CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761378Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW FOR BLA 761378

Application Type	BLA 351(k)
Application Number	BLA 761378
PIND Number	IND 144550
Received Date	June 28, 2023
BsUFA Goal Date	June 28, 2024
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Review Completion Date	See DARRTS stamped date
Product Code Name	FYB203
Proposed Nonproprietary Name[1]	aflibercept-mrbb
Proposed Proprietary Name[1]	Ahzantive
Pharmacologic Class	Vascular endothelial growth factor (VEGF) inhibitor
Applicant	Formycon AG (Formycon)
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Recommendation on Regulatory Action	Approval of FYB203, injection, for intravitreal use as biosimilar to US-Eylea (aflibercept) for the product described below: • 2 mg (0.05 mL of 40 mg/mL) in a single-dose vial (vial) as biosimilar to US-Eylea 2 mg (0.05 mL of 40 mg/mL) in a vial kit and single-dose pre-filled syringe (PFS). (b) (4)

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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Reviewers of Biosimilar Multidisciplinary Evaluation and Review

DO = Division of Ophthalmology
OSM = Office of Specialty Medicine
OTBB = Office of Therapeutic Biologics and Biosimilars

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CDTL	Rhea Lloyd
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Scientific Reviewers, OTBB	Carol Kim, Pharm.D., Nina Brahme, Ph.D., M.P.H
OTBB Regulatory Project Manager	Wendy Streight, Ph.D.
Pharmacology/Toxicology Reviewer	Muriel Saulnier / Kim Hatfield
Statistical Reviewer	Martin Klein/ Jessica Kim
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OPDP Reviewer	Carrie Newcomer
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Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
AMD	Age-Related-Macular Degeneration
BCVA	Best Corrected Visual Acuity
BLA	Biologics License Application
BOCF	Baseline Observation Carried Forward
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFB	Change from Baseline
CFR	Code of Federal Regulations
CFT	Central Foveal Thickness
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CMH	Cochran-Mantel-Haenzel
CNV	Choroidal Neovascularization
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DP	Drug Product
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
eCTD	Electronic Common Technical Document
ETDRS	Early Treatment Diabetic Retinopathy
EU-Lucentis	EU-approved Lucentis
FA	Fluorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFAS	FDA Full Analysis Set
FISH	Fluorescence In Situ Hybridization

GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
ICH	International Conference on Harmonization
IE	Intercurrent Event
IND	Investigational New Drug
ITT	Intention to Treat
IVT	Intravitreal
IWRS	Interactive Web Response System
LLOQ	Lower Limit of Quantitation
LOCF	Last Observation Carried Forward
LS	Least Square
MAPP	Manual of Policy and Procedure
MAR	Missing at Random
mCNV	Myopic Choroidal Neovascularization
mITT	Modified Intention to Treat
MI	Multiply Imputed
MMRM	Mixed Effects model with Repeated Measures
MOA	Mechanism of Action
NAb	Neutralizing Antibody
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NCT	National Clinical Trial
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OCT	Optical Coherence Tomography
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedures

TEAE	Treatment-Emergent Adverse Events
ULOQ	Upper Limit of Quantitation
US-Lucentis	U.S.-licensed Lucentis
VEGF	Vascular Endothelial Growth Factor

1. Executive Summary

1.1. Product Introduction

FYB203 (Ahzantive, aflibercept-mrbb) is a recombinant fusion protein consisting of portions of human vascular endothelial growth factor (VEGF) receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 developed as a proposed (b) (4) biosimilar to US-licensed Eylea (US-Eylea). US-Eylea acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF), and thereby can inhibit the binding and activation of these cognate VEGF receptors.

The Applicant is seeking licensure for FYB203 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial (b) (4) US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS. A 2 mg (0.05 mL of 40 mg/mL) dose is for the following indications which are the same as those previously approved for US-Eylea[2]:

- Neovascular (wet) age-related macular degeneration (AMD): 2 mg (0.05 mL of 40 mg/mL) solution to be administered by intravitreal injection every 4 weeks (approximately 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL of 40 mg/mL) via intravitreal injection once every 8 weeks (2 months).

- Macular edema following retinal vein occlusion (RVO): 2 mg (0.05 mL of 40 mg/mL) solution to be administered by intravitreal injection every 4 weeks (approximately every 25 days, monthly).

- Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR): 2 mg (0.05 mL of 40 mg/mL) solution to be administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL of 40 mg/mL) via intravitreal injection once every 8 weeks (2 months).

The strength, dosage form, route of administration, indications, and dosing regimens for FYB203 will be the same as those of US-Eylea, 2 mg (0.05 mL of 40 mg/mL) solution.

The applicant is not seeking licensure for Retinopathy of Prematurity (ROP) (b) (4)
(b) (4)

[2] U.S. Prescribing Information, US-licensed Eylea, approved 12/14/23, under BLA 125387/S-84. Accessed April 30, 2024 from : https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s084lbl.pdf

(b) (4)

1.2. Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

Not applicable.

1.3. Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

This BLA contains sufficient data and information to demonstrate that FYB203 and US-Eylea utilize the same mechanism of action (MOA) to the extent known for the proposed neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic retinopathy (DR), diabetic macular edema (DME) (b) (4) indications. FYB203 binds to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to contribute to retinal neovascularization and retinal leakage. The binding of FYB203 to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

To support the demonstration that FYB203 is highly similar to US-Eylea, the applicant performed a comparative analytical assessment of FYB203 and US-Eylea. The comparative analytical assessment data provided support for the conclusion that FYB203 is highly similar to US-Eylea. FYB203 has the same mechanism(s) of action as that of US-Eylea.

US-Eylea is licensed in 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and in a PFS. The applicant is seeking licensure of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial. The route of administration (ROA), dosage form, and the strength of the proposed product are the same as that of the US-reference product.

The condition(s) of use for which the applicant is seeking licensure have been previously approved for US-Eylea.

[3] U.S. Prescribing Information, US-licensed Eylea, approved 12/14/23, under BLA 125387/S-84. Accessed April 30, 2024 from : https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/125387s084lbl.pdf

1.4. Inspection of Manufacturing Facilities

All facilities used for the manufacture and quality control testing were acceptable. On-site pre-licensing inspections (PLIs) for the DS manufacturing facility (b) (4) (b) (4) and the DP manufacturing facility (b) (4) were conducted in (b) (4) and (b) (4), respectively. Both PLIs were classified as "Voluntary Action Indicated (VAI)", and the responses to FDA Form 483 were satisfactory. Thus, per Office of Biotechnology Product's BLA executive Summary Assessment dated 5/8/2024, this BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

The following facilities were inspected and found to be in compliance with cGMPs:

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)			Approve - Based on Inspection
			Approve - Based on Inspection

1.5. Scientific Justification for Use of a Non-U.S.-Licensed Comparator Product

The comparative analytical data provided by the Applicant established the scientific bridge between FYB203, US-Eylea, and EU-approved Eylea (EU-Eylea), which justifies the relevance of comparative data generated using EU-Eylea to the assessment of biosimilarity.

1.6. Biosimilarity (b) (4) Assessment

Table 1: Summary and Assessment of Biosimilarity

Comparative Analytical Studies[4]	
Summary of Evidence	• FYB203 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components. • The comparative analytical data establish the scientific bridge that justifies the relevance of comparative data generated using EU-Eylea to the assessment of biosimilarity. • FYB203 (2 mg (0.05 mL of 40 mg/mL) in a single dose vial is the same strength as US-Eylea in a vial kit and PFS. • The dosage form and route of administration is the same as that of US-Eylea.
Assessment of Residual Uncertainties	• There are/are no residual uncertainties from a product quality perspective.
Animal/Nonclinical Studies	
Summary of Evidence	• The nonclinical development program of FYB203 was focused on *in vitro* assays including inhibition of VEGF-A165 induced VEGFR-2 dimerization (potency), endothelial cell proliferation, target binding, and Fc receptor binding/activity, to confirm its nonclinical similarity to US-Eylea in terms of biological activity. • Animal studies were not required to support this 351(k) application. • The information relating to toxicity supports the demonstration of biosimilarity.
Assessment of Residual Uncertainties	• There are no residual uncertainties.
Clinical Studies	
Clinical Pharmacology Studies	

[4]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter therein for additional information regarding comparative analytical studies.

Summary of Evidence	• Systemic exposure of FYB203 and EU-Eylea was evaluated in a subset of subjects with neovascular AMD (nAMD) in study FYB203-03-01. Comparable systemic exposure between FYB203 and EU-Eylea based on descriptive analysis supports a demonstration that there are no clinically meaningful differences between FYB203 and US-Eylea. • Comparable incidence of ADA/Nab formation between FYB203 and EU-Eylea in patients with nAMD supports a demonstration that there are no clinically meaningful differences between FYB203 and US-Eylea.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective.
Additional Clinical Studies	
Summary of Evidence	• In Study FYB203-0301, the study eye was treated with either FYB203 or EU-Eylea in subjects with neovascular AMD. The study was a randomized, active-controlled, double-masked, multicenter, comparative clinical study with a total of 433 subjects treated. There were no meaningful differences in terms of efficacy or safety. The data from this study support a demonstration of no clinically meaningful differences between FYB203 and US-Eylea.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or clinical statistical perspectives.
[redacted] (b) (4)	
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	

Summary of Evidence	The Applicant has provided adequate data and information, including analytical and clinical data, to support a demonstration that FYB203 can be expected to produce the same clinical result as that of US-Eylea in any given patient.
Assessment of Residual Uncertainties	There are no residual uncertainties from the clinical perspective.
Extrapolation	
Summary of Evidence	• The information submitted in the original BLA supports a demonstration that FYB203 and US-Eylea are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. • The data and information provided by the Applicant are sufficient to demonstrate that FYB203 can be expected to produce the same clinical result as US-Eylea in any given patient (b) (4) [redacted] • Division of Ophthalmology (DO) has determined that the Applicant has provided adequate scientific justification and agrees with the applicant's justification for extrapolation to the other indications listed in the US-Eylea package insert being sought for licensure based on: 1) the mechanism of action of aflibercept, including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, diabetic macular edema, diabetic retinopathy and retinopathy of prematurity by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known

	safety and immunogenicity profiles of aflibercept across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication. • The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of FYB203 as (b) (4) biosimilar to US-Eylea for the following indications for which US-Eylea has been previously approved: ○ Neovascular (Wet) Age-Related Macular Degeneration (AMD) ○ Macular Edema Following Retinal Vein Occlusion (RVO) ○ Diabetic Macular Edema (DME) ○ Diabetic Retinopathy (DR) (b) (4)
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.

1.7. Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB203 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB203 and US-Eylea in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that FYB203 can be expected to produce the same clinical result as US-Eylea in any given patient (b) (4)

Therefore, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrate that FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial is biosimilar to (b) (4) US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS for each of the following indications for which US-Eylea has been previously approved and for which the Applicant is seeking licensure of FYB203:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)

Healthcare providers administer US-Eylea to all patient populations using either a vial kit (single-dose glass vial co-packaged with injection components) or a single-dose PFS. While we note that US-Eylea is currently labeled only for use as a vial kit and a PFS, (b) (4)

The review team recommends (b) (4) an Approval for FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

(b) (4)

This BLA has been administratively split so that the Approval of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS will remain in BLA 761378/Original 1. BLA 761378/Original 1 will receive an Approval letter.

(b) (4)

2. Introduction and Regulatory Background

2.1. Summary of Presubmission Regulatory History Related to Submission

The Applicant sought guidance on the development program under Pre-Investigational New Drug Application (PIND) 144550 and under drug code name FYB203. ***Table 2*** below provides some highlights from the relevant interactions between FDA and the Applicant during product development for FYB203.

Table 2. Interactions between FDA and Applicant for FYB203 development

Date	Interaction Type	Comment/ Recommendations
9/11/2019	BPD Type 2	-Discussed the design of the PK subgroup analysis, including the number of nAMD patients for evaluation of study drug in plasma concentration
7/24/2020 (initial) 12/7/2020 (agreed)	IPSP	-An Initial Pediatric Study Plan was submitted on July 24, 2020 -Agreed iPSP was submitted under PIND 144550 on December 7, 2020 and included in BLA submission
3/1/2021	BPD2 Type 2	-Discussed timelines for filing of a prospective 351(k) BLA for FYB203 with regard to exclusivity protection of US-Eylea - (b) (4)
5/18/2022	Advice Letter	-FDA sent an advice letter stating that (b) (4)
2/15/2023	BPD Type 4	-Discussed (b) (4) comparative analyses -Discussed the content of a complete initial BLA submission and agreed on the data which may be submitted in the 120-day safety update.

2.2. Studies Submitted by the Applicant

Table 3. Listing Submitted Animal Studies

Species/ Strain	Study Number	MoA	Duration of Dosing	Test Substance and Dose (mg/eye)*	Testing Facility
Animal Studies					
Rabbit/ New Zealand White	F21D03018	Intravitreal	3 weeks	FYB203 (F18198); 2 mg/mL EU-Eylea (72477C): 2 mg/mL	(b) (4)
Rabbit/ New Zealand White	F21DE24318	Intravitreal	1 week	FYB203 (F18146): 2 mg/mL FYB203 (F18198): 2 mg/mL FYB203 (180180): 2 mg/mL EU-Eylea (81020C): 2 mg/mL	
Rabbit/ New Zealand White	F21D03118 (35933)	Intravitreal	1 month	FYB203: 2 mg/mL EU-Eylea: 2 mg/mL Placebo FYB203: 0 mg/mL Placebo EU-Eylea: 0 mg/mL	

*bilateral

Table 4. Listing All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study(ies)					
FYB203-03-01	NCT04522167	Comparative PK, efficacy, and safety of FYB203 and EU-Eylea	A comparative clinical study, Double-blind, Parallel-Group, Multi-center (US and international study sites)	434 Subjects with newly diagnosed neovascular macular degeneration	FYB203: 215 (n=31 subset for PK) EU-Eylea: 219 (n=26 subset for PK)

3. Summary of Conclusions of Other Review Disciplines

3.1. Office of Pharmaceutical Quality (OPQ)

Aflibercept is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1. VEGF-A and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes.

Activation of these receptors by VEGF-A can result in neovascularization and vascular permeability. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF, and thereby can inhibit the binding and activation of these cognate VEGF receptors. All potency results are reported as percentage relative to a qualified reference material.

The totality of the CAA evidence supports that FYB23 is highly similar to US-Eylea, notwithstanding minor differences in clinically inactive components. FYB203 2 mg (0.05 mL of 40 mg/mL) in a single dose vial is the same strength as US-Eylea in a vial kit and PFS.

The overall conditions used in the manufacturing process have been adequately validated, and the product has been consistently manufactured from multiple production runs. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from product quality, microbiology, and sterility assurance perspectives.

3.2. Division of Medication Error Prevention and Analysis (DMEPA)

The Applicant's proposed nonproprietary name for FYB203, aflibercept-mrbb, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated March 25, 2024.

The proposed proprietary name for FYB203 is conditionally approved as Ahzantive. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) who concluded the name was conditionally acceptable in a letter to the applicant dated February 9, 2024.

3.3. Office of Study Integrity and Surveillance (OSIS)

Not applicable.

3.4. Office of Scientific Investigations (OSI)

Not applicable.

4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1. Nonclinical Executive Summary and Recommendation

The Applicant submitted the results of 1) one week PK (F21D03018), ocular and systemic exposure/toxicity study following a single intravitreal administration in New Zealand White rabbits, 2) 3-week PK (F21DE24318), ocular and systemic exposure/toxicity study following a single intravitreal administration in New Zealand White rabbits, and 3) 1 month PK (35933), ocular and systemic toxicity study following two intravitreal administration in New Zealand White rabbits.

From a nonclinical perspective, because the toxicity of aflibercept products, barring differences in clinical parameters, is a direct function of their affinity to VEGF-A and PlGF and related activity, the comprehensive battery of in vitro cell-free and cell-based studies are considered more sensitive than animal studies in detecting functional differences and toxicities, should they exist, between FYB203 and US-Eylea.

The applicant's development program was designed to support a demonstration that FYB203 is highly similar to US-Eylea using physicochemical and biological assays. Comparative analytical data between FYB203 and US-Eylea was assessed by the Quality discipline. From a nonclinical perspective, the comparative analytical data show that FYB203 is similar to US-Eylea and the final determination was made by the Quality discipline. In the absence of specific clinical, physicochemical, or other identifiable concerns, in vivo assays are not anticipated to provide additional meaningful information to inform the evaluation of toxicity. In summary, no animal studies with FYB203 and US-Eylea were needed to support this 351(k) application and the results of the in vitro studies support a demonstration of biosimilarity.

4.1.1. Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2. Product Information

Product Formulation

FYB203 is a clear, colorless to pale yellow solution, sterile and preservative-free solution in a single-use vial designed to deliver by intravitreal injection 2 mg (0.05 mL of 40 mg/mL) solution. The solution includes histidine HCL, (b) (4) mM sodium chloride, 0.03% polysorbate 20, and 5% sucrose, with a pH of 6.2. ***Table 5*** shows a comparison of the composition of FYB203 DP and that of US-Eylea.

Table 5. Comparison of FYB203 and US-Eylea

US-Eylea Formulation	FYB203 Formulation
40 mg/mL aflibercept	40 mg/mL FYB203
(b) (4) mM sodium phosphate	-
5% w/v sucrose	5% w/v sucrose
0.03% w/v polysorbate 20	0.03 %w/v polysorbate 20
(b) (4) mM sodium chloride	(b) (4) mM sodium chloride
-	(b) (4) mM (b) (4) histidine/L-histidine HCl monohydrate
pH 6.2	pH 6.2

No impurities of concern were identified.

The proposed commercial presentation is a single-use glass vial only designed to provide 2 mg (0.05 mL of 40 mg/mL) solution for intravitreal injection in a vial.

5. Clinical Pharmacology Evaluation and Recommendations

5.1. Clinical Pharmacology Executive Summary and Recommendation

Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of FYB203 and EU-Eylea evaluated in a subset of subjects with nAMD in Study FYB203-03-01 were comparable based on descriptive analysis, supporting a demonstration of no clinically

	meaningful differences between FYB203 and US-Eylea.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB203 and US-Eylea in subjects with nAMD supports a demonstration of no clinically meaningful differences between FYB203 and US-Eylea.

5.1.1. Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding the PK and immunogenicity assessments for FYB203 and US-Eylea.

5.2. Clinical Pharmacology Studies to Support the Use of a Non-US-Licensed Comparator Product

Not applicable.

5.3. Human Pharmacokinetic and Pharmacodynamic Studies

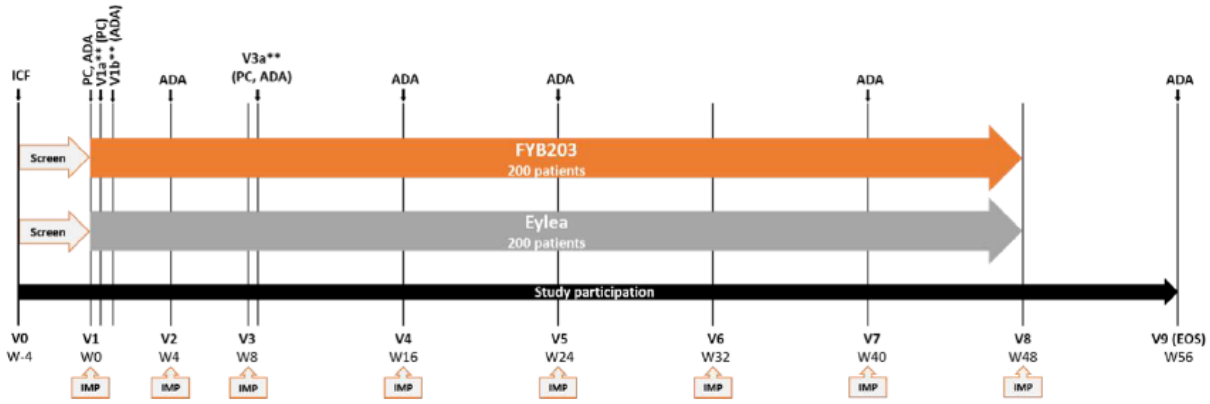
A PK similarity study using traditional PK endpoints, such as AUC and Cmax, in healthy subjects is not considered to be feasible for the following reasons: 1) aflibercept is administered by intravitreal (IVT) injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following IVT injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of IVT injections. Therefore, a PK sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

Clinical Pharmacology Study Design Features and Endpoints

Study FYB203-03-01 was a multicenter, double-masked, randomized, parallel group study in subjects with neovascular AMD (n=434). Subjects were randomized in a 1:1 ratio to receive either FYB203 2 mg (0.05 mL of 40 mg/mL solution) or EU-Eylea 2 mg (0.05 mL of 40 mg/mL solution) in the study eye by IVT once every four weeks for 3 consecutive doses starting at baseline (visit 1) through week 8 (visit 3) followed by 1 IVT every 8 weeks up to and including week 48 (visit 8), for a total of 8 IVT injections. The study design is illustrated in Figure 1 below.

Figure 1. Study Design of Study FYB203

Figure 9-1 Schematic of Study Design for Protocol FYB203-03-01



ADA = anti-drug antibody, EOS = end of study, ICF = informed consent form, IMP = investigational medicinal product, PC = plasma concentration, V = visit, W = week

Source: Figure 2 of the CSP (Appendix 16.1.1.3)

Source: Figure 9-1, CSR FYB203-03-01, page 40

The PK profiles of FYB203 and EU-Eylea were descriptively evaluated within up to 60 subjects participating in the PK sub-study as part of the comparative clinical study. The PK data were pre-specified to be analyzed qualitatively. Analyses included:

- Systemic exposure measured at Baseline prior to 1st IVT dose, 48 hours after 1st IVT dose close to Cmax after the first dose, and at 48 hours after the 3rd IVT dose close to Cmax after the 3rd dose in a subgroup of patients from both treatment groups.

The immunogenicity of FYB203 and EU-Eylea were descriptively evaluated in all neovascular AMD subjects in the comparative clinical study. Analyses included:

- Incidence of anti-drug antibodies (ADAs) to FYB203 and EU-Eylea
- Incidence of neutralizing antibodies (NAbs) to FYB203 and EU-Eylea

Of the 434 subjects randomized, 31 of 215 and 26 of 219 subjects in the FYB203 an EU-Eylea treatment groups, respectively, were included in PK subgroup analysis set.

Bioanalytical PK Method and Performance

Free concentrations of FYB203 or EU-Eylea in serum of patients with nAMD were measured using a validated Electrochemiluminescent immunoassay (ECLIA) assay. The lower and upper quantification limits for plasma study drug concentrations were 1 ng/mL and 60 ng/mL, respectively. The maximum storage time of all PK samples from Study FYB203-03-01 from sample collection to the end of sample analysis did not exceed 227 days. All PK samples were initially stored at a nominal temperature of -20°C for a maximum of 68 days and at a nominal temperature of -80°C for the remaining period. Study samples were analyzed within the validated long-

term stability periods (373 days stored at -20 ºC, 647 days stored at -80°C). Refer to Appendix 1 of the clinical pharmacology review dated 2/23/24 in DARRTs) for more detailed information regarding the bioanalytical method validation.

PK Similarity Assessment

In Study FYB203-03-01, 57 of 434 (13.1%) subjects were included in the PK subgroup analysis, including 31 of 215 (14.4%) and 26 of 219 (11.9%) subjects in the FYB203 and EU-Eylea treatment groups, respectively. Blood samples for PK assessments were collected at baseline prior to 1st IVT dose, 48 hours after 1st IVT dose, and at 48 hours after the 3rd IVT dose in the PK subgroup.

The descriptive PK comparison of free study drug by treatment in Study FYB203-03-1 showed that the systemic concentrations close to Cmax after the first and the third IVT injections were highly variable and generally in the same range in both treatment groups. Similar PK comparison was also observed for total study drug concentrations. Refer to Table 5, Figure 3 and Appendix 2 of the clinical pharmacology review dated 2/23/24 in DARRTs for more detailed information.

Overall, systemic exposure of FYB203 and EU-Eylea evaluated in a subset of subjects with nAMD in study FYB203-03-01 were comparable and support a demonstration that FYB203 has no clinically meaningful differences from US-Eylea.

PD similarity assessment: Not applicable.

5.4. Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity (ADA and NAb) was evaluated in Study FYB203-03-01 as one of the secondary endpoints.

Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed bridging electrochemiluminescence (ECL) assay and competitive ligand-binding assay ECL assays that are suitable for detecting ADA and NAb, respectively, in the presence of expected levels of FYB203 and EU-Eylea.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood samples for immunogenicity assessment were collected in all subjects at prior to IVT injection at baseline (Day 1), Week 4, Week 16, Week 24, Week 40, and at Week 56 (EOS visit). Additional ADA/NAb samples were also collected one week after the first and 48 hours after the third injection in the 57 patients in the PK subgroup.

Comparison of Incidence of ADA and NAb

The incidence of ADA and NAb by treatment group and time points in Study FYB203-03-01 were summarized in Table 6. The incidence of an ADA or NAb positive response was generally low and comparable between treatment groups throughout the study. None of the patients in the PK subgroup was positive for ADA in either the FYB203 or EU-Eylea treatment groups.

Table 6. Incidence of anti-drug antibody and neutralizing antibodies by visit **(Study FYB203-03-01 (Safety Analysis Set**, N=433 and PK subgroup, N=57)

	FYB203 (N=215)			Eylea (N=218)		
Analysis Visit	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**
Baseline (V1)	4 (1.9) n=213	0.71 (41.68)	Re 0 (0.0) Ne 4 (1.9) n=213	3 (1.5) n=204	0.63 (41.68)	Re 0 (0.0) Ne 3 (1.5) n=204
V1b; V1 + 7d[1]	0 (0) n=31	NA	NA	0 (0) n=25	NA	NA
Week 4 (V2)	2 (1.0) n=209	0.71 (52.11)	Re 0 (0.0) Ne 2 (1.0) n=209	1 (0.5) n=201	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=201
Week 8 (V3a; V3 + 48h)[1]	0 (0) n=32	NA	NA	0 (0) n=27	NA	NA
Week 16 (V4)	3 (1.5) n=195	1.59 (94.74)	Re 0 (0.0) Ne 3 (1.5) n=195	1 (0.5) n=191	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=191

	FYB203 (N=215)			Eylea (N=218)		
Analysis Visit	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**
Week 24 (V5)	4 (2.1) n=195	1.19 (106.76)	Re 0 (0.0) Ne 4 (2.1) n=195	1 (0.5) n=193	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=193
Post-treatment only[2]	2 (1.0) n=209	NA	Re 0 (0.0) Ne 5 (2.3) n=213	0 (0.0) n=201	NA	Re 0 (0.0) Ne 1 (0.5) n=204

ADA = anti-drug antibody, d = day, Geom. CV = geometric coefficient of variation, Geomean = geometric mean, h = hours, N = number of patients per group, n = number of patients per category, NA = not applicable, NAb = neutralizing antibody, n.c. = not calculable, Ne = negative, PKS = plasma concentration analysis set (used only for V1b and V3a), Re = reactive, SAF = safety analysis set (used only for V1, V2, V3, V4, V5 and post-treatment only), V = visit

[1] Plasma concentration analysis set (PKS) only, patients from PK subgroup with measurable aflibercept concentrations at prior to 1st injection were excluded

[2] The immunogenicity analysis "post-treatment only" excludes patients without any post-treatment ADA or NAb sample, excludes patients from ADA analysis who were ADA positive at pre-treatment (denominator n=209) and excludes patients from NAb analysis who were NAb reactive at pre-treatment (denominator n=213). Any patient who was NAb negative at pre-treatment could test NAb reactive during at any time during the treatment phase, independent of the ADA status pre-treatment.

Source: Table 12-23, Study FYB203-03-01CSR

Source: Table 3 in clinpharm review dated 2/23/24, pages 7-8

Comparison of ADA Titers

The ADA titers is comparable between the FYB203 and EU-Eylea treatment groups as seen in Table 6.

Comparison of Immunogenicity Impact on PK

None of the patients in the PK subgroup was positive for ADA in either the FYB203 or EU-Eylea treatment groups up to Week 24. Therefore, no conclusion could be made regarding the correlation between systemic levels and antibody rates.

Comparison of Immunogenicity Impact on Efficacy

The primary efficacy endpoint of Study FYB203-03-01 is the change from baseline in best corrected distance visual acuity (BCVA) at Week 8 with FYB203 or EU-Eylea treatments. At Week 8, none of the patients in the FYB203 or EU-Eylea group had positive ADA result (Table 6). Therefore, no conclusion could be made regarding the correlation between efficacy and antibody rates.

Comparison of Immunogenicity Impact on Safety
Two patients in the FYB203 group had treatment-emergent ADA signals, no drug hypersensitivity or anaphylaxis-type or ocular inflammatory treatment-emergent adverse events (TEAEs) of special interest were reported up to Week 24.

In conclusion, in SAF, 4 (1.9%) patients in FYB203 group and 3 (1.5%) patients in EU-Eylea group were tested positive for ADAs at baseline (pre-dose). None of these ADAs were neutralizing at baseline. Post-dose, 2 patients (1.0%) were newly tested positive for ADAs at least once in FYB203 group compared to no patient in EU-Eylea group. None of these were neutralizing post-dose. No patient in the PK subgroup was tested positive for ADAs either pre-dose or post-dose. Based on limited data, no apparent differences were noted regarding the impact of immunogenicity on comparative safety and efficacy between treatment groups.

6. Statistical and Clinical Evaluation

The totality of the efficacy and safety data from Study FYB203-03-01 supports the conclusion that there are no clinically meaningful differences between FYB203 and US-Eylea. As summarized above, the Applicant provided data demonstrating that FYB203 and US-Eylea are highly similar notwithstanding minor differences in clinically inactive components and established the scientific bridge to justify the relevance of data generated from the comparative clinical study using EU-Eylea to the assessment of biosimilarity. Therefore, Study FYB203-03-01 supports, in the context of the totality of the evidence, the conclusion that FYB203 is biosimilar to US-Eylea. The clinical and statistical review teams recommend approval of FYB203 for the same indications as US-Eylea for which the Applicant is seeking licensure.

6.1. Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the statistical and clinical analyses.

6.2. Review of Comparative Clinical Studies with Statistical Endpoints

6.2.1. Data and Analysis Quality

No major issues were identified regarding the quality and integrity of the submitted datasets under BLA 761378, and the overall quality of the submitted data and analysis is acceptable. Refer to Statistical Review dated 3/11/24 and Clinical Review dated 6/28/24 for details.

6.2.2. Study Design and Endpoints

The comparative clinical study FYB203-03-01 was a multicenter, double-masked, randomized, parallel-group study in subjects with neovascular AMD, where 434 subjects were randomized in a 1:1 ratio to receive 2 mg (0.05 mL of 40 mg/mL) solution of either EU-Eylea or FYB203 in the study eye once every four weeks for 3 consecutive doses through Week 8 followed by 1 IVT injection every 8 weeks over approximately 48 weeks (a total of 8 IVT injections per subject). Refer to ***Figure 1*** for study Design. The randomization scheme included stratification parameters to ensure a balanced distribution of assignment to the two treatments based on eye color (light, medium, dark iris); geographical region; and BCVA letters at baseline. Subjects were followed up for changes in efficacy variables and safety for 48 weeks.

One of the main objectives of the study FYB203-03-01 was to support a demonstration that there are no meaningful differences between FYB203 and US-Eylea in subjects with neovascular AMD over 8 weeks, as assessed by change from baseline to Week 8 in best corrected visual acuity (BCVA). This study was conducted in 77 clinical sites across 9 countries (Bulgaria, Czech Republic, Hungary, Israel, Italy, Japan, Poland, Russia and Ukraine). The randomization was stratified by country. The primary endpoint was the mean change in BCVA from baseline to Week 8 using the ETDRS protocol for the study eye.

6.2.3. Statistical Methodologies

For a detailed discussion on the statistical methods refer to the statistical review in DARRTS dated 3/11/2024.

Determination of Sample Size

The total sample size of approximately 400 patients was calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 9.0 ETDRS letters in BCVA. An equivalence test of means using two 1-sided tests with sample sizes of 180 in each treatment group (360 patients in total) achieves 90.0% power at a 2.5% significance level when no difference between the means is assumed, the SD is 9.0 letters, and the equivalence interval is [-3.5; 3.5] letters. Considering that about 10% of patients might drop-out and/or would be non- evaluable, 400 patients in total were planned to be included in the Week 24 analysis.

Analysis Population

Full Analysis Set

The full analysis set (FAS) included all patients who received at least 1 injection of study medication in the study eye. Patients were analyzed according to their randomized treatment. The FAS was used for the analysis of all efficacy data.

Safety Analysis Set
The safety analysis set (SAF) included all patients who received at least 1 injection of study medication in the study eye. Patients were analyzed according to the treatment they actually received in the study eye irrespective of their randomized treatment. The SAF was used for the analysis of all safety and tolerability data.

Per Protocol Set
The per protocol set (PPS) included all patients that were in the FAS and

- Had no major protocol deviations until Week 8 that would interfere with the interpretation of the BCVA efficacy data at Baseline or at Week 8
- Had received treatment from the randomized treatment group only before Week 8
- Had a valid measurement of the BCVA at Baseline and at Week 8 available
- Had no positive total aflibercept concentration at Baseline (since this indicated use of prohibited prior treatment, even if no such treatment might have been explicitly documented. A total aflibercept concentration at Baseline documented as 'not reportable' was treated like a positive value, as the true value was unclear and values below limit of quantification would be documented as such)

Plasma Concentration Analysis Set
The plasma concentration analysis set (PKS) included patients that were in the SAF and had at least 1 valid post-dose plasma concentration measurement. Patients were analyzed according to the treatment they actually received in the study eye at Visit 1. Patients who received injections from different treatment groups at Visit 1 and Visit 3 were not included in the PKS. Furthermore, patients with a positive Baseline total aflibercept concentration were excluded from the PKS.

Efficacy Analysis
The difference between FYB203 and EU-Eylea with respect to the primary efficacy endpoint was assessed with an MMRM based on all available data collected for the study eye until Week 24 (Visit 5) for all patients in the FAS. The MMRM included the Baseline BCVA by ETDRS letters, region (Japan vs. ROW), treatment, visit, treatment-visit- interaction and Baseline-visit-interaction, the estimates were thus adjusted for these parameters.

The null hypothesis of non-equivalence was tested using the estimated difference between FYB203 and EU-Eylea in change from Baseline in BCVA by ETDRS letters to Week 8 (from Visit 1 to Visit 3). The comparison of the 2 treatment groups was performed by calculating 2-sided 90.4% (US analysis) or 95.2% (EU analysis) CIs and compare these to the pre-defined equivalence margin of (-3.5; +3.5) ETDRS letters.

The sensitivity analyses for the primary endpoint at Week 8 were performed using different MMRMs and ANCOVAs with and without MI.

6.2.4. Patient Disposition, Demographic and Baseline Characteristics

For a detailed discussion on the patient disposition, demographic and baseline characteristics, refer to the statistical review in DARRTS dated 3/11/2024.

Patient Disposition

A total of 434 subjects were randomized into two groups: 215 in FBY203 and 219 in EU-Eylea. The number of subjects completing the 24-week primary efficacy endpoint was similar between groups. Up to Week 24, 7 (3.3%) patients in the FYB203 group and 7 (3.2%) patients in the EU-Eylea group had discontinued the study prematurely. Until the end of the study, the number of discontinuations increased to 19 (8.8%) in the FYB203 group and to 12 (5.5%) in the EU-Eylea group. At the primary efficacy endpoint, Week 8 (Visit 3), 98.6% of patients in the FYB203 group and 99.1% of patients in the EU-Eylea group remained on the study in the FAS. The results were the same for the SAF analysis set.

Demographic and Baseline Characteristics

Most subjects in the study were White (91.9%). Slightly more subjects in the study were females (57.3%) compared to males (42.7%). The average age of the subjects in the study was about 74 years (range from 51 to 93 years). The average baseline BCVA in the study was around 58 letter score (range from 34 to 73 letter score). The demographic and baseline characteristics appear to be comparable between the two treatment groups.

6.2.5. Results and Conclusions

The primary endpoint of Study FYB203-0301 to evaluate whether there are any meaningful differences with respect to efficacy between FYB203 and EU-Eylea in subjects with neovascular AMD was the change from baseline (CFB) to Week 8 in BCVA letters. To support similarity, the confidence limits for the least square (LS) means difference had to be within the equivalence margin of 3.5 letters at Week 8 (90% CI for FDA analysis and 95% CI other health authority analysis). The 2-sided 90% CI of [-0.3; 2.2] ETDRS letters for the difference was completely contained in the pre-defined equivalence margin of (-3.5; 3.5) ETDRS letters. The following table presents change from baseline in the BCVA letter score, primary efficacy at Week 8.

The assessment of the primary efficacy variable is presented in Table 7.

Table 7. MMRM: Comparison of Change in BCVA (ETDRS letters) from Baseline to Week 8 including data up to Week 24-US Analysis- FAS (N=433)

		MMRM Least Squares estimation					
Week (Visit) Treatment group Difference	N	n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 90.4% CI	2-sided 95.2% CI
Week 8 (V3)							
FYB203	215	215	0	6.6	0.73	[5.4; 7.8]	[5.2; 8.0]
Eylea	218	218	0	5.6	0.73	[4.4; 6.9]	[4.2; 7.1]
Difference: FYB203 - Eylea				1.0	0.76	[-0.3; 2.2]	[-0.6; 2.5]
US analysis		2-sided 90.4% CI contained in (-3.5; 3.5)[c] : yes					
EU analysis		2-sided 95.2% CI contained in (-3.5; 3.5)[c] : yes					

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 8 assessments were considered if they have at least 1 Post-Baseline BCVA value until Week 24.

[b] Estimates are adjusted for Baseline BCVA, region (Japan vs. Rest of world), treatment, visit, treatment-visit-interaction and Baseline-visit-interaction.

[c] If the CI for the difference in LS means was completely contained in the interval (-3.5 letters; 3.5 letters), FYB203 and Eylea were considered equivalent.

Source: Table 14.1.4.1, Table 14.2.1.1, Table 14.2.1.2
Source: statistical review dated 3/11/24 Table 6.2-11.

Sensitivity Analysis of the Primary Efficacy Endpoint

The sensitivity analyses were performed on FAS and those results were consistent with the primary efficacy results. Refer to the statistical review in DARRTS dated 3/11/2024 for details.

Analysis of Secondary Clinical Endpoint(s)

There was no relevant key secondary endpoint evaluated.

Findings in Special/Subgroup Populations

Treatment effects in evaluable subgroups (e.g., by age, iris color) in the study were generally consistent with the results in the overall population. Age ≥75 years did not have a clinically significant effect on the primary efficacy endpoint. The differences by race (Asian and White) and [redacted] were comparable.

Potential Effects of Missing Data

In the Full Analysis Set, for the primary endpoint of change from baseline (visit 1) in BCVA by ETDRS letters to Week 8, there were 6 missing values in the FYB203 group

and 5 missing values in the EU-Eylea group. Overall, the primary efficacy study results do not appear to have been significantly impacted by missing data.

6.3. Safety Review Approach

The safety of FYB203 was compared to EU-Eylea in a single randomized, double-masked, active-controlled study in patients with age-related macular degeneration. The safety population included 433 subjects treated for 56 weeks and included all subjects who received at least 1 intravitreal injection of study drug (215 patients exposed to FYB203, 218 patients exposed to EU-Eylea).

6.4. Review of the Safety Database

6.4.1. Overall Exposure

The mean (SD) treatment duration for the W24 analysis had been 110.9 (14.15) days and the mean (SD) study duration at this point was 183.0 (17.59) days. For the final analysis, the mean (SD) treatment duration increased to 323.1 (58.97) days with a mean (SD) study duration of 398.7 (53.03) days. The treatment and study durations were well balanced between both treatment groups and no relevant differences were observed.

Adequacy of the safety database

The safety database and the clinical evaluations conducted during the development was adequate to comparatively assess the safety profile of this intravitreally administered biologic product.

6.4.2. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This BLA submission was of sufficient quality to perform a substantive review of this product.

Categorization of Adverse Events

All AEs (both ocular and non-ocular) were coded using MedDRA Version 23 or higher. An AE was considered a treatment emergent adverse event (TEAE) if it occurred or worsened on or after receipt of the first dose of study drug. AEs have been summarized

using the MedDRA preferred term (PT) as event category and/or MedDRA primary system organ class (SOC) as summary category.

Treatment-Emergent Adverse Events (TEAEs) for each study arm (FYB203 arm and EU-Eylea arm) were categorized as Serious TEAEs (SAEs), Fatal TEAEs, Nonfatal SAEs, Severe TEAEs, Related TEAEs to study treatment, Related TEAEs to Study Procedure (IVT injection.)

Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns of intravitreally administered products (i.e., biomicroscopy, fundoscopy, visual acuity, IOP, etc.) were adequately addressed in the design and conduct of the trials for this product. Refer to Table 6.1-2 Evaluation and Visit Schedule for procedures and scheduled assessments for laboratory evaluations.

6.4.3. Safety Results

Seven patients died during the course of the study through week 56, of which 5 patients were randomized and received study treatment and 2 patients were screen failures. The deaths were considered by the investigators to be unrelated to the study drugs. Refer to Clinical Review in DARRTS dated 6/28/24 for details.

Clinical Conclusions

There is no integrated assessment of safety across studies as the application includes only a single comparative clinical study (FYB203-03-01) to support FYB203. Study FYB203-03-01 demonstrated that FYB203 and EU-Eylea have comparable safety profiles including the change in best corrected visual acuity from baseline to Week 8. The adverse event safety profiles were also similar between patients treated with FYB203 and EU-Eylea.

6.5.

(b) (4)

(b) (4)

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(b) (4)

6.6. Extrapolation

The Applicant submitted data and information in support of a demonstration that FYB203 is highly similar to US-Eylea notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between FYB203 and US-Eylea in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that FYB203 can be expected to produce the same clinical results as US-Eylea in any given patient (b) (4)

The Applicant is seeking licensure of FYB203 for the following indication(s) for which US-Eylea has been previously licensed and for which FYB203 has not been directly studied: macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME) and diabetic retinopathy (DR).

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of FYB203 as (b) (4) biosimilar for each such indication for which licensure is sought and for which US-Eylea has been previously approved. Note that the Applicant is not seeking licensure for retinopathy of prematurity (ROP) (b) (4)

Therefore, the totality of the evidence provided by the Applicant supports licensure of FYB203 as (b) (4) biosimilar to US-Eylea for each of the following indication(s) for which the Applicant is seeking licensure of FYB203: neovascular (Wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR).

7. Labeling Recommendations

7.1. Nonproprietary Name

The Applicant's proposed nonproprietary name, aflibercept-mrbb, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated March 25, 2024.

7.2. Proprietary Name

The proposed proprietary name for aflibercept-mrbb, Ahzantive, has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was conditionally acceptable in a letter to the applicant dated February 9, 2024.

7.3. Other Labeling Recommendations

It was determined that the proposed labeling is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

Division of Medication Error Prevention and Analysis 1 (DMEPA 1) completed a review of the 5/23/2024, carton and container labeling and found the revisions to be acceptable.

The Office of Product Quality Assessment III (OPQA-III) completed a final review on 5/8/2024 and found the label and labeling to be acceptable.

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. No compensation was reported to be linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the Applicant.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (section 505B of the FD&C Act), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is generally required unless waived or deferred or inapplicable. Under the statute, an interchangeable product is not considered to have a "new active ingredient" for purposes of PREA.

This application included the 12/11/2020 agreed iPSP for the AMD, RVO, DME, and DR indications, (b) (4) For each of the AMD, RVO, DME, and DR indications, the Applicant requested a waiver (see Q.A.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act) for the full pediatric population. The Pediatric Review Committee (PeRC) discussed the assessment on November 21, 2023. The labeling for US-Eylea does not contain pediatric information for the indications for which the applicant is seeking licensure, and PREA requirements were waived for US-Eylea for those indications. Therefore, the Agency has determined that, no pediatric studies will be required under PREA for this BLA. See Q.A.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act.

(b) (4)

11. REMS and Postmarketing Requirements and Commitments

11.1. Recommendations for Postmarketing Requirements and Commitments

None.

12. Comments to Applicant

None.

13. Division Director (OND – Clinical) Comments

I concur with the review team's assessment of the data and information submitted in this BLA. Additionally, I concur with the team's recommendation that the action for this administratively split BLA is an Approval for biosimilarity of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial (b) (4) (b) (4)

As the review team notes above, the information submitted by the Applicant demonstrates that FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial (b) (4) with US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

Specifically, this FYB203 product (b) (4) the following indications for which US-Eylea has been previously approved and for which the Applicant is seeking licensure of FYB203:

- Neovascular (wet) age-related macular degeneration (AMD),
- Macular edema following retinal vein occlusion (RVO),
- Diabetic macular edema (DME), and
- Diabetic retinopathy (DR).

(b) (4)

(b) (4)

This BLA has been administratively split so that the Approval of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS will remain in BLA 761378/Original 1. BLA 761378/Original 1 will receive an Approval letter.

(b) (4)

14. Financial Disclosure

Refer to Clinical Review in DARRTS archived on June 28 2024, for Financial Disclosure.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIDIST BERHANU
06/28/2024 03:32:25 PM
to add several signers to the BMER before it was finalized

CAROL Y KIM
06/28/2024 03:34:04 PM

NINA N BRAHME
06/28/2024 03:35:24 PM

RHEA A LLOYD
06/28/2024 03:37:18 PM

WILLIAM M BOYD
06/28/2024 03:38:34 PM

BIOSIMILAR CLINICAL REVIEW

Application Type	351(k) BLA
Application Number(s)	BLA 761378
Received Date(s)	6/28/2023
BSUFA Goal Date	6/28/2024
Division/Office	Division of Ophthalmology/Office of Specialty Medicine
Reviewer Name	David B. Summer, MD
Review Completion Date	See DARRTS stamped date
Product Code Name	FYB203 (aflibercept-mrbb)
Proposed Proprietary Name	AHZANTIVE
Pharmacologic Class	Vascular endothelial growth factor (VEGF) inhibitor
Dosage Form	Injectable solution
Applicant	Formycon AG
Applicant Proposed Indication(s)	Same indications as those approved for US-licensed Eylea: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR)
Applicant Proposed Dosing Regimen(s)	Same regimen approved for US-licensed Eylea: Neovascular (Wet) Age-Related Macular Degeneration (AMD) • The recommended dose for AHZANTIVE is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). • Although AHZANTIVE may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week (monthly) dosing after the first 12 weeks (3 months). • Although not as effective as the recommended every 8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. Macular Edema Following Retinal Vein Occlusion (RVO) • The recommended dose for AHZANTIVE is 2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly).

	Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR) • The recommended dose for AHZANTIVE is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). (2.6, 2.7) • Although AHZANTIVE may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when aflibercept was dosed every 4 weeks compared to every 8 weeks. Some patients may need every 4-week (monthly) dosing after the first 20 weeks (5 months).
Recommendation on Regulatory Action	Approval of FYB203, injection, for intravitreal use as biosimilar to US-Eylea (aflibercept) for the product described below: • 2 mg (0.05 mL of 40 mg/mL) in a single-dose vial (vial) as biosimilar to US-Eylea 2 mg (0.05 mL of 40 mg/mL) in a vial kit and single-dose pre-filled syringe (PFS). (b) (4)

BLA 761378 Review Team Role	Reviewer
OND RPM	Kidist Berhanu
OTBB RPM	Wendy Streight
CDTL	Rhea Lloyd
Clinical Reviewer	David Summer
Pharmacology/Toxicology Reviewer	Muriel Saulnier / Kim Hatfield
Statistical Reviewer	Martin Klein/ Jessica Kim
Clinical Pharmacology Reviewer	Lei He/ Ping Ji
OND Labeling Reviewer	Derek Alberding
OPQ Review Team	
Review Chief	Maria-Teresa Gutierrez-Lugo
ATL	Nailing Zhang
RBPM	Shazma Aftab
Microbiology	Yi Wang (DP)/ Jiangsong Jiang (DS)/ Michael Shanks secondary
Facility	Yi Wang (DP)/ Jiangsong Jiang (DS)/ Madushini Dharmasena secondary
Comparative Analytical Assessment (CAA), Immunogenicity Assay	Dilip Devineni/ Nailing Zhang
Drug Substance	Mercy Oyugi
Drug Product	Odile Engel
OBP Labeling	Liming Lu
OSE RPMs	Oyinlola Fashina
DMEPA Team Lead / Reviewer	Valerie Vaughn / Sofanit Getahun
OSI CSO	Roy Blay
OPDP Reviewer	Carrie Newcomer
Deputy Division Director	William Boyd
Office Director	Charles Ganley

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

FYB203 is developed to be a biosimilar to the biological reference product Eylea® which is marketed by Regeneron Pharmaceuticals, Inc. in the US and Bayer AG in the European Union. Its active substance is aflibercept (ATC code: S01LA05), a glycosylated, disulfide- stabilized homodimeric recombinant fusion protein consisting of domain 2 of human vascular endothelial growth factor receptor 1 (VEGFR-1 D2) and domain 3 of VEGFR-2 (VEGFR-2 D3) fused to the Fc domain of human IgG1. Aflibercept acts as a soluble decoy receptor that binds vascular endothelial growth factor receptor A (VEGF-A) and placental growth factor (PlGF), and thereby can inhibit the binding and activation of these cognate VEGF receptors.

The indications proposed for FYB203 are (b) (4) those for the reference product for use in adult patients. In the US, Eylea is approved for the treatment of patients with:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic retinopathy (DR)

The 0.4 mg (0.01 mL) dose administered using the 2 mg/0.05 mL (40 mg/mL) strength is for the following indication:

- Retinopathy of Prematurity (ROP)

This indication is approved for US licensed Eylea but the applicant is not seeking licensure for ROP (b) (4)

An extensive similarity assessment was performed to evaluate the similarity of FYB203 in comparison to Eylea. The results confirmed a high similarity between FYB203 and Eylea and show that bridging between Eylea US and Eylea EU is supported. Functional assays reflecting the mechanism of action, which is consistent across all approved indications, showed similar pharmacological action and did not indicate clinically significant or remarkable differences between FYB203 and Eylea. In addition, *in vivo* preclinical results add to the totality of evidence for FYB203 being highly similar to Eylea.

For clinical confirmation of biosimilarity, a randomized, parallel-group, active-controlled, double-masked, multi-center phase 3 efficacy and safety study comparing FYB203 and EU-

Eylea in patients with neovascular AMD was conducted in nine countries outside of the US. Based on these results, an application for licensure as biosimilar is being submitted.

1.2. Conclusions on Clinical Similarity

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB203 is highly similar to EU-licensed Eylea, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB203 and EU-licensed Eylea in terms of the safety, purity, and potency of the product. The comparative analytical data provided by the Applicant established the scientific bridge between FYB203, US-Eylea, and EU-approved Eylea (EU-Eylea), which justifies the relevance of comparative data generated using EU-Eylea to the assessment of biosimilarity. The data and information provided by the Applicant are sufficient to demonstrate that SB15 can be expected to produce the same clinical result as US-licensed Eylea in any given patient. (b) (4)

Therefore, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB203 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial is biosimilar to (b) (4) US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS for each of the following indications for which US-Eylea has been previously approved and for which the Applicant is seeking licensure of FYB203:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macula edema (DME)
- Diabetic retinopathy (DR)

(b) (4)

Healthcare providers administer US-Eylea to all patient populations using either a vial kit (single-dose glass vial co-packaged with injection components) or a single-dose PFS. While we note that US-Eylea is currently labeled only for use as a vial kit and a PFS, (b) (4)

(b) (4)

(b) (4)

The review team recommends (b) (4) an Approval for FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

(b) (4)

This BLA has been administratively split so that the Approval of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS will remain in BLA 761378/Original 1. BLA 761378/Original 1 will receive an Approval letter.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

In the Phase 3, randomized, double masked, multicenter, parallel group study, FYB203-03-01 (Magellan-AMD) evaluating FYB203 compared to EU-Eylea in patients with neovascular age-related macular degeneration (nAMD), the change in BCVA from baseline to Week 8 and corresponding 2-sided 90.4% confidence interval (CI) was contained within the equivalence margin of ±3.5 letters. Therefore, the results demonstrated similarity of the biosimilar candidate FYB203 to Eylea. The results of this trial demonstrate that there are no clinically meaningful differences between FYB203 and Eylea in treatment of nAMD patients.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	The following conditions if untreated will lead to visual loss: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy	Aflibercept has been approved to treat the listed conditions in the US and has been shown to prevent visual loss.
Current Treatment Options	• Lucentis (ranibizumab injection), Eylea (aflibercept), Beovu (brolucizumab), Byooviz (ranibizumab), Macugen (pegaptanib sodium injection) and Visudyne (verteporfin for injection), Vabysmo ™ (faricimab-svoa), Cimerli (ranibizumab-eqrn), Opuviz (aflibercept-yszy) and Yesafili (aflibercept-jbvf). Avastin (bevacizumab) is used off-label to treat nAMD.	FYB203 will add to the armamentarium of drugs to treat several retinal diseases that lead to vision loss.
Benefit	Eylea (aflibercept) is approved for the treatment of: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy	Study FYB203-03-01 (Magellan-AMD) compared the efficacy, safety, PK and immunogenicity between FYB203 (Ahzantive) and Eylea. This submitted data demonstrated biosimilarity between FYB203 and US-Eylea.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Eylea (aflibercept) is relatively safe for the treatment of the labeled indications listed above.	The results of Study FYB203-03-01 demonstrate that FYB203 has a similar safety profile to US-licensed Eylea, including adverse events, immunogenicity and PK

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X □	Clinical outcome assessment (COA) data, such as		6.1, 6.2
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X □	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Neovascular age-related macular degeneration (nAMD), although less prevalent than dry AMD, commonly causes acute and substantial central vision loss due to growth of pathologic choroidal neovascularization (CNV), which causes exudation of blood and/or fluid into the macula, leading to retinal edema and retinal thickening. The aberrant vascular growth and exudation in nAMD are driven by cascade of many cytokines involved in angiogenesis, primarily vascular endothelial growth factor-A (VEGF-A).

Neovascular age-related macular degeneration (nAMD) is characterized by the new growth of abnormal blood vessels (neovascularization) emanating from the subjacent choroid in the subretinal pigment epithelium (RPE) space and the subretinal space termed choroidal neovascular membranes (CNV or CNVM). These newly formed vessels have an increased likelihood to leak blood and serum causing separation of Bruch's membrane, RPE and retina from each other and resulting in the accumulation of sub-RPE, sub-retinal or intra-retinal fluid. Fluid accumulation leads to a generalized thickening of the retina and/or the formation of cystic spaces causing photoreceptors to become misaligned and eventually degenerative changes occur with cell loss and eventual fibrosis and scar tissue formation. Untreated, most affected eyes will have poor central vision (20/200) within 12 months. Although the neovascular form of the disease is only present in about 10% of all AMD cases, it has accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments.

2.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection), US Eylea (aflibercept), Beovu (brolucizumab-dbll) injection, Byooviz (ranibizumab), Vabysmo ™ (faricimab-svoa), Cimerli (ranibizumab-eqrn, Opuviz (aflibercept-yszy) and Yesafili (aflibercept-jbvf) are approved for the treatment of wAMD. Macugen (pegaptanib sodium injection) and Visudyne (verteporfin for injection) are also approved for the treatment of AMD.

Avastin (bevacizumab) injection is used off-label to treat AMD.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

AHZANTIVE is a VEGF- inhibitor formulated for intravitreal administration which has been developed under IND 144550 as a proposed biosimilar (b) (4) to US Eylea. It has not yet been marketed.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Sponsor consulted the Agency concerning the overall development program in the following meetings:

- A BPD Type Type 2 meeting was held September 11, 2019, to discuss the design of the PK subgroup analysis, including the number of nAMD patients for evaluation of aflibercept plasma concentration and the sampling timepoints.
- An initial Pediatric Study Plan was submitted on July 24, 2020, requesting drug-specific waivers for all pediatric age groups. As requested in FDA's written response issued on October 21, 2020, an Agreed iPSP was submitted on December 7, 2020 (PIND 144550). A copy of this agreed iPSP is included in Section 1.9.1 of this application.
- A BPD Type 2 was held March 1, 2021. The meeting was held to discuss timelines for filing of a prospective 351(k) BLA for FYB203 as a biosimilar to US-licensed Eylea®, and (b) (4)
- On May 18, 2022, FDA sent advice to sponsor regarding (b) (4) for your proposed aflibercept product if the application otherwise meets the standards for licensure under section 351 (k) of the PHS Act.
- On Feb 15, 2023, a BPD Type 4 meeting was held between Formycon and the FDA to discuss the (b) (4) comparative analyses
    - The analysis for the initial BLA submission includes all efficacy, safety, PK, and immunogenicity data of all 433 treated patients collected up until Week 24.
    - Additionally, available data on serious AEs, AEs of special interest, discontinuation for any reason, and death cases are reported until the time of database lock in the initial BLA
    - The analysis for the initial BLA submission includes all efficacy, safety, PK, and immunogenicity data of all 433 treated patients collected up until Week 24.
    - Additionally, available data on serious AEs, AEs of special interest, discontinuation for any reason, and death cases are reported until the time of database lock in the initial BLA

3.3. Foreign Regulatory Actions and Marketing History

No foreign approvals or marketing.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspections were not requested for this application. Study FYB203-03-01 was conducted mostly in non-US investigational sites. No single investigational site included enough subjects to significantly alter the final result of the clinical trial. There is no evidence of data integrity issues which suggest that the clinical trial was not conducted in compliance with good clinical practices.

4.2. Product Quality

From the OPQ Executive Summary finalized May 8, 2024:

Dosage Form	Solution, injection		
Strength	2 mg/0.05 mL (40 mg/mL) solution in a single-dose vial		
Route of Administration	Intravitreal injection		
Primary Container Closure System	(b) (4) glass vial, closed with a (b) (4) stopper with (b) (4) and sealed by an aluminum seal with a plastic flip-off cap		
Device Information	Not applicable (Note: US-licensed Eylea also has a 2 mg/0.05 mL single-dose prefilled syringe presentation. Formycon AG is not seeking approval for the prefilled syringe presentation.)		
Co-packaged Product Information	Not applicable (Note: US-licensed Eylea vial presentation is co- packaged with the following device components: (1) one 19-gauge x 1½-inch, 5-micron, filter needle for withdrawal of the vial contents, (2) one 30-gauge x ½- inch injection needle for intravitreal injection, and (3) one 1-mL syringe for administration. AHZANTIVE (aflibercept-mrbb) does not include these co-packaged device components.)		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Mercy Oyugi	Nailing Zhang
	Drug product	Odile Engel	
	Comparative Analytical Assessment (CAA), Immunogenicity Assay	Dilip Devineni	
	Facility	Jiangsong Jiang (DS) / Yi Wang (DP)	Michael Shanks

	Microbiology	Jiangsong Jiang (DS) / Yi Wang (DP)	Madushini Dharmasena
	RBPM	Shazma Aftab	
	ATL	Nailing Zhang	
	Review Chief	Maria-Teresa Gutierrez-Lugo	
OPQ Issued Consults	None		

Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761378 for AHZANTIVE (aflibercept-mrbb) manufactured by Formycon AG. The data submitted in this application are adequate to support the conclusion that the manufacture of AHZANTIVE (aflibercept-mrbb) is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that AHZANTIVE (aflibercept-mrbb) is highly similar to US- licensed Eylea (aflibercept), notwithstanding minor differences in clinically inactive components. It is recommended that this product be approved for human use under conditions specified in the package insert.

CMC Information for Action Letter

- Manufacturing Location:
- Drug Substance: (b) (4)
- Drug Product:
  - Manufacturing: (b) (4)
  - Labeling and secondary packaging: (b) (4)

Fill size and dosage form:

- 2 mg/0.05 mL (40 mg/mL) solution in a single-dose vial

Dating Period:

- Drug Substance: (b) (4)
- Drug Product: 24 months at 2°C - 8°C, protected from light
- Stability Option:
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

Exempt from lot release:

- Yes
- AHZANTIVE is exempted from lot release per FR 95-29960.

Basis for Recommendation

Summary:

AHZANTIVE (aflibercept-mrbb) is (b) (4) to US-licensed Eylea (aflibercept) for the treatment of Neovascular (Wet) Age-Related Macular

Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR). Aflibercept is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1. It acts as a soluble decoy receptor that binds VEGF-A and Placental Growth Factor (PlGF), and thereby can inhibit the binding and activation of the VEGF receptors. Potency of AHZANTIVE (aflibercept-mrbb) is controlled using a cell-based reporter assay that measures its ability to inhibit VEGF-A-induced luciferase reporter activity in iLite VEGF cell line, a stably transfected HEK-239 cell line expressing VEGFR-2 together with GAL4-Elk1a responsive luciferase gene. Potency results are reported as percentage relative to a qualified reference material.

The totality of the comparative analytical evidence supports that AHZANTIVE (aflibercept-mrbb) is highly similar to US-licensed Eylea (aflibercept), notwithstanding minor differences in clinically inactive components. The strength of 2 mg/0.05 mL (40 mg/mL) AHZANTIVE in a single-dose vial demonstrated the same strength as that of US-licensed Eylea. Refer to Appendix for detailed summary on comparative analytical assessment.

The drug substance (DS) manufacturing process consists of (b) (4)

(b) (4)

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. On-site pre-licensing inspections (PLIs) for the DS manufacturing facility (b) (4) and the DP manufacturing facility (b) (4) were conducted in (b) (4) and (b) (4) respectively. Both PLIs were classified as "Voluntary Action Indicated (VAI)", and the responses to FDA Form 483 were reviewed and found satisfactory.

The overall AHZANTIVE (aflibercept-mrbb) control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for AHZANTIVE (aflibercept-mrbb) are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays

used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives.

Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
CAA	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for AHZANTIVE (i.e., there is no specific test method described in regulation for AHZANTIVE that establishes an official standard of potency). We next considered whether potency is a factor for AHZANTIVE within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for AHZANTIVE for purposes of § 610.61(r) because lot variability is not a concern for AHZANTIVE as AHZANTIVE's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

Life-Cycle Considerations
Established Conditions based on ICH Q12 principles: No
Drug Substance:

- Protocols approved:

(b) (4)

(b) (4)

- Residual risk: None

- Future inspection points to consider: None

Drug Product:

- Protocols approved:
  - Qualification protocol for commercial drug product shipping
  - Stability protocols for drug product shelf-life extension
  - Post-approval stability protocols for drug product
- Residual risk: None
- Future inspection points to consider: None

4.3. Clinical Microbiology

Not applicable to this application. This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

From the Pharmacology Toxicology reviewer finalized on March 8, 2024:

Brief Discussion of Nonclinical Findings

Formycon performed *in vivo* studies in animals in order to demonstrate similarities between the ocular and systemic pharmacokinetic (PK) and toxicological profiles between FYB203 and Eylea.

The *in vivo* preclinical data suggested that FYB203 and Eylea had slightly different systemic PK/TK and toxicity profiles.

Nevertheless, since new animal studies with FYB203 were neither required by the Agency nor recommended for a BLA type 351(k) application, the preclinical data reviewed in this report were merely informational.

Recommendations on Approvability

The product is approvable from a pharmacology and toxicology perspective.

4.5. Clinical Pharmacology

From the Clinical Pharmacology review finalized on February 23, 2024:

Clinical Pharmacology Executive Summary and Recommendation

Eylea (aflibercept) is a vascular endothelial growth factor (VEGF) inhibitor. The Applicant submitted this BLA application under section 351(k) of the Public Health Service Act (PHS Act) for FYB203, 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 immunoglobulin (Ig)G1 formulated as aqueous solutions for intravitreal (IVT) administration, as a proposed biosimilar to US-licensed Eylea (aflibercept). The proposed indications include neovascular age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR). The proposed dosage form is 2 mg/0.05 mL injection in a single-dose glass vial and the proposed dosage regimens for FYB203 are same as those approved for US-licensed Eylea.

BLA 761378 application consists of one comparative clinical study in patients with neovascular AMD (nAMD) (Study FYB203-03-01, n=434), in which the PK profiles of FYB203 and EU-approved Eylea were evaluated in a subgroup of nAMD patients.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) has reviewed the clinical pharmacology data submitted under this BLA application and had the following recommendations regarding clinical pharmacology review issues (Table 1).

Table 1. Clinical pharmacology major review issues and recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of FYB203 and EU-approved Eylea evaluated in a subset of subjects with nAMD in Study FYB203-03-01 were comparable based on descriptive analysis, supporting a demonstration of no clinically meaningful differences between FYB203 and US-licensed Eylea.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB203 and EU-approved Eylea in subjects with nAMD supports a demonstration of no clinically meaningful differences between FYB203 and US- licensed Eylea.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic issue. (b) (4)

(b) (4)

4.7. Consumer Study Reviews

There were no consumer study reviews.

5. Sources of Clinical Data and Review Strategy

APPEARS THIS WAY ON ORIGINAL

5.1. Table of Clinical Studies

Study Reports of Controlled Clinical Studies Perinent to the Claimed Indication

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status, Type of Report
Efficacy and Safety	FYB203-03-01	Module 5.3.5.1	To demonstrate therapeutic equivalence of FYB203 to Eylea and to compare the safety and immunogenicity in patients with nAMD.	Parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study	All eligible patients were 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 consisted of 1 IVT injection every 4 weeks for 3 consecutive doses starting at baseline (Visit 1) through Week 8 (Visit 3) followed by 1 IVT injection every 8 weeks over a period of approximately 48 weeks (Visit 8), resulting in a total of 8 IVT injections per patient.	434 enrolled; 433 treated	Newly diagnosed neovascular age-related macular degeneration (nAMD)	Approx. 12 months	Complete, Interim (24-Wk)

5.2. Review Strategy

Clinical data for Study Magellan-AMD FYB203-03-01 listed in Section 5.1 was reviewed to support safety and efficacy of FYB203 for the indication nAMD. Clinical data from the additional PK and immunogenicity sub-studies were reviewed as appropriate to support safety.

The clinical development program involves a single clinical study to demonstrate the similarity of SB15 to Eylea (aflibercept). The study evaluated the similarity of SB15 and EU-licensed Eylea in subjects dosed with 2 mg (0.05 mL) by intravitreal injection every 4 weeks for the first 3 months followed by once every 8 weeks with age-related macular degeneration.

The application includes a single, randomized, double-masked, parallel group, multicenter comparative clinical study of FYB203 to EU-Eylea among subjects with AMD. The study evaluated efficacy by comparing the primary endpoint of change in best corrected distance visual acuity (BCVA) from baseline to Week 8 between FYB203 and EU Eylea. Efficacy was compared using the primary endpoint of change in BCVA at week 8 from the baseline between FYB203 and EU licensed Eylea. Similarity was demonstrated if the treatment group difference of the mean change in BCVA, from baseline to Week 8 based on 90.4% CI was fully contained within the pre-defined margin of [-3.5; + 3.5] ETDRS letters.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study: FYB203-03-01: MAGELLAN-AMD: 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

Study Objectives

Primary:

- To demonstrate that the biosimilar candidate FYB203 is equivalent to Eylea ® in subjects with wet age-related macular degeneration (wAMD) as assessed by the change in best corrected visual acuity (BCVA) from Baseline to Week 8.

Secondary:

The secondary objectives of this study were to evaluate and compare:

- changes in foveal center point (FCP) retinal thickness
- changes in FCP retinal thickness and changes in foveal central subfield (FCS) retinal

thickness over time
- functional changes of the retina by BCVA over time
- the proportion of patients who gained or lost ≥5, 10, and 15 ETDRS letters compared to baseline
- the absence of disease activity (fluid-free macula) over time
- change in total lesion size
- systemic free and total aflibercept concentrations in a subgroup of up to 60 patients (up to 30 per group)
- change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25)
- the immunogenic profile (ADAs) in serum
- local and systemic AEs and SAEs

Primary Endpoint

The primary endpoint of the study was the change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3).

Secondary endpoints were:
- Change from Baseline (Visit 1) in FCP retinal thickness to Week 4 (Visit 2) (defined as key secondary endpoint for the EU analysis)
- Changes of FCP retinal thickness and FCS retinal thickness over the whole study from Baseline (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
- Change of BCVA by ETDRS letters over the whole study from Baseline (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
- Proportion of patients who gained or lost ≥5, 10, or 15 ETDRS letters from Baseline (Visit 1) to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
- Percentage of patients with fluid-free macula at each Visit, i.e., Baseline (Visit 1), Week 4 (Visit 2), Week 8 (Visit 3), Week 16 (Visit 4), Week 24 (Visit 5), Week 32 (Visit 6), Week 40 (Visit 7), Week 48 (Visit 8) and Week 56 (Visit 9)
- Change from Baseline (Visit 1) in total lesion size to Week 24 (Visit 5), Week 40 (Visit 7) and Week 56 (Visit 9)
- Systemic concentrations of free and total aflibercept in a PK subgroup at selected sites at Baseline (Visit 1) and close to predicted maximum concentration [Cmax] (based on estimated time to maximum concentration [tmax])
    - 48 hours after 1st dose (Visit 1a) and
    - 48 hours after the 3rd dose (Visit 3a)
- Change from Baseline (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)
- Number of patients with ADAs over time, i.e., at Baseline (Visit 1), 7 days after the first injection (Visit 1b, for PK subgroup only), Week 4 (Visit 2), 48 hours after the 3rd injection (Visit 3a, for PK subgroup only), Week 16 (Visit 4), Week 24 (Visit 5), Week 40

(Visit 7) and Week 56 (Visit 9)
- Frequency of local and systemic AEs and SAEs

Study Design

This was 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 sub-foveal nAMD or wet AMD.

The Screening period started with the ICF signature and had a maximum duration of 28 days. In addition to the Screening assessments on site, CRC GRADE received 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 (total lesion area). Patients had to meet all eligibility criteria during the Screening period, including positive evaluation of the Screening retinal images performed by the Central Reading Center (CRC).

All eligible patients received 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 were 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 was to receive a total of 8 IVT injections.

Systemic concentrations of free and total aflibercept were 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 Cmax, and at 48 hours after the 3rd IVT dose (Visit 3a) close to Cmax. Anti-drug antibodies formation against aflibercept were 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).

The study was conducted in 9 countries, where 77 sites screened at least 1 patient. For the 24-week analysis (W24 analysis) presented in this clinical study report (CSR), 72 sites in 9 countries randomized at least 1 patient: Bulgaria (4 sites), Czech Republic (9 sites), Hungary (8 sites), Israel (6 sites), Italy (5 sites), Japan (14 sites), Poland (9 sites), Russia (9 sites) and Ukraine (8 sites).

At each study site, there were at least 2 masked staff members: The PI and the Visual Acuity (VA) examiner. At each site, the PI was responsible for the study. A list of the PIs at each site, along with their affiliation and qualification, is located in Appendix 16.1.4.1.

Further, there was an unmasked intravitreal (IVT) administrator at each study site who was responsible for the study injections.

Only investigators (masked and unmasked) qualified by training and experience were selected as appropriate experts to investigate the study drugs. Eighty-five study centers, located in Europe, Israel and Japan have patients participating in this study.

Protocol Amendments
Protocol Version 1.0 (22-Oct-2019) was never implemented and never submitted in any country. The first patients were enrolled under protocol version 2.0.

Protocol Version 2.0 (16-Dec-2019) was the original protocol submitted and approved in all countries.

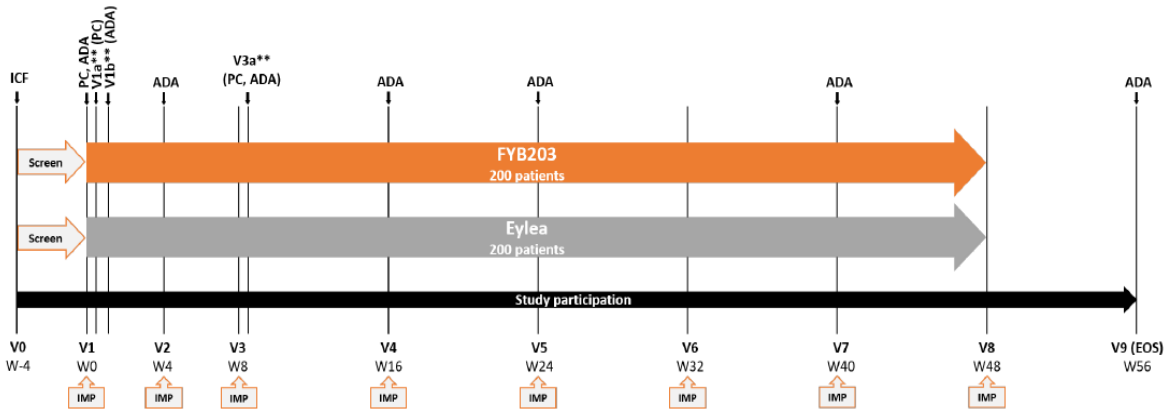
The clinical protocol Version 3.0 was the only amendment to Protocol Version 2.0. This substantial amendment 1.0 (dated 15-Jul-2022) updated the planned statistical analyses: (b) (4)

Due to enrollment delays caused by the COVID-19 pandemic and the geopolitical situation in Ukraine, the timing difference (b) (4) has been reduced sufficiently to justify conducting (b) (4) the final US analysis. About 9% more patients than originally planned, i.e., 434 instead of 400, are randomly assigned to study treatment to compensate for potentially incomplete treatment and evaluation of patients because of the geopolitical situation in Ukraine in 2022, which could impact the evaluation of safety.

The study was conducted between 21-Jul-2020 (first patient, first visit) and 13-Oct-2022 (last patient last visit for the W24 analysis). Patients were treated between 12-Aug-2020 and 18-Aug-2022.

Schematic of the study design

Figure 6.1-1 Design of confirmatory efficacy & safety study, FYB203-03-01



ADA = anti-drug antibody, EOS = end of study, ICF = informed consent form, IMP = investigational medicinal product, PC = plasma concentration, V = visit, W = week
Source: Figure 2 of the CSP (Appendix 16.1.1.3)

PK Assessment Systemic concentrations of free and total aflibercept were assessed and compared in a plasma concentration evaluation subgroup (PK subgroup) of up to 60 patients (up to 30 each for EU-approved Eylea and FYB203) at selected study sites at Baseline prior to 1st IVT dose, 48 hours after 1st IVT dose (Visit 1a) close to maximum concentration (Cmax), and at 48 hours after the 3rd IVT dose (Visit 3a) close to Cmax.

Immunogenicity Assessment ADA formation against aflibercept was evaluated in serum in all patients before they received the IVT injections at Visit 1, Visit 2, Visit 4, Visit 5, Visit 7 and Visit 9, and in addition, in patients from the PK subgroup 1 week after the 1st dose (Visit 1b) and 48 hours after the 3rd dose (Visit 3a).

Eligibility Criteria

Inclusion Criteria
Patients had to meet all the following criteria to be eligible to enter the study:
General
1. Age ≥50 years at Screening.
2. Male or female:

a. A male patient had to agree to use contraception as detailed in Appendix 6 of the protocol during the treatment period (48 weeks) and for at least 4 weeks after the last dose of study treatment.
b. A female patient was eligible to participate if she was not pregnant (see Appendix 6 of the protocol), not breastfeeding, and at least 1 of the following conditions applied:
    i. Not a woman of childbearing potential (WOCBP) as defined in Appendix 6 of the protocol OR
    ii. A WOCBP who agreed to follow the contraceptive guidance in Appendix 6 of the protocol 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 Appendix 2 of the protocol, which included compliance with the requirements and restrictions listed in the ICF and in the CSP.
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 nAMD:
    a. All subtypes of nAMD CNV lesions were eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Treatment- naïve CNV secondary to nAMD had to be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by SD-OCT or retinal pigment epithelium [RPE] detachment);
    b. Total area of whole lesion had to be ≤ 9 disc areas;
    c. Total CNV area encompassed ≥50% of total lesion area based on FA, including all subtypes of nAMD.

Term	Definition
nAMD	Clinical signs (including findings by retinal imaging) attributable to nAMD (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

CNV = choroidal neovascularization, FA = fluorescein angiography, nAMD = neovascular age-related macular degeneration, RPE = retinal pigment epithelium

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

Ocular (Fellow Eye)

9. BCVA in the fellow eye, determined by standardized ETDRS testing, at least 20/200 Snellen equivalent.

Inclusion Criteria to Remain Eligible for Randomization

1. There was no significant anatomical change in the study eye following ophthalmological and SD-OCT examination between the Screening Visit and Visit 1 (i.e., large subretinal hemorrhage, RPE tear, pigment epithelial detachment).
2. VA in the study eye was 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 was greater than 5 ETDRS letters (better or worse) between Screening and Visit 1, the patient was NOT to 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 was NOT to 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 had to use best medical judgement to exclude patients with a probable fellow eye treatment need during the course of the study.

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 study eye;
6. History of IVT or periocular injections of corticosteroids or device implantation within 6 months prior to Randomization in the study eye.
7. Prior treatment with verteporfin (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation) in the study eye;
8. Any other intraocular surgery (including cataract surgery) in the study eye 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 study eye.
10. Irreversible structural damage involving the center of fovea (e.g. advanced fibrosis > 50% of the total lesion in the study eye or atrophy) in the study eye 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 study eye.
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 study eye.
15. Current vitreous hemorrhage in the study eye.
16. Spherical equivalent of the refractive error in the study eye demonstrating more than 6 diopters of myopia.
17. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not exceed 6 diopters of myopia.
18. History of or current corneal transplant in the study eye.
19. Aphakia in the study eye. Absence of an intact posterior capsule was allowed if it occurred as a result of yttrium aluminum garnet laser posterior capsulotomy in association with prior posterior chamber intraocular lens 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 study eye (defined as IOP ≥30 mmHg, despite treatment with anti-glaucomatous medication).
22. Ocular disorders in the study eye (i.e., retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on VA) at the time of Screening that could have confounded interpretation of study results and compromise VA.

23. Any concurrent intraocular condition in the study eye (e.g., glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the PI or his/her delegate, would either have required surgical intervention during the study to prevent or treat visual loss that might have resulted from that condition or might 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 might have biased 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 nAMD requiring treatment with an IVT anti-VEGF agent (e.g., aflibercept, bevacizumab, ranibizumab) within the Screening period or the expectation, in the opinion of the PI or his/her delegate, to need such treatment in the fellow eye throughout the study. At the time of Screening and randomization, the PI or his/her delegate should have used best medical judgement to exclude patients with a probable fellow eye treatment need during the course of the study.

Study eye selection

The study was open to treatment naïve patients with recently diagnosed nAMD in one eye only. No patients had two eligible eyes at the time of randomization.

Test Product and Reference Therapy

- FYB203 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection
- EU- Eylea 2 mg (0.05 mL of 40 mg/mL solution) administered by intravitreal injection

Table 6.1-1 Study Medication Formulation, and Batch Numbers

Masked lot #	Product	Input batch #	Actual Expiry Date	Labeled Expiry Date	Quantity labeled & packaged	QP released on
E218374-0002L E218374-0008L[2]	FYB203	3-FIN-3355	~~May-2021~~ May-2022[1]	May-2021[2] Oct-2021[2]	(b) (4)	23-Jun-2020 06-Jul-2021[2]
	Eylea	KT057AP	Oct-2021			
E218374-0003L	FYB203	3-FIN-3355	May-2022	Oct-2021		18-Jan-2021
	Eylea	KT05T02	Oct-2021			
E218374-0005L	FYB203	3-FIN-3684	Jul-2023	Oct-2021		19-Apr-2021
	Eylea	KT05T02	Oct-2021			
E218374-0007L	FYB203	3-FIN-3684	Jul-2023	Jun-2022		11-Aug-2021
	Eylea	KT07FL2	Jun-2022			
E218374-0009L	FYB203	3-FIN-3684	Jul-2023	Aug-2022		11-Aug-2021
	Eylea	KT095K0	Aug-2022			
E218374-0012L	FYB203	3-FIN-3684	Jul-2023	Oct-2022		03-Sep-2021
	Eylea	KT097VK	Oct-2022			
E218374-0010L	FYB203	3-FIN-3684	Jul-2023	Aug-2022		21-Oct-2021
	Eylea	KT095CJ	Aug-2022			
E218374-0013L	FYB203	3-FIN-3684	Jul-2023	Jun-2023		10-May-2022
	Eylea	KT0B625	Jun-2023			

QP = qualified person
[1] The shelf-life of FYB03 DP batch was extended from (b) (4) to (b) (4) months based on updated stability data
[2] Most remaining kits from this IMP batch were re-labeled at the applicable sites or depots with the expiry date of 10-2021. Masked lot # in IWRS system is the same, but (b) (4) lot # for re-labeled kits is E218374-0008L

Study Schedule of Events

Table 6.1-2 Evaluation and Visit Schedule

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

Table 6.1-2 Evaluation and Visit Schedule (continued)

	V0 Scree-ning	V1 Base-line	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8****	V9 (EOS/ Early Termina-tion)****
Week (Day)	W-4 to W-1 (-28 to -1)	W0 (1)	W0+48h V1+48h (±6h)	W0+7d V1 + 7 (±1)	W4 (29±7)	W8 (57±7)	W8+48h V3+48h (±12h)	W16 (113±7)	W24 (169±7)	W32 (225±7)	W40 (281±7)	W48 (337±7)	W56 (393±7)
Urine sampling[14]	X								X		X		X
Plasma concentration evaluation**[8]		X**	X**				X**						
ADAs[9]		X		X**	X		X**	X	X		X		X
Concomitant medications	X	X			X	X		X	X	X	X	X	X
AEs[10]	X	X	X**	X**	X	X	X**	X	X	X	X	X	X
IVT treatment[11]		X			X	X		X	X	X	X	X	
3-Day Post-IVT Telephone Safety Check		X			X	X		X	X	X	X	X	

ADA =anti-drug antibody, AE = adverse event, BCVA = best corrected visual acuity, d = day, EOS = end of study, ETDRS = early treatment diabetic retinopathy study, FSH = follicle stimulating hormone, h = hours, hCG = human chorionic gonadotropin, IMP = investigational medicinal product, IOP = intraocular pressure, IVT = intravitreal, NAb = neutralizing antibody, NEI VFQ-25 = national eye institute visual function questionnaire 25, SD-OCT = spectral domain optical coherence tomography, V = visit, W = week

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

** Plasma concentration evaluation subgroup only.

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

**** Visit 6, Visit 7, Visit 8 and Visit 9 will be analyzed in a separate CSR. Early termination visits are included in the analysis if patients terminated prior to Visit 7.

[1] Before any blood sample collection on the same day.

[2] Refraction and visual acuity testing had to 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 were performed on both eyes. Ocular assessments at all other study visits were performed on the study eye only.

[4] Goldmann applanation tonometry had to be performed at Screening. The Tonopen or Perkins Tonometer could be used at other times, however Goldmann applanation tonometry had to be used to verify any IOP ≥30 mmHg.
[5] Tonometry had to be measured prior to the injection and within 30 to 60 minutes after the injection.
[6] A complete ophthalmic examination had to 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 were evaluated. Additional ADA sampling and evaluation were performed in patients experiencing signals of unexpected ocular inflammation.
[10] AEs starting after signing the informed consent had to be recorded on relevant AE page. Between Screening and 1st dose only study related AEs had to be collected.
[11] A safety check (Light Perception Ophthalmoscopy and Tonometry) was performed within 60 minutes post IVT.
[12] No significant anatomical change in the study eye compared to Screening and visual acuity in the study eye within the defined inclusion criteria range (Snellen equivalent 20/40 [0.5] to 20/200 [0.1]) and within 5 letters of the Screening BCVA.
[13] See Appendix 3 of the CSP (Appendix 16.1.1.3) for the list of clinical laboratory tests to be performed.
[14] Urine sampling for clinical laboratory test were collected at Screening, at Visit 5 and Visit 7 prior to IVT injection of IMP and at EOS Visit (Appendix 3 of the CSP [Appendix 16.1.1.3]). Urine samples had to be collected before performing FA (when applicable) to avoid false elevations in urine protein values.
All assessments of a particular visit had to be performed during 1 day, except for Screening.
Source: Section 1.3 of the CSP (Appendix 16.1.1.3)

Table 6.1-4 List of Investigators (*Sites without randomized patients were not included in the list below)*

The study was conducted in 9 countries, where 77 sites screened at least 1 patient. For the 24-week analysis (W24 analysis) presented in this clinical study report (CSR), 72 sites in 9 countries randomized at least 1 patient: Bulgaria (4 sites), Czech Republic (9 sites), Hungary (8 sites), Israel (6 sites), Italy (5 sites), Japan (14 sites), Poland (9 sites), Russia (9 sites) and Ukraine (8 sites).

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Hungary	11001	Budapest Retina Intézet Váciút 76. Capital Square, II. torony, 3. emelet 1133 Budapest	András Seres	Beáta Gáspár, Béla Csákány, Judit Radnóti, Tamás Pregun, Norbert Czumbel, Fanni Balogi, Timea Gulyás, Edina Nagyné Hadnagy, Bernadett Szabó-Bacsek	2	1
Hungary	11002	Debreceni Egyetem Szemklinika Nagyerdei krt. 98. 4032 Debrecen	Attila Vajas	Szabolcs Balla, Erika Papp, Beáta Bajdik, Bence Kolozsvári, Balázs Mazurka, Zita Steiber	20	16
Hungary	11003	Semmelweis Egyetem Szemészeti osztály Mária u. 41. 4. emelet 1085 Budapest	András Papp	Miklós Resch, György Barcsay, Illés Kovács, Gábor Sándor, Ágnes Borbándy, Antal Szabó, Zoltán Zsolt Nagy	32	23

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Hungary	11004	Magyar Honvédség Egészségügyi Központ Szemészeti osztály Dózsa György u.112. D. ép. 7.emelet 1068 Budapest	Gábor Vogt	Enikő Szathmáry, Orsolya Medgyaszay, Enikő Takács, András Rodler, Veronika Dudás, Zsuzsanna Kálmán	9	8
Hungary	11005	Ganglion Orvosi Központ Váradi Antal u. 10/A fszt. 5. 7621 Pécs	Balázs Varsányi	Réka Füstös, Beatrix Varga, Zsanett Dinnyés, Zsófia Kölkedy, Regina Katona, Adrienn Horváth, Krisztina Lantos	8	5
Hungary	11006	Zala Megyei Szent Rafael Kórház Szemészet Zrinyi M. u 1. 8900 Zalaegerszeg	Krisztina Fatalin	Katalin Kiss, Etelka Aradi, Lajos Szalcler, Miklósné Nyúl, Szabina Bohár	9	7
Hungary	11007	Fejér Megyei Szent György Egyetemi Oktató Kórház Szemészeti osztály Seregélyesi út 3. 8000 Székesfehérvár	Jenő Tóth	Dorottya Mihályi, Judit Rákóczi, Krisztina Barabás, Mónika Faragó, Helga Vándor	4	2
Hungary	11008	Szegedi Tudományegyetem Szent-Györgyi Albert Klinikai Központ Szemészeti Klinika Korányi fasor 10-11. 6720 Szeged	Edit Tóth-Molnár	Eszter Vizváry, Barbara B. Tóth, Attila Kovács, Lilla Smeller, Magdolna Vajda, Ágnes Metál	9	6
Bulgaria	12001	DCC "Alexandrovska", EOOD, 1, Georgi Sofiyski Str., 1431 Sofia	Alexander Oscar	Stanislava Kostova-Ivanova, Vasil Haykin, Yani Zdravkov, Galateya Tsvetkova, Rozaliya Hristova	10	5

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Bulgaria	12005	Specialized Hospital for Active Treatment of Ophthalmologic Diseases "Zora", OOD, Clinic of Ophthalmology, 4, Petar Protich str., 1784 Sofia	Iva Petkova	Miglena Metodieva, Maria Yaneva, Boryana Irinkova, Karolina Telbizova, Irina Kuneva-Parvanova, Ana Georgieva, Plamen Yordanov	14	8
Bulgaria	12006	Medical Center Vereya EOOD, 4, Kenali str., 6000 Stara Zagora	Nataliya Ivanova	Dimitar Dzhelebov, Radostina Markova-Dzhelebova, Rositca Stoinova, Elmira Mincheva – Gancheva, Tanya Kyoseva	10	7
Bulgaria	12007	Eye clinic Svetlina, 191, Maria Luiza Blvd, 1233 Sofia	Stefan Nedev	Irena Mazhlekova, Anna Deleva, Velina Miltenova, Mira Holevich, Evdokia Ilieva	1	1
Czech Republic	13001	Fakultní nemocnice Královské Vinohrady Oftalmologická klinika Šrobárova 1150/50 Praha 10 – Vinohrady, 100 00 Czech Republic	MUDr. Jan Hamouz	Lukas Magera, Ludovit Vesely, Yun Min Klimesova, Lucie Holubova, Anna Novotna	24	10
Czech Republic	13002	Fakultní nemocnice Hradec Králové Oční klinika Sokolská 581 Hradec Králové - Nový Hradec Králové, 500 05 Czech Republic	Doc. MUDr. Jan Studnička, PhD.	Alexandr Stepanov, Jan Marak, Nada Jiraskova, Marie Burova, Hana Langrova, Jana Breznayova, Jaroslava Dusova, Anna Tarkova, David Beran	20	13

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Czech Republic	13003	NEMOS SOKOLOV s.r.o. Oční oddělení Slovenská 545 Sokolov, 356 01 Czech Republic	MUDr. Andrej Farkaš	Katerina Skulavikova, Vadym Cheban, Josef Mendrek, Maria Dovhan, Zuzana Blazejova, Dominik Stevanak	13	7
Czech Republic	13004	Axon Clinical, s.r.o. Ostrovského 253/3 Praha 5, 150 00 Czech Republic	MUDr. Jan Ernest, PhD.	Bohdan Kousal, Katerina Kesslerova, Katerina Manethova, Michal Hrevus, Jarolslav Romanek, Adam Ernest, Vladimir Strasmajer, Martin Wallisch	23	15
Czech Republic	13005	Fakultní nemocnice Ostrava Oční klinika 17. listopadu 1790 Ostrava - Poruba, 708 52 Czech Republic	MUDr. Jan Němčanský, Ph.D., MBA	Sabina Nemcanska, Frantisek Benda, Michal Koubek, Jana Dvorakova, Radovan Krejcha	9	7
Czech Republic	13006	Oční centrum Praha, a.s. Jankovcova 1569/2c Praha 7 - Holešovice, 170 00 Czech Republic	Doc. MUDr. Jiří Pašta, CSc., FEBO	Radan Zugar, Lucie Frantlova, Andrea Janekova, Michaela Klementova, Dana Cernohuba-Fillova	19	7
Czech Republic	13008	Oftex, s.r.o. Rokycanova 2798 530 02 Pardubice Czech Republic	MUDr. Vladimír Korda, PhD., MBA	Eva Kovacikova, Ivana Harcubova, Lucie Russnakova, Jiri Spisek, Jaroslav Toninger	2	2
Czech Republic	13009	Fakultní Thomayerova nemocnice Oční oddělení Vídeňská 800	MUDr. Kateřina Myslík Manethová, FEBO	Tereza Novotna, Julius Lukes, Jana Habalova, Katerina Kesslerova, Hedvika	6	5

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
		140 59, Praha 4 – Krč Czech Republic		Polodnova, Tomáš Koupa		
Czech Republic	13010	Všeobecná fakultní nemocnice v Praze Oční klinika U nemocnice 499/2 128 08, Praha 2 Czech Republic	MUDr. Bohdan Kousal, PhD.	Andrea Havlikova, Jan Dvorak, Magdalena Kovacova, Alena Loukotova, Eva Uherkova	5	4
Poland	14001	Centrum Medyczne Uno- Med St. Gumniska 11, 33-100 Tarnów	Piotr Oleksy	Halina Wykrota, Izabella Karska-Basta, Weronika Płutniak, Karolina Florek- Opioła, Konrad Duda	7	3
Poland	14002	OFTALMIKA Sp. zo.o. St. Modrzewiowa 15, 85-631 Bydgoszcz	Jakub Kałużny	Ilona Piotrkowiak-Slupska, Beata Danek, Iwona Jaworowska-Cieslinska, Agata Cieslinska-Rypolc, Anna Majer, Przemyslaw Zabel, Jagoda Rzeszewska-Zamiara, Magdalena Kaszuba-Modrzejewska, Damian Jaworski, Dzmitry Atlivanau, Jaroslaw Makowski, Patryk Mlyniuk, MariaKaluzna	8	6

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Poland	14003	Szpital Świętego Łukasza S. A., Poradnia Okulistyczna St. Bystrzanska 94b, 43-309 Bielsko-Biała	Bogumił Wowra	Katarzyna Lepska, Anna Pawlowska, Anna Kies, Aneta Pilny-Brzoska, Jakub Kolodziejczyk	23	14
Poland	14004	Centrum Diagnostyki i Mikrochirurgii Oka LENS St. Budowlana 3A, 10-424 Olsztyn	Dominik Zalewski	Malgorzata Dabrowska, Damian Dawid, Slawomir Zalewski Magdalena Gorczyca-Bojko, Agnieszka Kondratowicz, Ewa Sierpinska-Bialczak, Agata Kozlowska, Iwona Kuta, Anna Borgosz	15	10
Poland	14006	Retina Okulistyka Sp. z o.o., Sp. Komandytowa St. Gimnazjalna1, 01-364 Warszawa	Piotr Fryczkowski	Piotr Tesla, Anna Borucka, Michal Szot, Agnieska Siennicka	3	1
Poland	14007	Szpital Zakonu Bonifratrów im. Św. Jana Bożego w Łodzi, Oddział Okulistyczny St. Kosynierów Gdyńskich 61, 93-357 Łódź	Piotr Gozdek	Mariusz Maroszynski, Dominik Odrobina, Iwona Laudanska-Olszewska, Kinga Raurowicz, Katarzyna Piasecka, Joanna Skupinska-Bitner, Marta Owidzka	6	3

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Poland	14008	Centrum Zdrowia MDM St. Waryńskiego 10a, 00-631 Warszawa	Piotr Wnorowski	Filip Grabowski, Dominika Romanczak, Beata Klimaszewska, Agnieszka Sekulska-Pietak, Anna Wolska, Anna Wegrzecka, Piotr Banka, Agnieszka Warpas	30	15
Poland	14009	Specjalistyczny Ośrodek Okulistyczny Oculomedica St. Ogrody 14, 85-870 Bydgoszcz		Adriana Laudencka, Grzegorz Czajkowski, Katarzyna Skoczylas-Piechowiak, Pawel Suchon, Izabela Wawra, Zofia Sikorska, Pawel Reisner, Magdalena Pol	6	4
Poland	14010	Centrum Medyczne Uno-Med St. Dietla 19/3, 31-070 Kraków	Piotr Oleksy	Izabella Karska-Basta, Weronika Pociej-Marciak, Weronika Plutniak, Konrad Duda, Katarzyna Zuber-Laskawiec, Piotr Bujak	37	21
Russian Federation	15001	"Republican Clinical Ophthalmological Hospital of the Ministry of Health of the Republic of Tatarstan named after Professor E.V. Adamyuk" Butlerova str.,14 420012, Kazan, Russian Federation,	Roza Nikolaevna Tokinova	Nargiza Davletshina, Elina Minkhuzina, Sergey Usmanov, Nadiia Mansurova, Daria Maksyutova, Nursultan Sultanov, Elena Zhidenko, Irida Zainutdinova, Leysan Shulaeva, Alexander Kuskov	6	3

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Russian Federation	15003	Federal State Budgetary Educational Institution of Higher Education "First St. Petersburg State Medical University named after Academician I.P. Pavlova" of the Ministry of Health of the Russian Federation, Department and Clinic of Ophthalmology 6/8, bld 16, Lva Tolstogo str. 197022, St.Petersburg Russian Federation	Sergei Yurievich Astakhov	Svetlana Belekhova, Alla Lisochkina, Pavel Nechiporenko, Alexsey Rukhovets, Aleksandra Titarenko, Svetlana Tultseva, Ghassan Shaar	5	3
Russian Federation	15004	Federal State Budgetary Scientific Institution "Research Institute of Eye Diseases 11 A/B Rossolimo str. 119021, Moscow Russian Federation,	Mariya Viktorovna Budzinskaya	Maria Afanasyeva, Anna Plyukhova, Anait Khalatyan, Aleksandra Ahelankova, Aleksey Kuznetsov, Aletvina Stoyukhina, Ekaterina Sakalova, Aleksandra Kurguzova, Madina Durzinskaya, Nino Zhorzholadze	12	6

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Russian Federatioon	15005	FSAI Intersectoral scientific and technical complex "Eye Microsurgery" named after academician S.N. Fedorov, of MOH the RF, Novosibirsk branch , 10, Kolhidskaya str. 630071, Novosibirsk Russian Federation	Galina Viktorovna Bratko	Yulia Filatova, Daria Cherepanova, Veronica Dulidova, Dmitry Chernykh, Evgeniy Smirnov, Olga Nepomnyaschaya, Anna Rago zina, Tatiana Chekhova, Ludmila Retulskikh, Liliya Dudnikova	10	6
Russian Federation	15007	SBHI NR "State Novosibirsk Regional Clinical Hospital" 130, Nemirovicha Danchenko str. 630087, Novosibirsk, Russian Federation,	Angella Zhannovna Fursova	Mariya Vasilyeva, Anna Derbeneva, Mikhael Tarasov, Liliya Serebrova, Evgenia Shutovich, Nadezhda Chubar, Ida Nikulich	20	11
Russian Federation	15010	FSBI “National medical research center of eye diseases n. a. Helmholtz” of MoH of Russian Federation 14/19, Sadovaya-Chernogriazskaja str. 105062, Moscow Russian Federation,	Tatiana Dmitrievna Okhotsimskaya	Maria Ryabina, Nadezhda Shvetsova, Pavel Bychkov, Olga Zaitseva, Pavel Ilyukhin, Anna Skyarova, Anastasia Ivanova, Ksenia Letnikova, Natalia Urakova, Ekaterina Bolkvadze, Natalia Shabatina	17	13

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Russian Federation	15011	LLC HI "Optic-Center" 15, 40th anniversary of October Str. 454007, Chelyabinsk, Russian Federation,	Elena Vladimirovna Tur	Konstantin Verein, Irina Sorokina, Marina Boiko, Olga Avdeeva	6	3
Russian Federation	15012	LLC X7 Clinical Research Lit T, 27, Engelsa avenue, office 50 H, room 28 194156, St.Petersburg, Russian Federation	Pavel Nechiporenko	Aleksandra Titarenko, Sergei Chub, Aleksandra Godlevskaya, Ekaterina Dvoretskaya, Svetlana Belekhova, Nataliya Chernova, Maryana Rybina, Evgenia Simonova, Svetlana Ponasenkova, Vadim Stepanov, Alexey Arguneev, Margarita Mukhortova	35	24
Japan	16001	Hyogo Prefectural Amagasaki General Medical Center 2-17 -77 Higashinaniwacho, Amagasaki-shi, Hyogo, 660-8550, Japan	Hideyasu Oh	Mio Hirose, Mariko Hasegawa, Yumiko Ojima, Maasa Ogata, Nao Aono, Akiko Sawa, Ai Nakata, Makito Tamiya, Hiroki Nakayama, Ayaka Doi, Takahiro Okumura, Mel Nakahara, Yuya Terubayahi	6	1

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Japan	16002	Keneikai Hayashi Eye Hospital Hakataekimae 4-23-35, Hakata-ku, Fukuoka-shi, Fukuoka, 812-0011, Japan	Ken Hayashi	Soichiro Ogawa, Miki Masumoto, Sumie Kawahara, Keiko Mine, Nina Sagara, Koichi Yoshimura, Akira Hirata, Shinichi Manabe, Hiroshi Sasaki, Tatsuhiko Sato, Motoaki Yoshida, Sosuke Ishiyama, Sho Ota, Sayaka Yoshitake, Emiko Iimori, Ryuya Kukita, Shunsuke Shibata	8	5
Japan	16003	Yokosuka Kyosai Hospital Yonegahamadori 1-16, Yokosuka-shi, Kanagawa-Ken, 238-8558, Japan	Satoshi Takeuchi	Soichiro Inokuchi, Kenichi Yamaguchi, Yu Sato, Shinichi Aoki	5	1
Japan	1604	JCHO Chukyo Hospital 1-1-10 Minami-ku 3jo, Nagoya-shi, Aichi-Ken, 457-8510, Japan	Tatsushi Kaga	Taisuke Matsuda, Sho Yokoyama, Yoshimi Yokoyama, Ayako Sawaki, Asato Hasegawa, Yuki Takagi, Kazuki Yoshioka, Kenta Hozumi, Shota Shiroyama, Midori Senda, Yuri Esaka, Kaito Noguchi, Taiga Tanino, Akihiro Masuda, Ryota Hashizume, Shiyomi Ito	6	2

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Japan	16006	Nihon University Hospital 1-6 Kandasurugadai, Chiyoda-ku, Tokyo, 101-8309, Japan	Koji Tanaka	Hiroyuki Nakashizuka, Ryusaburo Mori, Hajime Onoe, Yumiko Machida, Michiteru Kono, Takuya Sakakibara, Keisuke Miyata, Reina Miyamoto, Rumi Adachi, Naoya Nakagawa, Mai Kitaoka, Mao Nakayama, Ichihiko Takeuchi, Aki Yoshida, Miki Sato, Ruri Yamamoto, Mai Omori, Koyo Takase, Aayaka Noguchi, Hiromi Hirosawa, Kazuki Tamura, Chiho Shada, Yorihisa Katagawa, Hiroyoki Kaneko, Akira Ono, Yu Wakatsuki Chiho Tsukatani, Yoshiki Kamimoto, Mayumi Yamano, Toshie Kawano, Hanayo Saito, Yukako Kikuchi	8	3
Japan	16007	Sapporo City General Hospital 13 Chome Kita 11 Jonishi 1-1, Chuo-ku, Sapporo Hokkaido, 060-8604, Japan	Hiroko Imaizumi	Hirotomo Miyamoto, Miho Shimizu, Takamasa Kinoshita, Junya Mori, Hikari Sakakima - Yamasaki, Kenji Kobayashi, Takaki Morita, Akira Hatanaka, Shuichiro Aoki, Kei Akaiwa,	2	2

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
				Masanori Iwasaki, Yuya Kimura		
Japan	16009	Saneikai Tsukazaki Hospital Waku 68-1, Aboshi-ku, Himeji-shi, Hyogo, 671-1227, Japan	Tomofusa Yamauchi	Toshihiko Nagasawa, Daisuke Nagasato, Yuki Yoshizumi Nanami Kuroda, Sakurako Miya	3	0
Japan	16011	Fukushima Medical University Hospital Hikarigaoka 1, Fukushima-shi, Fukushima-Ken, 960-1295, Japan	Tetsuju Sekiryu	Kanako Itagaki, Yukinori Sugano, Akihito Kasai, Yusuke Iitaka, Ryo Mukai, Junichiro Honjo, Yutaka Kato, Shohei Matsumoto, Keiichiro Tanaka, Yasuharu Oguchi, Ayaka Kasai, Akira Ojima, Masashi Ogasawara, Hiroaki Shintake, Ryutaro Tomita, Kanae Takama	3	1

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Japan	16012	Kurume University Hospital 67 Asahi-machi, Kurume-shi, Fukuoka, 830-0011, Japan	ShigeoYoshida	Kensaku Iwata, Takuya Tsuji, Shotaro Dake, Masatoshi Haruta, Mariko Tanaka, Hodaka Akune, Kensuke Sasaki, Kei Furushima, Nobuhiro Kato, Yoshinori Hashimoto, Yoshiki Kojima, Naoko Sako, Shuntaro Ikeda, Daiki Ishio, Tomohiro Kurose, Koki Ishibashi, Yuka Nishihara, So Handa, Yumi Ishibashi, Akito Nagae, Ryo Hayashi, Yasunobu Saneyoshi, Masako Ishibashi, Yurie Shimokobe, Yu Matsuo, Kumi Honda, Makiko Yamaguchi, Yusho Koyanagi	9	1
Japan	16013	Suita Tokushukai Hospital 21-1 Senrioka Nishi, Suita-shi, Osaka, 565-0814, Japan	Tomiya Mano	Yuko Moriyama, Toshitaka Bun, Tomoko Miyake, Yu Kimura, Rino Fujimori, Serika Moriyama, Sheishiro Fujii, Kuo-Chung Chang, Kanae Fukui, Akiko Hosoki	5	4

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Japan	16014	Seirei Hamamatsu General Hospital Sumiyoshi 2-12-12, Naka-ku, Hamamatsu-shi, Shizuoka, 430-8558, Japan	Akira Obana	Yuko Ghoto, Risa Nakazawa, Kaori Ishii, Saki Noma, Takahito Seto, Chikako Nagasaka, Yuri Fujino, Honami Fukuyo	9	3
Japan	16017	Nagasaki University Hospital Sakamoto 1-7-1, Nagasaki-shi, Nagasaki, 852-8501, Japan	Eiko Tsuiki	Takashi Kitaoka, Mao Kusano, Kazuko Kinoshita, Akiko Matsukuma, Ryota Kono, Takehito Sato, Daisuke Inoue, Akio Oishi, Akira Machida, Yuki Hirata, Yusuke Doi, Makiko Matsumoto, Yuki Maekawa, Genichiro Tokimura, Kanako Yamada, Miwa Takahashi, Shogo Ikeda, Misaki Morita	3	2
Japan	16021	NHO Tokyo Medical Center 2-5-1 Higashigaoka Meguro-ku Tokyo, 152-8902, Japan	Kunihiko Akiyama	Toru Noda, Ken Watanabe, Katsuyuki Kuwabara, Asako Naruo, Takaaki Matsuki, Shota Fujii, Hirohiko Kawashima, Yasuyuki Nakae, Takuhiro Hayakawa, Mariko Sasaki, Junichiro Yajima, Shih-Wei Chen, Ayane Hirose	8	4

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Japan	16022	Akita University Hospital 44-2, Hasunuma Hiroomote Aza Akita-shi Akita, 010-8543, Japan	Shungo Nishiyama	Mariko Sato, Ryoma Kamada, Nanako Yokota, Naoyuki Serita	4	2
Japan	16023	Asahikawa Medical University Hospital Midorigaoka-higashi 2-1-1-1 Asahikawa-shi Hokkaido, 078-8510, Japan	Tsuneaki Omae	Tsubasa Abe, Masataka Murono, Yonung-Soek, Song, Kengo Takahashi, Yoshitaka Takizawa, Akito Shimouchi, Shinji Ono, Ami Konno, Miki Sato	2	2
Ukraine	17001	V.P.Filatov Institute of Eye Diseases and Tissue Therapy AMSU , 49/51, Frantsuskyi Blvd. Dept. of Ophthalmoendocrinology&Microsurgery of Glaucoma 65061 Odesa	Andriy Korol	Illia Nasinnyk, Serhii Drachenko, Olga Guzun, Taras Kustryn, Alla Nevska, Oleh Zadorozhnii, Victoriia Rostel	9	5
Ukraine	17002	M.V. Sklifosovskyi Poltava RCH Ophthalmology Dept, 23, Shevchenka St. 36011 Poltava	Iryna Bezkorovayna	Andriy Shatkun, Nina Bezega, Polina Gorlachova, Marina Klochko, Vita Riadnova, Iryna Steblovska	12	11

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Ukraine	17003	Limited Liability Company Vizus, Medical Center of LLC Vizus, Treatment and Diagnostic Department #1 34, Nezalezhnoi Ukrainy St., Zaporizhzhia, Ukraine	Nataliya Zavgorodnya	Olga Bezdenezgna, Sergii Bezdenezhnyi, Kateryna Kostrovska, Nadiia Mykhailenko, Sergii Mykhalchyk	18	16
Ukraine	17004	14th Girshman City clinical hospital, Str. Olesya Gonchara 5 61023 Kharkiv	Olena Muzhychuk	Omar Salamin, Yurii Kovalenko, Igor Saienko, Yevheniia Hontar, Inna Duras, Anna Filatova	7	4
Ukraine	17005	Medical Center Oftalmika, 16-H, Otakara Yarosha St 61045 Kharkiv	Lydia Nikitina	Iryna Chubenko, Sergii Fesenko, Vardui Sardaryan, Roman Shebanov, Svitlana Skrynnyk2	2	2
Ukraine	17006	Treatment-Diagnostic Center of Private Enterprise of PPC Atsynus, 65, Velyka Perspektyvna St. 25006 Kropyvnytskyi	Vyacheslav Povkh	Olena Popova, Tamara Oliinyk, Elena Bondarchuk, Oleh Parkhomenko, Dmitriy Zhaboedov, Iliia Pinchuk	17	11
Ukraine	17007	Communal Enterprise Volyn Regional Clinical Hospital of Volyn Regional Council, 21, Prosp. Prezydenta Hrushevskoho Av. 43005 Lutsk	Roksolana Sydor	Mariia Vashcheniuk Yurii Valetskiy Lidiya Rudavska Ihor Stadnytskyi Liudmyla Kyrychuk	14	11

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Ukraine	17009	Communal Nonprofit Enterprise Afanasii and Olha Tropiny Kherson City Clinical Hospital of Kherson City Counsil, Ophthalmology Department, 2 Komarova St, 73000 Kherson	Olena Platonova	Iryna Reshetniak, Mariia Obukhova	6	4
Israel	18001	Kaplan Medical Center, 1 Pasternak St. Rehovot 7661041	Alexandra Goz	Amir Bukelman, Ariel Marcovich Haia Morori-Katz Majd Arow, Oren Yovel, Ortal Zaks, Ran Maltov Kormas, Reut Parness Yossifon, Tamir Weinberg, Yochai Shohani, Yoel Greenwald, Efraim Berco, Chaim Nissen, Emad Borsha, Gabriel Avraham	2	2
Israel	18002	Hadassah Medical Center, Ein-Karem, Kiryat Hadassah, Jerusalem, 9112001	Samer Khateb	Edward Averbukh, Itay Chowers, Jaime Levy, Jose Antonio Rivera Vasquez, Liran Tiosano, Radgonde Amer, Tareq Z. Jaoni, Yitzchac Hemo, Noa Epelbaum	2	1

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Israel	18003	Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 6423906	Michaella Goldstein	Adiel Barak, Anat Loewenstein, Assaf Hilely, Avraham Ohayon, Dinah Zur, Efrat Fleissig, Gilad Rabina, Michael Regenbogen, Omer Trivizki, Shulamit Schwartz, Zohar Habot-Wilner, Nathanel Silam, Karen Rehany-Hen, Dana Wolters, Ariella Koffler	4	2
Israel	18004	Rabin Medical Center, Beilinson Campus, Derech Ze'ev Jabotinsky 39, Petah Tikva, 4941492	Irit R Rosenblatt	Alon Tiosano, Amir Hadayer, Amit Meshi, Assaf Dotan, Assaf Ben-Arzi, Gal Antman, Isaac Levy, Judith Kramarz, Karny Shouchane Blue, Maureen Yogev, Meydan Ben Ishai, Michal Schaap Fogler, Noa Stockhammer-Kaner, Orly Gal-Or, Rabeei Haj Daood, Rita Ehrlich, Ruth Axer Siegel, Yair Pesoa, Yariv Keshset, Yehonatan Weinberger, Iliya Simantov, Avraham Abudi, Halleluya Rosen, Michelle Cahn	1	1

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Israel	18004	Rabin Medical Center, Beilinson Campus, Derech Ze'ev Jabotinsky 39, Petah Tikva, 4941492	Irit R Rosenblatt	Alon Tiosano, Amir Hadayer, Amit Meshi, Assaf Dotan, Assaf Ben-Arzi, Gal Antman, Isaac Levy, Judith Kramarz, Karny Shouchane Blue, Maureen Yogev, Meydan Ben Ishai, Michal Schaap Fogler, Noa Stockhammer-Kaner, Orly Gal-Or, Rabeei Haj Daood, Rita Ehrlich, Ruth Axer Siegel, Yair Pesoa, Yariv Keshset, Yehonatan Weinberger, Iliya Simantov, Avraham Abudi, Halleluya Rosen, Michelle Cahn	1	1
Israel	18005	Meir Medical Center, 59 Tchernichovski St. Kfar Saba 4428164	Alexander Rubowitz	Alon Roy, Elad Moisseiev, Nimrod Dar, Ori Segal, Raz Gepstein, Galut Kabaso	3	3

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Israel	18007	Rambam Health Care Campus, 8 HaAliya HaShniya St. Haifa, 3109601	Barak Yoreh	Alexey Rapoport, Dalia Dori, Efrat Naaman, Elie Zaher, Rina Leibu, Shadi Safuri, Tarek Debes, Rajeid Waked Al Qutub, Cecilia Labardini, Waseem Nasser	5	3
Italy	19001	Azienda Ospedaliera Universitaria Careggi, Largo Brambilla, 3 Padiglione 15 Piastra dei Servizi Piano terra, stanza 31 50134 Firenze	Fabrizio Giansanti	Vittoria Murro, Chiara Lenzetti, Lorenzo De Angelis	3	2
Italy	19003	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi Oftalmologia, Via Pelagio Palagi 9, 40138 Bologna,	Antonio Ciardella	Maria Chiara Morara, Anna Rita Piccinini, Nicole Balducci	1	1
Italy	19004	Azienda Sanitaria Universitaria Friuli Centrale ASU-FC, Clinica Oculistica – P.le Santa Maria della Misericordia, 15 33100 Udine, ITALY	Paolo Lanzetta	Daniele Veritti, Valentina Sarao	2	1

Country	Site no.	Address	Name of Principal Investigator	Name of Sub-Investigator	Number of Screened Patients	Number of Randomized Patients
Italy	19005	Azienda Ospedaliera Universitaria Policlinico Tor Vergata, Viale Oxford, 81 Azienda Ospedaliera Univ Pol Tor Vergata – Dermatologia 00133 Roma	Federico Ricci	Filippo Missiroli, Cecilia De Felici, Alessia Di Stefano	1	0
Italy	19006	Fondazione IRCCS CA' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35 Neurology 20122 Milano	Francesco Viola	Marco Nassisi	0	0
Italy	19008	Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Largo Agostino Gemelli, 8 Pharmacy 00168 Roma	Angelo Minnella	Martina Maceroni, Maria Graza Sammarco, Laura Guccione, Patrizio Bernardinelli, Antonio Baldascino	14	8

Safety Assessments
Adverse events (AEs), clinical laboratory test, physical examination, vital signs, full ophthalmic examinations (slit-lamp biomicroscopy, IOP measurements, and fundus examinations), digital imaging, fluorescein angiogram, and visual function questionnaire were monitored.

Pharmacokinetics Assessments:
Blood samples of approximately 24 mL were collected for measurement of plasma concentrations of systemic free and total aflibercept at Week 0 (Visit 1) prior to 1st IVT dose, 48 hours after 1st IVT dose (Visit 1a), and at 48 hours after the 3rd IVT dose (Visit 3a). The 48-hour post- administration timepoint were chosen to approximate to the

estimated plasma Cmax, thereby permitting maximal sensitivity to detect differences between the treatment groups. In case of a delayed IVT dose, the collection of blood for plasma concentration assessment was postponed accordingly to keep the required time intervals (48 hours) between IVT dose and sample collection. Concentrations of free and total aflibercept were measured using a validated assay by (b) (4)

Immunogenicity Assessments:
Anti-drug antibody formation was evaluated in serum in all patients in Study FYB203-03-01 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); in addition, for patients participating in the PK subgroup, samples for ADA testing were collected 1 week after the 1st dose (Visit 1b) and 48 hours after the 3rd dose (Visit 3a).

Statistical Methodologies
Determination of Sample Size

The total sample size of approximately 400 patients for the EU analysis was calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 9.0 ETDRS letters in BCVA. An equivalence test of means using two 1-sided tests with sample sizes of 180 in each treatment group (360 patients in total) achieves 90.0% power at a 2.5% significance level when no difference between the means is assumed, the SD is 9.0 letters, and the equivalence interval is [-3.5; 3.5] letters. Considering that about 10% of patients might drop-out and/or would be non- evaluable, 400 patients in total were planned to be included in the W24 analysis.

Analysis populations

Full Analysis Set
The full analysis set (FAS) included all patients who received at least 1 injection of study medication in the study eye. Patients were analyzed according to their randomized treatment. The FAS was used for the analysis of all efficacy data.

Per Protocol Set
The per protocol set (PPS) included all patients that were in the FAS and

- Had no major protocol deviations until Week 8 that would interfere with the interpretation of the BCVA efficacy data at Baseline or at Week 8
- Had received treatment from the randomized treatment group only before Week 8
- Had a valid measurement of the BCVA at Baseline and at Week 8 available
- Had no positive total aflibercept concentration at Baseline (since this indicated use of prohibited prior treatment, even if no such treatment might have been explicitly documented. A total aflibercept concentration at Baseline documented as 'not reportable' was treated like a positive value, as the true value was unclear and values below limit of quantification would be documented as such)

Safety Analysis Set
The safety analysis set (SAF) included all patients who received at least 1 injection of study medication in the study eye. Patients were analyzed according to the treatment they actually received in the study eye irrespective of their randomized treatment. The SAF was used for the analysis of all safety and tolerability data.

Plasma Concentration Analysis Set
The plasma concentration analysis set (PKS) included patients that were in the SAF and had at least 1 valid post-dose plasma concentration measurement. Patients were analyzed according to the treatment they actually received in the study eye at Visit 1. Patients who received injections from different treatment groups at Visit 1 and Visit 3 were not included in the PKS. Furthermore, patients with a positive Baseline total aflibercept concentration were excluded from the PKS.

Efficacy Analysis
The difference between FYB203 and EU Eylea with respect to the primary efficacy endpoint was assessed with an MMRM based on all available data collected for the study eye until Week 24 (Visit 5) for all patients in the FAS. The MMRM included the Baseline BCVA by ETDRS letters, region (Japan vs. ROW), treatment, visit, treatment-visit- interaction and Baseline-visit-interaction, the estimates were thus adjusted for these parameters.

The null hypothesis of non-equivalence was tested using the estimated difference between FYB203 and Eylea in change from Baseline in BCVA by ETDRS letters to Week 8 (from Visit 1 to Visit 3). The comparison of the 2 treatment groups was performed by calculating 2-sided 90.4% (US analysis) or 95.2% (EU analysis) CIs and compare these to the pre-defined equivalence margin of (-3.5; +3.5) ETDRS letters.

The sensitivity analyses for the primary endpoint at Week 8 were performed using different MMRMs and ANCOVAs with and without MI. Table 11-2 summarizes the sensitivity analyses. All sensitivity analyses and the primary efficacy analysis for the primary endpoint showed a similar difference in BCVA change from Baseline between the FYB203 and Eylea treatment groups; all the 90.4% as well as 95.2% CIs for the LS mean difference were completely contained within the pre-defined equivalence margin.

6.2. Study Results

Compliance with Good Clinical Practices
The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with International Council for Harmonization (ICH) guideline on Good Clinical Practice (GCP).

Patient Disposition

The study was conducted between 21-Jul-2020 (first patient, first visit) and 18-May-2023 (last patient last visit). Patients were treated between 12-Aug-2020 and 30-Mar-2023.
Patient disposition is summarized in Table 6.2-1.

Subject Disposition by Treatment Group

Table 6.2-1 Patient Disposition (All Screened Patients and FAS for Discontinuation)[1]

	FYB203		Eylea		Total	
	n	(%)	n	(%)	n	(%)
Number of Screenings (including re-screenings)[2]					719	
Number of re-Screenings					7	
Number of Screening failures (including re-screenings)					285	
Screened and enrolled patients (signed ICF)[3]					712	
Re-screened patients					7	
Screening failure patients					278	
Patients randomized[3]	215	(100.0)	219	(100.0)	434	(100.0)
Patients randomized but not treated[4]	0	(0.0)	1	(0.5)	1	(0.2)
Patients treated[3]	215	(100.0)	218	(99.5)	433	(99.8)
Patients completed study until Week 24	208	(96.7)	211	(96.3)	419	(96.5)
Patients completed study until Week 56	*196*	*(91.2)*	*206*	*(94.1)*	*402*	*(92.6)*
Patients Completing and Discontinuing Study – Week 8 (V3) FAS						
Completed	*212*	*(98.6)*	*216*	*(99.1)*	*428*	*(98.8)*
Prematurely discontinued	*3*	*(1.4)*	*2*	*(0.9)*	*5*	*(1.2)*
Premature discontinuation of study until Week 24 (FAS)[3]	7	(3.3)	7	(3.2)	14	(3.2)
Adverse event	2	(0.9)	0	(0.0)	2	(0.5)
Death	0	(0.0)	1	(0.5)	1	(0.2)
Lost to follow-up	1	(0.5)	0	(0.0)	1	(0.2)
Protocol violation	1	(0.5)	0	(0.0)	1	(0.2)
Physician decision	0	(0.0)	1	(0.5)	1	(0.2)
ICF withdrawal by patient	1	(0.5)	4	(1.8)	5	(1.2)
Other[5]	2	(0.9)	1	(0.5)	3	(0.7)
Premature discontinuation of treatment Week 24 (FAS)[3]	5	(2.3)	8	(3.7)	13	(3.0)
Adverse event	2	(0.9)	0	(0.0)	2	(0.5)
Death	0	(0.0)	1	(0.5)	1	(0.2)
Lost to follow-up	1	(0.5)	0	(0.0)	1	(0.2)
Physician decision	0	(0.0)	2	(0.9)	2	(0.5)
ICF withdrawal by patient	1	(0.5)	4	(1.8)	5	(1.2)
Other[6]	1	(0.5)	1	(0.5)	2	(0.5)
Premature discontinuation of study until Week 56 (FAS)[3]	*19*	*(8.8)*	*12*	*(5.5)*	*31*	*(7.2)*
Adverse event	*5*	*(2.3)*	*0*	*(0.0)*	*5*	*(1.2)*
Death	*4*	*(1.9)*	*1*	*(0.5)*	*5*	*(1.2)*
Lost to follow-up	*1*	*(0.5)*	*1*	*(0.5)*	*2*	*(0.5)*
Protocol violation	*1*	*(0.5)*	*0*	*(0.0)*	*1*	*(0.2)*
Physician decision	*0*	*(0.0)*	*2*	*(0.9)*	*2*	*(0.5)*
ICF withdrawal by patient	*3*	*(1.4)*	*7*	*(3.2)*	*10*	*(2.3)*
Other[5]	*5*	*(2.3)*	*1*	*(0.5)*	*6*	*(1.4)*
Premature discontinuation of treatment until Week 56 (FAS)[3]	*20*	*(9.3%)*	*10*	*(4.6%)*	*30*	*(6.9%)*
Adverse event	*5*	*(2.3%)*	*0*	*(0.0%)*	*5*	*(1.2%)*

Death	*4*	*(1.9%)*	*1*	*(0.5%)*	*5*	*(1.2%)*
Lost to follow-up	*1*	*(0.5%)*	*0*	*(0.0%)*	*1*	*(0.2%)*
Physician decision	*1*	*(0.5%)*	*2*	*(0.9%)*	*3*	*(0.7%)*
ICF withdrawal by patient	*3*	*(1.4%)*	*6*	*(2.8%)*	*9*	*(2.1%)*
Other[6]	*6*	*(2.8%)*	*1*	*(0.5%)*	*7*	*(1.6%)*

FAS = full analysis set, ICF = informed consent form
[1] Patients are displayed according to the randomized treatment assigned, even if a different treatment was administered
[2] n = number of screening procedures
[3] n = number of patients in corresponding class
[4] Patient (b) (6) was randomized to Eylea but not treated due to ICF withdrawal
[5] Other: Patients (b) (6) treated with FYB203 and patient (b) (6) treated with Eylea discontinued the study due to other reasons related to the geopolitical situation in Ukraine. Patient (b) (6) treated with FYB203 refused to participate in the continuation of the study due to the improvement of vision
[6] Other: Patients (b) (6) treated with FYB203 and patient (b) (6) treated with Eylea discontinued the treatment due to other reasons related to the geopolitical situation in Ukraine. Patient (b) (6) treated with FYB203 refused to participate in the continuation of the study due to the improvement of vision
Source: Listing 1.1, Listing 1.2; Table 14.1.2.8.2

Reviewer's comment:
At the primary efficacy endpoint, Week 8 (Visit 3), 98.6% of patients in the FYB203 group and 99.1% of patients in the Eylea group remained on the study in the FAS. The results were the same for the SAF analysis set.

Up to Week 24, 7 (3.3%) patients in the FYB203 group and 7 (3.2%) patients in the Eylea group had discontinued the study prematurely. Until the end of the study, the number of discontinuations increased to 19 (8.8%) in the FYB203 group and to 12 (5.5%) in the Eylea group. Reasons for discontinuation are summarized in Table 6.2-1.

The number of subjects completing the 24-week primary efficacy endpoint was similar between groups.

Protocol Violations/Deviations

Table 6.2-2 Major Protocol Deviations or Major Intercurrent Event Occurring in ≥ 1% (FAS, N=433)

	FYB203 N=215		Eylea N=218		Total N=433	
	n	(%)	n	(%)	n	(%)
Any major protocol deviation or intercurrent event[1,2]	14	(6.5)	13	(6.0)	27	(6.2)
BCVA schedule deviation	6	(2.8)	7	(3.2)	13	(3.0)
BCVA schedule deviation at V3 (programmed protocol deviation)	6	(2.8)	7	(3.2)	13	(3.0)
IMP schedule deviation	2	(0.9)	3	(1.4)	5	(1.2)
IMP schedule deviation at V2 (programmed protocol deviation)	2	(0.9)	3	(1.4)	5	(1.2)

BCVA = best corrected visual acuity, CRA = clinical research associate, FAS = full analysis set, IMP = investigational medicinal product, N = total number of patients in analysis set, n = number of patients in corresponding class, PI = principal investigator, V = Visit

[1] All protocol deviations except 'Violation of inclusion criterion 08: Foveal center point retinal thickness is not taken at Screening' interfered with the interpretation of the BCVA efficacy data at Baseline or Week 8

[2] A patient can have several major protocol deviations / intercurrent events in different categories. Visit schedule deviations reported by clinical research associates can include the same patients as programmed BCVA schedule deviations.

Source: Table 14.1.3.1.2, Table 14.1.3.2.2

Reviewer's Comment:
In total, there were 27 (6.2%) patients with major protocol deviations, which led to the exclusion from the PPS, 14 patients in the FYB203 group and 13 patients in the Eylea group.

The most frequent deviation was 'BCVA schedule deviation at Visit 3 or Week 8 the primary efficacy timepoint, 6 patients in the FYB203 group and 7 patients in the Eylea group.

Data Sets Analyzed

There were 4 analysis sets. Table 6.2-3 provides the number of patients in each analysis set and the reason for exclusion for all randomized patients.

In total, 27 treated patients were excluded from the PPS. Patients could be excluded for multiple reasons at the same time. The most frequent reason for exclusion from the PPS was the lack of BCVA measurement at Week 8 (analysis visit), which affected 11 (2.5%) patients, followed by major IMP schedule or administration deviations (7 patients; 1.6%) and violation of inclusion/exclusion criteria (4 patients; 0.9%). Furthermore, 3 patients were excluded due to a positive Baseline total aflibercept concentrations and 2 patients due to measured BCVA values invalid/affected due to protocol deviation. One patient was excluded after possible unmasking of study site staff or subject. As described above, 2 patients received injections from different treatment than randomized. These patients were also excluded from the PPS. Therefore, the PPS consisted of 406 patients.

Out of the 60 patients who were recruited into the plasma concentration sub-study, 3 patients (b) (6) had positive Baseline total aflibercept concentrations. No clear root cause for these positive concentrations could be identified. Therefore, they were excluded from the PPS and PKS as potential prior treatment with aflibercept could not be conclusively ruled out. This resulted in a PKS of 57 patients.

In both treatment groups, similar numbers of patients were excluded from the SAF, FAS, PPS and PKS.

Table 6.2-3 Number of Patients in Each Analysis Set and Reasons for Exclusion From Each Analysis Set (All Randomized Patients, N=434)

Analysis set	FYB203 N=215		Eylea N=219		Total N=434	
Reason for exclusion	n	(%)	n	(%)	n	(%)
Patients in SAF	215	(100.0)	218	(99.5)	433	(99.8)
Reason for exclusion from SAF: No injection of study medication	0	(0.0)	1	(0.5)	1	(0.2)
Patients in FAS	215	(100.0)	218	(99.5)	433	(99.8)
Reason for exclusion from FAS: No injection of study medication	0	(0.0)	1	(0.5)	1	(0.2)
Patients in PPS	201	(93.5)	205	(94.0)	406	(93.8)
Patients in SAF/FAS	215	(100.0)	218	(100.0)	433	(100.0)
Reasons for exclusion from PPS:						
No BCVA measurement at Week 8	6	(2.8)	5	(2.3)	11	(2.5)
Major IMP schedule or administration deviation	3	(1.4)	4	(1.8)	7	(1.6)
Violation of inclusion/exclusion criteria	2	(0.9)	2	(0.9)	4	(0.9)
Positive Baseline total aflibercept concentration	1	(0.5)	2	(0.9)	3	(0.7)
Measured BCVA values invalid/affected due to protocol deviation	1	(0.5)	1	(0.5)	2	(0.5)
Injections from different treatment than randomized until Week 8	1	(0.5)	1	(0.5)	2	(0.5)
Possible unmasking of study site staff or subject	0	(0.0)	1	(0.5)	1	(0.2)
No BCVA measurement at Baseline	0	(0.0)	0	(0.0)	0	(0.0)
Patients in PKS*	31	(96.9)	26	(92.9)	57	(95.0)
Patients recruited into plasma concentration sub-study	32	(100.0)	28	(100.0)	60	(100.0)
Reasons for exclusion from PKS:						
Positive Baseline total aflibercept concentration	1	(3.1)	2	(7.1)	3	(5.0)

BCVA = best corrected visual acuity, FAS = full analysis set, IMP = investigational medicinal product, N = total number of patients in analysis set, n = number of patients in corresponding class, PKS = plasma concentration analysis set, PPS = per protocol set, SAF = safety analysis set

* For patients in PKS block, % = number of patients in corresponding class / number of patients recruited into plasma concentration sub-study

Source: Table 14.1.4.1

Demographic and Baseline Characteristics

Table 6.2-4 Demographics (FAS, N=433)

Parameter Category	FYB203 N=215	Eylea N=218	Total N=433
[n (%)]			
Male	94 (43.7%)	91 (41.7%)	185 (42.7%)
Female	121 (56.3%)	127 (58.3%)	248 (57.3%)
Of childbearing potential	0 (0.0%)	1 (0.5%)	1 (0.2%)
Not of childbearing potential	121 (56.3%)	126 (57.8%)	247 (57.0%)
Country [n (%)]			
Bulgaria	10 (4.7%)	11 (5.0%)	21 (4.8%)
Czech Republic	34 (15.8%)	35 (16.1%)	69 (15.9%)
Hungary	34 (15.8%)	34 (15.6%)	8 (15.7%)
Israel	6 (2.8%)	6 (2.8%)	12 (2.8%)
Italy	9 (4.2%)	9 (4.1%)	18 (4.2%)
Japan	17 (7.9%)	16 (7.3%)	33 (7.6%)
Poland	37 (17.2%)	40 (18.3%)	77 (17.8%)
Russian Federation	35 (16.3%)	36 (16.5%)	71 (16.4%)
Ukraine	33 (15.3%)	31 (14.2%)	64 (14.8%)
Race [n (%)]			
White	197 (91.6%)	201 (92.2%)	398 (91.9%)
Asian	17 (7.9%)	16 (7.3%)	33 (7.6%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Ethnicity [n (%)]			
Hispanic or Latino	3 (1.4%)	5 (2.3%)	8 (1.8%)
Not Hispanic or Latino	212 (98.6%)	213 (97.7%)	425 (98.2%)
Age at Screening [years]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	73.7 (7.72)	73.3 (7.70)	73.5 (7.71)
Median	74.0	74.0	74.0
Min–Max	51–93	51–92	51–93
Q1–Q3	68.0–79.0	68.0–79.0	68.0–79.0
Age categories 1 at Screening [n (%)]			
50–64 years	17 (7.9%)	25 (11.5%)	42 (9.7%)
65–75 years	105 (48.8%)	111 (50.9%)	216 (49.9%)
> 75 years	93 (43.3%)	82 (37.6%)	175 (40.4%)

FAS = full analysis set, Max = maximum, Min = minimum, N = total number of patients in analysis set, n = number of patients with non-missing assessments, Q1 = first quartile, Q3 = third quartile, SD = standard deviation

Source: Table 14.1.5.1.2

Table 6.2-5 Baseline Diagnosis Characteristics (FAS, N=433)

Parameter Category	FYB203 N=215	Eylea N=218	Total N=433
Study eye [n (%)]			
OD (right eye)	112 (52.1%)	99 (45.4%)	211 (48.7%)
OS (left eye)	103 (47.9%)	119 (54.6%)	222 (51.3%)
Iris color [n (%)]			
Light	76 (35.3%)	84 (38.5%)	160 (37.0%)
Medium	96 (44.7%)	86 (39.4%)	182 (42.0%)
Dark	43 (20.0%)	48 (22.0%)	91 (21.0%)
Baseline BCVA Snellen equivalent in study eye [n (%)]			
20/40	39 (18.1%)	40 (18.3%)	79 (18.2%)
20/50	50 (23.3%)	46 (21.1%)	96 (22.2%)
20/63	32 (14.9%)	33 (15.1%)	65 (15.0%)
20/80	32 (14.9%)	35 (16.1%)	67 (15.5%)
20/100	23 (10.7%)	17 (7.8%)	40 (9.2%)
20/125	5 (2.3%)	15 (6.9%)	20 (4.6%)
20/160	13 (6.0%)	13 (6.0%)	26 (6.0%)
20/200	21 (9.8%)	19 (8.7%)	40 (9.2%)
Lesion type at Baseline in the study eye [n (%)]			
Type 1 MNV	71 (33.0%)	72 (33.0%)	143 (33.0%)
Type 2 MNV	49 (22.8%)	51 (23.4%)	100 (23.1%)
Mixed type 1 and type 2 MNV	74 (34.4%)	76 (34.9%)	150 (34.6%)
Type 3 MNV	19 (8.8%)	19 (8.7%)	38 (8.8%)
Missing	2 (0.9%)	0 (0.0%)	2 (0.5%)
Time since first diagnosis of nAMD to randomization [days]			
N	182	191	373
Missing values	33	27	60
Mean (SD)	55.0 (101.64)	53.1 (108.75)	54.1 (105.20)
Median	32.0	29.0	30.0
Min–Max	7–975	6–1226	6–1226
Q1–Q3	20.0–53.0	19.0–54.0	20.0–53.0

BCVA = best corrected visual acuity, FAS = full analysis set, Max = maximum, Min = minimum, MNV = macular neovascularization, N = total number of patients in analysis set, n = number of patients with non-missing assessments, nAMD = neovascular age-related macular degeneration, OD = oculus dexter, OS = oculus sinister, Q1 = first quartile, Q3 = third quartile, SD = standard deviation

Source: Table 14.1.5.1.2

Reviewer's Comment: Baseline ophthalmologic parameters were balanced between the FYB203 and Eylea groups.

Overall, mean (SD) Baseline BCVA was 57.9 (11.27) letters, Baseline FCP retinal thickness was 476.6 (154.55) µm, Baseline FCS retinal thickness was 504.1 (139.31) µm, total lesion area was 9.6 (5.84) mm² and Baseline IOP was 15.3 (2.67) mmHg. For patients with a missing FCP measurement at Visit 1 (Baseline) (N=9), the measurement from the Screening visit was taken as Baseline value for the analysis.

Table 6.2-6 Baseline Ophthalmologic Parameters (FAS, N=433)

	FYB203 N=215	Eylea N=218	Total N=433
Baseline (V1) BCVA [ETDRS letters]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	58.0 (11.35)	57.8 (11.22)	57.9 (11.27)
Median	60.0	60.0	60.0
Min–Max	34–73	34–73	34–73
Q1–Q3	51.0–67.0	50.0–67.0	51.0–67.0
Baseline (V1) FCP retinal thickness [µm]			
N	208	216	424
Missing values	7	2	9
Mean (SD)	465.9 (157.06)	487.0 (151.73)	476.6 (154.55)
Median	432.5	448.5	439.0
Min–Max	188–1161	269–930	188–1161
Q1–Q3	347.0–550.5	364.0–598.5	353.0–573.5
Baseline (V1) FCS retinal thickness [µm]			
N	213	218	431
Missing values	2	0	2
Mean (SD)	493.5 (140.50)	514.5 (137.68)	504.1 (139.31)
Median	463.0	484.0	472.0
Min–Max	226–1152	292–911	226–1152
Q1–Q3	393.0–558.0	402.0–611.0	397.0–585.0
Screening[1] total lesion area [mm^2]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	9.5 (5.74)	9.6 (5.95)	9.6 (5.84)
Median	8.4	8.9	8.6
Min–Max	0–23	1–34	0–34
Q1–Q3	4.9–13.4	4.8–13.0	4.8–13.2
Baseline (V1) IOP [mmHg]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	15.0 (2.60)	15.6 (2.71)	15.3 (2.67)
Median	15.0	16.0	15.0
Min–Max	8–21	10–23	8–23
Q1–Q3	13.0–17.0	14.0–17.0	13.0–17.0

BCVA = best corrected visual acuity, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, FCP = foveal center point, FCS = foveal central subfield, IOP = intraocular pressure, Max = maximum, Min = minimum, N = total number of patients in analysis set, n = number of patients with non-missing assessments, Q1 = first quartile, Q3 = third quartile, SD = standard deviation, V = visit

[1] Total lesion was not assessed at the Baseline Visit (Visit 1).

Source: Table 14.1.5.7.2

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline ophthalmologic parameters were balanced between the FYB203 and Eylea groups. Overall, mean (SD) Baseline BCVA was 57.9 (11.27) letters, Baseline FCP retinal thickness was 476.6 (154.55) µm, Baseline FCS retinal thickness was 504.1 (139.31) µm, total lesion area was 9.6 (5.84) mm^2 and Baseline IOP was 15.3 (2.67) mmHg (Table 10-8). For patients with a missing FCP measurement at Visit 1 (Baseline) (N=9), the measurement from the Screening visit was taken as Baseline value for the analysis.

Reviewer's comment: Baseline ophthalmologic parameters for the SAF, PPS and PKS were comparable.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Reviewer's comment: *There were no clinically relevant difference between treatment groups regarding treatment compliance, concomitant medications, or rescue medications.*

Efficacy results –Primary Endpoint

The primary efficacy endpoint, the change from Baseline in BCVA by ETDRS letters to Week 8 (from Visit 1 to Visit 3) was calculated to evaluate and compare functional changes in BCVA by ETDRS letters following treatment with FYB203 or Eylea at Week 8 compared to Baseline. The difference between FYB203 or Eylea with respect to the primary efficacy endpoint was assessed with an MMRM based on all available data collected for the study eye until Week 24 (Visit 5) for all patients in the FAS. The MMRM included the Baseline BCVA by ETDRS letters, region (Japan vs. ROW), treatment, visit, treatment-visit- interaction and Baseline-visit-interaction, the estimates were thus adjusted for these parameters.

The null hypothesis of non-equivalence was tested using the estimated difference between FYB203 and Eylea in change from Baseline in BCVA by ETDRS letters to Week 8 (from Visit 1 to Visit 3). The comparison of the 2 treatment groups was performed by calculating 2-sided 90.4% (US analysis) or 95.2% (EU analysis) CIs and compare these to the pre-defined equivalence margin of (-3.5; 3.5) ETDRS letters.

Table 6.2-7 MMRM: Comparison of Change in BCVA (ETDRS letters) from Baseline to Week 8 including data up to Week 24-US Analysis- FAS (N=433)

		MMRM Least Squares estimation					
Week (Visit) Treatment group Difference	N	n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 90.4% CI	2-sided 95.2% CI
Week 8 (V3)							
FYB203	215	215	0	6.6	0.73	[5.4; 7.8]	[5.2; 8.0]
Eylea	218	218	0	5.6	0.73	[4.4; 6.9]	[4.2; 7.1]
Difference: FYB203 - Eylea				1.0	0.76	[-0.3; 2.2]	[-0.6; 2.5]
US analysis		2-sided 90.4% CI contained in (-3.5; 3.5)[c] : yes					
EU analysis		2-sided 95.2% CI contained in (-3.5; 3.5)[c] : yes					

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 8 assessments were considered if they have at least 1 Post-Baseline BCVA value until Week 24.

[b] Estimates are adjusted for Baseline BCVA, region (Japan vs. Rest of world), treatment, visit, treatment-visit- interaction and Baseline-visit-interaction.

[c] If the CI for the difference in LS means was completely contained in the interval (-3.5 letters; 3.5 letters), FYB203 and Eylea were considered equivalent.

Source: Table 14.1.4.1, Table 14.2.1.1, Table 14.2.1.2

Reviewer's comment: *The 2-sided 90.4% CI of [-0.3; 2.2] ETDRS letters for the difference was completely contained in the pre-defined equivalence margin of (-3.5; 3.5) ETDRS letters for the US analysis. The study was successful in meeting its primary efficacy endpoint.*

The 2-sided 95.2% CI of [-0.6; 2.5] ETDRS letters for the difference was completely contained in the pre-defined equivalence margin of (-3.5; 3.5) ETDRS letters for the EU analysis.

Table 6.2-8 Summary of Sensitivity Analyses Displaying Least Squares Mean Difference Between FYB203 and Eylea in BCVA Change From Baseline to Week 8 (US and EU Analysis, FAS, N=433)

Method, Set, Data	LS mean difference in ETDRS letters[1]	SE	2-sided 90.4% CI Source	2-sided 95.2% CI Source	Within equivalence margin]-3.5; 3.5[
MMRM, FAS Data up to Week 24, including patient discontinuation status prior to Week 24 (Yes/No) as additional covariate	1.0	0.76	[-0.3; 2.2] Table 14.2.2.1	[-0.6; 2.5] Table 14.2.3.1	yes
MMRM, FAS Data up to Week 24, including patient discontinuation of treatment prior to Week 24 (Yes/No) as additional covariate	0.9	0.76	[-0.3; 2.2] Table 14.2.2.2	[-0.6; 2.5] Table 14.2.3.2	yes
MMRM, FAS Data up to Week 24, including patient any major protocol deviation status (Yes/No) as additional covariate	0.9	0.76	[-0.3; 2.2] Table 14.2.2.3	[-0.6; 2.5] Table 14.2.3.3	yes
MMRM, FAS Data up to Week 24, including ancillary chart use (Yes/No) as additional covariate	1.0	0.77	[-0.3; 2.3] Table 14.2.2.4	[-0.5; 2.5] Table 14.2.3.4	yes
MMRM, FAS Data up to Week 8	0.9	0.77	[-0.3; 2.2] Table 14.2.2.5	[-0.6; 2.5] Table 14.2.3.5	yes
ANCOVA, FAS, observed cases	1.0	0.77	[-0.3; 2.3] Table 14.2.2.6	[-0.5; 2.5] Table 14.2.3.6	yes
ANCOVA, FAS, multiple imputation	1.1	0.77	[-0.2; 2.4] Table 14.2.2.7	[-0.4; 2.6] Table 14.2.3.7	yes

[1] Difference calculated as FYB203 – Eylea Sources: directly in table.

Reviewer's comment: *The sensitivity analyses performed confirmed the primary efficacy result.*

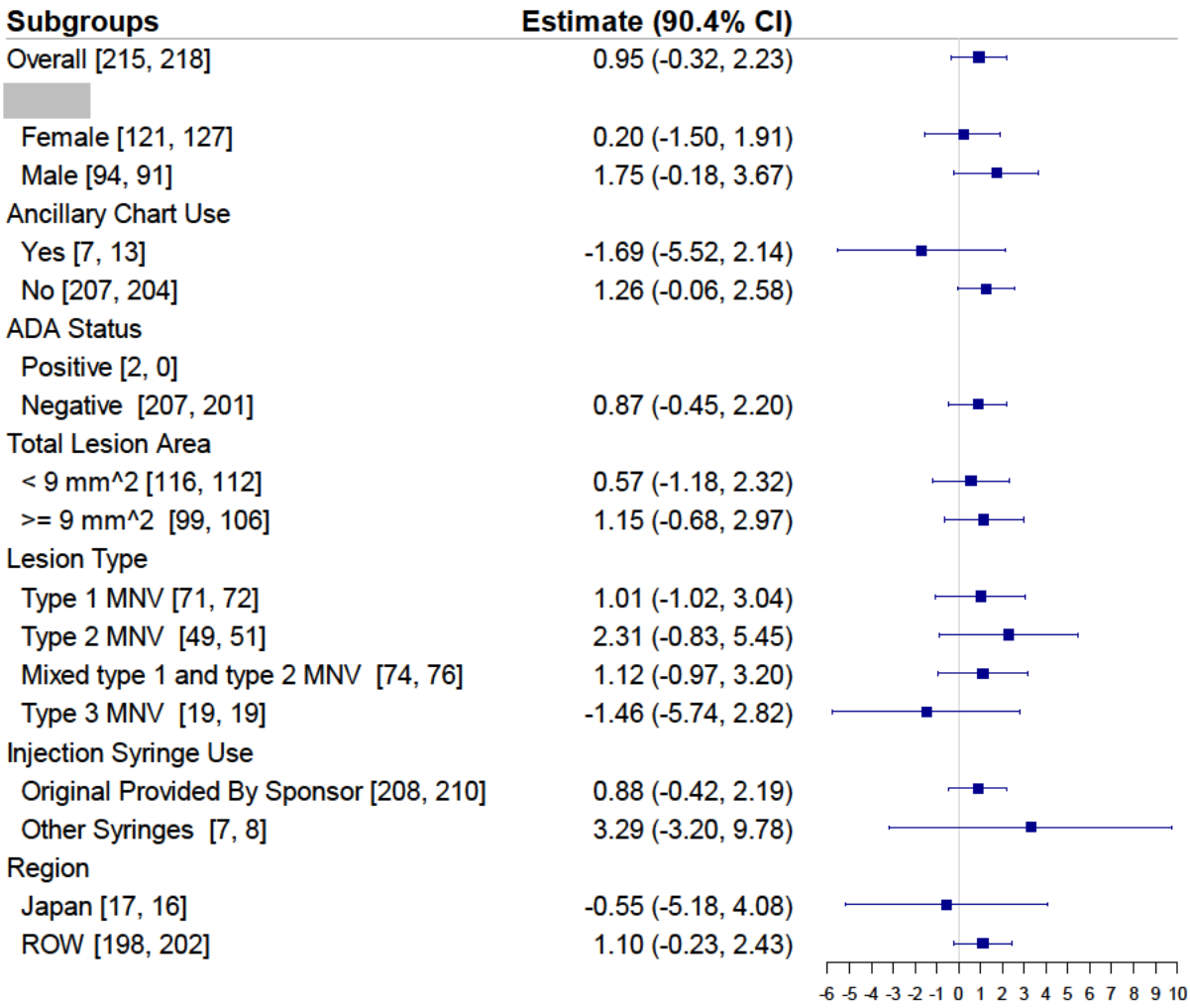
Data Quality and Integrity

The application was of sufficient quality to conduct a substantive review of the data. There were no data integrity issues uncovered during the review of this NDA.

Efficacy Results – Secondary and other relevant endpoints

For the US specific analysis there was no key secondary endpoint.

Figure 6.2-1 Subgroup analysis for change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8.



Reviewer comment: Treatment effects in evaluable subgroups (e.g., by age, iris color) in the study were generally consistent with the results in the overall population. Age ≥75 years did not have a clinically significant effect on the primary efficacy endpoint. The differences by race (Asian and White) and [redacted] were comparable.

Persistence of Effect

The change in visual acuity was similar for both treatment groups over the entire study period. Initial improvements were sustained showing a stable treatment response for both FYB203 and Eylea.

Reviewer's Comment:
As per agency discussion a biosimilar may demonstrated similarity to the reference listed drug with a single adequate and well controlled clinical efficacy trial. the submitted study demonstrated that FYB203 demonstrated non-inferior efficacy to EU-Eylea and was , therefore, biosimilar to Eylea.

7. Review of Safety

7.1. Safety Review Approach

The safety of FYB203 was evaluated in a single randomized, double-masked, active-controlled study compared to EU-Eylea in patients with age-related macular degeneration. The safety population included 433 subjects treated for 56 weeks and included all subjects who received at least 1 intravitreal injection of study drug (215 patients exposed to FYB203, 218 patients exposed to the reference product Eylea).

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The mean (SD) treatment duration for the W24 analysis had been 110.9 (14.15) days and the mean (SD) study duration at this point was 183.0 (17.59) days. For the final analysis, the mean (SD) treatment duration increased to 323.1 (58.97) days with a mean (SD) study duration of 398.7 (53.03) days. The treatment and study durations were well balanced between both treatment groups and no relevant differences were observed.

Study and Treatment Duration (SAF, N=433)

Parameter Category	FYB203 N=215	Eylea N=218	Total N=433
N	215	218	433
Missing values	0	0	0
Mean (SD)	110.6 (14.64)	111.2 (13.67)	110.9 (14.15)
Median	113.0	113.0	113.0
Min–Max	29–128	30–129	29–129
Q1–Q3	112.0–114.0	113.0–115.0	112.0–114.0
Study duration until Week 24 [days]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	183.6 (17.71)	182.4 (17.49)	183.0 (17.59)
Median	184.0	184.0	184.0
Min–Max	50–209	41–210	41–210
Q1–Q3	179.0–191.0	178.0–190.0	178.0–191.0

Source: Table 14.3.1.1

Reviewer comment: The treatment and study durations were well balanced between both treatment groups and no relevant differences were observed.

7.2.2. Relevant characteristics of the safety population:

Refer to Section 6.2, Demographics.

7.2.3. Adequacy of the safety database:

The size of the safety database and the clinical evaluations conducted during the development were adequate to assess the safety profile of FYB203.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

This BLA submission was of sufficient quality to perform a substantive review of this product.

7.3.2. Categorization of Adverse Events

All AEs (both ocular and non-ocular) were coded using MedDRA Version 23 or higher. An AE was considered a treatment emergent adverse event (TEAE) if it occurred or worsened on or after receipt of the first dose of study drug. AEs have been summarized using the MedDRA preferred term (PT) as event category and/or MedDRA primary system organ class (SOC) as summary category.

Treatment-Emergent Adverse Events (TEAEs) for each study arm (FYB203 arm and Eylea arm) were categorized as Serious TEAEs (SAEs), Fatal TEAEs, Nonfatal SAEs, Severe TEAEs, Related TEAEs to study treatment, Related TEAEs to Study Procedure (IVT injection.)

7.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns of intravitreally administered products (i.e., biomicroscopy, fundoscopy, visual acuity, IOP, etc.) were adequately addressed in the design and conduct of the trials for this product. Refer to Table 6.1-2 Evaluation and Visit Schedule for procedures and scheduled assessments for laboratory evaluations.

7.4. Safety Results

7.4.1. Deaths

Deaths during Treatment

Patient	Age / Sex	MedDRA preferred term / (Start day–Stop / Death day)	AESI/ Severity/ Serious	Related to Study Procedure / Study Treatment	Outcome
Until Week 24 Treatment Group: Eylea					
(b) (6)	69 / Male	Cardiac failure/ Day 41–Day 41	No/Severe/ Yes	Unrelated / unlikely to be related	Fatal
After Week 24 Treatment Group: FYB203					
(b) (6)	86 / Female	Pulmonary fibrosis/ Day 296–Day 325	No/Severe/ Yes	Unrelated / unrelated	Fatal
		Cardiac failure/ Day 321–Day 325	No/Moderate/ Yes	Unrelated / unrelated	Fatal
	70 / Male	COVID-19/ Day 260–Day 265	No/Severe/ Yes	Unrelated / unrelated	Fatal
		COVID-19 pneumonia/ Day 261–Day 265	No/Severe/ Yes	Unrelated / unrelated	Fatal
		Cardiac failure/ Day 265–Day 265	No/Severe/ Yes	Unrelated / unrelated	Fatal
	72 / Male	Ileus/ Day 273–Day 274	No/Severe/ Yes	Unrelated / unrelated	Fatal
	77 / Male	Acute myeloid leukaemia/ Day 243–Day 270	No/Severe/ Yes	Unrelated / unrelated	Fatal

AESI = adverse event of special interest, MedDRA = medical dictionary for regulatory activities
Source: Listing 16.2.7.12, Listing 16.2.7.13, Listing 16.2.4.1

Seven patients died during the course of the study through week 56, of which 5 patients were randomized and received study treatment and 2 patients were screen failures. The deaths were considered by the investigators to be unrelated to the study drugs.

7.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment-Emergent Adverse Events Leading to Withdrawal of Study Treatment and/or Discontinuation of Study Until Week 56

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
Any TEAE leading to withdrawal of study treatment/premature discontinuation of study	10	(4.7)	18	2	(0.9)	2	12	(2.8)	20
Eye disorders, overall	3	(1.4)	5	1	(0.5)	1	4	(0.9)	6
Eye disorder[1]	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Macular hole[2]	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Rhegmatogenous retinal detachment	1	(0.5)	3	0	(0.0)	0	1	(0.2)	3
Subretinal fluid	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Cardiac disorders, overall	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Cardiac failure	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Infections and infestations, overall	3	(1.4)	4	0	(0.0)	0	3	(0.7)	4
COVID-19	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
COVID-19 pneumonia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Toxic shock syndrome	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), overall	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Acute myeloid leukaemia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Oesophageal carcinoma stage 0[3]	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Respiratory, thoracic and mediastinal disorders, overall	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Aspiration	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Pulmonary fibrosis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Gastrointestinal disorders, overall	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Abdominal adhesions	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Ileus	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Nervous system disorders, overall	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Cerebrovascular accident	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1

Ev = number of adverse events of the specified preferred term or system organ class, MedDRA = medical dictionary for regulatory activities, N = total number of patients in analysis set, n = number of patients with at least 1 TEAE of the specified preferred term or system organ class, SAF = safety analysis set, TEAE = treatment-emergent adverse event

[1] Patient discontinued from study and treatment due to ICF withdrawal.

[2] Patient discontinued from treatment while study continued.

[3] Patient discontinued from study and treatment based on physician's decision.

Source: Listing 1.1 and Listing 1.2

7.4.3. Serious Adverse Events

Table 7.4.3-1 Serious Treatment-Emergent Ocular Adverse Events until Week 56

Patient	Age / Sex	MedDRA PT / (Start day–Stop day)	Eye Affected	AESI / Severity	Related to Study Procedure / Study Treatment	Outcome
Treatment Group: FYB203						
(b) (6)	78 / Male	Iridocyclitis / (Day 237–Day 252)	Study Eye	Yes / severe	Probably related / Probably related /	Recovered / Resolved with sequelae
		Uveitis / (Day 237–Day 252)	Study Eye	Yes / severe	Probably related / Probably related	Recovered / Resolved with sequelae
	65 / Male	Rhegmatogenous retinal detachment / (Day 44–Day 51)	Study Eye	No / moderate	Possibly related / unrelated	Recovered / Resolved with sequelae
Treatment Group: Eylea						
(b) (6)	81 / Female	Neovascular age-related macular degeneration / (Day 57–Day 113)	Fellow eye	No / severe	Unrelated / Unrelated	Recovered / Resolved with sequelae
	71 / Female	Visual impairment / (Day 58–Day 225)	Study Eye	No / moderate	Unrelated / Unrelated	Recovered / Resolved with sequelae
	67 / Male	Corneal dystrophy / (Day 337–Day 375)	Study Eye	No / mild	Unrelated / unrelated	Recovered / Resolved
	79 / Female	Retinal degeneration/ (Day 400–Ongoing)	Fellow Eye	No / moderate	Unrelated / unrelated	Not recovered/ Not resolved
	80 / Male	Glaucoma / (Day 386–Ongoing)	Fellow Eye	No / severe	Unrelated / unrelated	Not recovered/ Not resolved

AESI = adverse event of special interest, MedDRA = medical dictionary for regulatory activities, PT = preferred term

Source: Listing 1.4

Reviewer's comment: *Iridocyclitis/Uveitis in one study eye in the FYB203 group is considered a TEAE of special interest.*

Table 7.4.3-2 Serious Systemic Treatment-Emergent Adverse Events until Week 56 (SAF, N=433)

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	n	FYB203 N=215 (%)	Ev	n	Eylea N=218 (%)	Ev	n	*Total* N=433 (%)	Ev
Any serious systemic TEAE	17	(7.9)	35	23	(10.6)	35	40	(9.2)	70
Infections and infestations, overall	8	(3.7)	13	7	(3.2)	8	15	(3.5)	21
COVID-19	4	(1.9)	4	1	(0.5)	1	5	(1.2)	5
COVID-19 pneumonia	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3
Appendicitis	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Pneumonia	1	(0.5)	3	1	(0.5)	1	2	(0.5)	4
Bronchitis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Colonic abscess	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Coronavirus infection	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Gallbladder empyema	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Peritonitis	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Toxic shock syndrome	1	(0.0)	1	0	(0.0)	0	1	(0.2)	1
Urosepsis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps), overall	4	(1.9)	4	4	(1.8)	5	8	(1.8)	9
Acute myeloid leukaemia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Adenocarcinoma gastric	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Adenocarcinoma of colon	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Colon cancer	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Gallbladder cancer	0	(0.0)	0	1	(0.5)	2	1	(0.2)	2
Gastric cancer	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Oesophageal carcinoma stage 0	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Parathyroid tumour benign	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	n	FYB203 N=215 (%)	Ev	n	Eylea N=218 (%)	Ev	n	*Total* N=433 (%)	Ev
Cardiac disorders, overall	2	(0.9)	2	4	(1.8)	4	6	(1.4)	6
Cardiac failure	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Angina pectoris	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Tachycardia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Ventricular tachycardia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Gastrointestinal disorders, overall	4	(1.9)	5	2	(0.9)	4	6	(1.4)	9
Abdominal adhesions	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Diverticulum intestinal	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Gastritis	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Ileus	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Intestinal obstruction	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Large intestinal stenosis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Oesophageal obstruction	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Small intestinal obstruction	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Nervous system disorders, overall	1	(0.5)	1	4	(1.8)	4	5	(1.2)	5
Cerebrovascular accident	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Dementia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Ischaemic stroke	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Transient global amnesia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Transient ischaemic attack	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Musculoskeletal and connective tissue disorders, overall	2	(0.9)	2	2	(0.9)	2	4	(0.9)	4
Intervertebral disc disorder	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Myalgia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Osteoarthritis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Rheumatoid arthritis	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Injury, poisoning and procedural complications, overall	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	n	FYB203 N=215 (%)	Ev	n	Eylea N=218 (%)	Ev	n	*Total* N=433 (%)	Ev
Clavicle fracture	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Ligament injury	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Nerve root injury	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Metabolism and nutrition disorders, overall	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3
Diabetic metabolic decompensation	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Hyponatraemia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Type 2 diabetes mellitus	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Hepatobiliary disorders, overall	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Biliary dilatation	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Gallbladder disorder	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Respiratory, thoracic and mediastinal disorders, overall	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Aspiration	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Pulmonary fibrosis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Vascular disorders, overall	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Aortic aneurysm	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Varicose vein	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Blood and lymphatic system disorders, overall	0	(0.0)	0	1	(0.5)	2	1	(0.2)	2
Anaemia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Iron deficiency anaemia	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Renal and urinary disorders, overall	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Calculus urinary	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Renal failure	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1

Ev=number of adverse events of the specified preferred term or system organ class, MedDRA= medical dictionary for regulatory activities, N = total number of patients in analysis set. n = member of patients with at least 1 TEAE of the specified preferred term or system organ class, SAF = safety analysis set TEAE = treatment-emergent adverse event

7.4.4. Significant Adverse Events

Treatment-Emergent Adverse Events of Special Interest Until Week 56 (SAF, N=433)

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
Any TEAE of special interest[1]	6	(2.8)	10	7	(3.2)	12	13	(3.0)	22
Eye disorders, overall	4	(1.9)	7	4	(1.8)	6	8	(1.8)	13
Iritis	1	(0.5)	1	3	(1.4)	4	4	(0.9)	5
Iridocyclitis	2	(0.9)	3	1	(0.5)	1	3	(0.7)	4
Vitritis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Uveitis	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Investigations, overall	1	(0.5)	2	3	(1.4)	5	4	(0.9)	7
Intraocular pressure increased	1	(0.5)	2	3	(1.4)	5	4	(0.9)	7
Nervous system disorders, overall	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Cerebrovascular accident	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Ischaemic stroke	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1

Ev = number of adverse events of the specified preferred term or system organ class, MedDRA = medical dictionary for regulatory activities, N = total number of patients in analysis set, n = number of patients with at least 1 TEAE of the specified preferred term or system organ class, SAF = safety analysis set, TEAE = treatment-emergent adverse event

[1] TEAEs of special interest are TEAEs documented as adverse events of special interest by the Investigator in the eCRF according to study protocol criteria

Reviewer's Comment: Three TEAEs of special interest were observed in the FYB203 treatment group (single events of iridocyclitis, iritis, and intraocular pressure increased), one event was reported in the Eylea group (vitritis).

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 7.4.5-1 Frequency of Treatment-Emergent Adverse Events in ≥ 2.0% of Patients in Either of the Treatment Groups Until Week 56 (SAF, N=433)

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
Any TEAE	165	(76.7)	498	158	(72.5)	536	323	(74.6)	1034
Eye disorders, overall	84	(39.1)	149	95	(43.6)	171	179	(41.3)	320
Neovascular age-related macular degeneration	28	(13.0)	31	28	(12.8)	35	56	(12.9)	66
Cataract	11	(5.1)	16	10	(4.6)	11	21	(4.8)	27
Conjunctival hemorrhage	5	(2.3)	5	14	(6.4)	24	19	(4.4)	29
Visual acuity reduced	9	(4.2)	9	6	(2.8)	6	15	(3.5)	15
Eye pain	6	(2.8)	6	6	(2.8)	9	12	(2.8)	15
Vision blurred	6	(2.8)	6	3	(1.4)	4	9	(2.1)	10
Visual impairment	3	(1.4)	3	5	(2.3)	5	8	(1.8)	8
Infections and infestations, overall	58	(27.0)	92	55	(25.2)	76	113	(26.1)	168
COVID-19	19	(8.8)	21	18	(8.3)	18	37	(8.5)	39
Nasopharyngitis	10	(4.7)	11	6	(2.8)	6	16	(3.7)	17

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
Conjunctivitis	6	(2.8)	11	6	(2.8)	6	12	(2.8)	17
Coronavirus infection	6	(2.8)	6	1	(0.5)	1	7	(1.6)	7
Musculoskeletal and connective tissue disorders, overall	22	(10.2)	29	22	(10.1)	33	44	(10.2)	62
Back pain	5	(2.3)	5	6	(2.8)	6	11	(2.5)	11
Osteoarthritis	10	(4.7)	11	1	(0.5)	1	11	(2.5)	12
Investigations, overall	20	(9.3)	37	23	(10.6)	56	43	(9.9)	93
Intraocular pressure increased	8	(3.7)	11	9	(4.1)	26	17	(3.9)	37
Vascular disorders, overall	21	(9.8)	28	17	(7.8)	23	38	(8.8)	51
Hypertension	15	(7.0)	16	9	(4.1)	12	24	(5.5)	28
Gastrointestinal disorders, overall	22	(10.2)	28	15	(6.9)	30	37	(8.5)	58
Injury, poisoning and procedural complications, overall	15	(7.0)	19	15	(6.9)	20	30	(6.9)	39
Nervous system disorders, overall	16	(7.4)	20	13	(6.0)	19	29	(6.7)	39
Headache	4	(1.9)	4	7	(3.2)	12	11	(2.5)	16
Metabolism and nutrition disorders, overall	12	(5.6)	17	10	(4.6)	14	22	(5.1)	31
Respiratory, thoracic and mediastinal disorders, overall	12	(5.6)	14	10	(4.6)	10	22	(5.1)	24
General disorders and administration site conditions, overall	6	(2.8)	9	11	(5.0)	13	17	(3.9)	22
Neoplasms benign, malignant and unspecified (incl cysts and polyps), overall	7	(3.3)	10	9	(4.1)	14	16	(3.7)	24
Renal and urinary disorders, overall	9	(4.2)	10	6	(2.8)	9	15	(3.5)	19
Cardiac disorders, overall	5	(2.3)	8	9	(4.1)	12	14	(3.2)	20
Ear and labyrinth disorders, overall	4	(1.9)	5	7	(3.2)	7	11	(2.5)	12
Blood and lymphatic system disorders, overall	5	(2.3)	7	4	(1.8)	6	9	(2.1)	13
Hepatobiliary disorders, overall	5	(2.3)	6	4	(1.8)	4	9	(2.1)	10
Skin and subcutaneous tissue disorders, overall	2	(0.9)	2	6	(2.8)	7	8	(1.8)	9

Reviewer's comment: The reported rates in both treatment groups were similar. The ocular and systemic adverse events were consistent with those seen in this study population. No unexpected safety signals were seen.

7.4.6. Laboratory Findings

Over the 56 weeks of the study, there were no notable trends or differences between treatment groups in hematology and clinical chemistry results.

7.4.7. Vital Signs

Over the 56 weeks of the study, there were no notable trends in changes from baseline or notable differences between treatment groups in any of the vital sign parameters (systolic blood pressure, diastolic blood pressure, and pulse rate).

7.4.8. Electrocardiograms (ECGs)

Electrocardiograms were not obtained during the development program for this product.

7.4.9. QT

Not applicable.

7.4.11. Immunogenicity

No significant differences were observed between both treatments at any of the timepoints. No drug hypersensitivity or anaphylaxis-type or ocular inflammatory TEAEs of special interest were reported up to Week 56 in patients with ADA positive status at any time during the study period. (Therefore, it was concluded that neither FYB203 nor Eylea induced adverse events that could potentially be related to immunogenicity.

Table 7.4.10-1 ADA/Nab prevalence and ADA titer Until Week 56 (SAF, N=433)

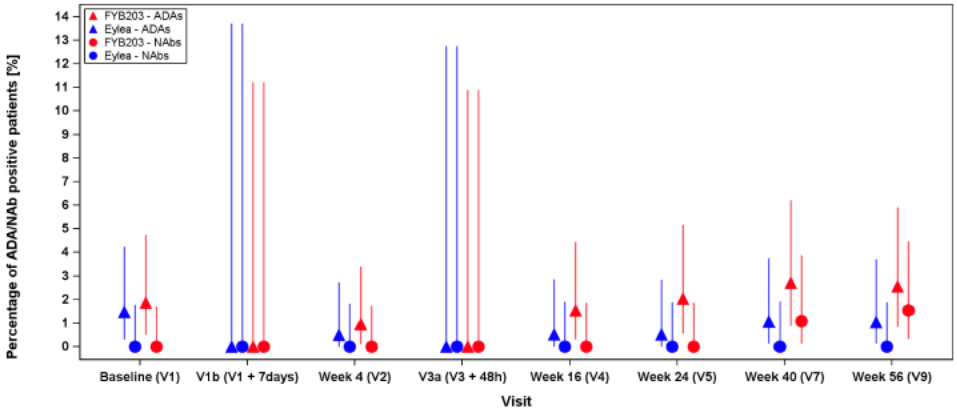
	FYB203 (N=215)			Eylea (N=218)		
Analysis Visit	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**
Baseline (V1)	4 (1.9) n=213	0.71 (41.68)	Re 0 (0.0) Ne 4 (1.9) n=213	3 (1.5) n=204	0.63 (41.68)	Re 0 (0.0) Ne 3 (1.5) n=204
V1b; V1 + 7d[1]	0 (0) n=31	NA	NA	0 (0) n=25	NA	NA
Week 4 (V2)	2 (1.0) n=209	0.71 (52.11)	Re 0 (0.0) Ne 2 (1.0) n=209	1 (0.5) n=201	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=201
Week 8 (V3a; V3 + 48h)[1]	0 (0) n=32	NA	NA	0 (0) n=27	NA	NA
Week 16 (V4)	3 (1.5) n=195	1.59 (94.74)	Re 0 (0.0) Ne 3 (1.5) n=195	1 (0.5) n=191	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=191
Week 24 (V5)	4 (2.1) n=195	1.19 (106.76)	Re 0 (0.0) Ne 4 (2.1) n=195	1 (0.5) n=193	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=193
Week 40 (V7)	5 (2.7) n=184	2.64 (142.10)	Re 2 (1.1) Ne 3 (1.6) n=184	2 (1.1) n=189	1.00 (0.00.)	Re 0 (0.0) Ne 2 (1.1) n=189
Week 56 (V9)	5 (2.6) n=194	3.81 (391.52)	Re 3 (1.5) Ne 2 (1.0) n=194	2 (1.0) n=192	1.41 (52.11)	Re 0 (0.0) Ne 2 (1.0) n=192
Post-treatment Until Week 56 only[2]	4 (1.9) n=209	NA	Re 3 (1.4) Ne 4 (1.9) n=213	2 (1.0) n=201	NA	Re 0 (0.0) Ne 3 (1.5) n=204

ADA = anti-drug antibody, d = day, Geom. CV = geometric coefficient of variation, Geomean = geometric mean, h = hours, N = number of patients per group, n = number of patients per category, NA = not applicable, NAb = neutralizing antibody, n.c. = not calculable, Ne = negative, PKS = plasma concentration analysis set (used only for V1b and V3a), Re = reactive, SAF = safety analysis set (used only for V1, V2, V3, V4, V5, V7, V9 and post-treatment only), V = visit

[1] Plasma concentration analysis set (PKS) only, patients from PK subgroup with measurable aflibercept concentrations prior to 1st injection were excluded

[2] The immunogenicity analysis "post-treatment only" excludes patients without any post-treatment ADA or NAb sample, excludes patients from ADA analysis who were ADA positive at pre-treatment (denominator n=209) and excludes patients from NAb analysis who were NAb reactive at pre-treatment (denominator n=213). Any patient who was NAb negative at pre-treatment could test NAb reactive during at any time during the treatment phase, independent of the ADA status pre-treatment.

Figure 7.4.10-1 Percentage of patients with positive ADA and NAb by scheduled eCRF visit including 95% confidence intervals until Week 56 (SAF, N=433)



ADA = Anti-Drug Antibody; NAb = Neutralizing Antibody; eCRF = Electronic Case Report Form; 95% CI = 95% Clopper-Pearson Confidence Intervals; SAF = Safety Analysis Set

The start and end of the whisker represents the lower and upper limits of the confidence interval respectively and the dots (circles, triangles) represent the estimate.

Table 7.4.10-2 Listing of ADA titers for all samples with ADA confirmed positive result in Study FYB203-03-01 until Week 56 – SAF

a) **FYB203**

Patient ID	Timepoint	ADA confirmatory	ADA titer	NAb assay result
Subjects with treatment-emergent (treatment-induced) ADA [1]				
(b) (6)	Week 16	Positive	1	Negative
	Week 24	Positive	1	Negative
	Week 40	Positive	2	Positive
	Week 56	Positive	1	Positive
	Week 16	Positive	4	Negative
	Week 24	Positive	4	Negative
	Week 40	Positive	16	Positive
	Week 56	Positive	50	Positive
	Week 40	Positive	2	Negative
	Week 56	Positive	8	Negative
	Week 40	Positive	2	Negative
	Week 56	Positive	2	Positive
Baseline positive subjects without a treatment-boosted response [2]				
(b) (6)	Pre-treatment	Positive	1	Negative
	Pre-treatment	Positive	<1	Negative
	Week 4	Positive	<1	Negative
	Pre-treatment	Positive	1	Negative
	Week 4	Positive	1	Negative
	Week 16	Positive	1	Negative
	Week 24	Positive	1	Negative
	Week 40	Positive	1	Negative
	Week 56	Positive	1	Negative
	Pre-treatment	Positive	<1	Negative
	Week 24	Positive	<1	Negative

b) Eylea

Patient ID	Timepoint	ADA confirmatory	ADA titer	NAb assay result
Subjects with treatment-emergent (treatment-induced) ADA [1]				
(b) (6)	Week 56	Positive	1	Negative
	Week 40	Positive	1	Negative
Baseline positive subjects without a treatment-boosted response [2]				
(b) (6)	Pre-treatment	Positive	1	Negative
	Week 4	Positive	1	Negative
	Week 16	Positive	1	Negative
	Week 24	Positive	1	Negative
	Week 40	Positive	1	Negative
	Week 56	Positive	2	Negative
	Pre-treatment	Positive	<1	Negative
	Pre-treatment	Positive	<1	Negative

ADA = anti-drug antibody; NAb = neutralizing antibody;

[1] A patient was defined as having treatment-induced ADAs if ADA results were positive post-treatment only. Any pre-treatment ADA assessment was either negative or not assessable. Patients with missing pre-treatment ADA samples were not evaluable for the ADA analysis

[2] A patient was defined as having treatment-boosted ADA if they were ADA positive pre-treatment and the signal was boosted to a higher level following study treatment, i.e. pre-treatment positive ADA titer that was boosted by at least 2 dilution steps (4-fold increase in ADA titer) following study treatment.

7.5. Analysis of Submission-Specific Safety Issues

There were no submission-specific safety issues.

7.6. Safety Analyses by Demographic Subgroups

See subgroup analyses for demographic subgroups performed on the primary efficacy endpoint in Section 6.2.

7.7. Specific Safety Studies/Clinical Trials

There were no specific safety issues.

7.8. Additional Safety Explorations

7.8.1. 120 Day Safety Update

On October 24, 2023, Formycon AG submitted the 120-day Safety Update Report (SUR). The Day 120 safety update included the results of key efficacy, safety, and immunogenicity over the whole 56-week study period.

The safety profiles of FYB203 and Eylea were highly comparable throughout the whole 56-week study period. No new safety signals were observed after the Week 24 analysis. Data from the Week 56 analysis corroborate that ocular events are similar throughout. No unexpected

systemic events were observed and immunogenicity was similarly low for both treatment groups.

7.8.2. Human Carcinogenicity or Tumor Development

Animal studies have not been conducted to determine the carcinogenic potential of aflibercept.

7.8.3. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

7.8.4. Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of aflibercept in pediatric patients has been established by the innovator. Pediatric studies were waived since the proposed indications for FYB203 do not occur in the pediatric population. Due to unexpired exclusivity for the orphan Retinopathy of Prematurity (ROP) indication, the applicant is seeking licensure only for Eylea's licensed adult indications:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic Retinopathy (DR)

An initial Pediatric Study Plan was submitted on July 24, 2020, requesting drug-specific waivers for all pediatric age groups of the adult indications listed above. As requested in FDA's written response issued on October 21, 2020, an Agreed iPSP was submitted on December 7, 2020 (PIND 144550). A copy of this agreed iPSP is included in Section 1.9.1 of this application. On January 19, 2024, Formycon AG submitted (b) (4).

7.8.5. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

FYB203 is not a narcotic and does not have abuse potential.

7.9. Safety in the Postmarket Setting

FYB203 has not yet been marketed.

7.9.1. Additional Safety Issues From Other Disciplines

7.10. Integrated Assessment of Safety

There is no integrated assessment of safety across trials as the application includes only a single pivotal study (FYB203-03-01) to support the safety assessment of FYB203. Study FYB203-03-01 demonstrated that FYB203 and Eylea have comparable safety profiles including eh change in best corrected visual acuity from baseline to Week 8. The adverse event safety profiles were also similar between patients treated with FYB203 and Eylea.

8. Advisory Committee Meeting and Other External Consultations

The application did not raise any efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the BLA.

9. Risk Evaluation and Mitigation Strategies (REMS)

None.

10. Postmarketing Requirements and Commitments

None.

11. Appendices

11.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): MAGELLAN-AMD / FYB203-03-01

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 734 investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes 734	No ☐ (Request explanation from Applicant)

12. Labeling Recommendations

Following is the final labeling submitted by the applicant with the original submission on 06/19/24.

29 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

13. Regulatory Action

The review team recommends [redacted] (b) (4) an Approval for FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS.

[redacted] (b) (4)

This BLA has been administratively split so that the Approval of FYB203, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial as biosimilar to US-Eylea, 2 mg (0.05 mL of 40 mg/mL) injection, for intravitreal use in a vial kit and PFS will remain in BLA 761378/Original 1. BLA 761378/Original 1 will receive an Approval letter.

[redacted] (b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RHEA A LLOYD
06/27/2024 03:22:19 PM
Signed in DARRTS for Medical Officer, David Summer, MD

WILLIAM M BOYD
06/27/2024 03:32:33 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Number	761378
Drug Name	FYB203 (Aflibercept) – proposed [redacted] (b) (4) biosimilar to Eylea
Applicant	Formycon AG
Reference Product	US-licensed Eylea (Aflibercept 2 mg/0.05 mL [40 mg/mL]), BLA 125387
Indications	Neovascular (wet) age-related macular degeneration (AMD), Macular edema following retinal vein occlusion (RVO), Diabetic macular edema (DME), Diabetic Retinopathy (DR).
Dates	Receipt Date: June 28, 2023 Statistical Review Completion Date: March 11, 2024 BsUFA Goal Date: June 28, 2024
Biometrics Division Statistical Reviewer Statistical Concurring Reviewer	Division of Biometrics VIII, Office of Biostatistics Martin Klein, PhD, Division of Biometrics VIII Jessica Kim, PhD, Division of Biometrics VIII
Medical Division Clinical Primary Reviewer Clinical Secondary Reviewer	Division of Ophthalmology, Office of Specialty Medicine David Summer, MD, Division of Ophthalmology Rhea Lloyd, MD, Division of Ophthalmology
Keywords	Best Corrected Visual Acuity, Biosimilar, Estimand, Multiple Imputation.

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1 EXECUTIVE SUMMARY

The Applicant, Formycon AG, submitted biologics license application (BLA) 761378 for FYB203 (Aflibercept 2 mg/0.05 mL [40 mg/mL]) as a proposed (b) (4) biosimilar product to US-licensed Eylea. To compare the efficacy and safety of FYB203 with European Union approved Eylea (EU-Eylea), the Applicant conducted Study FYB203-03-01, a parallel group, 1-1 randomized, active-controlled, double masked, multicentered study in patients with neovascular age-related macular degeneration (nAMD).

Patients were randomized to receive either FYB203 or EU-Eylea in a dose of 2 mg (0.05 mL of a 40 mg/mL solution). Randomization was stratified by country and participation in the pharmacokinetic subgroup (yes/no). A total of 434 patients were randomized to receive treatment with FYB203 (215 patients) or EU-Eylea (219 patients). After consent withdrawal by 1 patient randomized to EU-Eylea, 433 patients started treatment with FYB203 (215 patients) or EU-Eylea (218 patients).

The primary endpoint was the change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3). The primary efficacy analysis was conducted to assess whether there is any clinically meaningful difference between FYB203 and EU-Eylea in the primary efficacy endpoint based on the Full Analysis Set which included all randomized patients who received at least 1 injection of study medication in the study eye.

The primary endpoint analysis yielded a 90.4% confidence interval for the difference of means (mean of FYB203 – mean of EU-Eylea) of (-0.3213, 2.2266), which is contained in the pre-specified similarity margin of (-3.5, 3.5). Thus, the study demonstrated similarity of FYB203 and EU-Eylea for the primary endpoint. Sensitivity, supplementary, exploratory, and descriptive analyses support the robustness of the primary analysis results and support similarity of FYB203 and EU-Eylea.

Based on the totality of statistical evidence from Study FYB203-03-01, the reviewer concluded that the Applicant provided adequate evidence for similarity of FYB203 and EU-Eylea in the primary efficacy endpoint.

2 INTRODUCTION

2.1 OVERVIEW

The Applicant, Formycon AG, submitted biologics license application (BLA) 761378 for FYB203 (Aflibercept 2 mg/0.05 mL [40 mg/mL]) as a proposed (b) (4) biosimilar product to US-licensed Eylea.

With this application, the Applicant is seeking licensure for the following indications:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Diabetic macular edema (DME)
- Diabetic Retinopathy (DR)

To compare the efficacy and safety of FYB203 with European Union approved Eylea (EU-Eylea), the Applicant conducted Study FYB203-03-01, a parallel group, 1-1 randomized, active-controlled, double masked, multicentered study in patients with neovascular age-related macular degeneration (nAMD). Table 1 displays a summary of Study FYB203-03-01.

Table 1. Summary of study reviewed.

Study ID	Design*	Duration	Treatment/Sample Size	Study Population
FYB203-03-01	Parallel group, randomized, active controlled, double-masked, multicentered study.	56 weeks (48 weeks duration of treatment, 24 weeks analyzed duration of treatment)	FYB203 / 215 patients[1] EU-Eylea / 218 patients[1]	Patients with nAMD

[1]434 patients were randomized to receive treatment with FYB203 (215 patients) or EU-Eylea (219 patients). After consent withdrawal by 1 patient randomized to EU-Eylea, 433 patients started treatment with FYB203 (215 patients) and EU-Eylea (218 patients). These 433 patients formed the Full Analysis Set and the Safety Analysis Set. Patient (b) (6) was randomized to FYB203 but treated with EU-Eylea throughout the complete study, while patient (b) (6) was randomized to EU-Eylea but treated with FYB203 throughout the complete study.
Source: Reviewer's summary based on the Clinical Study Report.

2.2 DATA SOURCES

The materials used for this review are from the electronic submission received on June 28, 2023, and these materials are in the directories indicated below.

Clinical Study Report, Protocol, Statistical Analysis Plan (SAP), and Other Documents:

\\CDSESUB1\evsprod\BLA761378\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\namd\5351-stud-rep-contr\fyb203-03-01

Datasets and Documentation:

\\CDSESUB1\evsprod\BLA761378\0001\m5\datasets\fyb203-03-01

3 STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

No major issues were identified regarding the quality and integrity of the submitted datasets.

3.2 EVALUATION OF EFFICACY BASED ON STUDY FYB203-03-01

3.2.1 Study Design and Endpoints

Study Design

Study FYB203-03-01 was a parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study to compare efficacy, safety, and immunogenicity of FYB203 with EU-Eylea in patients with nAMD.

The primary objective of this study was to 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 EU-Eylea compared to Baseline.

The study was conducted in 9 countries, where 77 sites screened at least 1 patient. For the 24-week analysis, 72 sites in 9 countries randomized at least 1 patient: Bulgaria (4 sites, 21 patients), Czech Republic (9 sites, 70 patients), Hungary (8 sites, 68 patients), Israel (6 sites, 12

patients), Italy (5 sites, 18 patients), Japan (14 sites, 33 patients), Poland (9 sites, 77 patients), Russia (9 sites, 71 patients) and Ukraine (8 sites, 64 patients).

Patients were randomized to receive either FYB203 or EU-Eylea in a dose of 2 mg (0.05 mL of a 40 mg/mL solution). Randomization was stratified by country and participation in the pharmacokinetic subgroup (yes/no).

A total of 434 patients were randomized to receive treatment with FYB203 (215 patients) or EU-Eylea (219 patients). After consent withdrawal by 1 patient randomized to EU-Eylea, 433 patients started treatment with FYB203 (215 patients) or EU-Eylea (218 patients). The identity of the study treatments is shown in Table 2.

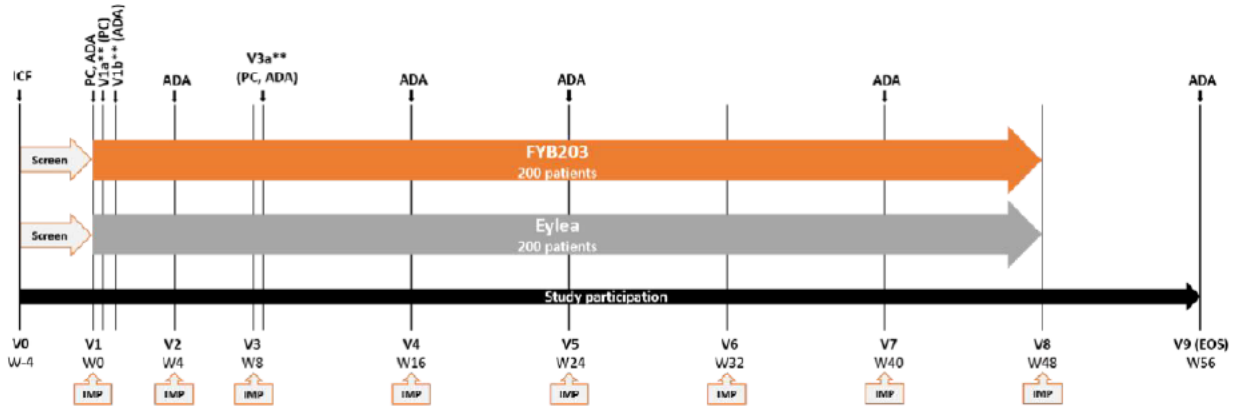
Table 2. Treatments administered.

	FYB203	**European Union-approved Eylea (EU-Eylea)**
Trade name	Not applicable	Eylea
Vials	Vial containing 100 µL, equivalent to 4 mg aflibercept	Vial containing 100 µL, equivalent to 4 mg aflibercept
Dose	2 mg in a glass vial designed to deliver 50 µL solution	2 mg in a glass vial or prefilled syringe designed to deliver 50 µL of solution
Route	Intravitreal	Intravitreal
Formulation	Solution for injection	Solution for injection
Strength	40 mg/mL solution	40 mg/mL solution

Source: Table 9-1 of the Clinical Study Report.

The screening period started with informed consent form signature and had a maximum duration of 28 days. After the screening period, eligible patients were randomized in a 1:1 ratio to receive either FYB203 or EU-Eylea at a dose of 2 mg (0.05 mL of a 40 mg/mL solution). After randomization, the treatment consisted of 1 intravitreal (IVT) injection every 4 weeks for 3 consecutive doses starting at Baseline (Visit 1) through Week 8 (Visit 3) followed by 1 IVT injection every 8 weeks up to and including Week 48 (Visit 8). For each patient a total of 8 IVT injections were planned (Baseline [Visit 1], Week 4 [Visit 2], Week 8 [Visit 3], Week 16 [Visit 4], Week 24 [Visit 5], Week 32 [Visit 6], Week 40 [Visit 7] and Week 48 [Visit 8]). A follow-up visit for safety (Early Termination Visit/End of Study [EOS]) occurred at Week 56 (Visit 9) after the administration of 8 IVT doses of the IMPs. If the patient discontinuation happened before the 8 planned IVT doses, an Early Termination Visit was conducted. Figure 1 shows a schematic of the study design.

Figure 1: Schematic of study design for Study FYB203-03-01.



ADA = anti-drug antibody, EOS = end of study, ICF = informed consent form, IMP = investigational medicinal product, PC = plasma concentration, V = visit, W = week

Source: Figure 9-1 of the Clinical Study Report.

Reviewer's comment. The reviewer noted that the study design (b) (4) .

Study Endpoints

The primary endpoint of the study was the change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3). Table 3 shows a summary of the efficacy endpoints in the study.

Table 3. Summary of efficacy endpoints in Study FYB203-03-01.

Primary	Change from Baseline (Visit 1) in best corrected visual acuity (BCVA) by early treatment diabetic retinopathy Study (ETDRS) letters to Week 8 (Visit 3).
Secondary	• Changes in foveal center point (FCP) retinal thickness at Week 4 (defined as the key secondary endpoint for the EU analysis). • Changes in foveal center point (FCP) and changes in foveal central subfield (FCS) retinal thickness. • Change in BCVA by ETDRS letters. • Gain or loss of best corrected visual acuity by ≥5, 10, and 15 ETDRS letters. • Fluid-free macula. • Changes in total lesion area. • Change in vision-related functioning and well-being from baseline to Week 24 (NEI VFQ-25).

Source: Reviewer's summary based on Section 8 and Section 11 of the Clinical Study Report.

3.2.2 Statistical Methodologies

Analysis Sets

The SAP defines the following analysis sets.

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

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

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

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

The plasma concentration analysis set (PKS) included patients that were in the SAF and had at least 1 valid post-dose plasma concentration measurement. Patients were analyzed according to the treatment they actually received in the study eye at Visit 1. Patients who received injections from different treatment groups at Visit 1 and Visit 3 were not included in the PKS. Furthermore, patients with a positive Baseline total aflibercept concentration were excluded from the PKS.

Sample Size Determination

The Applicant’s sample size calculation was based on the following assumptions.

- Similarity margin of (-3.5, 3.5) letters.
- Standard deviation of 9.0 ETDRS letters in BCVA, and 1:1 randomization ratio.
- No difference between means.
- 5.0% significance level for US analysis, 2.5% significance level for EU analysis.

Under these assumptions, the Applicant determined that 180 patients in both treatment groups (360 patients total) achieves 90% power at a 2.5% significance level, and 144 in both treatment groups (288 patients in total) achieves 90% power at a 5.0% significance level. Assuming a difference of 10% between the Full Analysis Set and Per Protocol Set, that Applicant determined that it was required to randomize 400 patients for the Full Analysis Set for a 2.5% significance level, and 320 patients for the Full Analysis Set for a 5.0% significance level.

(b) (4)

. Due to regulatory feedback from the FDA in February 2023, the planned 24W analysis on all patients was performed for the US criteria using a 5% overall significance level and for the EU (b) (4) criteria using a 2.5% significance level overall.

Reviewer's comment. Under the assumptions described above, the reviewer's calculations indicated that at 2.5% significance level, 180 patients in both treatment groups (360 patients total) yielded a power of 91.45%, and at a 5.0% significance level, 144 patients in both treatment groups (288 patients in total) yielded a power of 90.05%. Thus, confirming the Applicant's sample size determination.

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

However, a simulation study had been conducted prior to the initiation of the study to assess the impact of a possible sample size increase on the overall study-wise type-I error rate alpha. The simulations using the US criteria (i.e., using a significance level of 5% for both one-sided tests) suggested that an adjustment of alpha to 4.8% would be needed to control the possible inflation of the type 1 error rate (b) (4). This corresponded to a 2-sided 90.4% confidence interval (CI) for the assessment of equivalence. Similarly, simulations using the EU criteria suggested a necessary adjustment of alpha to 2.4% for all EU specific statistical analyses.

Reviewer's comment. Regarding the alpha adjustment to 4.8% for the primary analysis, the reviewer conducted simulation studies using similar assumptions as the Applicant, and the results agreed with the Applicant's finding that an alpha adjustment to 4.8% (hence using the 90.4% confidence interval) could control the type 1 error probability for (b) (4) 288 patients. Again, using similar assumptions as the Applicant, the reviewer conducted further simulation studies which indicated that an alpha adjustment to 4.8% could control the type 1 error probability at 5% if the originally planned sample size was assumed to be 360 patients.

Analysis of Primary Efficacy Endpoint

The primary efficacy estimand was defined as shown in Table 4.

Table 4. Primary estimand

Treatment Condition	FYB203 vs Eylea (at least 1 IVT injection with a dose of 2 mg).
Population	Patients with nAMD who were randomized to receive either FYB203 or Eylea and who received at least 1 dose of IMP, i.e., the FAS.
Endpoint	Absolute change from Baseline to Week 8 in BCVA by ETDRS letters: $CHG_{BCVA,Week\ 8} = BCVA_{Week\ 8} - BCVA_{Base}$, using analysis visits as defined in Table 9-5 of the Clinical Study Report.
Intercurrent events and strategies	All intercurrent events were handled according to the treatment policy strategy, i.e., all values of interest were analyzed whether or not the intercurrent event occurs. The following intercurrent events were considered: • Discontinuation of treatment • Discontinuation of study (including death of the patient) related to safety of the IMP without any Post-Baseline assessment of the BCVA • Discontinuation of study (including death of the patient) unrelated to safety of the IMP without any Post-Baseline assessment of the BCVA • Major Protocol Deviations, which impacted the BCVA assessment until Week 8 as defined during the DRM
Population level summary	Difference in means between FYB203 and Eylea treatment groups.

Source: Table 9-6 of the Clinical Study Report.

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

The hypotheses to be tested are

$$H_0: |\mu_{BCVA,\,FYB203} - \mu_{BCVA,\,Eylea}| \geq 3.5 \text{ versus } H_1: |\mu_{BCVA,\,FYB203} - \mu_{BCVA,\,Eylea}| < 3.5$$

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

The difference between the least squares (LS) means of the treatment groups and the corresponding 2-sided 90.4% CI was estimated from the MMRM for the US analysis. The significance level alpha was reduced from 0.05 to 0.048 to control the overall type 1 error in the light of the masked sample size review. Analogously, the 2-sided 95.2% CI was estimated from the same MMRM model for the EU analysis.

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

If the respective CI was completely contained in the interval (-3.5, 3.5) ETDRS letters, H_0 could be rejected and similarity of FYB203 and EU-Eylea with respect to the primary endpoint could be concluded.

Reviewer's comments.

1. Recently a similarity margin of (-3, 3) has been used for proposed biosimilar products referencing US-licensed Eylea using the same primary endpoint as in this study.
2. Regarding the hierarchical testing strategy described above, this appears to have been put in place under the Applicant's original proposal to (b) (4) . However, this plan was changed based on feedback from the FDA in February 2023 so that the planned 24W analysis (b) (4) was performed on all patients.

<u>Handling of Missing Data</u>

It was assumed that there would be no missing data for Baseline because the Baseline BCVA needed to be available to confirm the inclusion criteria. A patient without any post-Baseline BCVA measurement until Week 24 could not be included in the primary efficacy analysis. The number of patients in the FAS without any Post-Baseline BCVA value was assessed during the DRM, and it was seen that all treated patients had at least 1 Post-Baseline BCVA assessment and therefore, no further imputation method would be needed.

Missing data were not explicitly imputed, however if a patient had 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.

Sensitivity and Supplementary Analyses

The following sensitivity analyses were performed as planned in the SAP.

- MMRM analysis with patient discontinued study prior to Week 24 (yes/no) as an additional covariate.
- MMRM analysis with patient discontinued treatment prior to Week 24 (yes/no) as an additional covariate.
- MMRM analysis with patient has any major protocol deviation (yes/no) as an additional covariate.
- MMRM analysis with use of an ancillary chart (yes/no) at each visit as additional covariate.
- MMRM analysis including only data until Week 8.
- Analysis of the primary endpoint using an analysis of covariance (ANCOVA) model instead of MMRM. The ANCOVA model included the change from baseline to Week 8 in BCVA as the dependent variable, the baseline BCVA value as covariate and region (Japan vs. ROW) and treatment group as fixed effects. This analysis was be performed based on observed cases, i.e., only patients with a BCVA at Week 8 analysis visit will be included.
- Analysis of the primary endpoint using the same ANCOVA model as described above, but now using multiple imputation for missing values.
- To investigate the impact of missing data, a tipping point analysis was performed using the ANCOVA model described above, with shift parameters δ_1 and δ_2 introduced for imputation models in the FYB203 and EU-Eylea groups, respectively.

The following supplementary analyses were performed as planned in the SAP.

- MMRM analysis using data up to Week 24, excluding patients from the FAS with major protocol deviations which impact BCVA assessments until Week 8 (Visit 3).
- MMRM analysis using data up to Week 24, excluding patients from the FAS who discontinued treatment before Week 8 or do not have a Week 8 BCVA assessment.
- MMRM analysis using data up to Week 24 based on the PPS.
- Analysis of the primary endpoint using an ANCOVA model based on the FAS where all patients excluded from the PPS were imputed using a multiple imputation approach, regardless of whether a BCVA value at Week 8 was collected.
- MMRM analysis excluding assessments following missed injection visits.
- MMRM analysis excluding assessments following a major protocol deviation.

If at least 10 patients present BCVA values until Week 24 that were assessed after discontinuation of treatment, then an MMRM analysis was to be conducted excluding all assessments following discontinuation of treatment. Less than 10 patients had BCVA values until Week 24 that were assessed after discontinuation of treatment, and this analysis was not performed. Also, if a substantial number of protocol deviations which impact only single BCVA measurements were identified, then an MMRM analysis with those single impacted measurements excluded could be conducted. The Applicant determined that the number of such protocol deviations was low and therefore did not conduct this analysis.

Key Secondary Efficacy Endpoint for EU Analysis

For the EU specific analysis, change from Baseline to Week 4 in FCP retinal thickness was defined as the key secondary endpoint. A similar MMRM model as specified for the primary efficacy analysis was used to derive 2-sided 95.2% CIs for the difference between the treatment groups. The following hypotheses were tested:

$$H_0: |\mu_{FCP,\,FYB203} - \mu_{FCP,\,Eylea}| \geq 45.0 \text{ versus } H_1: |\mu_{FCP,\,FYB203} - \mu_{FCP,\,Eylea}| < 45.0$$

where $\mu_{FCP,\,FYB203}$ and $\mu_{FCP,\,Eylea}$ denote the mean changes of FCP retinal thickness from Baseline to Week 4 in the respective treatment groups.

The difference between the LS means of the treatment groups and the corresponding 2-sided 95.2% CI were estimated from the MMRM. The significance level alpha was reduced from 0.025 to 0.024 to control the overall type 1 error in the light of the masked sample size review. If the CI is completely contained in the interval [-45.0 µm; 45.0 µm], H_0 can be rejected and equivalence of FYB203 and EU-Eylea can be concluded with respect to change in FCP retinal thickness, based on all patients in the FAS. The analysis was repeated based on all patients in the PPS and consistency between the results based on the FAS and the PPS is regarded as essential.

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

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

Other Secondary Endpoints

Other secondary endpoints were analyzed descriptively and included the following.

- Changes in foveal center point (FCP) and changes in foveal central subfield (FCS) retinal thickness.
- Change in BCVA by ETDRS letters.
- Gain or loss of best corrected visual acuity by ≥5, 10, and 15 ETDRS letters.

- Fluid-free macula.
- Changes in total lesion area.
- Change in vision-related functioning and well-being from baseline to Week 24 (NEI VFQ-25).

Subgroup Analysis

The primary endpoint analysis was performed within the following subgroups, using the FAS, as defined in the SAP.

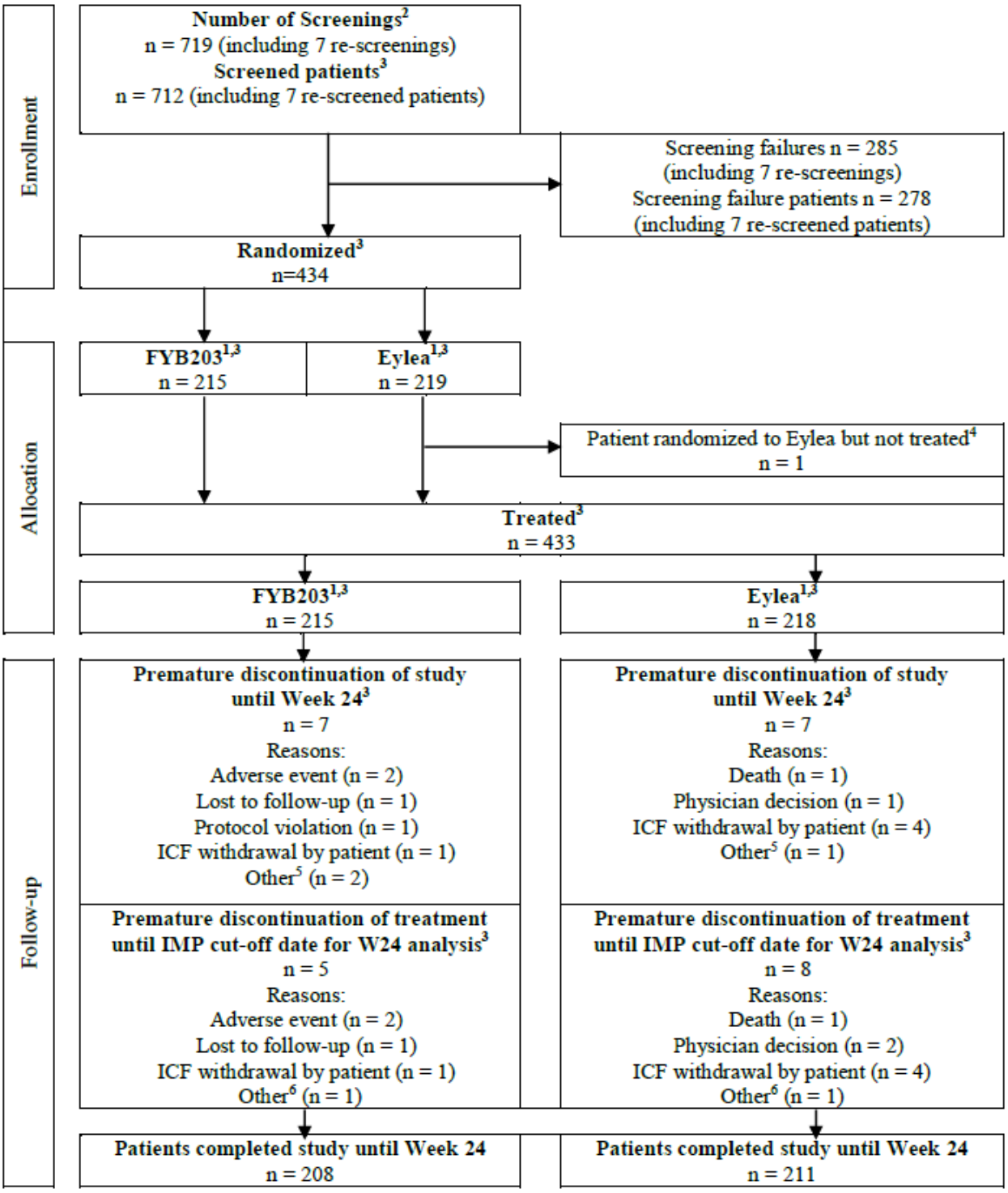
- [redacted] (female and male)
- Use of an ancillary chart up to Week 24 (yes/no, patients who only used the ancillary chart for single assessments will be excluded from this analysis)
- ADA status (any positive treatment emergent ADA during study versus no positive treatment emergent ADA during study up to Week 24)
- Total lesion area at baseline ($< 9mm^2$ versus $>= 9mm^2$)
- Lesion type at baseline (types as reported by GRADE)
- Syringe use (original syringes provided by sponsor versus other syringes used (at any time during study))
- Region (Japan versus Rest of World (ROW))

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The patient disposition is summarized in Figure 2 and Table 5. A total of 434 patients were randomized into one of two groups: 215 patients were allocated to receive treatment with FYB203. and 219 patients were allocated to receive treatment with EU-Eylea. Since 1 patient was randomized to the EU-Eylea treatment group but not treated due to informed consent form (ICF) withdrawal by the patient, 215 patients started treatment with FYB203 and 218 patients started treatment with EU-Eylea. Up to Week 24, 7 patients in the FYB203 group and 7 patients in the EU-Eylea group discontinued the study prematurely. Table 6 provides a summary of the Full Analysis Set and the Per Protocol Set, and the reasons for exclusion from each analysis set.

Demographic and baseline characteristics are summarized in Table 7 for the Full Analysis Set, and in Table 8 for the Per Protocol Set. These tables indicated that, in general, the demographic and baseline characteristics were balanced between the two treatment groups.

Figure 2. Patient disposition diagram.



Source: Figure 10-1 of the Clinical Study Report.

Table 5. Patient disposition.

	FYB203	EU-Eylea	Total
Number of screenings (including re-screens)	-	-	719
Number of re-screenings	-	-	7
Number of screening failures	-	-	285
Screened and enrolled patients (signed ICF)	-	-	712
Re-screened patients	-	-	7
Screening failure patients	-	-	278
Patients randomized	215	219	434
Patients randomized but not treated[1]	0	1	1
Patients treated	215	218	433
Patients completed study until Week 24	208	211	419
Premature Discontinuation of study until Week 24 in Full Analysis Set	7	7	14
Adverse event	2	0	2
Death	0	1	1
Lost to follow-up	1	0	1
Protocol violation	1	0	1
Physician decision	0	1	1
ICF withdrawal by patient	1	4	5
Other[2]	2	1	3
Premature discontinuation of treatment until IMP cut-off date for Week 24 analysis in Full Analysis Set	5	8	13
Adverse event	2	0	2
Death	0	1	1
Lost to follow-up	1	0	1
Physician decision	0	2	2
ICF withdrawal by patient	1	4	5
Other[3]	1	1	2

[1]Patient (b) (6) was randomized to EU-Eylea but not treated due to ICF withdrawal.
[2]Patient (b) (6) and patient (b) (6) treated with FYB203 and patient (b) (6) treated with EU-Eylea discontinued the study due to other reasons related to the geopolitical situation in Ukraine.
[2]Patient (b) (6) treated with FYB203 and patient (b) (6) treated with EU-Eylea discontinued treatment due to other reasons related to the geopolitical situation in Ukraine.
Source: Table 10-1 of the CSR.

Table 6. Summary of Full Analysis Set and Per Protocol Set.

	FYB203 N=215	EU-Eylea N=219	Total N=434
Patients in Full Analysis Set	215	218	433
Reasons for exclusion			
No injection of study medication	0	1	1
Patients in Per Protocol Set	201	205	406
Reasons for exclusion			
Major IMP schedule or administration deviation	1	2	3
Major IMP schedule or administration deviation, Injections from different treatment than randomized until Week 8	1	1	2
Major IMP schedule or administration deviation, No BCVA measurement at baseline or Week 8	1	1	2
Measured BCVA values invalid/affected due to protocol deviation	1	0	1
Measured BCVA values invalid/affected due to protocol deviation, No BCVA measurement at baseline or Week 8	0	1	1
No BCVA measurement at baseline or Week 8	5	3	8
Positive baseline total aflibercept concentration	1	2	3
Possible Unmasking of study site staff or subject	0	1	1
Violation of inclusion/exclusion criteria	2	2	4
In Full Analysis Set, not in Per Protocol Set, but exclusion reason not provided in PPSREAS variable of ADSL dataset[1]	2	0	2

[1]The reviewer noted that the 2 patients falling in this category are patient (b) (6) and patient (b) (6) treated with FYB203, and according to Data Review Meeting Minutes (see page 246 of 613 of the SAP) these two patients had a major protocol deviation related to use of IMP kits which were in quarantine.
Source: Reviewer's analysis.

Table 7. Demographic and baseline characteristics in the Full Analysis Set.

	FYB203 N=215	EU-Eylea N=218	Total N=433
, n (%)			
Male	94 (43.7%)	91 (41.7%)	185 (42.7%)
Female	121 (56.3%)	127 (58.3%)	248 (57.3%)
Country, n (%)			
Bulgaria	10 (4.7%)	11 (5.0%)	21 (4.8%)
Czech Republic	34 (15.8%)	35 (16.1%)	69 (15.9%)
Hungary	34 (15.8%)	34 (15.6%)	68 (15.7%)
Israel	6 (2.8%)	6 (2.8%)	12 (2.8%)
Italy	9 (4.2%)	9 (4.1%)	18 (4.2%)
Japan	17 (7.9%)	16 (7.3%)	33 (7.6%)
Poland	37 (17.2%)	40 (18.3%)	77 (17.8%)
Russian Federation	35 (16.3%)	36 (16.5%)	71 (16.4%)
Ukraine	33 (15.3%)	31 (14.2%)	64 (14.8%)
Race, n (%)			
White	197 (91.6%)	201 (92.2%)	398 (91.9%)
Asian	17 (7.9%)	16 (7.3%)	33 (7.6%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Ethnicity			
Hispanic or Latino	3 (1.4%)	5 (2.3%)	8 (1.8%)
Not Hispanic or Latino	212 (98.6%)	213 (97.7%)	425 (98.2%)
Age (years)			
N	215	218	433
Missing values	0	0	0
Mean (SD)	73.7 (7.72)	73.3 (7.70)	73.5 (7.71)
Median	74	74	74
Min, Max	51, 93	51, 92	51, 93
Q1, Q3	68, 79	68, 79	68, 79
Age Categories			
50-64 years	17 (7.9%)	25 (11.5%)	42 (9.7%)
65-75 years	105 (48.8%)	111 (50.9%)	216 (49.9%)
> 75 years	93 (43.3%)	82 (37.6%)	175 (40.4%)
Baseline (V1) BCVA [ETDRS Letters]			
N	215	218	433
Missing values	0	0	0
Mean (SD)	58.0 (11.35)	57.8 (11.22)	57.9 (11.27)
Median	60	60	60
Min, Max	34, 73	34, 73	34, 73
Q1, Q3	51, 67	50, 67	51, 67

Source: Reviewer's analysis.

Table 8. Demographic and baseline characteristics in the Per Protocol Set.

	FYB203 N=201	EU-Eylea N=205	Total N=406
[redacted], n (%)			
Male	87 (43.3%)	85 (41.5%)	172 (42.4%)
Female	114 (56.7%)	120 (58.5%)	234 (57.6%)
Country, n (%)			
Bulgaria	7 (3.5%)	10 (4.9%)	17 (4.2%)
Czech Republic	31 (15.4%)	31 (15.1%)	62 (15.3%)
Hungary	33 (16.4%)	34 (16.6%)	67 (16.5%)
Israel	6 (3.0%)	6 (2.9%)	12 (3.0%)
Italy	9 (4.5%)	9 (4.4%)	18 (4.4%)
Japan	16 (8.0%)	16 (7.8%)	32 (7.9%)
Poland	35 (17.4%)	39 (19.0%)	74 (18.2%)
Russian Federation	31 (15.4%)	31 (15.1%)	62 (15.3%)
Ukraine	33 (16.4%)	29 (14.1%)	62 (15.3%)
Race, n (%)			
White	184 (91.5%)	188 (91.7%)	372 (91.6%)
Asian	16 (8.0%)	16 (7.8%)	32 (7.9%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Ethnicity			
Hispanic or Latino	3 (1.5%)	5 (2.4%)	8 (2.0%)
Not Hispanic or Latino	198 (98.5%)	200 (97.6%)	398 (98.0%)
Age (years)			
N	201	205	406
Missing values	0	0	0
Mean (SD)	73.7 (7.66)	73.5 (7.74)	73.6 (7.69)
Median	74	74	74
Min, Max	51, 93	51, 92	51, 93
Q1, Q3	68.0, 79.0	68.0, 79.0	68.0, 79.0
Age Categories			
50-64 years	16 (8.0%)	23 (11.2%)	39 (9.6%)
65-75 years	98 (48.8%)	104 (50.7%)	202 (49.8%)
> 75 years	87 (43.3%)	78 (38.0%)	165 (40.6%)
Baseline (V1) BCVA [ETDRS Letters]			
N	201	205	406
Missing values	0	0	0
Mean (SD)	57.8 (11.46)	58 (11.25)	57.9 (11.34)
Median	60	60	60
Min, Max	34, 73	34, 73	34, 73
Q1, Q3	51, 67	50, 68	51, 67

Source: Reviewer's analysis.

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoint

The primary objective of this study was to 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 EU-Eylea compared to Baseline. Table 9 presents the primary analysis results of the primary endpoint.

Table 9. Primary analysis results for change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8 (Full Analysis Set).

	n	LS Mean	SE	90.4% CI	95.2% CI
FYB203	215	6.5976	0.7283	(5.3831, 7.8121)	(5.1541, 8.0412)
EU-Eylea	218	5.6450	0.7292	(4.4290, 6.8610)	(4.1997, 7.0903)
Difference (FYB203)-(EU-Eylea)		0.9526	0.7636	(-0.3213, 2.2266)	(-0.5617, 2.4670)

Source: Reviewer's analysis.

As shown in Table 9 the 90.4% confidence interval for the difference of means between the FYB203 group and EU-Eylea group was (-0.3213, 2.2266) and the corresponding 95.2% confidence interval (pertaining to the EU-analysis) was (-0.5617, 2.4670). Both confidence intervals are fully contained within the pre-defined similarity margin of (-3.5, 3.5). Thus, similarity of FYB203 and EU-Eylea with respect to the primary endpoint can be concluded.

Sensitivity analysis results are shown in Table 10, and each of these results is consistent with the primary analysis result because each 90.4% and 95.2% confidence interval for the difference of means between the FYB203 and EU-Eylea groups is fully contained in the (-3.5, 3.5) similarity margin. The supplementary analysis results are shown in Table 11, and each of these results is also consistent with the primary analysis result.

Table 10. Sensitivity analysis results for the primary efficacy endpoint (Full Analysis Set).

	FYB203	EU-Eylea	Difference
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE) 90.4% CI 95.2% CI
MMRM, Data up to Week 24, including patient discontinuation status (yes/no) prior to Week 24 as additional covariate	5.7737 (1.0970)	4.8201 (1.0982)	0.9536 (0.7629) (-0.3191, 2.2264) (-0.5593, 2.4665)
MMRM, Data up to Week 24, including patient discontinuation of treatment prior to Week 24 (Yes/No) as additional covariate	6.3714 (1.1145)	5.4254 (1.0965)	0.9460 (0.7642) (-0.3289, 2.2210) (-0.5695, 2.4616)
MMRM, Data up to Week 24, including patient any major protocol deviation status (Yes/No) as additional covariate	7.1811 (0.9315)	6.2355 (0.9365)	0.9456 (0.7638) (-0.3286, 2.2198) (-0.5690, 2.4602)
MMRM, Data up to Week 24, including ancillary chart use (Yes/No) as additional covariate	7.0942 (0.8657)	6.0853 (0.8392)	1.0089 (0.7657) (-0.2683, 2.2862) (-0.5094, 2.5272)
MMRM, Data up to Week 8	6.6416 (0.7297)	5.6964 (0.7304)	0.9452 (0.7652) (-0.3313, 2.2216) (-0.5722, 2.4625)
ANCOVA, observed cases[1]	6.8383 (0.8255)	5.8460 (0.8238)	0.9923 (0.7716) (-0.2950, 2.2796) (-0.5379, 2.5225)
ANCOVA, multiple imputation[1]	6.8765 (0.8220)	5.7957 (0.8229)	1.0808 (0.7689) (-0.1991, 2.3607) (-0.4396, 2.6012)

[1]There are 6 missing values in the FYB203 arm and 5 missing values in the EU-Eylea arm.
Source: Reviewer's analysis.

Table 11. Supplementary analysis results for the primary efficacy endpoint.

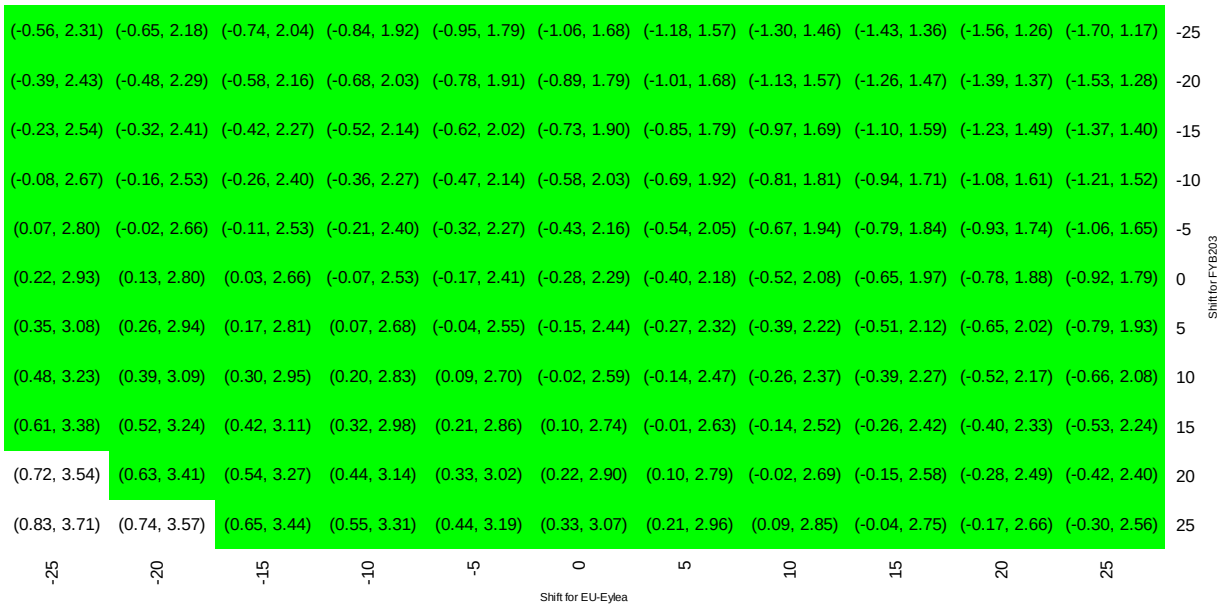
	FYB203	EU-Eylea	Difference
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE) 90.4% CI 95.2% CI
MMRM, FAS, Data up to Week 24, excluding patients with major protocol deviations influencing BCVA until Week 8	6.4186 (0.7490)	5.6150 (0.7460)	0.8036 (0.7899) (-0.5143, 2.1215) (-0.7630, 2.3702)
MMRM, FAS, Data up to Week 24, excluding patients who discontinued treatment before Week 8 or did not have a Week 8 BCVA	6.5233 (0.7404)	5.5298 (0.7379)	0.9935 (0.7715) (-0.2936, 2.2806) (-0.5365, 2.5235)
MMRM, PPS, Data up to Week 24	6.4186 (0.7490)	5.6150 (0.7460)	0.8036 (0.7899) (-0.5143, 2.1215) (-0.7630, 2.3702)
ANCOVA, FAS, Multiple imputation for all patients excluded from the PPS	6.7454 (0.8284)	5.9055 (0.8316)	0.8399 (0.7889) (-0.4732, 2.1530) (-0.7200, 2.3998)
MMRM, FAS, Data up to Week 24 excluding assessments after missed injections	6.5691 (0.7297)	5.6572 (0.7311)	0.9119 (0.7662) (-0.3664, 2.1901) (-0.6076, 2.4313)
MMRM, FAS, Data up to Week 24 excluding assessments after major protocol deviations	6.4913 (0.7356)	5.6932 (0.7366)	0.7981 (0.7811) (-0.5051, 2.1012) (-0.7510, 2.3472)

Source: Reviewer's analysis.

In the Full Analysis Set, for the primary endpoint change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8, there were 6 missing values in the FYB203 arm and 5 missing values in the EU-Eylea arm. In the primary analysis, the missing values were handled using the MMRM model under a missing at random (MAR) assumption. To explore the sensitivity of results to various missing not at random situations, a tipping point analysis was conducted. The tipping point analysis used shift parameters δ_1 and δ_2 for adjustment of imputed values in the FYB203 and EU-Eylea groups, respectively. The reviewer considered combinations of shift parameters δ_1 and δ_2 ranging over $\{-25, -20, -15, -10, -5, 0, 5, 10, 15, 20, 25\}$, for a total of $11 \times 11 = 121$ combinations of δ_1 and δ_2. The reviewer's tipping point analysis results are shown in Figure 3, and out of these 121 combinations, the following three tipping points were identified: $(\delta_1 = 20, \delta_2 = -25)$, $(\delta_1 = 25, \delta_2 = -20)$, and $(\delta_1 = 25, \delta_2 = -25)$. In consideration of the distribution of the observed data on the primary endpoint (refer to Figure 4),

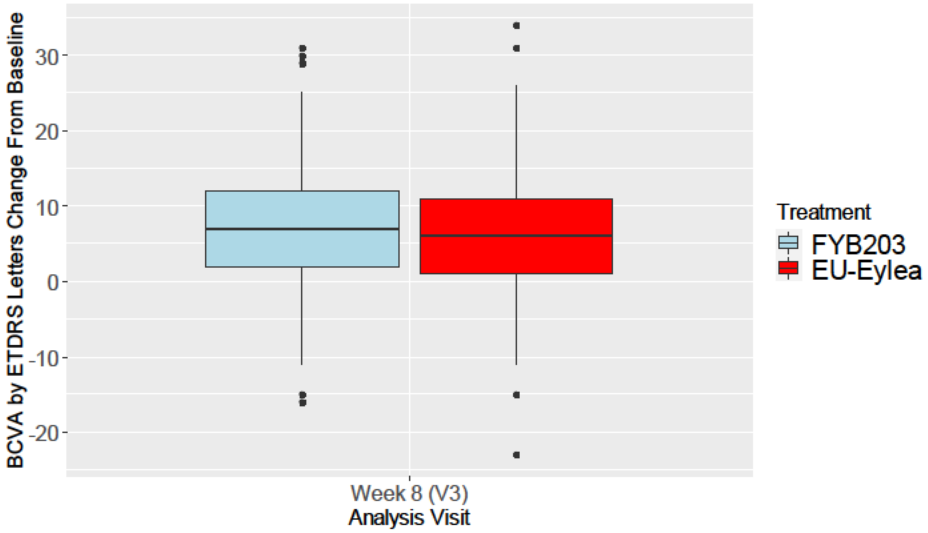
the tipping point analysis results support the robustness of the conclusions of the primary analysis to plausible departures from the missing at random assumption.

Figure 3. Tipping point analysis for change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8.



Notes: (1) The vertical axis shows the value of the shift parameter δ_1 for the imputed values in the FYB203 group, the horizontal axis shows the value of the shift parameter δ_2 for the imputed values in the EU-Eylea group. (2) Green shaded cells correspond to combinations of shift parameters yielding a 90.4% confidence interval that is contained in the similarity margin of (-3.5, 3.5). (3) The 90.4% confidence interval for the corresponding combination of shift parameters is displayed in each cell.
Source: Reviewer's analysis.

Figure 4. Boxplots of the primary endpoint by treatment group.



Source: Reviewer's analysis.

Reviewer's comments.

1. The reviewer noted the following.
    a. Patient [redacted] (b) (6) was randomized to FYB203 but treated with EU-Eylea throughout the complete study, while Patient [redacted] (b) (6) was randomized to EU-Eylea but treated with FYB203 throughout the complete study. As an exploratory analysis the reviewer applied the primary analysis method using actual treatment received instead of randomized treated. Patient [redacted] (b) (6) and Patient [redacted] (b) (6) are both included in the FAS and excluded from the PPS, and within the FAS, only these two patients have actual treatment different from randomized treatment.
    b. The supplementary analyses shown in Table 11 included an analysis based on the PPS using MMRM. As an additional exploratory analyses, the reviewer conducted the ANCOVA analysis using the PPS, using the same ANCOVA model as used in the sensitivity analysis.
    c. The Applicant's simulation studies used to determine the alpha adjustment of 0.048 (used to account for the interim analysis and hence control the overall type 1 error probability at the 0.05 level) for the primary analysis, used the two-sample t-test to evaluate similarity, where the similarity hypotheses were tested using two one-sided t tests. Therefore, as an exploratory analysis, the reviewer calculated confidence intervals for the difference of means between the FYB203 and EU-Eylea groups using the two-sample t confidence interval assuming both groups have equal variance.

    Table 12 shows the results of each of the exploratory analyses described above and each of these results is consistent with the primary analysis result.

2. While this study used a pre-specified similarity margin of (-3.5, 3.5), the reviewer noted that recently a similarity margin of (-3, 3) has been used for proposed biosimilar products referencing US-licensed Eylea using the same primary endpoint as in this study. If the margin (-3, 3) was used in this study, the conclusions of the primary analysis results in Table 9, sensitivity analysis results in Table 10, supplementary analysis results in Table 11, and exploratory analysis results in Table 12 would remain the same. Usage of the margin (-3, 3) instead of (-3.5, 3.5) would introduce additional tipping points in the tipping point analysis described above, but nevertheless the results would still appear to be reasonably robust to plausible departures from the MAR assumption.

Table 12. Exploratory analyses conducted by the reviewer.

	FYB203	EU-Eylea	Difference
	LS Mean (SE)	LS Mean (SE)	LS Mean (SE) 90.4% CI 95.2% CI
Primary analysis method except uses actual treatment[1], FAS	6.5342 (0.7286)	5.7086 (0.7294)	0.8256 (0.7640) (-0.4488, 2.1001) (-0.6893, 2.3406)
ANCOVA, PPS	6.7284 (0.8338)	5.9259 (0.8316)	0.8025 (0.7900) (-0.5155, 2.1206) (-0.7643, 2.3694)
2-sample , t confidence interval, FAS, observed cases	7.0813 (0.5473)	6.0845 (0.5421)	0.9968 (0.7704) (-0.2884, 2.2820) (-0.5309, 2.5246)
2-sample t confidence interval, PPS	6.9652 (0.5601)	6.1659 (0.5546)	0.7993 (0.7883) (-0.5159, 2.1145) (-0.7641, 2.3628)

[1]Patient (b) (6) was randomized to FYB203 but treated with EU-Eylea throughout the complete study, while Patient (b) (6) was randomized to EU-Eylea but treated with FYB203 throughout the complete study.
Source: Reviewer's analysis.

3.2.4.2 Secondary Efficacy Endpoints

FCP Retinal Thickness at Week 4

For the EU analysis, the key secondary endpoint was the change from Baseline (Visit 1) in FCP retinal thickness to Week 4 (Visit 2). As shown in Table 13, the 95.2% confidence intervals for the difference of means based on the FAS and PPS were (-24.3664, 15.4235) and (-28.1551, 13.1246), respectively. Both confidence intervals are contained in the pre-specified margin of (-45.0, 45.0). The 95% confidence intervals are also shown as a descriptive analysis.

Table 13. Analysis of change in foveal center point retinal thickness at Week 4.

	n	LS Mean	SE	95% CI	95.2% CI
Full Analysis Set					
FYB203	206	-171.38	10.3227	(-191.67, -151.09)	(-191.85, -150.91)
EU-Eylea	210	-166.91	10.3891	(-187.33, -146.48)	(-187.51, -146.30)
Difference (FYB203)-(EU-Eylea)		-4.4715	10.0303	(-24.1904, 15.2475)	(-24.3664, 15.4235)
Per Protocol Set					
FYB203	192	-172.80	10.6316	(-193.70, -151.90)	(-193.89, -151.71)
EU-Eylea	198	-165.28	10.5979	(-186.12, -144.45)	(-186.31, -144.26)
Difference (FYB203)-(EU-Eylea)		-7.5152	10.4037	(-27.9725, 12.9420)	(-28.1551, 13.1246)

Patients with at least one post-baseline FCP value until Week 24 were included in the analysis.
Source: Reviewer's analysis.

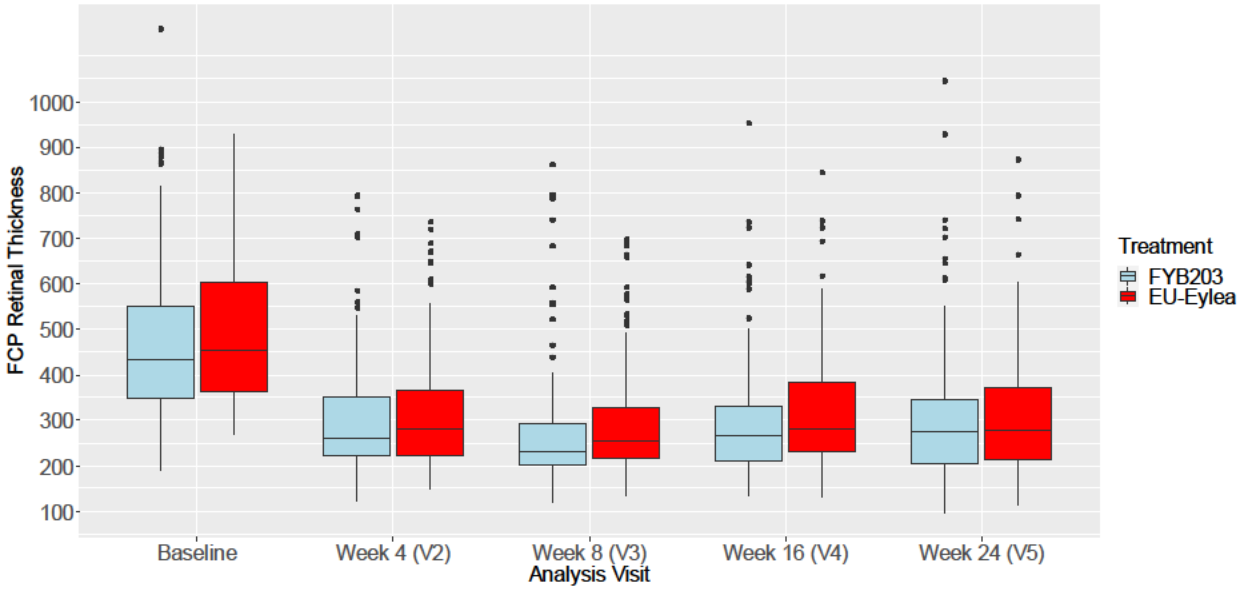
Additional Secondary Endpoints

The reviewer conducted the following descriptive analyses of secondary endpoints using the Full Analysis Set.

- Comparative boxplots of FCP retinal thickness over analysis visits, and of FCP retinal thickness change from baseline over analysis visits (Figure 5 and Figure 6).
- Comparative boxplots of FCS retinal thickness over analysis visits, and of FCS retinal thickness change from baseline over analysis visits (Figure 7 and Figure 8).
- Comparative boxplots of BCVA by ETDRS Letters over analysis visits, and of change from baseline in BCVA by ETDRS Letters over analysis visits (Figure 9 and Figure 10).
- Comparison of change categories of BCVA by ETDRS letters from baseline to Week 24 (Table 14).
- Comparison of number/percentage of patients with Fluid-Free Macula (Table 15).
- Comparative boxplots of total lesion area at baseline and Week 24, and of change from baseline in total lesion area at Week 24 (Figure 11 and Figure 12).
- Comparative boxplots of composite NEI VFQ-25 Score at Baseline and Week 24, and of change from baseline in Composite NEI VFQ-25 Score at Week 24 (Figure 13 and Figure 14).

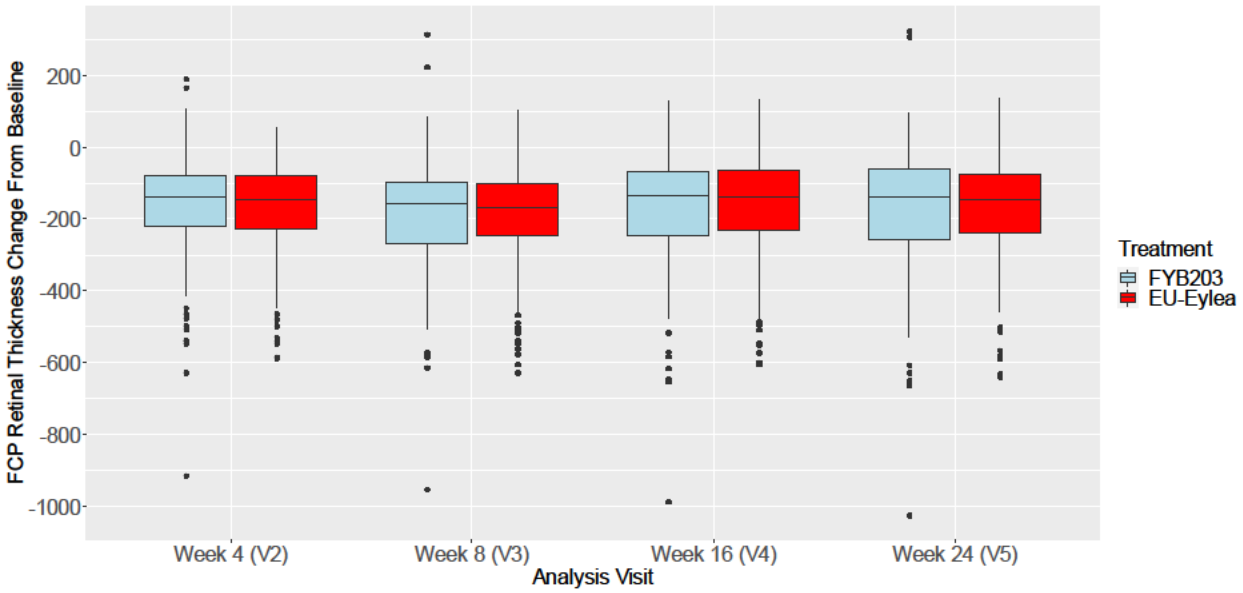
The results described above are descriptive in nature, and the results generally appear to be comparable between the FYB203 group and EU-Eylea group.

Figure 5. FCP retinal thickness to Week 24, Full Analysis Set.



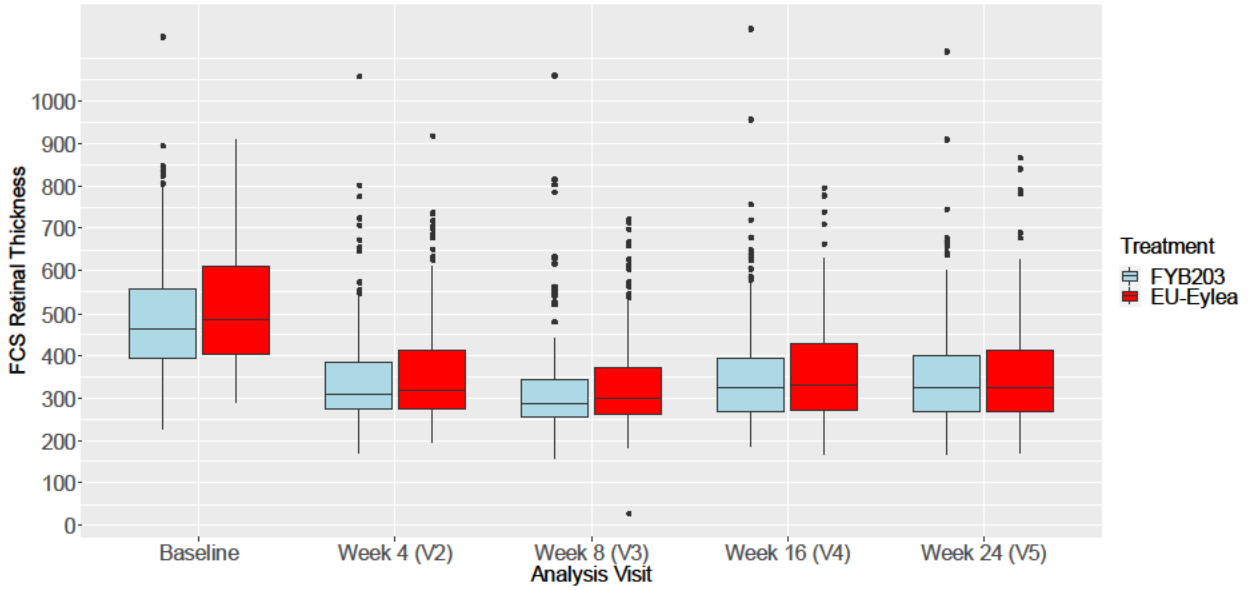
Source: Reviewer's analysis.

Figure 6. FCP retinal thickness change from baseline to Week 24, Full Analysis Set.



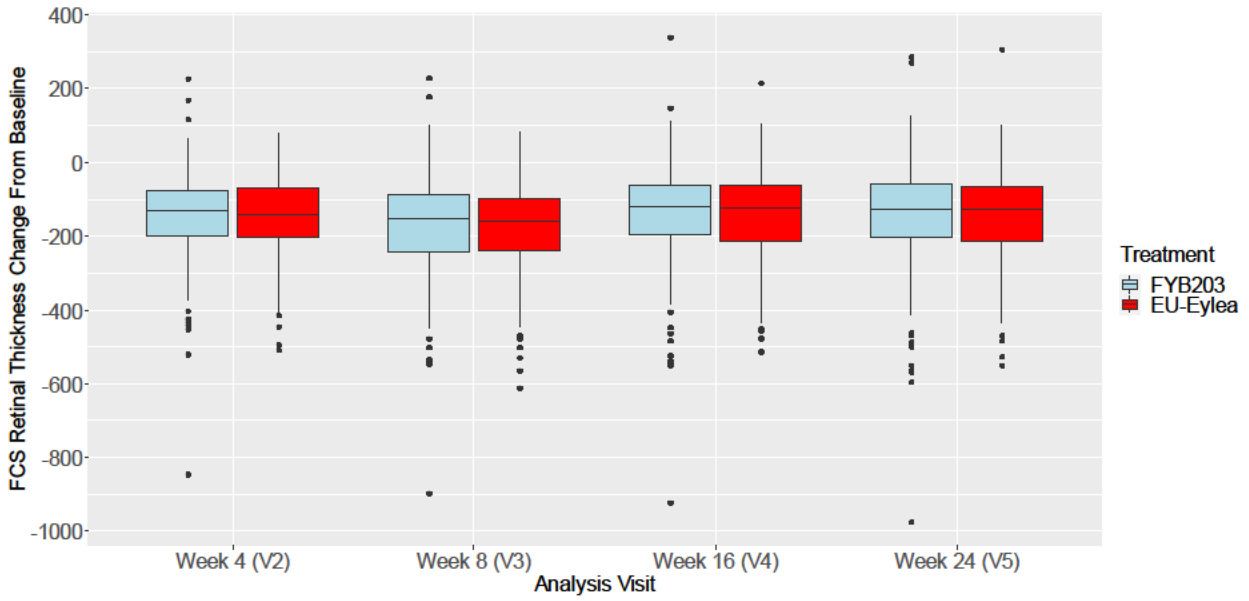
Source: Reviewer's analysis.

Figure 7. FCS retinal thickness to Week 24, Full Analysis Set.



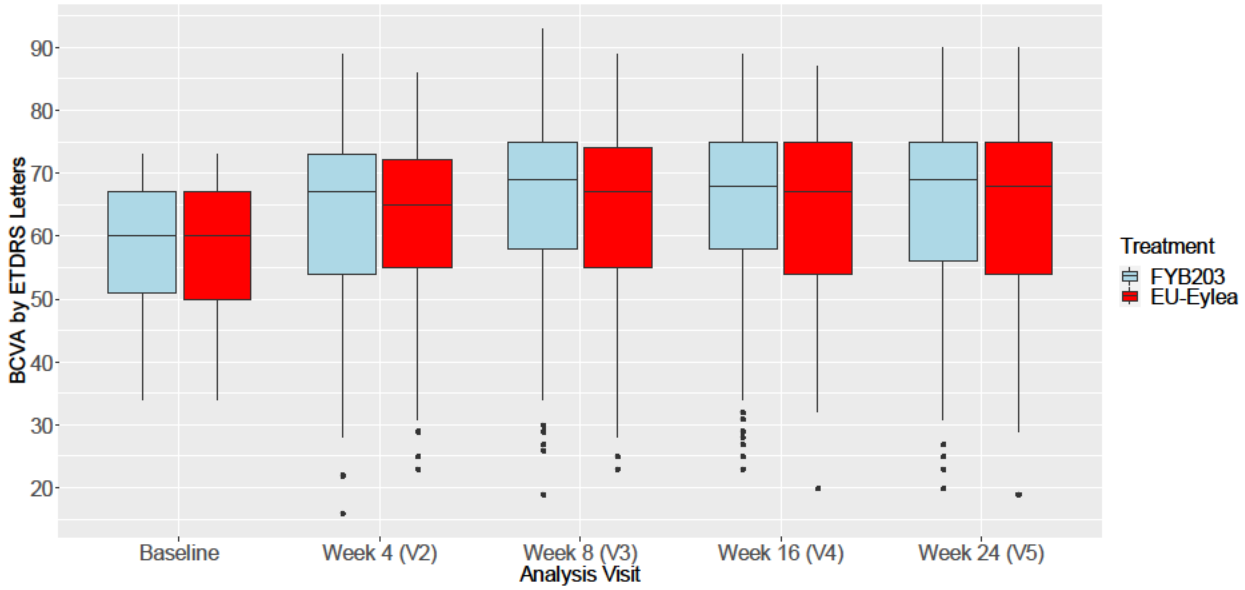
Source: Reviewer's analysis.

Figure 8. FCS retinal thickness change from baseline to Week 24, Full Analysis Set.



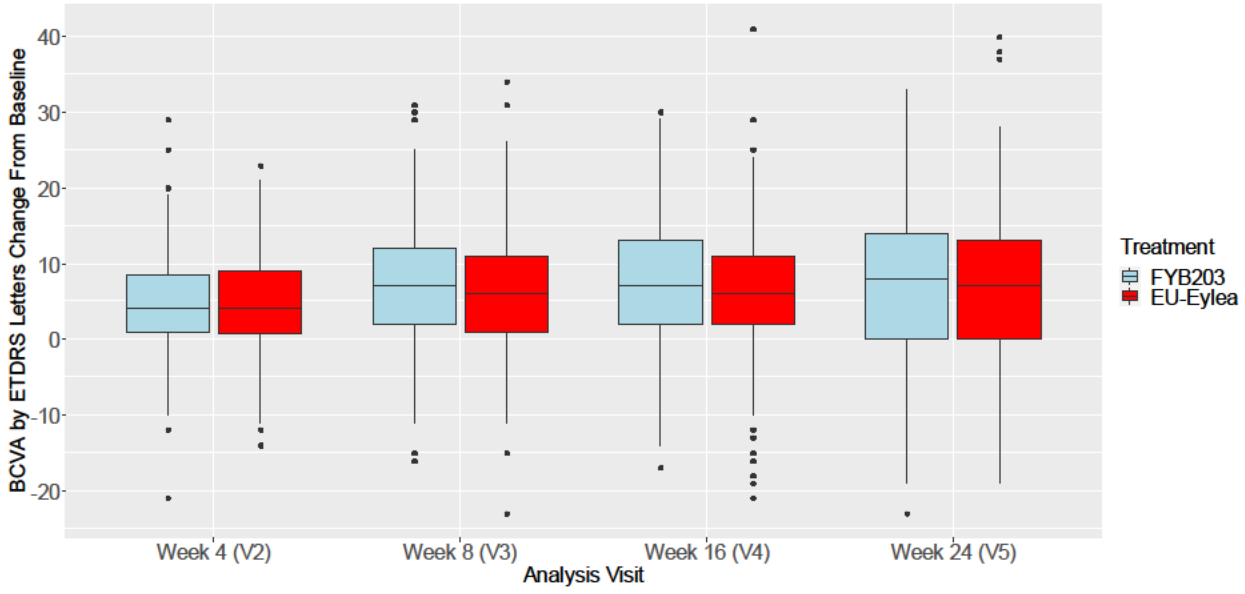
Source: Reviewer's analysis.

Figure 9. BCVA by ETDRS Letters to Week 24, Full Analysis Set.



Source: Reviewer's analysis.

Figure 10. Change from baseline in BCVA by ETDRS Letters to Week 24, Full Analysis Set.



Source: Reviewer's analysis.

Table 14. Change categories of BCVA by ETDRS letters from baseline to Week 24, Full Analysis Set.

		FYB203 (N=215)		EU-Eylea (N=218)		Total (N=433)	
		n_1	%	n_1	%	n_1	%
≥ 15 letters	(gain 15 or more)	45	22.39%	38	18.72%	83	20.54%
≥ 10 and < 15 letters	(gain 10-14)	41	20.40%	39	19.21%	80	19.8%
≥ 5 and < 10 letters	(gain 5-9)	41	20.40%	47	23.15%	88	21.78%
> -5 and < 5	(gain or loss up to 4)	52	25.87%	58	28.57%	110	27.23%
> -10 and ≤ -5 letters	(loss 5-9)	12	5.97%	13	6.40%	25	6.19%
> -15 and ≤ -10 letters	(loss 10-14)	6	2.99%	2	0.99%	8	1.98%
≤ -15 letters	(loss 15 or more)	4	1.99%	6	2.96%	10	2.48%
Missing		14		15		29	

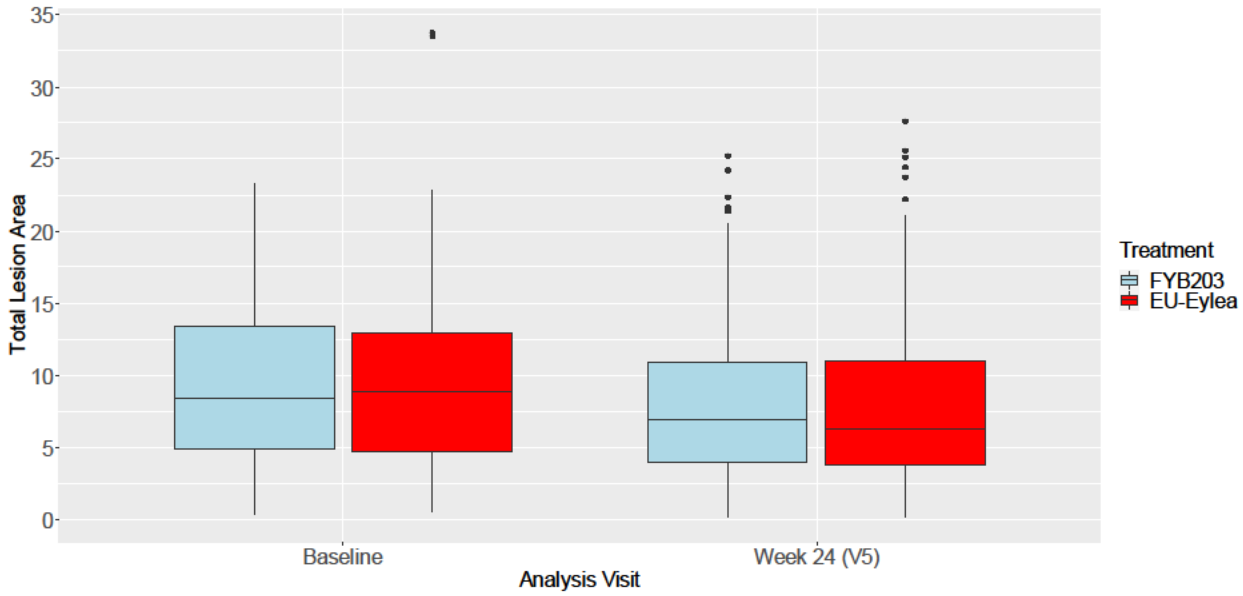
Source: Reviewer's analysis.

Table 15. Summary of patients with Fluid-Free Macula, Full Analysis Set.

	FYB203		EU-Eylea		Total	
	n_1/n	%	n_1/n	%	n_1/n	%
Baseline (V1)	0/214	0%	0/217	0%	0/431	0%
Week 4 (V2)	85/215	39.53%	87/214	40.65%	172/429	40.09%
Week 8 (V3)	118/208	56.73%	114/210	54.29%	232/418	55.50%
Week 16 (V4)	70/203	34.48%	73/204	35.78%	143/407	35.14%
Week 24 (V5)	71/198	35.86%	65/200	32.50%	136/398	34.17%

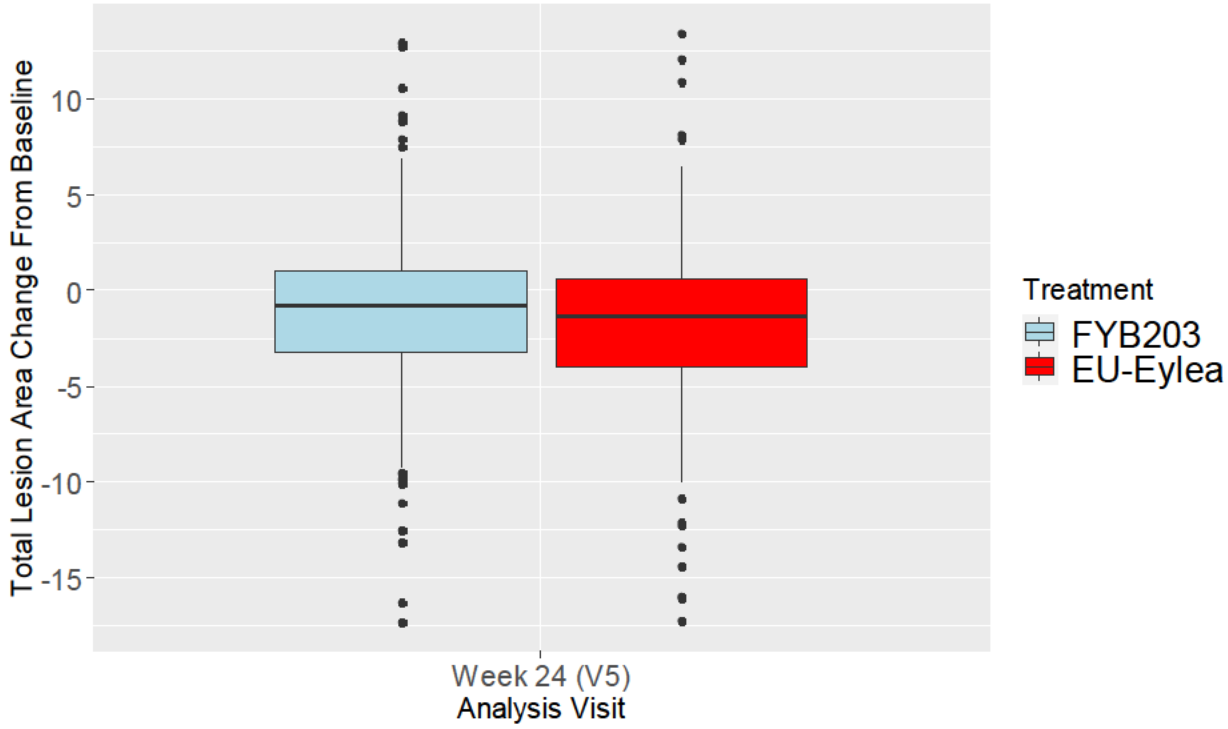
Source: Reviewer's analysis.

Figure 11. Total lesion area at baseline and Week 24, Full Analysis Set.



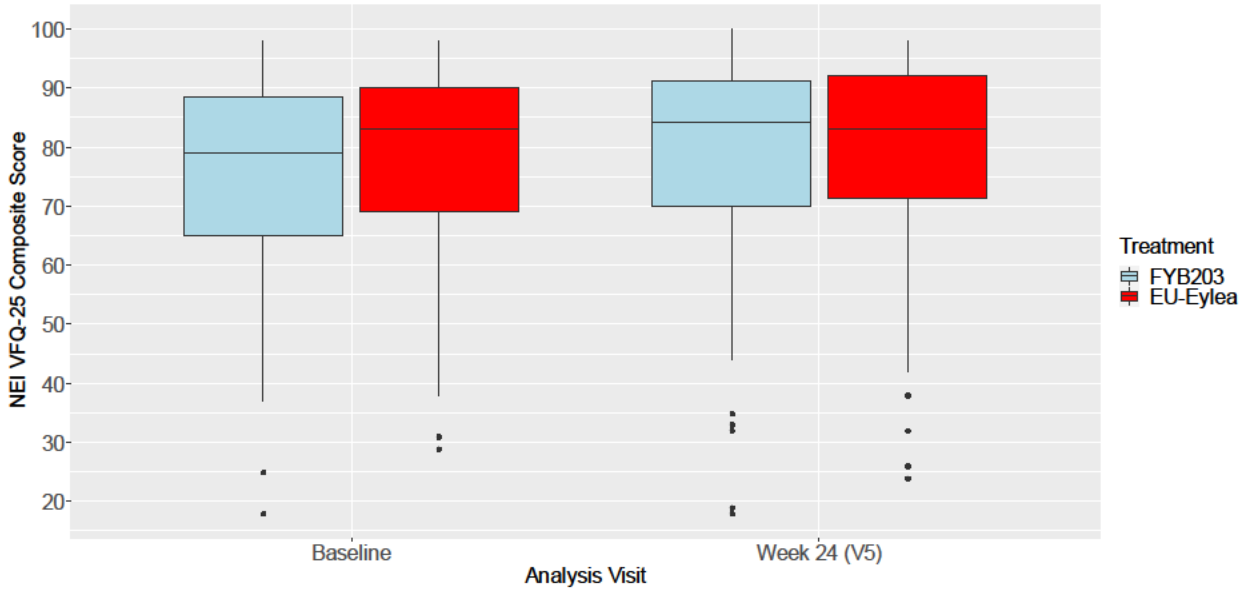
Source: Reviewer's analysis.

Figure 12. Change from baseline in total lesion area at Week 24, Full Analysis Set.



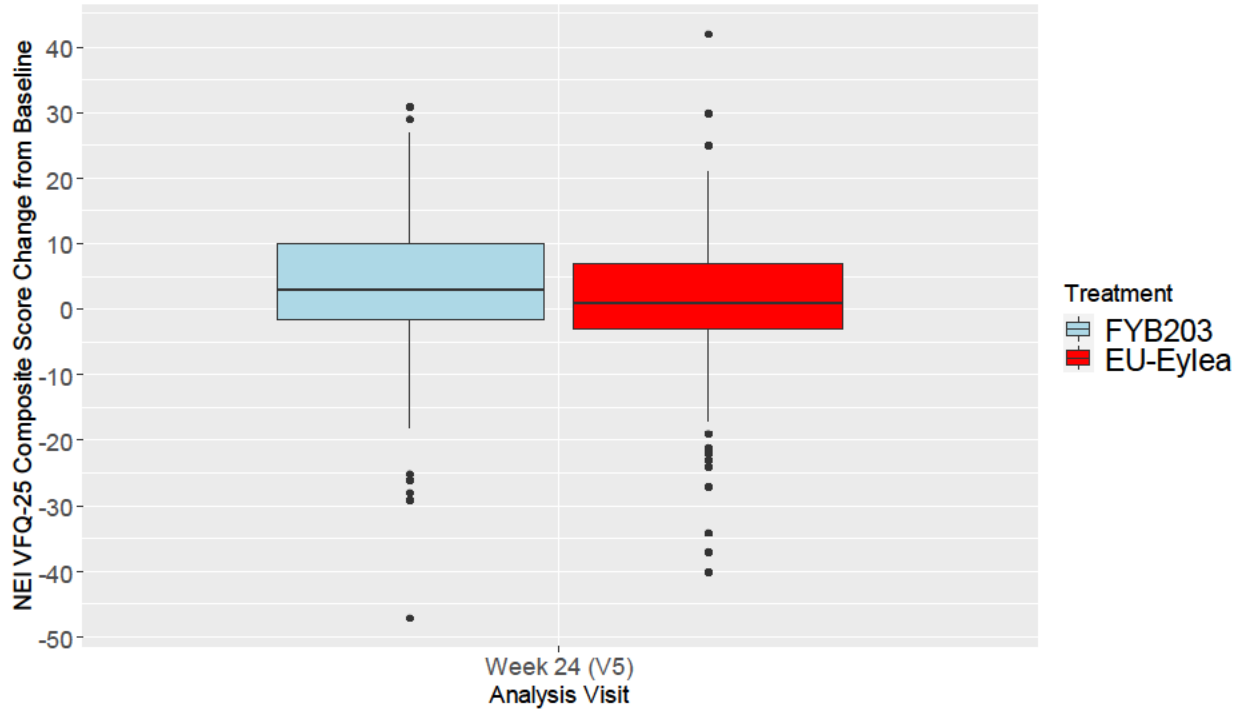
Source: Reviewer's analysis.

Figure 13. Composite NEI VFQ-25 Score at Baseline and Week 24, Full Analysis Set.



Source: Reviewer's analysis.

Figure 14. Change from baseline in Composite NEI VFQ-25 Score at Week 24, Full Analysis Set.



Source: Reviewer's analysis.

3.2.4.3 Efficacy Conclusion

Study FYB203-03-01 provided adequate statistical evidence that there is no clinically meaningful difference between FYB203 and EU-Eylea with respect to mean change in BCVA from Baseline to Week 8 according to the prespecified similarity margin. Sensitivity, supplementary, exploratory, and descriptive analyses support the robustness of the primary analysis results and support similarity of FYB203 and EU-Eylea.

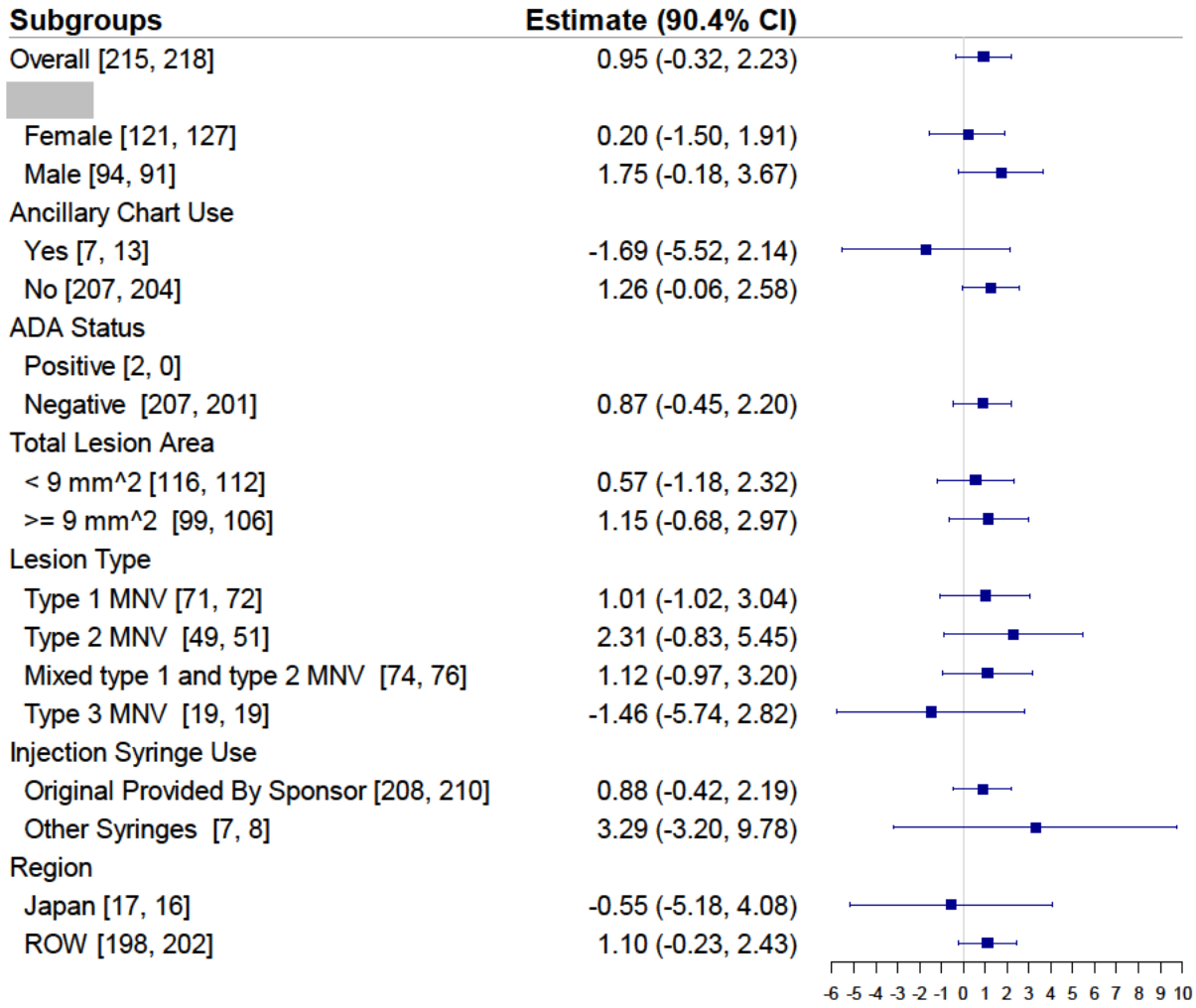
4 SUBGROUP ANALYSES

Figure 15 displays the primary endpoint analysis results within the following subgroups which were prespecified in the SAP, using the Full Analysis Set.

- [redacted] (female and male)
- Use of an ancillary chart up to Week 24 (yes/no, patients who only used the ancillary chart for single assessments will be excluded from this analysis)
- ADA status (any positive treatment emergent ADA during study versus no positive treatment emergent ADA during study up to Week 24)
- Total lesion area at baseline (< $9mm^2$ versus >= $9mm^2$)
- Lesion type at baseline (types as reported by GRADE)
- Syringe use (original syringes provided by sponsor versus other syringes used (at any time during study))
- Region (Japan versus Rest of World (ROW))

These analyses are descriptive in nature. There were no notable efficacy trends favoring FYB203 or EU-Eylea. Note that some subgroups have small sample sizes, and observations should be considered as exploratory.

Figure 15. Subgroup analysis for change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8.



Notes: The numbers $[N_1,N_2]$ in the column labeled "Subgroups" represent the number of patients in the FYB203 and EU-Eylea groups, respectively, for the subgroup. (2) In the "Subgroups" column "Overall" represents the primary analyses results shown in Table 9. (3) The "Estimate" column provides the estimate of the difference of means between the FYB203 group and EU-Eylea group and the corresponding 90.4% confidence interval. (4) For the Positive ADA Status subgroup, the sample size was insufficient to perform the subgroup analysis. (5) Patients were excluded from a particular subgroup analysis if the relevant subgroup variable was missing.
Source: Reviewer's analysis.

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES

The reviewer did not identify any major statistical issues that can impact the overall conclusions.

5.2 COLLECTIVE EVIDENCE

The Applicant seeks approval of FYB203 as a proposed (b) (4) biosimilar product to US-licensed Eylea. Similarity of FYB203 and EU-Eylea was evaluated in Study FYB203-03-01.

The primary endpoint was the change from Baseline (Visit 1) in BCVA by ETDRS letters to Week 8 (Visit 3). The primary endpoint analysis yielded a 90.4% confidence interval for the difference of means (mean of FYB203 – mean of EU-Eylea) of (-0.3213, 2.2266), which is contained in the pre-specified similarity margin of (-3.5, 3.5). Thus, the study demonstrated similarity of FYB203 and EU-Eylea for the primary endpoint. Sensitivity, supplementary, exploratory, and descriptive analyses support the robustness of the primary analysis results and support similarity of FYB203 and EU-Eylea.

5.3 CONCLUSIONS AND RECOMMENDATIONS

Based on the totality of statistical evidence from Study FYB203-03-01, the reviewer concluded that the Applicant provided adequate evidence for similarity of FYB203 and EU-Eylea in the primary efficacy endpoint.

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION

Application number:	BLA 761378
Supporting document/s:	SN0001
Applicant's letter date:	June 28, 2023
CDER stamp date:	June 28, 2023
Product:	FYB203 (aflibercept, 2 mg)
Pharmacological class:	VEGF inhibitor
Indication:	Neovascular (Wet) Age-Related Macular Degeneration (AMD) Macular Edema Following Retinal Vein Occlusion (RVO) Diabetic Macular Edema (DME) Diabetic Retinopathy (DR)
Applicant:	Formycon AG
Clinical Review Division:	Ophthalmology
Reviewer:	Muriel Saulnier, DVM, PhD, DABT
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	currently vacant
Project Manager:	Kidist Berhanu

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

Formycon AG (Formycon) is submitting a Biologic License Application (BLA) type 351(k) for the (b) (4) biosimilar product FYB203 (aflibercept) for intravitreal injection, which has the same dosage form, route of administration, dosing regimen and presentation as the reference product Eylea® (aflibercept for intravitreal injection, 2 mg/0.05 mL (40 mg/mL)) reviewed under BLA 125387.

The Applicant is seeking licensure for Eylea's indications of neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR).

To support the BLA approval, Formycon performed an extensive *in vitro* similarity assessment of their product compared to Eylea (results of similarity between FYB203 and Eylea to be confirmed by the OFFICE OF BIOTECHNOLOGY PRODUCTS OBP), *in vivo* preclinical studies, and a clinical study, i.e., a randomized, parallel-group, active-controlled, double-masked, multi-center phase 3 efficacy and safety study comparing FYB203 and Eylea in patients with neovascular AMD (title: MAGELLAN-AMD).

1.2 Brief Discussion of Nonclinical Findings

Formycon performed *in vivo* studies in animals in order to demonstrate similarities between the ocular and systemic pharmacokinetic (PK) and toxicological profiles between FYB203 and Eylea.

The *in vivo* preclinical data suggested that FYB203 and Eylea had slightly different systemic PK/TK and toxicity profiles.

Nevertheless, since new animal studies with FYB203 were neither required by the Agency nor recommended for a BLA type 351(k) application, the preclinical data reviewed in this report were merely informational.

1.3 Recommendations

1.3.1 Approvability

The product is approvable from a pharmacology and toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

2 Drug Information

2.1 Drug

CAS Registry Number
862111-32-8

Generic Name
Aflibercept

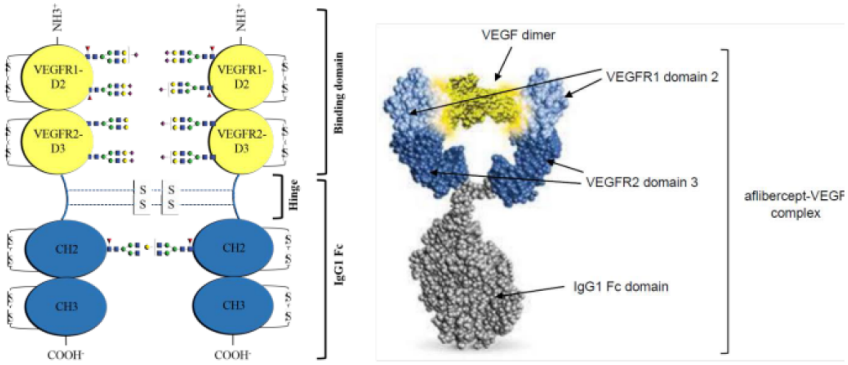
Code Name
FYB203

Chemical Description
Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. Aflibercept has five N-glycosylation sites on each polypeptide chain which can be occupied with carbohydrates and exhibit some degree of heterogeneity, including heterogeneity in terminal sialic acid residues.

Molecular Formula/Molecular Weight
$C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$/96.9 kDa (deglycosylated)

Structure

Left: schematic structure of aflibercept. Right: model showing aflibercept bound to a VEGF dimer, adapted from https://ophthalmologie.bayer.de



Pharmacologic Class
Vascular endothelial growth factor (VEGF) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- Pre-IND 144550 for FYB203 reviewed by Dr. McDougal, Division of Ophthalmology at FDA

  This reviewer's comment: Note that IND 144550 was not formally opened, although one of the goals of the pre-IND meeting held on September 11, 2019 (Minutes archived in DARRTS on October 17, 2019A) was to discuss the adequacy of the animal studies performed by the Sponsor to open an IND with a Phase 3 trial planned in Q1 2020. The IND remains in pre-submission phase.
- BLA 125387 for Eylea®

(b) (4)

2.3 Drug Formulation

FYB203 is produced in recombinant Chinese Hamster Ovary (CHO) cells. The strength, dose, and volume (40 mg/mL, 2 mg intravitreal (IVT) dose in 50 µL) are similar to Eylea. The drug product (DP) is delivered in single dose glass vials with a nominal fill volume of (b) (4) mL/vial.

The FYB203 formulation differs from Eylea in the (b) (4). FYB203 drug product (DP) contains (b) (4) mmol/L (b) (4) histidine / L-histidine HCl monohydrate, (b) (4) mmol/L sodium chloride, 5 % (w/v) sucrose and 0.3 mg/mL polysorbate 20 at pH 6.2 (Table 1).

Table 1: Formulation of FYB203 DP

Component	Function	Reference to standard [1]	Quantity per unit (vial)	Quantity per mL
Aflibercept	API	N/A	(b) (4)	40 mg
(b) (4) histidine	(b) (4)	USP, EP		0.917 mg
L-histidine hydrochloride monohydrate		EP		0.857 mg
Sodium chloride	(b) (4)	USP, EP	(b) (4)	2.34 mg
Sucrose		USP-NF, EP		50 mg
Polysorbate 20		USP-NF, EP		0.3 mg
Water for injection (WFI)		USP, EP		q.s. to 1.00 mL

[1] For compendial monographs the current version is applied as appropriate.

(Copied from Module 2.2.3 Drug Product on pp 9,10)

2.4 Comments on Novel Excipients

There are no novel excipients.

This reviewer's comment: According to the Inactive Ingredient Database at FDA, sucrose and polysorbate 20 have not been qualified in ophthalmic products. However, the clinical formulation was used in a GLP toxicity study in the rabbit which qualifies the excipients.

2.5 Comments on Impurities/Degradants of Concern

Drug Product (DP)

Process-related impurities of the drug substance (DS) which could be carried over into the DP, e.g., leachables and host cell proteins (HCPs), were investigated and are monitored (b) (4), if applicable. These are not expected to increase/differ in the DP compared to the DS.

Extractables and Leachables

Compatibility of the elastomeric and plastic product contacting the biomaterial (drug product) was determined. All identified compounds (b) (4) were found well below their respective permissible daily exposure (PDE).

Compatibility of the container closure system, including the leachables from the vial/stopper combination (b) (4) (b) (4) with the biomaterial (drug product) was studied and no relevant impact on the product quality was found, i.e., they were all below the PDE.

Drug Substance (DS)

FYB203-related impurities are (b) (4) resulting in DS batches that consistently met the DS release specification for the respective parameters.

Process-related impurities, (b) (4) The DS release results for these impurities were either close to (b) (4) or below method limit of quantitation (LOQ) (b) (4) (b) (4)

This reviewer's comment: This reviewer defers to OBP for the acceptability of these limits.

2.6 Proposed Clinical Population and Dosing Regimen

Clinical population

From the proposed label of FYB203, the product is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema

Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

Dosing regimen

Neovascular (Wet) Age-Related Macular Degeneration (AMD)

2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).

Macular Edema Following Retinal Vein Occlusion (RVO)

2 mg (0.05 mL) administered by intravitreal injection once every 4 weeks (approximately every 25 days, monthly)

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR)

2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months)

2.7 Regulatory Background

The Sponsor had several prior interactions with the Agency to obtain advice on their development program for FYB203. Minutes of each meeting were archived in DARRTS on March 15, 2023, May 18, 2022, March 25, 2021, and October 17, 2019. At the meeting on September 11, 2019 (meeting minutes dated October 17, 2019), one purpose was to confirm that the data from the rabbit PK and toxicology studies sufficiently addressed the differences in certain quality attributes (specifically the degree of sialylation) between Eylea and FYB203 for entry into a clinical study. This was the only meeting addressing pharmacology and toxicology.

3 Studies Submitted

3.1 Studies Reviewed

F21D03018: FYB203: 3-week ocular and systemic pharmacokinetic study following a single intravitreal administration in albino rabbits

F21DE24318: FYB203: Comparative ocular and systemic pharmacokinetic study following a single intravitreal administration of aflibercept in albino rabbits

35933: FYB203: 1 month ocular and systemic tolerance/toxicity study following two intravitreal administrations in albino rabbits

3.2 Studies Not Reviewed

All Methods and Validation studies

3.3 Previous Reviews Referenced

Pre-IND 144550 for FYB203 reviewed by Dr. McDougal, Division of Ophthalmology at FDA

4 Pharmacology

4.1 Primary Pharmacology

Mechanism of action

Aflibercept is a glycosylated, disulfide-stabilized homodimeric recombinant fusion protein consisting of domain 2 of human vascular endothelial growth factor receptor 1 (VEGFR-1 D2) and domain 3 of VEGFR-2 (VEGFR-2 D3) fused to the Fc domain of human IgG1. Aflibercept acts as a soluble decoy receptor that binds VEGF-A and placental growth factor (PlGF), and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Biosimilarity assessment

It was based on *in vitro* functional characterization of FYB203 compared to Eylea.

This reviewer's comment: Biosimilarity is reviewed by OBP.

Methods

The *in vitro* assessment of the pharmacodynamic (PD) properties of FYB203 addressed its mode of action using a battery of functional assays (Table 2).

Table 2: Assays performed to assess functional activities

Type of study / Quality attribute	Method
VEGF-A binding	iLite VEGF-A_{165} potency assay VEGF-A_{165} HUVEC proliferation assay VEGF-A_{165} relative potency (ELISA) VEGF-A_{121} relative potency (ELISA) VEGF-A_{189} relative potency (ELISA) VEGF-A_{165} binding kinetics

Type of study / Quality attribute	Method
PlGF binding	PlGF-2 relative potency (ELISA) PlGF-1 relative potency (ELISA)
VEGF-B binding	VEGF-B_{186} relative potency (ELISA)
Galectin-1 binding	Galectin-1 (ELISA)
FcRn binding	FcRn binding kinetics (BLI)
Fc gamma receptor binding	FcγRI binding kinetics (SPR) FcγRIIIA(V) binding kinetics (SPR) FcγRIIIA(F) binding kinetics (SPR)
C1q binding	C1q binding (ELISA)
ADCC	ADCC assays
CDC	CDC assays
Absence of VEGF-C binding	VEGF-C non-binding (BLI)
Absence of VEGF-D binding	VEGF-D non-binding (ELISA)

BLI = Bio-Layer Interferometry; ELISA = Enzyme-linked immunosorbent assay; SPR = Surface Plasmon Resonance

(Copied from Module 2.2.4 Non-Clinical Overview on pp 24, 25)

Results

- In a Bio-Layer Interferometry (BLI), Surface Plasmon Resonance (SPR), and Enzyme-Linked Immunosorbent Assay (ELISA), FYB203 bound to VEGF-A165 (BLI + ELISA), VEGF-A121(BLI + ELISA), VEGF-A189 (BLI + ELISA), VEGF-B186 (ELISA), PlGF-2 (SPR + ELISA), PlGF-1 (SPR + ELISA), and Galectin (SPR + ELISA), -similarly to Eylea

- In an iLite reporter gene assay (luciferase assay), FYB203 dose-dependently inhibited the binding of VEGF-A165 to its cognate receptors, and inhibited VEGF-A165-induced proliferation of VEGF-receptor expressing human umbilical vein endothelial cells (HUVECs) in a similar fashion as Eylea

- Like Eylea, FYB203 bound to FcRn (BLI), FcγRI (SPR) and did not bind to target related proteins VEGF-C and VEGF-D (BLI and ELISA), or to C1q (ELISA), and

did not induce Antibody Dependent Cell Cytotoxicity (ADCC) or Complement Dependent Cell Cytotoxicity (CDC)

Although differences between FYB203 and Eylea in binding to FcγRIIIA (158V)) and FcγRIIIA (158F) (determined by SPR) due to differences in afucose levels were detected, the differences did not translate in induction of ADCC with FYB203.

4.2 Secondary Pharmacology

No information was provided (the Sponsor referred to Eylea).

4.3 Safety Pharmacology

No information was provided (the Sponsor referred to Eylea).

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

ABSORPTION/OCULAR DISTRIBUTION

The ocular and plasma PK of FYB203 compared to Eylea following a single IVT dose of either product was assessed in the albino New Zealand White rabbit. In plasma, free and total aflibercept were measured. All bioanalytical assays were validated.

1) F21D03018: FYB203: 3-week ocular and systemic pharmacokinetic study following a single intravitreal administration in albino rabbits (GLP)

Methods

Male New Zealand White (NZW) rabbits (2 groups of 48, 6/group/time point) received a single intravitreal injection of 2 mg/eye/OU Eylea (batch # 72477C) or 2 mg/eye/OU FYB203 (batch # F18198). The exposure to each drug product was evaluated in the vitreous humor (VH), aqueous humor (AH), retina/choroid (R/C), optic nerve (ON), and plasma at 1-, 6-, 24-, 48-, 72-, 120- (plasma only), 168-, 336-, and 504-hours post-dose. The presence of antidrug antibodies (ADAs) was evaluated at baseline and at 504 hours. Ophthalmoscopy was performed at baseline and at 24-, 72-, 144-, 312-, and 480 hours post-dose. An ELISA with VEGF-A165 was used to evaluate free aflibercept in plasma (Lower Level of Quantitation (LLOQ) = 6.25 ng/mL), in the VH (LLOQ = 0.3 ng/mL), in AH and R/C (LLOQ = 0.45 ng/mL). An ELISA with an anti-aflibercept antibody was used to evaluate total aflibercept in plasma LLOQ = 5.0 ng/mL). Total aflibercept = free aflibercept + VEGF-bound aflibercept.

Results
Test items were well tolerated.

Plasma (Tables 3, 4, 6):

- Free and total aflibercept exposures (C_{max} and AUC_{0-t}) were 2-fold lower with FYB203 compared to Eylea but the levels of calculated bound aflibercept (total aflibercept minus free aflibercept) for FYB203 were in the range of the reference product Eylea
- Eylea T_{max} was 72 hours (free and total) while FYB203 free T_{max} was 120 hours, and bound T_{max} was 168 hours
- 2/6 rabbits treated with FYB203 were ADA positive compared with 3/6 with Eylea

The assumption was that the lower levels of sialylation with FYB203 resulted in faster clearance from the blood *via* the liver resulting in different elimination kinetics of the free (and total) aflibercept compared to Eylea.

Table 3: Summary of free and total aflibercept levels in plasma

Time-point after dosing	FYB203 Tech Batch 2 (F18198) treatment		Eylea® treatment	
	Concentration (ng/mL, mean ± SD)			
	Free aflibercept in plasma (a)	Total aflibercept in plasma (b)	Free aflibercept in plasma (a)	Total aflibercept in plasma (b)
1 h	6 ± 15	6 ± 15	2 ± 4	1 ± 3
6 h	126 ± 28	127 ± 31	225 ± 231	237 ± 230
12h	211 ± 77	232 ± 65	284 ± 117	265 ± 92
24 h	403 ± 122	663 ± 162	608 ± 197	684 ± 159
48 h	583 ± 186	890 ± 87	1 117 ± 120	1 328 ± 96
72 h	625 ± 108	1 001 ± 143	1 518 ± 362	1 718 ± 328
120 h	626 ± 161	1 136 ± 205	1 326 ± 36	1 552 ± 81
168 h	564 ± 159	1 232 ± 484	1 000 ± 170	1 500 ± 165
336 h	52 ± 111	151 ± 283	160 ± 214	327 ± 365
504 h	14 ± 25	41 ± 70	48 ± 73	129 ± 172
N (PK time-points)	10	10	10	10
AUC_{last} [h*ng/mL]	147 215	NP	298 776	NP
SE AUC_{last} [h*ng/mL]	11 171	NP	17 791	NP
C_{max} [ng/mL]	626	1 232	1 518	1 718
SE C_{max} [ng/mL]	66	NP	148	NP
AUC_{inf} [h*ng/mL]	148 313	NP	303 631	NP
AUC_{time} [h*ng/mL]	89 909	NP	183 837	NP
$T_{1/2}$ [h]	63	NP	77	NP
T_{max}	120	168	72	72
MRT_{Inf} [h]	138	NP	149	NP
CL/f [(mg*mL)/(h*ng)]	0.0004	NP	0.0002	NP
Vz/f [(mg*mL)/ng]	0.0325	NP	0.0198	NP

NP = Not performed, PK parameters calculations for total aflibercept in plasma were not performed in accordance with the Sponsor.
(a) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.182 (see deviation in section **10.2**).
(b) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.155 (see deviation in section **10.2**).

(Copied from F21D03018 on p 9)

Table 4: Summary of calculated bound aflibercept levels in plasma

	Calculated bound aflibercept in plasma (ng/mL)			
	FYB203 Tech Batch 2 (F18198)		Eylea®	
Time (hours)	Mean	SD	Mean	SD
1	0.2	0.6	0.0*	0.5
6	4.6	8.9	16.8	11.1
12	27.0	72.0	0.0*	36.3
24	275.8	101.4	92.2	119.1
48	328.6	191.4	242.6	122.2
72	399.9	189.9	240.8	270.2
120	535.2	147.5	262.1	96.7
168	696.9	368.4	534.6	123.5
336	102.0	179.0	175.0	165.5
504	27.2	46.8	83.7	104.7

* Negative value replaced by 0.0

(Copied from F21D03018 on p 9)

Ocular (Tables 5,6):

- For VH, AH, and R/C, the equivalence for AUC_{0-t} between treatment with FYB203 or Eylea was high with ratios being close to 1.00. The related Fieller-type confidence intervals (CIs) for the AUC ratios were within the limits of 0.8 to 1.25.

- For VH and AH, the equivalence for C_{max} between both treatments was high with ratios being close to 1.00 and related Fieller-type CIs within the limits of 0.8 to 1.25, and 0.8 to 1.3 for VH and AH, respectively.

- For R/C, the equivalence for C_{max} between both treatments was 1.78 and the related Fieller-type CIs were outside the limits of 0.8 to 1.25. However, taking into account the inhomogeneous distribution of aflibercept in vitreous humor at early time-points resulted in a ratio for C_{max} of 0.97 with related Fieller-type CIs being within the limits of 0.8 to 1.25.

Table 5: Summary of free aflibercept levels in ocular tissues

Time-point after dosing	FYB203 Tech Batch 2 (F18198) treatment			Eylea® treatment		
	Concentration (µg/mL for VH and AH and in µg/g for R/CH, mean ± SD)					
	Vitreous humor (a)	Aqueous humor (a)	Retina-Choroid (b)	Vitreous humor (a)	Aqueous humor (a)	Retina-Choroid (b)
1 h	1 548 ± 245	5 ± 7	371 ± 145	1 578 ± 312	14 ± 13	205 ± 115
6 h	1 428 ± 187	41 ± 10	184 ± 68	1 541 ± 473	41 ± 28	149 ± 41
24 h	1 413 ± 179	53 ± 16	184 ± 32	1 439 ± 82	55 ± 8	174 ± 28
48 h	1 178 ± 377	63 ± 10	198 ± 40	1 270 ± 151	59 ± 14	203 ± 44
72 h	946 ± 140	53 ± 12	124 ± 24	1 115 ± 71	55 ± 7	165 ± 40
168 h	584 ± 74	33 ± 3	75 ± 20	493 ± 36	26 ± 3	71 ± 12
336 h	238 ± 51	11 ± 3	32 ± 10	208 ± 36	13 ± 7	35 ± 7
504 h	28 ± 19	5 ± 2	8 ± 4	34 ± 13	5 ± 1	8 ± 4
N (PK time-points)	8	8	8	8	8	8
AUC_{last} [h*µg/mL]	255 210	12 763	NP	252 992	12 278	NP
SE AUC_{last} [h*µg /mL]	7 553	441	NP	4 595	602	NP
C_{max} [µg /mL or µg/g]	1 548	63	371	1 578	59	205
SE C_{max} [µg /mL]	100	4.3	NP	127	5.8	NP
AUC_{inf} [h*µg /mL]	260 672	13 502	NP	258 755	13 116	NP
AUC_{time} [h*µg /mL]	Not calculated	7 868	NP	Not calculated	7 605	NP
$T_{1/2}$ [h]	93	119	NP	94	125	NP
T_{max} [h]	1	48	1	1	48	1
MRT_{Inf} [h]	143	174	NP	135	182	NP
CL/f [(mg*mL)/(h*µg)]	0.0002	0.0039	NP	0.0002	0.0041	NP
Vz/f [(mg*mL)/µg]	0.0271	0.6672	NP	0.0281	0.7440	NP

NP = Not performed, PK parameters calculations for retina-choroid were performed in accordance with the Sponsor.
(a) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.182 (see deviation in section **10.2**).
(b) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.155 (see deviation in section **10.2**).

(Copied from F21D03018 on p 8)

Table 6: Ratios and two-sided 90% Fieller-type CIs

Parameter	Comparison	AUC_{0-t} ratio	90% CI
AUC_{0-t}	Vitreous humor	1.009	[0.951; 1.068]
	Aqueous humor	1.039	[0.942; 1.151]
	Retina-choroid [1 h – 504 h]	1.04	[0.97; 1.11]
	Retina-choroid [6 h – 504 h]	1.05	[0.99; 1.12]
	Plasma	0.493	[0.418; 0.577]
C_{max}	Vitreous humor	0.981	[0.828; 1.171]
	Aqueous humor	1.059	[0.874; 1.301]
	Retina-choroid [1 h – 504 h]	1.78	[0.97; 2.77]
	Retina-choroid [6 h – 504 h]	0.97	[0.81; 1.15]
	Plasma	0.413	[0.323; 0.524]

(Copied from F21D03018 on p 11)

2) F21DE24318: FYB203: Comparative ocular and systemic pharmacokinetic study following a single intravitreal administration of aflibercept in albino rabbits (GLP)

Methods

Male New Zealand White (NZW) (4 groups of 12) received a single intravitreal injection of 2 mg/eye/OU Eylea (batch # 81020C) or 2 mg/eye/OU FYB203 (batch # F18146, F18198, or ADM-2019-001). The exposure to Eylea and to each batch of FYB203 was evaluated in the vitreous humor (VH), aqueous humor (AH), retina/choroid (R/C), optic nerve (ON), and plasma at 12- (plasma only), 48- (plasma only), 72-, and 120 hours post-dose. Ophthalmoscopy was performed at baseline and at 72 hours post-dose. An ELISA with VEGF-A165 was used to evaluate free aflibercept in plasma (LLOQ = 6.39 ng/mL), in the VH (LLOQ = 0.3 ng/mL), in AH and R/C (LLOQ = 0.45 ng/mL). An ELISA with an anti-aflibercept antibody was used to evaluate total aflibercept in plasma LLOQ = 5.0 ng/mL). Total aflibercept = free aflibercept + VEGF-bound aflibercept.

Study design

Group n°	Treatment	Time-points	Rabbit identification ocular tissues	Rabbit identification plasma
1	FYB203 Tech Batch 1 (F18146)	12 h ± 24 min	-	1 to 12
		48 h ± 96 min	-	1 to 12
		72 h ± 2 h	1 to 6	1 to 12
		120 h ± 3 h	7 to 12	7 to 12
2	FYB203 Tech Batch 2 (F18198)	12 h ± 24 min	-	13 to 24
		48 h ± 96 min	-	13 to 24
		72 h ± 2 h	13 to 18	13 to 24
		120 h ± 3h	19 to 24	19 to 24
3	FYB203 GMP Batch 1 (ADM-2019-001)	12 h ± 24 min	-	25 to 36
		48 h ± 96 min	-	25 to 36
		72 h ± 2h	25 to 30	25 to 36
		120 h ± 3h	31 to 36	31 to 36
4	Eylea®	12 h ± 24 min	-	37 to 48
		48 h ± 96 min	-	37 to 48
		72 h ± 2h	37 to 42	37 to 48
		120 h ± 3h	43 to 48	43 to 48

Results

Test items were well tolerated.

Plasma (Tables 7-9):

- Free and total aflibercept exposures were comparable in rabbits treated with Eylea or FYB203 batch F18146, whereas plasma levels of free and total aflibercept in

rabbits treated with Eylea were increased when compared to rabbits treated with either FYB203 batch F18198, or FYB203 batch ADM-2019-001

- The calculated bound aflibercept exposures in animals dosed with FYB203 (all batches) were in the same range as those of animals treated with Eylea considering the variability of the data

The assumption was that decreased systemic distribution of FYB203 with lower levels of sialylation in the different batches of FYB203 resulted in different elimination kinetics of the free aflibercept molecule. In fact, it resulted in lower systemic exposure with FYB203 *versus* Eylea, hence enhancing the systemic safety of the proposed drug product.

Table 7: Summarized data - Free aflibercept levels in plasma

	Free aflibercept in plasma [(b)]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD
12	499	380	348	180	312	107	502	386
48	1348	264	936	295	1081	315	1538	423
72	1210	236	880	395	957	273	1413	287
120	1397	149	950	261	964	120	1367	367

(Copied from F21D03018 on p 8)

Table 8: Summarized data - Total aflibercept levels in plasma

	Total aflibercept in plasma [(b)]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD
12*	479	276	482	202	405	168	584	425
48*	1461	156	1277	336	1274	430	1660	502
72*	1806	239	1846	974	1459	289	1802	261
120**	2005	661	1537	389	1481	709	1654	778

(a) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.182 (see deviation in section **10.2**).
(b) = Sample analyzed with calibration curve and QC performed with protein concentration calculated by using an extinction coefficient of 1.155 (see deviation in section **10.2**).
* n= 12 ; ** n = 6

(Copied from F21D03018 on p 9)

Table 9: Summarized data - Calculated bound aflibercept levels in plasma

	Calculated bound aflibercept in plasma [b]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD	Mean (ng/mL)	SD
12*	0°	145	134	87	93	133	82	187
48*	113	201	341	246	193	318	122	295
72*	596	252	965	1 020	502	397	389	271
120**	608	710	586	163	517	696	287	673

SD = Standard Deviation
* n= 12 ; ** n = 6 ; ° Negative value set to zero

(Copied from F21D03018 on p 9)

Ocular (Tables 10-12):
In VH, AH and R/C, 72 hours post IVT injection, the concentrations of free aflibercept were in the same range for all treatment groups (i.e., 770 to 1009 µg/mL for VH, 54 to 58 µg/mL for AH, and 114 to 125 µg/g for R/C), and declined to the same extent up to the terminal endpoint of 120 hours post IVT (i.e., 607 to 738 µg/mL in VH, 38 to 41 µg/mL in AH, and 88 to 128 µg/g in R/C).

Table 10: Summarized data - Free aflibercept levels in vitreous humor

	Free aflibercept concentration in vitreous humor [a]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP Batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD
72	1009	318	897	154	812	220	770	247
120	674	161	737	72	738	90	607	125

(Copied from F21D03018 on p 8)

Table 11: Summarized data - Free aflibercept levels in aqueous humor

	Free aflibercept concentration in Aqueous humor [a]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP Batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD	Mean (µg/mL)	SD
72	57	11	58	1	55	11	54	16
120	38	10	41	3	41	5	38	8

(Copied from F21D03018 on p 8)

Table 12: Summarized data - Free aflibercept levels in retina-choroid

	Free aflibercept concentration in retina-choroid [b]							
	FYB203 Tech Batch 1 (F18146)		FYB203 Tech Batch 2 (F18198)		FYB203 GMP Batch 1 (ADM-2019-001)		Eylea®	
Time (hours)	Mean (µg/g of tissue)	SD	Mean (µg/g of tissue)	SD	Mean (µg/g of tissue)	SD	Mean (µg/g of tissue)	SD
72	125	34	118	33	117	37	114	35
120	110	32	128	31	115	25	88	41

(Copied from F21D03018 on p 8)

SYSTEMIC DISTRIBUTION/METABOLISM/EXCRETION
No information was provided (the Sponsor referred to Eylea).

5.2 TK

See Toxicity Section.

6 General Toxicology

6.1 Single-Dose Toxicity

Not performed.

6.2 Repeat-Dose Toxicity

Study title: FYB203: One Month Ocular and Systemic Tolerance/Toxicity Study Following Two Intravitreal Administrations in Albino Rabbits

Study no.: 35933
Study report location: SDN0001
Conducting laboratory and location: (b) (4)
Date of study initiation: 23 July, 2018
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: FYB203, Lot # F18198, purity 99%

Key Study Findings

In this protocol, the toxicity of FYB203, FYB203 placebo, Eylea and Eylea placebo was compared in groups of New Zealand White rabbit. Males and females received intravitreally twice (on Day 1 and Day 15) 2 mg test article or placebo in each eye. Test

article-related adverse, moderate to severe anterior uveitis involving the aqueous humor, iris, ciliary processes, the Harderian glands by extension, and extending to pars plana, vitreous and the optic nerve associated with inflammation and neovascularization (FYB203 only) was observed with Eylea (3/12 rabbits) and FYB203 (5/12 rabbits) at terminal necropsy on Day 22. At recovery necropsy on Day 36 there were no findings in the FYB203 group, while 2 rabbits treated with Eylea had a moderate pan-uveitis in both eyes. The uveitis usually correlated with the presence of systemic ADAs in affected rabbits but not always. Overall, there were no differences in the nature and severity of the uveitis with both test articles. Nevertheless, there was a somewhat higher incidence of findings of uveitis with FYB203 compared to Eylea. Also, during the treatment period, other non-adverse ophthalmoscopic findings, e.g., conjunctival congestion, corneal opacity and/or corneal staining happened at higher incidence (more eyes involved), frequency and/or of higher grade with FYB203 placebo compared to Eylea. In toxicokinetic analysis, beside free, total, and calculated bound concentrations of aflibercept at Days 4, 22 and 36, no other TK parameters were evaluated and the comparison of the TK profiles of FYB203 and Eylea was not possible. The concentrations of aflibercept on Days 4, 22 and 36 suggested though, that the 2 test articles had slightly different kinetics profiles consistent with a slower elimination phase for FYB203 *versus* Eylea.

Methods

Doses:	2 mg/eye/OU
Frequency of dosing:	Twice on Day 1 and Day 15
Route of administration:	Intravitreal
Dose volume:	50 µL
Formulation/Vehicle:	(b) (4) mmol/L histidine / histidine HCl, mmol/L sodium chloride, 5% (w/v) sucrose and 0.03% (w/v) polysorbate 20, pH 6.2
Species/Strain:	Rabbit
Number/Sex/Group:	New Zealand White
Age:	2-3 months at start of study
Weight:	2-2.5 kg
Satellite groups:	No
Unique study design:	See Study design below
Dosing Solution Analysis:	Acceptable

Study design

Group n°	Treatment	Dose regimen	Animal's identification											
			Males						Females					
			Set 1	Set 3	Set 2	Set 5	Set 4	Set 6	Set 6	Set 4	Set 5	Set 2	Set 1	Set 3
1	FYB203	50 µL IVT administration in both eyes on Day 1 and Day 15	1	2	3	4	5	6	7	8	9	10	11	12
2	Placebo FYB203		13	14	15	16	17	-	18	19	20	21	22	-
3	Placebo Eylea		23	24	25	26	27	-	28	29	31 Bis (*)	30	31 (*)	32	-
4	Eylea		33	34	35	36	37	38	39	40		41	42	43	44

FYB203 = FYB203 Tech Batch 2 (F18198)
In grey animals involved in recovery endpoint.
(*) The rabbit n°31 (set 2) was euthanized for ethical reason on Day 8. This animal was replaced in the set 4 by animal n°31 bis. See

Terminal necropsy occurred on Day 22, i.e., 7 days after the second injection, and recovery necropsy occurred on Day 36, i.e., 14 days later.

> ***This reviewer's comment:*** *Based on ocular PK data in the rabbit, the terminal necropsy did not happen at the end of treatment considering that T_{max} was 1 hour in the retina, while the recovery necropsy was an acceptable endpoint considering $T_{1/2}$ ranged between 90 and 120 hours in the eye (five half-lives = 15 - 25 days).*

Observations and Results

Mortality

There were no mortalities on study.

Clinical Signs

There were no test article related findings except for ocular signs (see below).

Body Weights

Body weights were not affected by the test articles.

Feed Consumption

Feed consumption was not affected by the test articles.

Ophthalmoscopy

Slit lamp examination and indirect ophthalmoscopy were performed on both eyes at baseline and on Days 4, 8, 14, 16, 18, 20, 22, and 36. The observations were scored using McDonald-Shadduck's and the Nussenblatt's scale. Fluorescein staining of the cornea was used to detect eventual lesions.

From Day 14 to Day 20, test article-related aqueous flare (McDonald-Shadduck's scale), hyperemia of iris (McDonald-Shadduck's scale) and blurred vitreous (Nussenblatt's scale) were observed with FYB203 (2/24 eyes) and Eylea (1/24 eyes), while synechiae iris-lens were only seen with FYB203 on Day 14 (2/24 eyes (Table 13)). They were not observed at the end of the recovery period. Other findings up to Day 20 were transient, and either

observed with placebos as well and/or were procedural-related. Among those non adverse findings, conjunctival congestion, corneal opacity, and/or corneal staining happened at higher incidence (more eyes involved), frequency and/or of higher grade with FYB203 placebo than with Eylea placebo (Table 13).

Table 13: Summary of ophthalmoscopy

Ocular findings			Treatment			
			FYB203 (both eyes: n = 24)	Placebo FYB203 (both eyes: n = 20)	Placebo Eylea (both eyes: n = 20)	Eylea (both eyes: n = 24)
Conjunctival congestion	Score 1		2 eyes on D14 2 eyes on D16 2 eyes on D20	4 eyes on D4 2 eyes on D16 1 eye on D18 2 eyes on D20	3 eyes on D4	1 eye on D4 2 eyes on D14 4 eyes on D16 2 eyes on D18
	Score 2		-	-	-	2 eyes on D16
	Score 3		-	1 eye on D4	-	-
Corneal opacity	Score 1	25% area	1 eye on D8 2 eyes on D20	1 eye on D8	-	2 eyes on D20
	Score 2	25% area	1 eye on D8	1 eye on D4 1 eye on D20	-	1 eye on D16
	Score 3	25% area	-	1 eye on D8 1 eye on D14	-	-
Corneal staining	Score 1	25% area	1 eye on D4 6 eyes on D8 3 eyes on D14 2 eyes on D18 4 eyes on D20	2 eyes on D4, D8 1 eye on D14 2 eyes on D16, D18 2 eyes on D20	2 eyes on D8 1 eye on D14 5 eyes on D20	1 eye on D4 6 eyes on D20
		50% area	10 eyes on D1 3 eyes on D20	1 eye on D8 4 eyes on D16 1 eye on D20	2 eyes on D8 4 eyes on D16 5 eyes on D20	1 eye on D8 9 eyes on D16 2 eyes on D20
		75% area	3 eyes on D8 3 eyes on D16 4 eyes on D20	5 eyes on D8 1 eye on D16 6 eyes on D20	4 eyes on D8 2 eyes on D16 2 eyes on D20	5 eyes on D8 2 eyes on D16 4 eyes on D20
		100% area	-	1 eye on D16	-	-
	Score 2	25% area	1 eye on D16	2 eyes on D20	1 eye on D14	1 eye on D16

			1 eye on D20		1 eye on D16 2 eyes on D20	1 eye on D20
		50% area	5 eyes on D20	2 eyes on D16 2 eyes on D20	3 eyes on D16 1 eye on D20	5 eyes on D16 6 eyes on D20
		75% area	2 eyes on D8 3 eyes on D16 1 eye on D20	1 eye on D16	4 eyes on D16	1 eye on D8 1 eye on D16
		100% area	1 eye on D8 1 eye on D16	1 eye on D16	-	1 eye on D8
	Score 3	**25% area**	-	-	-	1 eye on D8
		75% area	-	1 eye on D16	-	-
	Score 4	**25% area**	-	-	-	1 eye on D16
Aqueous flare	**Score 1**		2 eyes on D14 3 eyes on D20	-	-	2 eyes on D18 2 eyes on D20
	Score 2		1 eye on D20	-	-	-
Iris (hyperhemia)	**Score 1**		2 eyes on D16 2 eyes on D20	-	-	2 eyes on D14 2 eyes on D16 2 eyes on D18
	Score 2		2 eyes on D14 1 eye on D20	-	-	2 eyes on D20
Fundus			2 eyes on D14 3 eyes on D20	-	-	2 eyes on D14 2 eyes on D16 2 eyes on D20
Nussenblatt	**Score 1**		2 eyes on D14	-	-	2 eyes on D14
	Score 2		4 eyes on D20	-	-	2 eyes on D16 1 eye on D18
	Score 3		-	-	-	2 eyes on D20
Other findings	**Partial or no mydriasis** *(after application of mydriatic agent)*		2 eyes on D14, D16 5 eyes on D20	-	-	2 eyes from D14-D20
	Shining particles *(anterior or posterior face of lens)*		2 eyes on D14, D16 3 eyes on D20	1 eye from D4-D14 1 eye from D14-D20	4 eyes on D4-D8 4 eyes on D16-D18 2 eyes on D14 3 eyes on D20	1eye on D4, D8 5 eyes on D14, D18 4 eyes on D16 6 eyes on D20
	Synecchia *(iris-lens)*		2 eyes on D14	-	-	-
	Fibrin *in vitreous*		2 eyes from D16-D20	-	1 eye from D4-D16 1 eye from D4-D20	2 eyes from D16-D20

Note: n = number of eyes per group; «-»: Nothing to observe; FYB203 = FYB203 Tech Batch 2 (F18198)

(Copied from 35933 report # 1 on pp 33-34)

Intra Ocular Pressure (IOP)

It was measured with a tonometer on both eyes at baseline and on Days 2, 7, and 18.

The IOP values at each time-point were stable during the measurement and similar between groups (between 21.9 ± 1.9 and 25.0 ± 1.6 mmHg).

Electroretinogram (ERG) (Non GLP)

Full field electroretinographic responses were performed on both eyes of all animals at baseline and on Days 1, 8, and 20 on 3-hours-dark-adapted eyes. Scotopic condition was employed with 0 dB stimuli (duration 0.4 msec) of 6 flashes were applied and the readings were averaged to obtain a full field ERG (a-wave and b-wave). Time and amplitude were recorded for a-wave and b-wave.

This reviewer's comment: Photopic condition was not used without justification and the statistical method to analyze the data was not indicated.

The a- and b-waves and implicit times were similar between both sexes in the same group and between each group from Baseline to Day 20. Hence, either treatment had no effects on the ERG.

Fluorescein Retina Angiography (Non GLP)

It was performed at baseline and on Days 8 and 16. Three images were taken to record the nasal, central, and temporal sides of the retinal vasculature oriented from the optic nerve head.

There were no test article-related effects reported on the retina angiography.

ECG

Non applicable.

Clinical Pathology

For hematology, clinical chemistry and urinalysis, blood was collected at baseline, Day 4, Day 22 (Terminal Necropsy), and Day 36 (Recovery Necropsy, except urine).

There were no test article-related effects on the clinical pathology parameters. All mean changes in all groups stayed in the normal range for the laboratory.

Hematology/Coagulation

Parameters evaluated: Total leukocyte count, differential leukocyte count (lymphocytes, monocytes, neutrophils, eosinophils, basophils), total erythrocyte count, mean corpuscular volume (MCV), hematocrit, mean corpuscular hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), hemoglobin, platelet counts.

This reviewer's comment: *Coagulation parameters were not included.*

Clinical Chemistry

Parameters evaluated: Sodium, potassium, total carbon dioxide (CO_2), chloride, glucose, calcium, urea, creatinine, alkaline phosphatase, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), total bilirubin, albumin, total protein, total cholesterol, triglycerides.

Urinalysis

Parameters evaluated: leukocytes, nitrites, pH, protein (albumin), glucose, ketones, urobilinogen, bilirubin, blood (erythrocyte/hemoglobin).

Gross Pathology

All animals underwent a complete necropsy and gross pathology observation.

No treatment-related gross observations occurred.

Organ Weights

Organs weighed:
Testis, uterus, ovary, spleen, thymus, heart, lungs, liver, adrenal glands, kidneys, Harderian lachrymal glands, submandibular lymph nodes, thyroid/parathyroids, brain/cerebellum.

Paired organs were weighed together. Absolute and relative weights to body weight and brain/cerebellum weights were calculated.

No treatment effects on organ weights were observed.

Histopathology

List of organs/tissues examined under the microscope:

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Block – No.	Organ
1	Kidney left, Adrenal left
2	Kidney right, Adrenal right
3	Liver (lobus caudatus), Spleen
3a	Liver (left and right medial lobe)
4	Heart (ventricle left and right, septum)
5	Lungs, Pancreas, Thymus
6	Stomach (pylorus, fundus)
7	Duodenum, Jejunum, Ileum (incl. Peyer's patches)
8	Colon, Rectum, Caecum
9	Lymph node (mesenteric), Salivary glands (mandibular, sublingual)
10	Muscle, Ureter left and right
11	Mammary complex, Skin (left flank)
12	Testis left, Epididymis left
12a	Testis right, Epididymis right
12	Ovary left and right, Vagina
13	Prostate, Seminal vesicle
13	Uterus
14	Brain (Cerebellum, Cerebrum, Brain stem), Pituitary gland
14a	Brain (Hippocampus, Paraventricular parts)
15	Esophagus, Trachea, Lymph node (mandibular) left and right
16	Nerve (sciatic)
17	Tongue
18	Thyroid left with Parathyroid left, Aorta
19	Thyroid right with Parathyroid right
20	Urinary bladder, Gall bladder
21	Femur with bone marrow and articular surface
22	Spinal cord
23	Larynx, Pharynx

APPEARS THIS WAY ON ORIGINAL

Slide – No.	H.-E.-Stained Organ
1	Kidney left, Adrenal left
2	Kidney right, Adrenal right
3	Liver (*lobus caudatus*), Spleen
3a	Liver (left and right medial lobe)
4	Heart (ventricle left and right, septum)
5	Lungs, Pancreas, Thymus
6	Stomach (pylorus, fundus)
7	Duodenum, Jejunum, Ileum (incl. Peyer's patches)
8	Colon, Rectum, Caecum
9	Lymph node (mesenteric), Salivary glands (mandibular, sublingual)
10	Muscle, Ureter left and right
11	Mammary complex, Skin (left flank)
12	Testis left, Epididymis left
12a	Testis right, Epididymis right
12	Ovary left and right, Vagina
13	Prostate, Seminal vesicle
13	Uterus
14	Brain (Cerebellum, Cerebrum, Brain stem), Pituitary gland
14a	Brain (Hippocampus, Paraventricular parts)
15	Esophagus, Trachea, Lymph node (mandibular) left and right
16	Nerve (sciatic)
17	Tongue
18	Thyroid left with Parathyroid left, Aorta
19	Thyroid right with Parathyroid right
20	Urinary bladder, Gall bladder
21	Femur with bone marrow and articular surface
22	Spinal cord
23	Larynx, Pharynx
	Oil-Red-O-Stain
24	Heart, Liver
25	Kidney

Bone marrow smears were also prepared. The myeloid : erythroid ratio was determined by cell differentiation (counting of 200 nuclei-containing cells).

Adequate Battery: Yes

Both eyeballs (3 nasal, central (including optic nerve) and temporal sections per eye), Harderian and Lacrimal glands (cut in two parts) were cut into three 5 to 7 µm-thick sections (spaced out 100 µm) each and stained for microscopic observation.

Peer Review: Not indicated in the report. The slides of the systemic organs were viewed by a Veterinarian with a European Board Certification in Toxicologic Pathology while the slides of the eyes and adnexa were viewed by a PhD, “Expert in Histology and Histopathology”.

Terminal Necropsy (Day 22)
Eyes and Adnexa
Test article-related moderate to severe anterior uveitis involving the aqueous humor, iris, ciliary processes, the Harderian glands by extension, and extending to pars plana, vitreous and the optic nerve associated with inflammation and neovascularization (FYB203 only) was observed with Eylea (3/12 rabbits) and FYB203 (5/12 rabbits).

Incidence, severity:
Rabbit # 42 (female); 2 eyes; Eylea; severe

Rabbit # 2 (male), 3 (male); 4 eyes; FYB203; severe
Rabbit # 1 (male), 7 (female), 10 (female); 6 eyes; FYB203; moderate

Recovery Necropsy (Day 36)
There were no findings in the FYB203 group, while rabbits # 38 (male, 2 eyes) and 43 (female, 2 eyes), treated with Eylea, had a moderate pan-uveitis in both eyes.

> ***This reviewer’s comment:*** *Considering that the severity of the uveitis might have decreased at Day 36 compared to Day 22, this reviewer judged that overall, there were no differences in the nature and severity of the uveitis with both compounds but nevertheless, there was a somewhat higher incidence of uveitis with FYB203 compared to Eylea.*

The uveitis usually correlated with the presence of systemic ADAs in affected rabbits but not always.

Other organs
No test article-related findings occurred in the systemic organs at Day 22 and Day 36. In addition, no morphological difference was noted in the organs between the animals treated with FYB203, Placebo FYB203, Placebo Eylea or Eylea.

Special Evaluation

Antidrug antibodies (ADAs) were measured at baseline, Day 22 (Terminal Necropsy), and Day 36 (Recovery Necropsy).

The results revealed no differences in the rates of ADA formation between treatment groups (5 positive with FYB203 and 4 positive with Eylea).

> ***This reviewer's comment:*** *The impact of the presence of ADAs on exposure to the test items was not reported.*

Toxicokinetics

Blood samples were collected at baseline, Day 4, Day 22 (Terminal Necropsy), and at Day 36 (Recovery Necropsy). Free and total aflibercept was measured using validated ELISAs. Bound aflibercept was calculated as the result of [total aflibercept – free aflibercept].

> This reviewer's comment: Note that once absorbed into the systemic circulation, aflibercept exists in the plasma as free aflibercept (unbound to VEGF) and a more predominant stable inactive form bound to circulating endogenous VEGF (bound aflibercept). The ratios of free and total aflibercept (Free aflibercept + Bound aflibercept) in the circulation of rabbits change over time as bound aflibercept was found to have a slower apparent clearance and elimination rate compared to free aflibercept. The majority of total drug concentration in blood plasma is expected to be the free form shortly after IVT administration, decreasing thereafter while bound aflibercept comprises the majority of the total concentration at later time points.

FREE AFLIBERCEPT

Day 4

Mean plasma concentrations of free aflibercept in male rabbits on Day 4 were 0.866 µg/mL for FYB203 and 1.453 µg/mL for Eylea. In females, it was 0.903 µg/mL (FYB203) and 1.666 µg/mL (Eylea).

Day 22

Mean plasma concentrations of free aflibercept in male rabbits on Day 22 were 0.297 µg/mL for FYB203 and 0.226 µg/mL for Eylea. In females, it was 0.250 µg/mL (FYB203) and 0.506 µg/mL (Eylea).

Day 36
Mean plasma concentrations of free aflibercept in male rabbits on Day 36 were 0.101 µg/mL for FYB203 and not detected for Eylea (< 5ng/mL). In females, it was 0.105 µg/mL (FYB203) and 0.049 µg/mL (Eylea).

> ***This reviewer's comment:*** *No TK parameters were calculated. These results had limited purpose.*

TOTAL AFLIBERCEPT
Mean C_{max} was on Day 3 with both test articles and concentrations declining thereafter. There was about 2-fold differences between FYB203's and Eylea's C_{max}, with FYB203 levels being lower than Eylea's until Day 22 (1.5X lower), but not on Day 36 where FYB203 mean concentration was 4X higher than Eylea's (Table 14).

Table 14: Total aflibercept in plasma

	Concentration of corrected total aflibercept in plasma (µg/mL)			
	FYB203 Tech Batch 2 (F18198)		Eylea (72477C)	
Time (Days)	Mean	SD	Mean	SD
Baseline	0	0	0	0
D4	1.054	0.216	1.813	0.343
D22	0.629	0.586	0.902	0.894
D36	0.322	0.073	0.087	0.155

SD = Standard Deviation

(Copied from 35933 report # 2 on p 7)

> ***This reviewer's comment****: On Day 22, based on the standard deviation (SD), mean results for both test articles can be considered equivalent but not on Day 36 though, where much less variability existed. The data suggested that the 2 test articles had slightly different kinetic profiles consistent with a slower elimination phase for FYB203 versus Eylea.*

CALCULATED BOUND AFLIBERCEPT

As expected, levels of mean bound aflibercept increased until Day 21 post first-IVT injection and declined thereafter. Mean C_{max} bound aflibercept on Day 21 was 1.5-fold higher for Eylea compared to FYB203. On Day 35 though, mean bound aflibercept concentration was 3.5-fold higher for FYB203 compared to Eylea (Table 15).

Table 15: Bound aflibercept in plasma

	Calculated bound aflibercept in plasma (µg/mL)			
	FYB203 Tech Batch 2 (F18198)		Eylea (72477C)	
Time (Days)	Mean	SD	Mean	SD
Baseline	0	0	0	0
D4	0.170	0.103	0.256	0.271
D22	0.366	0.311	0.536	0.489
D36	0.219	0.044	0.062	0.106

SD = Standard Deviation

(Copied from 35933 report # 2 on p 8)

> ***This reviewer's comment:*** *Again, based on the SD on Day 22, the data seemed equivalent for both test articles, but not on Day 36 where the data suggested different elimination kinetics between the test articles, with FYB203 being eliminated more slowly.*

7 Genetic Toxicology

Based on ICH S6 guidance (ICH S6(R1), 2011) genotoxicity studies are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed.

8 Carcinogenicity

Carcinogenicity studies were not performed with aflibercept. With their application for bio similarity to Eylea, the Sponsor did not perform carcinogenicity studies with FYB203.

9 Reproductive and Developmental Toxicology

Reproductive and developmental toxicity has been addressed with aflibercept under the Eylea BLA. With their application for biosimilarity to Eylea, the Sponsor did not perform new reproductive and developmental toxicity studies with FYB203.

10 Special Toxicology Studies

No special toxicity studies were performed with FYB203.

11 Integrated Summary and Safety Evaluation

FYB203 (aflibercept) for IVT injection, a proposed biosimilar (b) (4) has the same dosage form, route of administration, dosing regimen and presentation as the reference product Eylea® reviewed under BLA 125387.

The Sponsor, Formycon, performed *in vivo* studies in animals which goals were to demonstrate similarities between the ocular and systemic pharmacokinetic (PK) and toxicological profiles between FYB203 and Eylea.

The *in vivo* preclinical data suggested that FYB203 and Eylea had slightly different systemic PK/TK and toxicity profiles.

Nevertheless, since new animal studies with FYB203 were neither required by the Agency nor recommended for a BLA type 351(k) application, the preclinical data reviewed in this report were merely informational. Consequently, as a biosimilar (b) (4) to Eylea, the product is approvable from this reviewer's perspective.

12 Appendix/Attachments

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MURIEL J SAULNIER
03/08/2024 02:46:07 PM

KIMBERLY P HATFIELD
03/08/2024 03:10:19 PM
I concur with the review and recommendations of Dr. Saulnier.

CLINICAL PHARMACOLOGY REVIEW

BLA	761378
Submission Date	06/28/2023
Applicant	Formycon AG
Proposed Brand Name	(b) (4)
Nonproprietary Name	FYB203 (aflibercept-xxxx), a proposed biosimilar to aflibercept
Proposed Indications	• Neovascular age-related macular degeneration • Macular edema following retinal vein occlusion • Diabetic macular edema • Diabetic retinopathy
Dosage form	Injection: 2 mg/0.05 mL in a single-dose glass vial
Route of Administration	Ophthalmic intravitreal injection
Dosage Regimen	Proposed the same dosing regimens as those approved for US-licensed Eylea
Primary Clinical Pharmacology Reviewer	Lei He, Ph.D.
Secondary Clinical Pharmacology Reviewer	Ping Ji, Ph.D.
OCP Division	Division of Inflammation and Immune Pharmacology
OND Division	Division of Ophthalmology Products
Submission Type; Code	351(k), standard review

1. Clinical Pharmacology Executive Summary and Recommendation

Eylea (aflibercept) is a vascular endothelial growth factor (VEGF) inhibitor. The Applicant submitted this BLA application under section 351(k) of the Public Health Service Act (PHS Act) for FYB203, 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 immunoglobulin (Ig)G1 formulated as aqueous solutions for intravitreal (IVT) administration, as a proposed biosimilar to US-licensed Eylea (aflibercept). The proposed indications include neovascular age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic macular edema (DME), and diabetic retinopathy (DR). The proposed dosage form is 2 mg/0.05 mL injection in a single-dose glass

vial and the proposed dosage regimens for FYB203 are same as those approved for US-licensed Eylea.

BLA 761378 application consists of one comparative clinical study in patients with neovascular AMD (nAMD) (Study FYB203-03-01, n=434), in which the PK profiles of FYB203 and EU-approved Eylea were evaluated in a subgroup of nAMD patients.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) has reviewed the clinical pharmacology data submitted under this BLA application and had the following recommendations regarding clinical pharmacology review issues (Table 1).

Table 1. Clinical pharmacology major review issues and recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of FYB203 and EU-approved Eylea evaluated in a subset of subjects with nAMD in Study FYB203-03-01 were comparable based on descriptive analysis, supporting a demonstration of no clinically meaningful differences between FYB203 and US-licensed Eylea.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB203 and EU-approved Eylea in subjects with nAMD supports a demonstration of no clinically meaningful differences between FYB203 and US-licensed Eylea.

1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding the PK and immunogenicity assessment for FYB203 and US-licensed Eylea.

2. Clinical Pharmacology Studies to Support the Use of a Non-US-licensed Comparator Product

In Study FYB203-03-01, including the PK sub-study, EU-approved Eylea was used as the comparator product. The Applicant submitted pairwise comparisons of comparative analytical data and analysis for FYB203, US-licensed Eylea, and EU-approved Eylea to support the use of EU-approved Eylea in Study FYB203-03-01. In the previous communications with the Applicant, the Agency agreed that the Applicant can use comparative clinical data generated using EU-approved Eylea as long as there is adequate comparative analytical data of the proposed biosimilar, EU-approved and US-licensed product (refer to Pre-IND Meeting Minutes dated 10/17/2019). Refer to the review by Office of Product Quality regarding the adequacy of the comparative analytical assessment

3. Human Pharmacokinetic and Pharmacodynamic Studies

A PK similarity study using traditional PK endpoints, such as AUC and C_{max}, in healthy subjects is not considered to be feasible for the following reasons: 1) aflibercept is administered by IVT injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following IVT injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of IVT injections. Therefore, a PK sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

Clinical Pharmacology Study Design Features and Endpoints

Study FYB203-03-01 was a phase 3, parallel-group, 1:1 randomized, active-controlled, double-masked, multicenter study to demonstrate therapeutic equivalence of FYB203 to Eylea and to compare the safety and immunogenicity in patients with nAMD (Figure 1). Patients were 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 consisted of 1 IVT injection every 4 weeks for 3 consecutive doses starting at Baseline (Visit 1) through Week 8 (Visit 3) followed by 1 IVT injection every 8 weeks up to and including Week 48 (Visit 8).

The PK profiles of FYB203 and EU-approved Eylea were descriptively evaluated within up to 60 patients participating in the PK sub-study as part of the comparative clinical study. The PK data were pre-specified to be analyzed qualitatively. Analyses included:

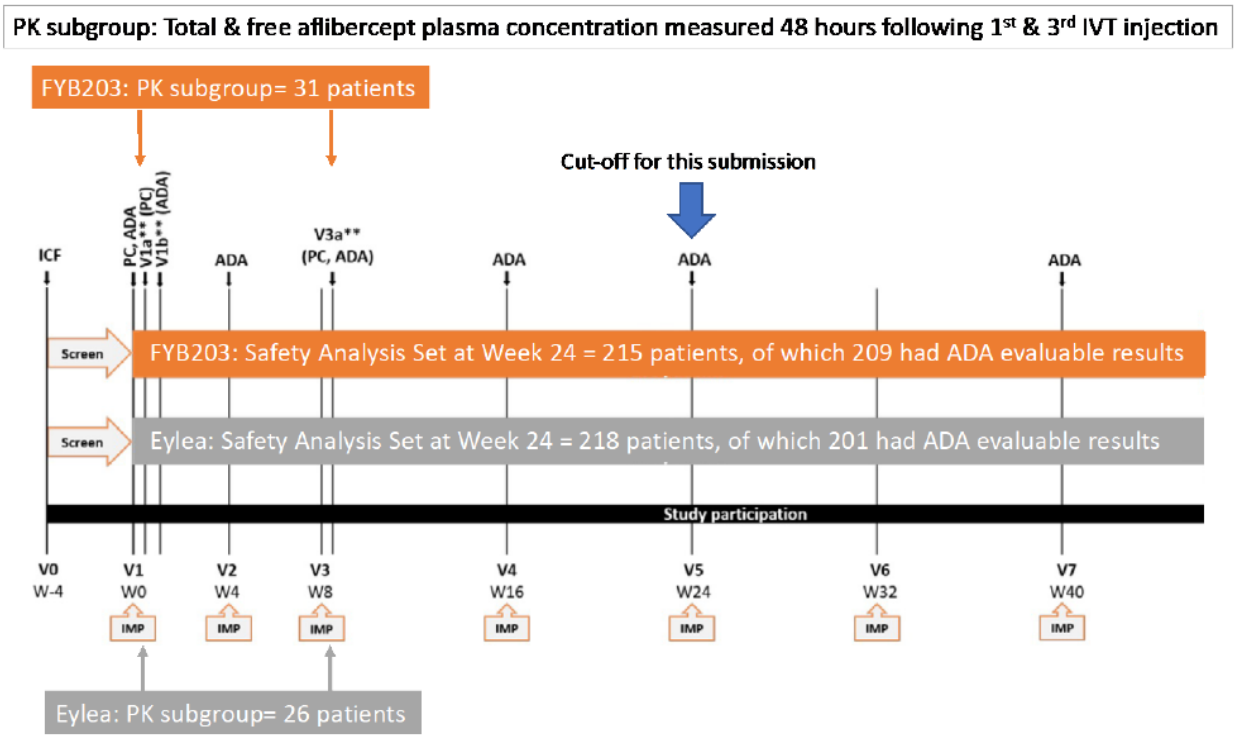
- Systemic exposure measured at Baseline prior to 1st IVT dose, 48 hours after 1st IVT dose close to Cmax after the first dose, and at 48 hours after the 3rd IVT dose close to Cmax after the 3rd dose in a subgroup of patients from both treatment groups

The immunogenicity of FYB203 and EU-approved Eylea were descriptively evaluated in all neovascular AMD patients in the comparative clinical study. Analyses included:

- Incidence of anti-drug antibodies (ADAs) to FYB203 and EU-approved Eylea
- Incidence of neutralizing antibodies (NAbs) to FYB203 and EU-approved Eylea

Of the 434 subjects randomized, 31 of 215 and 26 of 219 subjects in the FYB203 and EU-approved Eylea treatment groups, respectively, were included in PK subgroup analysis set.

Figure 1. Study design of Study FYB203-03-01



ADA = Anti-drug antibody; EOS = End of Study; IMP = Investigational Medicinal Product; ICF = informed consent form; PC = plasma concentration; V = visit; W = week.
Note: 219 patients were randomized in Eylea treatment group, in which one patient ((b) (6) was not treated due to ICF withdrawal.
Source: Figure 4, Study FYB203-03-01 Patient PK and Initial Tolerability Study Reports

Bioanalytical PK method and performance

Free concentrations of FYB203 or aflibercept in serum of patients with nAMD were measured using a validated Electrochemiluminescent immunoassay (ECLIA) assay. The lower and upper quantification limits for plasma study drug concentrations were 1 ng/mL and 60 ng/mL, respectively. The maximum storage time of all PK samples from Study FYB203-03-01 from sample collection to the end of sample analysis did not exceed 227 days. All PK samples were initially stored at a nominal temperature of -20°C for a maximum of 68 days and at a nominal temperature of -80°C for the remaining period. Study samples were analyzed within the validated long-term stability periods (373 days stored at -20 ºC, 647 days stored at -80°C). Refer to Appendix 1 for more detailed information regarding the bioanalytical method validation.

PK of FYB203 and EU-approved Eylea in patients with nAMD (Study FYB203-03-01)

In Study FYB203-03-01, 57 of 434 (13.1%) patients were included in the PK subgroup analysis, including 31 of 215 (14.4%) and 26 of 219 (11.9%) subjects in the FYB203 and EU-approved Eylea treatment groups, respectively. Blood samples for PK assessments were collected at baseline prior to 1st IVT dose, 48 hours after 1st IVT dose, and at 48 hours after the 3rd IVT dose in the PK subgroup.

The PK results of free aflibercept by treatment in Study FYB203-03-01 are presented in Table 2 and Figure 2. The descriptive PK comparison showed that the systemic concentrations close to Cmax after the first and the third IVT injections were highly variable and generally in the same range in both treatment groups. Similar PK comparison was also observed for total aflibercept concentrations (Table 5, Figure 3) (see Appendix 2).

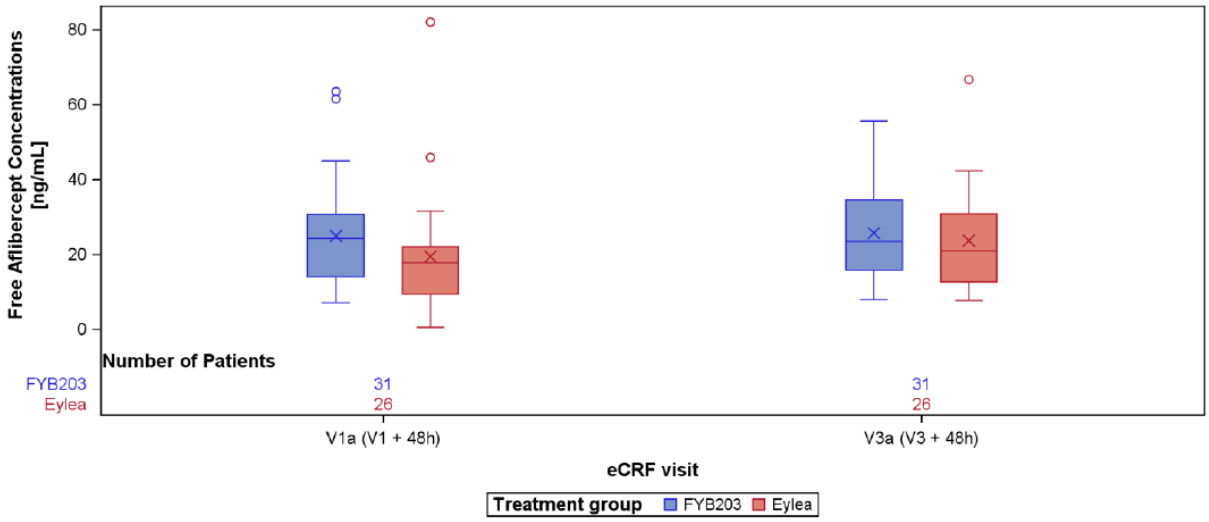
Table 2. Systemic concentration of free aflibercept (ng/mL) 48 hours after 1st and 3rd IVT injection

	V1a (V1 + 48h)		V3a (V3 + 48h)	
Analysis Visit	**FYB203**	**Eylea**	**FYB203**	**Eylea**
n	31	26	31	26
nmiss	0	0	0	0
Mean (SD)	24.965 (13.8995)	19.482 (16.1314)	25.735 (12.5649)	23.712 (13.4233)
CV (%)	55.677	82.803	48.824	56.610
Geom. mean	21.667	14.235	22.773	20.512
Geom.CV [%]	58.922	119.312	55.552	59.891
Geom. mean 95%CI	17.735 - 26.470	9.735 - 20.817	18.828 - 27.545	16.402 - 25.652
Median	24.300	17.800	23.500	21.000
Min-Max	7.12 - 63.60	0.50 - 82.00	7.96 - 55.70	7.68 - 66.80
P10 – P90	10.300 - 40.600	6.600 - 31.600	10.600 - 42.700	8.860 - 41.200
Q1 – Q3	14.100 - 30.800	9.460 - 22.100	15.800 - 34.600	12.700 - 30.900

eCRF = Electronic Case Report Form; n.c. = not calculable; n/nmiss = number of non-missing/ missing assessments; SD = standard deviation; Min = minimum; Q1 = first quartile; Q3 = third quartile; Max =maximum; CV = coefficient of variation; Geom. Mean = geometric mean; Geom. CV = Geometric coefficient of variation; P10/P90 = 10th / 90th Percentile; CI = Confidence Interval.
Values below the lower limit of quantification (1.00 ng/mL) are set to half of the lower limit of quantification and values above the upper limit of quantification (60 ng/mL) are set to the upper limit of quantification for the purpose of summary statistics.
PKS = Plasma Concentration Analysis Set

Source: Table 5, Study FYB203-03-01 Patient PK and Initial Tolerability Study Reports

Figure 2. Systemic concentrations of free aflibercept (ng/mL) by visit in Study FYB203-03-01 (PK subgroup analysis set)



X = arithmetic mean; Circles = outliers; The horizontal lines of the box plots are defined as follows (from bottom to top): lower whisker, 25th percentile, median, 75th percentile, upper whisker.

The lower and upper whiskers are defined as the lowest/largest observed data point that falls within the range of 1.5 times the IQR from the 25th/75th percentile. Interquartile range (IQR): distance between the 25th and 75th percentile.

A general cut-off date is applied for the 24 week analysis: all data up to and including study day 182 (analysis visit Week 24 (V5)) is included.

PKS = Plasma Concentration Analysis Set

Source: Figure 6, Study FYB203-03-01 Patient PK and Initial Tolerability Study Reports

PD similarity assessment

Not applicable.

4. Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity (ADA and NAb) was evaluated in Study FYB203-03-01 as one of the secondary endpoints.

Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed bridging electrochemiluminescence (ECL) assay and competitive ligand-binding assay ECL assesy that are suitable for detecting ADA and NAb, respectively, in the presence of expected levels of FYB203 and EU-approved Eylea. Refer to the review by Office of Product Quality regarding the immunogenicity assay assessment.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood samples for immunogenicity assessment were collected in all subjects at prior to IVT injection at baseline (Day 1), Week 4, Week 16, Week 24, Week 40, and at Week 56 (EOS visit). Additional ADA/NAb samples were also collected one week after the first and 48 hours after the third injection in the 57 patients in the PK subgroup.

Comparison of Incidence of ADA and NAb

The incidence of ADA and NAb by treatment group and time points in Study FYB203-03-01 were summarized in Table 3. The incidence of an ADA or NAb positive response was generally low and comparable between treatment groups throughout the study. None of the patients in the PK subgroup was positive for ADA in either the FYB203 or Eylea treatment groups.

Table 3. Incidence of anti-drug antibody and neutralizing antibodies by Visit (Study FYB203-03-01 (Safety Analysis Set (N=433))

	FYB203 (N=215)			Eylea (N=218)		
Analysis Visit	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**
Baseline (V1)	4 (1.9) n=213	0.71 (41.68)	Re 0 (0.0) Ne 4 (1.9) n=213	3 (1.5) n=204	0.63 (41.68)	Re 0 (0.0) Ne 3 (1.5) n=204
V1b; V1 + 7d[1]	0 (0) n=31	NA	NA	0 (0) n=25	NA	NA
Week 4 (V2)	2 (1.0) n=209	0.71 (52.11)	Re 0 (0.0) Ne 2 (1.0) n=209	1 (0.5) n=201	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=201
Week 8 (V3a; V3 + 48h)[1]	0 (0) n=32	NA	NA	0 (0) n=27	NA	NA
Week 16 (V4)	3 (1.5) n=195	1.59 (94.74)	Re 0 (0.0) Ne 3 (1.5) n=195	1 (0.5) n=191	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=191

	FYB203 (N=215)			Eylea (N=218)		
Analysis Visit	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**	**ADA Positive n (%) non-missing assessments**	**Titer geomean (Geom. CV %)**	**NAb Reactive/ Negative n (%)**
Week 24 (V5)	4 (2.1) n=195	1.19 (106.76)	Re 0 (0.0) Ne 4 (2.1) n=195	1 (0.5) n=193	1.00 (n.c.)	Re 0 (0.0) Ne 1 (0.5) n=193
Post-treatment only[2]	2 (1.0) n=209	NA	Re 0 (0.0) Ne 5 (2.3) n=213	0 (0.0) n=201	NA	Re 0 (0.0) Ne 1 (0.5) n=204

ADA = anti-drug antibody, d = day, Geom. CV = geometric coefficient of variation, Geomean = geometric mean, h = hours, N = number of patients per group, n = number of patients per category, NA = not applicable, NAb = neutralizing antibody, n.c. = not calculable, Ne = negative, PKS = plasma concentration analysis set (used only for V1b and V3a), Re = reactive, SAF = safety analysis set (used only for V1, V2, V3, V4, V5 and post-treatment only), V = visit

[1] Plasma concentration analysis set (PKS) only, patients from PK subgroup with measurable aflibercept concentrations at prior to 1st injection were excluded

[2] The immunogenicity analysis "post-treatment only" excludes patients without any post-treatment ADA or NAb sample, excludes patients from ADA analysis who were ADA positive at pre-treatment (denominator n=209) and excludes patients from NAb analysis who were NAb reactive at pre-treatment (denominator n=213). Any patient who was NAb negative at pre-treatment could test NAb reactive during at any time during the treatment phase, independent of the ADA status pre-treatment.

Source: Table 12-23, Study FYB203-03-01CSR

Comparison of ADA Titers

The ADA titers is comparable between the FYB203 and EU-approved Eylea treatment groups as seen in Table 3.

Comparison of Immunogenicity Impact on PK

None of the patients in the PK subgroup was positive for ADA in either the FYB203 or Eylea treatment groups up to Week 24. Therefore, no conclusion could be made regarding the correlation between blood levels and antibody rates.

Comparison of Immunogenicity Impact on Efficacy

The primary efficacy endpoint of Study FYB203-03-01 is the change from baseline in best corrected distance visual acuity (BCVA) at Week 8 with FYB203 or EU-approved Eylea treatments. At Week 8, none of the patients in the FYB203 or Eylea group had positive ADA result (Table 3). Therefore, no conclusion could be made regarding the correlation between efficacy and antibody rates.

Comparison of Immunogenicity Impact on Safety

Two patients in the FYB203 group had treatment-emergent ADA signals, no drug hypersensitivity or anaphylaxis-type or ocular inflammatory treatment-emergent adverse events (TEAEs) of special interest were reported up to Week 24.

Appendix 1. Summary of Bioanalytical Method Validation

Free concentrations of FYB203 or aflibercept in serum of patients with nAMD were measured using a validated ECLIA assay (Table 4). The lower and upper quantification limits for plasma study drug concentrations were 1 ng/mL and 60 ng/mL, respectively.

Table 4. Summary method performance of the bioanalytical method to measure free aflibercept in human plasma

Method description	• Assay format: Electrochemiluminescent immunoassay (ECLIA) to detect active drug • Platform: Meso Scale Diagnostics (MSD) MESO QuickPlex® SQ 120 Imager with MSD GOLD® 96 well small spot streptavidin SECTOR® plate • Test matrix: human plasma (CTAD) • Primary incubation: 50 µl sample/control are incubated on a blocked and biotin-VEGF-A165 coated streptavidin small spot plate. • Secondary incubation: Plate is washed and 50 µl polyclonal rabbit antibody directed against aflibercept without Fc-part are added to the wells and incubated. • Detection: Plate is washed and 100 µl sulfo-tagged anti-rabbit antibody are added and incubated. Plate is washed and 150 µl per well of MSD Read buffer are added.
Materials used for calibration curve & concentration	FYB203 Batch No. 3-FIN-3355 1.00, 2.00, 4.00, 10.0, 15.0, 30.0, 50.0, and 60.0 ng/mL (prepared in bulk; aliquots stored at -80°C)

Validated assay range	1.00 to 60.0 ng/mL
Material used for QCs & concentration	FYB203 Batch No. 3-FIN-3355 EU-Eylea (Bayer Batch No. KT0373P) 1.00 (LLOQ QC), 3.00 (Low), 10.0 (Medium), 15.0 (free QC containing in addition 2.00 ng/mL VEGFA-165), 45.0 (High) and 60.0 (ULOQ QC) ng/mL (prepared in bulk; aliquots stored at -80°C)
Minimum required dilutions (MRDs)	1:50
Source & lot of reagents (LBA)	• Reference standard: FYB203 Batch No. 3-FIN-3355 • Analyte for Bioanalytical Comparison: EU-Eylea (Bayer Batch No. KT0373P) • Control human plasma (CTAD), (b) (4) • ActiveMax® human VEGF-A165 protein, Tag Free (HPLC-verified), Acro Biosystems, Catalog No. VE5-H4210 • Anti-aflibercept antibody (0.44 mg/mL), rabbit polyclonal, Formycon ID ADM-2018-310-01, (b) (4) • Biotinylated human VEGF-A165, (b) (4) (b) (4) (b) (4) • Histidine (b) (4) (formulation (b) (4) for biosimilar), FYB203 histidine (b) (4) Formycon AG • Ultrapure deionized water (H2O), Type-1, (b) (4) • MSD® Blocker A, Meso Scale Discovery, Catalog No. R93BA • MSD® Read Buffer T (4X) with surfactant, Meso Scale Discovery, Catalog No. R92TC • MSD® SULFO-TAG labeled anti-rabbit antibody (goat), 500 µg/mL, Meso Scale Discovery, Lot No. W0017418S, Lot No. W0019719S, Lot No. W0020326S, Lot No. W0020508S and W0020719S, Catalog No. R32AB • PBS-Tween® Tablets, (b) (4) (b) (4) • MSD GOLD® 96 well small spot streptavidin SECTOR® plate, Meso Scale Discovery

Regression model & weighting	5PL, $1/Y^2$		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 5 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01
	Cumulative accuracy (%bias) from LLOQ to ULOQ FYB203	-3.4 to 5.0%	Table 5 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01
	Cumulative precision (%CV) from LLOQ to ULOQ FYB203	≤ 4.1%	Table 5 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01
QCs performance during accuracy & precision (runs meeting acceptable A&P evaluation criteria only)	**Cumulative accuracy (%bias) in 5 QCs** QCs: FYB203 EU Eylea	 -9.9 to 5.2% -12.7 to -3.2%	Table 3 and Table 4 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01
	Inter-batch %CV QCs: FYB203 EU Eylea	 ≤ 14.5% ≤ 14.0%	Table 3 and Table 4 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01
	Total Error (TE) QCs: FYB203 EU Eylea	 ≤ 24.4% ≤ 26.7%	Table 3 and Table 4 of Attachment 5 of [redacted] amendment 4 to report no. CA28351-01

Validation parameters	Method validation summary	Source location (hyperlinked)
Selectivity & matrix effect	12 or 17 plasma (CTAD) lots from special population human subjects (diagnosed with nAMD) spiked with FYB203 or EU Eylea: FYB203: LLOQ (1.00 ng/mL): -28.6 to 5.7 %bias in 12 lots (-24.7 to 5.7 %bias in 11/12 lots) HQC (45.0 ng/mL): -21.8 to -1.5 %bias in 17 lots (-16.5 to -1.5 %bias in 16/17 lots) EU Eylea: LLOQ (1.00 ng/mL): -32.8 to 24.8 %bias in 17 lots (-23.8 to 24.8 %bias in 14 of 17 lots) HQC (45.0 ng/mL): -22.4 to -0.5 %bias in 17 lots (-18.5 to -0.5 %bias in 15/17 lots)	Table 14 and 16 of (b) (4) amendment 4 to report no. CA28351-01
Interference & specificity	No quantitation greater than the LLOQ in 16 of the 17 human plasma (CTAD) lots from special population human subjects (diagnosed with nAMD) FYB203 • 0, 100, 200, 400 pg/mL VEGFR-1 spikes – at LLOQ (1.00 ng/mL): -18.5 to 3.3 %bias – at HQC (45.0 ng/mL): -5.6 to 5.8 %bias • 0, 10.000, 15.000, 20.000 pg/mL VEGFR-2 spikes – at LLOQ (1.00 ng/mL): -6.3 to 2.0 %bias – at HQC (45.0 ng/mL): -11.7 to -2.5 %bias1 Eylea • 0, 100, 200, 400 pg/mL VEGFR-1 spikes – at LLOQ (1.00/ng/mL): -3.7 to 10.2 %bias, 25.6 %bias in case of 400 pg/mL spike – at HQC (45.0 ng/mL): -15.3 to -10.6 %bias • 0, 10.000, 15.000, 20.000 pg/mL VEGFR-2 spikes – at LLOQ (1.00 ng/mL): -18.3 to -6.2 %bias – at HQC (45.0 ng/mL): -16.7 to -1.0 %bias	Section 2.3.2 of (b) (4) amendment 4 to report no. CA28351-01 Table 17 and Table 18 of (b) (4) amendment 4 to report no. CA28351-01 Table 21 and Table 22 of (b) (4) amendment 4 to report no. CA28351-01

Validation parameters	Method validation summary	Source location (hyperlinked)
Hemolysis effect	5 hemolyzed human plasma (CTAD) lots fortified with 5% whole blood spiked with FYB203 or EU Eylea: FYB203: LLOQ (1.00 ng/mL): -26.1 to 1.0 %bias (-18.4 to 1.0 %bias in 4/5 lots) HQC (45.0 ng/mL): -15.8 to 0.4 %bias in 5 lots EU Eylea: LLOQ (1.00 ng/mL): -19.1 to -11.6 %bias in 5 lots HQC (45.0 ng/mL): -20.0 to -13.8 %bias in 5 lots	Table 25 and Table 26 of (b) (4) amendment 4 to report no. CA28351-01
Lipemic effect	5 lipemic human plasma (CTAD) lots spiked with FYB203 or EU Eylea: FYB203: LLOQ (1.00 ng/mL): -22.3 to -11.8 %bias in 5 lots HQC (45 ng/mL): -23.8 to 1.3 %bias (-17.6 to 1.3 %bias in 4/5 lots) EU Eylea: LLOQ (1.00 ng/mL): -31.2 to -18.4 %bias (-23.7 to -18.4 %bias in 4/5 lots) HQC (45 ng/mL): -27.1 to -13.2 %bias (-19.1 to -13.2 %bias in 4/5 lots)	Table 27 and Table 28 of (b) (4) amendment 4 to report no. CA28351-01
Dilution linearity & hook effect	• Highest concentration tested: 600 ng/mL FYB203 or EU Eylea – No hook effect (prozone) observed • 3 dilution factors tested: 20, 50, 100 • Range of observed % bias: FYB203: -3.8 to -1.7 %bias EU Eylea: -10.8 to -5.8 %bias	Table 67 to Table 70 of (b) (4) amendment 4 to report no. CA28351-01
Bench-top/process stability	24 hours in polypropylene tubes at ambient temperature under white light (FYB203 & EU Eylea)	Table 55 and Table 56 of (b) (4) amendment 4 to report no. CA28351-01
Freeze-Thaw stability	6 freeze (-80°C) - thaw (ambient temperature) cycles in polypropylene tubes under white light (FYB203 & EU Eylea)	Table 53 and Table 54 of (b) (4) amendment 4 to report no. CA28351-01
Long-term storage	FYB203: 373 days stored at -20 °C, 647 days stored at -80°C EU Eylea: 373 days stored at -20 °C, 647 days stored at -80 °C	Table 29 to Table 52 of (b) (4) amendment 4 to report no. CA28351-01
Parallelism	Five study samples at or above ULOQ (60.0 ng/mL) and 7 samples with the highest concentration below 60.0 ng/mL, 5 dilutions per sample: 100% of study samples with acceptable dilution series.	Table 11 of amendment 1 to (b) (4) report no. CA31109-01
Carry over	Not applicable for LBA	

Source: Table 5, Summary of Biopharmaceutic Studies

Appendix 2. Additional PK Results

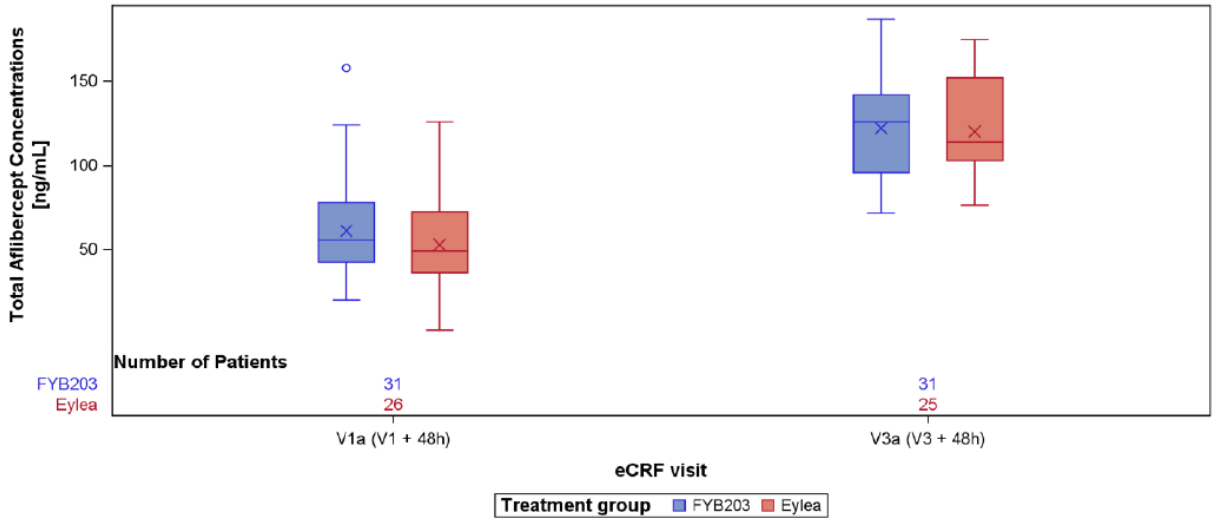
Table 5. Systemic concentration of total aflibercept (ng/mL) 48 hours after 1st and 3rd IVT injection

	V1a (V1 + 48h)		V3a (V3 + 48h)	
Analysis Visit	**FYB203**	**Eylea**	**FYB203**	**Eylea**
n	31	26	31	25
nmiss	0	0	0	1
Mean (SD)	61.106 (29.9909)	52.869 (29.4998)	122.116 (30.5161)	120.112 (28.9556)
CV (%)	49.080	55.798	24.989	24.107
Geom. mean	54.731	42.000	118.282	116.821
Geom.CV [%]	51.169	102.113	26.569	24.443
Geom. mean 95%CI	45.858 - 65.322	29.854 - 59.089	107.477 - 130.174	105.764 - 129.035
Median	55.600	49.200	126.000	114.000
Min-Max	19.80 - 158.00	2.00 - 126.00	71.50 - 187.00	76.20 - 175.00
P10 – P90	30.100 - 85.200	17.700 - 87.600	79.500 - 164.000	86.200 - 163.000
Q1 – Q3	42.500 - 77.800	36.000 - 72.300	95.600 - 142.000	103.000 - 152.000

eCRF = Electronic Case Report Form; n.c. = not calculable; n/nmiss = number of non-missing/ missing assessments; SD = standard deviation; Min = minimum; Q1 = first quartile; Q3 = third quartile; Max =maximum; CV = coefficient of variation; Geom. Mean = geometric mean; Geom. CV = Geometric coefficient of variation; P10/P90 = 10th / 90th Percentile; CI = Confidence Interval.
Values below the lower limit of quantification (4.00 ng/mL) are set to half of the lower limit of quantification and values above the upper limit of quantification (500 ng/mL) are set to the upper limit of quantification for the purpose of summary statistics.
PKS = Plasma Concentration Analysis Set
Source: Table 1.2.1.1 in ISI TFLs for Study FYB203-03-01

Source: Table 4, Study FYB203-03-01 Patient PK and Initial Tolerability Study Reports

Figure 3. Systemic concentrations of total aflibercept (ng/mL) by visit in Study FYB203-03-01 (PK subgroup analysis set)



X = arithmetic mean; Circles = outliers; The horizontal lines of the box plots are defined as follows (from bottom to top): lower whisker, 25th percentile, median, 75th percentile, upper whisker.

The lower and upper whiskers are defined as the lowest/largest observed data point that falls within the range of 1.5 times the IQR from the 25th/75th percentile. Interquartile range (IQR): distance between the 25th and 75th percentile.

A general cut-off date is applied for the 24 week analysis: all data up to and including study day 182 (analysis visit Week 24 (V5)) is included.

PKS = Plasma Concentration Analysis Set

Source: Figure 1.2.1.2 in ISI TFLs for Study FYB203-03-01

Source: Figure 5, Study FYB203-03-01 Patient PK and Initial Tolerability Study Reports

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