will be summarized by subgroup and overall for the SAF, and will include:

- Duration of exposure to ranibizumab for both study eye and fellow treated eye, as well as total duration of exposure (study eye and fellow eye). Duration of exposure will be calculated as date of last ranibizumab injection – date of first ranibizumab injection + 1, for study eye, fellow treated eye and both eyes together
- Total number of injections overall the study course and number of injections by visit (including unscheduled visits), for both study eye and fellow treated eye
- Number and percentage of patients who received bilateral injections of ranibizumab (both the study eye and fellow eye injected at the same visit) by visit
- Reason for PRN treatment (BCVA decline, or OCT criteria) by visit during the PRN treatment period, for study eye
- Reason for no dosing by visit, for study eye. Prior to database lock, a complete list of reasons for no dosing during the Monthly treatment period, as recorded on the eCRF, will be provided by [redacted] to Novartis in an Excel spreadsheet. Novartis will review them and classify them as ocular or non-ocular.
- Compliance to treatment regimen, for study eye

Compliance to treatment regimen will be assessed as follows

- Monthly treatment period, compliance=100*(number of injections in study eye/3)
- PRN treatment period, compliance=100*(number of injections done in study eye / number of required injections in study eye based on changes in patient symptoms, BCVA or OCT)
  An injection will be considered as required if:
  - in the opinion of the Investigator persistent or worsening visual symptoms are attributed to nAMD and/or
  - there is evidence of worsening early treatment diabetic retinopathy study (ETDRS) BCVA (>1 letter decline since last Study Visit) and/or
  - the presence of persistent or worsening disease activity on OCT (presence of sub-retinal fluid, persistent or increased number, size or total volume of IRC, or increased central retinal or foveal thickness)

All treatment exposure to ranibizumab details, including derived variables, will be listed.

2.2 Efficacy evaluation

2.2.1 Primary objective

The primary objective is to demonstrate that the mean change from baseline in CSRT as determined by OCT at Day 90 is less than zero.

2.2.1.1 Variables

The primary variable will be the difference from baseline to Day 90 in CSRT.

2.2.1.2 Descriptive analyses

The change in CSRT from baseline to Day 90 will be summarized together with the 95% CI for the mean and absolute values of CSRT at baseline and at Day 90.

In the event that CSRT is missing for Day 90, the analysis will follow an LOCF (Last Observation Carried Forward) approach for the FAS.

The primary analysis will be performed on the FAS.

For sensitivity purposes, the primary analysis will be repeated using the PPS.

2.2.2 Secondary objectives

2.2.2.1 Variables

Secondary variables are:

From OCT

- Change from baseline to visits up to Day 180 in
    - Subfoveal Retinal Thickness (SRT) (*GRADE*: SUBFOVTK),
    - Central Subfield Retinal Thickness (CSRT) (*GRADE*: CSTTHK),
    - Central Subfield Retinal Volume (CSRV) (*GRADE*: CSRVVOL).
- Presence or absence of qualitative OCT parameters:
    - Intraretinal fluid (*GRADE:* RETFL),
    - Intraretinal fluid of cystoid origin (*GRADE*: RETIRC)
    - Subretinal fluid (SF) (*GRADE:* RETFLSF)
    - Intraretinal/subretinal fluid within the central subfield (diameter 1000 microns) (*GRADE:* RETSF)
    - Pigment epithelial detachments (PEDs) (*GRADE*: PEDDET),

  - Dry retina. Dry retina is defined as eye without intraretinal fluid (RETFL from derived.grade) AND eye without subretinal fluid (RETFLSF from derived.grade) AND eye without intraretinal cysts (RETIRC from derived.grade)

- Change from baseline to visits up to Day 180 in PED height (*GRADE*: PEDHEIGH) and diameter (*GRADE*: PEDDIAM) and IRC height (*GRADE*: IRCHEIGH).
- Frequency of qualitative change OCT parameters:
  - Change from previous visit, each visit up to Day 180 in intraretinal fluid (*GRADE*: INTRAFL)
  - Change from previous visit, each visit up to Day 180 in subretinal fluid (SF) (*GRADE*: SUBRETFL)
  - Change from previous visit, each visit up to Day 180 in intraretinal/subretinal fluid within the central subfield (*GRADE*: SUBCENT)
  - Change from previous visit, each visit up to Day 180 in the pigment epithelium detachment (PED). (*GRADE*: CHAGPED)

or **From visual acuity (for study eye and fellow eye)**

- Change in BCVA from baseline to visits up to Day 180.
- Change in BCVA from Day 90 to Day 180.
- Proportions of patients with change from baseline in ETDRS letters for the following categories:≤-15, >-15 to <0, ≤0 to <5, ≥5 to <10, ≥ 10 to <15 and ≥15 ETDRS letters from baseline at visits up to Day 180.

2.2.2.2 Descriptive analyses

The analysis of the secondary efficacy objectives will be performed on the FAS.

No replacement of missing data will be done.

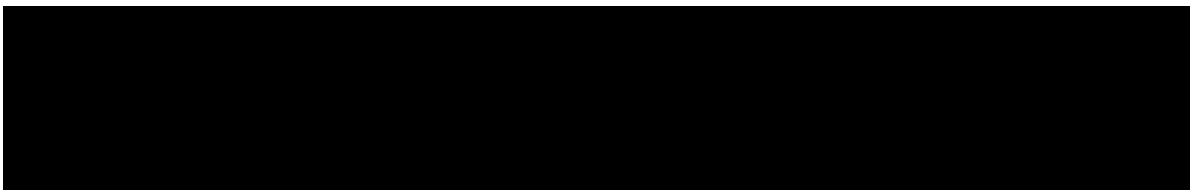
Data from visual acuity will be summarized for study eye and fellow eye separately.

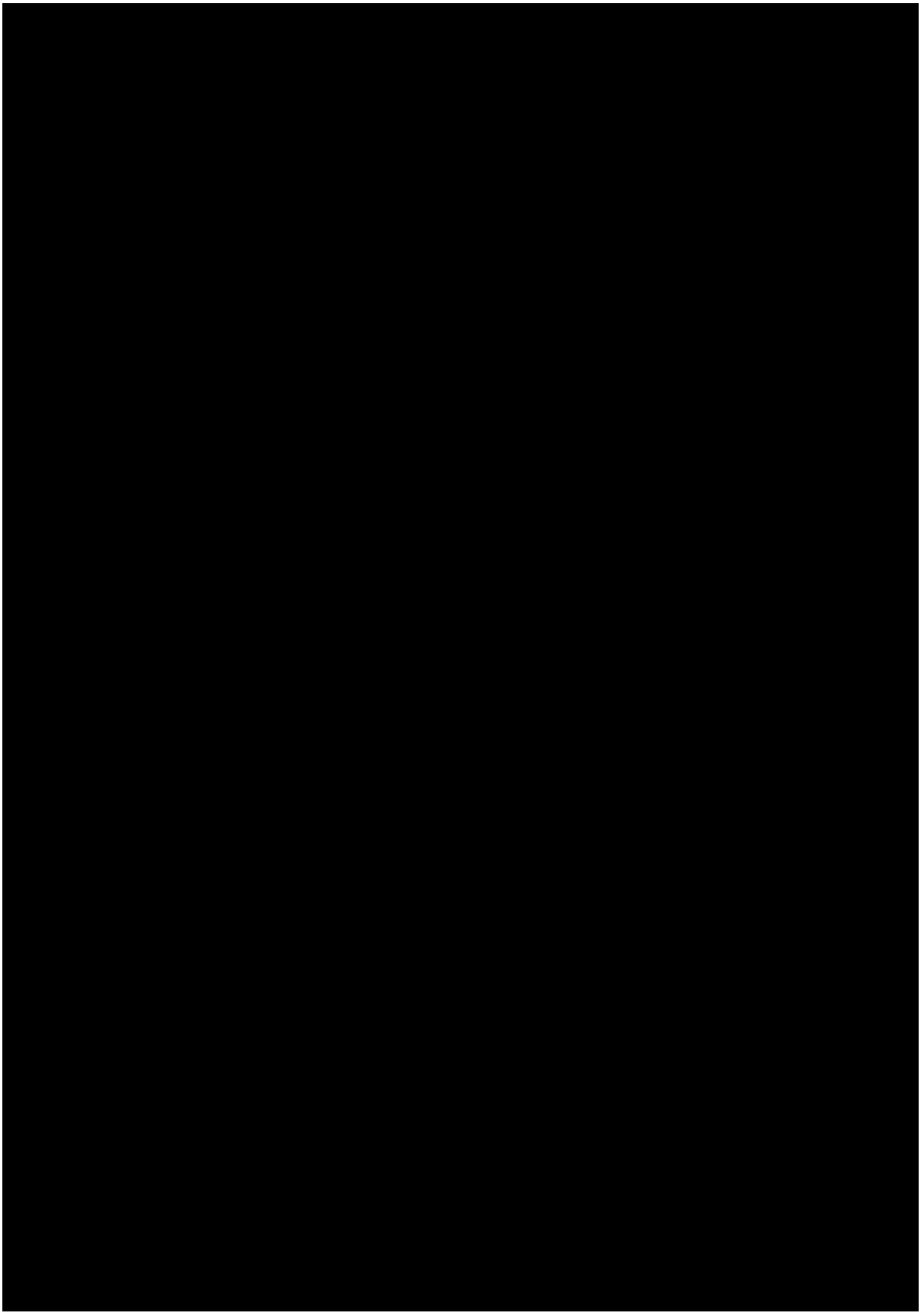
Continuous secondary variables will be summarized presenting the absolute values and changes from baseline by visit, and will also be plotted over time.

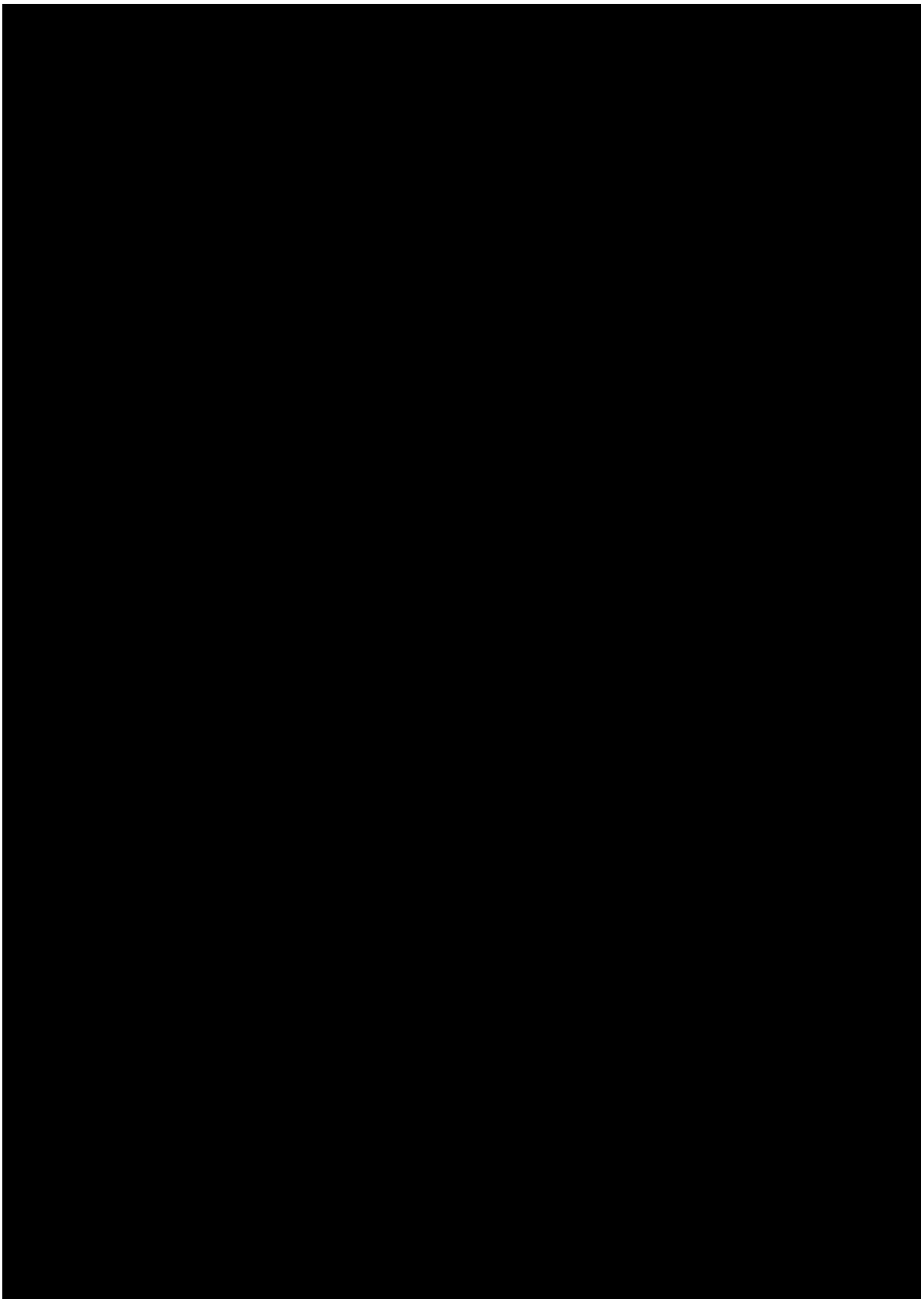
Waterfall plot for change in number of letters for BCVA will be presented.

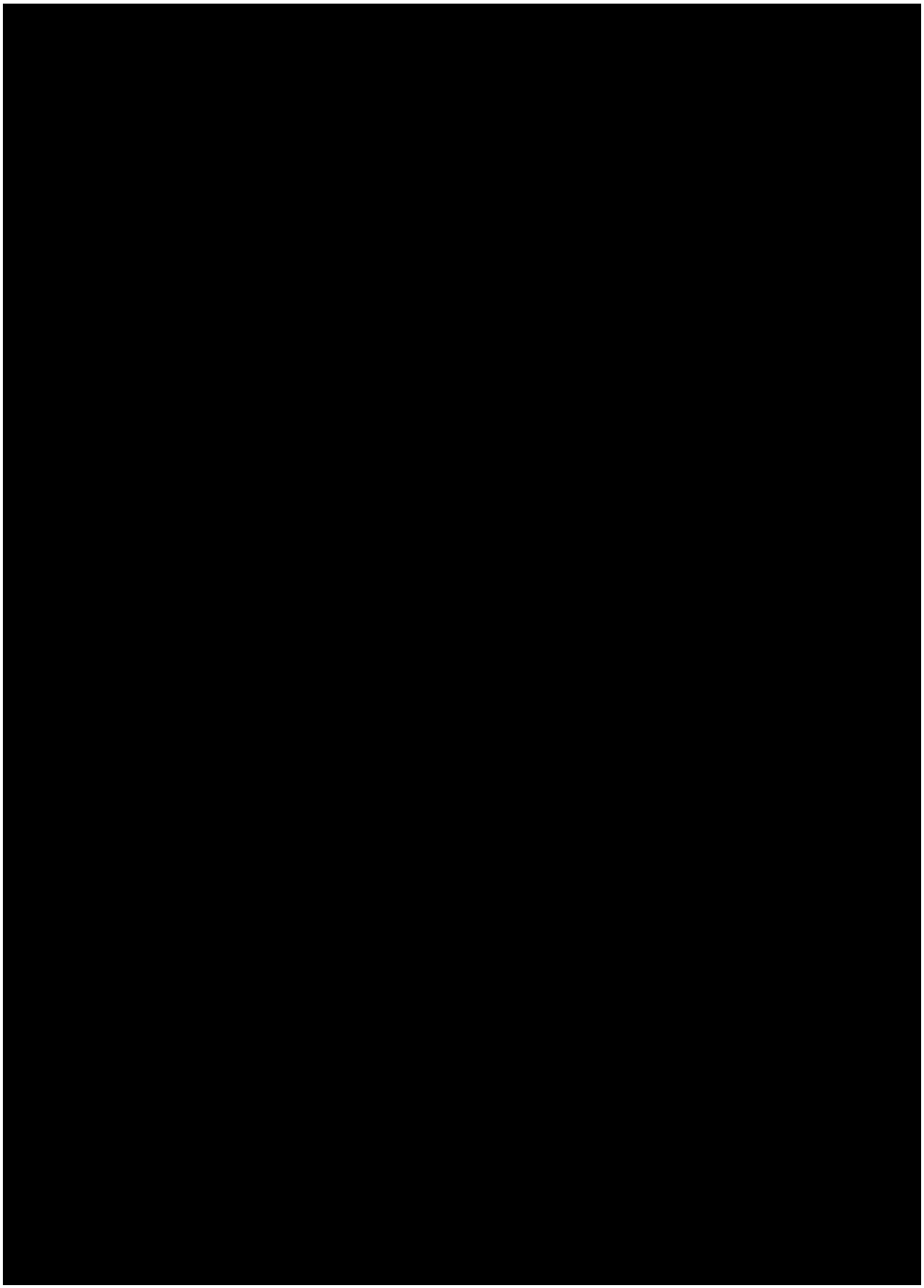
Qualitative secondary variables will be summarized presenting the number and percentage of patients for each modality by visit, and will also be presented graphically over time using bar charts.

All secondary variables details, including derived variables, will be listed.









2.4 Safety evaluation

All safety analyses will be performed using the Safety Set, by subgroups and overall.

2.4.1 Adverse events

Adverse events (AEs) will be coded according to MedDRA version 18.1 or higher.

A treatment-emergent adverse event (TEAE) is defined as an AE with start date/time on or after the first dose of study treatment, or AEs with worsening severity on or after the first dose of study treatment.

AEs with unknown start date/time will be assumed to be treatment-emergent unless the end date/time is known to be before the first dose of study treatment.

An overview summary of TEAEs will be created, including the number of events and the number and percentage of patients reporting: TEAEs, serious TEAEs, eye-related TEAEs, TEAEs leading to study discontinuation, TEAEs leading to death, TEAEs by severity and TEAEs by relationship to study treatment.

Summary tables of TEAEs presenting the number of events and the number and percentage of patients by SOC and PT will be created for:

- All TEAEs
- TEAEs by severity, patient will be counted once for each SOC and once for each PT at the maximum severity
- Study treatment related TEAEs
- Eye-related TEAEs
- Serious TEAEs
- Deaths
- TEAEs leading to study discontinuation

- TEAEs leading to dose adjustment (including study treatment discontinuation)

SOC and PT will be presented in decreasing frequency of the total number of patients with TEAEs. If a patient experienced more than one TEAE, the patient will be counted once for each SOC and once for each PT.

All AEs details will be listed with a flag for TEAEs.

Separate listings of all serious adverse events (SAEs) and of all eye-related AEs will also be presented with a flag for TEAEs. Eye-related AEs will be listed according to whether they occurred in the study eye, the fellow treated eye or both.

2.4.2 Vital signs

Vital signs include pulse rate, systolic blood pressure, and diastolic blood pressure.

Vital signs will be summarized by visit presenting shift tables using clinically notable abnormal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from baseline.

All vital signs data will be listed with a flag for values outside the clinically notable range.

2.4.3 Intraocular pressure

Intraocular pressure (IOP) measurements will be summarized by visit including absolute values and change from baseline.

All ophthalmic examination details will be listed.

2.5 Interim analysis

An interim analysis will be conducted after the first 50 patients have completed visits up to Day 90. This will be used primarily to provide preliminary data on the safety of ranibizumab in patients with nAMD with either primary treatment failure or suboptimal treatment response to aflibercept. The results from this Day 90 analysis will be submitted for publication. As no hypothesis tests will be carried out, no statistical adjustments are required.

Descriptive analyses will be carried out on the main safety and efficacy variables, as follows:

- Demographics and baseline characteristics
- Adverse events – All summary tables and listings mentioned in Section 2.4.1
- Primary efficacy variable
- Secondary efficacy variables – All summary tables and listings mentioned in Section 2.2.2.
- [redacted]

2.6 Other topics

None

[redacted]

3 Appendices

[redacted]

3.2 Appendix 2 Latest version of the VAP Module 3 - Protocol Deviations

[redacted]

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Final VAP M3 PDs V5