Bioeq GmbH: FYB203-03-01

(BQ03)

Statistical Analysis Plan for US and EU Analysis

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Study Title:	A Phase 3 Randomized, Double-masked, Multicenter Study to Compare the Efficacy and Safety of the Proposed Aflibercept FYB203 Biosimilar in Comparison to Eylea® in Patients with Neovascular Age-Related Macular Degeneration (MAGELLAN-AMD)
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1 DOCUMENT HISTORY

Version	Date	Author / editor of new version	Main changes / comments
Final v01	29-Mar-2023		

2 LIST OF ABBREVIATIONS

Abbreviation	Text
ADA	Anti-Drug Antibody
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical (classification)
BCVA	Best Corrected Visual Acuity
BDRM	Blind Data Review Meeting
BLA	Biologics License Application
CI	Confidence Interval
CFP	Color Fundus Photography
CHG	Change from Baseline
CM	Concomitant Medication
CS	Clinically Significant
CSR	Clinical Study Report
D	Day
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
EOS	End of Study
EU	European Union
FA	Fluorescein Angiography
FAS	Full Analysis Set
FCP	Foveal Center Point
FCS	Foveal Central Subfield
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
h	hours
hCG	human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ID	Identity
IMP	Investigational Medicinal Product
IOP	Intraocular Pressure
IVT	Intravitreal
IWRS	Interactive Web Response System

Abbreviation	Text
LS	Least Square
MAR	Missing At Random
Max	Maximum
MedDRA	Medical Dictionary of Regulatory Activities
Min	Minimum
mmHg	Millimeters of Mercury (unit of pressure)
MMRM	Mixed Model Repeated Measures
NA	Not Applicable / Not Available
nAMD	neovascular Age-Related Macular Degeneration
NAb	neutralizing antibody
NCS	Not Clinically Significant
NEI VFQ-25	National Eye Institute Visual Function Questionnaire 25
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
PD	Protocol Deviation
PK	Pharmacokinetic
PKS	Plasma Concentration Analysis Set
PPS	Per Protocol Set
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
QC	Quality Control
ROW	Rest of World
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SDR	Source Data Review
SDTM	Study Data Tabulation Model
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
US	United States
UTC	Universal Time Coordinated
V	Visit
VA	Visual Acuity
W	Week
WHO	World Health Organization
WHODrug	World Health Organization Drug Dictionary

3 GENERAL

This statistical analysis plan (SAP) reflects study protocol FYB203-03-01 version 3.0 dated 15-Jul-2022. It follows the principles of the Guidelines ICH Topic E3 and ICH Topic E9.

Throughout this document, symbols indicating proprietary names (®, ™) may not be displayed for ease of readability; the appearance of product names without these symbols does not imply that these names are not protected.

In agreement with section 10.4 of the study protocol, four analyses are described in total: A masked sample size review, the originally planned unmasked final United States (US) analysis, the unmasked 24 week analysis and the unmasked 56 week analysis. The focus of reporting for the US changed in February 2023 after regulatory feedback from the FDA.

This SAP covers and describes all analyses for the 24 week and 56 week analysis of this study. There is a separate SAP for the masked sample size review and a further separate SAP for the originally planned final US analysis. This is due to the fact that there are substantial differences in the statistical analyses conducted for the masked sample size review and the distinct region-specific analyses.

Table 1 Planned clinical study reports and statistical analysis plans

CSR	SAP
not applicable	DMC SAP
not applicable	SAP for masked sample size review
None	SAP for originally planned US Analysis
24 week CSR intended for the initial EU and US regulatory submissions	SAP for US and EU analysis (this document)
56 week CSR intended as supplementary submission for the EU, as 120 day safety update for the US and for regulatory submission in Japan	

3.1 Analyses planned and already performed

The following analysis has already been performed:

- **Masked sample size review:** After the first 200 treated patients from all regions have completed Week 8 of the study or terminated the study prematurely before Week 8.

The following analyses were planned:

- **Originally planned analysis for US:** After the first 320 treated patients (or the adapted sample size for the US analysis) have completed 40 weeks of treatment or terminated the study prematurely before Week 40, and all treated patients have completed the best corrected visual acuity (BCVA) assessment at Week 8 or terminated the study prematurely before Week 8.
- **24 week analysis (Main analysis for EU and US):** After all treated patients have completed 24 weeks of treatment or terminated the study prematurely before Week 24.
- **56 week analysis (Final analysis for EU/Japan and parts for Day 120 Safety Update for US):** After all treated patients have completed the whole study period of 56 weeks

or terminated the study prematurely.

For the ease of notation, the main analysis and the final analysis will be named simply **24 week** or **56 week analysis**.

For the statistical analyses, the term 24 week analysis and 56 week analysis will be used throughout since the focus of reporting was adapted in 2023.

In addition, an independent Data Monitoring Committee (DMC) reviewed safety data on a regular basis and ad hoc if needed. All further details are defined in a separate DMC Charter.

This SAP only refers to the 24 week and 56 week analyses. The masked sample size review and the originally planned final US analysis were described in separate documents.

The 24 week analysis will be based on data up to Week 24 and will be described in the 24 week clinical study report (CSR). The final 56 week analysis will be based on data up to Week 56 (i.e. all data collected) and will be described in the 56 week CSR.

3.2 SOPs to be followed

The analysis will be carried out according to Standard Operating Procedures (SOPs).

The clinical study reports as described in Section 3 will be written according to the ICH E3 and other applicable ICH guidelines.

4 OVERVIEW OF THE PROTOCOL

The purpose of this study is to demonstrate the equivalence of efficacy of FYB203 to Eylea and to evaluate the safety and immunogenicity in patients with neovascular Age-Related Macular Degeneration (nAMD). In addition, systemic exposure of FYB203 and Eylea will also be evaluated in patients participating in plasma concentration evaluation.

4.1 Objectives of the study

The primary objective of the study is to evaluate and compare functional changes in BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at Week 8 of treatment with FYB203 or Eylea compared to baseline.

The primary estimand is the difference in means between the randomized treatment groups FYB203 and Eylea for the primary efficacy endpoint, i.e. change from baseline to Week 8 in BCVA in the study eye, regardless of treatment adherence, usage of concomitant medications and any other major protocol deviation (PD) until Week 8, which have an impact on BCVA, using data on all patients within the FAS with at least one post-treatment BCVA measurement until Week 24 available.

The following objectives are secondary objectives of the study:

- Evaluate and compare changes in foveal center point (FCP) retinal thickness
- Evaluate and compare changes in FCP retinal thickness and changes in foveal central subfield (FCS) retinal thickness over time
- Evaluate and compare functional changes of the retina by BCVA over time
- Evaluate and compare the proportion of patients who gain or lose ≥ 5, 10, and 15 ETDRS letters compared to baseline

- Evaluate and compare the absence of disease activity (fluid-free macula) over time
- Evaluate and compare changes in total lesion area
- Evaluate and compare systemic free and total aflibercept concentrations in a subgroup of up to 60 patients (up to 30 per arm)
- Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25)
- 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 the EU analysis, the first secondary objective to evaluate and compare changes in foveal center point (FCP) retinal thickness is defined as key secondary objective. If equivalence of FYB203 and Eylea can be shown with respect to the primary objective, the equivalence of FYB203 and Eylea with respect to the key secondary objective will be investigated in a formal statistical test. All other secondary objectives are weighed equally.

4.2 Study design

This study is a Phase 3 parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study to demonstrate clinical equivalence in terms of clinical efficacy, safety, and immunogenicity of FYB203 with EU-approved Eylea over 48 weeks of treatment in patients with subfoveal nAMD or wet AMD.

All eligible patients will receive 1 intravitreal (IVT) injection every 4 weeks for 3 consecutive doses starting at Week 0 (Visit 1) through Week 8 (Visit 3) followed by 1 IVT injection every 8 weeks over a period of approximately 48 weeks up to Visit 8.

Patients will be randomized in a 1:1 ratio to receive either FYB203 or EU-approved Eylea at a dose of 2 mg (0.05 mL of a 40 mg/mL solution). Randomization is performed stratified by country and participation in the plasma concentration evaluation subgroup (yes/no).

Each patient will receive a total of 8 IVT injections.

4.3 Sample size

The total sample size of approximately 400 patients for the EU/Japan analysis was calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 9.0 ETDRS letters in BCVA. An equivalence test of means using two one-sided tests with sample sizes of 180 in both treatment groups (360 patients in total) achieves at least 90.0% power at a 2.5% significance level when no difference between the means is assumed, the SD is 9.0 letters, and the equivalence interval is]-3.5; 3.5[letters. Assuming a difference in the number of patients of 10% between the PPS and the FAS, 400 patients in total are planned to be included in the EU specific analysis.

Reflecting different regulatory requirements regarding the significance level for equivalence testing, the required sample size for a US specific analysis using a 90% confidence interval corresponding to a significance level of 5% under otherwise identical assumptions is 320. The study was therefore planned to have a US specific analysis performed once the first 320 treated patients had completed their Week 40 assessments or discontinued the study. Following interactions with FDA in February 2023, it was agreed that the initial BLA

submission will also be based on the data of all patients enrolled instead of the subset of the first 320 patients.

The fixed sample size is based on the fixed assumed standard deviation of 9.0 letters. As there was some uncertainty about this parameter at the time of initial sample size calculation, a masked sample size review was performed after the first 200 treated patients had completed Week 8 (in November 2021). It revealed that the observed variability overall does not require an increase in sample size to maintain the intended statistical power. Details about this procedure are described in the corresponding SAP for the masked sample size review.

4.4 Endpoints for the analyses

The primary endpoint corresponding to the primary objective described in section 4.1 is the change from baseline in BCVA by ETDRS letters to Week 8 (Visit 3).

The key secondary endpoint corresponding to the key secondary objective for the EU analysis described in section 4.1 is the change from baseline in FCP retinal thickness to Week 4 (Visit). For the US analysis, this endpoint is not a key secondary endpoint but equally weighted as the other secondary endpoints below.

The following secondary endpoints correspond to the other secondary objectives listed in section 4.1, with timepoints after Week 24 only being relevant for the 56 week analysis:

- Changes of FCP retinal thickness and FCS retinal thickness over the whole study from baseline to Week 24 (Visit 5), to Week 40 (Visit 7) and to Week 56 (Visit 9)
- Change of BCVA by ETDRS letters over the whole study from baseline to Week 24 (Visit 5) to Week 40 (Visit 7) and to Week 56 (Visit 9)
- Proportions of patients who gain or lose ≥ 5, 10, or 15 ETDRS letters from baseline to Week 24 (Visit 5), to Week 40 (Visit 7) and to Week 56 (Visit 9)
- Percentage of patients with fluid-free macula at each Visit (baseline, Week 4 (Visit 2), Week 8 (Visit 3), Week 16 (Visit 4), Week 24 (Visit 5), Week 32 (Visit 6), Week 40 (Visit 7) and Week 56 (Visit 9)
- Change from screening in total lesion area to Week 24 (Visit 5), to Week 40 (Visit 7) and to Week 56 (Visit 9)
- Systemic concentrations of free and total aflibercept in a plasma concentration evaluation subgroup at selected sites at baseline (Visit 1) and close to predicted maximum concentration [C_{max}] (based on estimated t_{max}) at
    - 48 hours after 1st dose (Visit 1a) and
    - 48 hours after the 3rd dose (Visit 3a)
- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 to Week 24 (Visit 5), to Week 40 (Visit 7) and to Week 56 (Visit 9)
- Number of patients with ADAs at baseline (Visit 1), 7 days after the first injection (Visit 1b, for plasma concentration evaluation subgroup only), Week 4 (Visit 2), 48 hours after the 3rd injection (Visit 3a, for plasma concentration evaluation subgroup only), Week 16 (Visit 4), Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
- Frequency of local and systemic AEs and SAEs

Additional analyses not specified as an endpoint above may be defined in the respective

section of chapter 7.

4.5 Study flow chart

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8	V9 (EOS/Early Termination)
Week (Day)	**W-4 – W-1 (-28 to -1)**	**W0 (1)**	**W0+48h V1+48h (±6h)**	**W0+7D V1 + 7 (±1)**	**W4 (29±7)**	**W8 (57±7)**	**W8+48h V3+48h (±12h)**	**W16 (113±7)**	**W24 (169±7)**	**W32 (225±7)**	**W40 (281±7)**	**W48 (337±7)**	**W56 (393±7)**
Patient information/Informed consent	x												
Demographics information* **	x												
Medical history	x												
Prior treatments	x												
Physical assessment	x								x		x		x
Vital signs[1]	x								x		x		x
BCVA[2,3]	x	x			x	x		x	x	x	x	x	x
Tonometry[3,4,5]	x	x			x	x		x	x	x	x	x	x
Slit lamp exam [3,6]	x	x			x	x		x	x	x	x	x	x
Ophthalmoscopy [3,6]	x	x			x	x		x	x	x	x	x	x
Inclusion/Exclusion	x	x[12]											
Randomization		x											
Fluorescein angiography*[3]	x								x		x		x
Color Fundus Photography[3]	x								x		x		x
SD-OCT[3]	x	x			x	x		x	x	x	x	x	x
NEI VFQ-25[7]		x							x		x		x
Laboratory tests[13]	x								x		x		x
Pregnancy (serum hCG and FSH) *(only women)*	x												

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8	V9 (EOS/Early Termination)
Week (Day)	**W-4 – W-1 (-28 to -1)**	**W0 (1)**	**W0+48h V1+48h (±6h)**	**W0+7D V1 + 7 (±1)**	**W4 (29±7)**	**W8 (57±7)**	**W8+48h V3+48h (±12h)**	**W16 (113±7)**	**W24 (169±7)**	**W32 (225±7)**	**W40 (281±7)**	**W48 (337±7)**	**W56 (393±7)**
Urine sampling[14]	x								x		x		x
Plasma concentration evaluation[/8]**		x**	x**				x**						
ADAs[9]		x		x**	x		x**	x	x		x		x
Concomitant medications	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
IVT treatment[11]		x			x	x		x	x	x	x	x	
3-Day Post-IVT Telephone Safety Check		x			x	x		x	x	x	x	x	

* Additional fluorescein angiography may be performed at any time at the discretion of the Investigator/s.

** Plasma concentration evaluation subgroup only.

*** Demographic data includes the date of birth (or year of birth), gender, race and ethnicity.

1 Before any blood sample collection on the same day.

2 Refraction and visual acuity testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.

3 Ocular assessments at Screening, Visit 7 and on EOS are performed on both eyes. Ocular assessments at all other study visits are performed on the study eye 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 mmHg.

5 Tonometry should be measured prior to the injection and within 30 to 60 minutes after the injection.

6 A complete ophthalmic examination should be performed prior to the IVT injection.

7 Prior to any ophthalmic procedures or any other assessments.

8 Evaluation of systemic aflibercept concentration only.

9 In case of confirmed ADAs, the ADA titer and NAbs will be evaluated. Additional ADA sampling and evaluation will be performed in patients experiencing signals of unexpected ocular inflammation.

10 AEs starting after signing the informed consent must be recorded on relevant AE page. Between screening and 1st dose only study related AEs have to be collected.

11 A safety check (Light Perception Ophthalmoscopy and Tonometry) will be performed within 60 minutes post IVT.

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 equivalent 20/40 [0.5] to 20/200 [0.1]) and within 5 letters of the Screening BCVA.

[13] See Table 7 for the list of clinical laboratory tests to be performed.

[14] Urine sampling for clinical laboratory test will be collected at Screening, at Visit 5 and Visit 7 prior to IVT injection of IMP and at EOS Visit (Appendix 3). Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.

ADA = Anti-drug antibody; AE = Adverse event; BCVA = Best-corrected visual acuity; d = day; EOS = End of Study; ETDRS = Early treatment diabetic retinopathy study;
FA = Fluorescein angiography; FSH = follicle stimulating hormone; h = hours; hCG = Human chorionic gonadotropin; IMP = Investigational Medicinal Product; IOP = Intraocular pressure; IVT = Intravitreal;
NAb = neutralizing antibody; NEI VFQ-25 = National eye institute visual function questionnaire 25; SD-OCT = Spectral domain optical coherence tomography; V = Visit; VA = Visual acuity; W = Week.

All assessments of a particular visit have to be performed during 1 day, except for screening.

5 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

5.1 Analysis sets

Decisions on the allocation of patients to the analysis sets were made prior to unmasking of the randomization code for all patients and documented in the Blind Data Review Meeting (BDRM) minutes before the originally planned final US analysis. Since all treated patients had completed Week 8 at that time point, all allocations to analysis sets were done prior to unmasking the individual treatment group for the purpose of statistical analysis. Updates on protocol deviations and intercurrent events will be provided for each analysis and CSR, but the allocation of each patient to the analysis sets will only change in exceptional cases (for example detection of data errors that are relevant for allocation of analysis sets) and only for patients not yet unmasked.

Screening failures are not included in any analysis set but will be included in disposition tables and listings.

The following analysis sets are defined for the statistical analysis after 24 and after 56 weeks.

Safety Analysis Set:

The safety set (SAF) includes all patients who receive at least 1 injection of study medication in the study eye. Patients will be analyzed according to the treatment they actually received in the study eye irrespective of their randomized treatment. The safety set will be used for the analysis of all safety and tolerability data.

Full Analysis Set:

The full analysis set (FAS) includes all patients who receive at least 1 injection of study medication in the study eye. Patients will be analyzed according to the treatment they were randomized to. The full analysis set will be used for the analysis of all efficacy data.

Per Protocol Set:

The per protocol set (PPS) includes all patients that are in the FAS and

- Have no major protocol deviations until Week 8 (defined as protocol deviations that will interfere with the interpretation of the BCVA efficacy data at baseline or at Week 8 in any way (directly or indirectly))
- Have received treatment from the randomized treatment group only before Week 8
- Have a valid measurement of the BCVA at baseline and at Week 8 available
- Have no positive total aflibercept concentration at baseline (since this indicates use of prohibited prior treatment, even if no such treatment is explicitly documented. A total aflibercept concentration at baseline documented as “not reportable” will be treated like a positive value, as the true value is unclear and values below limit of quantification would be documented as such)

Plasma Concentration Analysis Set:

The plasma concentration analysis set (PKS) includes patients that are in the SAF and have at least 1 valid post-dose plasma concentration measurement. Patients will be analyzed according to the treatment they actually received in the study eye at Visit 1. Patients who

receive injections from different treatment groups at Visit 1 and Visit 3 will not be included in the PKS. Furthermore, patients with a positive baseline total aflibercept concentration will be excluded from the PKS.

Analysis strategies for patients receiving treatment outside their randomized treatment group:

If only single injections from the wrong treatment were administered, it will be decided on a case by case basis in which treatment group the patients will be analyzed.

Adverse events that occurred after a wrong treatment will be listed separately.

5.2 Protocol deviations

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 BDRM 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 for all treated patients were reviewed during the BDRM before database lock and unmasking for the originally planned US analysis in order to allocate all patients into the different analysis sets. The deviations were assessed as major or minor during the BDRM before the originally planned US analysis with regard to their influence on the primary efficacy endpoint prior to locking the database. Updates on protocol deviations and intercurrent events will be provided for the 24 and 56 week analyses and reports, but the allocation of each patient to the analysis sets will only change in exceptional cases (for example detection of data errors that are relevant for assignment to analysis sets) and only for patients not yet unmasked. All PDs will be kept and included in the analysis, even if programmed and CRA reported PDs might be the same. Issues identified during the DRM as being not a PD or a PD that is not CSR reportable will be kept in the original PD lists but will not be included in the TFLs.

All protocol deviations will be listed by patient and treatment group. For the 24-week analysis, only protocol deviations that occurred until the individual general cut-off date (study day 182) will be used for tables and listings.

Deviations from inclusion and exclusion criteria will be listed together with the treatment group, center ID, patient ID and inclusion/exclusion criteria for all enrolled patients including screen failures.

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

5.3 Changes or deviations from planned analyses

The following table summarizes the deviations from the planned analysis as described in the study protocol.

Table 2 Changes or deviations from planned analysis

Summary of protocol content including reference to section	Summary of SAP content including reference to section	Description and rationale for change
3 Objectives and Endpoints	4.4 Endpoints	The term "Change from baseline Visit (V1)" was replaced by "Change from baseline" to include all baseline values according to the definition in section 6.6
10.4.1.2 Primary analysis The primary estimand will be assessed through a mixed model for repeated measures (MMRM) including the BCVA at Baseline as covariate, country, visit, randomized treatment group, the baseline-by-visit interaction, and the treatment-by-visit interaction as fixed effects.	Section 7.9.1.3 The primary estimand will be assessed through a MMRM including the BCVA at baseline as covariate, region, visit, randomized treatment group, the baseline-by-visit interaction and the treatment-by-visit interaction as fixed effects	Variable country was replaced by region, using the definition of region as Japan versus Rest of World (ROW), since the differences between study population in Japan versus the other countries is regarded as more important than possible differences between countries.
10.4 Statistical Analyses Originally, it was planned to perform a final US analysis based on 40 week data and on the first 320 treated patients. Further, the planned analysis on 24 week data based on all patients was planned to be submitted in the EU only. Due to regulatory feedback by FDA in February 2023, the planned 24 week data analysis on all patients will now be performed both according to the US criteria using a 5% overall significance level **and** according to the EU/Japan criteria using a 2.5% significance level overall.	Section 3.1 The 24 week analysis is planned to be submitted to the EU and the FDA. Elements of the 56 week analysis will also be submitted to the FDA as part of the 120-Day Safety Update Report.	The scope of reporting changed after regulatory feedback from the FDA in February 2023.

6 DEFINITIONS FOR STATISTICAL ANALYSIS

All definitions in chapters 6 and 7 that involve study drug administration are only relevant for patients who received at least one injection of study drug.

6.1 Reference day / Day 1

Day 1 is defined as the date of first injection of study treatment. Study days for statistical analysis will be calculated relative to Day 1.

The study day will be calculated as follows:

- Assessment/Visit Date – date of first injection of study treatment + 1; for

assessments after first injection of study treatment or on the same day

- Assessment/Visit Date – date of first injection of study treatment; for assessments before first injection of study treatment

There is no study day 0.

In case a study day calculation is needed for patients who did not receive any study treatment, the date of randomization will be used instead. For patients who were not randomized, no calculation of study days will be done.

6.2 Framework for the 24 week statistical analysis

The 24 week statistical analysis will be performed after completion of the following working steps:

- All treated patients have completed Week 24 (Visit 5) (including corresponding delayed IMP visit if applicable) or terminated the study prematurely before Week 24 (for definition see section 7.3).
- All relevant data are available and clean. The confirmation of the cleaning status has to be available at xxx(see Table 3).
- All data items relevant for the 24 week analysis as defined below have been locked in the database, i.e. further changes of database contents relevant for the 24 week analysis are not permitted and physically impossible. The only data that might change afterwards are AE/CM end dates, maximum severities and outcomes.
- A BDRM has been performed to confirm the assignment of all patients to the respective analysis sets. The analysis set of a patient can only change in exceptional cases (for example detection of data errors that are relevant for assignment to analysis sets) and only for patients who had not yet been unmasked for the originally planned US analysis.
- The randomization codes of all randomized patients have been unmasked to a restricted number of predefined persons that perform and review the statistical analyses.
- All relevant data are available at xxxfor statistical analysis.

Table 3 Description of data needed for all enrolled patients at the time point of the 24 week analysis

Type of data	Source	Data that has to be available	Cleaning status
Randomization	eCRF/ Interactive Web Response System (IWRS)	All patients have been randomized.	Data cleaning and reconciliation performed, check for completeness performed by xxx
First treatment date	eCRF	Data for all treated patients has to be available.	Source Data Review (SDR) performed.
Premature termination	eCRF	For any patient that terminated the study prematurely before Week 24 (for definition see 7.3), the disposition page	SDR performed

Type of data	Source	Data that has to be available	Cleaning status
information		on the eCRF has to be filled and at least the primary reason and the date of discontinuation have to be available.	
Visit dates	eCRF	Visit dates of all performed visits, including unscheduled visits, have to be available until analysis visit Week 24 (V5), i.e. up to study day 182 if necessary (see 6.5). If a patient terminated the study prematurely before analysis visit Week 24 (V24), all visit dates until the premature termination date have to be available. Any data after analysis visit Week 24 (V5) will not be included in the 24 week analysis, however to minimize data changes after unmasking, all further data should be cleaned as far as possible.	Data cleaning performed, check for completeness performed by XXX
BCVA assessments	eCRF	All performed assessments for all visits as described above have to be available for the study eye.	Confirmed by investigator via signature on the respective eCRF page, SDV performed
SD-OCT information	eCRF	All performed assessments for all visits as described above have to be available.	Data cleaning performed, check for completeness performed by XXX
Other eCRF data	eCRF	All data generated and collected up to analysis visit Week 24 (V5) have to be available.	Data cleaning (and SDR/SDV where applicable) performed
Laboratory data	External data	All performed assessments for all visits as described above have to be available.	SDR and reconciliation between external and eCRF data performed
Imaging data (XXX)	External data	All performed assessments for all visits as described above have to be available.	SDR and reconciliation between external and eCRF data performed
FCP data	External data	Results of all performed assessments until analysis visit Week 24 (V5) have to be available for the study eye for all treated patients. If a result cannot be provided, a reason has to be given. All further results that are available should also be transferred.	Reconciled with SD-OCT data
Investigator confirmation	eCRF	The investigator has to confirm that the case report forms until Week 24 (V5) of	Confirmed by investigator via

Type of data	Source	Data that has to be available	Cleaning status
		the patients have been reviewed and the information contained herein is true to the best of his/her knowledge.	signature on the respective eCRF page
External data		All external data collected until analysis visit Week 24 (V5), i.e. up to study day 182 if necessary (see 6.5), as defined above is reconciled with the eCRF. Confirmation has to be present at XXX.	Reconciled with eCRF data
Queries		All queries pertaining to the data as defined above have been answered and necessary editing of the database has been performed.	
Medical Coding		All medical coding for any data as defined above has been done and coding review has been performed.	

6.3 Individual patient cut-off dates for the 24 week statistical analysis

The following cut-off dates are calculated individually for each treated patient and will be used for the 24 week analysis (no cut-off dates are needed for the final 56 week analysis since all data will be included there):

- **General cut-off date:** The general cut-off date for each patient, defines which data are included in the 24 week analysis, and is equal to the date of the latest study visit/assessment performed up to and including study day 182, regardless of the type of visit/assessment. Thus, all data assigned to any analysis visit up to and including analysis visit Week 24 (Visit 5) will be included in the 24 week analysis. If multiple values for the same parameter fall into the same analysis visit window, the values used for analysis are selected as specified in section 6.5.
- **IMP administration cut-off date:** Since the study drug is administered after all efficacy assessments have been performed at eCRF Visit 5 (Week 24), all study drug administration information collected up to and including eCRF Visit 4 (including delayed IMP visits corresponding to eCRF Visit 4) will be included for the 24 week analysis, will be assigned to analysis visits and will be displayed in summary tables and patient data listings. Thus, the cut-off date for all IMP administration data is the date of the IMP injection at eCRF Visit 4 (Week 16) or the corresponding delayed IMP visit. For patients who do not have a documented IMP administration at V4 or discontinued the study before, all documented IMP data (including “not-done” visits in the eCRF and end of treatment date from End of Treatment form) before V5 or study discontinuation date are included in the 24 week analysis.
- **Safety cut-off date:** The safety cut-off date for each patient is equal to the date of the IMP injection performed at eCRF Visit 5 (Week 24) (including delayed injections that are allocated to eCRF Visit 5) minus 1 day. If no injection was performed at Visit 5, the date of the injection performed at Visit 4 plus 55 days is used. If this is also not documented, the safety cut-off date is set equal to the general cut-off date as defined above. This cut-off date is used for all medication and surgical procedure as well as general adverse event data. All medications/procedures/events with a start date up to and including the safety cut-off date are included in the 24 week analysis, all

medications/procedures/events with a start date after the safety cut-off date will be excluded from the 24 week analysis. If the exact start time of an AE is known and the AE is known to have started prior to the injection at Visit 5 (Week 24), then this AE will still be included in the 24 week analysis. Medications/procedures/events with partial start dates that might have occurred before or on the safety cut-off date will also be included in the 24 week analysis. However, all SAEs, AEs of special interest, AEs leading to discontinuation of treatment or study and deaths will be included in patient listings.

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

Discontinued or withdrawn patients will not be replaced. Data from patients who prematurely discontinue the study will be used to the maximum extent possible.

For the primary analysis, a mixed model for repeated measures (MMRM) will be used. Missing data will not be explicitly imputed, however if a patient has a missing data point at a specific post-baseline visit the model assumes that the patient's missing value is comparable to the observed value of another patient having identical baseline characteristics and a comparable course of change from baseline until the respective Week/Visit.

Using an MMRM approach, only patients will be included in the analysis of each parameter, if at least the baseline assessment and one further post-baseline assessment is available for the respective parameter. For patients who do not have a baseline measurement or no post-baseline value, no course of change from baseline can be assumed and consequently, these patients are excluded from the analysis. For the definition of baseline refer to section 6.6.

As a sensitivity analysis for the primary analysis regarding the handling of missing values, an analysis of covariance (ANCOVA) model will be used and missing values will be imputed using multiple imputation (see section 7.9.1.4 for details).

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 masked manner prior to the BDRM and the strategy for handling missing data will be reconsidered if deemed necessary prior to database lock and unmasking.

If not specified otherwise, the number of missing values will be displayed for all summaries. If not specified otherwise, the number of missing values for summaries by visit will be based on the number of patients in the respective treatment group and/or analysis set. For overall summaries, the number of missing values will also be based on the number of patients in the respective treatment group and/or analysis set.

6.5 Visit windows and analysis visits

Visit windows of +/- 7 days calculated from the planned visit day (target day) are originally defined in the protocol for all relevant post-baseline visits. In order to include assessments from unscheduled visits in the best way, visit-based assessments will be analyzed according to analysis visits and thus not necessarily according to the visit indicated in the eCRF (referred to as 'eCRF-visit' in the analysis).

Analysis visits are defined in Table 4. A range of +/- 14 days is considered. Measurements

that cannot be matched to any of the analysis visits will not be included in any summary tables but will be included in by-patient listings. The number of assessments that cannot be mapped to any analysis visit and the definition of analysis visit windows were reviewed during the BDRM for the originally planned US analysis and it was confirmed that the definition will not be changed and assessments that fall out of any window will not be mapped. This strategy will not be changed.

If more than one assessment for the same parameter 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.

Table 4 Definition of analysis visits

Analysis visit name	Target study day	Definition
Baseline	NA	All baseline assessments as defined in section 6.6
Week 4 (V2)	29	15 ≤ Study day ≤ 42 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 8 (V3)	57	43 ≤ Study day ≤ 70 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 16 (V4)	113	99 ≤ Study day ≤ 126 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 24 (V5)	169	155 ≤ Study day ≤ 182 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 32 (V6)	225	211 ≤ Study day ≤ 238 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 40 (V7)	281	267 ≤ Study day ≤ 294 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 48 (V8)	337	323 ≤ Study day ≤ 350 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.
Week 56 (V9)	393	379 ≤ Study day ≤ 406 Assessments performed in the framework of unscheduled visits will be assigned to this analysis visit if applicable.

Visits that are only applicable for the Plasma Concentration Sub-Study will be analyzed as collected in the eCRF.

The analysis of all plasma concentration data and all anti-drug antibody (ADA) related data will not make use of this concept of analysis visits, but will be analyzed by eCRF visits as specified in sections 7.12 and 7.13. Safety data will also be analyzed by eCRF visit as described in section 7.10.

6.6 Baseline

In general, the assessments performed at Visit 1 (Baseline) prior to the first injection of study treatment will be considered as baseline values. If multiple assessments for the same parameter or variable are available at Visit 1, the latest assessment prior to study drug administration will be considered as baseline value.

Assessments that are defined as pre-IVT in the study protocol and that are performed at the same date as the first injection of study treatment are considered to have been performed prior to the injection if no time is collected. Assessments that are defined as post-IVT in the study protocol and that are performed at the same date as the first injection of study treatment are considered to have been performed after the injection if no time is collected.

If the assessment at Visit 1 is missing or if no assessment is planned at Visit 1 for a certain parameter, the assessment at Screening will be considered as baseline value. All assessments performed during the screening period prior to the first injection of study treatment will also be considered for identifying the baseline assessment. For re-screened patients, also all assessments during the initial screening will be considered.

6.7 Screening failures

The classification of a patient as a screening failure needs to be clearly documented in the eCRF by selecting “Screen failure” as the reason for early discontinuation. Screening failures are defined as patients who were enrolled in the study but were not randomized.

For screening failures, the informed consent date and the screening date will be listed. If available, the reason why the patient has not been randomized will be included as well. Furthermore, failing of inclusion/exclusion criteria will be listed for screening failures as available. All AEs collected from screening failures during the screening period will be listed as pre-treatment AEs

The number of screening failures will be summarized overall, and by study center in the respective disposition table. Basic demographic data of screen failures will be included in a respective table, as defined in section 7.6. Screening failures will not be considered in any further summary table or figure.

7 STATISTICAL ANALYSIS SPECIFICATION

7.1 Specifications related to whole analysis

7.1.1 Tables

If not specified otherwise, all collected data will be summarized for the study eye. Data for the fellow eye will be summarized descriptively if available.

Data will be summarized descriptively and will be presented by treatment group (FYB203, Eylea and overall) and analysis visit/time point if applicable and not specified otherwise.

Continuous data will be presented as number of patients (with non-missing value, termed as “n”), number of missing data (termed as “nmiss”), arithmetic mean, 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 the first and third quartile; 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). Number of patients will be displayed with no decimal place, percentages will be displayed with one decimal place. If not specified otherwise, the number of patients in the respective treatment group and/or analysis set will be used as denominator for all corresponding percentage calculations. The number of missing data will also be displayed.

Separate summary tables for the SAF and the FAS will only be provided if for at least one patient a different actual treatment group was assigned than the randomized one.

7.1.2 Data listings

All individual patient data will be listed as documented in the eCRF. All relevant generated and transformed variables will be included in listings as well, next to the original data items. In all listings, patient ID (which includes the center ID), treatment group, and analysis set (in terms of the most restrictive analysis set, PPS is more restrictive than FAS) for each patient will be included. As applicable, either only the eCRF visit or both the eCRF and the analysis visit will be listed. The listings will be sorted by patient ID, visit date and study eye/fellow eye if applicable.

7.1.3 Figures

The time course of all continuous efficacy variables which are measured at every visit is presented in terms of boxplots by analysis visit and treatment. The arithmetic mean will additionally be presented in the grouped boxplots. These plots will be displayed for absolute values and changes from baseline.

The time course of all binary and categorical efficacy variables which are measured at every visit is presented in terms of bar plots by analysis visit and treatment.

The difference in the percentage of patients experiencing a certain type of adverse event between the treatment groups will be visualized with forest plots including 95% confidence intervals (according to Miettinen and Nurminen (1985)).

Discontinuation from study and discontinuation of treatment will be presented in terms of Kaplan-Meier plots.

7.2 Overall study duration and treatment duration

Overall study duration for 24 week analysis (expressed in [days]):

- Date of last chronological individual patient general cut-off day (see Section 6.3) – date of Screening of first patient +1, based on all patients in the analysis set

Overall treatment duration for 24 week analysis (expressed in [days])

- Date of last chronological individual patient IMP administration cut-off day (see Section

6.3) – date of first chronological IMP administration + 1, based on all patients in the analysis set

Overall study duration for 56 week analysis (expressed in [days]):

- Date of last patient last visit – date of Screening of first patient +1, based on all patients in the analysis set

Overall treatment duration for 56 week analysis (expressed in [days])

- Date of last chronological IMP administration – date of first chronological IMP administration + 1, based on all patients in the analysis set

The overall study duration and the overall treatment duration will be displayed in days and months (1 month=30.5 days), together with the respective start and end dates as defined above.

7.3 Disposition of patients

For the 24 week and 56 week analyses, all treated patients will be included in any disposition analyses with their data until analysis visit week 24 (Visit 5) (see section 5.1) / all data as applicable for the respective analysis, and additionally all screen failures and randomized but not treated patients. All specifications below refer to this population of patients (i.e. all enrolled patients).

A patient is defined as completing the study until Week x, if

a) at least one eCRF visit is documented that can be mapped to the corresponding analysis visit (for details see section 6.5) and the disposition page of the eCRF is not filled with a date prior to this visit *or*

b) at least one eCRF visit is documented with a date after the respective analysis visit Week x.

A patient is defined as 'terminating the study prematurely before Week x' if the patient is marked as early discontinued on the disposition page of the eCRF and no eCRF visit is available that could be mapped to analysis visit Week x or has a date after analysis visit Week x (for details see section 6.5).

The disposition includes the following categories:

- screening procedures (including rescreenings)
- rescreening procedures
- screening failure procedures (including rescreenings)
- screened and enrolled patients (signed the informed consent form [ICF])
- rescreened patients
- screening failure patients
- patients who were randomized
- patients who were randomized but not treated
- patients who were treated
- patients who completed the study until Week 24 (Visit 5) / Week 56 (Visit 9)

- patients who discontinued the study prior to Week 24 (Visit 5) / Week 56 (Visit 9)
- patients who discontinued treatment but not the study prior to Week 24 (Visit 5) / Week 56 (Visit 9)

The number and percentage of patients in all categories will be summarized by treatment group and overall. In addition, these summaries will be created by study center, by age group, by gender as well as by age group and gender.

Additionally, the reason for discontinuation of the study and for discontinuation of treatment prior to Week 24 (Visit 5) / Week 56 (Visit 9) will be summarized.

The number of patients who completed the study until week x and who discontinued the study prior to Week x as defined above will be summarized for all applicable analysis visits Week x until Week 24 (Visit 5) / Week 56 (Visit 9).

Additionally, the number of patients who discontinued the study in each time period between the planned study days of the visits (see section 6.5) will be summarized by treatment group and overall.

Discontinuation from study and discontinuation of treatment over time will be presented in terms of Kaplan-Meier plots (both probability of discontinuation as well as probability of not discontinuing will be displayed).

Disposition related summary tables are included in Section 14.1 of the summary tables (see SAP appendix).

A patient data listing for patient enrollment will list all patients enrolled in the study with country, patient ID, details on informed consent (date and version), details on informed consent for participation in the plasma concentration evaluation subgroup (date and version, if applicable), rescreening details, and BCVA at screening (Snellen equivalent). Another patient data listing for randomization will list all patients with treatment group, patient ID, informed consent date, screening date, randomization date, randomization number, inclusion in the plasma concentration evaluation subgroup, rescreening details, and country for all randomized patients. A further listing for not randomized patients will include patient ID, informed consent date, screening date, date of declared screening failure, reason for not being randomized (if available), rescreening details, and country for all patients who were not randomized.

A patient data listing will list all treated patients who prematurely discontinued the study prior to Week 24 (Visit 5) / Week 56 (Visit 9) including treatment group, patient ID, date of discontinuation, reason for discontinuation and specification, last available visit, and unmasking details if applicable. Similarly, a listing for discontinuation of treatment will be created.

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

7.4 Protocol deviations

The analysis of protocol deviations is detailed in section 5.2.

7.5 Analysis datasets

The number of patients in each analysis set and the categorized reason for exclusion from

each analysis set will be summarized by treatment group and overall. Reasons for exclusion from any analysis set will be presented in patient listings individually with more specific reasons in addition if available.

7.6 Demographics and baseline characteristics

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 or subgroup analyses might be added.

Age at Screening will be categorized in two different ways:

- 50-64 years; 65-75 years and >75 years
- 18-64 years; 65-84 years; >=85 years

Demographic data and other baseline characteristics including age, age categories, gender, childbearing potential, race, ethnicity, country, region (EU versus non-EU, as well as Japan versus Rest of World), study eye, iris color for the study eye, time since first diagnosis of nAMD, and lesion type at baseline for the study eye will be summarized by treatment group and overall for the SAF, the FAS, the PPS and the PKS.

Time since first diagnosis of nAMD will be defined as time between the earliest start date of documented nAMD medical history (MH with preferred term “Neovascular age-related macular degeneration”, relevant term confirmed during BDRM) and date of randomization. This calculation will not be done if only partial start dates of nAMD MH are documented.

Additionally, baseline BCVA Snellen equivalent will be summarized by treatment group for each analysis set for the study eye.

Demographic data and other baseline characteristics will also be summarized by region (Japan vs. ROW), by gender, by age group as well as by gender and age group for the SAF and the FAS and the PPS.

Additionally, there will be a reduced demographics table that includes all patients that signed the informed consent, thus also screen failures (rescreened patients will be included once with the enrollment that led to randomization). It will include country, age, age categories, and gender.

Furthermore, there will be a separate table for screening and baseline values of efficacy parameters BCVA, FCP and FCS retinal thickness, and total lesion area, as well as IOP. This table will be created for the same analysis sets as defined above for the demographics and baseline characteristics tables.

All summary tables related to demographics and baseline characteristics are included in Section 14.1 of the summary tables (see SAP appendix).

All demographic data and other baseline characteristics will be listed including patient ID, treatment group, and analysis set.

All patient data listings related to demographic data and other baseline characteristics are included in Section 16.2.4 of the patient data listings (see SAP appendix).

7.7 Medical history and current medical conditions

Medical history and current medical conditions will be recorded at Screening and summarized. Reported terms will be coded using the Medical Dictionary of Regulatory Activities (MedDRA), in the version and using the update strategy that is defined in the medical coding specification of this 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 current medical condition.

For each medical history/current medical condition, it is collected in the eCRF whether it is related to the left eye, related to the right eye or non-eye-related. Conditions that are related to both eyes must be entered separately for both eyes. Based on the information which eye is the study eye collected in the demography section of the eCRF all medical history and current medical conditions will be categorized into “related to the study eye”, “related to the fellow eye” or “not eye related” medical history/current medical conditions.

Medical history and current medical conditions will be analyzed separately, and each again separated into ophthalmological related to study eye, ophthalmological related to fellow eye, and general not eye related, by display of their absolute and relative frequency by treatment group for the SAF and the FAS. 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, all medical history and current medical conditions will be listed. The listings will be sorted by treatment group, patient ID and medical history number.

Summary tables related to medical history and current medical conditions are included in Section 14.1 of the summary tables and the corresponding listings are included in Section 16.2.4 of the patient data listings (see SAP appendix).

7.8 Prior and concomitant medication and non-drug treatment

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/occurrence after the first injection of IMP (i.e. medications/therapies with a start and/or stop date later than the first injection of IMP, or no stop date [ongoing]). Hence follows, some medications/therapies will be considered as both, prior and concomitant. If the medication/therapy started on the same day as the first IMP administration and the time of medication/therapy is missing, the medication/therapy will be classified as prior and concomitant.

Prior and concomitant medications, as well as surgical procedure history and (concomitant) non-drug treatments are documented separately in the eCRF. However, for analysis, the classification into prior and concomitant medications (respectively, surgical procedure history and non-drug treatments) will be conducted as described above if a complete start and/or stop date is available that allows unique classification. If such classification is not possible because of missing/incomplete dates, the medication/therapy will be analyzed according to the documentation as prior or concomitant in the eCRF.

Prior and concomitant medications and non-drug treatments as well as surgical procedure history are recorded in the eCRF. All medications (other than IMP) and significant non-drug treatments administered after the patient starts treatment with the IMP muss be recorded in the eCRF. If a treatment is given due to an adverse event or medical history, this is documented in the eCRF via the respective cross-reference.

Prior and concomitant medications will be coded using the WHO Drug Global dictionary (WHODrug), in the version and using an update strategy that is defined in the medical coding specification of this study. Surgical procedure history and non-drug treatments/interventions will be coded using the MedDRA dictionary, in the version and using the update strategy that is defined in the medical coding specification of this study.

For the 24 week analysis, safety cut-off dates as defined in section 6.3 will be applied for concomitant medications/therapies: all concomitant medications/therapies with a start date up to and including the safety cut-off date will be included in the analysis. All concomitant medications/therapies with partial start dates which might have occurred prior to or at the safety cut-off date are considered in the respective analysis.

For non-drug treatments as well as prior and concomitant medications, the information whether its purpose is to treat the eyes or not (and if used for the study or fellow eye) is collected in the eCRF. For surgical procedure history, it is collected whether the procedure was related to the left eye, the right eye, both eyes, or no eye. This information will be mapped to study eye/fellow eye/no eye based on the information which eye is the study eye collected in the demography section of the eCRF. Procedures documented as “related to both eyes” in the CRF will be categorized as both, related to the study eye and related to the fellow eye.

Prior and concomitant medications will be analyzed by display of their absolute and relative frequencies using as denominator the number of patients in the respective treatment group in the SAF. In these tables, medications will be classified according to ATC level 3 and WHODrug preferred name and will be sorted by decreasing frequency in the total column within levels.

Surgical procedure history and non-drug treatments will be analyzed similarly, classified according to MedDRA SOC and PT.

Analyses for prior/concomitant medications, non-drug treatments and surgical procedure history will be done separately for study eye, fellow eye and all other indications.

Additionally, the number of patients who received Eylea treatment in the fellow eye as well as the number of Eylea injections they received will be summarized (Concomitant medications documented in the fellow eye with preferred name “Aflibercept”).

These summary tables are included in Section 14.1 of the summary tables (see SAP appendix).

Prior and concomitant medications, surgical procedure history and non-drug treatments will be listed separately and sorted by treatment group, patient ID, start date and eye, if applicable. These patient data listings will include flags indicating whether the medication/therapy is classified as prior, concomitant, or both and whether the purpose was to treat the study eye, the fellow eye and all other indications if available. These patient data listings are included in Section 16.2.9 of the patient data listings (see SAP appendix).

7.9 Efficacy

7.9.1 Primary efficacy analyses

7.9.1.1 Primary estimand

The primary estimand is the difference in means between the randomized treatment groups FYB203 and Eylea for the primary efficacy endpoint, i.e. change from baseline to Week 8 in BCVA in the study eye, regardless of treatment adherence, usage of concomitant medications and any other major protocol deviation (PD) until Week 8, which have an impact on BCVA, using data on all patients within the FAS with at least one post-treatment BCVA measurement available until Week 24.

Hence, the attributes as defined in the ICH E9 addendum of this estimand are:

- **Treatment condition:** FYB203 vs Eylea (at least one IVT injection with a dose of 2 mg)
- **Population:** Patients with nAMD who were randomized to receive either FYB203 or Eylea and who received at least one dose of IMP, i.e. the FAS
- **Endpoint:** Absolute change from baseline to Week 8 in BCVA by ETDRS letters
- **Intercurrent events and strategies:**
  All intercurrent events will be handled according to the treatment policy strategy, i.e. all values of interest will be analyzed whether or not the intercurrent event occurs.
  The following intercurrent events are considered for this estimand:
  - Discontinuation of treatment
  - Discontinuation of study (including death of the patient) related to safety of the IMP without any post-baseline assessment of the BCVA
  - Discontinuation of study (including death of the patient) unrelated to safety of the IMP without any post-baseline assessment of the BCVA
  - Major Protocol Deviations which impact the BCVA assessment until Week 8 as defined during the Data Review Meeting (e.g. wrong treatment administered, missing injections, use of prohibited medication etc.)
- **Population level summary:** Difference in means between FYB203 and Eylea treatment groups

This estimand will be used for the US specific and EU specific analyses. In order not to inflate the overall study-wise significance level, a hierarchical test strategy will be applied: the EU specific analysis will only be performed in a confirmatory way if the US specific analysis has already shown equivalence between FYB203 and Eylea.

7.9.1.2 Primary efficacy variable and primary efficacy endpoint

The primary efficacy variable is the change from baseline in ETDRS BCVA for the study eye.

The ETDRS BCVA for the study eye is collected at each visit in the eCRF. These measurements will be mapped to analysis visits as described in section 6.5. The change from baseline in ETDRS BCVA at each analysis visit (Week x) is calculated for each patient via:

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

For the definition of the baseline assessment, see section 6.6.

The primary efficacy endpoint is the change from baseline to Week 8 in ETDRS BCVA for

the study eye.

7.9.1.3 Primary efficacy analysis

The primary estimand will be assessed through a MMRM including the BCVA at baseline as covariate and region (Japan vs. Rest of World), visit, randomized treatment group, the baseline-by-visit interaction and the treatment-by-visit interaction as fixed effects. Within patients' correlations will be modeled using an unstructured variance-covariance matrix. Kenward-Roger degrees of freedom approximation will be used. The MMRM will use all available data collected until Week 24 (Visit 5) for the study eye for all patients in the FAS for model estimation.

It is assumed that there will be no missing data for baseline because the baseline BCVA needs to be available to confirm the inclusion criteria. A patient without any post-baseline BCVA measurement until Week 24 cannot be included in the primary efficacy analysis. The number of patients in the FAS without any post-baseline BCVA value will be assessed during the BDRM, and it will be evaluated whether an imputation approach will be added for the primary analysis for these patients.

Missing data will not be explicitly imputed, however if a patient has a missing data point at a specific post-baseline visit, the model assumes that the patient's missing value at that visit is comparable to the observed values of another patient having identical baseline characteristics and a comparable course of change from baseline until Week 24.

The hypothesis that both treatments FYB203 and Eylea are biosimilar with respect to the primary efficacy 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 corresponding to the primary estimand:

$$H_0: \left|\mu_{BCVA,FYB203} - \mu_{BCVA,Eylea}\right| \geq 3.5$$

$$H_1: \left|\mu_{BCVA,FYB203} - \mu_{BCVA,Eylea}\right| < 3.5$$

where $\mu_{BCVA,FYB203}$ and $\mu_{BCVA,Eylea}$ denote the mean changes of ETDRS letters from baseline to Week 8 in the respective treatment groups.

The difference between the least square (LS) means of the treatment groups and the corresponding two-sided 95.2% (EU analysis) and two-sided 90.4% (US analysis) confidence intervals (CIs) will be estimated from the MMRM to address regulatory requirements in the EU and the US, respectively. The significance level alpha from the one-sided test was reduced from 0.025 (0.05) to 0.024 (0.048) to control the overall type 1 error in the light of the masked sample size review, see section 10.2 of the protocol. If the CI is completely contained in the interval]-3.5;3.5[ETDRS letters, H_0 can be rejected and equivalence of FYB203 and Eylea can be concluded (rounded to the next integer, this corresponds to an equivalence margin of 3 ETDRS letters).

In order not to inflate the overall study-wise significance level, a hierarchical test strategy will be applied: the EU specific analysis will only be performed in a confirmatory way if the US specific analysis has already shown equivalence between FYB203 and Eylea.

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

```
proc mixed;
      class subject region treatment visit;
      model CHG_BCVA = BASE_BCVA region treatment visit
```

```
                    treatment*visit BASE_BCVA*visit/s ddfm = kr;
      repeated visit / subject = subject type = UN;
      lsmeans treatment*visit / diff=all cl <alpha=0.048 or alpha=0.096>;
run;
```

The MMRM assumption of normality of the residuals will be assessed via respective residual plots.

The summary tables for the primary efficacy analysis will be included in Section 14.2 of the summary tables (see SAP appendix). Appendix 16.2.6 will contain a listing showing the raw BCVA assessment values together with the analyzed changes from baseline at the CRF visits and the corresponding analysis visits.

7.9.1.4 Sensitivity analyses

For the primary estimand, the following sensitivity analyses are planned for the 24 week and 56 week analyses. The relevance of the sensitivity analyses will be evaluated during the BDRM considering the number of patients that fall into the respective category.

- For the primary statistical analysis using the MMRM, it is assumed that post-treatment assessments are missing at random (MAR) and that missing assessments are thus not related to any efficacy or safety difference between the two treatments. To investigate this assumption, the MMRM will be repeated including additional covariates:
  - Patient discontinued study prior to Week 24 (Yes/No)
  - Patient discontinued treatment prior to Week 24 (Yes/No)
  - Patient has any major protocol deviation (Yes/No)
- For the primary MMRM, it was assumed that the use of an ancillary chart does not influence the BCVA results. To investigate this assumption, the MMRM is repeated including the use of an ancillary chart (yes/no) at each visit as additional covariate.
- For the primary MMRM, it was assumed that patients with similar post-treatment values until Week 24 behave similarly. To investigate this assumption, the MMRM is repeated including only data until Week 8.
- The primary analysis as specified in section 7.9.1.3 will be repeated, but with all available data collected up to and including Week 56 (Visit 9) included and used for model estimation (56 week analysis only).
- For the primary analysis, it was assumed that there is a correlation between the different visits within a patient. To investigate this further, the change from baseline to Week 8 in BCVA by ETDRS letters will be analyzed with an ANCOVA model instead of an MMRM. The model will include the change from baseline to Week 8 in BCVA as the dependent variable, the baseline BCVA value as covariate and region (Japan vs. ROW) and treatment group as fixed effects. This analysis will be performed based on observed cases, i.e. only patients with a BCVA at Week 8 analysis visit will be included.
  The analysis will be conducted using SAS code similar to the following statement:

```
proc mixed data=BCVA_data;
   where visit eq 'V3';
   class region treatment;
   model CHG_BCVA = BASE_BCVA region treatment /s;
   lsmeans treatment / diff cl <alpha=0.048 or alpha=0.096>;
run;
```

- The primary efficacy analysis model cannot include patients without any post treatment assessments of the BCVA. To compensate, a sensitivity analysis will be performed

where missing BCVA assessments at Week 8 will be imputed using multiple imputation (MI) and an ANCOVA model will be used on the imputed dataset to analyze the primary efficacy endpoint. MI will use the baseline BCVA value as well as region and treatment group as covariates for imputation. A monotone imputation approach is used since it is expected that the covariates baseline BCVA, region and treatment group will not be missing for any patient. The predictive mean matching method is used to impute missing values of the BCVA change from baseline to ensure that imputed values are in the range of observed values. Instead of the default of 25 imputations, 100 imputations and a seed of 2143 will be used. The ANCOVA model will be the same as specified above for the previous sensitivity analysis and will be conducted separately for each of the 100 imputed datasets. The results will then be combined to the final result.
The analysis will be conducted using SAS code similar to the following statement:

```
PROC MI data=BCVA_data(where=(visit eq 'V3')) out=BCVA_MI nimpute=100
        seed=2143;
   class region treatment;
   monotone regpmm(CHG_BCVA = BASE_BCVA region treatment);
   var  BASE_BCVA region treatment CHG_BCVA;
run;

PROC MIXED data=BCVA_MI;
   BY _IMPUTATION_;
   where visit eq 'V3';
   class region treatment;
   model CHG_BCVA = BASE_BCVA region treatment /s;
   lsmeans treatment / e diff cl <alpha=0.048 or alpha=0.096>;
   ods output Diffs = LsMeans_Diffs_ANCOVA_MI;
run;

   PROC MIANALYZE data=LsMeans_Diffs_ANCOVA_MI <alpha=0.048 or
alpha=0.096>;
      modeleffects estimate;
      stderr stderr;
   run;
```

- To further investigate the assumption of MAR, a tipping point analysis assuming missing not at random may be performed where a sensitivity parameter (θ) will be introduced for each treatment. The MAR assumption with θ = 0 will be the starting point and will be changed in steps of 5 ETDRS letters in both directions to increase the difference between the treatment groups. Missing values will be imputed within the same treatment group. An ANCOVA will then be used to analyze the imputed datasets. The relevance of this analysis, dependent on the number and pattern of missing data with respect to the primary endpoint, was confirmed during the BDRM prior to the unmasking for the originally planned US analysis. To put the resulting tipping point into context of the distribution of the primary endpoint in the study population, an additional descriptive table will be created displaying the following summary statistics for the change from baseline to Week 8 in BCVA: N, nmiss, n, Mean, SD, Minimum, Maximum, and 1st, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 99th percentile.

7.9.1.5 Supplemental estimands for the primary endpoint

The following supplemental estimands (referring to the primary efficacy endpoint) are defined in the protocol:

- The mean difference between the randomized treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, excluding patients from the FAS with major protocol deviations which impact the BCVA assessments until Week 8 (Visit 3)
- The mean difference between the randomized treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, excluding patients from the FAS who discontinued treatment before Week 8 or do not have a Week 8 BCVA assessment
- The mean difference between the randomized treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, based on the PPS (this secondary estimand is a combination of the previous ones stated above)

The supplemental estimands described above will be assessed using the same statistical method as described in Section 7.9.1.3 for the primary efficacy analysis.

Additionally, the following supplemental estimand will be assessed:

- The mean difference between the randomized treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, based on the FAS with all patients excluded from the PPS analyzed with an imputed (hypothetical) BCVA value. The BCVA values at Week 8 will be imputed for all patients excluded from the PPS using a multiple imputation approach, regardless of whether a BCVA value at Week 8 was collected. This estimand will be assessed with the same ANCOVA model as specified above as sensitivity analysis.

To investigate the assumptions for the primary estimand further, the following supplemental estimands will be investigated

- For the primary analysis, it was assumed that discontinuation of treatment will have the same impact on the following measurements in both treatment groups and can therefore be neglected. To investigate this assumption, the primary MMRM will be repeated on data where all assessments following discontinuation of treatment are set to missing. This strategy follows the While on treatment strategy as described in the ICH E9 addendum on estimands. This analysis will only be done, if at least 10 patients present BCVA values until Week 24 that were assessed after discontinuation of treatment.
- For the primary analysis, it was assumed that single missed injections will not have an influence on the following assessments. To investigate this assumption, the primary MMRM will be repeated on data where all assessments following missed injection visits are set to missing. Missed injection visits are defined as analysis visits where no injection could be mapped to the defined visit window as defined in section 6.5. Only the BCVA assessment following this missed injection visit will be set to missing and assessments collected thereafter may still be included in the analysis.
- For the primary analysis, it was assumed that major protocol deviations will have the same impact on the following measurements in both treatment groups and can therefore be neglected. To investigate this assumption, the primary MMRM will be repeated on data where all assessments following major protocol deviations are set to missing.

- Certain protocol deviations will only have an impact on single BCVA measurements, e.g. prohibited medications that where taken only for a certain time period and are washed out thereafter. These deviations will be identified during the BDRM and all corresponding BCVA assessments will be set to missing and the primary MMRM will be repeated on this data. This analysis will only be performed if a substantial number of such PDs are identified, this decision is documented in the BDRM minutes.

The extent and pattern of missing data relevant for the primary analysis was reviewed during the BDRM and no further sensitivity analyses or supplemental were deemed necessary.

7.9.2 Secondary efficacy analyses

The secondary efficacy analyses described below will be included in Section 14.2 of the summary tables (see SAP appendix). In general, the 24 week analysis will only include efficacy data until the general cut-off date for the 24 week analysis (analysis visit Week 24 (Visit 5)). The 56 week analysis will include all data.

7.9.2.1 Definitions for variables assessed by the XXX reading center

All color fundus photographs, fluorescein angiography and SD-OCT images, which are collected at protocol-specified times, are sent to the (XXX) reading center for central evaluation by trained personnel who are masked to the patient's treatment.

Two independent readers perform the grading; in case of discrepancy a third reader is consulted for arbitration. The final reading data resulting from the centrally performed evaluation of the images is provided.

Color fundus photography (CFP) is used for assessing the image quality and to support FA and SD-OCT results and measurements. Therefore, no CFP results are explicitly available.

The variables FCP retinal thickness, FCS retinal thickness, total lesion area, and fluid-free macula are determined based on the images evaluated at the XXX reading center.

FCP retinal thickness is measured by SD-OCT and hence is assumed to be available at all eCRF visits planned for all patients, including *Screening* and *Baseline Visit 1* because this parameter is also relevant for checking inclusion and exclusion criteria. FCP is not available at visits that are performed for the plasma concentration evaluation subgroup only. In addition to the FCP measurement itself, the parameter "Does the finding affect the FCP measurement?" need to be considered. If the finding affects the FCP measurement, the measured FCP value is compromised and is not analyzed 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 planned for all patients except for Screening because this parameter is not relevant for the assessment of any in- or exclusion criterion.

Total lesion area is measured by Fluorescein Angiography (FA) and is available at Screening, Week 24 (Visit 5),Week 40 (Visit 7), and Week 56 (Visit 9). In the raw data transfer from XXX, lesion area is included in the record for Visit 1 due to XXX internal processes regarding the grading, however the values are based on screening images, thus the visit Screening will be mapped to all V1 lesion area assessments in Study Data

Tabulation Model (SDTM) data.

Fluid-free macula is measured by SD-OCT and is available at all eCRF visits planned for all patients except for at Screening because this parameter is not relevant for the evaluation of any in- or exclusion criterion. For fluid-free macula, the two XXX parameters “presence of intraretinal fluid” and “presence of subretinal fluid” need to be considered:

- Only if both parameters “presence of intraretinal fluid” and “presence of 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

Mapping rules for categorical XXX parameters:

The following mapping rules apply for all categorical XXX 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: Grader suspects about 50-90% probability that a finding is positive; will be summarized 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 summarized 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 summarized 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 summarized in category “Yes” and will be listed as “Yes, definitive” or “Yes, subtle” as applicable

7.9.2.2 Analysis of the key secondary endpoint based on FCP retinal thickness

For the 24 week and 56 week analyses, a similar MMRM model as specified for the primary efficacy analysis to derive two-sided 95.2% CIs for the difference between the treatment groups, will be used to analyze the key secondary endpoint of

Change from baseline to Week 4 in FCP retinal thickness (including data up to Week 24 (Visit 5)).

The hypothesis that both treatments FYB203 and Eylea are biosimilar with respect to the key secondary efficacy endpoint will be tested in terms of a two-sided equivalence test. The equivalence margin of 45.0 µm will be tested by the following hypotheses:

$$H_0: \left|\mu_{FCP,FYB203} - \mu_{FCP,Eylea}\right| > 45.0 \text{ µm}$$

$$H_1: \left|\mu_{FCP,FYB203} - \mu_{FCP,Eylea}\right| \leq 45.0 \text{ µm}$$

where $\mu_{FCP,FYB203}$ and $\mu_{FCP,Eylea}$ denote the mean changes of FCP retinal thickness from

baseline to Week 4 in the respective treatment groups.

The difference between the least square (LS) means of the treatment groups and the corresponding two-sided 95.2% confidence interval (CI) will be estimated from the MMRM. The significance level alpha was reduced from 0.025 to 0.024 to control the overall type 1 error in the light of the masked sample size review, see section 10.2 of the protocol. If the CI is completely contained in the interval [-45.0 µm; 45.0 µm], H_0 can be rejected and equivalence of FYB203 and Eylea can be concluded with respect to change in FCP retinal thickness can be concluded, based on all patients in the FAS. The analysis will be repeated based on all patients in the PPS and consistency between the results based on the FAS and the PPS is regarded as essential.

This conclusion is statistically valid only when equivalence of FYB203 and Eylea could already be shown for the primary efficacy endpoint.

For the US analysis, there is no key secondary endpoint and the change from baseline in FCP to Week 4 will be analyzed with the same MMRM as described above to derive 95% CIs, but without formal hypothesis testing.

7.9.2.3 Analyses of BCVA, FCP and FCS retinal thickness, and total lesion area

Any data available from the XXX reading center, for which no specific analysis is specified below, will be listed including treatment group, patient ID, analysis set and eCRF visit for both eyes separately (study eye/fellow eye), if applicable. The listing(s) for the study eye will be included in Appendix 16.2.6, listing(s) for the fellow eye will be included in Appendix 16.2.9.

Analyses of BCVA, FCP and FCS retinal thickness, and total lesion area for the 24 week analysis

All values of the study eye for BCVA, FCP and FCS retinal thickness, and total lesion area will be summarized by analysis visit until Week 24 (Visit 5) and treatment group, including the absolute change from baseline per analysis visit. Available BCVA data for the fellow eye will be summarized by analysis visit until Week 24 and treatment group similar as for the study eye. The other parameters are not available for the fellow eye.

The time course of BCVA as well as FCP and FCS retinal thickness, and total lesion area will be presented in terms of boxplots by analysis visit and treatment until Week 24. The following values will be presented in different figures:

- Absolute values for the study eye
- Changes from baseline (change from screening for total lesion area) for all post-baseline visits for the study eye

For the 24 week analysis, a similar MMRM model as specified for the primary efficacy analysis to derive two-sided 95.0% CIs for the difference between the treatment groups, but without formal hypothesis testing, will be used to analyze the

- Change from baseline to Week 4 in FCS retinal thickness (including data up to Week 24 (Visit 5))
- Change from baseline to Week 24 (Visit 5) in BCVA (including data up to Week 24 (Visit 5))
- Change from baseline to Week 24 (Visit 5) in FCP retinal thickness (including data up

to Week 24 (Visit 5))
- Change from baseline to Week 24 (Visit 5) in FCS retinal thickness (including data up to Week 24 (Visit 5))
- Change from screening to Week 24 in total lesion area (including data up to Week 24 (Visit 5))

The change from baseline to Week 24 (Visit 5) in BCVA will be categorized as follows:

- ≥ 15 ETDRS letters (i.e. gain 15 letters or more)
- ≥ 10 and < 15 ETDRS letters (i.e. gain between 10 and 14 letters)
- ≥ 5 and < 10 ETDRS letters (i.e. gain between 5 and 9 letters)
- > -5 and < 5 ETDRS letters
- > -10 and ≤ -5 ETDRS letters (i.e. loss between 5 and 9 letters)
- > -15 and ≤ -10 ETDRS letters (i.e. loss between 10 and 14 letters)
- ≤ -15 ETDRS letters (i.e. loss of 15 letters or more)

Absolute and relative frequencies of patients in each of the categories will be displayed. Additionally, the proportions of patients with gains/losses in the described categories will be visualized using a bar plot.

These analyses will be conducted on the FAS, and additionally for the PPS.

Analyses of BCVA, FCP and FCS retinal thickness, and total lesion area for the 56 week analysis

All values of the study eye for BCVA, FCP and FCS retinal thickness, and total lesion area will be summarized by analysis visit and treatment group, including the absolute change from baseline per analysis visit. Available BCVA data for the fellow eye will be summarized by analysis visit and treatment group similar as for the study eye. The other parameters are not available for the fellow eye.

The time course of BCVA as well as FCP and FCS retinal thickness, and total lesion area will be presented in terms of boxplots by analysis visit and treatment. The following values will be presented in different figures:

- Absolute values for the study eye
- Changes from baseline (change from screening for total lesion area) for all post-baseline visits for the study eye

In the final 56 week CSR, all analysis related to the 24 week analysis will be included.

For the 56 week analysis, a similar MMRM model as specified for the primary efficacy analysis to derive two-sided 95.0% CIs for the difference between the treatment groups, but without formal hypothesis testing will be used to analyze additionally the

- Change from baseline to Week 40 in BCVA (including data up to Week 56 (Visit 9))
- Change from baseline to Week 40 in FCP retinal thickness (including data up to Week 56 (Visit 9))
- Change from baseline to Week 40 in FCS retinal thickness (including data up to Week 56 (Visit 9))
- Change from screening to Week 40 in total lesion area (including data up to Week 56

(Visit 9))
- Change from baseline to Week 56 in BCVA (including data up to Week 56 (Visit 9))
- Change from baseline to Week 56 in FCP retinal thickness (including data up to Week 56 (Visit 9))
- Change from baseline to Week 56 in FCS retinal thickness (including data up to Week 56 (Visit 9))
- Change from screening to Week 56 in total lesion area (including data up to Week 56 (Visit 9))

The MMRM will be performed as an observed case analysis, i.e. only patients will be included who have at least the baseline assessment and one further post-baseline assessment for the analyzed parameter until Week 24 (Visit 5) / Week 40 (Visit 7) / Week 56 (Visit 9), respectively.

To account for missing values in secondary endpoints FCP/FCS retinal thickness and total lesion area, multiple imputation followed by an ANCOVA analysis, similarly as defined for the primary endpoint in section 7.9.1.4 will be performed: The change in FPC and FCS at Week 4 compared to baseline and the change in total lesion area at Week 24 compared to Screening will be analyzed. Patients with missing baseline assessment cannot be included in these analyses.

The change from baseline to Week 40 (Visit 7) and Week 56 (Visit 9) in BCVA will be categorized as follows:

- ≥ 15 ETDRS letters (i.e. gain 15 letters or more)
- ≥ 10 and < 15 ETDRS letters (i.e. gain between 10 and 14 letters)
- ≥ 5 and < 10 ETDRS letters (i.e. gain between 5 and 9 letters)
- > -5 and < 5 ETDRS letters
- > -10 and ≤ -5 ETDRS letters (i.e. loss between 5 and 9 letters)
- > -15 and ≤ -10 ETDRS letters (i.e. loss between 10 and 14 letters)
- ≤ -15 ETDRS letters (i.e. loss of 15 letters or more)

Absolute and relative frequencies of patients in each of the categories will be displayed for Week 40 (Visit 7) and Week 56 (Visit 9) separately. Additionally, the proportions of patients with gains/losses in the described categories will be visualized using a bar plot.

These analyses will be conducted on the FAS, and additionally for the PPS.

7.9.2.4 Analyses of fluid-free macula

The number and percentage of patients with fluid-free macula will be tabulated by analysis visit and treatment group by considering all applicable records/analysis visits for the study eye. The table will include the difference in proportions of patients with fluid-free macula between the treatment groups with the corresponding approximate 95% CIs according to Miettinen and Nurminen (1985).

In addition, a bar plot will be created displaying the percentage of patients with fluid-free macula per analysis visit and treatment group for the study eye.

For the 24 week analysis, only data until Week 24 will be analyzed.

Fluid-free macula will be analyzed based on the FAS, and additionally based on the PPS.

7.9.2.5 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 orientated domains related to daily visual functioning. NEI VFQ-25 questionnaires will be answered at Baseline (Visit 1), Week 24 (Visit 5),Week 40 (Visit 7), and Week 56 (Visit 9).

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 (see Appendix II to this SAP).

Scoring is performed according to the following two-step process and the composite score is calculated afterwards in a third step:

- First, original numeric values from the questionnaire are re-coded following the scoring rules outlined in Table 5 (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 6 (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 sued to generate sub-scale scores. Hence, the sub-scale scores represent the average for all items in the sub-scale that the respondent answered.
- Composite score calculation: To calculate the composite score, all vision-targeted sub-scale scores are averaged, excluding the general health rating question. By averaging the sub-scale scores rather that the individual items, equal weights are given to each sub-scale, whereas averaging the item would give more weight to scales with more items. The composite score will be missing only if all sub-scales are missing. In case of single missing sub-scales, the composite score will be calculated by averaging all available sub-scales.

All collected sub-scales and the composite score will be summarized descriptively by analysis visit and treatment group by considering all applicable analysis visits, including the absolute change from baseline for each analysis visit.

In addition, boxplots as defined for the primary efficacy analysis will be created for the composite score absolute values to display the time course. No figures for the changes from baseline will be created as the NEI VFQ-25 questionnaires will only be answered at Baseline (Visit 1), Week 24 (Visit 5),Week 40 (Visit 7), and Week 56 (Visit 9).

For the 24 week analysis, only data until Week 24 will be analyzed.

These analyses will be conducted using the FAS, and additionally using the PPS.

Table 5 NEI-VFQ-25: 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	1	100
	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25	1	0
	2	25
	3	50
	4	75
	5	100

(a) Pre-coded response choices as printed in the questionnaire

(b) Item 15c has four response levels, but is expanded to five levels using item 15b as follows:

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.

* Response choice "6" ("7" for item 2) 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 6 VFQ-25 Sub-Scales generation: averaging of items

Scale	Number of items	Items to be averaged (after recoding per Table 5)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance	3	8, 9, 14
Vision Specific:		
Social	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

Scale	Number of items	Items to be averaged (after recoding per Table 5)
Peripheral Vision	1	10

7.9.2.6 Subgroup analyses

Analyses of subgroups with respect to the following variables will be performed:

- Gender (female and male)
- Use of an ancillary chart up to Week 24 / 56 (yes/no, Patients who only used the ancillary chart for single assessments will be excluded from this analysis)
- ADA status (any positive treatment emergent ADA as defined in section 7.13 during study versus no positive treatment emergent ADA during study up to Week 24 / 56)
- Total lesion area at baseline (< 9mm^2 versus >= 9mm^2, cut-off confirmed during BDRM)
- Lesion type at baseline (types as reported by XXX, calculations not to be done in subgroups where the sample size is too small leading to non-calculable estimates)
- Syringe use (original syringes provided by sponsor versus other syringes used (at any time during study))
- Region (Japan versus Rest of World (ROW))

The primary efficacy analysis will be repeated for all subgroups for the FAS, which will be graphically displayed in a forest plot. In addition, the summary tables and figures for BCVA will be repeated for all subgroups for the FAS.

For the subgroups regarding syringe use, also safety and PK subgroup analyses will be performed, refer to section 7.10 and 7.12, respectively.

7.10 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 summarized according to the treatment they actually received irrespective of their randomized treatment.

All visit-based safety data will be analyzed by eCRF visit and will thus not make use of the concept of analysis visits described in section 6.5.

7.10.1 Study drug exposure and compliance

7.10.1.1 Definitions related to study drug administration and compliance for the 24 week analysis

For the 24 week analysis, a patient is defined as having prematurely discontinued study medication if the patient prematurely discontinued study medication prior to or at the IMP cut-off date and did not receive the planned number of IMP injections i.e. it is marked on the End of Treatment page of the eCRF that the patient did not complete the full course of study treatment and the date of discontinuation is before or on the IMP cut-off date, and the total number of administered IMP injections before is less than 4.

A patient is defined as having interrupted study medication if the administration was omitted at least at one eCRF visit (either the visit was performed but no IMP was given, or the whole visit was not performed) up to and including eCRF Visit 4 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.

A patient is defined as having a delayed injection for an injection visit, if the study treatment for this visit (documented in the eCRF under the scheduled visit number or a corresponding delayed IP visit) was administered on a date other than the documented date of the scheduled visit.

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 the IMP administration cut-off date for the 24 week analysis (see section 6.3) will be included for the 24 week analysis and will be displayed in summary tables and patient data listings.

Treatment duration and study duration will be calculated according to the following definitions (only dates are used, calculation in complete days):

Individual patient study duration for 24 week analysis (expressed in [days]):

- General cut-off date for the 24 week analysis (see Section 6.3) will be used for the calculation of study duration
- General cut-off date - date of eCRF Screening/ V0 + 1
- In case of (partially) missing date of Screening/ V0 or (partially) missing date of general cut-off date no calculation will be done

Individual patient treatment duration for 24 week analysis (expressed in [days]):

The IMP administration cut-off date for the 24 week analysis (see Section 6.3) will be used to calculate the individual treatment duration:

- Treatment duration = IMP administration cut-off date – date of first IMP administration +1
- In case of (partially) missing date of first or last injection no calculation will be done.

7.10.1.2 Definitions related to study drug administration and compliance for the 56 week analysis

For the 56 week analysis, a patient is defined as having prematurely discontinued study medication if the patient prematurely discontinued study medication i.e. it is marked on the End of Treatment page of the eCRF that the patient did not complete the full course of study treatment and the date of discontinuation.

A patient is defined as having interrupted study medication if the administration was omitted at least at one eCRF visit (either the visit was performed but no IMP was given, or the whole visit was not performed) up to end of study 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.

A patient is defined as having a delayed injection for an injection visit, if the study treatment for this visit (documented in the eCRF under the scheduled visit number or a corresponding delayed IP visit) was administered on a date other than the documented date of the scheduled visit.

Treatment duration and study duration will be calculated according to the following definitions (only dates are used, calculation in complete days):

Individual patient study duration for the 56 week analysis (expressed in [days]):

- End of study date - date of eCRF Screening/ V0 + 1
- In case of (partially) missing date of Screening/ V0 or (partially) missing date of general cut-off date no calculation will be done

Individual patient treatment duration for the 56 week analysis (expressed in [days]):

- Treatment duration = latest IMP administration date – date of first IMP administration +1
- In case of (partially) missing date of first or last injection no calculation will be done.

7.10.1.3 Analysis of study drug administration and compliance

The following summary tables will be presented for study drug administration for the SAF and will be included in Section 14.3 of the summary tables (see SAP Appendix):

- Individual patient treatment duration and study duration [days] (see definition in Section 7.10.1.1) will be summarized by treatment group
- For the 24 week analysis, the number of IVT injections of IMP administered up to the IMP administration cut-off for the 24 week analysis (see definition in Section 6.3) and the number of delayed IVT injections per patient will be summarized by treatment group, as well as the number of patients with at least one interruption of study medication, and the number of patients with premature discontinuation of treatment up to the IMP administration cut-off date.
- For the 56 week analysis, the overall number of IVT injections of IMP administered and the number of delayed IVT injections per patient will be summarized by treatment group, as well as the number of patients with at least one interruption of study medication, and the number of patients with premature discontinuation of treatment.
- The number and percentage of injections with a correct/incorrect dose per patient will be summarized by treatment group. For the 24 week analysis, only doses until IMP administration cut-off date will be taken into account.
- The number of patients receiving an IVT injection as planned (injection documented at date of visit), the number of patients receiving a delayed IVT injection, the number of patients performing the visit, but not receiving the injection (omitted injection), and the number of patients completely missing a visit or having the visit after end of treatment will be summarized by treatment group and eCRF visit. This table will be repeated distinguishing if the correct dose was given or not. For the 24 week analysis, only doses until IMP administration cut-off date will be taken into account.

There will be a patient data listing for overview of study treatment administration, including study and treatment duration, number of injections, number of delayed injections, number of omitted injections, and number and percentage of correct/incorrect doses for each patient. Additionally, there will be a patient data listing for details on study treatment administration, including all collected data for all individual injection visits for all patients, including reasons for delayed/omitted injections and incorrect doses. For the 24 week analysis, only study drug exposure related information up to the IMP administration cut-off for the 24 week analysis (see definition in Section 6.3) will be included in these listings.

Study drug administration information will be listed for all patients and additionally 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 of the patient data listings (see SAP Appendix).

7.10.2 Adverse events

7.10.2.1 Definitions for adverse events

General considerations:

For the 24 week analysis, only AEs with a start date up to and including the respective safety cut-off date will be considered and will be listed and summarized accordingly (see section 6.3). AEs with missing or partial start dates that might theoretically have occurred before the respective safety-cut-off date will be included in the 24 week analysis. However, all SAEs, AEs of special interest, AEs leading to discontinuation of treatment or study and deaths will be included in patient listings.

For the 56 week analysis, all AEs reported until the final end of study visit at week 56 will be summarized.

AEs will be coded according to the MedDRA dictionary, in the version and using the update strategy that is defined in the medical coding specification of this study.

Treatment-emergent AEs:

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

Temporally associated AEs are AEs with a start 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. If the imputed date would be prior to the first IMP administration, the AE onset date will be imputed with 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.

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 AEs:

The duration of AEs 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 AEs where the start and/or end of the AE were not documented with the exact time of the day.

The duration of AEs will not be calculated (i.e. be missing) if end or start date of the adverse

event is completely missing. If the AE start/end date is partially missing, a worst-case imputation will be used to calculate the duration of the event. 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. If an imputed start date is before study day 1, then the date of study day 1 will be imputed. If an imputed end date is after date of death then the date of death will be imputed.

Definition of local (ocular) and systemic AEs:

A local (ocular) AE is defined as any AE documented as occurring in the eye. These will be further categorized as ocular AEs in the study eye and ocular AEs in the fellow eye. Any AE not occurring in the eye is defined as a systemic AE.

Definition of frequent (TE)AEs:

Frequent AEs are defined as AEs which are observed in at least 5% of the patients in at least one of the two treatment groups, taking into account all TEAEs regardless of seriousness, severity etc. by preferred term. All terms identified as frequent overall will be included in all tables for frequent TEAEs within one analysis, also if the specific subgroup of AEs (for example serious AEs) are observed in less than 5% of the patients.

The terms identified as frequent TEAEs can differ between the 24 week analysis and the 56 week analysis, since for the 24 week analysis only TEAEs until the safety cut-off date are considered for identifying frequent AEs, whereas for the 56 week analysis all TEAEs are considered.

Related AE:

An AE is defined as being related to study treatment, if the relationship to study treatment was documented as probably or possibly related, as unknown or if the relationship to study treatment is missing.

Adverse event of special interest (AESI):

AEs of special interest are AEs documented as adverse events of special interest by the investigator in the eCRF according to study protocol criteria.

Ocular inflammatory adverse events of special interest:

Ocular inflammatory AESIs are identified during the medical review process by review of all AESIs documented.

7.10.2.2 Analysis of adverse events

Summary tables for AEs will be included in Section 14.3 of the summary tables and patient data listings for AEs will be included in Section 16.2.7 of the patient data listings (see SAP Appendix).

TEAEs will be analyzed by display of the number and percentage of patients (absolute and relative frequencies) reporting the adverse event as well as the total number of events by treatment group. Hence, the number of patients in the SAF in each treatment group will be the denominator for the relative frequencies.

In these tables, AEs will be summarized by MedDRA PT and grouped by MedDRA SOC. The SOCs as well as the PTs within will be sorted by frequency in the total column in decreasing order. Additionally, the number and percentage of patients with AEs will be further grouped by maximum severity (mild, moderate, severe) and strongest relationship

to study treatment / strongest relationship to study procedure (probably related, possibly related, unlikely to be related, unrelated and unknown).

Non-treatment-emergent AEs will be listed but will not be summarized.

(Serious) AEs will be presented overall and by maximum severity and strongest relationship to study treatment / strongest relationship to study procedure by treatment group.

For summary tables displaying AEs by maximum severity or strongest relationship, the maximum severity/relationship per patient, preferred term or system organ class is displayed.

Furthermore, separate frequency tables will be provided for all patients with

- Serious TEAEs
- Non-serious TEAEs
- Severe TEAEs
- TEAEs leading to withdrawal of study treatment
- TEAEs leading to interruption of study treatment
- TEAEs leading to premature discontinuation of study
- Local (ocular) TEAEs in the study eye
- Local (ocular) TEAEs in the study eye leading to withdrawal of study treatment
- Local (ocular) TEAEs in the study eye leading to interruption of study treatment
- Serious (ocular) local TEAEs in the study eye
- Non-serious local (ocular) TEAEs in the study eye
- Local (ocular) TEAEs in the fellow eye
- Local (ocular) TEAEs in the fellow eye leading to withdrawal of study treatment
- Local (ocular) TEAEs in the fellow eye leading to interruption of study treatment
- Serious (ocular) local TEAEs in the fellow eye
- Non-serious local (ocular) TEAEs in the fellow eye
- Systemic TEAEs
- Serious systemic TEAEs
- Non-serious systemic TEAEs
- TEAEs of special interest
- Ocular inflammatory TEAEs of special interest
- TEAEs to related to study treatment, and
- TEAEs related to study procedure

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

- Any AE
- any treatment-emergent AE (TEAE)
- any serious TEAE
- any severe TEAE
- any related TEAE
- any related serious TEAE
- any related severe TEAE

- any local (ocular) TEAE in the study eye
- any related local (ocular) TEAE in the study eye
- any serious local (ocular) TEAE in the study eye
- any serious related local (ocular) TEAE in the study eye
- any severe local (ocular) TEAE in the study eye
- any severe related local (ocular) TEAE in the study eye
- any local (ocular) TEAE in the fellow eye
- any related local (ocular) TEAE in the fellow eye
- any serious local (ocular) TEAE in the fellow eye
- any serious related local (ocular) TEAE in the fellow eye
- any severe local (ocular) TEAE in the fellow eye
- any severe related local (ocular) TEAE in the fellow eye
- any systemic TEAE
- any related systemic TEAE
- any serious systemic TEAE
- any serious related systemic TEAE
- any severe systemic TEAE
- any severe related systemic TEAE
- any TEAE of special interest
- any ocular inflammatory TEAE of special interest
- any TEAE leading to withdrawal of study drug
- any TEAE leading to interruption 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 approximate 95% confidence intervals (according to Miettinen and Nurminen (1985)) by MedDRA PT will be displayed for

- frequent TEAEs
- frequent serious TEAEs
- frequent severe TEAEs
- frequent local (ocular) TEAEs in the study eye

AE listings 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, severity, relationship to study treatment and study procedure, action taken and outcome) will be provided. The listing will be sorted by treatment group, patient ID and AE onset date.

Treatment-emergent and non-treatment-emergent AEs will be listed separately. Deaths, serious TEAEs, severe TEAEs and TEAEs leading to study discontinuation will additionally be listed separately, if applicable. The Serious Event details collected in the eCRF will be

included in the respective listing and will not be displayed in any summary table.

7.10.2.3 Subgroup analyses

For the subgroups regarding syringe use as defined in section 7.9.2.6, the following tables will be repeated for each subgroup:

- Local (ocular) TEAEs in the study eye
- TEAEs of special interest
- Ocular inflammatory TEAEs of special interest

Additionally, subgroup analyses for Japan vs. ROW will be performed for

- Overall incidence of adverse events
- Serious TEAEs
- Local (ocular) TEAEs in the study eye
- TEAEs of special interest

7.10.3 Safety laboratory

Safety laboratory analyses comprise clinical chemistry, hematology, coagulation, urine analysis and other laboratory assessments. The corresponding planned measurements are displayed in Table 7. Urinalysis results will be analyzed according to the data collected in the eCRF, no further data on a parameter level is expected.

In the eCRF, the information if a laboratory result is “clinically significant” (CS) or “not clinically significant” (NCS) is only collected for entire laboratory categories (hematology, chemistry, urinalysis, coagulation profile) but not for individual parameters. Further categorizations are not available in the eCRF.

On a parameter level, values will be categorized as below normal range, within normal range or above normal range based on reference ranges provided with external data transfers.

If appropriate, all CS laboratory results will be repeated to ensure the validity of the abnormal result. If any CS abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered CS by the masked investigator, or an explanation for the change is obtained. CS 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 as well as unscheduled laboratory assessments later than the first administration of study treatment will not be summarized but will be listed only. All laboratory assessments performed prior to the first administration of study treatment, including re-tests and unscheduled assessments, will be considered for the determination of the baseline laboratory assessment.

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. This classification will only be done if not already provided by the laboratory.

Results performed by local laboratories and entered into the eCRF will be included in summary tables, if no central laboratory result is available for a certain patient and visit. If both central and local laboratory results are documented, the central laboratory results will be preferred for summary tables and figures. All data from all laboratories will be listed.

Summary tables for safety laboratory will be included in Section 14.3 of the summary tables and patient data listings for safety laboratory assessments will be included in Section 16.2.8 of the patient data listings (see SAP appendix).

Safety laboratory analyses for the 24 week and 56 week analysis:

Safety laboratory tests are performed at Screening, Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9) and will be analyzed by eCRF visit.

The 24 week analysis will be restricted to the eCRF visits Screening and Week 24 (Visit 5). If end of study visits were performed as early termination visits and the visit date is before the individual safety cut-off date, then this data will be included in data listings. Data listing will only contain data until the individual general cut-off date for the 24 week analysis (see section 6.3).

The 56 week analysis will include all eCRF visits and data.

For each laboratory parameter, summary statistics of the observed laboratory values and the absolute change from baseline (see section 6.6) will be provided by eCRF visit and treatment group. Since safety laboratory is only performed at eCRF visits Screening, Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9) unscheduled laboratory assessments at other visits will only be listed.

The number and percentage of abnormal and clinically significant samples will be tabulated by eCRF visit and treatment group separately for each laboratory category (hematology, chemistry, urinalysis, coagulation profile). The categories “normal”, “not clinically significant”, “clinically significant”, and “missing” will be used in this frequency table.

The number and percentage of values below/within/above normal range will be tabulated by eCRF visit and treatment group separately for each laboratory parameter. The categories “below normal range”, “within normal range”, “above normal range” and “missing” will be used in this frequency table.

Separate corresponding laboratory shift tables will display changes in both categorizations defined above compared to Screening by eCRF visit.

Separate patient data listings will be generated for clinical chemistry, hematology, urinalysis, and coagulation laboratory assessments including the result, the reference range and flags if the result is below or above normal range for each laboratory parameter. Results from local laboratories will also be included in these listings with a flag identifying if the data was analyzed in the central or local laboratory.

Additionally, all laboratory assessments which are not within normal range will be listed separately. This listing will also include the flag if the respective laboratory category was considered as clinically significant or not in the eCRF at the respective visit.

All listings will be sorted by treatment group, patient ID, laboratory parameter and visit.

Results from serum pregnancy tests and FSH for female patients (performed at Screening

only) will only be listed separately and sorted by treatment group and patient ID.

Table 7 Planned safety laboratory parameters

Laboratory Assessments	Parameters
Hematology	hemoglobin, hematocrit, red blood cells, platelets and white blood cells (total and differential)
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), FSH

Further laboratory parameters that might be present in the data which are not planned according to the protocol will be listed only.

7.10.4 Vital signs

Vital signs assessments include systolic and diastolic blood pressure [mmHg], pulse rate [beats per minute] and body temperature [°C]. Vital signs assessments are performed at Screening, Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9).

The observed vital signs measurements and the absolute changes from baseline will be summarized by eCRF visit and treatment group.

All vital signs related data will be listed including the reason for not performed assessments.

The 24 week analysis will be restricted to the eCRF visits Screening and Week 24 (Visit 5). If end of study visits were performed as early termination visits and the visit date is before the individual safety cut-off date, then this data will be included in data listings. Data listing will only contain data until the individual general cut-off date for the 24 week analysis (see section 6.3).

The 56 week analysis will include all eCRF visits and data.

7.10.5 Other safety data

All available other safety data falling into one of the categories listed below for which no specific analysis is specified in one of the subsections below will be listed only.

The 24 week analysis will be restricted to the eCRF visits until and including Week 24 (Visit 5). If end of study visits were performed as early termination visits and the visit date is before the individual safety cut-off date, then this data will be included in data listings. Data listing will only contain data until the individual general cut-off date for the 24 week analysis (see section 6.3).

The 56 week analysis will include all eCRF visits and data.

7.10.5.1 Ophthalmological safety data

Selected assessments resulting from the ophthalmological external examination, slit lamp examination, tonometry and indirect ophthalmoscopy will be summarized by treatment group and eCRF visit. These assessments are performed at all visits for the study eye, and additionally at Screening, Week 40 (Visit 7) and Week 56 (Visit 9) for the fellow eye.

Data will be summarized for the study eye for all applicable visits, data for the fellow eye will separately be summarized for all visits where available.

Tonometry:

The intraocular pressure (IOP) will be summarized by treatment group, eCRF visit and time point. Additionally, summary statistics of the change in IOP within one visit (post injection value – pre-injection value) will be displayed by eCRF visit. Furthermore, there will be a frequency table by eCRF visit and timepoint displaying the number of patients with an IOP >= 30 mmHg.

External examination, slit lamp exam and indirect ophthalmoscopy:

The number and percentage of patients with at least one clinically significant abnormal ophthalmological assessment will be summarized by eCRF visit and/or time point.

The parameters listed below are collected in the eCRF with categorical result and will be summarized by category, time point (by eCRF visit and by pre-/post injection if applicable) and treatment group:

- External examination and slit lamp exam
  - Lids/Adnexa examination
  - Pupil examination
  - Conjunctiva examination
  - Cornea examination
  - Iris examination
  - Lens examination
  - Anterior chamber examination
- Indirect ophthalmoscopy
  - Optic nerve head (Papilla) examination
  - Macula examination
  - Retinal Periphery examination
  - Retinal Vasculature
  - Vitreous examination

Additionally, there will be a table for indirect ophthalmoscopy post IVT, summarizing the number and percentage of patients with changes from pre-IVT by eCRF visit.

All ophthalmological examination, tonometry and indirect ophthalmoscopy related data will be listed including method of assessment and the assessment if the observed result is abnormal and/or clinically significant as well as the reported term of an abnormal result. If any of these assessments was not performed, the respective reason will be listed.

7.10.5.2 Safety check after injection of study treatment

In addition to the tonometry assessment (described in Section 7.10.5.1), a light perception test is performed after each IVT injection as part of the safety check. The number and

percentage of patients with present/absent light perception after IVT injection will be summarized by eCRF visit and treatment group. All data related to light perception tests after IVT injection will be listed and the listing will be sorted by treatment group, patient ID and eCRF visit, including all relevant records, respectively.

7.10.5.3 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 potential complications. Data related to telephone safety calls will be listed only.

7.10.5.4 General physical examination

Physical examination will be performed at Screening, Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9). The results of the physical examination (normal/abnormal not clinically significant [NCS]/abnormal clinically significant [CS]) will be summarized by body system, eCRF visit, and treatment group. Unscheduled assessments will be listed only.

The following body systems will be presented

- General appearance
- Head, eyes, ears, nose and throat (HEENT)
- Cardiovascular
- Chest
- Abdominal
- Genitourinary
- Musculoskeletal
- Skin
- Neurological

All data related to physical examination will be listed including reported terms of abnormal findings and reasons for not performed physical examinations.

7.11 Other data

7.11.1 Corrected refraction data

Corrected refraction data will be included in the patient data listings for BCVA, including all relevant records, respectively. No summary tables will be created. All values will be displayed as recorded in the eCRF, no conversion calculations will be performed.

7.12 Pharmacokinetic data

Plasma concentration evaluation subgroup:

Up to 60 patients (n=30 per group) at selected sites will be included into a plasma concentration evaluation subgroup. Plasma concentrations of systemic free and total aflibercept will be assessed in this subgroup at additional visits as specified below.

Systemic concentration of aflibercept:

Samples for measuring the systemic concentration of aflibercept will be obtained pre-first dose (at baseline/ Visit V1), at 48 +/- 6 hours after first IVT injection (close to C_{max}) and at 48 +/- 12 hours after third IVT injection (close to C_{max}). To guarantee an accurate assessment of the systemic concentration of aflibercept, all patients in the plasma

concentration evaluation subgroup are not allowed to receive Eylea treatment in the fellow eye until and including Visit V1 and within 7 days prior to Visit 3 and until the blood sample at Visit 3a has been taken.

Observed systemic aflibercept concentrations below the lower limit of quantitation will be set to 0.5 x lower limit of quantitation and concentrations above the upper limit of quantitation will be set to the upper limit of quantitation for the purpose of calculating summary statistics. Such values will be marked in patient data listings.

The aflibercept concentrations at baseline and 48 hours after the first and the third injection with study treatment will be summarized using the arithmetic mean and standard deviation, coefficient of variation, geometric mean, geometric coefficient of variation, two-sided 95% confidence intervals for geometric mean, median, minimum and maximum, 10^{th} and 90^{th} percentile, and first and third quartile by eCRF Visit and treatment group. Additionally, the aflibercept concentrations will be presented in boxplots by treatment group, separately for visits V1a and V3a.

All PK related information will be listed for the patients in the plasma concentration evaluation subgroup and will be sorted by treatment group, patient ID, and visit of assessment. All PK analyses are performed using the PKS analysis set and patients are summarized according to the treatment they actually received in the study eye.

The summary tables of the systemic aflibercept concentrations will be included in Section 14.4 in the summary tables and PK-related information will be listed in Section 16.2.6 of the patient data listings (see SAP appendix).

Subgroup analyses:

The summary tables of systemic free and total aflibercept concentration as defined above will be repeated stratified by syringe use, as defined in section 7.9.2.6.

7.13 Immunogenicity analysis

A blood sample will be collected for ADA assessments at baseline (pre-dose; Visit 1), Week 4 (Visit 2), Week 16 (Visit 4), Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9). For all patients in the plasma concentration evaluation subgroup, ADAs are additionally assessed at Visit 1b (7 +/- 1 days after V1) and Visit 3a (48h +/-12h after V3).

ADA positivity will be based solely on positive results from the ADA confirmatory assay, which is performed after the ADA screen result gave a positive signal.

For the 24 week analysis, only data from eCRF visits at baseline (pre-dose; Visit 1), Week 4 (Visit 2), Week 16 (Visit 4), Week 24 (Visit 5) will be included. Definitions provided below will be derived based on this restricted data.

Samples which underwent the ADA confirmatory assay without having a positive signal from the ADA screen result will be excluded from the ADA analyses, regardless of the result.

Only ADA / NAb evaluable patients, defined as patients who have at least one valid assessment both prior and post first IMP administration, will be included in immunogenicity analyses. For the 24 week analysis, patients without any valid ADA / Nab assessment until and including Week 24 (Visit 5) will not be ADA / Nab evaluable.

A patient is defined as having treatment-induced ADAs if ADA results are positive post-treatment only. Any pre-treatment ADA assessment is either negative or not assessable.

Patients with missing pre-treatment ADA samples are not evaluable for the ADA analysis. For the 24 week analysis, treatment-induced ADA is based on results until and including eCRF visit Week 24 (Visit 5) only.

A patient is defined as having treatment-boosted ADAs if they have pre-existing ADA pre-treatment that were boosted to a higher level following study treatment, i.e. pre-treatment positive ADA titer that was boosted by at least 2 dilution steps (4-fold) following study treatment. For the 24 week analysis, treatment-boosted ADA is based on results until and including eCRF visit Week 24 (Visit 5) only.

A patient is defined as having treatment-emergent ADAs if they meet the definition of treatment-induced or treatment-boosted ADA. For the 24 week analysis, treatment-emergent ADA is based on results until and including eCRF visit Week 24 (Visit 5) only.

ADA related data will not be assigned to analysis visits as described in section 6.5 because anti-drug antibodies are only measured at selected visits. ADA related data will be analyzed and summarized by scheduled eCRF visit. All ADA results, which were assessed at regular visits where no ADA assessment was planned, or at unscheduled visits will be assigned to the previous scheduled visit for ADA assessments for the statistical analysis (based on the planned schedule of assessments, regardless of whether an assessment already exists at this previous scheduled visit or not). 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 assessment 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.

ADA titer 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 titers will be summarized by treatment group and scheduled eCRF visit, using the arithmetic mean and standard deviation, coefficient of variation, geometric mean, geometric coefficient of variation, two-sided 95% confidence intervals for geometric mean, median, minimum and maximum, 10^{th} and 90^{th} percentile, and first and third quartile.

Furthermore, any pre-first-dose/post-first-dose detection of ADAs will be tabulated by treatment group. A sample is denoted as pre-treatment if it has been taken before first administration of study drug. Similarly, a sample is denoted as post-treatment if it has been taken after first administration of study drug. If a sample is documented at the exact same date and time as first administration of study drug, it will be considered as pre-treatment. 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.

For the 24 week analysis, post-first-dose ADAs are classified as positive if at least one post-

first-dose ADA assessment until and including eCRF visit Week 24 (Visit 5) is positive. If at least one post-first-dose ADA assessment is negative and no post-first-dose ADA assessment is positive until and including eCRF visit Week 24 (Visit 5), post-first-dose ADAs are classified as negative. If all post first-dose ADA assessments until and including eCRF visit Week 24 (Visit 5) are either missing, not reportable or insufficient samples have been taken, post-first-dose ADAs are classified as missing.

For the 56 week analysis, 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 assessments are either missing, not reportable or insufficient samples have been taken, post-first-dose ADAs are classified as missing.

The 95% Farrington-Manning CI of the difference in percentages (FYB203 - Eylea) will be used. SAS code similar to the following will be used for calculation:

```
PROC FREQ;
  tables TRT*ADA_STATUS /riskdiff(CL=FM method=FM);
RUN;
```

Programming Note:
ADA_STATUS = ADA status (positive/negative)
TRT = Treatment (Eylea, FYB203)

Additionally, the number and percentage of patients who have neutralizing ADAs (nABs) in serum will be tabulated by treatment group and scheduled eCRF visit. For the 24 week analysis, only samples until and including eCRF visit Week 24 (Visit 5) will be taken into account.

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

ADA related summary tables will be included in Section 14.4 of the summary tables, the corresponding listings will be included in Section 16.2.6 of the patient data listings.

Subgroup analyses:

The analyses will be repeated for the subgroups Japan vs. ROW.

7.14 Stratification variables

Randomization was performed stratified by country and participation in the PK sub study (yes/no). Since the differences between the study population in Japan versus other countries is deemed more important than differences between other countries, and to account for low numbers of patients in some countries, region (Japan vs. Rest of World) is included in all statistical models for primary and secondary analyses instead of country. Participation in the PK sub study is only used for randomization to ensure that treatment groups are also comparable within the PKS, but not included in any statistical model. Patients participating in the PK sub study only have three additional blood samples taken for plasma concentration/ADA evaluation, otherwise all assessments performed are identical as for patients who do not participate in the sub study. Thus, no impact on evaluation of study data is expected.

8 SOFTWARE AND STATISTICAL PROGRAMMING

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.4 or higher).

SAS programming will be performed according to XXX standards as defined in SOP and related work instructions. Special attention will be paid to planning and performance of quality control (QC) measures as documented in the QC plan for the analysis of this study.

9 REFERENCES

ICH Topic E3: Note for Guidance on Structure and Content of Clinical Study Reports. Consensus Guideline; 30 November 1995, adopted by CPMP, December 95, issued as CPMP/ICH/137/95

ICH Topic E9: Statistical Principles for Clinical Trials, 5 February 1998, adopted by CPMP, March 1998, issued as CPMP/ICH/363/96

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ICH Topic E10: Choice of Control Group and Related Issues in Clinical Trials, adopted by CPMP, 20 July 2000, issued as CPMP/ICH/364/96

Miettinen, O. S. and Nurminen, M. M. (1985), Comparative Analysis of Two Rates, Statistics in Medicine, 4, 213–226.

SAS 9.4 https://support.sas.com/documentation/94/index.html. Copyright © SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved.