TITLE PAGE

Protocol 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)

Protocol Number: FYB203-03-01

Protocol Version: 15 July 2022/Version 3.0

Amendment Number: Amendment 1.0

Product: Aflibercept FYB203

Short Title: Efficacy and Safety of the Aflibercept FYB203 Biosimilar in Comparison to Eylea® in Patients with Neovascular Age-Related Macular Degeneration (MAGELLAN-AMD)

Study Phase: Phase 3

Sponsor Name: bioeq GmbH

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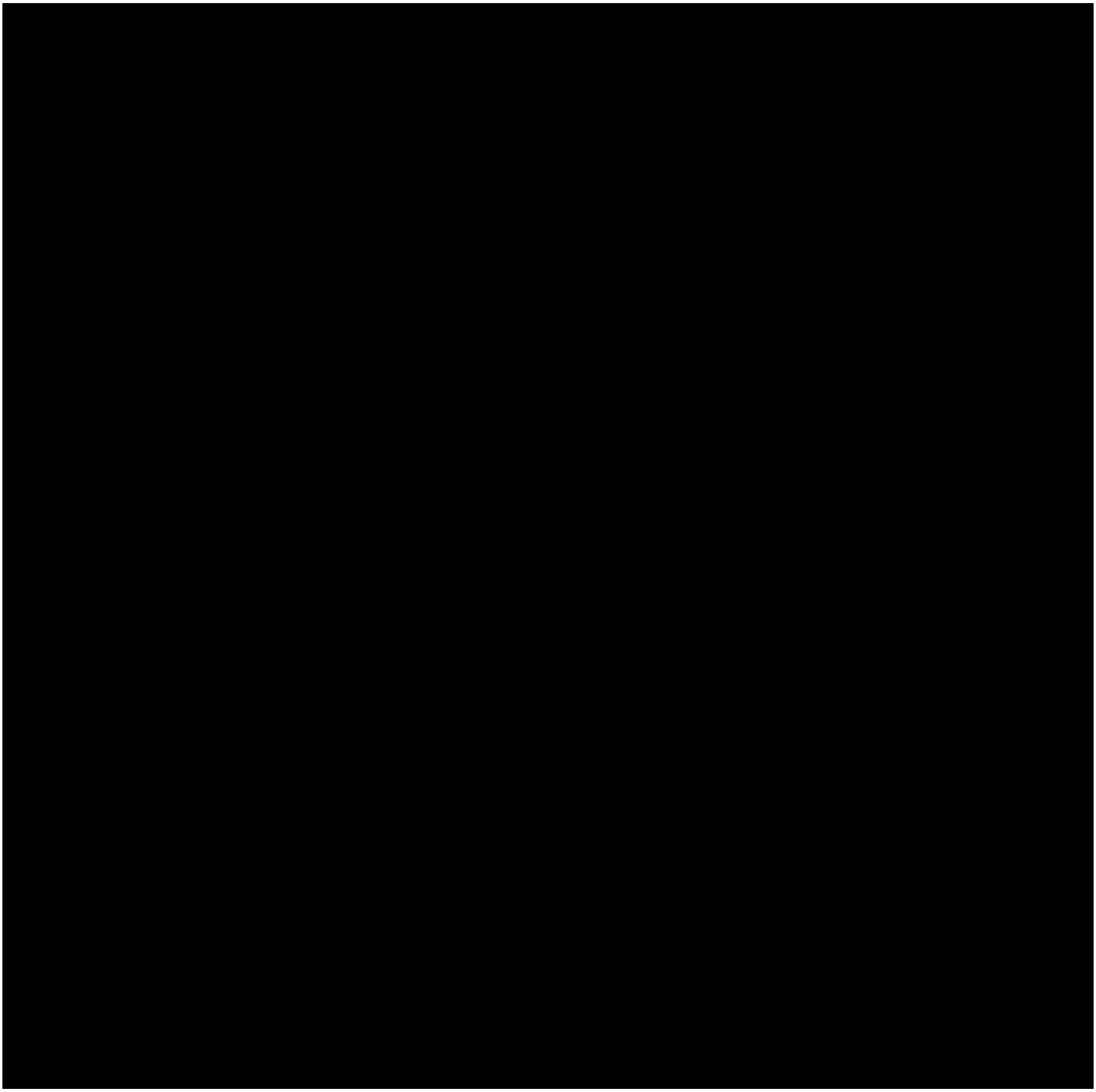
Regulatory Agency Identifying Number(s): EudraCT No 2019-003923-39

Date of Protocol: 15 July 2022

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:



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DOCUMENT HISTORY		
Document	**Date**	**Region**
Amendment 1.0	15 July 2022	Global

[redacted]

Amendment 1.0 (15 July 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to update the planned statistical analyses.

Section # and Name	[redacted]
1.1 Synopsis 10.4 Statistical Analyses	
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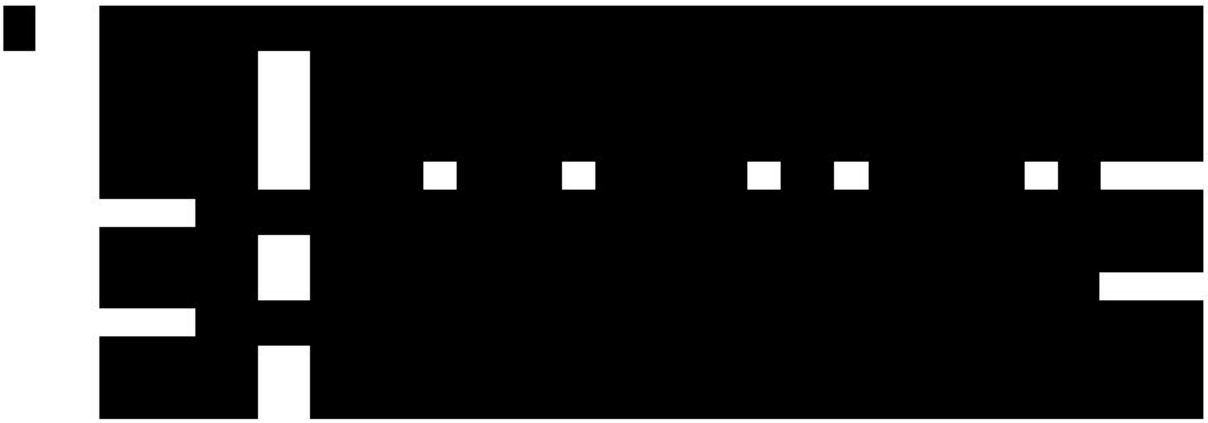

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1.1 Synopsis

Protocol 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)

Short Title: Efficacy and Safety of the Aflibercept FYB203 Biosimilar in Comparison to Eylea® in Patients with Neovascular Age-Related Macular Degeneration (MAGELLAN-AMD)

Rationale:

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.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate and compare functional changes in best corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at Week 8 of treatment with FYB203 or Eylea compared to baseline	• Changes from Baseline Visit (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3)
Secondary	
• Evaluate and compare changes in foveal center point (FCP) retinal thickness	• Change from Baseline Visit (Visit 1) in FCP retinal thickness to Week 4 (Visit 2)
• Evaluate and compare changes in FCP retinal thickness and changes in foveal central subfield (FCS) retinal thickness over time	• Changes of FCP retinal thickness and FCS retinal thickness over the whole study from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare functional changes of the retina by BCVA over time	• Change of BCVA by ETDRS letters over the whole study from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare the proportion of patients who gain or lose ≥ 5, 10, and 15 ETDRS letters compared to baseline	• Proportion of patients who gain or lose ≥ 5, 10, or 15 ETDRS letters from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7), and Week 56 (Visit 9)
• Evaluate and compare the absence of disease activity (fluid-free macula) over time	• Percentage of patients with fluid-free macula at each Visit

Objectives	Endpoints
• Evaluate and compare change in total lesion size	• Change from baseline in total lesion size to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare systemic free and total aflibercept concentrations in a subgroup of up to 60 patients (up to 30 per arm)	• Systemic concentrations (close to maximum concentration [C_{max}]) of free and total aflibercept in a subgroup at selected sites – 48 hours after the 1st dose (Visit 1a) – 48 hours after the 3rd dose (Visit 3a)
• Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25)	• Change from Baseline Visit (Visit 1) in vision-related functioning and well-being measured by NEI VFQ-25 to Week 24 (Visit 5), Week 40 (Visit 7), and Week 56 (Visit 9)
• Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum	• Number of patients with ADAs over time
• Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs)	• Frequency of local and systemic AEs and SAEs

Overall 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 (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). Each patient will receive a total of 8 IVT injections.

Systemic concentrations of free and total aflibercept will be assessed and compared in a subgroup of up to 60 patients (up to 30 each for EU-approved Eylea and FYB203) at selected study sites at Baseline Visit (Visit 1) prior to 1st IVT dose, 48 hours after 1st IVT dose (Visit 1a) close to C_{max}, and at 48 hours after the 3rd IVT dose (Visit 3a) close to C_{max}. Anti-drug antibodies formation against aflibercept will be evaluated in serum in all patients prior to receiving the IVT injections at Visit 1, Visit 2, Visit 4, Visit 5, Visit 7 and Visit 9, and in addition in the subgroup 1-week after the 1st dose (Visit 1b) and 48 hours after the 3rd dose (Visit 3a).

Number of Investigators and Study Centers:

Originally 400 patients were planned to be randomized, including 52 patients in Japan. However, the actual number of patients randomized are 434 including 33 patients in Japan.

Eighty-five study centers, located in Europe, Israel and Japan have patients participating in this study.

Number of Patients:

A total of 434 patients have been randomly assigned to study treatment and 433 patients have received at least 1 injection of study treatment in the study eye, including 33 patients in Japan, such that 433 patients will be included in the Full Analysis Set (FAS) population, where the FAS population is defined as all patients randomly assigned to study treatment who receive at least 1 injection of study treatment in the study eye (SE). The fixed sample size could have been increased following the interim masked review of sample size after the first 200 treated patients had completed Week 8 (Visit 3) up to a maximal sample size of 800 patients. However, this interim masked review of sample size revealed that the observed variability overall does not require an increase in sample size to maintain the intended statistical power of 90% for the primary endpoint, and of 80% for the key secondary endpoint (EU/Japan only).

Inclusion Criteria:

General

1. Age ≥ 50 years at Screening.
2. Male or female:
   - Male:
     - A male patient must agree to use contraception as defined in this protocol during the treatment period (48 weeks) and for at least 4 weeks after the last dose of study treatment.
   - Female:
     - A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies:

     i) Not a woman of childbearing potential (WOCBP)
     OR
     ii) A WOCBP who agrees to follow the contraceptive guidance during the treatment period (48 weeks) and for at least 4 weeks after the last dose of study treatment
3. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
4. Willingness and ability to undertake all scheduled visits and assessments.

Ocular (Study Eye)

5. Newly diagnosed (within 6 months of Screening Visit), angiographically documented, treatment-naïve choroidal neovascularization (CNV) lesion secondary to wet AMD:

    a) All subtypes of wet AMD CNV lesions are eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Treatment-naïve CNV secondary to wet AMD must be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by spectral domain optical coherence tomography [SD-OCT] or retinal pigment epithelium [RPE] detachment);

    b) Total area of whole lesion must be ≤ 9 disc areas;

    c) Total CNV area encompasses ≥ 50% of total lesion area based on fluorescein angiography (FA), including all subtypes of wet AMD.

Term	Definition
Wet AMD	Clinical signs (including findings by retinal imaging) attributable to wet AMD (e.g. pigmentary changes, drusen) and no other likely etiologic explanations for the degenerative changes
Subfoveal	Including the center of the fovea
Juxtafoveal	At least some part of CNV lesion must be in an area up to 199 µm from the geometric center of the fovea
Total area of whole lesion	A contiguous area of abnormal tissue that contains a CNV (as documented by FA) with possible additional components of hemorrhages, blocked fluorescence not from hemorrhage, serous detachment of the RPE, atrophy, and subretinal fibrosis

6. Sufficiently clear ocular media and adequate pupillary dilation to permit good quality ocular imaging.
7. Best corrected visual acuity (BCVA) in the SE, determined by standardized ETDRS testing, between 20/40 and 20/200 Snellen equivalent.
8. Foveal center point retinal thickness at Screening ≥ 300 µm and < 800 µm. (FCP thickness is defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea).

Ocular (Fellow Eye)

9. Best corrected visual acuity (BCVA) in the fellow eye, determined by standardized ETDRS testing, at least 20/200 Snellen equivalent.

Exclusion Criteria:

Patients are not eligible for the study if any of the following criteria apply:

General

1. Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who are legally institutionalized.
2. Study eye requiring immediate treatment.

Prior or Current Ocular Treatment

3. Any prior treatment with anti-Vascular Endothelial Growth Factor (VEGF) agent (e.g. bevacizumab, aflibercept, ranibizumab) or any investigational products to treat AMD, in either eye.
4. Prior treatment with any investigational products to treat ocular diseases other than wet AMD within 30 days or 5 half-lives prior to Randomization, whichever is longer.
5. History of vitrectomy, macular surgery or other surgical intervention for AMD in the SE;
6. History of IVT or periocular injections of corticosteroids or device implantation within 6 months prior to Randomization in the SE.
7. Prior treatment with verteporfin (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the SE;
8. Any other intraocular surgery (including cataract surgery) in the SE within 3 months prior to Randomization.

CNV Lesion Characteristics

9. Sub- or intra-retinal hemorrhage that comprises more than 50% of the entire lesion in the SE.
10. Irreversible structural damage involving the center of fovea (e.g. advanced fibrosis > 50% of the total lesion in the SE or atrophy) in the SE that is considered sufficient to irreversibly impair visual acuity (VA).
11. CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.

Current Ocular Conditions

12. Retinal pigment epithelial tear involving the macula in the SE.
13. History of or current full-thickness macular hole (stage 2 and above by clinical examination or full-thickness macular hole by SD-OCT imaging of any size) in the SE.
14. History of or current retinal detachment in the SE.
15. Current vitreous hemorrhage in the SE.
16. Spherical equivalent of the refractive error in the SE demonstrating more than 6 diopters of myopia.
17. For patients who have undergone prior refractive or cataract surgery in the SE, the preoperative refractive error in the SE should not exceed 6 diopters of myopia.

18. History of or current corneal transplant in the SE.
19. Aphakia in the SE. Absence of an intact posterior capsule is allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation.
20. Active or recent (within 4 weeks prior to Randomization) intraocular inflammation of clinical significance in either eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis, or endophthalmitis.
21. Uncontrolled ocular hypertension or glaucoma in the SE (defined as intraocular pressure [IOP] ≥ 30 mmHg, despite treatment with anti-glaucomatous medication).
22. Ocular disorders in the SE (i.e. retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on VA) at the time of Screening that may confound interpretation of study results and compromise VA.
23. Any concurrent intraocular condition in the SE (e.g. glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results.

Systemic Medical History and Treatments and Conditions at Screening

24. Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives prior to Randomization, whichever is longer.
25. Systemic treatment with anti-VEGF agent (e.g. bevacizumab) within 90 days prior to Randomization.
26. Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
27. Stroke or myocardial infarction within 6 months prior to Randomization.
28. Presence of uncontrolled systolic blood pressure > 160 mmHg or uncontrolled diastolic blood pressure > 100 mmHg within 4 weeks prior to Randomization.
29. Known hypersensitivity to the investigational drug (aflibercept or any component of the aflibercept formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation.
30. Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, and ethambutol.
31. History of recurrent significant infections and/or current treatment for active systemic infection.

Ocular (Fellow Eye)

32. Any diagnosis and/or signs of wet AMD requiring treatment with an IVT anti-VEGF agent (e.g. aflibercept, bevacizumab, ranibizumab) within the Screening period or are expected, in the opinion of the investigator, to need such treatment in the fellow eye throughout the study. At the time of Screening and Randomization, the Investigator should use best medical judgement to exclude patients with a probable FE treatment need during the course of the study.

Treatment Groups and Duration:

The Investigational Medicinal Products (IMPs) are FYB203 and Eylea.

Experimental product: FYB203 – proposed aflibercept biosimilar (International Nonproprietary Name [INN]: aflibercept) 40 mg/mL solution for IVT injection.

Comparator: Eylea (INN: aflibercept), EU-approved, 40 mg/mL solution for IVT injection.

All eligible patients will receive 1 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 (Visit 8). Each patient will receive a total of 8 IVT injections.

Statistical Methods:

Primary Endpoint:

The FAS, defined as all randomized patients who receive at least 1 injection of study treatment in the SE, will be used for all efficacy analyses. Sensitivity analyses based on the Per Protocol Set (PPS; defined as all patients from the FAS with available BCVA assessments at Baseline and Week 8 for the SE without major protocol deviations that might influence the BCVA assessments at Baseline Visit (Visit 1) or Week 8) will be performed for the primary and secondary efficacy endpoints (see below). For the final assessment of bioequivalence, it is essential that the analyses of the primary efficacy endpoint based on the FAS and on the PPS as well as other sensitivity analyses yield consistent results.

The primary estimand is the mean difference between the randomized treatment groups, FYB203 and Eylea for the primary endpoint, i.e. change from Baseline to Week 8 in BCVA, in the SE regardless of treatment adherence and usage of concomitant medications and using data on all patients within the FAS. Also patients randomized and treated although inclusion or exclusion criteria were violated will be analyzed within the FAS according to the randomized treatment group.

The primary estimand will be assessed through a mixed model for repeated measures (MMRM), which uses all available data collected until Week 24 (Visit 5) for the SE for all patients for model estimation. The difference in the treatment group least square means and the corresponding two-sided 90.4% [redacted] confidence intervals (CI) will be estimated from the MMRM to address regulatory requirements in the US [redacted]. If the respective CI is completely contained in the interval]-3.5; 3.5[ETDRS letters, equivalence of FYB203 and Eylea can be concluded (rounded to the next integer, this corresponds to an equivalence margin of 3 ETDRS letters).

Supplemental estimands are defined by excluding patients with major protocol deviations which impact the BCVA assessments until Week 8 and/or patients who discontinue treatment before Week 8 or do not have a Week 8 BCVA assessment. By excluding all these patients, an estimand will be defined that repeats the primary analysis based on the PPS.

Secondary Endpoints:

Specifically, for the European Medicines Agency (EMA), the endpoint of change in FCP retinal thickness from Baseline to Week 4 in the SE will be analyzed as a key secondary endpoint using an equivalence interval from [-45; 45] µm. The difference in the treatment group least square means and the corresponding two-sided 95.2% CI will be estimated from the MMRM using all patients in the FAS. If the CI is completely contained in the interval [-45; 45] µm, equivalence of FYB203 and Eylea with respect to the FCP retinal thickness can be concluded. For all non-EU regulatory submissions, the CI will not be compared to any equivalence margin and descriptive statistical analyses will performed.

The change from baseline in the SE over time for BCVA, FCP and FCS retinal thickness and total lesion area will be analyzed using a similar MMRM model than the one used for the primary estimand. The absolute values and the changes from baseline for each parameter will also be summarized descriptively by visit and treatment group for all scheduled time points for the SE. Data for the fellow eye at Screening Visit, Visit 7, and EOS Visit will be summarized descriptively.

NEI VFQ-25 total scores will be determined as described in the official manual. The absolute values and the change from baseline for each parameter will also be summarized descriptively by visit and treatment group for the SE and fellow eye separately.

The percentage of patients with fluid-free macula at each visit, based on all patients with evaluation at each given visit, will be presented in descriptive summary tables.

Interim Analysis:

An interim masked review of sample size was planned to re-assess the assumptions for the sample size calculation with respect to the standard deviation after the first 200 patients had completed the primary efficacy endpoint of change in BCVA at Week 8 and the key secondary endpoint for the EU-specific analysis of change in FCP retinal thickness at Week 4. Variability of the primary and the secondary endpoint were planned to be estimated as the common covariance from the MMRM model used for the primary analysis, but with the treatment and treatment-by-time interaction terms excluded. This was used to calculate the conditional power for the study to show bioequivalence. A target power of 90% to show bioequivalence is intended for the primary efficacy endpoint for the PPS (assuming 10% of patients will be excluded from the FAS) and a target power of 80% for the EU-specific key secondary endpoint for the FAS. An independent statistician who will otherwise not be involved in the planning and performance of the statistical analysis of the study data has performed the calculations and provided recommendations on possible sample size adaptations. The recommendation followed the following rules: The sample size will not be decreased, even if the conditional power will be higher than targeted. If the conditional power is lower than the target power, the sample size will be increased up to a pre-determined maximal sample size. If the target power for the primary endpoint can only be reached by including more patients than the maximal sample size, the recommendation will indicate this fact and the Sponsor will stop the study.

This interim masked review of sample size was performed in November 2021 and revealed that the observed variability overall does not require an increase in sample size to maintain the intended statistical power of 90% for the primary endpoint, and of 80% for the key secondary endpoint (EU/Japan only).

Main Analyses:

Three analyses are planned on unmasked data: (1) the final US analysis intended for the US regulatory submission (Biologics License Application [BLA]), (2) the main EU, and (3) the final EU/Japan analyses intended for the EU and Japan regulatory submissions respectively. Only a restricted number of pre-defined persons not otherwise involved in the direct conduct and management of the study and the study sites, will have access to any unmasking information to perform and review the first two planned analyses.

The final US analysis intended for the US regulatory submission (BLA) is planned to be performed when the first 320 treated patients have completed 40 weeks of treatment (or discontinued the study prematurely) and all randomized and treated patients have completed the primary efficacy endpoint assessment at Week 8 (or discontinued the study prematurely).

Due to the geopolitical situation in Ukraine in 2022, more patients than the originally planned 320 treated patients may be included in the US analysis. The exact number of patients will be determined prior to providing any access regarding treatment unmasking information to any personnel involved in the analysis of this data and will depend on the extent of missing treatments and possibly missing information related to safety and efficacy assessments in affected sites and patients. Formal records on this decision will be kept in the blind data review meeting minutes together with time points of decision and partial unmasking.

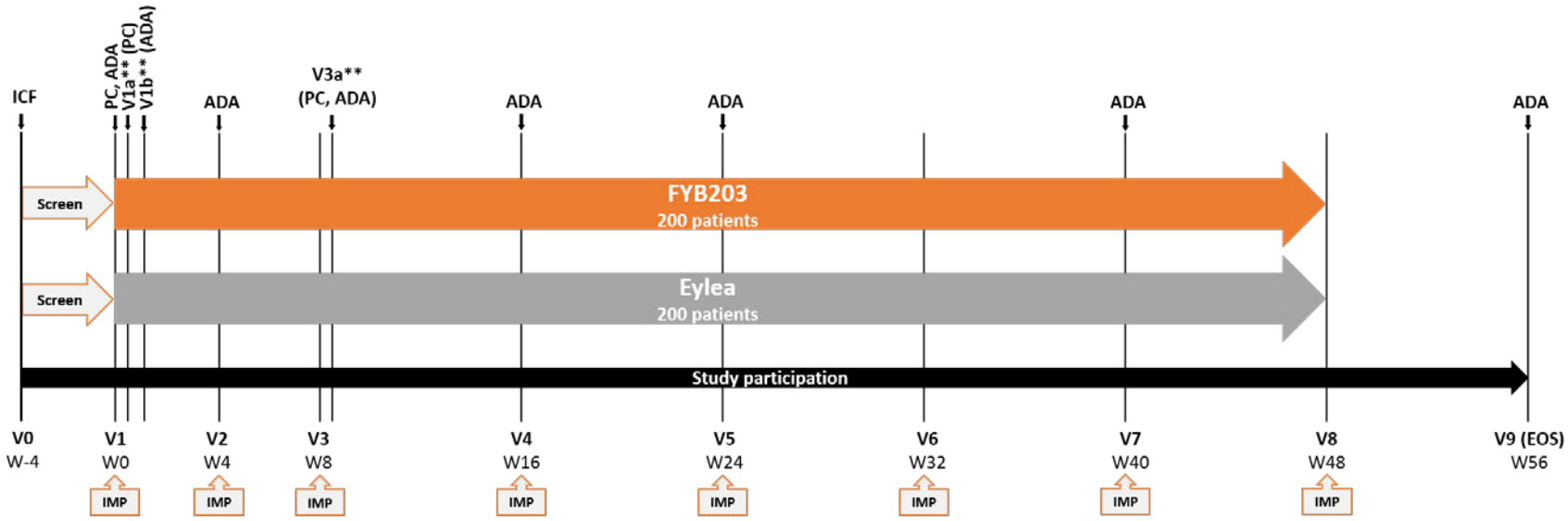
The main EU analysis intended for initial regulatory submission is planned when all randomized and treated patients have completed 24 weeks of treatment or discontinued the study prematurely.

The final EU/Japan analysis intended for the EU and Japan regulatory submissions is planned when all randomized and treated patients have completed the whole study period of 56 weeks.

Data Monitoring Committee (DMC): Yes

1.2 Schema

Figure 1 Overall Study Design



ADA = Anti-drug antibody; EOS = End of Study; IMP = Investigational Medicinal Product; ICF = informed consent form; PC = plasma concentration; V = visit; W = week.

1.3 Schedule of Activities

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8	V9 (EOS/Early Termination)
Week (Day)	W-4–W-1 (-28to-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 (-28to-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.

** 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 SE only.

[4] Goldmann applanation tonometry must be performed at Screening. The Tonopen or Perkins Tonometer, may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP $\geq$ 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 SE compared to Screening and visual acuity in the SE 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 [redacted] 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 [redacted] 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; SE = Study eye; V = Visit; VA = Visual acuity; W = Week.

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

2 INTRODUCTION

Age-related macular degeneration (AMD) is a progressive degenerative macular disease affecting the region of highest visual acuity (VA) of the eye. Characteristically, it is a disease affecting individuals over 50 years of age and is the leading cause of visual loss in developed countries (1,2,3,4,5,6).

In developed countries, AMD is a leading cause of severe visual loss in people 65 years of age and older. In the US, an estimated 6% of individuals aged 65 to 74 years, and 20% of those older than 75 years are affected with some stage of AMD. Also, among white people aged 40 years and older, AMD is the number one cause of visual impairment and blindness in the US.

Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities. Age-related macular degeneration is classified into 2 general subgroups: the non-neovascular (non-exudative or dry) form of the disease and the neovascular (exudative or wet) form of the disease. The non-neovascular form of AMD is more prevalent, accounting for approximately 85% to 90% of all AMD cases in the US and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years. By contrast, neovascular AMD (nAMD) or wet AMD, although less prevalent, accounts for 10% to 15% of clinical forms in the US and commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of VA in this disease (7). This type of AMD results from abnormal blood vessels (neovascularization) proliferation under and/or within the retina. The neovascular form develops due to an angiogenic process in which newly formed choroidal vessels (choroidal neovascularization; CNV) invade the macular area, resulting in rapid vision loss and often total blindness (8,9).

Choroidal neovascularization can be associated with fibrous replacement of the retinal photoreceptors and retinal pigment epithelium (RPE), as well as atrophy of these portions of the retina in the macula, leading to severe visual decline with loss of reading vision, driving vision, and the ability to recognize faces. Vascular Endothelial Growth Factor (VEGF), a protein growth factor that stimulates angiogenesis and increases vascular permeability, is a major pathogenic factor in CNV due to AMD. Counteracting these effects of VEGF can provide significant therapeutic benefit to patients suffering from this disorder.

The pathogenesis of AMD is poorly understood. It is characterized by development of focal deposits of long-spacing collagen and phospholipid vesicles within and beneath the basement membrane of the RPE, called “drusen” which can be accompanied by gradual degeneration of photoreceptors and RPE (atrophy), which often results in slow deterioration of central VA. This thickening and degeneration of Bruch’s membrane can predispose to abnormal growth of blood vessels from the choriocapillaris, termed CNV. The occurrence of CNV heralds the onset of wet

AMD. Leakage from the CNV can cause macular edema with collection of fluid and blood beneath and within the macula, resulting in loss of vision. Growth of the lesions with accompanying fibrovascular or fibroglial tissue further destroys retinal tissue. Over time, the CNV promotes scarring that damages photoreceptors and the RPE, resulting in permanent vision loss.

In addition to wet AMD, ocular neovascularization occurs in various other ocular diseases, including proliferative diabetic retinopathy, retinopathy of prematurity, and ocular hemangioma. Several lines of evidence have linked VEGF to the development of ocular vascular conditions. Vascular endothelial growth factor-A, VEGF-B, and Placental Growth Factor (PlGF) have all been detected in choroidal neovascular membranes. Placental Growth Factor may play an important role in the pathological angiogenesis, in a coordinated way with other VEGF family members. However, the exact effect of PlGF on neovascularization may be case-dependent.

All pharmacologic therapies currently available for wet AMD target and inhibit VEGF and are administered by the intravitreal (IVT) route. These include Lucentis® (ranibizumab), Eylea (aflibercept), and Macugen® (pegaptanib sodium) (10,11,12). The primary mode of action (MoA) of these anti-VEGF agents is prevention of local angiogenesis and the decrease of the intra-retinal and subretinal fluid associated with abnormal blood vessels. Today anti-VEGF therapy is the mainstay and gold standard in the treatment of wet AMD (13).

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, thereby inhibiting the binding and activation of these cognate VEGF receptors. Aflibercept binds VEGF-dimers 1:1 and cannot form multimeric complexes. Binding and neutralization of VEGF dimers inhibits dimerization of the transmembrane receptors, VEGF receptor (VEGFR)-1 and VEGFR-2 and prevents activation of vascular endothelial cells.

Inhibition of VEGF-A, VEGF-B, and PlGF-mediated effects is aflibercept's exclusive MoA and is identical for all indications for which Eylea is licensed (14).

2.1 Eylea: Aflibercept Reference Product

Eylea (aflibercept) (15) is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human immunoglobulin (Ig)G1 formulated as an iso-osmotic solution for intravitreal administration. Aflibercept is a homodimeric glycoprotein with a protein molecular weight of 97 kilodaltons (kDa) and contains glycosylation, constituting an additional 15% of the total molecular mass, resulting in a total molecular weight of 115 kDa. Aflibercept is produced in recombinant CHO cells.

Eylea is a sterile, clear, and colorless to pale yellow solution and supplied as a preservative-free, sterile, aqueous solution for intravitreal injection in a single-dose glass vial or a prefilled syringe designed to deliver 50 µL of solution containing 2 mg of aflibercept (40 mg/mL in 10 mM sodium phosphate, 40 mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, at pH 6.2).

2.2 FYB203: Proposed Aflibercept Biosimilar

FYB203 is developed as a biosimilar to Eylea as the reference medicinal product. The recommended dose of Eylea and FYB203 is 2 mg administered every 4 weeks for the first 3 months, followed by a 2 mg dose once every 8 weeks (2 months).

Like the originator Eylea, FYB203 is a glycosylated, disulfide-stabilized homodimeric recombinant fusion protein consisting of domain 2 of VEGFR-1) and domain 3 of VEGFR-2 fused to the Fc domain of human IgG1. [redacted]

Like Eylea, FYB203 is supplied as a 40 mg/mL sterile, aqueous solution for IVT injection in a glass vial containing the same amount of solution. Each vial contains 100 µL, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single-dose of 50 µL containing 2 mg aflibercept. [redacted] Storage conditions of FYB203 will be same as for the reference product Eylea.

In vitro data obtained with representative FYB203 drug substance and drug product batches from production scale demonstrated similar pharmacological results in binding assays and cell-based assays when compared to Eylea. Since the main mechanism of action is through binding of aflibercept to members of the VEGF family and consequently blocking of downstream effects, it is expected that also the in vivo human pharmacological effects will be highly similar between FYB203 and Eylea.

2.3 Study Rationale

The reference product Eylea (15) is currently approved in the EU for the treatment of:

- Neovascular (wet) AMD
- Visual impairment due to macular edema secondary to retinal vein occlusion (RVO) (branch RVO or central RVO)
- Visual impairment due to diabetic macular edema
- Visual impairment due to myopic CNV

In the US, the reference product, Eylea is currently approved for:

- Neovascular (wet) AMD
- Macular edema following RVO
- Diabetic macular edema
- Diabetic Retinopathy

In Japan, Eylea is currently approved in the following indications:

- Age-related macular degeneration with subfoveal CNV
- Macular edema secondary to RVO
- Choroidal neovascularization in pathologic myopia (myopic CNV)
- Diabetic macular edema

Regarding the treatment of wet AMD, there is an unmet need for an affordable treatment with a highly effective substance and the approved reference product, Eylea, is approaching patent expiration. For these reasons, the Sponsor has developed an aflibercept biosimilar version to Eylea.

A biosimilar is a biological medicinal product that is highly similar to an already authorized original biological medicinal product (reference medicinal product) in terms of quality, tolerability, and efficacy based on a comprehensive comparability exercise (16, 17, 18). The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have developed specific guidelines for a biologic drug to be approved as a biosimilar (16, 18, 19). These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological characterization before initiating clinical studies for the comparison of the efficacy, tolerability, plasma concentration properties, and immunogenicity of the biosimilar.

This Phase 3 study aims to demonstrate the biosimilarity between FYB203 (proposed aflibercept biosimilar) and Eylea (approved originator medicinal product) in terms of efficacy, safety, and immunogenicity, in patients with wet AMD, and to obtain approval in all granted indications for the originator biological medicinal product Eylea in the European Economic Area, Japan, and the US.

This study will be conducted in compliance with the clinical study protocol, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Topic E6, and all applicable regulatory requirements including the principles outlined in the Declaration of Helsinki.

2.4 Background

Age-related Macular Degeneration, left untreated, is a leading cause of adult blindness in the developed world. Neovascular or wet AMD accounts for only 10% of cases of AMD yet results in 90% of the severe vision loss. Epidemiological studies suggest that “wet” AMD will develop in almost 1 million persons in the US within the next 5 years (20, 21).

Aflibercept acts as a soluble decoy receptor that binds VEGF-A, VEGF-B, and PlGF with higher affinity than their natural receptors and thereby can inhibit the binding and activation of these cognate VEGF receptors. Aflibercept has been shown to prevent abnormal, leaky blood vessel growth (CNV) observed in wet AMD and other intraocular disease manifestations related to exaggerated levels of VEGF which also cause macular edema and impaired vision. Today anti-VEGF therapy is the mainstay and gold standard in the treatment of wet AMD (13).

A detailed description of the chemistry, pharmacology, nonclinical efficacy, and clinical safety of aflibercept is provided in the most recent Investigator's Brochure (IB).

2.5 Benefit/Risk Assessment

As this study is being conducted in patients diagnosed with wet AMD, a benefit to the patient is expected. As other compounds of this class are approved for the intended indications, the risks are well understood at this time. The potential risks associated with this study are:

1. Risks related to the intravitreal injection procedure: common risks associated with intravitreal injections include conjunctival hyperemia and hemorrhage at the injection site. Uncommon risks include endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract, increase in intraocular pressure, and vitreous hemorrhage.
2. Risks related to aflibercept study treatment: hypersensitivity, non-ocular hemorrhages and arterial thromboembolic events, and pigment epithelial retinal detachment.

Based on the physical/chemical and preclinical data, FYB203 is expected to have the same safety and efficacy profile as the originator. Intravitreal aflibercept was generally well tolerated and without notable differences in ocular or non-ocular treatment-emergent adverse events (TEAEs) compared to ranibizumab. The incidence of anti-drug antibodies (ADAs) was low with no difference between pre- and post-dose values.

The potential benefit of FYB203 is to bring new treatment options to patients with retinal diseases since there is a need for more easily accessible anti-VEGF therapeutic agents. That need can be met by developing biosimilars to approved anti-VEGFs.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of FYB203 may be found in the IB.

3 OBJECTIVES AND ENDPOINTS

The primary and secondary objectives are shown in Table 1 below along with their corresponding endpoints.

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate and compare functional changes in best corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at Week 8 of treatment with FYB203 or Eylea compared to baseline	• Changes from Baseline Visit (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3)
Secondary	
• Evaluate and compare changes in foveal center point (FCP) retinal thickness	• Change from Baseline Visit (Visit 1) in FCP retinal thickness to Week 4 (Visit 2)
• Evaluate and compare changes in FCP retinal thickness and change in foveal central subfield (FCS) retinal thickness over time	• Changes of FCP retinal thickness and FCS retinal thickness over the whole study from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare functional changes of the retina by BCVA over time	• Change of BCVA by ETDRS letters over the whole study from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare the proportion of patients who gain or lose ≥ 5, 10, and 15 ETDRS letters compared to baseline	• Proportion of patients who gain or lose ≥ 5, 10, or 15 ETDRS letters from Baseline Visit (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7), and Week 56 (Visit 9)
• Evaluate and compare the absence of disease activity (fluid-free macula) over time	• Percentage of patients with fluid-free macula at each Visit
• Evaluate and compare change in total lesion size	• Change from baseline in total lesion size to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
• Evaluate and compare systemic free and total aflibercept concentrations in a subgroup of up to 60 patients (up to 30 per arm)	• Systemic concentrations (close to maximum concentration [Cmax]) of free and total aflibercept in a subgroup at selected sites – 48 hours after 1st dose (Visit 1a) – 48 hours after the 3rd dose (Visit 3a)
• Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25)	• Change from Baseline Visit (Visit 1) in vision-related functioning and well-being measured by NEI VFQ-25 to Week 24 (Visit 5), Week 40 (Visit 7), and Week 56 (Visit 9)
• Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum	• Number of patients with ADAs over time

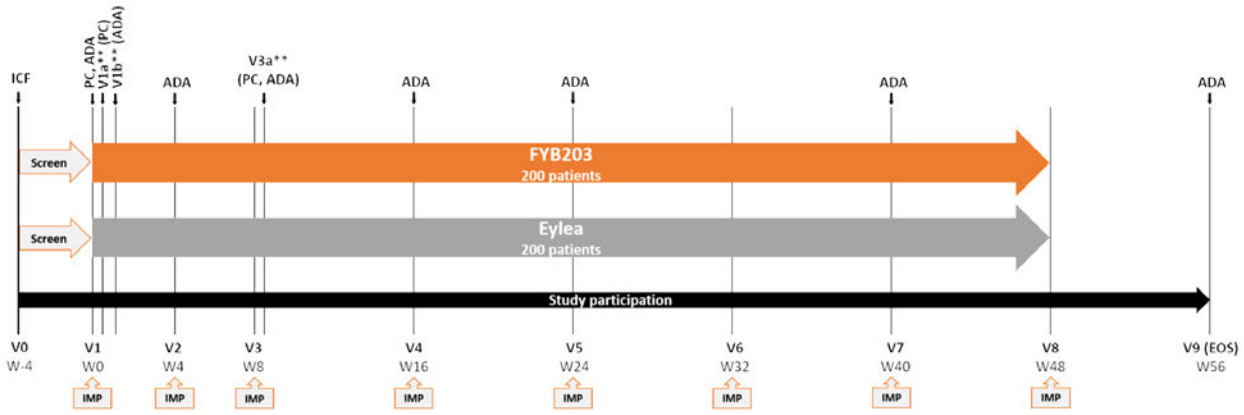
• Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs)	• Frequency of local and systemic AEs and SAEs

ADA = Anti-drug antibody; AE = Adverse event; ETDRS = Early treatment diabetic retinopathy study; FCP = foveal central point; FCS = foveal central subfield; NEI VFQ-25 = National eye institute visual function questionnaire 25.

4 STUDY DESIGN

4.1 Overall Design

Figure 2 Overall Study Design



ADA = Anti-drug antibody; EOS = End of Study; IMP = Investigational Medicinal Product; ICF = informed consent form; PC = plasma concentration; V = visit; W = week.

This is a Phase 3, parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study to demonstrate the equivalence of efficacy of FYB203 to Eylea and to evaluate the safety and immunogenicity in patients with nAMD. During the Screening period (maximum 28-day starting with the informed consent form [ICF] signature), the central reading center will receive the patient's retinal images in order to provide an independent, masked assessment of patient eligibility regarding FCP, lesion classification, lesion size, and area of CNV. Patients must meet all eligibility criteria during the Screening period, including positive evaluation of the screening retinal images performed by the central reading center. After this period, potential patients who satisfy the entry criteria 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).

The treatment will consist of 1 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 (Visit 8). Each patient will receive a total of 8 IVT injections.

This study is designed to be evaluation-masked, neither the patient nor the Investigator(s) performing the evaluations and masked study personnel will know which treatment the patient is assigned to.

At each study site there will be at least 2 masked staff members (Investigator and VA examiner) and 1 unmasked Injector (who will administer the investigational medicinal product [IMP]). There

may be also other masked study site staff (e.g. study coordinator, study nurse, optical coherence tomography technician, photographer). The unmasked Injector should have a back-up person.

The Principal Investigator (PI) (or his/her masked study team to whom tasks have been delegated) will do all pre- and post-injection assessments (Tonometry and Ophthalmologic Examination, spectral domain optical coherence tomography [SD-OCT], fluorescein angiography [FA] and color fundus photography [FP], blood samples collection, and National eye institute visual function questionnaire 25 [NEI VFQ-25 questionnaire administration]), except measurements of refraction and VA. The masked Investigator(s) will also assess the relationship of all AEs to IMP, including those noted by the unmasked Injector.

Only the masked VA examiners will measure refraction and BCVA. The masked VA examiners will not be permitted to have any further roles in obtaining data from a patient; however, they may perform additional study support tasks such as read-out of the temperature logger.

Only the unmasked Injector will perform IVT injections. He/she can also perform the post-dose safety check or tonometry, according to the clinical practice of the study site. The systemic concentrations of free and total aflibercept will be assessed and compared in a subgroup of up to 60 patients (up to 30 per arm) at Baseline Visit (Visit 1) prior to 1st IVT dose, 48 hours after 1st IVT dose (Visit 1a) close to C_{max}, and at 48 hours after the 3rd IVT dose (Visit 3a) close to C_{max}.

Anti-drug antibodies formation against aflibercept will be evaluated in serum in all patients prior to the patient receiving the IVT injections administered at Baseline Visit (Visit 1), Week 4 (Visit 2), Week 16 (Visit 4), Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9), and in addition, in patients participating in the subgroup 1 week after the 1st dose (Visit 1b) and 48 hours after the 3rd dose (Visit 3a). In case, patients experiencing signals of an unexpected ocular inflammation, as this may indicate an immune response, additional sampling of an ADA sample should be conducted.

A follow-up visit for safety (Early Termination Visit/End of Study [EOS]) will occur at Week 56 (Visit 9) after the administration of 8 IVT doses of IMP. If the patient discontinuation happens before the 8 planned IVT doses, an Early Termination Visit should be conducted.

The total study duration for a patient will be approximately 56 weeks, excluding the Screening period.

A Data Monitoring Committee (DMC) will be established to monitor safety throughout the study. The DMC is independent of the Sponsor and of the contract research organization (CRO) and will consist of external experts who will review the safety and tolerability data from the study. Details of the analysis will be specified in the DMC Statistical Analysis Plan (SAP) and referenced in the DMC Charter.

4.2 Scientific Rationale for Study Design

The purpose of this study is to demonstrate the biosimilarity between FYB203 and Eylea in patients with wet AMD, the most sensitive indication. The planned confirmatory study is expected to rule out any clinically meaningful differences between both biological medicinal products. FYB203 is developed in the same indications and route of administration as the reference product Eylea.

For supporting the assessment of overall systemic safety of FYB203 relative to Eylea, systemic exposures will be collected and compared in the subgroup population (approximately 60 patients, 30 patients per treatment group) in this study.

No clinical studies have been performed with FYB203 to date. The clinical development program of FYB203 builds on an extensive analytical and functional characterization which compares FYB203 and Eylea. Similarity will be confirmed in a parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study to demonstrate clinical equivalence of efficacy of FYB203 to Eylea and evaluate the safety and immunogenicity over 56 weeks in patients with subfoveal wet AMD. The product characteristics of the reference product Eylea are well known for human use. After close to 10 years on the EU and US market, the medicinal product continues to be an effective agent for the treatment in all approved indications.

4.3 Justification for Dose

The dose of FYB203 and Eylea selected for use in this study is the approved dose for patients with subfoveal wet AMD treatment.

4.4 End of Study Definition

A patient is considered to have completed the study if he/she has completed the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA) (Section 1.3).

The end of the study is defined as the date of the last visit of the last patient in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last patient in the study globally.

5 STUDY POPULATION

The study population for this study are patients with subfoveal wet AMD.

Prospective approval of protocol deviations to eligibility criteria, also known as protocol waivers or exemptions, will not be granted.

Eligibility for participation in this study will be based on the inclusion/exclusion criteria. Only 1 eye will be designated as the study eye (SE). For patients who meet eligibility criteria in both eyes, the eye with the worse VA will be selected as the SE. If both eyes have equal VA, the eye with better visual prognosis (e.g. clearer lens and ocular media and less amount of subfoveal scar or geographic atrophy) will be selected at the Investigator's discretion. If there is no objective basis for selecting the SE, factors such as ocular dominance, other ocular pathology, and patient preference should be considered by the Investigator in making the selection.

5.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

General

1. Age ≥ 50 years at Screening.
2. Male or female:

- Male:
  - A male patient must agree to use contraception as detailed in [redacted] of this protocol during the treatment period (48 weeks) and for at least 4 weeks after the last dose of study treatment.
- Female:
  - A female patient is eligible to participate if she is not pregnant [redacted], not breastfeeding, and at least 1 of the following conditions applies:
    - i) Not a woman of childbearing potential (WOCBP) as defined in [redacted]
      OR
    - ii) A WOCBP who agrees to follow the contraceptive guidance in [redacted] during the treatment period (48 weeks) and for at least 4 weeks after the last dose of study treatment

3. Capable of giving signed informed consent as described in [redacted], which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
4. Willingness and ability to undertake all scheduled visits and assessments.

Ocular (Study Eye)

5. Newly diagnosed (within 6 months of Screening Visit), angiographically documented, treatment-naïve CNV lesion secondary to wet AMD:

    a) All subtypes of wet AMD CNV lesions are eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Treatment-naïve CNV secondary to wet AMD must be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intra-retinal fluid by SD-OCT or RPE detachment);

    b) Total area of whole lesion must be ≤ 9 disc areas;

    c) Total CNV area encompasses ≥ 50% of total lesion area based on FA, including all subtypes of wet AMD.

Term	Definition
Wet AMD	Clinical signs (including findings by retinal imaging) attributable to wet AMD (e.g. pigmentary changes, drusen) and no other likely etiologic explanations for the degenerative changes
Subfoveal	Including the center of the fovea
Juxtafoveal	At least some part of CNV lesion must be in an area up to 199 µm from the geometric center of the fovea
Total area of whole lesion	A contiguous area of abnormal tissue that contains a CNV (as documented by FA) with possible additional components of hemorrhages, blocked fluorescence not from hemorrhage, serous detachment of the RPE, atrophy, and subretinal fibrosis

AMD = Age-Related Macular Degeneration; CNV = choroidal neovascularization; FA = fluorescein angiography; RPE = Retinal pigment epithelium.

6. Sufficiently clear ocular media and adequate pupillary dilation to permit good quality ocular imaging.
7. Best corrected visual acuity in the SE, determined by standardized ETDRS testing, between 20/40 and 20/200 Snellen equivalent [redacted].
8. Foveal center point retinal thickness at Screening ≥ 300 µm and < 800 µm. (FCP thickness is defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea).

Ocular (Fellow Eye)

9. Best corrected visual acuity in the fellow eye, determined by standardized ETDRS testing, at least 20/200 Snellen equivalent [redacted].

5.2 Exclusion Criteria

Patients are not eligible for the study if any of the following criteria apply:

General

1. Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who are legally institutionalized.
2. Study eye requiring immediate treatment.

Prior or Current Ocular Treatment

3. Any prior treatment with anti-VEGF agent (e.g. bevacizumab, aflibercept, ranibizumab) or any investigational products to treat AMD, in either eye.
4. Prior treatment with any investigational products to treat ocular diseases other than wet AMD within 30 days or 5 half-lives prior to Randomization, whichever is longer.
5. History of vitrectomy, macular surgery or other surgical intervention for AMD in the SE.
6. History of IVT or periocular injections of corticosteroids or device implantation within 6 months prior to Randomization in the SE.
7. Prior treatment with verteporfin (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the SE.
8. Any other intraocular surgery (including cataract surgery) in the SE within 3 months prior to Randomization.

CNV Lesion Characteristics

9. Sub- or intra-retinal hemorrhage that comprises more than 50% of the entire lesion in the SE.
10. Irreversible structural damage involving the center of fovea (e.g. advanced fibrosis > 50% of the total lesion in the SE or atrophy) in the SE that is considered sufficient to irreversibly impair VA.
11. CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia.

Current Ocular Conditions

12. Retinal pigment epithelial tear involving the macula in the SE.
13. History of or current full-thickness macular hole (Stage 2 and above by clinical examination or full-thickness macular hole by SD-OCT imaging of any size) in the SE.
14. History of or current retinal detachment in the SE.
15. Current vitreous hemorrhage in the SE.
16. Spherical equivalent of the refractive error in the SE demonstrating more than 6 diopters of myopia.
17. For patients who have undergone prior refractive or cataract surgery in the SE, the preoperative refractive error in the SE should not exceed 6 diopters of myopia.

18. History of or current corneal transplant in the SE.
19. Aphakia in the SE. Absence of an intact posterior capsule is allowed if it occurred as a result of yttrium aluminum garnet laser posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation.
20. Active or recent (within 4 weeks prior to Randomization) intraocular inflammation of clinical significance in either eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis, or endophthalmitis.
21. Uncontrolled ocular hypertension or glaucoma in the SE (defined as intraocular pressure [IOP] ≥ 30 mmHg, despite treatment with anti-glaucomatous medication).
22. Ocular disorders in the SE (i.e. retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on VA) at the time of Screening that may confound interpretation of study results and compromise VA.
23. Any concurrent intraocular condition in the SE (e.g. glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the Investigator, would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results.

Systemic Medical History and Treatments and Conditions at Screening

24. Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives prior to Randomization, whichever is longer.
25. Systemic treatment with anti-VEGF agent (e.g. bevacizumab) within 90 days prior Randomization.
26. Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
27. Stroke or myocardial infarction within 6 months prior to Randomization.
28. Presence of uncontrolled systolic blood pressure > 160 mmHg or uncontrolled diastolic blood pressure > 100 mmHg within 4 weeks prior to Randomization.
29. Known hypersensitivity to the IMP (aflibercept or any component of the aflibercept formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation.
30. Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol.
31. History of recurrent significant infections and/or current treatment for active systemic infection.

Ocular (Fellow Eye)

32. Any diagnosis and/or signs of wet AMD requiring treatment with an IVT anti-VEGF agent

(e.g. aflibercept, bevacizumab, ranibizumab) within the Screening period or are expected, in the opinion of the Investigator, to need such treatment in the fellow eye throughout the study. At the time of screening and randomization, the Investigator should use best medical judgement to exclude patients with a probable fellow eye treatment need during the course of the study.

5.3 Lifestyle Considerations

No restrictions are required.

Please see Section 7.5 for medications that are prohibited during this study.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any adverse event.

5.5 Re-screening Procedures

The decision for re-screening of a patient is at the discretion of the Investigator and may be performed under certain circumstances. Re-screening may only be performed once per screened patient and 1 of the following criteria has to apply:

1. The patient was already consented and fulfilled all eligibility criteria but the enrollment was delayed due to an unexpected change in the patient's personal situation (e.g. an issue in the family).
2. The patient did not fulfill all eligibility criteria previously due to an event (e.g. laboratory test result, physical exam finding, planned surgery, uncontrolled medical condition) or any other technical/logistical reason (e.g. laboratory samples lost by courier, malfunction of a device) that has been resolved.
3. The patient did not fulfill all eligibility criteria previously but becomes eligible due to a protocol amendment and change of inclusion and exclusion criteria.

In cases where previous screening procedures were discontinued, and the patient was not randomized, the following procedures have to be undertaken:

1. The patient has to sign and date a new ICF prior to being re-screened.
2. A new unique patient identification number will be assigned to the patient.

3. Data of the patient has to be entered in a new eCRF with the new unique patient identification number.
4. Re-screening has to be documented in the source data.

The re-screened patient can be randomized if all eligibility criteria are met.

6 SCHEDULE OF STUDY VISITS

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

6.1 Visit 0 (Screening)

Prior to participation in the study patients will be informed both verbally and in writing about the purpose of the study, its procedures and any potential risks or discomforts resulting from participation. Informed consent will be obtained by the patient before any study specific procedures. Only those patients who fulfill all eligibility criteria will be enrolled into the study.

However, if a routine procedure (e.g. FA, SD-OCT) is performed to diagnose AMD independent of this clinical study, and subsequently the patient provides informed consent, procedures performed prior to informed consent may be used as Screening assessments for this study, provided the 28-day period of Screening evaluations is respected. In addition, the assessments must meet the standards defined in this protocol and SD-OCT images must be obtained by central reading center-certified SD-OCT operators and evaluated by the central reading center.

At Screening (Visit 0), the following activities and assessments will be performed within 28 days prior to Visit 1:

- Patient information/Informed consent
- Demographic information (date of birth [or year of birth], gender, race and ethnicity)
- Medical history:
    - General medical conditions:
        - All conditions present at the time of ICF signature
        - All conditions/surgeries that occurred within 1 year prior to ICF signature
        - History of arterial thromboembolic events (defined as nonfatal stroke or nonfatal myocardial infarction) regardless of the time of occurrence
    - Ophthalmologic conditions: all data regardless of the time of occurrence including SE and fellow eye information
- Prior treatments:
    - All medications the patient is receiving until the time of ICF
    - All medications related to ophthalmologic conditions, regardless of the time of occurrence
    - All medications related to arterial thromboembolic events (defined as nonfatal stroke or nonfatal myocardial infarction) regardless of the time of occurrence
    - Ocular and systemic: ocular and systemic anti-VEGF treatment, regardless of the indication
- Physical assessment

- Vital signs (before any blood sample collection on the same day)
- BCVA (both eyes): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (both eyes): Goldmann applanation tonometry must be performed at Screening
- Slit lamp exam (both eyes)
- Ophthalmoscopy (both eyes)
- Verification of inclusion and exclusion criteria
- Urine sampling [redacted]. Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.
- Fluorescein angiography (both eyes)
- Color FP (both eyes)
- SD-OCT (both eyes)
- Laboratory tests [redacted]
- Pregnancy test, serum human chorionic gonadotropin (hCG) and follicle stimulating hormone (FSH) (only women)
- Concomitant medications
- AEs recorded from the day the informed consent was signed

6.2 Visit 1 (Baseline)

At Visit 1, the following activities and assessments will be performed:

Prior to randomization:

- Concomitant medications
- AEs
- NEI VFQ-25 (prior to any ophthalmic procedures or any other assessments)
- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- SD-OCT (SE)
- Verification of inclusion and exclusion criteria

To remain eligible for randomization at Day 1 (Visit 1), the following 3 criteria must be met:

1. There is no significant anatomical change in the SE following ophthalmological and SD-OCT examination between the Screening Visit and Visit 1 (i.e. large subretinal hemorrhage, RPE tear, pigment epithelial detachment).

2. Visual acuity in the SE is within the defined inclusion criteria range (using ETDRS testing Snellen equivalent 20/40 [0.5] to 20/200 [0.1]) and within 5 letters (better or worse) of the Screening VA. Thus:
    - If difference in BCVA is greater than 5 ETDRS letters (better or worse) between Screening and Visit 1, the patient must NOT be randomized.
    - If the Snellen equivalent at Visit 1 is no longer within the inclusion criteria (Snellen equivalent 20/40 to 20/200), the patient must NOT be randomized.
3. No diagnosis and/or signs of wet AMD requiring treatment during the study with an IVT anti-VEGF agent in the fellow eye (e.g. aflibercept, bevacizumab, ranibizumab). The Investigator should use best medical judgement to exclude patients with a probable FE treatment need during the course of the study.

Randomization:

After completing the Screening period and being confirmed eligible for participation in the study by the central reading center and the masked Investigator, patients will be centrally randomized via Interactive Web Response System (IWRS) into 1 of the two study groups in a 1:1 ratio (FYB203:Eylea).

Post-randomization:

- Blood sampling for ADAs
- Blood sampling for systemic evaluation of aflibercept plasma concentration (Subgroup only)

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
    - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
    - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
    - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP $\geq$ 30 mmHg.

6.2.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs or symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.3 Visit 1a (Subgroup only)

- Blood sampling for evaluation of systemic aflibercept plasma concentration
- AEs

6.4 Visit 1b (Subgroup only)

- Blood sampling for ADAs
- AEs

6.5 Visit 2

The following activities and assessments will be performed:

<u>During the visit:</u>

- Concomitant medications
- AEs

<u>Pre-IVT injection:</u>

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP $\geq$ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- SD-OCT (SE)
- Blood sampling for ADAs

<u>IVT injection:</u>

- IVT administration (FYB203 or Eylea) by unmasked IVT administrator

<u>Post-IVT injection:</u>

- Safety check including:

- Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
- Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
- Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.5.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.6 Visit 3

The following activities and assessments will be performed:

<u>During the visit:</u>

- Concomitant medications
- AEs

<u>Pre-IVT injection:</u>

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- SD-OCT (SE)
- Additional ADA sampling and evaluation will be performed in patients experiencing signals of unexpected ocular inflammation

<u>IVT injection:</u>

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
  - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
  - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
  - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.6.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.7 Visit 3a (Subgroup only)

- Blood sampling for evaluation of systemic aflibercept plasma concentration
- AEs
- Blood sampling for ADAs

6.8 Visit 4

The following activities and assessments will be performed:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection:

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)

- SD-OCT (SE)
- Blood sampling for ADAs

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
  - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
  - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
  - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.8.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.9 Visit 5

The following activities and assessments will be performed:

During the visit:

- NEI VFQ-25 (prior to any ophthalmic procedures or any other assessments)
- Physical assessment
- Vital signs (before any blood sample collection on the same day)
- Laboratory tests [redacted]
- Concomitant medications
- AEs

Pre-IVT injection:

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.

- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- Urine sampling [redacted]. Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.
- Fluorescein angiography (SE)
- Color FP (SE)
- SD-OCT (SE)
- Blood sampling for ADAs

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
  - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
  - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
  - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.9.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.10 Visit 6

The following activities and assessments will be performed:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection:

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- SD-OCT (SE)
- Additional ADA sampling and evaluation will be performed in patients experiencing signals of unexpected ocular inflammation

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
  - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
  - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
  - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.10.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.11 Visit 7

The following activities and assessments will be performed:

During the visit:

- NEI VFQ-25 (prior to any ophthalmic procedures or any other assessments)

- Physical assessment
- Vital signs (before any blood sample collection on the same day)
- Laboratory tests [redacted]
- Concomitant medications
- AEs

Pre-IVT injection:

- BCVA (both eyes): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (both eyes): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (both eyes)
- Ophthalmoscopy (both eyes)
- Urine sampling [redacted]. Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.
- Fluorescein angiography (both eyes)
- Color FP (both eyes)
- SD-OCT (both eyes)
- Blood sampling for ADAs

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
  - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
  - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
  - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.11.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections

such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.12 Visit 8

The following activities and assessments will be performed:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection:

- BCVA (SE): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (prior to the injection) (SE): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (SE)
- Ophthalmoscopy (SE)
- SD-OCT (SE)
- Additional ADA sampling and evaluation will be performed in patients experiencing signals of unexpected ocular inflammation.

IVT injection:

- IVT administration (aflibercept biosimilar FYB203 or Eylea) by unmasked IVT administrator

Post-IVT injection:

- Safety check including:
    - Check for light perception: within 15 minutes after the injection (SE). Absence of light perception may indicate central retinal artery occlusion. In this case, paracentesis is indicated as an attempt to restore central retinal artery perfusion immediately.
    - Ophthalmoscopy: within 30 minutes after the injection (SE) to assess central retinal artery perfusion and identify injection-related complications (i.e. hemorrhage or retinal detachment).
    - Tonometry: 30 to 60 minutes after the injection (SE). The Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg.

6.12.1 Telephone Safety Call

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

6.13 Visit 9 (EOS/Early Termination Visit)

The following activities and assessments will be performed:

<u>During the visit:</u>

- NEI VFQ-25 (prior to any ophthalmic procedures or any other assessments)
- Physical assessment
- Vital signs (before any blood sample collection on the same day)
- Laboratory tests [redacted]
- Concomitant medications
- AEs
- BCVA (both eyes): refraction and VA testing must be performed by a certified masked visual acuity examiner using an ETDRS chart prior to any ophthalmic assessments.
- Tonometry (both eyes): the Tonopen or Perkins Tonometer, may be used, however Goldmann applanation tonometry must be used to verify any IOP ≥ 30 mmHg
- Slit lamp exam (both eyes)
- Ophthalmoscopy (both eyes)
- Urine sampling [redacted]. Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.
- Fluorescein angiography (both eyes)
- Color FP (both eyes)
- SD-OCT (both eyes)
- Blood sampling for ADAs

7 STUDY TREATMENT

The IMPs are FYB203 and Eylea.

The term experimental product refers to FYB203 (aflibercept biosimilar).

The term comparator refers to Eylea (EU-approved).

7.1 Study Treatment(s) Administered

This study is designed to be evaluation-masked, neither the patient nor the Investigator(s) performing the evaluations and masked study personnel will know which treatment the patient is assigned to.

The PI (or his/her masked study team to whom tasks have been delegated) will do all pre- and post-injection assessments (Tonometry and Ophthalmologic Examination, SD-OCT, FA and color FP, blood samples collection and, NEI VFQ-25 questionnaire administration), except measurements of refraction and VA. The masked Investigator/s will also assess the relationship of all AEs to IMP, including those noted by the unmasked IVT administrator.

Only the unmasked IVT administrator will perform IVT injections. He/she can also perform the post-dose safety check or tonometry, according to the clinical practice of the study center.

Each eligible patient will receive a total of 8 IVT injections of FYB203 or Eylea according to the details in Table 2.

Table 2 Study Treatment Details

Study Treatment Name:	FYB203 (experimental product)	Eylea (comparator)[1]
INN:	aflibercept	
Pharmaceutical Form:	Solution for injection; clear, colorless to pale yellow and iso-osmotic solution	
Route of Administration	Intravitreal	
Unit Dose Strength(s):	2 mg (0.05 mL of 40 mg/mL solution)	
Storage conditions	Store in a refrigerator (2ºC to 8ºC). Do not freeze. Protect from light (keep the outer carton unopened). Prior to usage, the unopened carton may be stored at room temperature (below 25°C) for up to 24 hours.	
Dosing Instructions:	IMP is for IVT injection only and may only be administered according to medical standards and applicable guidelines by a qualified ophthalmologist in IVT injections.	
Packaging and Labeling	Study treatment packaging and labeling will comply with Good manufacturing practices regulations and local regulatory requirements.	

[1] Eylea® (15)

IMP = investigational medicine product; IVT = intravitreal.

7.2 Preparation/Handling/Storage/Accountability

1. Detailed instructions for storage and handling will be provided within a separate IMP Handling Manual.
2. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
3. Only patients randomized in the study may receive study treatment and only a qualified ophthalmologist experienced in IVT injections should administer the injection.
4. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.
5. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for maintaining complete documentation of IMP handling up from receipt until destruction or return, respectively, such as study treatment accountability, reconciliation, and record maintenance. This documentation must be available for inspection at any time.
6. Further guidance and information for the final disposition of unused study treatment are provided in the IMP Handling Manual.

7.3 Measures to Minimize Bias: Randomization and Masking

The randomization will occur after the written informed consent has been obtained and eligibility has been confirmed for participation in the study at Visit 1 (Baseline). Patients will be randomized 1:1 to either FYB203 or Eylea.

All patients will be centrally assigned to randomized study treatment using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each study center.

Study treatment will be dispensed at the study visits summarized in SoA (Section 1.3).

This is a double-masked study with limited access to the randomization code. The experimental product (FYB203) and comparator will be identical in physical appearance. Due to differences in the products presentation, the IMPs will be administered by an unmasked IVT administrator which will be responsible for the study injections only. The treatment each patient will receive will only be disclosed to the unmasked IVT administrator but not to other study center staff, patient, Sponsor, or study vendors. The treatment codes will be held by the IWRS vendor.

Except for the unmasked IVT administrator, unmasking should be considered only when knowledge of the treatment assignment is deemed essential for the patient's medical care by the Investigator or a regulatory body. Investigators are strongly discouraged from requesting the mask be broken for an individual patient, unless there is a patient safety issue that requires unmasking and would change patient management. The process for breaking the mask will be handled through

the IWRS. Any center that breaks the mask under inappropriate circumstances may be asked to discontinue its participation in the study. If the mask is broken, it may be broken only for the patient in question.

The Sponsor and CRO must be notified immediately if a patient and/or Investigator/site personnel is unmasked during the course of the study. Pertinent information regarding the circumstances of unmasking of a patient's treatment code must be documented in the patient's source documents and electronic case report forms (eCRFs). This includes who performed the unmasking, the patient(s) affected, the reason for the unmasking, the date of the unmasking and the relevant IMP information.

7.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any deviations from the intended regimen must be recorded in the respective eCRF page.

All IMP injections will be given by the unmasked Investigator or back-up to ensure compliance. The exact date and time of IMP injection must be recorded in the source documentation and the eCRF.

Patients who miss any scheduled dosing visit should be counseled on the importance of good compliance to the study dosing regimen.

If the IMP is not given within 7 days of the scheduled dosing visit date, the IMP should be given at the discretion of the PI but the interval between two doses injected into one eye should be at least 4 weeks. If the next dose is scheduled in less than 4 weeks time, dosing should not be performed at the previous late visit.

If IMP is given outside of the visit window, this will be captured as protocol deviation. Next scheduled dosing visit date and visit window should not be altered even if previous dosing is not performed on the exact scheduled dosing visit date. It is the Investigator's responsibility to make every effort to return to the dosing schema summarized in SoA (Section 1.3).

7.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines) that the patient is receiving at the time of Screening or receives during the study must be recorded in the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

A list of excluded medications/therapy is provided in [redacted].

7.5.1 Fellow Eye Treatment

If during the course of the study the patient develops wet AMD in the fellow eye (non-SE) with an acute treatment need, the fellow eye will not be considered as an additional SE. For the fellow eye treatment, the patient could ONLY receive Eylea after Visit 3 and should remain in the study. Patients in the plasma concentration subgroup should not receive fellow eye treatment until after the plasma concentration blood sample collection at Visit 3a has been taken.

Fellow eye injection will be performed by the Investigator for this study and the details about the injection will be documented in the eCRF. However, fellow eye visit is not part of study but should be timely separated by at least 14 days from study eye treatment. Ocular AEs for the fellow eye will be monitored and recorded after the written informed consent is obtained from the patient until Week 56 (Visit 9).

7.6 Treatment After the End of the Study

The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with the medical condition.

8 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Treatment

The patient must be discontinued from study treatment in the event of any of the following:

- Consent withdrawal by patient:
  - If patients withdraw his/her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (e.g. documented lack of efficacy, AE or pregnancy); however, the patient could refuse to provide such reason;
  - If the main reason for consent withdrawal is considered related to the study, the Investigator may select appropriate reason among the reasons listed below other than consent withdrawal.
- Any newly developed or aggravated ophthalmic abnormality other than AMD in the SE which could interfere with evaluation of efficacy or safety of IMP including but not limited to retinal vascular abnormality;
- Any AEs in the SE (e.g. intraocular inflammation, VA loss, increased IOP [≥ 30 mmHg], subretinal hemorrhage, vitreous hemorrhage, and local or systemic infection) which in the opinion of the Investigator and/or patient would require IMP discontinuation;
- Protocol deviations which may adversely affect the patient's safety and/or integrity of data as agreed by the masked Investigator and/or upon request from the Sponsor;
- IMPs non-compliance (Section 7.4):
  - A patient misses any of the first 2 doses (IVT injection of IMPs at Week 0 [Day 1] and Week 4) after randomization.
  - A patient misses 2 consecutive doses during the study period after randomization.
- Decision by the masked Investigator that the patient requires alternate treatment (e.g. other anti-VEGF agents such as bevacizumab or ranibizumab, PDT, PPV etc.) to treat wet AMD in the SE;
- Decision by the Sponsor that IMP discontinuation is in the patient's best medical interest or administrative decision for a reason (e.g. a suspicion of fraud, the patient enrolling in multiple clinical studies, lack of compliance, etc.) other than that of an AE;
- Lost to follow-up;
- Pregnancy;
- Rhegmatogenous retinal detachment or full-thickness macular hole.

Any significant change in the posterior pole (e.g. subretinal hemorrhage, macular hole, vitreous hemorrhage or opacity, retinal detachment, etc.) that is detected with fundus examination should be confirmed and documented with FP and/or FA. The masked Investigator should decide IMP

discontinuation based on the FP and/or FA. The images taken at unscheduled visits will be sent to the central reading center within 72 hours.

If a patient is prematurely discontinued from study treatment due to any of the above described reasons excluding death, the patient will complete the Early Termination Visit procedures (except for plasma concentration sampling) as described for Week 56 (Visit 9) immediately.

If a patient agrees to continue follow-up for associated clinical outcome information until Week 56 irrespective of IMP injection status, the patient's clinical outcome information such as BCVA, AEs and concomitant medication will be collected through non-invasive chart review, if available.

If a patient does not agree to continue follow-up of associated clinical outcome information, the patient will be terminated from the study accordingly. The data and blood samples collected on the patient up to the Early Termination Visit remains in the study database and no further data will be collected.

In all cases, the reason for IMP discontinuation must be recorded in the patient's medical records and in the eCRF.

8.1.1 Temporary Investigational Medicinal Product Withhold

- Intraocular inflammation:
  - Interrupt study treatment if intraocular inflammation (iritis, iridocyclitis, or vitritis) is ≥ 2+ in the SE;
  - Patients with ≥ 2+ intraocular inflammation may be allowed to resume study treatment subsequently, as determined by Medical Monitor and Investigator.
- Intraocular surgery in the SE (e.g. cataract operation, vitrectomy, glaucoma surgery, etc.) which in the opinion of the Investigator would require IMP discontinuation:
  - Interrupt study treatment after intraocular surgery in the SE;
  - Study treatment may be resumed no earlier than 28 days after an uncomplicated cataract surgery and no evidence of post-operational inflammation at that time. For cataract surgery or other intraocular surgery with complications, study treatment may be permitted, as determined by Medical Monitor and Investigator.
- BCVA decrease:
  - Interrupt study treatment if there is a study treatment-related decrease of ≥ 30 letters in BCVA in the SE compared with the last assessment of BCVA prior to the most recent treatment;
  - Study treatment may be permitted subsequently, as determined by Investigator.

- Elevated IOP:
  - Interrupt study treatment if pre-treatment IOP in the SE is ≥ 30 mmHg;
  - Treatment may be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or with treatment, as determined by Investigator.
- Rhegmatogenous retinal break:
  - Interrupt study treatment if a retinal break is present in the SE;
  - Study treatment may be resumed no earlier than 28 days after successful laser retinopexy, as determined by Investigator.
- Active infection:
  - Interrupt study treatment if active or suspected ocular or periocular infections present (e.g. infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis) in either eye or if the patient requires treatment for an active non-ocular infection;
  - Study treatment may be subsequently permitted after discussion with Medical Monitor;
  - Additional ADA sampling and evaluation will be performed in patients experiencing signals of unexpected ocular inflammation.
- On-study prohibited medications:
  - See Section 8 for additional reasons for study treatment interruption or discontinuation;
- Any other reason for treatment interruption per the discretion of the masked Investigator has to be discussed upfront with the medial monitor.

8.1.2 Replacement

Patients who are discontinued from IMP after randomization will not be replaced.

8.2 Patient Discontinuation/Withdrawal from the Study

- A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she misses a study visit and subsequent visits despite attempts to contact the patient. The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 contact attempts and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.4 Premature Termination of the Study

The Sponsor may terminate this study prematurely for any reasonable cause. The Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) and Competent Authority(ies) (CAs) should be informed in accordance with applicable regulations.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study, or potential study patients.
- A decision on the part of the Sponsor to suspend or discontinue development of FYB203. If the study is prematurely terminated or suspended for any reason, the masked Investigator/institution should promptly inform the study patients and should ensure appropriate therapy and follow-up for the patients. The masked Investigator should also attempt to complete the final study assessments as outlined in the Section 6.13. Patients with an ongoing AE should be followed until resolution of the AE, or the masked Investigator or delegated staff member decides that the AE is stable and needs no further follow-up. All AEs should be followed up according to Section 9.3.3.

9 STUDY ASSESSMENTS

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not granted.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon awareness to determine if the patient should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).
- The maximum amount of blood collected from the selected subgroup of patients for the evaluation of systemic aflibercept concentration over the duration of the study will be approximately 24 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

9.1.1 Best Corrected Visual Acuity

Visual Acuity examiners and VA lanes at study centers must be certified to ensure consistent measurement of BCVA prior to start of study.

Refraction and VA testing will be assessed by a certified masked visual acuity examiner using an ETDRS chart **prior to any ophthalmic assessments**. VA should only be performed by site personnel with active certification by the site certification vendor and must be a different person than the Investigator administering the IVT injections. Visual Acuity will be assessed with ETDRS charts. Please refer to the VA Specifications for full details. Patient must use the same chart consistently from Screening to Week 56 (Visit 9). Visual Acuity testing must be performed before dilation of pupils and FP/FA and OCT assessment.

A decrease in VA of ≥ 15 letters from the last assessment of VA should be reported as AEs/Serious Adverse Events (SAEs) as appropriate.

If the event meets 1 or more of the following criteria, it should be reported as SAE.

- A decrease in VA of ≥ 30 letters from the last assessment of VA;
- A decrease in VA to the level of light perception or worse.

9.1.2 Ophthalmological Examination

The ophthalmological examination will consist of an external examination of the eye and adnexa routine screening for eyelid/pupil responsiveness (including but not limited to blepharoptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light, and afferent pupillary defect), slit lamp exam, indirect ophthalmoscopy, and IOP measurements.

Grading scales for slit lamp exam are provided in [redacted].

9.1.2.1 Slit Lamp Exam

The slit lamp exam (cornea, lens, iris, aqueous reaction [cells and flare]) will be performed on both eyes at Screening, Visit 7, and EOS Visit and on the SE at each other IVT administration visit until Week 56 (Visit 9) Visit. At the dosing visits, slit lamp exam should be performed prior to IVT injection by a masked Investigator. Anterior segments will be assessed with the slit lamp.

9.1.2.2 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed on both eyes at Screening, Visit 7, and EOS Visit and on the SE at each other IVT administration visit until Week 56 (Visit 9) prior to the IVT injection by a masked Investigator. The fellow eye will be followed to determine if wet AMD develops.

The posterior segment will be examined after dilation of pupil with 2 to 3 drops of phenylephrine-tropicamide (or any other mydriatic drug), applied topically to the eye.

The posterior segment assessment method can be performed using 1 of the 2 methods at the discretion of the PI and must remain consistent for a patient throughout the study: (1) indirect ophthalmoscopy at the slit lamp with a lens for indirect ophthalmoscopy (e.g. 90D) or (2) indirect binocular ophthalmoscopy (performed with a head mounted indirect binocular ophthalmoscope and a lens, e.g. 20D).

9.1.2.3 Tonometry

IOP will be measured on both eyes at Screening, Visit 7, and EOS Visit and on the SE at each other IVT administration visit until Week 56 (Visit 9) prior to the IVT injection by a masked Investigator and within 30 to 60 minutes after the injection either by the unmasked IVT administrator or the masked Investigator.

IOP must be measured using Goldmann applanation tonometry at Screening. The Tonopen or Perkins Tonometer may be used at other times in each patient after Screening. The method used for the IOP measurement for a patient could be performed at the discretion of the PI and must remain consistent throughout the study. However, Goldmann applanation tonometry must be used to verify any IOP $\geq$ 30 mmHg.

9.1.3 Color Fundus Photography and Fluorescein Angiography

Color FP and FA will be performed by a masked Investigator on both eyes at Screening, Visit 7 (prior to the IVT administration), and EOS Visit and the images will be sent to the central reading center within 72 hours.

Color FP and FA will also be performed on the SE prior to IVT injection of IMP at Visit 5. The images will be sent to the central reading center within 72 hours. Additional FA may be performed at any time at the discretion of the Investigator(s).

At least 1 site staff performing FA/FP must be certified by the central reading center before study start at the site.

Only FP/FA devices certified by central reading center should be used. If 1 or more FP/FA devices are certified in a study center, sites should use the same FP/FA device consistently from Screening to EOS Visit for a patient.

All original FP/FA images will be kept at the investigational site and copies will be sent to the central reading center for analysis and archiving within 72 hours. A detailed protocol for FP/FA image acquisition and transmission will be provided in the Imaging Manual.

If any significant change in the posterior pole (e.g. subretinal hemorrhage, macular hole, vitreous hemorrhage or opacity, retinal detachment, etc.) is detected with fundus examination, additional FP and/or FA can be performed at the Investigator's discretion, and images will be sent to the central reading center within 72 hours.

9.1.4 Spectral Domain Optical Coherence Tomography (SD-OCT)

The SD-OCT will be performed on both eyes at Screening, Visit 7, and EOS; the SE will be examined at each other IVT administration visit until Week 56 (Visit 9) prior to IVT injection of IMP.

At least 1 site staff who will perform SD-OCT scans in this study must be certified by the central reading center before study start at the site.

The SD-OCT devices registered in a study center should meet the minimum requirements (including software) as defined in the Imaging Manual. The site should use the OCT devices registered by central reading center during the study period. The site should use the same device throughout the study for a patient; if there is more than 1 device approved at the site and/or the primary is going out of order, any of them can be used.

All original SD-OCT images will be kept at the study center and copies will be sent to the central reading center for analysis and archiving within 72 hours. A detailed protocol for SD-OCT image acquisition and transmission will be provided in the Imaging Manual.

9.1.5 National Eye Institute Visual Function Questionnaire (NEI VFQ-25)

Vision-related Quality of Life will be assessed by a masked Investigator using NEI VFQ-25 [redacted] questionnaire. NEI VFQ-25 should be performed at Week 0 (Visit 1) prior to randomization, and at Visit 5, Visit 7, and EOS Visit. NEI VFQ-25 should be performed prior to any ophthalmic procedures or any other assessments.

All questionnaires will be administered in the local language. The Investigator or delegated site staff will conduct a questionnaire survey with the patient. The results of the questionnaire will be recorded in a paper questionnaire and then entered into the eCRF.

9.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

9.2.1 Physical Assessment

Physical assessment will be performed at Screening, at Visit 5 and Visit 7 prior to IVT injection of IMP and at EOS Visit by a masked Investigator. The patients will be examined before any blood sample collection on the same day. A safety check will be performed within 60 minutes post-IVT.

All patients will undergo verbal health status assessments. Additionally, at any time, other physical assessments may be performed at the Investigators' discretion.

The assessment will consist of a routine interrogation of the patients' general health. The assessment is divided into 9 categories: general appearance; head, eye, ear, nose, and throat (HEENT); chest; cardiovascular; abdominal; genitourinary; musculoskeletal; skin; and neurological. The findings will be recorded as either "normal" or "abnormal" for each category and any abnormal findings will be described.

9.2.2 Vital Signs

Vital signs will be assessed at Screening, at Visit 5 and Visit 7 prior to IVT injection of IMP and at EOS Visit. The patients will be examined before any blood sample collection on the same day. The Investigator should assess all vital signs and any clinically significant abnormalities should be reported as AE.

The following vital signs will be assessed:

- Body temperature, pulse rate, blood pressure.
- Blood pressure and pulse measurements will preferably be assessed with an automated device. Manual techniques will be used only if an automated device is not available.
- Vital signs will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute) in supine position after at least 5 minutes of rest in supine position. The average of the 3 blood pressure readings will be recorded in the CRF.

9.2.3 Clinical Safety Laboratory Assessments

Blood (approximately 30 mL) and 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. Blood and urine sampling for clinical laboratory test will also be collected at any time during the Visit at EOS Visit. Urine samples must be collected before performing FA (when applicable) to avoid false elevations in urine protein values.

Blood samples will be analyzed in central laboratory and urine samples will be tested at each study center by using a dipstick which will be provided by the Sponsor. A detailed process for clinical laboratory sampling, handling, storage and shipping will be provided in the Central Laboratory Manual for safety laboratory testing.

- See [redacted] for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The masked Investigator must review the laboratory report as soon as possible but prior to the next IVT administration visit, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline values of Visit 1 or are no longer considered clinically significant by the Investigator or Medical Monitor.
    - If such values do not return to normal/baseline values of Visit 1 within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in [redacted], must be conducted in accordance with the Laboratory Manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (e.g. SAE, AE, or dose modification), then the results must be recorded in the CRF.

9.2.4 Pregnancy and Follicle Stimulating Hormone Tests

Serum pregnancy and FSH tests must be performed for all women at Screening. The serum samples taken at Screening will be analyzed in the central laboratory.

Additional serum or urine pregnancy test can be performed at each study center during the study period, if necessary (at the Investigator's discretion).

Deleted pregnancy test result at Screening, such as handling error, lost/damaged during shipment, sampling error or tube breakage, should be followed by re-test. Result of re-test will be considered as that of an initial.

9.2.5 3-Day Post-IVT Injection Telephone Safety Check

The study center staff will call the patient for an AE assessment 3 days after each IVT injection to determine if there are any signs and symptoms of potential complications of the IVT injections such as but not limited to endophthalmitis, retinal detachment, etc. If a potential AE is suspected, the masked Investigator or delegated staff member will be responsible for further patient assessments and treatment, if applicable.

9.3 Adverse Events

The definitions of an AE or SAE can be found in [redacted].

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following-up AEs. The Investigator should follow up each AE until the event has resolved completely or to the baseline values of Visit 1, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported. If after follow-up (Week 56), complete recovery, return to baseline status, or stabilization cannot be established, an explanation should be recorded on the AE eCRF.

During the study period, resolution of AEs (with dates) should be documented in the patient's medical records to facilitate source data verification and in the Adverse Event eCRF page. If, after follow-up, complete recovery, return to the baseline values of Visit 1 or stabilization cannot be established, an explanation should be recorded in the AE eCRF page. (Section 8).

9.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until Week 56 (Visit 9; EOS/Early Termination) Visit, at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before ICF signature will be recorded on the Medical History/Current Medical Conditions section of the CRF, not in the AE section.

All SAEs will be recorded and reported to the [redacted] Lifecycle Safety within 24 hours of awareness, as indicated in [redacted]. The Investigator will submit any updated SAE data or follow-up information to the [redacted] Lifecycle Safety within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the [redacted] Lifecycle Safety.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in [redacted].

9.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient by a masked Investigator is the preferred method to inquire about AE occurrences.

9.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in [redacted].

9.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the [redacted] Lifecycle Safety of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor and [redacted] Lifecycle Safety will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor or [redacted] Lifecycle Safety policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SUSAR or other specific safety information (e.g. summary or listing of SUSARs) from the [redacted] Lifecycle Safety will review, document the review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5 Pregnancy

- Details of all pregnancies in female patients and, if indicated and a respective ICF was signed, female partners of male patients will be collected after the start of study treatment and until Week 56 (Visit 9).
- If a pregnancy is reported, the Investigator should inform the [redacted] Lifecycle Safety within 24 hours of learning of the pregnancy and should follow the procedures outlined in [redacted].
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.3.6 Adverse Events of Special Interest

The following AEs in the SE will be classified as Adverse Events of Special Interests (AESIs) in this study:

- Any case of new onset IOP of > 21 mmHg that does not respond to treatment, except the transient pressure rise observed within an hour after IVT injection of IMP;
- Any case of IOP ≥ 35 mmHg, at any time, that required treatment;
- Any case of intraocular infection such as endophthalmitis;
- Any case of intraocular inflammation such as iritis, vitritis, and iridocyclitis;
- Iatrogenic traumatic cataract;
- Arterial thromboembolic events defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death;
- Death of unknown cause.

9.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in patients with wet AMD and can be serious:

- Macular hemorrhage
- Macular edema

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. These events will be recorded on the corresponding CRF page in the patient's CRF within the appropriate time frame. These DREs will be monitored by a DMC on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual patient.*
  OR
- *The Investigator considers that there is a reasonable possibility that the event was related to study treatment.*

9.4 Plasma Concentration

Blood samples for plasma concentration evaluation will be collected in approximately 60 patients (30 patients per arm) participating in plasma concentration evaluation.

The sites which are interested in taking part in the plasma concentration evaluation will be selected before the study starts. Patients screened at these sites will be asked to participate in the plasma concentration sub-study. If the patient consents to the blood sampling, the patient will be recruited in this sub-study. When the expected number of patients in the plasma concentration sub-study is reached, no more plasma concentration patients will be recruited.

Blood samples of approximately 24 mL will be collected for measurement of plasma concentrations of systemic free and total aflibercept as specified in the SoA at Week 0 (Visit 1) prior to 1st IVT dose, 48 hours after 1st IVT dose (Visit 1a) close to C_{max}, and at 48 hours after the 3rd IVT dose (Visit 3a) close to C_{max}. In case of a delayed IVT dose the collection of blood for plasma concentration assessment should be postponed accordingly to keep the required time intervals (48 hours) between IVT dose and sample collection. Concentrations of free and total aflibercept will be measured using a validated assay by the central laboratory. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded in the eCRF. The exact time and date of study treatment administration will also be recorded.

A detailed process of plasma concentration sampling, handling, storage, and shipping will be provided in the Laboratory Manual.

9.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6 Genetics

Genetics parameters are not evaluated in this study.

9.7 Immunogenicity Assessments

Anti-drug antibodies (ADAs) to aflibercept will be evaluated in serum samples collected from all randomized patients according to the SoA (Section 1.3). Blood samples of approximately 26 mL will be collected for measurement of ADAs. To note, the plasma concentration subgroup will have additional ADA samples collected, (resulting in a total of 34 mL) as described in the SoA

(Section 1.3). In case of a delayed IVT dose the collection of blood for ADA assessment should be postponed accordingly to keep the required time intervals between IVT dose and sample collection.

Additionally, serum samples should also be collected at the Early Termination Visit from patients who discontinued study treatment or were withdrawn from the study.

The exact date and time of sample collection will be recorded in the eCRF. Serum samples will be screened for ADA and the titer of confirmed positive samples will be reported, as well as assessment of neutralizing antibodies (nAbs).

The detection and characterization of ADA will be performed using a validated assay method.

A detailed process for immunogenicity sampling, handling, storage, and shipping will be provided in the Laboratory Manual.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

The test for equivalence will be performed with respect to FYB203 versus Eylea.

The following hypotheses will test the null hypothesis for nonequivalence against the alternative hypothesis of equivalence:

$$H_0: |\mu_{FYB203} - \mu_{Eylea}| \geq 3.5$$

$$H_A: |\mu_{FYB203} - \mu_{Eylea}| < 3.5$$

where μ_{FYB203} is the mean change from Baseline to Week 8 in BCVA, measured in ETDRS letters, for patients randomized to receive FYB203 and μ_{Eylea} is the mean change from Baseline to Week 8 in BCVA, measured in ETDRS letters, for patients randomized to receive Eylea.

10.2 Sample Size Determination

Originally 400 patients were planned to be randomized [redacted]. However, actual number of patients randomized are 434 [redacted].

The total sample size of approximately 400 randomized patients has been calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 9.0 ETDRS letters in BCVA. The calculation considers that overall, an application of a two-sided 90% CI for the US and a two-sided 95% CI for the EU is required for assessing biosimilarity and that consistency between analyses based on the Full Analysis Set (FAS) and the Per Protocol Set (PPS) is required for a conclusion of bioequivalence of FYB203 and Eylea.

An equivalence test of means using two one-sided tests with sample sizes of 180 patients in both treatment groups achieves at least 90.3% power at a 2.5% significance level when there is no true difference between the means, the SD is 9.0, and the equivalence interval is]-3.5; 3.5[letters. Three hundred and sixty patients overall are thus an adequate sample size for the PPS analysis; if a difference of 10% between the FAS and the PPS is assumed, it is required to randomize 400 patients for the FAS.

Applying the US criterion for assessing biosimilarity, the equivalence test of means using two one-sided tests with sample sizes of 144 in both treatment groups (288 patients in total) achieves 90.0% power at a 5.0% significance level when no difference between the means is assumed, the SD is 9.0, and the equivalence interval is]-3.5; 3.5[letters. Assuming a difference of 10% between the PPS and the FAS, 320 patients in total should be included in any US-specific analysis.

Further, the change of FCP retinal thickness at Week 4 (Visit 2) compared to Baseline Visit (Visit 1), shall be evaluated as a key secondary endpoint for EU/Japan regulatory submissions. The sample size of 200 patients in each treatment group (400 patients in total) provides a power of 82.8% at a 2.5% significance level (e.g. a two-sided 95% CI) when the true difference between the means is 0, the SD is 135 µm and the equivalence interval is [-45.0; 45.0] µm.

The fixed sample size described above could have been increased following the interim masked review of sample size after the first 200 treated patients had completed Week 8 (Visit 3) up to a maximal sample size of 640 patients for the US analysis and a maximum sample size of 800 patients for the EU analysis, see Section 10.5. This interim masked review of sample size was performed in November 2021 and revealed that the observed variability overall does not require an increase in sample size to maintain the intended statistical power of 90% for the primary endpoint, and of 80% for the key secondary endpoint (EU/Japan only).

The interim masked review of sample size (Section 10.5) however, may increase the type 1 error rate (22). Simulation results using the US criterion suggest that for true SDs of the change in BCVA lower than about 12 letters, an interim analysis after 200 patients, a maximal sample size of 640 patients and a target power of 90% for the US analysis based on the PPS, a slight increase of the type one-error rate may occur. Therefore, an adjusted significance level of 4.8%, corresponding to a two-sided 90.4% confidence interval (CI) will be used in the US-specific analysis, which was shown to keep the overall type 1 error of the US-specific analysis below 5%. Similarly, simulation results using the EU/Japan criterion, when the interim analysis is performed after 200 patients, the maximal sample size is 800 patients and the target power is 90% for the primary endpoint based on the PPS and 80% for the key secondary endpoint based on the FAS, show that an alpha of 2.4% ensures the overall type 1 error in the EU/Japan-specific analysis to not be higher than 2.5%. Therefore, 2-sided 95.2% CIs for the difference between the two treatment arms will be used in the EU/Japan-specific analysis.

The US-and EU/Japan-specific analyses will be performed sequentially. Only if the US-specific analysis based on the first 320 treated patients (or the adapted sample size for the US analysis) shows bioequivalence using the 4.8% significance level, then EU/Japan-specific analysis based on the bigger sample size of all treated patients will be performed, using a 2.4% significance level. Bioequivalence with respect to the key secondary endpoint will only be assessed if bioequivalence with respect to the primary efficacy endpoint has been shown. Therefore, no inflation of the overall type 1 error due to multiple testing can occur.

10.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 3 are defined.

Table 3 Analysis Sets

Analysis Set	Description
FAS	All patients randomly assigned to study treatment who receive at least 1 injection of study treatment in the study eye. Patients will be analyzed according to the study treatment they have been randomized to.
PPS	All patients included in the FAS who have no major protocol deviations until Week 8 that will interfere with the interpretation of the BCVA efficacy data at Baseline or at Week 8 and have received treatment from the randomized treatment group only, and have a valid measurement of the BCVA at Baseline and at Week 8 available.
Safety Analysis Set	All patients who receive at least 1 injection of study treatment in the SE. Patients will be analyzed according to the treatment they actually received in the SE.
Plasma concentration Analysis Set	All patients randomly assigned to study treatment, who receive at least 1 dose of study treatment in the SE and who have at least 1 valid post-dose plasma concentration measurement. Patients will be analyzed according to the treatment they actually received in the SE.

FAS = Full Analysis Set; PPS = Per Protocol Set.

10.4 Statistical Analyses

The SAP(s) will be developed and finalized before the first unmasked analysis is performed.

The following analyses are planned on unmasked data:

The final US analysis, which is intended for the US regulatory submission (Biologics License Application [BLA]), is planned to be performed when the **first** 320 treated patients have completed 40 weeks of treatment (or discontinued the study prematurely) and all randomized and treated patients have completed the primary efficacy endpoint assessment at Week 8 (or discontinued the study prematurely).

Due to the geopolitical situation in Ukraine in 2022, more patients than the originally planned **first** 320 treated patients may be included in the US analysis. The exact number of patients will be determined prior to providing any access regarding treatment unmasking information to any

personnel involved in the analysis of this data and will depend on the extent of missing treatments with study medication, and possibly missing information related to safety and efficacy assessments in affected sites and patients. Patients to be included in the US analysis will be chosen based on the exact sequence of the first treatment UTC date/time. Formal records on this decision will be kept in the blind data review meeting minutes together with time points of decision and partial unmasking.

The main EU analysis intended for initial regulatory submission in EU is planned when all randomized and treated patients have completed 24 weeks of treatment or have discontinued the study prematurely.

The final EU/Japan analysis intended for the EU and Japan regulatory submissions is planned when all randomized and treated patients have completed the whole study period of 56 weeks or discontinued the study prematurely.

The decisions on inclusion or exclusion of any patient into any of the analysis sets and on inclusion into the US analysis will be finalized prior to the US analysis (i.e. the first unmasked analysis), and will be documented in the blind data review meeting minutes. Only patients included in the US analysis will be unmasked for the pre-defined group of persons and functions who will have access to the results of the analysis.

Updates on protocol deviation listings and intercurrent events will be provided for EU/Japan analysis and report, but the allocation of each patient to the analysis sets will not change after the first unmasked analysis.

Prior to the US analysis, the first unmasked analysis, a database lock will be performed on all data up to and including at least the Week 40 visit for all randomized and treated patients planned to be included in the US analysis and for all data until the individual last visit up to the cut-off date for all other randomized and treated patients. A second database lock will be performed for the main EU analysis, including all available data for all treated patients up to the cut-off date (at least up to and including Week 24 visit). At this second database lock, all data from visits that were already performed will be cleaned and locked although some data might not be included in the statistical analysis. The third and final database lock will be performed prior to the final EU/Japan analysis. The data in the EU/Japan analyses is not expected to change compared to the US analysis data and the data in the final EU/Japan analysis is not expected to change compared to the Week 24 EU analysis data. Data from visits performed after data cut-off, new concomitant medication and new AEs might be new; and only stop dates of any ongoing AEs and medications and final outcome of ongoing AE might be subject to change.

Only a restricted number of pre-defined persons not otherwise involved in the direct conduct and management of the study and the study sites, will have access to any unmasking information to perform and review this analysis. All personnel directly involved in the management of sites, patients and data (i.e. Clinical Research Associate [CRA]s, Investigators, study nurses, most

Sponsor personnel, data management) will not have access to any information with respect to the individual treatment group of patients or unblinded summary result; and the medical safety review will be performed by independent masked review personnel.

The following conventions will be used in all planned statistical analyses:

All collected data will be summarized using descriptive statistics by visit (when applicable) and treatment group for the SE and fellow eye separately, unless otherwise specified. Summary statistics will consist of the number of observations, mean, SD, minimum, median, quartiles and maximum for continuous parameters, and number and percent of patients for categorical parameters.

For each eye, baseline value, for each measured parameter, will be defined as the last non-missing, including unscheduled assessments prior to the first injection of study drug, unless otherwise specified.

Individual patient data will be presented in listings.

Statistical analysis will be performed using Statistical Analysis Software (SAS) version 9.4 or higher.

10.4.1 Efficacy Analyses

The FAS will be used for all efficacy analyses. Sensitivity analyses based on the PPS will be performed for the primary and secondary efficacy endpoints (see below). For the final assessment of bioequivalence, it is essential that the analyses of the primary efficacy endpoint based on the FAS and on the PPS as well as other sensitivity analyses yield consistent results.

10.4.1.1 Primary Estimand

The primary estimand is the mean difference between the randomized treatment groups, FYB203 and Eylea for the primary endpoint, i.e. change from Baseline to Week 8 in BCVA, in the SE regardless of treatment adherence and usage of concomitant medications and using data on all patients within the FAS. Also, patients randomized and treated although inclusion or exclusion criteria were violated will be analyzed according to the randomized treatment group.

Any other currently unknown intercurrent events or any possible major protocol deviation in the time between Baseline and Week 8 will be handled in the SAP or the data review prior to database lock for the first unmasked analysis (final US analysis). This estimand is following a treatment policy strategy.

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.

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 SE for all patients for model estimation. Missing data will not be explicity 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 (Visit 5).

The difference in the treatment group least square means and the corresponding two-sided 90.4% and 95.2% CIs will be estimated from the MMRM to address regulatory requirements in the US and the EU/Japan, respectively.

If the respective CI is completely contained in the interval]-3.5; 3.5[ETDRS letters, equivalence of FYB203 and Eylea can be concluded (rounded to the next integer, this corresponds to an equivalence margin of 3 ETDRS letters).

10.4.1.3 Sensitivity Analyses and Supplemental Estimands

Sensitivity analyses of the primary estimand may be defined in the SAP, if appropriate.

A supplemental estimand will be the mean difference between the randomized treatment groups, FYB203 and Eylea in the primary endpoint for the SE, excluding patients from the FAS with major protocol deviations which impact the BCVA assessments until Week 8 (Visit 3).

Another supplemental estimand will be the mean difference between the randomized treatment groups, FYB203 and Eylea in the primary endpoint for the SE, excluding patients from the FAS who discontinue treatment before Week 8 or do not have a Week 8 BCVA assessment.

A further supplemental estimand will be a combination of the 2 estimands mentioned above and will be the mean difference between the randomized treatment groups, FYB203 and Eylea in the primary endpoint for the SE, based on the PPS.

Other supplemental estimands, which will impute the BCVA hypothetically of those patients excluded from the PPS as if the intercurrent event had not happened will be considered in addition and finally described in the SAP.

The supplemental estimands will be assessed using the same methods described for the primary analysis.

Further supplemental estimands and sensitivity analyses of the supplemental estimands may be defined in the SAP, if appropriate. All supplemental estimands and sensitivity analyses will be performed using appropriate CIs.

10.4.1.4 Analysis of Secondary Endpoints

The secondary endpoint of change in FCP retinal thickness from Baseline to Week 4 will be analyzed in a similar way as the primary endpoint using the equivalence interval from [- 45; 45] µm. The difference in the treatment group least square means and the corresponding two-sided 95.2% CI will be estimated from the MMRM using all patients in the FAS. If the two-sided 95.2% CI is completely contained in the equivalence interval [-45; 45] µm, equivalence of FYB203 and Eylea with respect to the FCP retinal thickness can be concluded. This secondary endpoint will be analyzed and reported as key secondary for any report intended for the EMA.

The change from baseline in the SE over time for BCVA, FCP, and FCS retinal thickness and total lesion area will be analyzed using a similar MMRM model than the one used for the primary estimand. The absolute values and the change from baseline for each parameter will also be summarized descriptively by visit and treatment group for all scheduled time points for the SE. Data for the fellow eye will be summarized descriptively.

NEI VFQ-25 total scores will be determined as described in the official manual. The absolute values and the change from baseline for each parameter will also be summarized descriptively by visit and treatment group for the SE and fellow eye separately.

The proportion of patients who gain or lose ≥ 5, 10 or 15 ETDRS letters and the percentage of patients with fluid-free macula at each visit, based on all patients with relevant evaluations at each given visit, will be presented in descriptive summary tables.

Statistical tests of secondary endpoints will be exploratory in nature and reported with nominal p-values. For differences or ratios between the treatment groups, two-sided 95% and possibly 90% CI will be provided as appropriate.

10.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

Treatment-emergent adverse events (TEAEs) are defined as AEs that first occurred or worsened in severity after the first administration of study treatment.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, numbers of ocular TEAEs and incidence rates will be tabulated by preferred term, system organ class, and treatment group for the SE and FE separately. Number of non-ocular TEAEs and incidence rates will be tabulated by preferred term, system organ class, and treatment group.

Similarly, ocular and non-ocular TEAEs by maximum severity, TEAEs by relationship to study treatment, SAEs and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group.

All laboratory test results, vital signs measurements will be summarized using descriptive statistics at each visit for absolute values and change from baseline.

10.4.3 Other Analyses

10.4.3.1 Plasma Concentrations

Concentrations of free and total systemic aflibercept will be listed, summarized, and presented graphically by treatment and time point as appropriate. No plasma concentration parameters will be estimated.

Concentration summaries will be based on the plasma concentration analysis set.

Concentrations that are below the lower limit of quantitation will be set to 0 for the computation of descriptive statistics.

Further details will be provided in the SAP.

10.4.3.2 Immunogenicity

Immunogenicity ADA results (positive, negative, and titer, and if appropriate, nAbs result), will be listed by patient and sampling time.

The number and proportion of patients with positive and negative ADA will be summarized by treatment group and sampling time.

10.4.4 Subgroup Analyses

Subgroup analyses will be defined in the SAP in all details.

10.5 Interim Analyses

No formal interim analyses for efficacy are planned; however, an interim masked review of sample size was planned after the first 200 treated patients reached the Week 8 time point. This interim analysis was planned to safeguard the study from a power loss due to a possible higher variability of more than the assumed SDs of 9.0 EDTRS letters in BCVA or of 135 µm in FCP retinal thickness

Variability of the primary endpoint and of the EU-specific key secondary endpoint was estimated as the common covariance from the MMRM model used for the primary analysis, but with the treatment and treatment-by-time interaction terms excluded. This was used to calculate the conditional power for the study to show bioequivalence using the formula as described in Friede 2003 (22). A target power of 90% to show bioequivalence is intended for the primary efficacy endpoint for the PPS and a target power of 80% for the EU-specific key secondary endpoint of FCP retinal thickness for the FAS.

An independent statistician who will otherwise not be involved in the planning and performance of the statistical analysis of the study data performed the calculations and provide recommendations on possible sample size adaptations. The recommendation followed the following rules:

i) The total sample size shall not be lower than the currently planned 320 or 400 patients.

ii) If the target power is reached for US and the EU/Japan the total sample size will not be changed.

iii) If the conditional power for the equivalence testing at the time of the interim analysis will be lower than the target power based on the observed results, then the statistician will recommend to increase the sample size for the US analysis to reach at least a power of 90% for a 4.8% significance level for the PPS (assuming 10% of patients will be excluded from the FAS). For the EU analysis at least a 90% power for a 2.4% significance level for the primary efficacy endpoint for the PPS and of 80% for a 4.8 significance level for the key secondary endpoint for the FAS shall be reached. These calculations assume that the observed overall SDs reflect the true SDs of the population and no difference between the two treatment groups.

iv) If this power can only be reached by including more than 640 for the US analysis or 800 patients for the EU/Japan analysis overall, the recommendation will indicate this fact and the Sponsor will stop the study.

This interim masked review of sample size was performed in November 2021 and revealed that the observed variability overall does not require an increase in sample size to maintain the intended statistical power of 90% for the primary endpoint, and of 80% for the key secondary endpoint (EU/Japan only).

10.6 Data Monitoring Committee

A DMC consisting of members who are independent from the Sponsor will be established. The DMC membership will have 5 members, including 4 specialists with expertise in Ophthalmology and an independent statistician, as appropriate. The DMC is responsible for reviewing and evaluating masked safety data collected at regularly scheduled meetings. The details of the safety data and time points for review will be described in the DMC Charter. The committee may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. The DMC will be responsible for making recommendations as to whether it is scientifically and ethically appropriate to continue recruitment or stop the study.

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