FYB201-C2015-01-P3
(BQ01)

Statistical Analysis Plan

Statistical Analysis Plan for Main and Final Analysis

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Study title:	Efficacy and Safety of the Biosimilar Ranibizumab FYB201 in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)
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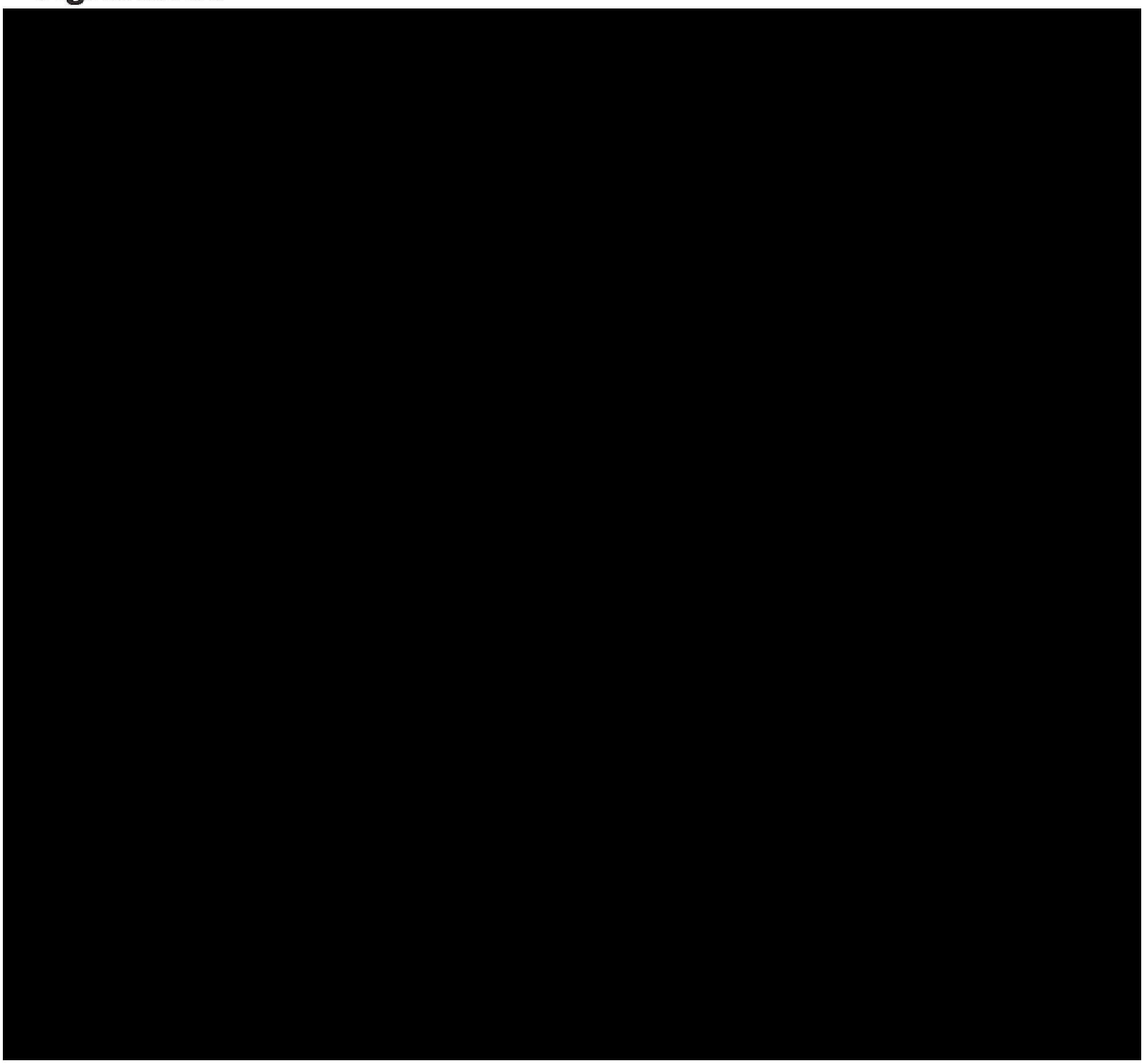
Sponsor:	Bioeq GmbH Bergfeldstraße 9 83607 Holzkirchen Germany

[redacted]

Signatures



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1 LIST OF ABBREVIATIONS

Abbreviation	Text
ADA	Anti-Drug Antibody
AE	Adverse event
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
BCVA	Best-Corrected Visual Acuity
BDRM	Blind Data Review Meeting
BMI	Body mass index
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
C_{max}	Maximum concentration
CM	Concomitant medication
CNV	Choroidal Neovascularization
CRC	Central Reading Centre
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report From
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FAS	Full Analysis Set
FCP	Foveal Centre Point
FCS	Foveal Central Subfield
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IOL	Intraocular Lens
IOP	Intraocular Pressure
ITT	Intention-to-treat
IVT	Intravitreal
IV/WRS	Interactive Voice/Web Response System
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MMRM	Mixed Model Repeated Measures
nAMD	Neovascular AMD

Abbreviation	Text
NEI VFQ-25	National Eye Institute Visual Function Questionnaire
OCT	Optical Coherence Tomography
OU	Both Eyes
PDT	Photodynamic Therapy
PK	Pharmacokinetic
PPS	Per Protocol Set
PSC	Posterior Subcapsular
PT	Preferred term
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-Emergent Adverse Event
US	United States
VA	Visual Acuity
WHO	World health organization

2 GENERAL

This statistical analysis plan (SAP) reflects the final study protocol version 9.0 incorporating amendment 7 dated 29 August 2017. It follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9.

In agreement with Section 12 of the final study protocol, two analyses will be conducted: A main analysis after all patients randomised have either completed the Week 24 assessments or have discontinued the study; a final analysis after all patients randomised have either completed the Week 48 assessments or have discontinued the study.

This SAP covers and describes all analyses for the main and the final analysis of this study. In contrast to Section 12.1 of the final study protocol, no separate SAPs are written for the main and the final analysis. This is due to the fact that the statistical analyses for the main and the final analysis overlap to a broad extent and both analyses will be reported in one clinical study report (CSR).

2.1 Analyses planned and already performed

No formal interim analysis was planned or was performed for this study.

The main analysis will be performed after all patients have either completed the Week 24 assessments or have discontinued the study. At this point, all relevant data will be cleaned and the database will be locked for unblinding. The main analysis will be described in a six month clinical study report (CSR) for internal use.

The final analysis will be performed when all randomised patients have either completed the Week 48 assessments or have discontinued the study. At this point, all newly added or modified data will be cleaned and the database will be locked for the analysis. In general, all data collected up to main analysis will be locked and cannot be modified later. Exceptions are concomitant medications and adverse events with a start date prior to the main analysis, where records such as end dates or outcomes are allowed to be modified after the main analysis if applicable and necessary. The analyses based on the whole study period will be described in a 12-month CSR, which will be an updated version of the six month CSR.

This SAP covers and describes all analyses for the main and the final analysis.

The SAP specifies different analysis sets taking into account different EU and US specific primary analyses. The CSR will contain all analyses specified in the SAP and will contain separate sections according to the region specific definitions and requirements.

An independent Data Safety Monitoring Board (DSMB) reviewed safety data on a regular basis and ad hoc if needed. The corresponding analyses are not covered or defined in this SAP and all further details are defined in a separate Data Safety Monitoring Board Charter.

2.2 SOPs to be followed

The statistical analysis will be carried out according to [redacted] Standard Operating Procedures (SOPs). The report will be written according to the ICH Guidelines Topic E3 and Topic E9.

3 OVERVIEW OF THE PROTOCOL

3.1 Objectives of the study

3.1.1 Objectives of the study for the main analysis

Primary objective:

- Evaluate and compare functional changes in best corrected visual acuity (BCVA) after 2 months (8 weeks) of treatment with FYB201 or Lucentis, compared to baseline BCVA

Secondary objectives:

The secondary objectives evaluated at the main analysis are to:

- Evaluate and compare functional changes of the retina by BCVA over time
- Evaluate and compare changes in foveal centre point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness over time
- Evaluate and compare presence of active choroidal neovascularization (CNV) leakage at Month 6 compared to baseline
- Evaluate and compare the absence of disease activity (fluid-free macula) over time
- Evaluate and compare total lesion size at Month 6 compared to baseline
- Evaluate and compare systemic ranibizumab concentrations close to C_{max} after the first and the sixth doses (24 hours post-dose [±3 hours]) in a subgroup of up to 60 patients
- Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) at Month 6 compared to baseline
- Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum
- Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs)

For all objectives evaluated over time at the main analysis, this refers to all assessments performed up to and including Month 6 [Week 24] and final visit assessments for patients who discontinued early prior to Month 6 [Week 24].

3.1.2 Objectives of the study for the final analysis

The primary objective will be evaluated based on fully clean data at the main analysis. The primary objective will be re-run at the final analysis but no changes of the results are expected. Similarly, all secondary objectives evaluated at the main analysis will be re-run at the final analysis but no changes of the results are expected. Additionally, the following

secondary objectives will be evaluated at the final analysis:

Secondary objectives:

- Evaluate and compare functional changes of the retina by BCVA over time
- Evaluate and compare changes in foveal centre point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness over time
- Evaluate and compare presence of active choroidal neovascularization (CNV) leakage at Month 12 compared to baseline
- Evaluate and compare the absence of disease activity (fluid-free macula) over time
- Evaluate and compare total lesion size at Month 12 compared to baseline
- Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) at Month 12 compared to baseline
- Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum
- Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs)

For all objectives evaluated over time at the final analysis, this refers to all assessments performed up to and including the final visits of all randomised patients.

3.2 Study design

The COLUMBUS-AMD study is a parallel-group, 1:1 randomised, active-controlled, evaluation-masked, multicentre study to demonstrate clinical equivalence in terms of clinical efficacy, pharmacology, and safety of FYB201 with Lucentis over 12 months of treatment in patients with subfoveal neovascular age-related macular degeneration (nAMD).

Patients must meet all eligibility criteria at the screening visit, including positive evaluation of the screening retinal images performed by the central reading centre. After all eligibility requirements are confirmed, patients who are found to be eligible will be randomised into one of the two treatment groups in a 1:1 ratio (FYB201:Lucentis) using an interactive voice response system (IVRS) or interactive web response system (IWRS). Randomization will be stratified by site and screening BCVA category (20/32 (0.63) Snellen equivalent, or 20/40 (0.50) – 20/100 (0.2) Snellen equivalent) based on the dynamic allocation method. Once a maximum of 48 patients with a screening BCVA of 20/32 (0.63) are enrolled, randomization to this stratum will be stopped.

All patients will receive monthly intravitreal (IVT) injections over a time period of approximately 12 months (48 weeks). Patients will receive FYB201 or Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as monthly (every 4 weeks) IVT injections starting at Visit 1 (Week 0) through Visit 12 (Week 44) (total of 12 injections).

Systemic ranibizumab concentration close to C_{max} after first and sixth IVT injections (24 hours post-dose [±3 hours]) and ADA formation one week after first IVT injection will be assessed in a subgroup of up to 60 patients of selected study centres.

Treatment allocation in the PK subgroup may not be fully balanced between FYB201 and Lucentis, as the inclusion in the PK subgroup was independent of the randomization.

3.3 Sample size

The required sample size for the primary endpoint is calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. The calculation is based on using a 95% confidence interval, i.e. a two-sided significance level of 2.5, to establish equivalence in line with EMA requirements.

Requesting a power of the trial of 90%, assuming no difference between the treatment groups, and using an equivalence margin of 3.5 ETDRS letters requires a total of 412 evaluable patients (206 patients each to be treated with FYB201 and Lucentis, respectively). Since the EU specific analysis will be limited to patients with a screening Snellen equivalent of 20/40 or worse and assuming that approximately 10% of all patients randomised will be in the 20/32 strata, a total of 460 patients will need to be enrolled.

A sample size of 460 is also sufficient for the US specific analysis. In particular, 230 patients per treatment group will provide at least 95% power for assessing equivalence in the change in BCVA using a 90% confidence interval, a standard deviation of 10 letters, no expected difference between the treatment groups, and an equivalence margin of 3.5 letters.

3.4 Endpoints

3.4.1 Endpoints for the main analysis

Primary endpoint:

- Change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment. For the US, this endpoint will be evaluated in all patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent, while for the EU the endpoint will be evaluated in the group of patients with a screening BCVA between 20/40 and 20/100 Snellen equivalent.

Secondary endpoints:

- Change from baseline in BCVA by ETDRS letters over time
- Changes from baseline in FCP retinal thickness and FCS retinal thickness over time
- Percentage of patients with active CNV leakage at Month 6
- Percentage of patients with fluid-free macula at each visit
- Change from baseline in total lesion area at Month 6
- Summary of systemic ranibizumab concentrations close to C_{max} after the first and sixth IVT injections (24 hours post-dose [±3 hours]) in a subgroup of up to 60 patients
- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 at Month 6

- Number of patients with anti-drug antibodies over time
- Frequency of local and systemic AEs and SAEs (up to the safety cut-off date; see Section 5.1)

For all endpoints evaluated over time at the main analysis, this refers to all assessments performed up to and including Month 6 [week 24] and final visit assessments for patients who discontinued early prior to Month 6 [week 24].

3.4.2 Endpoints for the final analysis

The primary endpoint will be evaluated based on fully clean data at the main analysis. The analysis of the primary endpoint will be re-run at the final analysis but no changes of the results are expected. Similarly, all analyses for secondary endpoints evaluated at the main analysis will be re-run at the final analysis but no changes of the results are expected. Additionally, the following secondary endpoints will be evaluated or updated at the final analysis:

Secondary endpoints:

- Change from baseline in BCVA by ETDRS letters over time
- Change from baseline in BCVA by ETDRS letters after 12 months (averaged over Months 10 [Week 40], 11 [Week 44] and 12 [Week 48])
- Changes from baseline in FCP retinal thickness and FCS retinal thickness over time
- Percentage of patients with active CNV leakage at Month 12
- Percentage of patients with fluid-free macula at each visit
- Change from baseline in total lesion area at Month 12
- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 at Month 12
- Number of patients with anti-drug antibodies over time
- Frequency of local and systemic AEs and SAEs

For all endpoints evaluated over time at the final analysis, this refers to all assessments performed up to and including the final visits of all randomised patients.

3.5 Study flow chart

Table 1 Schedule of Study Events - Visits for ALL patients

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V4	V5	V6	V6a**	V7	V8	V9	V10	V11	V12	Final Visit
Week (Day)	W-4–W-1 (-28to-1)	W0 (0)	D1 (1±3 h)	W1 (7±1)	W4 (28±3)	W8 (56±3)	W12 (84±3)	W16 (112±3)	W20 (140±3)	W20+24 h (±3 h)	W24 (168±3)	W28 (196±3)	W32 (224±3)	W36 (252±3)	W40 (280±3)	W44 (308±3)	W48 (336±3)
Patient information / informed consent	x																
Demographics information	x																
Medical History	x																
Prior treatments	x																
Physical assessment, vital signs[1]	x										x						x
BCVA[2,3]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
Tonometry[3,4,5]/ ophthalmological examination[3,6]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
Inclusion/Exclusion	x	x[12]															
Randomization		x															
Fluorescein angiography*[3]	x										x						x
Color Fundus Photography[3]	x										x						x
SD-OCT[3]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
NEI VFQ-25[7]		x									x						x
Laboratory tests	x										x						x
Pregnancy (serum HCG) *(only women)*	x																
PK*/8		x**	x**							x**							
ADAs[9]		x		x**	x		x				x						x

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V4	V5	V6	V6a**	V7	V8	V9	V10	V11	V12	Final Visit
Week (Day)	W-4–W-1 (-28 to -1)	W0 (0)	D1 (1±3 h)	W1 (7±1)	W4 (28±3)	W8 (56±3)	W12 (84±3)	W16 (112±3)	W20 (140±3)	W20+24 h (±3 h)	W24 (168±3)	W28 (196±3)	W32 (224±3)	W36 (252±3)	W40 (280±3)	W44 (308±3)	W48 (336±3)
Concomitant med.		x	x**	x**	x	x	x	x	x	x**	x	x	x	x	x	x	x
AEs[10]	x	x	x**	x**	x	x	x	x	x	x**	x	x	x	x	x	x	x
IVT treatment[11]		x			x	x	x	x	x		x	x	x	x	x	x	
3-Day Post-Injection Telephone Safety Check		x			x	x	x	x	x		x	x	x	x	x	x	

* Additional fluorescein angiography may be performed at any time at the discretion of the Masked Investigator/s.
** Subgroup only.
1 Before any blood sample collection on the same day.
2 Refraction and VA testing must be performed prior to any other visual examination that requires eye drops (i.e. ophthalmological examination, FA, color fundus photography and SD-OCT) using ETDRS charts.
3 Ocular assessments at Screening and Final visit are performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.
4 Goldmann applanation tonometry must be performed at Screening. The Tonopen or Perkins Tonometer, may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30 mm Hg.
5 Tonometry should be measured prior to the injection and at least 30 minutes after the injection.
6 A complete ophthalmic examination should be performed prior to the IVT injection. For details and examinations after the IVT injection please see Section 10.4.
7 Before any invasive procedure.
8 Evaluation of systemic ranibizumab concentration only
9 In case of confirmed anti-drug antibodies, the titer and neutralizing capacity of ADAs (nAbs titer) will be evaluated
10 AEs starting after signing the informed consent must be recorded on relevant AE page.
11 A safety check will be performed just after the injection.
12 No significant anatomical change in the study eye compared to screening and visual acuity in the study eye within the defined inclusion criteria range (Snellen equivalent20/32 [0.63] to 20/100 [0.2]) and within 5 letters of the Screening BCVA.

ADA: Anti-drug antibody, AE: Adverse event, BCVA: Best-corrected visual acuity, D: day, ETDRS: Early treatment diabetic retinopathy study, h: hours, HCG: Human chorionic gonadotropin, IOP: Intraocular pressure, IVT: Intravitreal, nAb: neutralizing antibody, NEI VFQ-25: National eye institute visual function questionnaire 25, OU: Both eyes, PK: Pharmacokinetic, SD-OCT: Spectral domain optical coherence tomography, V: Visit, VA: Visual acuity.

VISIT WINDOWS:
It is essential that patients adhere to their scheduled study visits within the following visit windows:
- **Visits 1a and 6a (Subgroup only):** **24 hours after first and sixth IVT injections (respectively) ± 3 hours**
- **Visit 1b (Subgroup only):** **± 1 day**
- **Visit 2 to Visit 12 (all patients):** **± 3 days**

4 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

4.1 Analysis Sets

The following analysis sets are defined for the statistical analysis of all data. Decisions on the allocation of patients will be made prior to unblinding of the randomization code and will be documented in the Blind Data Review Meeting (BDRM) minutes for the main analysis prior to the Week 24 database lock (see section 4.2).

Safety Set (SAF):

The safety set includes all patients who receive at least one injection with investigational medicinal product (IMP). The safety set will be used as general analysis set for all kinds of safety and tolerability data. Patients will be analysed according to the treatment they actually received irrespective of their randomised treatment. If only single injections from the wrong treatment were administered it will be decided on a case by case basis how the patient will be analysed.

For all other analysis sets, different analysis sets are considered for the EU and for the US specific analyses:

Full Analysis Set for the EU (FAS_EU):

The FAS_EU is based on the intention to treat (ITT) principle (i.e., patients will be analysed according to their randomised treatment irrespective of the treatment they actually received) and includes all patients

- who receive at least one injection of IMP and
- for whom BCVA results at least after 1 month are available and
- who have a screening BCVA between 20/40 and 20/100 Snellen equivalent in the study eye.

Full Analysis Set for the US (FAS_US):

The FAS_US is based on the ITT principle (i.e., patients will be analysed according to their randomised treatment irrespective of the treatment they actually received) and includes all patients

- who receive at least one injection of IMP and
- for whom BCVA results at least after 1 month are available and
- who have a screening BCVA between 20/32 and 20/100 Snellen equivalent in the study eye.

Per-Protocol Set for the EU (PPS_EU):

The PPS_EU includes all patients

- who belong to the FAS_EU and
- who have no major protocol deviations until V3 (visit after 8 weeks) that would interfere with the interpretation of BCVA efficacy data.

Per-Protocol Set for the US (PPS_US):

The PPS_US includes all patients

- who belong to the FAS_US and
- who have no major protocol deviations until V3 (visit after 8 weeks) that would interfere with the interpretation of BCVA efficacy data.

PK Subgroup Analysis Set:

The PKS includes all patients

- who receive an initial injection of IMP and
- who have a valid measurement close to C_{max} post-first dose and
- who have no major protocol deviations that would interfere with the interpretation of the ranibizumab concentration data (e.g., a high ADA titre may interfere with the PK assay and might lead to a major protocol deviation if the interpretation of the concentration data is disturbed or limited; such cases will be discussed on a by-patient basis in the main BDRM).

Patients in PKS will be analysed according to the treatment they actually received irrespective of their randomised treatment.

Patients have a valid measurement close to C_{max} post-first dose if they have a valid measurement close to C_{max} at eCRF Visit 1a or eCRF Visit 6a. The validity of the C_{max} measurement is confirmed by the PK laboratory if the specimen condition is classified as “OK” and if there are no comments which point to a non-validity of the C_{max} measurement.

4.2 Protocol deviations

A preliminary classification of protocol deviations in major or minor deviations was mutually agreed between bioeq GmbH and [redacted] at the start of the study. Deviations to the study protocol are documented in a Protocol Deviation Log during the study. Other protocol deviations will be identified via programming or manual medical review based on documented data. A Blind Data Review Plan will specify the criteria for these protocol deviations, the method to identify these and the specific statistical outputs that will be used for data review and protocol deviations. All protocol deviations relevant for the main analysis will be reviewed during the BDRM before database lock in order to allocate the patients into the different analysis sets. Protocol deviations observed later than the assessments at Week 24 for the final analysis will not affect the allocation of patients into the different analysis sets.

All protocol deviations will be listed by patient and treatment group. The deviations will be assessed as major or minor during the BDRM for the main analysis with regard to their influence on any of the primary efficacy or pharmacokinetic variables prior to locking the database. If applicable, the reasons for exclusion of patients from any of the analysis sets will be listed and, where relevant, the data of these patients will be described separately.

Summary tables will be used to tabulate the number and percentage of patients with major and minor protocol deviations additionally stratified by type of protocol deviation and treatment group.

4.3 Changes or deviations from planned analyses

The primary endpoint has been re-formulated as the stratification of patients has been changed to be performed based on the **screening BCVA** instead of based on the **baseline**

BCVA (this change has been documented in a corresponding protocol amendment):

Change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment. For the US, this endpoint will be evaluated in all patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent, while for the EU the endpoint will be evaluated in the group of patients with a screening BCVA between 20/40 and 20/100 Snellen equivalent.

The definitions of the Full Analysis Sets for the EU and the US have been amended accordingly and “baseline BCVA” was replaced by “screening BCVA” throughout.

Furthermore, the definition of the Full Analysis Sets for the EU and the US has been revised and instead of “for whom efficacy results at least after 1 month are available” has been changed to “for whom BCVA results at least after 1 month are available” to provide a more precise definition.

5 DEFINITIONS FOR STATISTICAL ANALYSIS

Any additional statistical analyses that are not described in the SAP will be documented in the final CSR.

5.1 Definitions for statistical analysis for the main analysis

The main statistical analysis will be performed after completion of the following working steps:

- All electronic case report form (eCRF) data relevant for the main analysis are available and have been checked for errors and/or inconsistencies.
- All queries relevant for the main analysis have been answered and necessary editing of the data base has been performed.
- The database has been closed and all eCRF pages relevant for the main analysis have been locked, i.e., further changes of database contents relevant for the main analysis are not permitted and physically impossible. All study personnel has been informed that continuously collected data (e.g., concomitant medications and adverse events) with start dates during the study period relevant for the main analysis has to be entered into the eCRF prior to data base lock for the main analysis.
- A detailed final statistical analysis plan is available and approved by responsible personnel.

Snapshot for the main analysis and related cut-off dates:

The analysis and reporting of the main analysis will be done based on a snapshot of the data once all relevant queries have been resolved. The snapshot for the main analysis will include all data collected up to and including the data assigned to eCRF Visit 7/Week 24 and all data collected at the final visits of all patients who discontinued the study early prior to eCRF Visit 7 /Week 24.This cut-off will be referenced as “general cut-off for the main analysis” in this SAP.

All visit-based collected data that were assigned to analysis visits (see section 5.4) up to the general cut-off for the main analysis will be included. An exception is valid for the visit-based data collected for study drug administration. Since the study drug is administered after all efficacy assessments have been performed at eCRF Visit 7, all study drug administration information collected up to and including eCRF Visit 6 will be included for the main analysis, will be assigned to analysis visits and will be displayed in summary tables and patient data

listings. For event-based data that were collected continuously during the study all events with a start date up to and including a safety cut-off date will be included in the analysis. This safety cut-off date is defined as the date of the injection performed at eCRF Visit 7 minus 1 day (i.e., the safety cut-off date is calculated individually for each patient). If no injection has been performed at eCRF Visit 7, the date of the injection performed at eCRF Visit 6 plus 27 days will be used as safety cut-off date.

Pooling algorithm for countries:

The country, in which the study centre is located, will be used as a covariate in the efficacy analyses. The following algorithm for pooling countries will be used:

- all countries including less than fifteen patients have to be pooled with another country.
- to avoid a too low number of patients for certain countries, Russia will be pooled with the Ukraine (both countries use Cyrillic letters), Austria will be pooled with Germany, and Great Britain will be pooled with France.

The decision about the final pooling of countries will be made during the main BDRM and will be documented in the main BDRM minutes.

5.2 Definitions for statistical analysis for the final analysis

The final statistical analysis will be performed after completion of the following working steps:

- All electronic case report form (eCRF) data are available and have been checked for errors and/or inconsistencies.
- All queries have been answered and necessary editing of the data base has been performed.
- The database has been closed, i.e., further changes of database contents are not permitted and physically impossible.

For the final analysis defined for the study period up to and including Week 48, all analyses defined for the main analysis in this SAP will be re-run based on the information gathered throughout the whole study period. Of course, all data which has been finally locked for the main/Week 24 analysis (this especially refers to the analysis of the primary efficacy endpoint at the main/Week 24 analysis) is not expected to be changed later. Summary tables based on data which is collected continuously during the study (e.g., adverse events and concomitant medication) will be updated accordingly without differentiating between data collected up to and including, and data collected after the main/Week 24 analysis. All by-visit summary tables and figures displaying the time course of variables which are assessed on a by-visit basis will be expanded for the Week 48 analysis. Some additional analyses will be included in the final analysis, for example, if efficacy endpoints are evaluated at Week 24 and Week 48, both analyses will be included.

The pooling algorithm for countries defined for the main analysis will also be used for the final analysis (see Section 5.1).

5.3 Handling of withdrawals (drop-outs), missing values and outliers

5.3.1 Handling of withdrawals (drop-outs), missing values and outliers in the main analysis

For the primary efficacy endpoint, the following strategy for handling missing data and/or withdrawals will be applied:

Discontinued or withdrawn patients will not be replaced. Data from patients who prematurely discontinue the trial will be used to the maximum extent possible. With the readouts for the primary endpoint being early in the trial, the impact of missing BCVA data is considered limited. However, the pattern and reasons for missing data will be carefully examined. As a sensitivity approach for handling missing data in the evaluation of the primary efficacy endpoint, a Mixed Model Repeated Measures (MMRM) approach will be used to model the change from baseline in BCVA depending on important baseline characteristics such as treatment group (FYB201 or Lucentis), baseline BCVA and Country. BCVA is determined at Visit 2, at Visit 3 (evaluation of primary endpoint), and Visit 4 to Visit 7, i.e., at four weeks, at eight weeks, and every four weeks thereafter, respectively and a change from baseline in BCVA can be calculated for all visits Visit 2, Visit 3, and Visit 4 to Visit 7.

The following MMRM will be estimated for the changes from baseline in BCVA at visits Visit 2 to Visit 7 because this model is able to handle missing values in the response variable, i.e., in the change from baseline in BCVA. The SAS code will be similar to the following statements:

```
proc mixed;
      class subjid country treatment visit;
      model CHG_BCVA = BCVA_base country treatment visit
                              treatment*visit /s ddfm = kr;
     repeated visit/ subject = subjid type = UN;
      lsmeans treatment*visit/ diff cl alpha=0.05/0.1*;
      estimate 'Visit 3' treatment -1 1
                        treatment*visit 0 -1 0 0 0 0 0 1 0 0 0 0/CL;
run;
```

** alpha levels depends on if the analysis is performed for FAS_EU (95% CI is required and thus, alpha is set to 0.05) or FAS_US (90% CI is required and thus, alpha is set to 0.1).

The MMRM model uses all available changes from baseline in BCVA for all patients in the respective analysis set for model estimation. If a patient has a missing change from baseline in BCVA at Visit 2 to Visit 7, the model assumes that the patient's missing change from baseline in BCVA is comparable to the observed change from baseline in BCVA of another patient having identical baseline characteristics and a comparable course of changes from baseline in BCVA. As the change from baseline in BCVA at Visit 3 (at Week 8) is relevant for the primary efficacy analysis, the corresponding difference in least square means for the two treatment groups is calculated together with the corresponding 90% confidence interval (CI) (for US) and the corresponding 95% CI (for the EU). If the respective CI is completely contained in the interval]-3.5; 3.5[letters, equivalence of FYB201 and Lucentis can be concluded in this sensitivity analysis. An unstructured correlation matrix for visits Visit 2 to Visit 7 is assumed for the MMRM. This MMRM model is different from the ANCOVA model which is specified for the primary efficacy analysis (see Section 6.8.2), where only the change from baseline in BCVA at week 8 is considered and all patients with missing change from baseline in BCVA at week 8 are excluded from the analysis.

Prior to the main BDRM, the pattern of missing changes from baseline in BCVA will be investigated in a blinded manner and the strategy for handling missing data will be reconsidered prior to database lock and unblinding. This SAP will be amended and finalized as necessary thereafter.

No other procedures for replacing missing data are intended and all other data will not be replaced. However, the pattern of missing data will be investigated in a blinded manner prior to the BDRM and the strategy for handling missing data will be reconsidered if deemed necessary prior to database lock and unblinding.

Sensitivity analyses using the PPS_US and PPS_EU will be performed for the primary efficacy endpoint (change from baseline in BCVA) and for the secondary efficacy endpoint change from baseline in FCP retinal thickness. If a considerable amount of patients (defined as at least 10% of the patients in the FAS_EU) is excluded from the FAS_US and FAS_EU due to major protocol deviations for definition of the corresponding PPS_US and PPS_EU, sensitivity analyses based on the PPS_US and PPS_EU will be performed for all defined efficacy analyses. The final decision about the allocation of patients to analysis sets will be drawn during the main BDRM and will be documented in the main BDRM minutes.

All sensitivity analyses for the primary efficacy analysis are included in Section 14.2.2 of the summary tables (see the SAP Appendix).

5.3.2 Handling of withdrawals (drop-outs), missing values and outliers in the final analysis

The same definitions specified for the main analysis apply for the final analysis. The MMRM will be re-run for the changes from baseline up to and including eCRF Visit 7 at the final analysis and the MMRM results are expected to be identical at the final analysis.

5.4 Visit windows and analysis visits

5.4.1 Visit windows and analysis visits for the main analysis

The following visit windows have been defined for the main analysis:

- Visit 1a and 6a **: 24 hours after first and sixth IVT injections (respectively) +/- 3 hours
- Visit 1b **: 7 days after first IVT injection +/- 1 day
- Visit 2 to Visit 7: +/- 3 days

** subgroup to analyse systemic ranibizumab concentrations only.

Potential influences of the visit window deviatons on the endpoints will be discussed in the main BDRM and might influence the allocation of patients to the analysis sets. The final decision of visit window deviations and the associated consequences will be documented in the main BDRM minutes.

In order to include assessments from unscheduled visits in the best way, all visit-based assessments will be analysed according to analysis visits and thus not necessarily according to the visit indicated in the eCRF. Analysis visits are defined as follows:

Analysis visit name	**Target day**	**Definition**
V0/Screening	NA	eCRF visit = “V0/Screening”

V1/Baseline	NA	eCRF vist = “V1/Baseline”, except for parameters and for assessments that are missing for eCRF visit = “V1/Baseline, in these cases eCRFvisit = “V0/Screening” The baseline assessment is defined as the last assessment prior to first injection of study treatment. Assessments performed at the same date as the first injection of study treatment are considered to have been performed prior to the injection. For safety laboratory, assessments performed in the framework of the RETEST procedure prior to the first injection of study treatment will be considered when identifying the baseline assessment. Any unscheduled assessments performed prior to the first injection of study treatment will be considered for indentifying the baseline assessment.
V1a/ Day 1	NA	eCRF visit = “V1a” Assessments at visit V1a are available for patients in the PK subgroup only.
V1b/ Week 1	NA	eCRF visit = “V1b” Assessments at visit V1b are available for patients in the PK subgroup only.
V2/Week 4	29	9 < Study day < 43 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V3/Week 8	57	43 ≤ Study day < 71 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V4/Week 12	85	71 ≤ Study day < 99 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V5/Week 16	113	99 ≤ Study day < 127 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V6/Week 20	141	127 ≤ Study day < 155 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V6a/ Week 20 + 24h	NA	eCRF visit = “V6a” Assessments at visit V6a are available for patients in the PK subgroup only.

V7/Week 24	169	155 ≤ Study day < 183 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V8/Week 28	197	183 ≤ Study day < 211 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V9/Week 32	225	211 ≤ Study day < 239 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V10/Week 36	253	239 ≤ Study day < 267 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V11/Week 40	281	267 ≤ Study day < 295 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
V12/Week 44	309	295 ≤ Study day < 323 Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Final Visit/Week 48	337	323 ≤ Study day Assessments performed in the framework of the RETEST procedure will not be assigned to this analysis visit. Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.

NA = not applicable

If more than one assessment falls into the same analysis visit window, the assessment closer to the target day will be selected as relevant assessment for the respective analysis visit. If assessments are equally close, the later assessment will be selected as relevant assessment for the respective analysis visit.

Unscheduled visits performed between study day 2 and study day 9 will not be assigned to any analysis visit.

All anti-drug antibody (ADA) related data will not be assigned to analysis visits as described above because anti-drug antibodies are only measured at selected visits. ADA related data will be analysed and summarised by scheduled eCRF visit. All ADA results which were

assessed at regular but unscheduled visits for ADA assessments or at unscheduled visits will be assigned to the previous scheduled visit for ADA assessments for the statistical analysis. If this procedure results in multiple ADA assessments being assigned to the same scheduled eCRF visit, the following rules apply:

- If at least one of the multiple ADA assessments is positive, a positive ADA assessment will be tabulated
- If no ADA assessment is positive and at least one ADA asssessment is negative, a negative ADA assessment will be tabulated
- If all ADA assessments are missing, not reportable or insufficient samples were taken, a missing ADA assessment will be tabulated

for the respective scheduled eCRF visit.

Please note that the baseline visit is referenced with study day 0 in the schedule of assessments (see Section 3.5), but the baseline visit/ day of first administration of study medication is referenced with study day 1 in the programming to be Clinical Data Interchange Standards Consortium (CDISC) compliant (see Section 5.6). The above definition of analysis visit windows is based on programmed study days and hence, the study days are always shifted by 1 day compared to the schedule of assessments.

5.4.2 Visit windows and analysis visits for the final analysis

The following visit windows have been defined for the final analysis:

- Visit 1a and 6a **: 24 hours after first and sixth IVT injections (respectively) +/- 3 hours
- Visit 1b **: 7 days after first IVT injection +/- 1 day
- Visit 2 - Visit 12 and the final visit: +/- 3 days

** subgroup to analyse systemic ranibizumab concentrations only.

The definition of analysis visits for the final analysis is identical to the definitions specified for the main analysis (see Section 5.4.1).

5.5 Baseline

The assessments performed at Visit 1 will be considered as baseline values. If multiple assessments are available for Visit 1 (also considering unscheduled and RETEST assessments), the latest assessment prior to study drug administration will be considered as baseline value. Assessments performed at the same date as the first injection of study treatment are considered to have been performed prior to the injection. If the assessment at Visit 1 is missing, the assessment at Screening will be considered as baseline value.

For all variables where no assessment is performed at Visit 1 (e.g., FA, color fundus photography), the Screening assessments will be considered as baseline values.

The definition of baseline assessments is identical for the main and the final analysis.

5.6 Reference day / Day 1 / Day 0

Day 1 is defined as the date of first injection of IMP. Study days for statistical analysis will be calculated relative to Day 1. There is no study day 0.

The definition of reference days is identical for the main and the final analysis.

5.7 Masked and unmasked data reporting

At each study centre, there are masked and unmasked study personnel. There are at least 2 masked staff members (the principal investigator and a visual acuity (VA) examiner) and at least one unmasked injector who administers the IMP. There may be further masked study centre staff (e.g., study coordinator, study nurse, SD-OCT technician, photographer, back-up mask investigator, back-up VA examiner) and the unmasked injector may also need a back-up.

Masked study centre personnel have full access to the whole eCRF to document data and sign eCRF pages. Unmasked study centre personnel have only limited access to the eCRF and can only collect and document data for study drug administration, safety checks after the injection, adverse events occurring after injection, and prior and concomitant medications. Therefore, a masked and an unmasked version exist of the adverse event (AE) and concomitant medication (CM) eCRF pages. For the statistical analyses, there will be no differentiation between masked and unmasked AEs and CMs. All information on AEs regardless whether it was documented by masked or unmasked personnel, will be included in patient data listings. The relationship of an AE had to be documented by the masked investigator for all AEs. If the same AE was reported by the masked and the unmasked investigator, the AE will be counted only once in summary tables and the worst relationship and worst severity will be tabulated. Both AEs will be included in listings and marked accordingly.

Masked and unmasked AEs and CMs will be handled identically in the main and the final analysis.

5.8 Screening failures

The classification of a patient as a screening failures needs to be clearly documented in the eCRF. Screening failures are defined as patients who were enrolled in the study but were not randomised.

For screening failures, the informed consent date, the screening date and the reason for screening failure will be listed. Screening failures will not be considered in any of the summary tables or figures. Separate listings will be generated for screening failures.

Screening failures will be handled and analysed identically in the main and in the final analysis.

6 STATISTICAL ANALYSIS SPECIFICATION

6.1 Specifications related to the main analysis

6.1.1 Tables

If not explained differently below, data will be summarised descriptively and will be presented by treatment group (FYB201, Lucentis, and overall) and analysis visit / time point if applicable. Continuous data will be presented as number of patients, arithmetic mean, standard deviation (SD), minimum (Min), first quartile (Q1), median, third quartile (Q3) and maximum (Max). Absolute values per analysis visit/ time point as well as absolute changes from baseline by analysis visit/ time point will be displayed using the defined summary statistics. In these

summary statistics, minimum and maximum will be displayed with the same number of decimal places which have been used for measuring the original continuous variable in raw data. One additional decimal place will be displayed for the arithmetic mean, the median, and all other summary statistics; two additional decimal places will be displayed for the SD.

Categorical data will be presented in frequency tables showing the number of observations and absolute and relative frequencies (counts and percentages). In the overview adverse event table, the number of events will be displayed in addition. Number of events and patients will be displayed with no decimal place, relative frequencies will be displayed with one decimal place.

In general, if missing data imputation is performed, the corresponding endpoints will be summarised with and without imputed missing values.

In all summary tables by analysis/eCRF visit, the total number of patients who are still in the study at the respective analysis/eCRF visit and did not discontinue early prior to the respective analysis/eCRF visit will be displayed.

For summary tables by analysis/eCRF visit for **continuous** variables, the number of non-missing (termed as “n”) and missing (termed as “nmiss”) assessments will be additionally displayed.

In summary tables for **categorical** variables, the number of patients with non-missing assessments will be displayed and this number serves as the denominator for corresponding percentage calculations. Missings will also be displayed but missings are not considered in any percentage calculations.

6.1.2 Data listings

All individual patient data will be listed as documented in the eCRF as well as all relevant generated and transformed variables next to the original data items. In all listings, treatment group, centre ID, patient ID and analysis sets for EU and US analyses (in terms of the most restrictive analysis sets; PPS is more restrictive than FAS which is more restrictive than SAF) for each patient will be included. As applicable, the eCRF visit or the eCRF (abbreviated label without specifying the respective week will be used) and the analysis visit (full label including the respective week will be used) will be listed. The listings will be sorted by patient ID, treatment group, visit date, and study eye/fellow eye, if applicable.

6.1.3 Figures

The time-course of all continuous efficacy variables which are measured every month is presented in terms of boxplots by analysis visit. The arithmetic mean will be additionally presented in the grouped boxplots.

6.2 Specifications related to the final analysis

Tables, figures and listings for the final analysis will have the same layout as tables, figures and listings specified for the main analysis. Analysis visit based summaries will be repeated for the final analysis by adding the additional analysis visits to tables and figures. Event based analyses will have the same layout as in the main analysis, but the events from the second half of the study will be added to the summaries. For detailed definitions of tables, listings and figures see Section 6.1.1, 6.1.2 and 6.1.3.

6.3 Disposition of patients

6.3.1 Disposition of patients for the main analysis

The disposition of patients

- who were enrolled in the study (i.e., signed the informed consent form),
- who were randomised,
- who were randomised but not treated,
- who were treated,
- who completed the main part of the study (the main part of the study includes all visits up to the general cut-off for the main analysis),
- who discontinued the study prior to eCRF Visit 7,
- and who discontinued treatment prior to eCRF Visit 7

will be summarised by treatment group and overall. Additionally, the reason for not being randomised and the reason for discontinuation of the study prior to eCRF Visit 7 will be summarised. The number of patients who discontinue the study prior to eCRF Visit 7 will be summarised by analysis visit as well.

The number of patients in each analysis set and the reasons for exclusion from each analysis set will be summarised by treatment group and overall.

Patient disposition will be displayed for all enrolled patients, i.e., for all patients who signed the informed consent form. Disposition related summary tables are included in Section 14.1.1 of the summary tables (see the SAP Appendix).

A patient data listing for patient enrollment will list all patients enrolled in the study together with centre ID, patient ID, date of informed consent, best corrected visual acuity at screening (Snellen equivalent) and US and EU compatibility. Another patient data listing for randomization will list all patients together with treatment group, informed consent date, screening date, randomization date, randomization number, inclusion in the PK/ADA subgroup, and reason for not being randomised and date of declared screening failure for all patients who were not randomised.

A patient data listing will list all patients who prematurely discontinued the study prior to eCRF Visit 7 including treatment group, centre ID, patient ID, date of discontinuation, reason for discontinuation and specification.

The fulfilment status of inclusion and exclusion criteria will be listed together with the treatment group, centre ID, patient ID and criteria.

Disposition and enrollment related patient data listings are included in Section 16.2.1 of the patient data listings (see SAP Appendix).

6.3.2 Disposition of patients for the final analysis

The disposition of patients

- who were enrolled in the study (i.e., signed the informed consent form),
- who were randomised,
- who were randomised but not treated,

- who were treated,
- who completed the whole study,
- who discontinued the study,
- and who discontinued treatment

will be summarised by treatment group and overall. Additionally, the reason for not being randomised and the reason for discontinuation of the study will be summarised. The number of patients who discontinue the study will be summarised by analysis visit as well.

All disposition-related TFLs defined for the main analysis will be repeated for the final analysis (see Section 6.3.1).

6.4 Demographics and baseline characteristics

6.4.1 Demographics and baseline characteristics for the main analysis

The homogeneity of the treatment groups will not be evaluated using statistical tests or confidence intervals. Instead, descriptive statistics will be compared between the treatment groups. If differences between the treatment groups are observed that are considered to be of potential clinical relevance, the corresponding variable may be incorporated as covariate in an additional analysis.

Age at Screening will be categorized into the categories 50-64 years; 65-75 years; > 75 years. Demographic data and other baseline characteristics including age, age categories, gender, childbearing potential, race, weight, height, BMI [kg/m^2], study eye, and iris color will be summarised by treatment group and overall for the SAF, the FAS_EU, the FAS_US, the PPS_EU, the PPS_US, and the PKS. Additionally, baseline BCVA Snellen equivalent will be summarised by treatment group for each analysis set. Demographic data and other baseline characteristics will also be summarised stratified by visual acuity and by country (see Section 6.13) for the SAF, the FAS_EU and the FAS_US; summary tables for the PPS_EU and the PPS_US will only be displayed for demographic data and other baseline characteristics also stratified by visual acuity if there is a considerable difference between the FAS and the PPS (see Section 5.3). Demographic data and other baseline characteristics stratified by country will not be displayed for the PPS_US and the PPS_EU.

Since the randomization was stratified by the screening BCVA category (20/32 (0.63) – 20/100 (0.2) Snellen equivalent, or 20/40 (0.50) – 20/100 (0.2) Snellen equivalent) and by site, demographics will also be presented by visual acuity stratum and by country.

All summary tables related to demographics and baseline characteristics are included in Section 14.1.2 of the summary tables (see SAP Appendix).

6.4.2 Demographics and baseline characteristics for the final analysis

All TFLs related to demographics and baseline characteristics will be repeated for the final analysis. All definitions are identical to the definitions specified for the main analysis (see Section 6.4.1).

6.5 Medical history and ophthalmologic history

6.5.1 Medical history and ophthalmologic history for the main analysis

Medical (ophthalmologic) history and current medical (ophthalmologic) conditions will be recorded at Screening and will be summarised. Reported terms for medical history and medical ophthalmologic history will be coded using the MedDRA dictionary Version 19.0. The MedDRA dictionary will not be updated during the conduct of the study.

Medical history is defined as any condition that stopped prior to Screening, whereas current medical conditions are any conditions which are ongoing at Screening. All medical history with missing end date and missing information if the medical history is ongoing or not ongoing at Screening will be considered as ongoing medical condition.

Medical (ophthalmologic) history and current medical (ophthalmologic) conditions will be analysed separately by display of their absolute and relative frequency by treatment group for the SAF, the FAS_EU, and the FAS_US. The summary tables will also be repeated for the PPS_EU and the PPS_US if there is a considerable difference between the FAS and the PPS (see Section 5.3). In these summary tables, the diagnoses and indications will be decoded by preferred term (PT) and grouped under the respective system organ class (SOC). The SOCs as well as the PTs within will be sorted by decreasing frequency in the total column.

Additionally, if the patient experienced any clinically relevant past or concomitant ocular diseases in addition to nAMD (yes/no), if the patients experienced any post ocular surgeries (yes/no) and if the patient planned ocular surgeries (yes/no) will be summarised by treatment group for the SAF, the FAS_EU, and the FAS_US. This information will be additionally presented for the PPS_EU and the PPS_US if there is a considerable difference between the FAS and the PPS (see Section 5.3). The type of planned ocular surgery will only be listed.

Additionally, medical history and medical ophthalmological history will be listed. The listings will be sorted by treatment group, centre ID, patient ID, and eye if applicable.

Medical history related summary tables are included in Section 14.1.3 of the summary tables and medical history related patient data listings are included in Section 16.2.4.3 and 16.2.4.4 (see SAP Appendix).

6.5.2 Medical history and ophthalmologic history for the final analysis

All TFLs related to medical and ophthalmologic history will be repeated for the final analysis. All definitions are identical to the definitions specified for the main analysis (see Section 6.5.1).

6.6 Prior and concomitant medication and prior and current ocular and non-ocular treatments

6.6.1 Prior and concomitant medication and prior and current ocular and non-ocular treatments for the main analysis

Prior ocular and non-ocular treatments within six months prior to signature of informed consent have to be recorded in the eCRF. All medications (other than IMP) and significant non-pharmacological therapies (including physiotherapy and blood transfusions) administered after the patient starts treatment with the IMP, must be recorded in the eCRF.

If a treatment is given due to an AE, MH or medical ophthalmological history, this is documented in the eCRF via the respective cross-reference.

Prior medication/therapy is defined as medication/therapy that started prior to first IMP administration. Concomitant medication/therapy is defined as medication/therapy with at least one dose taken after the first injection of IMP [i.e., medications with a start and/or stop date later than the first injection of IMP, or no stop date (ongoing medication)] Hence follows, some medications will be considered as both, prior and concomitant medications. For patients who did not receive any study drug, all medications will be considered as prior medications.

If only partial start and/or stop dates are reported for medications, a worst case imputation (first/last day of the month will be imputed in the start/stop date if only month and year are available; 1st January/ 31st December will be imputed in the start/stop date if only the year is available) will be applied for classifying medications into prior or concomitant medications or both. If start and/or end dates are completely missing, the medication will be classified as both previous and concomitant except for if a reported start or end date allows a unique classification as prior or concomitant medication. If time of medication is missing and the medication started at the day of 1st injection, the medication will be classified as prior and concomitant. Prior and concomitant medications and therapies will be coded using the WHO drug dictionary Enhanced Version March 2015. This dictionary will not be updated during the conduct of the study.

A safety cut-off will be applied for concomitant medications for the main analysis: all concomitant medications with a start date up to and including a safety cut-off date will be included in the main analysis. This safety cut-off date is defined as the date of the injection performed at Visit V7 minus 1 day (i.e., the safety cut-off date is calculated individually for each patient). If no injection has been performed at Visit V7, the date of the injection performed at Visit V6 plus 27 days will be used as safety cut-off date. All medications with partial start dates which might have occurred prior to or at the safety cut-off date are considered for the main analysis.

Prior and concomitant medications and therapies will be analysed separately by display of their absolute and relative frequency using as denominator the number of patients in the respective treatment group in the SAF. In these tables, medications and therapies will be classified according to ATC level 3 and WHO dictionary preferred term and will be sorted by decreasing frequency in the total column within levels. These summary tables are included in Section 14.1.4 of the summary tables (see SAP Appendix).

Prior and concomitant medications and therapies will be listed and sorted by treatment group, centre ID, patient ID and eye if applicable. This patient data listing will include a flag indicating whether the medication/therapy is classified as previous, concomitant, or both. The patient data listing is included in Section 16.2.9.1 of the patient data listings (see SAP Appendix).

6.6.2 Prior and concomitant medication and prior and current ocular and non-ocular treatments for the final analysis

All TFLs related to prior and concomitant medication will be repeated for the final analysis. Hence, all CM documented in the second half of the study will additionally be considered. All definitions are identical to the definitions specified for the main analysis (see Section 6.6.1).

6.7 Study drug exposure and compliance

6.7.1 Definitions related to study drug administration and compliance for the main analysis

For the main analysis, a patient is defined as having prematurely discontinued study medication if the patient prematurely discontinued study medication prior to or at eCRF Visit 7. The reason for non-administration of the next scheduled injection will be listed as reason for premature discontinuation of study medication.

A patient is defined as having interrupted study medication if the administration was omitted at least at one analysis visit up to and including eCRF Visit 6 (see also definition of cut-off dates in Section 5.1) but administered again at a later visit. The reason(s) for non-administration of the next scheduled injection(s) will be listed as reason(s) for interruption.

Since the study drug is administered after all efficacy assessments have been performed at eCRF Visit 7, all study drug administration information collected up to and including eCRF Visit 6 will be included for the main analysis, will be assigned to analysis visits and will be displayed in summary tables and patient data listings.

Treatment duration and study duration will be calculated according to the following definitions:

Duration of treatment for main analysis (expressed in [days]):

- Date/time of sixth injection – date/time of first injection
- In case of missing time of first or sixth injection: date of sixth injection – date of first injection +1
- In case of (partially) missing date of first or last injection no calculation will be done.

Duration of study for main analysis (expressed in [days]):

- General cut-off date will be used for the calculation of study duration for the main analysis
- General cut-off date - date of Screening/ V0 + 1
- In case of (partially) missing date of Screening/ V0 or (partially) missing date of general cut-off no calculation will be done

Calculation of amount of study medication administered in [mg]:

The total volume of study medication administered per injection is collected in [mL] in the eCRF. For both Lucentis and FYB201, the administered amount of study medication per injection in [mg] can be calculated by

amount of study medication [mg] = volume of study medication [mL] * 10,

since both study medications are provided using a 10 mg/mL solution. For the main analysis, only administered injections at eCRF Visits 1/ Baseline – eCRF Visit 6 (first – sixth injection) will be considered.

6.7.2 Definitions related to study drug administration and compliance for the final analysis

A patient is defined as having prematurely discontinued study medication if the last study drug administration was earlier than analysis visit 12. The reason for non-administration of the next scheduled injection will be listed as reason for premature discontinuation of study medication.

A patient is defined as having interrupted study medication if the administration was omitted at least at one analysis visit between Visit 1 and Visit 12 but administered again at a later visit. The reason(s) for non-administration of the next scheduled injection(s) will be listed as reason(s) for interruption.

Treatment duration and study duration will be calculated according to the following definitions:

Duration of treatment (expressed in [days]):

- Date/time of last injection – date/time of first injection
- In case of missing time of first or last injection: date of last injection – date of first injection +1
- In case of (partially) missing date of first or last injection no calculation will be done.

Duration of study (expressed in [days]):

- Date of last contact will be used for the calculation of study duration
- Date of last contact - date of Screening/ V0 + 1
- In case of (partially) missing date of Screening/ V0 or (partially) missing date of last contact no calculation will be done

Calculation of amount of study medication administered in [mg]:

The total volume of study medication administered per injection is collected in [mL] in the eCRF. For both Lucentis and FYB201, the administered amount of study medication per injection in [mg] can be calculated by

amount of study medication [mg] = volume of study medication [mL] * 10,

since both study medications are provided using a 10 mg/mL solution.

6.7.3 Analysis of study drug administration and compliance for the main analysis

The following summary tables will be presented for study drug administration for the SAF and will be included in Section 14.3.1 of the summary tables (see SAP Appendix):

- Treatment duration and study duration [days] for the main analysis (see definition in Section 6.7.1) will be summarised by treatment group.
- The number of IVT injections of study medication administered up to the general cut-off for the main analysis (see definition in Section 5.1) will be summarised by treatment group and analysis visit. The number of patients with at least one interruption and with premature discontinuation of study medication will be presented.
- The total amount of study medication administered [mg] up to the general cut-off for the main analysis (see definition in Section 5.1) will be summarised by treatment group and analysis visit. Additionally, the cumulative total amount of study medication administered in all performed injections up to the general cut-off for the main analyis will be summarised by treatment group.
- The percentage of the total amount of administered study medication relative to the amount of total planned study medication up to the general cut-off for the main analysis will be summarised by treatment group. The corresponding ratio is calculated by total amount of administered study medication/ total amount of planned study medication per patient.The total amount of planned study medication is 3 mg up to the general cut-

off for the main analysis (assuming six injections prior to all ophthalmological assessments at Week 24; the planned amount per injection is 0.5 mg).

All study drug exposure related information up to the general cut-off for the main analysis (see definition in Section 5.1) will be listed including the reason if no study drug was administered and the reason if not the expected volume of study drug was administered. The volume [mL] and the amount [mg] of study medication administered at each injection will both be listed.

Study drug administration information will be listed separately for all patients who prematurely discontinued or interrupted study medication.

These patient data listings for compliance and study drug exposure will be included in Section 16.2.5 (see SAP Appendix).

6.7.4 Analysis of study drug administration and compliance for the final analysis

The following summary tables will be presented for study drug administration for the SAF and will be included in Section 14.3.1 of the summary tables (see SAP Appendix):

- Treatment duration and study duration [days] for the final analysis (see definition in Section 6.7.2) will be summarised by treatment group.
- The number of IVT injections of study medication will be summarised by treatment group and analysis visit. The number of patients with at least one interruption and with premature discontinuation of study medication will be presented.
- The total amount of study medication administered [mg] will be summarised by treatment group and analysis visit. Additionally, the cumulative total amount of study medication administered in all performed injections will be summarised by treatment group.
- The percentage of the total amount of administered study medication relative to the amount of total planned study medication will be summarised by treatment group. The corresponding ratio is calculated by total amount of administered study medication/ total amount of planned study medication per patient.The total amount of planned study medication is 6 mg (assuming twelve injections prior to all ophthalmological assessments at the final visit/ Week 48; the planned amount per injection is 0.5 mg).

All study drug exposure related information will be listed including the reason if no study drug was administered and the reason if not the expected volume of study drug was administered. The volume [mL] and the amount [mg] of study medication administered at each injection will both be listed.

Study drug administration information will be listed separately for all patients who prematurely discontinued or interrupted study medication.

These patient data listings for compliance and study drug exposure will be included in Section 16.2.5 (see SAP Appendix).

6.8 Efficacy

6.8.1 Primary efficacy variable

The primary efficacy variable is the change from baseline in ETDRS BCVA calculated for the data at Week 8. The ETDRS BCVA for the study eye is collected by visit in the eCRF. The

change from baseline in ETDRS BCVA at Week 8 is calculated per patient via:

$\mathrm{CHG}_{\mathrm{BCVA}} = \mathrm{BCVA}_{\mathrm{Week\,8}} - \mathrm{BCVA}_{\mathrm{Base}}$,

where the baseline assessment is obtained at analysis visit V1.

The primary efficacy variable is only based on data which is collected up to the main analysis. The calculation of the primary efficacy variable will be identical for the main and for the final analysis.

6.8.2 Primary efficacy analysis

The hypothesis that both treatments FYB201 and Lucentis are biosimilar with respect to the primary endpoint will be tested in terms of a two-sided equivalence test. The equivalence margin of 3 ETDRS letters (as rounded to the nearest integer) will be tested by the following hypotheses:

$H_0: \left|\mu_{\mathrm{BCVA,FYB201}} - \mu_{\mathrm{BCVA,Lucentis}}\right| \geq 3.5$

$H_1: \left|\mu_{\mathrm{BCVA,FYB201}} - \mu_{\mathrm{BCVA,Lucentis}}\right| < 3.5$,

where $\mu_{\mathrm{BCVA,FYB201}}$ and $\mu_{\mathrm{BCVA,Lucentis}}$ denote the mean changes of ETDRS letters from baseline to Week 8.

An analysis of covariance (ANCOVA) model will be used for the analysis with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects. The model can be expressed as:

$\mathrm{CHG}_{\mathrm{BCVA,i}} = \mu + \alpha \cdot b_i + c_j + t_k + \varepsilon_{ijk}$,

where:

$\mathrm{CHG}_{\mathrm{BCVA,i}}$: Change of BCVA from baseline to Week 8 for patient i

μ: Intercept

b_i: Baseline value of BCVA for patient i

α: Regression coefficient for baseline BCVA

c_j: Effect of country j

t_k: Effect of treatment k (FYB201 or Lucentis)

$\varepsilon_{ijk} \sim N(0, \sigma_\varepsilon)$: Residual error.

All patients in the respective analysis set who do not have a non-missing change in BCVA between baseline and Week 8, or for whom at least one of the covariates in the model are missing will not be considered in the estimation of the ANCOVA model.

For the comparison between the treatment groups, the 90% (US) and 95% (EU) CIs for the treatment difference FYB201 – Lucentis will be calculated using Least Square Means. If the respective confidence interval is completely contained in the interval]-3.5 ; 3.5[letters, equivalence of FYB201 and Lucentis can be concluded for the primary endpoint.

This analysis will be conducted using SAS code similar to the following statement:

```
proc mixed;
      class subjid country treatment;
      model CHG_BCVA = BCVA_base country treatment;
      lsmeans treatment/ diff cl alpha=0.05/0.1; **
```

```
run;
```

** alpha levels depends on if the analysis is performed for FAS_EU (95% CI is required and thus, alpha is set to 0.05) or FAS_US (90% CI is required and thus, alpha is set to 0.1).

The main analysis of the primary endpoint will be based on all patients in the FAS_EU and the FAS_US, respectively. Sensitivity analyses will be conducted based on the per-protocol sets (PPS_EU and PPS_US, respectively) as well as using the MMRM specified in section 5.3.

The extent of missing data will be reviewed and further sensitivity analyses may be specified if deemed necessary.

The primary efficacy analysis and the related sensitivity analyses are only based on data which is collected up to the main analysis. These analyses will be re-run for the final analysis and the results from the ANCOVA models and the MMRM are expected to be identical for the main and for the final analysis.

The summary tables for the primary efficacy analysis will be included in Section 14.2.1 and the summary tables for the sensitivity analyses for the primary efficacy analysis will be included in Section 14.2.2 (see SAP Appendix). Summary statistics for the primary efficacy endpoint stratified by country will be included in Section 14.2.4.

6.8.3 Secondary efficacy analyses

The secondary efficacy analyses described below will be included in Section 14.2.3 of the summary tables (see SAP Appendix). Efficacy analyses stratified by country will be included in Section 14.2.4.

6.8.3.1 Definitions for variables assessed by the [redacted] reading centre

FCP retinal thickness, FCS retinal thickness and total lesion area are assessed based on images evaluated at the [redacted] Reading Centre.

FCP retinal thickness is measured by SD-OCT and hence, is available at all eCRF visits. FCP retinal thickness is available at Screening and at the Baseline Visit 1 because this parameter is also relevant for checking inclusion and exclusion criteria. Additionally, the parameter “Does the finding affect the FCP measurement” needs to be considered. If the finding affects the FCP measurement, the measured FCP value is compromised and is not analysed but set to missing instead. If the finding does not affect the FCP measurement, the FCP value is valid and can be used for the statistical analysis.

FCS retinal thickness is measured by SD-OCT and is available at all eCRF visits except for Screening because this parameter is not relevant for the assessment of any in- or exclusion criteria.

Total lesion area and CNV leakage is measured by Fundus Angiography (FA) and is available at Screening, Visit 7 and the Final Visit.

CNV leakage is captured in the [redacted] parameter “presence of active leakage (study eye)”. Fluid free macula is measured by SD-OCT and is available at all eCRF visits except for Screening because CNV leakage is not relevant for the evaluation of any inclusion or exclusion criteria

For fluid free macula, the two [redacted] parameters “presence of intraretinal fluid” and “presence of subretinal fluid” need to be considered:

- Only if both presence of intraretinal/subretinal fluid are “No”, fluid free macula is

categorized as “Yes”.

- If either presence of intraretinal or subretinal fluid is “Yes”, fluid free macula is categorized as “No”.
- Fluid free macula is missing in all other cases.

Assignment of [redacted] assessments to analysis visits:

For assigning [redacted] assessments to analysis visits, the following procedure will be used:

- If a date is printed on the image which has been taken for the SD-OCT, Fundus Photography (FP) or FA assessment, respectively, this date will be used for assigning the respective assessment to an analysis visit.
- If no date is printed on the image which has been taken for the SD-OCT, FP or FA assessment, the date of visit inserted by the site will be used for assigning the respective assessment to an analysis visit.
- Some specific rules apply for assessments at Screening and Baseline/ Visit 1:
  - For FCP retinal thickness, the respective date at Screening and at Baseline/ Visit 1 will be used and the corresponding eCRF Visit is specified as “Screening” or “Visit 1 (Baseline)”.
  - For FCS retinal thickness, the respective date at Baseline/Visit 1 will be used and the corresponding eCRF Visit is specified as “Visit 1 (Baseline)”
  - For Total lesion area, the respective date at Screening will be used and the corresponding eCRF Visit is specified as “Screening”.
  - For CNV leakage, the respective date at Screening will be used and the corresponding eCRF Visit is specified as “Screening”.
  - For fluid free macula, the date at Baseline/Visit 1 will be used and the corresponding eCRF Visit is specified as “Visit 1 (Baseline)”.

Mapping rules for categorical [redacted] parameters:

The following mapping rules apply for all categorical [redacted] parameters which have been collected using the respective categories:

- Yes: Grader is more than 90% sure that a finding is positive; will be evaluated as “Yes”
- No: Grader is more than 50% sure that a finding is negative; will be evaluated as “No”
- Questionable: Grade suspects about 50-90% probability that a finding is positive; will be summarised in category “Missing/NA/Not gradable/Questionable” and will be listed as “Questionable”
- Not gradable: image quality is not sufficient for grading or not all images needed for grading are available; will be summarised in category “Missing/NA/Not gradable/Questionable” and will be listed as “Not gradable”
- NA (not applicable): Question does not have to be or cannot be answered; will be summarised in category “Missing/NA/Not gradable/Questionable” and will be listed as “NA”
- Answers “Yes, definitive” and “Yes, subtle” (definitively present, but manifestation is less pronounced compared to standard images) will be summarised in category “Yes” and will be listed as “Yes, definitive” or “Yes, subtle” as applicable.

6.8.3.2 Analyses of BCVA, FCP, FCS and total lesion area

Please see Section 6.8.3.1 for further definitions of the variables FCP retinal thickness, FCS retinal thickness and total lesion area.

Analyses of BCVA, FCP, FCS and total lesion area for the main analysis:

All values for BCVA, FCP, and FCS retinal thickness as well as total lesion area will be summarised by analysis visit and treatment group, including the absolute change from baseline by analysis visit. At Screening, BCVA measurements are obtained for both eyes and thus, the absolute values will be summarised for both eyes ("study eye" and "fellow eye"). The change from baseline to Week 24 (analysis visit V7) will be compared between treatment groups for all four variables using the same ANCOVA model specified for the primary endpoint to derive the CIs for the difference between the treatment groups, but without formal hypothesis testing. The analysis sets for these analyses will be FAS_US and FAS_EU. FCP retinal thickness will also be analysed using PPS_US and PPS_EU in terms of sensitivity analyses. If a considerable amount of patients (defined as at least 10% of the patients in the FAS_EU) is excluded from the FAS_US and FAS_EU due to major protocol deviations for definition of the corresponding PPS_US and PPS_EU, sensitivity analyses based on the PPS_US and PPS_EU will be performed for FCS retinal thickness and for total lesion area as well.

Analyses of BCVA, FCP, FCS and total lesion area for the final analysis:

All values for BCVA, FCP, and FCS retinal thickness as well as total lesion area will be summarised by analysis visit and treatment group, including the absolute change from baseline by analysis visit. At Screening and at the final visit, BCVA is obtained for both eyes and thus, the absolute values will be summarised for both eyes ("study eye" and "fellow eye") at Screening and at the final analysis visit. The change from baseline to Week 24 (analysis visit V7) and to Week 48 (final analysis visit) will be compared for all four variables between treatment groups using the same ANCOVA model specified for the primary endpoint to derive the CIs for the difference between the treatment groups, but without formal hypothesis testing. The analysis sets for these analyses will be FAS_US and FAS_EU. FCP retinal thickness will also be analysed using PPS_US and PPS_EU in terms of sensitivity analyses. If a considerable amount of patients (defined as at least 10% of the patients in the FAS_EU) is excluded from the FAS_US and FAS_EU due to major protocol deviations for definition of the corresponding PPS_US and PPS_EU, sensitivity analyses based on the PPS_US and PPS_EU will be performed for FCS retinal thickness and for total lesion area as well.

For the Week 48 analyses of the absolute change from baseline in BCVA, an additional calculation will be performed: the patient-wise average of Weeks 40, 44, and 48 (analysis visits 11, 12, and the final analysis visit) will be additionally calculated to reduce the intrinsic variability of the measurements. If one or two of the three assessments are missing, the average will be calculated using all available assessments; if all three assessments are missing, the average will also be missing. This averaged patient-wise measurement at 12 months and the corresponding absolute change from baseline will also be summarised and displayed in the summary statistics for BCVA by treatment group and analysis visit. Additionally, the ANCOVA model for the absolute change from baseline for BCVA at 12 months will use the absolute change from baseline for the averaged measurements at 12

months as dependent variable.

6.8.3.3 Patient reported outcome – Questionnaire NEI VFQ-25:

The NEI VFQ-25 is a 25-question quality of life questionnaire created by the National Eye Institute to measure the influence of visual disability on general health and functioning. The questionnaire assesses the influence of visual disability and visual symptoms on general health domains such as emotional well-being and social functioning, in addition to task oriented domains related to daily visual functioning. NEI VFQ-25 questionnaires will be answered at Visits V1, V7, and at the final visit.

The NEI VFQ-25 consists of 25 vision-targeted items combined into 12 subscales: general health, general vision, ocular pain, near activities, distance activities, driving, color vision, peripheral vision and vision-specific social functioning, mental health, role difficulties and dependency. Each item of the NEI VFQ-25 is converted into a 0-100 scale; thus, the lowest and highest possible scores are set at 0 and 100 points. Higher scores represent better functioning, and scores decrease with worsening visual acuity (VA).

NEI VFQ-25 scores will be determined as described in the official manual:
https://www.nei.nih.gov/sites/default/files/nei-pdfs/manual_cm2000.pdf

Scoring is performed according to the following two-step process:

- First, original numeric values from the questionnaire are re-coded following the scoring rules outlined in Table 1 (see Table 2 in the official manual). All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format, scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.
- In step 2, items within each sub-scale are averaged together to create the 12 sub-scale scores. Table 2 (see Table 3 in the official manual) indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the sub-scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, the sub-scale scores represent the average for all items in the sub-scale that the respondent answered.
- **Composite score calculation:** Average the vision-targeted sub-scale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items, equal weights are given to each sub-scale, whereas averaging the items would give more weight to scales with more items. The composite score will be missing if all sub-scales are missing. In case of missing sub-scales, the composite score will be calculated by averaging all available sub-scales.

Questionnaire NEI VFQ-25 – Analyses for the main analysis:

Vision-targeted sub-scales and the composite score will be descriptively summarised by analysis visit and treatment group, including the absolute change from baseline for each analysis visit. The change from baseline to Week 24 (analysis Visit V7) for the composite total score will be compared between treatment groups using the same ANCOVA model specified for the primary endpoint to derive the CIs for the difference between the treatment groups, but without formal hypothesis testing. The analysis sets for these analyses will be the FAS_US and the FAS_EU.

Questionnaire NEI VFQ-25 – Analyses for the final analysis:

Vision-targeted sub-scales and the composite score will be descriptively summarised by analysis visit and treatment group, including the absolute change from baseline for each analysis visit. The change from baseline to Week 24 (analysis Visit V7) and to Week 48 (final analysis visit) for the composite total score will be compared between treatment groups using the same ANCOVA model specified for the primary endpoint to derive the CIs for the difference between the treatment groups, but without formal hypothesis testing. The analysis sets for these analyses will be the FAS_US and the FAS_EU.

Table 1 Scoring of single items

Item Numbers	Change original response category [a]	To recoded value of:
1,3,4,15c[b]	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a A3,A4,A5,A6,A7,A8,A9[c]	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25, A11a,A11b,A12,A13	1	0
	2	25
	3	50
	4	75
	5	100
A1,A2	0 to 10	0 to 100

[a] Precoded response choices as printed in the questionnaire.

[b] Item 15c has four-response levels, but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

[c] "A" before the item number indicates that this item is an optional item from the Appendix. If optional items are used, the NEI-VFQ developers encourage users to use all items for a given sub-scale. This will greatly enhance the comparability of sub-scale scores across studies.

* Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing."

Table 2 Scoring of single items

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

6.8.3.4 Binary efficacy endpoints

Please see Section 6.8.3.1 for further definitions of the variables CNV leakage and fluid-free macula.

The number and percentage of patients with active CNV leakage (yes/no) and fluid-free macula (yes/no) will be tabulated by analysis visit and treatment group for the main and for the final analysis by considering all applicable records/analysis visits, respectively (see Section 5.1). CNV leakage and fluid-free macula will be tabulated based on the FAS_EU and the FAS_US, and additionally based on the PPS_EU and the PPS_US if there is a considerable difference between the FAS and the PPS (see Section 5.3).

6.8.3.5 Stratified analyses

Stratified analyses for the main analysis:

All efficacy endpoints will be analysed taking the stratification factors into consideration (see section 6.13). All efficacy endpoints will be tabulated by patients with a screening BCVA between 20/40 and 20/100 Snellen equivalent (population for the EU specific analysis) and by patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent (population for the US specific analysis). This is considered in the analyses by calculating and estimating separate summary statistics and ANCOVA models for the EU- and US-specific analysis sets.

Additionally, all efficacy endpoints will be summarised stratified by country by pooling the sites within each country. If only few patients are randomised in a particular country, pooling of countries may be necessary for the analyses. The corresponding algorithm for pooling countries is defined in Section 5. The final decision for pooling countries will be made during the BDRM and will be documented in the BDRM minutes.

Stratified analyses for the final analysis:

Please see the definitions for the main analysis above.

6.8.4 Sensitivity analysis

Sensitivity analyses for the main analysis:

Sensitivity analyses using the PPS will be performed for the primary efficacy endpoint (change from baseline in BCVA) and for the secondary efficacy endpoint change from baseline in FCP retinal thickness. If a considerable amount of patients (defined as at least 10% of the patients in the FAS_EU) is excluded from the FAS_US and FAS_EU due to major protocol deviations for definition of the corresponding PPS_US and PPS_EU, sensitivity analyses based on the PPS_US and PPS_EU will be performed for all defined efficacy analyses. The final decision about the allocation of patients to analysis sets will be drawn during the main BDRM and will be documented in the main BDRM minutes.

An MMRM will be estimated for the primary efficacy endpoint to account for missing values (see section 5.3). No further sensitivity analyses will be applied unless relevant factors are identified during the main BDRM.

Sensitivity analyses for the final analysis:

Please see the definitions for the main analysis above.

6.9 Safety

If not mentioned otherwise in the respective section, all safety analyses will be performed for the SAF, i.e., for all patients who received study medication irrespective of the amount that has been administered. Patients are summarised according to the treatment they acutally received irrespective of the treatment they were randomised to.

6.9.1 Adverse events

All definitions for adverse events are identical for the main and for the final analysis. For the main analysis only adverse events with a start date up to and including the safety cut-off date will be considered (see Section 5.1). All analyses for adverse events will be repeated at the final analysis and all reported adverse events will be considered.

Summary tables for adverse events will be included in Section 14.3.2 of the summary tables and patient data listings for adverse events will be included in Section 16.2.7 of the patient data listings (see SAP Appendix).

General considerations:

Adverse events will be coded according to the Medical Dictionary of Regulatory Activities (MedDRA) Version 19.0. The MedDRA dictionary will not be updated during the conduct of the study.

Treatment emergent adverse events (TEAEs) will be analysed by display of the number and percentage of patients (absolute and relative frequencies) reporting the adverse event by treatment group. Hence, the number of patients in each treatment group will be the denominator for the relative frequencies. Counts will not be done by event. In these tables, adverse events will be summarised by MedDRA preferred term (PT) and grouped by MedDRA system organ classes (SOC). The SOCs as well as the PTs within will be sorted by frequency in decreasing order. Additionally, the number and percentage of patients with adverse events will be further grouped by severity (mild, moderate, severe) and relationship to IMP (probably related, possibly related, unlikely related, and not applicable).

(Serious) Adverse events will be presented overall and by intensity and relationship to IMP/ relationship to intravitreous injection procedure by treatment group. For summary tables

displaying adverse events by severity or relationship, the maximum severity/relationship per patient and preferred term is displayed. Furthermore, separate frequency tables for all patients with

- Serious TEAEs
- Non-serious TEAEs
- Severe TEAEs
- TEAEs leading to withdrawal of study drug
- TEAEs leading to premature discontinuation of study
- Local TEAEs
- Serious local TEAEs
- Non-serious local TEAEs
- Systemic TEAEs
- Serious systemic TEAEs
- Non-serious systemic
- Related TEAEs to study drug
- Related TEAEs to intravitreous injection procedure

will be provided.

The total number of events and the number and percentage of patients experiencing at least one adverse event will be summarised in an adverse event overview table by treatment group for

- any treatment-emergent AE (TEAE)
- any serious TEAE
- any severe TEAE
- any related TEAE
- any related serious TEAE
- any related severe TEAE
- any local TEAE
- any systemic TEAE
- any serious local TEAE
- any serious systemic TEAE
- any severe local TEAE
- any severe systemic TEAE
- any TEAE leading to withdrawal of study drug
- any TEAE leading to premature discontinuation of the study
- any non-fatal serious TEAE
- any fatal TEAE.

Forest plots visualizing the difference in the percentage of patients experiencing a certain type of adverse event between the treatment groups including exact 95% confidence intervals (according to Agresti and Min (2001)) by MedDRA PT will be displayed for

- frequent TEAEs
- frequent serious TEAEs
- frequent severe TEAEs

- frequent local TEAEs.

Frequent adverse events are defined as adverse events which are observed in at least 5% of the patients in at least one of the two treatment groups.

Adverse events will be listed and this listing will include the reported term and the coding of the respective adverse event in terms of PT and SOC. Thereby, the link of the original and the coded terms is established. Additionally, all further AE related information (e.g., onset relative to start of treatment, duration, intensity, relationship to IMP and injection procedure, action taken and outcome) will be listed and the listing will be sorted by treatment group, centre ID, patient ID and AE onset date.

Treatment-emergent and non-treatment-emergent adverse events will be listed separately. Deaths, serious TEAEs, severe TEAEs and TEAEs leading to study discontinuation will additionally be listed separately, if applicable.

Definitions for adverse events:

Safety cut-off for main analysis of adverse events:

A safety cut-off for adverse events is defined for the main analysis: all adverse events with a start date up to and including a safety cut-off date will be included in the main analysis and will be listed and summarised accordingly. This safety cut-off date is defined as the date of the injection performed at Visit 7 minus 1 day (i.e., the safety cut-off date is calculated individually for each patient). If no injection has been performed at Visit 7, the date of the injection performed at Visit 6 plus 27 days will be used as safety cut-off date.

Treatment emergent adverse events:

Treatment emergent adverse events (TEAEs) are defined as adverse events that are temporally associated with the use of an IMP, whether or not considered related to the IMP.

Temporally associated adverse events are adverse events with a start date later than the first administration of study treatment.

If the AE onset date is partially missing, a worst case imputation will be used to decide if the AE is treatment emergent or not. Worst case imputation means the first day of the month is imputed if only the day is missing and first January is imputed if day and month are missing, as long as the imputed date is later than the date of first IMP administration. AEs with completely missing AE onset date will be considered as treatment emergent in general except for non-missing end dates which allow to classify the AE as not treatment emergent. Pre-treatment adverse events will be displayed in a separate patient data listing but not summarised. All other adverse events (i.e., TEAEs) will be summarised by treatment group for the SAF.

AE onset time will be considered for classifying an AE as treatment emergent or not treatment emergent if available. Missing time of AE onset will not be imputed and only the AE onset date will be used for classifying an AE as treatment emergent or not in such cases. If an AE starts at the same date as the first administration of study treatment and no start time is given, the AE is considered as treatment emergent.

Duration of adverse events:

The duration of adverse events will be calculated by

Duration = AE end date/time – AE start date/time,

in days/hours/minutes for AEs with documented date and time for start and end dates; and

Duration = AE end date – AE start date + 1,

in days for all adverse events where only start and end date were documented.

Duration of adverse events will be missing if end or start date of the adverse event is completely missing. If start and end dates are partially missing the following rules apply: If the AE start/end date is partially missing, a worst case imputation will be used to calculate the treatment duration. Worst case imputation means the first/last day of the month is imputed if only the day is missing and first January/31st December is imputed if day and month are missing, respectively.

Definition of local and systemic adverse events:

Adverse events will be classified into “local adverse events” and “systemic adverse events”. All adverse events occurring in the study eye will be classified as “local adverse events” and all remaining adverse event not occurring in the study eye will be classified as “systemic adverse events”.

Masked and unmasked adverse events:

Adverse events can be reported and documented in the eCRF either by masked study personnel or by the unmasked injector (the person administering the injection of study medication) on the respective eCRF page for masked or unmasked adverse events, respectively. The masked investigator will assess the relationship of all adverse events including all unmasked adverse events. Hence, the relationship of all adverse events will be analysed according to the judgement of the masked investigator only.

6.9.2 Safety laboratory

Safety laboratory analyses comprise clinical chemistry, hematology, coagulation, and other laboratory assessments. The corresponding measurements are displayed in Table 3.

Based on the reference ranges, which are provided for each laboratory safety parameter, laboratory results are flagged accordingly if the result is below or above normal range.

Furthermore, laboratory values outside of normal range will be assessed as “clinically significant” or “not clinically significant” by the masked investigator and this information will be provided on the respective eCRF page. If appropriate, all clinically significant laboratory results will be repeated to ensure the validity of the abnormal result. If any clinically significant abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered clinically significant by the masked investigator, or an explanation for the change is obtained. Clinically significant laboratory results will be repeated by means of a re-test procedure according to the protocol. All laboratory assessments performed in the framework of the re-test procedure later than the first administration of study treatment will not be assigned to analysis visits but will be listed. All laboratory assessments performed in the framework of the re-test procedure prior to the first administration of study treatment will be considered for the determination of the baseline laboratory assessment. Unscheduled

laboratory assessments will be assigned to analysis visits as applicable.

If a laboratory measurement is collected as "<xx", then xx/2 will be used for calculation of summary statistics. If it is collected as ">xx", the numerical analysis value will be xx. For the classification if these values are out of normal ranges ("below normal range", "normal", "above normal range"), the original laboratory result in character format ("<xx" or ">xx") will be considered. For example, a laboratory result reported as ">5" will be considered having numerical value 5 and will be considered as "above normal range" if the upper reference range is 5.

Summary tables for safety laboratory will be included in Section 14.3.4 in the summary tables and patient data listings for safety laboratory assessments will be included in Section 16.2.8 in the patient data listings.

Safety laboratory analyses for the main analysis:

Laboratory tests are performed at Screening and at Visit 7.

If multiple laboratory assessments have been performed prior to the first administration of study medication, the last assessment prior to first administration of study treatment is considered as baseline laboratory assessment in summary tables. Only regular and unscheduled laboratory assessments will be assigned to analysis visit 7 and any assessments obtained in the framework of the re-test procedure will be omitted. The laboratory assessment closest to the target day will be considered for the analysis and in the summary tables (see Section 5.4).

For each laboratory parameter, summary statistics of the observed laboratory values and the absolute change from baseline (defined as the assessment at Screening for laboratory measurements) will be provided by analysis visit and treatment group. Since safety laboratory is only performed at eCRF visits Screening and Visit 7, laboratory values assigned to analysis visits 0 and 7 (closest values to the target days) will be summarised using descriptive statistics. All other laboratory results (including values assigned to other analysis visits) will only be listed.

The number and percentage of abnormal and clinically significant observations will be tabulated by analysis visit and treatment group separately for each laboratory parameter. The categories "within normal range", "below normal range not clinically significant", "below normal range clinically significant", "above normal range not clinically significant", "above normal range clinically significant", and "missing" will be used in this frequency table. Corresponding laboratory shift tables will display changes in this categorization compared to Screening by analysis visit. Separate patient data listings will be generated for clinical chemistry, hematology and coagulation laboratory assessments including the result, the reference range and flags if the result is below or above normal range and clinically significant for each laboratory parameter. Additionally, all laboratory assessments outside of normal range will be listed separately. This listing will also include the flag if the respective laboratory measurement was considered as clinically significant. Furthermore, the abnormal laboratory result will be displayed as multiple of the lower or upper reference range limit by dividing the result by the lower or upper reference range limit. All listings will be sorted by treatment group, centre ID, patient ID and laboratory parameter.

Results from serum pregnancy tests for female patients (performed at Screening only) will only

be listed separately and sorted by treatment group, centre ID, and patient ID.

Safety laboratory analyses for the final analysis:

Laboratory tests are performed at Screening, at Visit 7 and at the Final Visit.

If multiple laboratory assessments have been performed prior to first administration of study medication, the last assessment prior to first administration of study treatment is considered as baseline laboratory assessment in summary tables. Only regular and unscheduled laboratory assessments will be assigned to analysis visit 7 and the final analysis visit and any assessments obtained in the framework of the re-test procedure will be omitted. The laboratory assessment closest to the target day will be considered for the analysis and in the summary tables (see Section 5.4).

For each laboratory parameter, summary statistics of the observed laboratory values and the absolute change from baseline (defined as the assessment at Screening for laboratory measurements) will be provided by analysis visit and treatment group. Since safety laboratory is only performed at eCRF visits Screening, Visit 7, and the Final Visit, laboratory values assigned to analysis visits 0, 7 and 13 (closest values to the target days) will be summarised using descriptive statistics. All other laboratory results (including values assigned to other analysis visits) will only be listed.

Beyond that, the definitions of summary tables and patient data listings for the final analysis are identical to the definitions for the main analysis.

Table 3: Laboratory Safety Parameters

Category	Laboratory Parameter
Hematology	white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils and other cells)
Clinical chemistry	sodium, potassium, chloride, creatinine, total protein, albumin, total bilirubin, gamma-glutamyl transferase, uric acid, urea (blood urea nitrogen), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, calcium, C-reactive protein, glycosylated hemoglobin
Coagulation profile (screening only)	prothrombin time, partial thromboplastin time
Other tests (Screening only, female patients only)	Serum pregnancy test (HCG)

6.9.3 Vital signs

Vital signs assessments include radial pulse [beats per minute], and systolic and diastolic blood pressure [mmHg]. Absolute values will be recorded and assessed as “normal” or “abnormal” by the investigators. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”. Summary tables for vital signs will be included in Section 14.3.5 of the summary tables and will be listed in Section 16.2.9.4 of the patient data listings (see SAP Appendix).

Vital signs analyses for the main analysis:

Vital signs assessments are performed at Screening and at Visit 7.

The observed vital signs measurements and the absolute changes from baseline will be summarised by analysis visit (see Section 5.4) and treatment group. The number and percentage of patients with at least one clinically significant abnormal measurement will be tabulated by analysis visit and treatment group.

All vital signs related data will be listed including a flag if the observed measurement is outside normal ranges ("normal" or "abnormal") and if abnormal values are clinically significant. If vital signs assessments were not performed, the reason is listed. All abnormal vital signs measurements will additionally be listed separately.

Vital signs analyses for the final analysis:

Vital signs assessments are performed at Screening, at Visit 7 and at the Final Visit.

The definitions of summary tables and patient data listings for the final analysis are identical to the definitions for the main analysis.

6.9.4 Other safety data

Other safety data analyses for the main analysis:

Selected assessments resulting from the ophthalmological examination and tonometry will be summarised by treatment group and analysis visit. The intraocular pressure (IOP) will be summarised by treatment group, analysis visit and time point. Additionally, summary statistics of the change in IOP within one visit (post injection value –pre injection value) will be produced by analysis visit. Further, the number and percentage of patients with at least one clinically significant abnormal ophthalmological examination assessment will be summarised by analysis visit or time point.

Anterior chamber activity, lens status, cataract severity, nuclear grade, PSC grade, cortical grade, virteous haze, virteous hemorhage (present/absent), and posteriour vitreous detachment (present/absent) will be summarised by category, time point (by visit and by pre-/post-injection of applicable) and treatment group.

Tonometry and ophthalmological examinations will be performed for both eyes at Screening and thus, the observed values will be summarised separately for each eye ("study eye" and "fellow eye") at Screening. Ophthalmological assessments and tonometry will be performed at every study visit. All ophthalmological examination and tonometry related data will be listed including the assessment if the observed result is abormal and/or clinically significant. If no ophthalmological examination or tonometry has been performed, the reason is listed.

Physical examination will be performed at Screening and at Visit 7. It is assumed that any clinically relevant finding will be documented as medical history or as adverse event. Therefore, all data will be listed only.

All other safety data will be listed.

Other safety data analyses for the final analysis:

In general, the same summary tables and patient data listings as defined for the main analysis will be repeated for the final analysis by taking all records into account.

In the summary table for the IOP, the change from baseline in IOP for the final visit will be additionally displayed for the final analysis.

Tonometry and ophthalmological examinations will be additionally performed for both eyes at

the Final Visit and thus, the observed values will be summarised for both eyes ("study eye" and "fellow eye") at Screening and at the Final Visit for the final analysis.

Physical examination will additonally be performed at the Final Visit and all related data will also be listed for the final analysis.

6.10 Other data

6.10.1 Calculation of corrected refraction data

The cylindrical component of the refraction result should have been provided with the same algebraic sign throughout all measurements for the same patient. In cases where the documentation deviates from this convention the following rules will be applied:

Use the first refraction as reference and convert all other refraction results with cylindrical value having the opposite sign:

- The new sphere value is equal to the sum of the original sphere value and the original cylinder value. Make sure to respect the signs of the original values.
- Reverse the sign of the cylinder value
- Add or substract 90° to the original axis such that the new axis value is between 1° and 180°, i.e. add 90° if the original value is between 0° and 90° and substract 90° if the original value is between 91° and 180°.

Note that different signs of spheric values cannot be converted (see also http://www.virtuallens.com/transpose).

6.10.2 [redacted] parameters for the fellow eye

[redacted]parameters for the fellow eye for the main analysis:

For the fellow eye, the parameter "Are you certain that there is no CNV in the fellow eye?" (yes/no) is assessed at Screening and will be summarized based on the SAF in a frequency table in Section 14.1.2.5 of the summary tables (see SAP Appendix). All fellow eye related information for [redacted] assessments will be listed in Section 16.2.9.9 of the patient data listings (see SAP Appendix).

[redacted] parameters for the fellow eye for the final analysis:

For the fellow eye, the following parameters will be evaluated:

- "Are you certain that there is no CNV in the fellow eye?" (yes/no) is a binary variable which will be only assessed at Screening.
- "Diagnosis of non-study eye" is a categorical variable and will only be assessed at the Final Visit.

Both parameters will be summarised based on the SAF using frequency tables in Section 14.1.2.5 and Section 14.3.6.12 of the summary tables and all fellow eye related information will be listed in Section 16.2.9.9 of the patient data listings (see SAP Appendix).

6.10.3 Fundus photography and fluorescein angiography

Fundus photography and fluorescein angiography for the main analysis:

Color fundus photographs (CFP)and fluorescein angiography (FA) will be performed at Screening and at Visit 7. Both investigations are performed for both eyes at Screening. All

color fundus photographs and FA images which are collected at protocol-specified times are sent to the central reading centre (CRC) for central evaluation. Data resulting from the centrally performed evaluation of fundus photographs and FA images will be provided by an external data transfer. All FA related measurements and results will be listed and sorted by treatment group, centre ID, patient ID, (eCRF/analysis) visit and eye ("study eye" or "fellow eye") if applicable. Color fundus photography is used for assessing image quality and to support FA and SD-OCT results and measurements. Therefore, no CFP results are explicitly available and thus, will not be listed.

Fundus photography and fluorescein angiography for the final analysis:

Color fundus photographs and fluorescein angiography (FA) will be performed at Screening, at Visit 7 and at the Final Visit. Both investigations are performed for both eyes at Screening and at the Final Visit.

All FA related measurements will be listed for the final analysis and the listing layout will be the same as in the main analysis.

6.10.4 SD-OCT

Morphologic changes of retina FCP are evaluated by SD-OCT. SD-OCT will be performed at all visits and the secondary efficacy endpoints FCP and FCS retinal thickness are obtained based on this investigation. All FCP retinal thickness images will be evaluated centrally by trained personnel at the CRC, who will be masked to the patient's treatment, and will be provided by an external data transfer. Two independent readers will perform grading; in case of discrepancy a third reader will be consulted for abitration. The final reading SD-OCT related information will be listed and sorted by treatment group, centre ID, patient ID, (eCRF/analysis) visit, eye ("study eye" and "fellow eye") and reader if applicable for the main and for the final analysis including all relevant records, respectively.

6.10.5 Safety check after injection of study medication

A safety check will be performed just after each injection for all patients by the unmasked injector. All safety check related information will be listed and the listing will be sorted by treatment group, centre ID, patient ID, and (eCRF/analysis) visit for the main and for the final analysis including all relevant records, respectively.

6.10.6 Telephone safety call

A telephone safety call is performed 3 days after each injection for AE assessment to determine if there are any signs or symptoms of retinal detachment or endophthalmitis. Data related to telephone safety calls will not be listed.

6.11 Pharmacokinetic data

PK subgroup:

Up to 60 patients at selected sites will be included into a PK subgroup. Systemic ranibizumab concentration close to C_{max} after the first and the sixth IVT injection will be assessed in this subgroup. Additionally, ADAs will be analysed one week after first IVT injection in this subgroup (see section 3.2).

Systemic concentration of ranibizumab:

Samples for measuring the systemic concentration of ranibizumab will be obtained pre-first dose (at baseline/ Visit V1), at 24 +/- 3 hours after first IVT injection (close to C_{max}) and at 24 +/- 3 hours after sixth IVT injection (close to C_{max}). To guarantee an accurate assessment of the systemic concentration of ranibizumab, all patients in the PK subgroup are not allowed to receive Lucentis treatment in the fellow eye until and including Visit V1 and within 7 days prior to Visit V6 and until the blood sample at Visit V6a has been taken.The mean ranibizumab concentrations at 24 hours after the first and the sixth doses will be calculated and will be summarised using the arithmetic and geometric means, ranges, SDs and the coefficient of variation by analysis visit and treatment group.

Observed systemic concentrations of ranibizumab below the limit of quantification are set to 0 and concentrations above the limit of quantification are set to the upper limit of quantification for the purpose of calculating summary statistics. Such values are marked in patient data listings.

All PK related information will be listed for the patients in the PK subgroup and will be sorted by treatment group, centre ID, patient ID, and visit/timepoint of assessment.

All PK analyses are performed using the PKS analysis set and patients are summarised according to the treatment they acutally received.

All PK-related analyses are only based on data which is collected up to the main analysis. The summary tables and patient data listings are expected to be identical for the main and for the final analysis.

The summary table of the systemic ranibizumab concentrations will be included in Section 14.4.1 in the summary tables and PK-related information will be listed in Section 16.2.6.11 of the patient data listings (see SAP Appendix).

6.12 Immunogenicity analysis

6.12.1 Immunogenicity analysis for the main analysis

A blood sample will be collected for anti-drug antibodies (ADAs) assesssments at baseline (pre-dose; Visit 1), Visit 2, 4, and Visit 7. For all patients in the PK subgroup ADAs are additionally assessed at Visit 1b. ADA titre analyses will be performed by a central laboratory and provided by an external data transfer.

The number and percentage of patients who have binding ADAs in serum will be tabulated by treatment group and scheduled eCRF visit. The corresponding titres will be summarised by treatment group and scheduled eCRF visit. Furthermore, any pre-first-dose/post-first-dose detection of ADAs will be tabulated by treatment group. Thereby, pre-first-dose ADAs are classified as positive if the ADA assessment is positive, as negative if the ADA assessment is negative and as missing if the ADA assessment is missing, not reportable or an insufficient sample has been taken. Post-first-dose ADAs are classified as positive if at least one post-first-dose ADA assessment is positive. If at least one post-first-dose ADA assessment is negative and no post-first-dose ADA assessment is positive, post-first-dose ADAs are classified as negative. If all post first-dose ADA assessment are either missing, not reportable or insufficient samples have been taken, post-first-dose ADAs are classified as missing.

Additionally, the number and percentage of patients who have neutralizing ADAs (nABs) in serum will be tabulated by treatment group and scheduled eCRF visit.

ADA analyses will be performed based on the SAF, and the PKS. Patients are summarised according to the treatment they actually received for both analysis sets.

6.12.2 Immunogenicity analysis for the final analysis

Immunogenicity assessments are additionally performed at the Final Visit for the final analysis.

The definitions of summary tables and patient data listings for the final analysis are identical to the definitions for the main analysis.

6.13 Stratification variables

The following stratification variables will be considered:

- Patients with a screening BCVA between 20/40 and 20/100 Snellen equivalent (population for the EU specific analysis) and on patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent (population for the US specific analysis).
- Country by pooling the sites within each country.
  If only few patients are randomised in a particular country, pooling of countries may be necessary for the analyses. The corresponding algorithm for pooling countries is defined in Section 5. The final decision for pooling countries will be made during the main BDRM and will be documented in the main BDRM minutes.

Stratified analyses will only be conducted for the demographic data and for the efficacy endpoints by considering the stratification factors defined above in the respective efficacy analyses for the main and for the final analysis.

6.14 Interim analysis

No formal interim analysis will be performed for this study.

A main and a final analysis will be performed.

The main analysis will be performed when all randomised patients have either completed the Week 24/6 month assessments or have discontinued the study. Data will be cleaned and the database will be locked for unblinding. Decisions on the allocation of each patient to each analysis set will be made and documented prior to unblinding.

The analyses will include all data collected up to and including the general cut-off for the main analysis (see Section 5). To ensure an objective assessment of the ongoing trial, investigational sites, data management, site monitors, medical reviewers and patients will remain blinded to the treatment assignments and the medical/safety review will be performed by independent blinded personnel.

The final analysis will be performed when all randomised patients have either completed the Week 48/12 month assessments or have discontinued the study. Data will be cleaned and the database will be locked for the analyses. Patients will be analysed according to the analysis sets already defined for the main Week 24 analyses. The analyses will cover the whole study period.

7 SOFTWARE AND STATISTICAL PROGRAMMING

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.3 or higher) on a Windows 7 Professional System.

SAS programming will be performed according to [redacted]standards [redacted] Special attention will be paid to planning and performance of quality control (QC) measures as documented in the QC documentation for the analysis of this study [redacted]

8 REFERENCES

NEI-FVQ-25 official manual: https://www.nei.nih.gov/sites/default/files/nei-pdfs/manual_cm2000.pdf (accessed on 2017-09-14).

Agresti, A. and Min, Y. (2001), "On Small-Sample Confidence Intervals for Parameters in Discrete Distributions," *Biometrics*, 57, 963–971.

See separate document:

9 LIST OF TABLES, FIGURES AND LISTINGS (PROVIDED IN APPENDIX)

9.1 Table of contents for end-of-text tables and figures

9.2 Table of contents for patient data listings (Appendix 16.2 of the CSR)

9.3 Table shells for summary tables