14 November 2024
EMA/CHMP/565845/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ahzantive

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006607/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BLA	Biologics licence application
BLI	Biolayer interferometry
BMI	Body mass index
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CFP	Colour fundus photography
CI	Confidence interval
Cmax	Maximum serum concentration
CNV	Choroidal neovascularisation
CQA	Critical quality attributes
CSR	Clinical study report
CTAD	Citrate-theophylline-adenosine-dipyridamole
CTD	Common technical document
DME	Diabetic macular oedema
DR	Diabetic retinopathy
DRE	Disease-related event
ECL	Electrochemiluminescence
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FCP	Foveal centre point
FCS	Foveal centre subfield
FDA	Food and Drug Administration
FP	Fundus photography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
ICF	Informed consent form
Ig	Immunoglobulin
IgG	Immunoglobulin G
IOP	Intraocular pressure
IQR	Interquartile range
ISI	Integrated Summary of Immunogenicity
IVT	Intravitreal
L	Liter
LC-MS	Liquid chromatography-mass spectrometry
LloQ	Lower limit of quantification
LOQ	Limit of quantification
LS	Least squares
MAR	Missing at random
mCNV	Myopic choroidal neovascularisation
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measurements
MNAR	Missing not at random
MNV	Macular neovascularisation
MoA	Mechanism of action
MSD	Meso scale discovery
N	Total number of patients in the analysis set
n	Number of patients with non-missing assessments
NAb	Neutralising antibody

nAMD Neovascular AMD
n.c. Not calculable
NEI VFQ-25 National Eye Institute Visual Function Questionnaire 25
nmiss Number of patients with missing values/assessments
OCT Optical coherence tomography
PD Pharmacodynamics
PDE Pigment epithelium detachment
PI Prescribing information
PK Pharmacokinetics
PKS Plasma concentration analysis set
PlGF Placental growth factor
PMDA Pharmaceuticals and Medical Devices Agency
PPS Per protocol set
PT Preferred term
Ref. Reference
RDTS Repeat-dose toxicology study
RMP Reference medicinal product
ROW Rest of world
RVO Retinal vein occlusion
SAE Serious adverse event
SAF Safety analysis set
SAP Statistical analysis plan
SD Standard deviation
SD-OCT Spectral Domain Optical Coherence Tomography
SE Standard error
SmPC Summary of product characteristics
SOC System organ class
TEAE Treatment emergent adverse event
ULN Upper limit of normal
US Unites States
VA Visual acuity
VEGF Vascular endothelial growth factor
VEGFR Vascular endothelial growth factor receptor
vs. Versus
Δ Difference

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Klinge Biopharma GmbH submitted on 25 April 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Ahzantive, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2021.

The applicant applied for the following indication:

Ahzantive is indicated for adults for the treatment of

- *neovascular (wet) age-related macular degeneration (AMD) (see section 5.1)*
- *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1)*
- *visual impairment due to diabetic macular oedema (DME) (see section 5.1)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).*

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

This application is submitted as a multiple of Baiama simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/12/797/001-002
- Bioavailability study number(s): FYB203-03-01

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 July 2019	EMEA/H/SA/4194/1/2019/III	Prof Andrea Laslop, Dr Rune Kjeken and Dr Kerstin Wickström

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Quality: analytical similarity assessment plan, preliminary analytical similarity data, quality attributes, release and stability testing, analytical assessments, grouping
- Non-clinical: PK and toxicology studies
- Clinical: PK study, direct entry into patients, confirmatory efficacy and safety study (overall study design, safety parameter, immunogenicity assessment, population, proposed primary endpoint, therapeutic equivalence, secondary endpoints, statistical evaluation, sample size, interim analysis, adaptation of sample size).

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Radimersky Co-Rapporteur: Christian Gartner

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	25 April 2024
The procedure started on	28 May 2024
The CHMP Rapporteurs' first assessment report was circulated to all CHMP and PRAC members on	28 August 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	03 September 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	05 September 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 September 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	10 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	29 October 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs updated joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	07 November 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ahzantive on	14 November 2024

2. Scientific discussion

2.1. About the product

Ahzantive (also referred to as FYB203) 40 mg/mL solution for injection in a vial has been developed as a biosimilar to the reference product Eylea (INN: aflibercept; EMEA/H/C/002392).

Aflibercept is in the pharmaceutical group 'ophthalmologicals / antineovascularisation agents' (ATC code: S01LA05).

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin G1. It acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

The claimed therapeutic indications for Ahzantive are: in adults for the treatment of

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

The indication of treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease in preterm infants – granted to Eylea 40 mg/mL solution for injection in pre-filled syringe - is not claimed.

2.2. Type of application and aspects on development

Scientific advice: during the development of FYB203 a written scientific advice was obtained from the European Medicines Agency (EMA).

2.3. Quality aspects

2.3.1. Introduction

FYB203 (aflibercept company code) was developed as biosimilar to Eylea (aflibercept) as reference product.

The finished product is presented as a solution for injection in vial containing 40 mg/ml of Aflibercerpt as active substance.

Other ingredients are: polysorbate 20 (E 432), histidine hydrochloride monohydrate (for pH adjustment), histidine (for pH adjustment), sodium chloride, sucrose and water for injections.

The product is available in a vial (type I glass) with a stopper (elastomeric butyl rubber). Each vial contains an extractable volume of at least 0.1 mL. Pack size of 1 vial.

2.3.2. Active substance

2.3.2.1. General information

The active substance (INN: aflibercept; company code FYB203) is a recombinant fusion protein consisting of human vascular endothelial growth factor (VEGF) receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human IgG1 and is produced in Chinese hamster ovary (CHO) cells.

FYB203 active substance is a colourless to pale yellow solution, containing 36.0-44.0 mg/mL of aflibercept. The solution is stored frozen at ≤ -60°C.

FYB203 is a homodimeric recombinant fusion glycoprotein. Each molecule of aflibercept consists of the extracellular domain 2 (D2) of human vascular endothelial growth factor receptor (VEGFR- 1 D2) and domain 3 (D3) of VEGFR-2 (VEGFR-2 D3), fused to the Fc domain of human immunoglobulin G1 (IgG1).

Aflibercept acts as a soluble decoy receptor that binds VEGF-A, VEGF-B and P1GF and thereby can inhibit the binding and activation of their natural receptors. Pharmacological inhibition of VEGF-A has been demonstrated to be effective at preventing angiogenesis and vascular leakage associated with various

eye diseases. Inhibition of VEGF-A is aflibercept´s main mechanism of action and it is identical for all indications for which Eylea is licensed or approved. The biological activity of FYB203 active substance is monitored via the cell-based iLite potency assay.

The major structural characteristics of FYB203 active substance are summarised below.

Molecular formula: $C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$

Number of amino acids: 864 in total, the polypeptide chains of each molecule unit consist of 432 amino acids

Number of disulfide bridges: 8 intra-chain bonds, 2 inter-chain bonds

Theoretical molecular weight: Unglycosylated protein: 96.9 kDa, Glycosylated protein: 115 kDa

Isoelectric point value 5.8-8.3

Molecular absorption (280 nm): Specific extinction coefficient of aflibercept: 1.155 $L*g^{-1}*cm^{-1}$

The nomenclature, chemical description and the company code (FYB203) of aflibercept are clearly defined. The FYB203 structure consist of a homodimeric recombinant fusion glycoprotein of 864 AS length with each built of the extracellular D2 domain of human VEGF-1 receptor and D3 domain of human VEGFR-2 receptor fused to the Fc domain of human IgG1. Disulfide bonds, glycosylation and the mode of action of aflibercept are described in detail.

2.3.2.2. Manufacture, process controls and characterisation

All manufacturing and testing sites are covered by valid GMP certificates. Active substance manufacturing sites are appropriately listed in the dossier and responsibilities of individual quality control testing sites are specified.

Description of manufacturing process and process controls

The active substance manufacturing process has been adequately described. The FYB203 active substance manufacturing process is a standard process for recombinant protein production, starting with a single vial of working cell bank, expansion in shake flasks, wave bags, seed bioreactors and a cultivation in production bioreactor. The downstream process consists of chromatographic, filtrations and additional steps for virus removal/inactivation and formulation of bulk active substance. filling and freezing. Limits for the process parameters and in-process controls are derived from process characterisation and development activities.

The ranges of critical process parameters and the routine in-process controls (IPCs) along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The applicant provided a detailed description of the manufacturing process steps that is accompanied by flow charts and tables listing process parameters and IPCs with their classification and acceptable ranges/acceptance criteria/action limits. Information on Critical process parameter (CPP), Key process parameters (KPP), Critical performance attributes (CPA) and Key performance attributes (KPA) is included. Acceptance criteria, action limits and/or additional alert limits, as applicable to critical/key and non-key in-process controls are also presented. The active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented in the dossier. No human or animal derived materials are used in the active substance manufacturing process and

acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

Comprehensive testing of MCB and WCB in line with ICH Q5D and Q1A (R1) was performed with respect to the cell banks' identity, purity, viability, viral safety and genetic properties. Characterisation reports for the MCB, WCB and LIVCA cell banks were provided, as well as the testing reports for unprocessed bulk, and the applicant has established periodic testing of the cell banks during storage.

Raw materials and consumables are appropriately tested when released into the production process.

Control of critical steps and intermediates

The manufacturing process is well described and its control strategy, which includes input and output process parameters and in-process controls, is clearly defined. A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the FYB203 active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests. Limits are provided for both process parameters and IPCs (justified by process characterisation) and the consequences for failing to meet them are clearly described. In the main, the PPs and IPCs and their respective ranges/limits are considered adequate. Actions taken if limits are exceeded are specified.

Process validation

The FYB203 active substance manufacturing process has been validated adequately. Overall, the validation criteria are acceptable.

Process performance qualification and validation activities included process consistency (PPQ), *in vitro* cell age study, impurity clearance study, process hold study, membrane and chromatographic column performance, extractables and leachables evaluation, active substance transport validation and reprocessing/ repeated filtration evaluation. Process consistency validation (PV) is based on the commercial manufacturing process, using a sufficient number of consecutive batches. Following the process validation, the process was further refined using the available manufacturing scale data.

It has been demonstrated that differences in charge forms and sialylation do not impact the potency of the finished product. Additional detailed data and discussion support the appropriateness of the process characterisation strategy.

Impurities

Validation of process-related impurities and product-related impurities was performed by their measurement at the individual process steps of the PPQ runs. Impurities were consistently reduced to acceptable low levels/below the LOQ/LOD. Elemental impurities and their possible sources were tested and found below the respective PDE and were therefore considered negligible.

Hold-times

The maximum acceptable hold times were validated with respect to microbial and physicochemical stability.

Membrane and column performance

Resin lifetimes and potential carry-over, and re-usability have been investigated. The membrane and resin lifetimes were first investigated for a defined number of use cycles by performing prospective studies at small-scale using qualified scale-down models (SDM) loaded with representative material from

manufacturing scale batches. Further, in order to confirm the resin and membrane lifetime established at small-scale, a concurrent validation study at manufacturing scale is performed.

No carry-over was observed

In-vitro cell age

Following the ICH Q5D recommendations, an *in vitro* cell age (IVCA) study was carried out for the commercial scale FYB203 active substance manufacturing process to confirm the genetic stability and adventitious agents safety of the production cells at the end of production (EoP). Furthermore, a small-scale IVCA study was designed and performed to demonstrate genetic stability and consistent process performance and product quality over an extended cultivation period.

Qualification of scale-down models

Scale-down models (were appropriately qualified and offsets were determined for some of the product quality attributes at certain steps so that the comparability of the results from the small-scale models to the manufacturing scale could be established.

Extractables and leachables

Based on a comprehensive risk assessment for extractables and leachables a product-specific extractables study was performed for the identified high-risk equipment. A toxicological risk assessment was subsequently performed for the identified extractables above the analytical evaluation threshold, which did not reveal any safety concerns for patients.

Shipping validation

Data supporting shipment of the active substance from the manufacturing site to finished product manufacturing site have been provided and are considered acceptable.

Reprocessing and repeated filtration

Limited to refiltration in the event of equipment/technical failure at the bioburden reduction filtration, virus filtration and final filtration steps. Lack of impact on product quality was demonstrated in small-scale studies and an adequate protocol for concurrent validation of reprocessing was provided.

Manufacturing process development

The applicant has provided an extensive description of the activities performed in the course of the manufacturing process development (together with data from supportive studies) and it is acknowledged that the batch release data support the comparability of the relevant batches. A number of changes in the manufacturing process were introduced only after the validation campaign. These are generally justified or involve tightening of applied limits. The presented approach to process characterisation was deemed well described and acceptable.

The development of the FYB203 active substance manufacturing process was initiated in one manufacturing site at laboratory scale. Consequently, the process was transferred to the commercial manufacturing site, where confirmation runs were executed, which were followed by scale-up to pilot scale (for preclinical supply) and eventually a commercial scale process. The commercial process was further modified, which was established to support the clinical development and commercial production. Initial GMP batches were followed by process validation batches.

Quality by Design (QbD)

The manufacturing process has been evaluated using a combination of conventional univariate studies and elements of quality by design (QbD) process characterisation (PC) is a systematic re-evaluation of

development data and includes experiments aimed at evaluating and confirming process parameter criticality and acceptable ranges (AR) for the final manufacturing process. The overall goal of PC is to assess and subsequently ensure robustness of the process, which finally is capable of consistently delivering a product that is safe and efficacious.

PC was conducted in accordance with current ICH requirements including QbD principles. PC included systematic evaluation of representative small scale and manufacturing scale data, risk assessments, and laboratory scale studies.

As a major outcome of PC, a robust process with performance and product quality within defined ranges was established.

The main deliverables of PC were:

- Classification of the process parameters into critical, key, and non-key as well as definition of the respective acceptable ranges.
- Development of a control strategy including justifications for in-process controls (IPC) classifications into critical, key, and non-key.

The presented approach to process characterisation was deemed well described and acceptable.

Characterisation

The FYB203 active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a recombinant fusion protein. The characterisation overall is sufficiently detailed, and results/observations are discussed in the dossier. Where multiple batches are analysed by the same method, the results appear consistent across the batches, save small differences attributable to method variability. A detailed description of experiments focused on the investigation of the charge forms, glycosylation and their impact on potency is presented, demonstrating the determining role of sialylation of the abundance of acidic forms and confirming that neither charge forms nor sialylation have observable effect on potency of the finished product.

Impurities

The applicant has identified product-related impurities as well as process-related impurities.

2.3.2.3. Specification

The proposed release specification for FYB203 Active substance includes compendial tests for colour, clarity of solution, pH and osmolality. Microbial purity including bioburden (TAMC and TYMC) and Endotoxins respectively. Non-compendial tests comprise polysorbate 20 content, identity, quantity, potency, purity and process-related impurities as well as product related impurities

To derive acceptance criteria for release specifications, the applicant uses a combination of data from clinical trial material and PPQ batches. As the resulting acceptance criteria can be considered sufficiently tight, reflecting both the results of the clinical trial material and the capabilities of the manufacturing process, no objection is raised concerning the general approach and the majority of the acceptance criteria are considered justified.

Analytical methods

The analytical methods used have been adequately described and appropriately validated in accordance with ICH guidelines.

Panel of tests contains pharmacopoeial and in-house methods. References for Ph.Eur. monographs and sufficient descriptions of in-house methods were provided.

Validation of analytical procedures

Verification summaries for Ph.Eur. methods were provided, as well as validation summaries for in-house methods. Validations of analytical procedures were conducted in compliance with principles laid out in ICH Q2(R1).

Batch analysis

Batch analysis data of commercial scale batches of the FYB203 active substance were provided. The results are within the specifications and confirm consistency of the manufacturing process.

The presented batch release results are within specifications valid at the time of release and show good consistency of the manufacturing process output.

Reference materials

For routine release testing a two-tiered reference standard system is established. The stated criteria for qualification of the reference standards are considered adequate and potential drift in potency of the PRS is deemed to be well controlled. Furthermore, the applicant has provided detailed results for the replicates measured at reference standard qualifications.

2.3.2.4. Stability

The stability results indicate that the FYB203 active substance is sufficiently stable and justify the proposed shelf life in the proposed container.

A number of batches manufactured from the commercial process were stored in commercially representative primary containers, The stability studies are in line with ICH Q5C.

Stability of FYB203 active substance batches was investigated under long-term, accelerated, and stress conditions according to the ICH guidelines. Additionally, a freeze-thaw study was performed.

Most parameters tested are the same as for release where the same analytical methods and specifications apply. In support of the proposed shelf-life, long-term stability data stability studies were performed in representative batches. Overall, the stability data support the proposed shelf-life. As it has been shown that unprotected aflibercept is susceptible to photo-degradation, the applicant has confirmed that the active substance is stored protected from light.

No trends are observed in the long-term storage conditions. In accelerated and stressed studies the stability is demonstrated. Photostability studies were performed demonstrating that the active substance is susceptible to photo-degradation and hence should be stored protected from light.

A post-approval stability protocol was provided, together with a stability commitment of placing one batch of FYB203 active substance on stability each year which is acceptable. Overall, the studies have been carried out in accordance with current regulatory guidelines.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical development

FYB203 finished product is a sterile solution for intravitreal injection with 40 mg/mL aflibercept in a single-use vial. With the exception of active substance, all components are compendial to Ph. Eur.

For FYB203 finished product, an alternative formulation was developed compared to the reference product Eylea differing in the buffer system used. This alternative formulation is based on well-established compendial excipients L-histidine / L-histidine HCl monohydrate, sodium chloride, sucrose and polysorbate 20.

The container closure system for FYB203 finished product consists of a 2R borosilicate Type I glass vial and a butyl rubber stopper sealed by an aluminium crimp cap with a plastic flip-off cap attached.

The FYB203 finished product solution in vials is sterilised by use of sterile filtration. FYB203 finished product is a temperature-susceptible proteinaceous solution and thus a terminal sterilisation process with moist heat is not feasible. The method of sterilisation is sufficiently justified.

Process characterisation studies were performed to evaluate some of the process parameters. Results from process characterisation studies were further verified during process validation.

The toxicological assessment revealed no specific, highly potent extractables for the primary packaging of FYB203 finished product vials. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. FYB203 40 mg/mL vials have been designed to deliver the same therapeutic dose of aflibercept as the reference medicinal product (RMP) Eylea. Thus, a dose of 0.05 mL must be ensured for the intravitreal (IVT) injection, meaning that a deliverable volume of 0.05 mL must be guaranteed to deliver 2 mg aflibercept with one IVT injection.

The product should be supplied as a vial only. According to the SmPC, for preparation and intravitreal injection the following medical devices for single use are needed. A 5-micron sterile filter needle (18-gauge x 1½-inch), a 1-mL sterile Luer-lock syringe and a 30 G x ½-inch sterile injection needle are needed for the intravitreal injection. These medical devices are considered as referenced. Representative components were used for in-use compatibility study on the device combination.

There are no novel excipients used in the finished product formulation.

2.3.3.2. Manufacture of the product and process controls

The finished product is manufactured by standard process covering thawing and pooling of active substance, bioburden reduction filtration, sterile filtration, filling and stoppering, crimping, visual inspection, and packaging for shipment. Representative flow diagram was provided including IPCs. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Reprocessing for finished product is not considered.

Finished product manufacturing sites are appropriately listed in the dossier and responsibilities of the individual quality control sites are specified. A flow-chart indicating all manufacturing and control sites involved in the manufacturing process and control of the medicinal product was submitted.

All sites are covered by valid MIA/GMP certificates.

Process controls

An input process parameter whose variation has an impact on a CQA is defined as critical process parameter (CPP). Operating ranges (OR) and acceptable ranges (AR) were considered for process parameters. An output parameter whose variability has the potential to affect a CQA in the final product is defined as critical in-process control (CIPC). Acceptance criterion or action limit and optionally an additional alert limit was considered for process controls. The proposed control classification seems reasonable. The criticality assessment of the operational parameters and process controls is supported by FMEA evaluation. Hold times are clearly identified and controlled. Suitability of endotoxin testing and bioburden testing was demonstrated. The batch numbering system in place ensures uniqueness and traceability of manufactured batches.

Process validation

The manufacturing process has been validated. Process validation covers all finished product manufacturing steps and was performed following a classical approach. All PPQ batches met in-process controls and acceptance criteria. The provided data demonstrates that when operating within the proposed ranges, the performance controls meet relevant quality criteria. An ongoing process verification programme is implemented in order to maintain the process in validated state.

Hold time validation

Holding times for commercial manufacturing process are covered by hold time validation studies. Filling and crimping time is covered by performed media-fill runs. Results from physicochemical and microbial stability analyses are presented. Samples were analysed for certain quality attributes to demonstrate the physico-chemical and microbial stability of the interim finished product stages.

Filter validation

The filter validation demonstrated that the sterile filter is suitable for manufacturing.

Media fill

The aseptic filling operations were validated via media fill runs. A bracketing approach is applied to validate aseptic filling operations.

Transport validation

The suitability of the transport was determined using a transport simulation study. After simulation the pallets and all packaging levels have been optically checked for defects caused by exposure to the selected stress conditions. After transport simulation study the analytical testing of finished product samples was performed. No impacts on product quality were noted following mechanical stress, indicating that the shipping system can maintain product integrity during the transportation. The applicant is asked to provide corresponding results upon availability. Details of the temperature excursion studies as well as to the approved shipping container(s) have been provided upon request

Comparability studies

Comparability studies between different manufacturing sites at finished product were performed. Analytical comparability study assessing IPC results, extended characterisation data, release data, and stability profiles at different storage conditions was performed

2.3.3.3. Product specification

The release specifications include tests for identity, potency, purity, microbial purity as well as general attributes that were assessed using compendial methods. The limits are sufficiently justified and are considered adequate to control the quality of FYB203 drug product.

The limits are sufficiently justified and are considered adequate to control the quality of FYB203 drug product.

The sequential approach to define release and shelf-life specifications is described. The overall risk of a potential release of elemental impurities into the drug product caused by the sources like drug substance, excipients, process equipment with direct product contact and primary packaging components is assessed as low and an establishment of a special control strategy to control the elemental impurities in FYB203 finished product vials is not required. All processes for manufacturing FYB203 finished product vials are under control regarding the level of elemental impurities. Any future change made to the processes will be subjected to change control processes and the potential impact will be evaluated.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that a negligible potential safety risk for FYB203 active substance or the related finished product was identified. Therefore, no additional control measures are deemed necessary.

Analytical methods

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Analytical procedures

Majority of analytical procedures used are the same as described in active substance section, with addition of usual methods used for finished products, e.g. extractable volume test or container closure integrity test Sufficient descriptions were provided, comments regarding equipment or reagent changes remain the same as described in active substance section. Unique method identifiers are included for all methods, in order to maintain a clear link between specifications, methods and methods validations.

Validations of analytical procedures were conducted in compliance with principles laid out in ICH Q2(R1).

Batch analysis

Batch analysis data of finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Batch release results are presented in the dossier. Presented batch release data all met specifications and no significant changes between batches are observed.

Reference materials

For analysis of FYB203 finished product the same reference standards as for FYB203 active substance are used.

2.3.3.4. Stability of the product

Based on available stability data, the shelf-life of 24 months and storage at 2°C-8°C conditions as stated in the SmPC are acceptable.

A number of finished product batches were placed on stability studies. Stability studies are performed at the intended long-term storage temperature (5 ± 3°C), accelerated conditions (25 ± 2°C/60 ± 5% RH), and stressed conditions (40 ± 2°C/75 ± 5% RH). The container used in the stability studies is same as proposed for the routine storage. All vials were stored inverted to simulate worst-case conditions. Stability testing protocols are provided for all tested storage conditions and are according to ICH guidelines.

The majority of parameters tested during stability are the same as for release (colour, clarity, pH, subvisible particles, activity and sterility, where the same analytical methods and specifications apply. Only few quality attributes have different release and shelf-life specifications although the same testing procedures are used.

Stability data covering the shelf-life were provided. All results met acceptance criteria decreasing trends were observed for some purity parameters. At accelerated and stressed storage conditions the degradation trends are more significant. The proposed shelf-life of 24 months at 2°C-8°C based on the available stability data which is acceptable

Out-of-fridge stability studies were performed to cover potential temperature excursions during manufacturing and sample handling. The provided data met acceptance criteria and no impact on the stability behaviour is observed. Stability data for one clinical finished product batch storage is now available. Therefore, it is concluded that the proposed possibility defined in the SmPC to store the unopened vial outside the refrigerator below 25°C for up to 24 hours is covered with worst-case stability data and could be accepted.

Formulation robustness study data are also presented in this section. Solutions with different formulation variants of finished product were placed on stability at 5°C ± 3°C and at 25°C ± 2°C. All quality attributes assessed up to the current timepoint are well within the specification limits.

Additionally, the impact of agitation stress and photo stress on finished product was evaluated during the forced degradation study as a part of analytical similarity assessment. Based on the results it is concluded that agitation stress does not affect product quality, whereas photo stress has an impact on product stability. Therefore, it is stated in the SmPC that finished product has to be stored in the original package in order to protect from light.

The post-approval stability protocol and stability commitment was provided. One batch of finished product will be placed on stability each year.

In accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.3.3.5. Adventitious agents

Multiple complementing measures are implemented to ensure product safety in terms of potential contamination by non-viral and viral adventitious agents. The measures include selection and testing of materials, testing of cell banks, testing of microbial attributes as in-process controls and at release, implementation and validation of dedicated virus clearance steps and steps contributing to virus reduction. In addition, microbial quality is ensured by process design (microbial reduction filtrations, sterile filtration, aseptic processing) and adequate sanitisation procedures.

Materials of biological origin and testing of cell banks and intermediates

Materials of biological origin were identified and listed. No raw materials of animal or human origin are/were used during manufacture of FYB203 active substance/finished product. Origin of biological materials was provided and for animal derived materials, the source countries were identified and the applicant performed detailed assessment regarding safety from the perspective of potential non-viral and viral contamination. For all reagents with bovine constituents used during development, the geographic origin can be traced to countries with a negligible TSE risk or are certified to fulfil the requirements laid down in Note for Guidance EMEA/410/01, rev. 3NoOverall, the extensive characterisation testing of production cell banks demonstrated the absence of microbial and viral contamination.

Virus clearance studies

Virus clearance capacity of the manufacturing process has been assessed in virus clearance studies Overall, the performed validation study was performed in line with the applicable guidelines using process parameters representing the worst-case scenario in routine GMP production and data demonstrated sufficient viral clearance capability of the purification process In summary, the risk of potential contamination and transmission of bacterial, viral, or TSE agents is adequately controlled and negligible

2.3.3.6. GMO

Not applicable

2.3.3.7. Biosimilarity

The biosimilar development has been performed following principles of the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012). Analytical similarity of FYB203 was assessed in a comprehensive exercise with EU-authorised and US-licensed Eylea products. Conclusions of the EMA scientific advice (EMA/CHMP/SAWP/398725/2019) with regard to criticality ranking of quality attributes, statistical approach for data evaluation, sampling of batches, panel of comparability exercises, reporting of N-glycan structure groups, determination of extinction coefficient and discussion on the observed differences in quality attributes were taken into consideration in the biosimilar development and are addressed in the dossier.

CQA assessment

As part of initial development efforts, the criticality of the relevant quality attributes was performed following risk ranking approach as per ICH Q9. Standardised approach concerning evaluation of impact and uncertainty was applied and impact factor was established based on effect of each attribute on biological activity/efficacy, PK/PD, immunogenicity and safety. For some quality attributes describing identity and potency as well as for general finished product attributes and some process-related impurities, the impact on efficacy, PK/PD, safety or immunogenicity is well established. For those quality attributes, a default criticality is assigned independent of the product specificities. The information on the CQA assessment and its outcome that includes detailed assessment examples for some criticality categories (low, moderate, high, very high) is satisfactory. Overall, criticality ratings and their justification is supported.

Data evaluation approach

Quality attributes with quantitative data with very high to moderate criticality were subjected to quantitative comparison between FYB203 and Eylea EU reference product. Pre-defined limits were

applied for data, such as retention time and molecular mass. Low and very low ranked CQAs or qualitative data was evaluated by visual comparison (e.g. spectral overlays). For very high to high criticality attributes subjected to quantitative evaluation of results a tighter similarity criterion might have been considered to strengthen the conclusion based on statistical evaluation however, the evaluation approach and provided comprehensive justifications is in line with the current guidance as described in the Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) and is deemed acceptable.

Analytical methods and tested batches

Panel of analytical methods employed in analytical similarity assessment is considered sufficiently comprehensive

Methods used in similarity exercises are categorised as leading, orthogonal or methods for additional characterisation. All procedures were sufficiently described. Description of used equipment, reagents and solutions, sample preparation, method workflow steps, equipment setup and parameters of the method were provided as applicable. Data reporting, approach to results evaluation were described and system suitability testing were described. All analytical methods were appropriately qualified and the provided results demonstrate suitability for the intended purpose. Qualification reports were provided for all methods subjected to qualification and the provided data summarizing the method parameters are considered acceptable.

In general, all available independent FYB203 finished product batches and an independent active substance batch were tested by leading methods, while a reduced number of FYB203 batches were tested by orthogonal and additional characterisation methods. All batches used for purpose of analytical similarity were produced at the proposed commercial active substance manufacturing site by the current commercial scale active substance process. FYB203 finished product batches included in the analytical exercise were manufactured at commercial scale at the proposed commercial production site. Batches tested in analytical similarity study were used in non-clinical and clinical studies and finished product batches were produced from active substance PPQ material. The batch sampling strategy is considered clear and tested batches are considered representative for the proposed commercial manufacturing process.

Generally, a sufficient number of batches was employed for analytical characterisation to study the quality profile of the EU-authorised Eylea reference product. In addition, analytical data for US-licensed Eylea are shown as supportive data. EU-sourced RMP lots as well as US-sourced originator lots were sourced over a time span of several years. It is agreed that the number of lots sourced over these long time periods will provide a robust estimate of variability of the RMPs.

Analytical similarity exercise

To evaluate the similarity of FYB203 in comparison to Eylea EU, an analytical similarity assessment was performed consisting of the initial characterisation, forced degradation study and stability study under accelerated and stress conditions.

Brief summary of the identified peptide fragments from individual digestion techniques was provided. Based on the data it is concluded that the higher order structure of the products is highly similar.

Molecular heterogeneity was characterised for size and charge heterogeneity as well as for further modifications. Results indicate similar structural, size, and charge heterogeneity, in further functional characterisation it was demonstrated that differences in N-glycosylation profile do not have impact on relevant biological properties and potency. Furthermore, in relation to the available non-clinical data and with references to the available literature it was sufficiently justified that the differences identified in the N-glycosylation profile do not have impact on pharmacokinetic properties in the context of intravitreal administration. Characterisation of the potential Fc-mediated effector functions and biding affinities is considered adequate, and results are considered similar to the EU-Eylea reference product.

Comparative stress stability studies were performed under various conditions (agitation, photolytic stress, oxidation, acidic and basic pH and glycation stress) to evaluate degradation pathways Results demonstrated similar degradation pathways and degradation rates in tested quality attributes In dedicated comparative freeze-thaw study performed showed no significant changes of stability indicating quality attributes were observed. In conclusion, it is agreed that the overall response to product degrading stress conditions was well comparable for FYB203 and its reference product Eylea. Observed trends and kinetics were in good agreement among all products for all stress conditions.

A comprehensive analytical exercise was performed to evaluate FYB203 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics. In addition to initial characterisation study, comparative forced degradation study and stability study under accelerated and stress conditions were performed and study results provide supportive information with regard to totality of evidence. Overall, the FYB203 is considered similar to the Eylea reference medicinal product in majority of physical and chemical attributes and biological properties. Differences have been identified in N-glycosylation profile with regard to overall fucosylation, galactosylation, mannosylation and sialylation content. Also, lower levels of oxidation and deamidation were observed in FYB203. These findings contributed to different relative content and distribution of charged variants and lower FcγRIIIA affinity. Nonetheless, it has been justified that this heterogeneity does not significantly impact the primary or potential secondary mechanism of action of aflibercept as generally robust functional characterisation supports the similarity between FYB203 and EU-Eylea. Also, it is concluded that observed differences do not have impact on safety and immunogenicity of the FYB203. Potential impact of differences in N-glycosylation profile to pharmacokinetic properties is not expected in regard to the intravitreal application which is supported by scientifically sound discussion. Available non-clinical data for all tested FYB203 batches showed a high degree of similarity to treatment with Eylea in the relevant ocular matrices (vitreous humor, aqueous humor, retina/choroid tissue) which further support this conclusion. All residual uncertainty with regard to demonstration of analytical similarity has been sufficiently resolved. FYB203 is considered similar to EU-Eylea in relevant physical and chemical attributes and functional characteristics and identified differences in quality profile are not expected to affect clinical performance.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Active substance

FYB203 has been developed as biosimilar product to EYLEA. The provided data support the comparability of the relevant historical batches to the commercial manufacturing process and a comparability exercise presented in line with the ICH Q5E, complete with clear summary tables of the relevant manufacturing process was included in the dossier.

The process validation at commercial scale is deemed successful overall. The active substance specifications and limits are considered justified in general, and it is accepted that tightening of the sialylation acceptance criteria is not warranted given absence of its impact on potency or safety and the negligible impact of sialylation of aflibercept on pharmacokinetics with intravitreal administration. Validation of analytical procedures were conducted in compliance with principles laid out in ICH Q2(R1). Validation summaries have been provided for all declared testing sites.

For routine release testing a two-tier reference standard system is established. The applicant has provided a clear overview of the history of reference standards (RS) and qualification criteria. The applicant has also provided results for individual replicates from the qualification of the reference standards. The qualification criteria and overall approach to RS management are deemed to sufficiently control potential drift in potency.

The proposed shelf-life at ≤ –60°C is supported by long-term stability data from representative batches fully covering at least the proposed shelf-life, additional long-term and accelerated and stressed-conditions stability data.

Finished product

FYB203 finished product is developed as a proposed biosimilar to the reference product Eylea in the dosage form of solution for intravitreal injection in a single-use vial. It was sufficiently demonstrated that the target fill volume is sufficient for the desired deliverable volume of 0.05 mL. Based on the results of formulation development, finally chosen formulation differs from the formulation of Eylea by replacement of the sodium phosphate buffering system with a L-histidine/L-histidine HCl monohydrate buffering system.

Process characterisation studies were performed, and results were further verified during process validation on consecutive PPQ batches. Process validation covers all finished product manufacturing steps and was performed following a classical approach. The provided data demonstrates that when operating within the proposed ranges, the performance controls meet relevant quality criteria. Holding times for commercial manufacturing process including the cumulative hold times are covered by hold time validation studies. Sufficient level of details is provided on filters.

The finished product specifications and limits are considered justified. Acceptable panel of tests, their validations and verifications, with majority of shared methods and raised concerns with active substance, was presented.

The proposed shelf-life 24 months at 2°C – 8°C is acceptable based on the provided stability data. Also, the proposed possibility to store the unopened vial outside the refrigerator for up to 24 hours is supported with stability data covering the worst-case scenario.

Biosimilarity

A comprehensive analytical exercise using a broad panel of orthogonal state-of-the art analytical techniques was performed to evaluate FYB203 similarity with EU-Eylea reference medicinal product in

all relevant physical and chemical attributes and functional characteristics. Analysis covered primary and higher order structure, product related substances and impurities, variants related to cysteine chemistry, charge, isoaspartate formation, glycosylation, or molecular size, and finished product related attributes. Functional activity was compared by a large panel of binding assays and cell-based biological assays covering the mode of action for the targeted indications as well as Fc-related functions. Based on the provided information it is concluded that the analytical methods are suitable for the intended purpose. In addition, results for US-Eylea were presented. Batches/lots analysed can be expected to sufficiently reflect product variability of both the proposed biosimilar and the reference product. The FYB203 batches have been manufactured according to the intended active substance commercial process.

For quantitative data the applicant applied quality ranges based on RMP data. Low and very low ranked CQAs which result in qualitative data were, in general, evaluated visually. The evaluation approach and provided comprehensive justifications is in line with the current guidance as described in the Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (EMA/CHMP/138502/2017) and is deemed acceptable. All individual test results of the analytical similarity exercise are provided.

In addition to the initial characterisation study, a comparative forced degradation study and a stability study under accelerated and stress conditions were performed and study results provide supportive information with regard to totality of evidence.

Overall, the differences between FYB203 and EU-Eylea reference medicinal product have been identified in N-glycosylation profile with regard to overall fucosylation, galactosylation, mannosylation and sialylation content. Also, lower levels of oxidation and deamidation was observed in FYB203. These findings contributed to different relative content and distribution of charged variants and lower FcγRIIIA affinity. Nonetheless, it has been justified that this heterogeneity does not significantly impact the primary or potential secondary mechanism of action of aflibercept as generally robust functional characterisation supports the similarity between FYB203 and EU-Eylea. Potential impact of differences in N-glycosylation profile to pharmacokinetic properties in ocular matrices is not expected in regard to the intravitreal application which is supported by scientifically sound discussion. Available non-clinical data for all tested FYB203 batches showed a high degree of similarity to treatment with Eylea in the relevant ocular matrices (vitreous humor, aqueous humor, retina/choroid tissue) which further support this conclusion. All residual uncertainty with regards to demonstration of analytical similarity has been sufficiently resolved. FYB203 is considered similar to EU-Eylea in relevant physical and chemical attributes and functional characteristics and identified differences in quality profile are not expected to affect clinical performance.

Adventitious agents

The risk for transmission of adventitious agents is adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

N/A

2.4. Non-clinical aspects

2.4.1. Introduction

Ahzantive (FYB203) has been developed as a proposed biosimilar to Eylea (INN: aflibercept). Aflibercept is a glycosylated, disulfide-stabilised 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. The molecular weight of the intact deglycosylated aflibercept molecule, as measured by mass spectrometry, is 96.9 kDa. 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.

The intended route of FYB203 administration is intravitreal (IVT) injection.

In the Non-clinical Overview (NCO) the applicant claimed identical qualitative and quantitative composition of FYB203 to the RMP (EU Eylea) in contrary to other sections of NCO in which the applicant claimed alternative formulation. The applicant corrected the discrepancy declaring identical qualitative and quantitative composition of FYB203 to the RMP (EU-Eylea). Furthermore, the applicant provided conducted non-GLP pilot *in vivo* formulation study to complement the overall data package.

2.4.2. Pharmacology

The applicant provided detailed description of the *in vitro* studies conducted.

No *in vivo* studies were conducted for primary pharmacology assessment. Secondary pharmacology, pharmacodynamic drug-drug interaction, and safety pharmacology studies were deemed not necessary for FYB203 as respective data from these experiments would not add relevant nonclinical information for the proposed biosimilar. Overall approach and omission of *in vivo* studies is adequate.

2.4.3. Pharmacokinetics

The applicant conducted two *in vivo* pharmacokinetic studies to demonstrate similarity of PK profile of aflibercept (FYB203) to originator EU-Eylea at four different compartments i.e., vitreous humor, aqueous humor, retina/choroid tissue and plasma.

Validated ELISA and MSD assays were used to determine drug levels in vitreous humor, aqueous humor, retina/choroid tissue, and plasma of NZW rabbits. Although immunogenicity data in animal models is not regarded representative of the human situation, anti-drug antibodies were analysed in the plasma of NZW rabbits using a validated MSD assay.

In a first GLP-compliant study, the biosimilar candidate FYB203 was tested side-by-side to EU-approved Eylea. The PK profile of FYB203 in the relevant ocular matrices (vitreous humor, aqueous humor, retina/choroid tissue), showed a high degree of similarity to treatment with Eylea, whereas in plasma of rabbits treated with FYB203 levels of free aflibercept were approximately 2-fold lower when compared to rabbits treated with EU-Eylea.

The aim of the second GLP PK study in rabbits was to evaluate and compare the ocular and systemic pharmacokinetics of 3 different FYB203 batches manufactured under varying growth condition with different levels of sialylation, and EU-approved Eylea. Again, drug levels in vitreous humor, aqueous humor, and retina/choroid tissue revealed similar ocular PK for all FYB203 batches tested and EU-Eylea, whereas in plasma FYB203 levels were decreased when compared to Eylea. For a FYB203 batch manufactured at pilot scale with a sialylation degree most similar to Eylea, plasma levels were comparable to those of EU-approved Eylea.

Overall, the applicant concluded that the presence of more terminal galactose and GlcNAc (linked to lower levels of sialic acid) in FYB203 may explain the different PK properties in plasma exhibiting faster clearance from the blood via the liver compared to the originator Eylea. This was not fully accepted as the PK profile also shows variation in Tmax (e.g., non-linear PK in 48-72 hours in second study) across batches.

Generally, the PK of aflibercept after IVT administration are well described and no *in vivo* data is warranted for biosimilar products like FYB203 in accordance with currently effective guidance. Nevertheless, two PK studies in rabbit were conducted and study reports submitted. Due to the fact that such *in vivo* studies are regarded as insensitive to support biosimilarity, these data are regarded of supportive value only. In addition to support similarity on the PK level, different formulations for FYB203 were tested in one of the two studies to define the final formulation to be used for further FYB203 development.

However, all FYB203 batches with differences in receptor domain sialylation showed a high degree of similarity in target binding and potency. The applicant therefore argued that differences in sialylation did not impact potency or target binding as demonstrated by functional assays (see under Quality, Analytical similarity). Taking provided arguments altogether, the PK differences based on non-clinical PK studies are not considered as concern for biosimilarity.

2.4.4. Toxicology

2.4.4.1. Repeat dose toxicity

The applicant provided one repeat-dose toxicology study that was performed to evaluate the toxicological effects of repeated IVT injections of FYB203, in comparison with EU approved Eylea over a 5-week period in albino NZW rabbits. The study was performed in compliance with the OECD Principles of Good Laboratory Practice (GLP) regulations.

Published data (del Amo et al, 2015) and the derived pharmacokinetic parameters indicate that the rabbit is a useful animal model in intravitreal nonclinical studies. However, because the volume of the vitreous humor of NZW rabbits (approx. 1 mL) is smaller than that of humans (approx. 4 mL), the intraocular drug concentration in rabbit eyes after a single dose is higher than in human eyes. In addition, systemic exposure following intravitreal administration of aflibercept is higher in rabbits than in humans due to weight differences. These facts had to be taken into account.

Overall, the applicant conducted an extensive *in vivo* non-clinical programme for FYB203 biosimilars which is not in line with the current guidelines emphasizing avoidance of *in vivo* studies due to availability of more sensitive *in vitro* methods for comparability assessment. In addition to two *in vivo* pharmacokinetic studies, an *in vivo* 1-month repeat-dose toxicology study (2 applications on D1 and D15) with toxicokinetic and recovery groups was conducted with FYB203 manufactured at the intended commercial scale.

The toxicology study with inclusion of toxicokinetic measurements also support the notion that FYB203 Tech Batch and EU-Eylea cannot be considered as biosimilar in terms of free plasma aflibercept. However, repeated dose toxicity studies are usually not recommended for similar biological products (EMA/CHMP/BMWP/403543/2010) and observed differences are not expected to have impact on clinical efficacy and safety supported by *in vitro* functional biosimilarity assessment and low systemic exposures to free plasma aflibercept FYB203 in patients. Clinical data supersede over non-clinical studies provided and no further non-clinical studies are warranted.

2.4.5. Ecotoxicity/environmental risk assessment

Adequate justification for absence of ERA has been provided. Monoclonal antibodies are unlikely to pose a significant risk to the environment. Environmental risk assessment studies are therefore not required in accordance with EMEA/CHMP/SWP/4447/00.

2.4.6. Discussion on non-clinical aspects

Comparability data and *in vitro* functional characterisation (*in vitro* binding and potency assays) data were submitted. Please refer to the respective section of this assessment report and the Quality sections for discussion and conclusion on the similarity data for FYB203. The provided data supports similarity of FYB203 and the RMP.

In vivo studies conducted demonstrated similar ocular pharmacokinetic between tested products whereas in plasma FYB203 levels were lower when compared to Eylea. Yet, the applicant claimed *in vitro* functional biosimilarity. In accordance with stepwise approach, *in vitro* studies were conducted first, and a decision then was made that *in vivo* studies were required to demonstrate that the use of an alternative formulation has no impact on the similarity of PK parameters. Considering the observed differences in free plasma aflibercept, the applicant introduced manufacturing changes to increase sialylation levels, however difference in PK profile although in a reduced extent was still observed between products. The applicant was requested to justify extensive non-clinical testing strategy and clarify manufacturing and functional comparability between batches used for *in vitro* biosimilarity assessment and in clinical studies (see section 3).

Section 4.6 and 5.3 of the proposed SmPC are in line with the approved product information for Eylea.

The applicant concluded from the generated RDTS data that analysis of ocular tolerance and systemic toxicity in rabbits treated with FYB203 or EU-approved Eylea support the claim of similarity of FYB203 with regard to safety.

In particular, the RDT data submitted by the applicant is acknowledged and the discussion provided by can be followed. However, toxicity data in the context of a biosimilar development are regarded of supportive value only and no conclusions on similarity can be drawn due to general lack of sensitivity of *in vivo* (animal) models in regard to biosimilarity assessment.

2.4.7. Conclusion on the non-clinical aspects

There are no concerns arising from the functional biosimilarity exercise (see Quality section) triggering the need for further investigations and the difference in free plasma concentration of aflibercept in provided *in vivo* PK and toxicology studies in rabbits has not been considered an issue. The applicant revised the documentation to declare identical qualitative and quantitative composition of FYB203 to the RMP (EU-Eylea). The updated documentation clarified that the formulation comprises well-established compendial excipients for intraocular use. No further assessment of these excipients has been considered

necessary. Additionally, the applicant provided the *in vivo* pharmacokinetic study with different formulations. Based on the data provided, it was reasonable to conclude that the observed differences in the *in vivo* pharmacokinetics (PK) of free aflibercept in plasma may be attributed to variations in formulation in comparison to RMP (EU-Eylea) and differences in affinity for the asialoglycoprotein receptor (ASGPR), which is influenced by varying sialylation levels among the products. Nevertheless, the applicant has demonstrated that these differences do not affect the efficacy of DP with formulation 2, as confirmed by *in vitro* biosimilarity studies, nor do they impact its safety, as supported by *in vivo* GLP animal studies following intravitreal (IVT) administration.

The applicant has also provided an overview table detailing the batches used in non-clinical development, The overview reveals that the non-clinical batches were not a priori tested in *in vitro* studies for glycosylation and biological functions. As a cautionary note for potential future developments, the applicant was strongly urged to follow a stepwise approach, ensuring that *in vitro* studies are thoroughly conducted before initiating any *in vivo* studies, if they are deemed necessary.

Overall, nonclinical *in vivo* data in the context of a biosimilar development are regarded of supportive value only as no conclusions on similarity can be drawn due to general lack of sensitivity of *in vivo* (animal) models in regard to biosimilarity assessment.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

As stated by the applicant in the clinical overview (section 2.5.1.4.1) only one clinical study (MAGELLAN-AMD) has been conducted, then the tabular overview of clinical studies has not been provided. This is endorsed by the assessor.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods for pharmacokinetics: Free and total aflibercept assays

Two separate validated ligand-binding assays, one to measure total (free + bound to VEGF) aflibercept and the other for measuring free (active, not bound to VEGF) aflibercept in human plasma, were developed and validated in accordance with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). Based on the provided method validation documentation it is concluded that both methods are suitable for their intended use. The bioanalytical similarity assessment was performed. Detailed analytical reports have been provided for testing of the clinical samples. In-study method performance was demonstrated by back- calculated calibration standards, inter-batch precision and accuracy of QC samples and ISR. Study samples were analysed without exceeding the validated short-term, long-term or freeze-thaw stability periods. In summary, the presented data do not indicate any issue related to testing of the clinical samples.

Bioanalytical methods for immunogenicity testing: ADA and NAb assays

Two validated methods to monitor the relative humoral immune response to FYB203 vs. EU-approved Eylea were employed: bridging electrochemiluminescence (ECL) assay to detect ADA and competitive ligand-binding assay to detect NAb with capacity to block binding of aflibercept to the target, VEGF-A165. A multi-tiered approach for immunogenicity assays was applied including ADA screening assay, ADA confirmatory assay for samples screened positive, followed by titre estimation and NAb assay. Taken together, the adopted three-tiered approach for determination of ADAs was well described and developed. It is considered state of the art and valid for its intended use. The presented assay for determination of neutralising properties was well described and established. It was setup correctly and validated.

Overall, the immunogenicity assays were characterised by very good sensitivity and a low risk of false negative results.

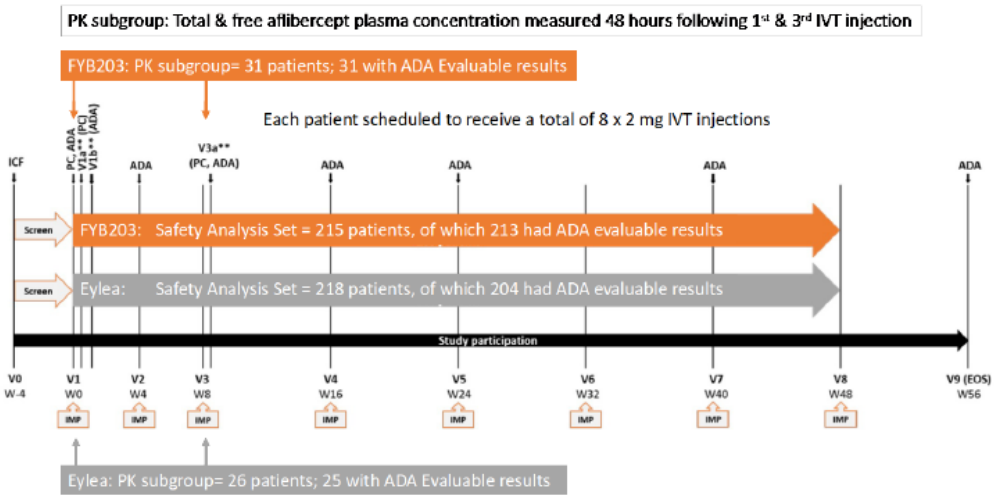
The bioanalytical methods for pharmacokinetics (total and free aflibercept in human plasma) and immunogenicity testing (ADA and NAb assays) have been considered reliable, well developed and validated and suitable for intended use. No concerns on bioanalytics have been identified.

Bioequivalence

No PK studies were conducted in healthy volunteers for ethical and safety reasons. The results of the assessment of comparative systemic free and total aflibercept exposure that were included as a safety endpoint in a subgroup of 57 patients within the confirmatory comparative clinical safety and efficacy study.

Study FYB203-03-01

The objective of the PK sub-group analysis was to compare systemic exposure of both total and free aflibercept by measurement of plasma concentration 48 hours following a first and third intravitreal (IVT) administration of either FYB203 or EU-approved Eylea at a dose of 2 mg (0.05 mL of a 40 mg/mL solution) in patients with subfoveal nAMD or wet AMD.



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

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

Blood samples 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).

Free as well as total aflibercept were measured and evaluated by the applicant. Free aflibercept is anticipated to be the active drug and levels of free aflibercept are considered more important, however total aflibercept levels add additional information on total levels and possibly differences in accumulation.

The number of patients included in the PK analysis is considered adequate, demographic characteristics were comparable between treatment groups and the method of selection of patients in the PK subset has been clarified.

Results:

Free and total aflibercept were assessed and compared in a subgroup of 57 patients (26 for Eylea and 31 for FYB203) at selected study sites at baseline prior to first IVT dose, 48 hours after first IVT dose (Visit 1a) and at 48 hours after the third IVT dose (Visit 3a). Systemic concentrations were assessed close to the predicted maximum concentration [Cmax] (based on estimated Tmax). Comparisons are based on descriptive statistics.

Table 1: Systemic total and free aflibercept plasma concentrations until week 8 by treatment group (ng/mL) (PKS, N=57)

eCRF Visit and Statistic	FYB203 (N=31)	Eylea (N=26)
Total aflibercept plasma concentration (ng/mL)		
V1a (V1 + 48h)		
n	31	26
Geom. Mean	54.731	42.000
Geom. CV (%)	51.169	102.113
Geom. Mean 95.0% CI	45.858–65.322	29.854–59.089
P10–P90	30.100–85.200	17.700–87.600
Week 8, V3a (V3 + 48h)		
n	31	25
Geom. Mean	118.282	116.821
Geom. CV (%)	26.569	24.443
Geom. Mean 95.0% CI	107.477–130.174	105.764–129.035
P10–P90	79.500–164.000	86.200–163.000
Free aflibercept plasma concentration (ng/mL)		
V1a (V1 + 48h)		
n	31	26
Geom. Mean	21.667	14.235
Geom. CV (%)	58.922	119.312
Geom. Mean 95.0% CI	17.735–26.470	9.735–20.817
P10–P90	10.300–40.600	6.600–31.600
Week 8, V3a (V3 + 48h)		
n	31	26
Geom. Mean	22.773	20.512
Geom. CV (%)	55.552	59.891
Geom. Mean 95.0% CI	18.828–27.545	16.402–25.652
P10–P90	10.600–42.700	8.860–41.200

CI = confidence interval, CV = coefficient of variation, eCRF = electronic case report form, Geom. Mean = geometric mean, h = hours, N = number of patients per group, n/nmiss = number of non-missing/missing assessments, PKS = Plasma concentration analysis set, P10/P90 = 10^{th} /90^{th} percentile, V = visit

Because none of the 57 patients in the PK subgroup developed ADA during the 56-week study period it was not possible to perform the planned analysis of the relationship of ADA status to systemic exposure.

In the absence of ADA formation, the geometric mean and 95% CI for the aflibercept (both total and free) concentrations measured 48 hours after the third IVT injection were similar for the FYB203 and Eylea treatment groups, supporting a conclusion of similar systemic exposure following repeated IVT administration in nAMD patients.

2.5.2.2. Pharmacodynamics

No dedicated PD study have been conducted as part of the clinical biosimilarity exercise and none is considered necessary.

Mechanism of action

The only known mechanism of action of aflibercept is its binding to VEGF-A and PlGF thereby inhibiting the binding and activation of VEGFR-1 and VEGFR-2, present on the surface of endothelial cells.

Aflibercept exerts inhibitory effects on angiogenesis and stabilizing actions on vessel permeability through the blocking of VEGF-A. IVT injection permits direct targeting of the areas of abnormal neovascularisation in the retina.

Immunological events

ADA formation against aflibercept was evaluated in serum in all patients before they received the IVT injections at baseline, Week 4, Week 16, Week 24, Week 40, at Week 56/early termination, and in addition, in patients participating in the PK subgroup one week after the first dose (baseline) and 48 hours after the third dose (Week 8).

The results provide compelling evidence of absence of clinically impactful ADA or NAb formation for either FYB203 or Eylea, consistent with very low incidence (1.9% of FYB203-treated nAMD patients) and minimal ADA titres detected, which is also in line with the accumulated clinical experience for Eylea.

Table 2: ADA / Nab prevalence and ADA titre in study FYB2023-03-01 - SAF

Category	Sample timepoint					
	Week 0/ Baseline	Week 4	Week 16	Week 24	Week 40	Week 56
FYB203 (N=215)						
No. of patients #	213	209	195	195	184	194
No. ADA positive	4	2	3	4	5	5
% ADA positive	1.9	1.0	1.5	2.1	2.7	2.6
Median titer *	0.75	0.75	1.0	1.0	2.00	2.00
Min/Max titer *	0.5 – 1.0	0.5 – 1.0	1.0 – 4.0	0.5 – 4.0	1.0 - 16.0	1.0 - 50.0
No. NAb positive	0	0	0	0	2	3
% NAb positive	0.0	0.0	0.0	0.0	1.1	1.5
Eylea (N=218)						
No. of patients #	204	201	191	193	189	192
No. ADA positive	3	1	1	1	2	2
% ADA positive	1.5	0.5	0.5	0.5	1.1	1.0
Median titer *	0.5	1.0	1.0	1.0	1.00	1.50
Min/Max titer *	0.5 – 1.0	1.0 – 1.0	1.0 – 1.0	1.0 – 1.0	1.0 - 1.0	1.0 - 2.0
No. NAb positive	0	0	0	0	0	0
% NAb positive	0.0	0.0	0.0	0.0	0.0	0.0

= number of patients with non-missing assessment; SAF = Safety Analysis Set

* ADA titer values do not include the MRD of 18

Table 3: Number and percentage of patients with treatment-induced / treatment-boosted positive ADA until Week 56 - SAF

Statistic	FYB203 (N=215)		Eylea (N=218)		Difference FYB203 – Eylea	
	n	(%)	n	(%)	Estimate (%)	95% CI (%)
Number of evaluable patients	213	(100.0)	204	(100.0)		
Patients with treatment-induced ADA	4	(1.9)	2	(1.0)	0.9	[-1.4 ; 3.2]
Patients with treatment-boosted ADA	0	(0.0)	0	(0.0)	NA	[NA ; NA]

ADA = Anti-Drug Antibody; NA = Not Applicable; 95% CI = 95% Farrington-Manning Confidence Intervals; n = number of patients within the specified category; % = number of patients within the specified category / total number of patients with non-missing assessment; N = total number of patients in analysis set; SAF = Safety Analysis Set

ADA incidence from baseline to Week 56 was very low, consistent with published results for Eylea: treatment-emergent (corresponding to the definition of "treatment-induced") ADA was detected in only 4 out of 213 (1.9%) evaluable patients in the FYB203 group compared to 2 out of 204 (1.0%) in the Eylea group. NAb was detected in 3 patients in the FYB203 treatment group; no patients treated with Eylea had a NAb positive result.

Four out of 213 (1.9%) evaluable patients in the FYB203 group were ADA positive at baseline compared to 3 out of 204 (1.5%) in the Eylea group, consistent with an expected false positive rate of 1% in the confirmatory ADA assay. Treatment with FYB203 or Eylea did not boost the ADA signals in any of these patients.

Impact of immunogenicity on PK:

No conclusion could be drawn regarding the impact of ADA / NAb formation on plasma drug levels because none of the 57 patients in the PK subgroup developed ADA or NAb during the 56-week study period.

Impact of immunogenicity on efficacy:

The low number of patients with ADA or NAb positive results at any time during the 56-week study period precluded a definitive analysis of the impact, if any, of treatment-induced ADA / NAb on efficacy parameters. Nevertheless, detection of ADA or NAb was not associated with any discernible downward inflexion in the efficacy response (BCVA, FCP or FCS) vs. time profiles for individual patients relative to earlier timepoints. Moreover, the profiles for ADA / NAb positive patients were fully contained within the range observed for ADA / NAb negative patients in each treatment group.

Impact of immunogenicity on safety:

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.

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

No dedicated human PK study was conducted, instead the comparability was evaluated in supportive PK analysis in the subset of patients enrolled in phase III study FYB203-03-01. This approach is acceptable in this case as aflibercept is applied intravitreally and PK comparison of systemic exposure is not suitable given the negligible and variable systemic concentrations.

The design of the PK subgroup analysis, including the number nAMD patients for evaluation of aflibercept plasma concentration and the sampling timepoints was discussed during EMA Scientific Advice (EMEA/H/SA/4194/1/2019/III) and the applicant followed the recommendations.

Free as well as total aflibercept were measured and evaluated by the applicant. Free aflibercept is anticipated to be the active drug and levels of free aflibercept are considered more important, however total aflibercept levels add additional information on total levels and possibly differences in accumulation.

A total of 57 patients were included in the PK subgroup (31 in FYB203 and 26 in Eylea group) and PK data were analysed only descriptively. All samples at baseline were below the lower limit of quantification in both treatment arms for free and total aflibercept. Out of the 60 patients who were recruited into the PK sub-study, there were 3 patients with positive baseline levels for total aflibercept detected and these 3 patients were excluded from the PK analysis. Predose plasma concentrations were measured only at Week 0.

The number of patients included in the PK analysis is considered adequate, demographic characteristics were comparable between treatment groups.

The post-dose plasma levels at Week 0 and at Week 8 were evaluated only on Day 2 (48 h) after IVT injection. It would have been preferable to conduct daily sampling on at least two days around the expected Tmax, since Cmax can occur at any time from Day 1 to Day 3 after administration, however this issue is not further pursued. The levels of free aflibercept were in the similar range as previously reported.

At Week 0, plasma concentrations of free aflibercept were slightly higher in the FYB203 group (GM 21.667 ng/mL) compared to Eylea group (GM 14.235 ng/mL), but with large variability (CV 58.9% vs 119.3%).

At Week 8, plasma concentrations of free aflibercept were comparable between treatment groups FYB203 group (GM 22.773 ng/mL) compared to Eylea group (GM 20.512 ng/mL), with reduced but still high variability (CV 55.6% vs 59.9%).

After the first dose the total aflibercept concentrations were somewhat higher with FYB203 compared to Eylea (geom. mean 54.731 ng/mL and 42.000 ng/mL, respectively), however the variability was larger for Eylea compared to FYB203 (geom. CV 102.113% and 51.169%, respectively). After the third dose, the total aflibercept concentrations (and variability) levelled out between treatments.

There was no accumulation of free aflibercept after the third dose as compared to after the first dose (as expected); measured concentrations were generally in the expected range, and very low, attesting that no relevant systemic exposure exists. Total aflibercept concentrations were higher than free aflibercept concentrations, as expected. Total aflibercept concentrations were higher after the third dose compared to after the first dose, reflecting accumulation (as expected).

The systemic exposure was similar between FYB203 and Eylea treatment groups.

Pharmacodynamics

No dedicated PD study have been conducted and none is considered necessary.

The analytical similarity assessment revealed minor differences between FYB203 and Eylea for some forms of glycosylation (FYB203 showing a higher amount of Asn68 non-glycosylation and lower amount of mannosylation, afucosylation and a tendency for lower sialylation). It is agreed that the glycosylation process is inherently variable and thus some variability for individual products as well as differences between products are to be expected. As glycosylation may in theory affect efficacy, PK/PD as well as

immunogenicity, the applicant provided a justification as to why these differences are not clinically relevant.

- VEGFR part:

It has been reported that glycosylation has no effect on target binding (TGA, 2012; Barleon et al., 1997). This was confirmed in all the functional assays investigating the mechanism of action (MoA) of aflibercept (similarity data presented in Analytical similarity section). Furthermore, charge variant fractionation experiments using free-flow electrophoresis showed that fractions differing in their glycosylation profile were highly comparable in their potency and additionally desialylated FYB203 displayed no changes in neutralisation of its targets (refer to quality section).

Theoretically, differences in binding to the mannose receptor and ASGPR could have an impact on PK. However, aflibercept is injected directly into the eye and ocular PK is driven mainly by protein size as the ASGPR is primarily expressed on hepatocytes (Berger et al., 2012; Roggenbuck et al., 2012,). This was confirmed as different levels in sialylation varying by about 7 % in the receptor domain had no impact on ocular PK in rabbits.

- Fc part:

As it was shown that ADCC and CDC are not part of aflibercept's MoA (refer to quality Assessment and section Analytical similarity characterisation), differences known to affect effector function (e.g. afucose levels) will not translate into any biological effects. Also, ASGPR cannot bind to the Fc part (Maverakis et al., 2015) and is not relevant for ocular PK and therefore galactosylation and sialylation levels of the Fc part have no impact on PK.

In summary, it has been shown that differing glycosylation profiles do not have an impact on FYB203 function.

The explanation is pharmacologically plausible.

Immunogenicity

The percentage of ADA-positive patients from the first IP administration through Week 56 was generally low in both treatment arms and ranged between 1.0% and 2.7% in the FYB203 group and between 0.5% and 1.5% for the Eylea overall treatment group. There were 2 patients at week 40 and 3 patients at week 56 who were Nab positive in FYB203 arm and no patient with positive Nab was observed in Eylea arm. The percentage of ADA-positive patients was slightly higher with FYB203 compared to Eylea across all timepoints up to Week 56 and the number of patients with treatment-induced ADA is also slightly higher in FYB203 arm - 4 patients vs 2 patients in Eylea arm. No treatment-boosted ADAs were observed in either treatment group. Based on the provided data and due to overall low incidence of ADAs, the impact of immunogenicity on efficacy and safety is very limited and no concerns arise regarding the impact of immunogenicity on efficacy and safety. Information on the risk of immunogenicity is described in sections 4.4 and 4.8 of SmPC in line with the reference medicinal product.

2.5.4. Conclusions on clinical pharmacology

Based on the data in nAMD patients no significant differences in systemic exposure were observed between FYB203 and Eylea treatment groups. The results are considered supportive of biosimilarity.

The incidence of ADA was low in both study arms and throughout the study and ranged between 1.0% and 2.7% in the FYB203 group and between 0.5% and 1.5% for the Eylea treatment group and most of the subjects were ADA negative. There were 3 patients at week 56 who were Nab positive in FYB203 arm and no patient with positive Nab was observed in Eylea arm.

The incidence of ADA-positive patients was slightly higher in the FYB203 treatment group during the study, but the total number of patients was very low in both study groups and no clinically relevant impact of immunogenicity on efficacy and safety was seen in the study.

2.5.5. Clinical efficacy

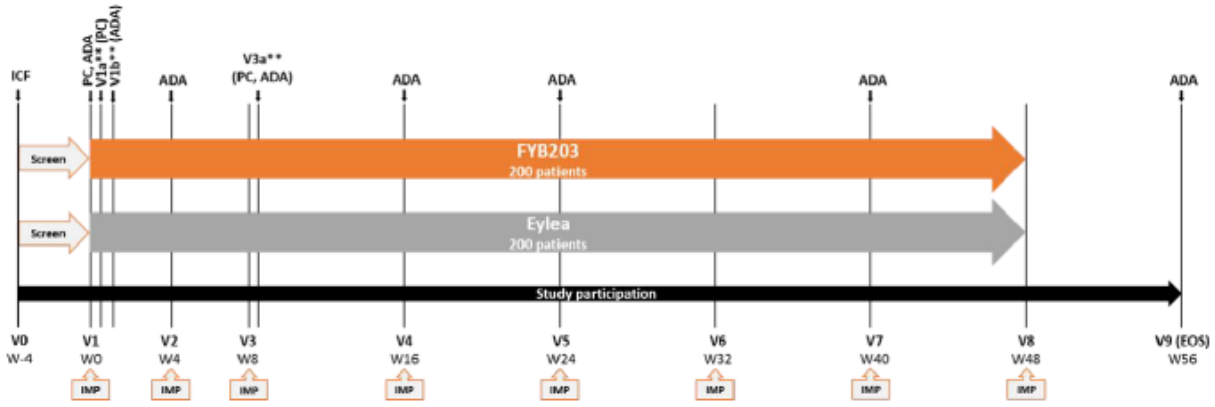
Table 4: Summary of the study FYB203-03-01

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
FYB203-03-01	Completed Randomised Set Total (RAN): N=434 FYB203: 215 Eylea: 219	Randomised, double-masked, parallel group, multicentre study Active Control/ Comparator	2 mg (0.05 mL) every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48	Patients with neovascular AMD

2.5.5.1. Main study(ies)

Study FYB203-03-01

This study was a parallel-group, randomised, active-controlled, double-masked, multi-centre study to demonstrate therapeutic equivalence of FYB203 to Eylea and to compare the safety and immunogenicity in subjects with neovascular age-related macular degeneration (nAMD).



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

Figure 2: Schematic outline of the study FYB203-03-01

Methods

Subjects were randomised 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 subject.

Four hundred (400) subjects were planned to be randomised. A total of 712 subjects were screened in the study of which 434 subjects were randomised. After consent withdrawal by 1 subject randomised to Eylea, 433 subjects started treatment with FYB203 (215) and Eylea (218). A total of 196 subjects in the FYB203 group and 206 subjects in the Eylea group completed the study until Week 56.

Study Participants

The study was conducted in 9 countries, where 77 sites screened at least 1 patient. In total, 72 sites in 9 countries randomised 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).

Main Inclusion criteria

Subjects had to provide written informed consent, be at least 50 years old, and suffer from newly diagnosed, angiographically documented, treatment-naïve CNV lesion secondary to nAMD in the study eye with a BCVA between 20/40 and 20/200 Snellen equivalent. Further, subjects had to have an FCP retinal thickness between ≥300 µm and <800 µm in the study eye and a BCVA of at least 20/200 Snellen equivalent in the fellow eye. Participants had to agree to follow the contraception guidance with exception of post-menopausal women.

Main Exclusion criteria

Subjects were not allowed to participate if they had prior or current ocular treatment, any prior anti-VEGF treatment in either eye, any investigational products to treat ocular diseases other than nAMD within 30 days or 5 half-lives prior to randomisation, any medical history of vitrectomy, macular surgery or other surgical intervention for AMD in the study eye, any history of IVT treatment with corticosteroids or device implantation within 6 months prior to Screening in the study eye. Further, they could not participate if they had particular CNV lesion characteristics or particular current ocular conditions or if they had any diagnosis and signs of nAMD requiring IVT treatment with an anti-VEGF agent within the Screening period or throughout the study in the fellow eye.

Treatments

After randomisation at the Baseline Visit, the subjects received either FYB203 or EU-approved Eylea at a dose of 2 mg (0.05 mL of a 40 mg/mL solution) at 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). The IVT injections were performed by the unmasked IVT administrator. Only a qualified ophthalmologist experienced in IVT injections administered the injection.

Table 5: Summary of treatments in the study FYB203-03-01

	FYB203 (experimental product, proposed biosimilar aflibercept)	Eylea (reference aflibercept, EU-approved)
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	IVT	IVT
Formulation	Solution for injection	Solution for injection
Strength	40 mg/mL solution	40 mg/mL solution

IVT= intravitreal

Prohibited Prior Therapy and Treatment

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

Prohibited Concomitant Therapy and Treatment

• Any IVT anti-VEGF treatment except IMP (FYB203 or Eylea)
• Systemic anti-VEGF agents (e.g., bevacizumab)
• Systemic medications known to be toxic to the lens, retina, or optic nerve including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, and ethambutol
• IVT injection of corticosteroid (e.g., triamcinolone acetonide), IVT device implantation, or periocular injections of corticosteroid
• Treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation)
• Ocular investigational products to treat nAMD
• Systemic investigational products to treat nAMD
• Ocular investigational products to treat ocular diseases other than nAMD

Objectives

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 Eylea compared to Baseline.

The **secondary objectives** were to evaluate and compare:

- changes in foveal centre 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 (anti-drug antibodies [ADAs]) in serum
- local and systemic AEs and SAEs

Outcomes/endpoints

Population	**Patients with nAMD who were randomized to receive either FYB203 or Eylea and who received at least 1 dose of investigational medicinal product, i.e., the FAS.**
Treatment condition	FYB203 vs Eylea (at least 1 IVT injection with a dose of 2 mg).
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.
Population-level summary	Difference in means between FYB203 and Eylea treatment groups.
Intercurrent events and strategy to handle them	
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: 1) discontinuation of treatment, 2) discontinuation of study (including death of the patient) related to safety of the IMP without any post-Baseline assessment of the BCVA, 3) discontinuation of study (including death of the patient) unrelated to safety of the IMP without any post-Baseline assessment of the BCVA and 4) major protocol deviations, which impacted the BCVA assessment until Week 8 as defined during the data review meeting (DRM).	

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 [C_{max}] (based on estimated time to maximum concentration [t_{max}])
    - 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

Sample size

The total sample size of approximately 400 patients for the "EU analysis" was calculated on the basis of a 1:1 randomisation 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.

Further, the change of FCP retinal thickness at Week 4 (Visit 2) compared to Baseline Visit (Visit 1), was planned to be evaluated as a key secondary endpoint for EU/Japan regulatory submissions. The sample size of 200 patients in each treatment group (400 patients in total) provides a power of 82.8% at a 2.5% significance level (e.g. a two-sided 95% CI) when the true difference between the means is 0, the SD is 135 µm and the equivalence interval is [-45.0; 45.0] µm. The equivalence margin of 45.0 µm was chosen in light of the Treat & Extend (T&E) regimen established for the treatment of nAMD with Eylea. Based on the ARIES study (NCT02581891), re-treatment / shortening of dosing intervals could be suspended as long as the subretinal fluid did not exceed 50 µm in thickness (in addition to the absence of intraretinal fluid and the absence of new neovascularisation or haemorrhage) (Mitchell et al. 2021). Therefore, the pre-defined equivalence margin of 45.0 µm ensures that there are no clinically relevant differences between FYB203 and Eylea in terms of changes in FCP thickness.

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 study.

Randomisation and blinding (masking)

Randomisation

Subjects were randomised 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). Randomisation was performed stratified by country and participation in the PK subgroup (yes/no).

All subjects were centrally assigned to randomised study treatment using the IWRS. Before the study was initiated, the login information and directions for the IWRS were provided to each study site.

Treatment masking and unmasking

This was a double-masked study with limited access to the randomisation code.

At each study site there were at least 2 masked staff members (the PI and the VA examiner). There could be also other masked study site staff (e.g., study coordinator, study nurse, OCT technician, photographer).

Due to differences in the products presentation, the IMPs were administered by an unmasked IVT administrator who was responsible for the study injections only. He/she could also perform the post-

dose safety check or tonometry, according to the clinical practice of the study site. The treatment each patient received was only disclosed to the unmasked IVT administrator but not to other study site staff, patient, Sponsor, or study vendors. The treatment codes were held by the IWRS vendor. The unmasked IVT administrator could also have a back-up person.

The PI (or his/her masked study team to whom tasks had been delegated) did all pre- and post-injection assessments (Ophthalmologic examination, SD-OCT, FA and CFP, blood samples collection, and NEI VFQ-25 administration), except measurements of refraction and VA. The masked Investigator(s) also assessed the relationship of all AEs to IMP, including those noted by the unmasked IVT administrator. The PI or the unmasked IVT administrator conducted tonometry to measure the IOP pre and post IVT injection.

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

Except for the unmasked IVT administrator, unmasking was considered only when knowledge of the treatment assignment was deemed essential for the patient's medical care by the PI (or his/her delegate) or a regulatory body. PIs or their delegates were strongly discouraged from requesting the mask be broken for an individual patient, unless there was a patient safety issue that required unmasking and would change patient management. The process for breaking the mask was handled through the IWRS.

Statistical methods

Planned analyses

Analysis sets

The **safety analysis set** (SAF) included all patients who received at least1 injection of study medication in the study eye. Patients were analysed according to the treatment they actually received in the study eye irrespective of their randomised treatment.

The **full analysis set** (FAS) included all patients who received at least 1 injection of study medication in the study eye. Patients were analysed according to the treatment they were randomised to.

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

• Had no major protocol deviations until Week 8 (defined as protocol deviations that would interfere with the interpretation of the BCVA efficacy data at Baseline or at Week 8)

• Had received treatment from the randomised 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.

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 who received treatment from different treatment groups at Visit 1 or Visit 3 or who had a positive total aflibercept concentration at Baseline were excluded from this analysis set.

Primary endpoint analysis

The primary estimand was assessed through a mixed model repeated measurements (MMRM) including the BCVA at Baseline as covariate and region (Japan vs. ROW), visit, randomised treatment group, the Baseline-by-visit interaction and the treatment-by-visit interaction as fixed effects. Within patients'

correlations were modelled 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 hypothesis that both treatments FYB203 and Eylea are therapeutically equivalent with respect to the primary efficacy endpoint was tested in terms of a 2-sided equivalence test. The equivalence margin of 3 ETDRS letters (as rounded to the nearest integer) was tested by the following hypotheses corresponding to the primary estimand:

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

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

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

The difference between the least squares (LS) means of the treatment groups and the corresponding 2-sided 90.4% and 95.2% CI were estimated from the MMRM to address different regulatory requirements regarding the confidence level. The significance level alpha was reduced from 0.5 to 0.48 and from 0.025 to 0.024, respectively, to control the overall type 1 error in the light of the masked sample size review.

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 Eylea.

If the respective CI was completely contained in the interval]-3.5;3.5[ETDRS letters, H_0 could be rejected and equivalence of FYB203 and Eylea could be concluded (rounded to the next integer, this corresponded to an equivalence margin of 3 ETDRS letters).

The MMRM assumption of normal distribution of the residuals was assessed via respective residual plots.

Handling of missing data

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.

Supportive analyses

For the primary estimand, sensitivity analyses as described below were planned. The relevance of the sensitivity analyses was evaluated during the DRM considering the number of patients that fell into the respective category.

For the primary statistical analysis using the MMRM, it was assumed that post-treatment assessments are missing at random (MAR) and that missing assessments were thus not related to any efficacy or safety difference between the 2 treatments. To investigate this assumption, the MMRM was repeated including additional covariates:

- Patient discontinued study prior to Week 24 (Yes/No)
- Patient discontinued treatment prior to Week 24 (Yes/No)
- Patient had any major protocol deviation (Yes/No)

For the primary MMRM, it was assumed that the use of an ancillary chart did not influence the BCVA results. To investigate this assumption, the MMRM was repeated including the use of an ancillary chart (yes/no) at each visit as additional covariate.

For the primary MMRM, it was assumed that patients with similar post-treatment values until Week 24 behave similarly. The MMRM was repeated including only data until analysis visit Week 8 or all data until Week 56 to investigate a possible influence of this definition on the estimation of treatment differences.

For the primary analysis, it was assumed that there is a correlation between the different visits within a patient. To investigate this further, the change from Baseline to Week 8 in BCVA by ETDRS letters was analysed with an analysis of covariance (ANCOVA) model instead of an MMRM. The 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 performed based on observed cases, i.e., only patients with a BCVA at Week 8 analysis visit were included.

A further sensitivity analysis to the MMRM was performed where missing BCVA assessments at Week 8 were imputed using multiple imputation (MI); and an ANCOVA model was used on the imputed datasets to analyse the primary efficacy endpoint. MI used the Baseline BCVA value as well as region and treatment group as covariates for imputation. A monotone imputation approach was used since it was expected that the covariates Baseline BCVA, region and treatment group would not be missing for any patient. The predictive mean matching method was used to impute missing values of the BCVA change from Baseline to ensure that imputed values would be in the range of observed values. Instead of the default of 25 imputations, 100 imputations and a seed of 2143 was used. The ANCOVA model was the same as specified above for the previous sensitivity analysis and was conducted separately for each of the 100 imputed datasets. The results were then combined to the final result.

To further investigate the assumption of MAR, tipping point analyses assuming "missing not at random" were performed. A sensitivity parameter (θ) was introduced for each treatment (-θ for the FYB203 treatment group and +θ for Eylea, +θ for the FYB203 and -θ for Eylea, 0 for FYB203 and +θ or -θ for Eylea, +θ or -θ for FYB203 and 0 for Eylea). The MAR assumption with θ = 0 for both treatments was the starting point and was changed in fixed steps of ETDRS letters in both directions or only in 1 direction to increase the difference between the treatment groups. Missing values were imputed within the same treatment group using a monotone regression imputation model, 100 imputations, and Baseline BCVA and region as covariates. An ANCOVA was used to analyse the imputed datasets, also including Baseline BCVA and region as covariates.

Supplemental estimands for the primary efficacy endpoint

The following supplemental estimands (referring to the primary efficacy endpoint) were assessed:

- The mean difference between the randomised treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, excluding patients from the FAS with major protocol deviations which directly impact the BCVA assessments until Week 8 (Visit 3).
- The mean difference between the randomised treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, excluding patients from the FAS who discontinued treatment before Week 8 or do not have a Week 8 BCVA assessment.

- The mean difference between the randomised treatment groups, FYB203 and Eylea, in the primary efficacy endpoint for the study eye, based on the PPS (this secondary estimand is a combination of the previous ones stated above).

The supplemental estimands described above were assessed using the same statistical method as for the primary efficacy analysis.

Additionally, the following supplemental estimand was assessed:

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

The following supplemental estimands were investigated to further investigate the assumptions for the primary estimand:

- For the primary analysis, it was assumed that discontinuation of treatment would have the same impact on the following measurements in both treatment groups and could therefore be neglected. To investigate this assumption, the primary MMRM was repeated on data where all assessments following discontinuation of treatment are set to missing. This strategy follows the "While on treatment strategy" as described in the ICH E9 addendum on estimands.

- For the primary analysis, it was assumed that single missed injections would not have an influence on the following assessments. To investigate this assumption, the primary MMRM was repeated based on data, where all assessments following missed injection visits are set to missing. Missed injection visits were defined as analysis visits where no injection could be mapped to the defined visit window. Only the BCVA assessment following this missed injection visit was set to missing and assessments collected thereafter could still be included in the analysis.

- For the primary analysis, it was assumed that major protocol deviations would have the same impact on the following measurements in both treatment groups and can therefore be neglected. To investigate this assumption, the primary MMRM was repeated based on data, where all assessments following major protocol deviations were set to missing.

- Certain protocol deviations would only have an impact on single BCVA measurements, e.g., prohibited medications that where taken only for a certain time period and are washed out thereafter. These deviations were identified during the DRM and all corresponding BCVA assessments would have been set to missing and the primary MMRM would have been repeated based on this data. However, since only very few of these protocol deviations occurred, this analysis was not performed.

Planned subgroup analyses

The primary efficacy analysis was repeated within pre-defined subgroups and results were displayed in a forest plot. The following subgroups were used:

- Gender (female and male)
- Use of an ancillary chart up to Week 56 (yes/no, Patients who only used the ancillary chart for single assessments will be excluded from this analysis)
- ADA status (any positive treatment-emergent ADA as defined in Section 7.13 of the SAP during study versus no positive treatment-emergent ADA during study up to Week 56)

- Total lesion area at Baseline (< 9mm2 versus ≥ 9mm2, cut-off confirmed during DRM)
- Lesion type at Baseline (types as reported by GRADE, calculations not to be done in subgroups where the sample size is too small leading to non-calculable estimates)
- Injection syringe use (medical devices for IMP preparation and administration procedure as provided by the Sponsor versus other syringes used (at any time during study))
- Region (Japan versus ROW)

Error probabilities, adjustment for multiplicity and interim analyses

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 1 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 for the originally planned "US analysis" of the first 320 patients. 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.

Changes from protocol-specified analyses

The following change, concerning the scope of reporting, occurred after regulatory feedback from the FDA in February 2023:

Originally, it was planned to perform a US-specific analysis based on 40-week data of the first 320 treated patients. Further, the planned analysis on 24-week data based on all patients was planned to be submitted in the EU only. Due to regulatory feedback from the FDA in February 2023, the planned 24-week analysis on all patients was performed for the US criteria using a 5% overall significance level and for the EU/Japan criteria using a 2.5% significance level overall.

Results

Participant flow

Study initiation date: Jul 21, 2020 (first patient, first visit), Study completion date: May 18, 2023 (last patient, last visit), Patients were treated between 12-Aug-2020 and 30-Mar-2023

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

Up to Week 56, 19 (8.8%) patients in the FYB203 group and 12 (5.5%) patients in the Eylea group discontinued the study prematurely, for the following reasons:

In the FYB203 group, 5 patients experienced AEs (PTs: Oesophageal carcinoma stage 0, Cerebrovascular accident, COVID-19, Rhegmatogenous retinal detachment and Subretinal fluid), 4 patients died (1 patient experienced PTs Pulmonary fibrosis and Cardiac failure, 1 patient experienced PTs COVID-19, COVID-19 pneumonia and Cardiac failure, 1 patient experienced PTs Aspiration, Toxic shock syndrome and Ileus, 1 patient experienced PT Acute myeloid leukaemia), 3 patients withdrew consent, 1 patient

was lost to follow-up, 1 patient had a protocol violation (related to the geopolitical situation in the Ukraine) and 5 patients discontinued due to other reasons (in 4 cases related to the geopolitical situation in the Ukraine, 1 patient refused to participate in the continuation of the study due to the improvement of vision).

In the Eylea group, 7 patients withdrew consent, 2 patients discontinued following physician decision, 1 patient died (PT: Cardiac failure), 1 patient was lost to follow-up and 1 patient discontinued due to other reasons (related to the geopolitical situation in the Ukraine.

A total of 196 (91.2%) patients in the FYB203 group and 206 (94.1%) patients in the Eylea group completed the study until Week 56.

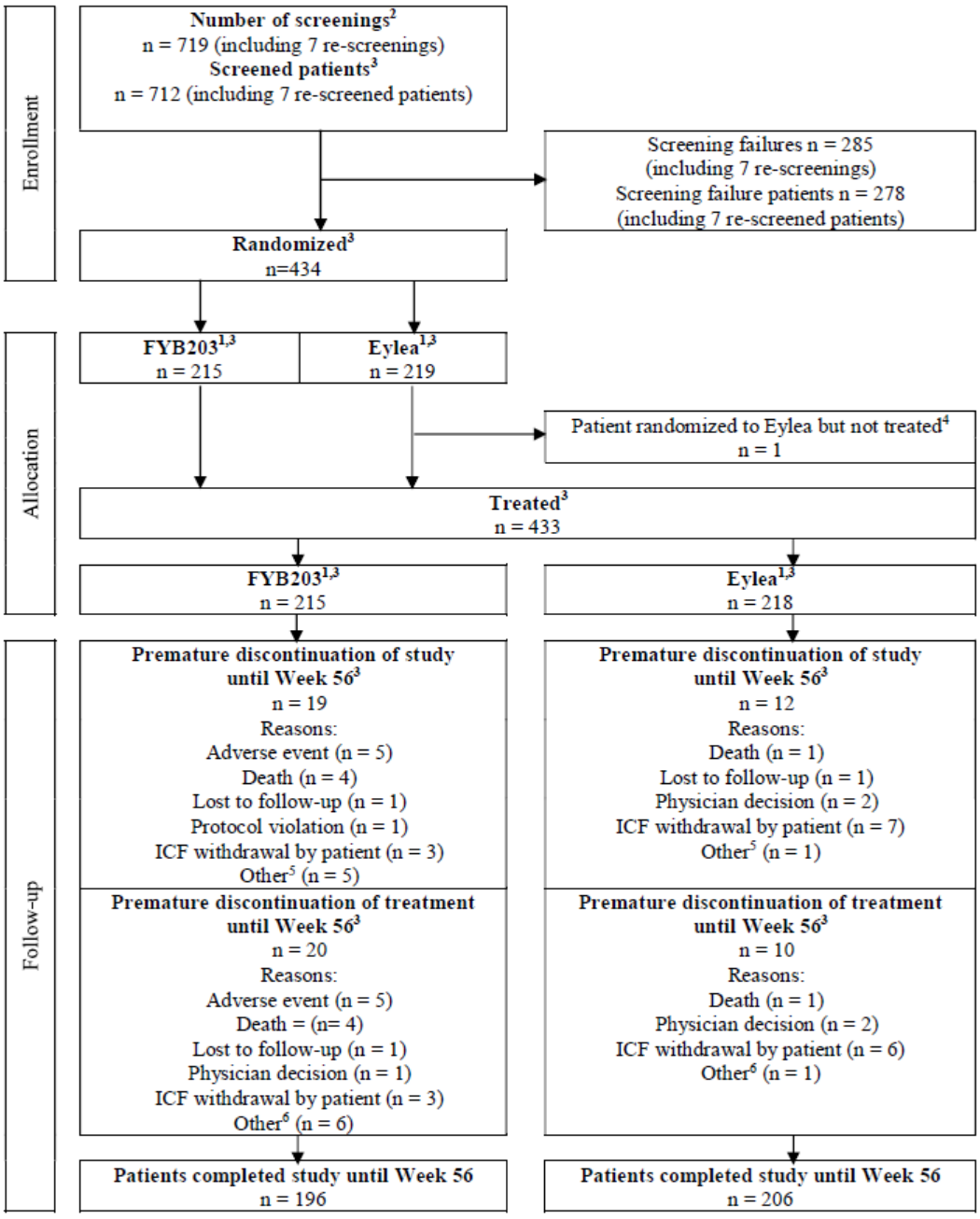


Figure 3: Patient disposition diagram

Conduct of the study

Protocol amendments

Protocol Version 1.0 was not implemented and the first patients were enrolled under Protocol Version 2.0.

The CSP was amended once; The most important changes introduced in Protocol Version 3.0 (Amendment 1.0) were as follows:

- The planned statistical analyses were updated: the originally planned main US analysis (after completion of 24 weeks of treatment) was removed. The final "US analysis" (after 40 weeks of treatment, US sample size), the main "EU analysis" (after 24 weeks, all patients), and the final

"EU/Japan analysis" (after 56 weeks, all patients) were to be performed sequentially instead, with 3 separate database locks.
- Potential increase in the sample size estimation for "US analysis".
- The number of patients were updated to reflect the final numbers of randomised patients (1) overall and (2) in Japan, including:
    - study sites updates (i.e., from 80 to 85 study sites and inclusion of additional countries enrolling participants).
    - interim masked review of sample size performed in November 2021 confirming that the original assumptions for the sample size calculation were correct.
- Details of MMRM model were adapted: removed patient as random effect and added Baseline-by-visit interaction as fixed effect.

The changes were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unmasking.

Protocol deviations

In total, there were 27 (6.2%, Table 6) patients with major protocol deviations, which led to the exclusion from the PPS. Overall, the number of patients with major protocol deviations was well balanced between the treatment groups (14 patients in the FYB203 group and 13 patients in the Eylea group).

Please note that programmed protocol deviations and clinical research associate (CRA) reported protocol deviations might overlap for some protocol deviations and patients.

Table 7, 8, 9, and 10, report respectively: demographics, baseline diagnosis characteristics, baseline ophthalmological parameters, number of patients in each analysis set/reasons for exclusion from each analysis set.

Table 6: Number and percentage of patients with any major protocol deviation or major intercurrent event (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)
IMP incompliance	2	(0.9)	2	(0.9)	4	(0.9)
Temperature excursion of IMP at Visit 2 (CRA reported protocol deviation)	2	(0.9)	0	(0.0)	2	(0.5)
Time window of IMP at Visit 2 (CRA reported protocol deviation)	0	(0.0)	2	(0.9)	2	(0.5)
Study treatment incompliance	2	(0.9)	2	(0.9)	4	(0.9)
Study treatment incompliance (programmed protocol deviation)	2	(0.9)	2	(0.9)	4	(0.9)
Visit schedule deviation	2	(0.9)	2	(0.9)	4	(0.9)
Visit schedule deviation, V3 (CRA reported protocol deviation)	1	(0.5)	2	(0.9)	3	(0.7)
Visit schedule deviation, V3, COVID19 related (CRA reported protocol deviation)	1	(0.5)	0	(0.0)	1	(0.2)
Inclusion criteria	1	(0.5)	2	(0.9)	3	(0.7)
Inclusion criterion 05 (CRA reported protocol deviation)	1	(0.5)	2	(0.9)	3	(0.7)
Positive Baseline total aflibercept concentration	1	(0.5)	2	(0.9)	3	(0.7)
Positive Baseline total aflibercept concentration (programmed protocol deviation)	1	(0.5)	2	(0.9)	3	(0.7)
Violation of inclusion criterion	1	(0.5)	2	(0.9)	3	(0.7)
Violation of inclusion criterion 05 (programmed protocol deviation)	1	(0.5)	2	(0.9)	3	(0.7)
Violation of inclusion criterion 08 (programmed protocol deviation)	1	(0.5)	2	(0.9)	3	(0.7)
BCVA: wrong sequence of assessments	1	(0.5)	1	(0.5)	2	(0.5)
BCVA at Baseline (CRA reported protocol deviation)	1	(0.5)	1	(0.5)	2	(0.5)
Randomization	1	(0.5)	1	(0.5)	2	(0.5)
Randomization (CRA reported protocol deviation)	1	(0.5)	1	(0.5)	2	(0.5)
Blinding	0	(0.0)	1	(0.5)	1	(0.2)
Possible unblinding of PI (CRA reported protocol deviation)	0	(0.0)	1	(0.5)	1	(0.2)
Exclusion criterion	1	(0.5)	0	(0.0)	1	(0.2)
Exclusion criterion 03 (CRA reported protocol deviation)	1	(0.5)	0	(0.0)	1	(0.2)
Violation of exclusion criterion	1	(0.5)	0	(0.0)	1	(0.2)
Violation of exclusion criterion 03 (programmed protocol deviation)	1	(0.5)	0	(0.0)	1	(0.2)

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

Table 7: Demographics (FAS, N=433)

Baseline data

Parameter Category	FYB203 N=215	Eylea N=218	Total N=433
Gender [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%)	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 [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%)

Table 8: 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

Table 9: Baseline ophthalmological 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 [mm²]			
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

Table 10: Number of patients in each analysis set and reasons for exclusion from each analysis set (all randomised patients, N=434)

Numbers analysed

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)

Outcomes and estimation

For all data derivations and statistical analyses, SAS® Version 9.4 was used.

Primary efficacy analysis

The primary efficacy endpoint, the change in BCVA by ETDRS letters from Baseline to Week 8 (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.

Table 11: MMRM: Comparison of change in BCVA (ETDRS letters) from baseline to week 8, including data up to week 24 (US and EU analyses, FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation 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					

BCVA = best corrected visual acuity, CI = confidence interval, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error of LS mean, V = Visit

[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; 3.5 letters[, FYB203 and Eylea were considered equivalent.

Source: Table 14.1.4.1, Table 14.2.1.1 ("US Analysis"), Table 14.2.1.2 ("EU Analysis")

Sensitivity analyses

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

All sensitivity analyses supported the result of the primary analysis, i.e., that the therapeutic equivalence of the 2 treatments with respect to the primary efficacy endpoint is given.

Table 12: Summary of sensitivity analyses displaying least squares mean difference between FYB203 and Eylea in BCVA (ETDRS letters) change from baseline to week 8 (US and EU analyses, FAS, N=433)

Method, set, data	LS mean difference[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 of study 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
MMRM, FAS Data up to Week 56	1.0	0.76	[-0.3; 2.2] Table 14.2.2.8	[-0.6; 2.5] Table 14.2.3.8	yes

ANCOVA = Analysis of covariance, BCVA = best corrected visual acuity, CI = confidence interval, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the analysis set, SE = standard error of LS mean

[1] Difference calculated as FYB203 – Eylea

Tipping point analyses

Additionally, tipping point analyses for the primary efficacy endpoint to assess possible deviations from the MAR assumption underlying the MMRM analyses were performed. The analyses used MI under a missing not at random assumption and added various constant shifts of θ in various directions to the imputed values in each treatment group. The imputed datasets were then analysed with an ANCOVA model to calculate the LS means and CIs. The shift was broadened with each analysis performed until the equivalence criterion was no longer achieved.

The smallest tipping point that would lead to a conclusion of lower efficacy of FYB203 compared to Eylea was a shift of 0 in the Eylea group and a shift of -88 or -79 letters in the FYB203 group for the US analysis and the EU analysis, respectively (last row in Table 13). Considering the observed data in the FYB203 group with a range of -16 to 31 letters for the change in BCVA from Baseline to Week 8 (Table 13) and the fact that imputed values would also be in this range, this would mean that changes for patients with missing data would have to be between -95 and -48 letters. The likelihood that all these patients would have much worse changes than the observed minimum changes is regarded as very low.

The tipping point analysis thus confirms the robustness of the therapeutic equivalence conclusion.

Table 13: Summary of Tipping Point Analyses Displaying Least Squares Mean Difference Between FYB203 and Eylea in BCVA (ETDRS Letters) Change From Baseline to Week 8, derived from ANCOVA after Multiple Imputation (US and EU Analyses, FAS, N=433)

Tipping points, Δ (FYB203–Eylea)	2-sided 90.4% CI		2-sided 95.2% CI	
	Eylea	FYB203	Eylea	FYB203
Shift in imputation (θ)	+53	-53	+48	-48
Δ (FYB203–Eylea)	**-1.7 [-3.54; 0.17]**		**-1.4 [-3.53; 0.67]**	
Shift in imputation (θ)	-22	+22	-18	+18
Δ (FYB203–Eylea)	**2.1 [0.71; 3.53]**		**1.9 [0.29; 3.54]**	
Shift in imputation (θ)	+103	0	+92	0
Δ (FYB203–Eylea)	**-1.3 [-3.52; 0.83]**		**-1.1 [-3.50; 1.31]**	
Shift in imputation (θ)	-44	0	-36	0
Δ (FYB203–Eylea)	**2.0 [0.51; 3.50]**		**1.8 [0.13; 3.53]**	
Shift in imputation (θ)	0	+38	0	+30
Δ (FYB203–Eylea)	**2.1 [0.59; 3.54]**		**1.8 [0.17; 3.51]**	
Shift in imputation (θ)	0	-88	0	-79
Δ (FYB203–Eylea)	**-1.4 [-3.53; 0.63]**		**-1.2 [-3.52; 1.12]**	

ANCOVA = analysis of covariance, BCVA = best corrected visual acuity, CI = confidence interval, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, N = total number of patients in the analysis set, Δ (FYB203–Eylea) = LS mean difference between FYB203 and Eylea

The 2-sided 90.4% and 95.2% confidence intervals were based on normal approximation.

Multiple imputation using Baseline BCVA, region (Japan vs. Rest of world) and treatment as covariates was used for imputation of missing assessments.

Δ (FYB203–Eylea) LS mean estimates were adjusted for region (Japan vs. Rest of world) and Baseline BCVA [letters].

If CIs for difference in LS means were completely contained in the interval]-3.5; 3.5[letters, FYB203 and Eylea were considered equivalent. This table presents the tipping points, i.e., the smallest imputation shifts where the CIs for difference in LS means were not contained in the interval of]-3.5; 3.5[letters.

Source: Table 14.2.2.9 ("US analysis"), Table 14.2.3.9 ("EU analysis")

Supplemental analyses

Supplemental analyses (Table 14) were performed using MMRM models restricted to the PPS population, to modified FAS populations, or using different approaches for handling of intercurrent events. As such, these analyses represent different (supplemental) estimands that differ in some properties from the primary estimand.

All supplemental analyses showed a similar difference between FYB203 and Eylea for the change in BCVA from Baseline to Week 8.

Table 14: Summary of supplemental analyses displaying least squares mean difference between FYB203 and Eylea in BCVA (ETDRS letters) change from baseline to week 8 (US and EU analyses)

Method, set, data	LS mean difference [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 Week 24, excluding patients with major protocol deviations influencing BCVA until Week 8	0.8	0.79	[-0.5; 2.1] Table 14.2.4.1	[-0.8; 2.4] Table 14.2.5.1	yes
MMRM, FAS Data up to Week 24, excluding patients who discontinued treatment before Week 8 or did not have a Week 8 BCVA	1.0	0.77	[-0.3; 2.3] Table 14.2.4.2	[-0.5; 2.5] Table 14.2.5.2	yes
MMRM, PPS Data up to Week 24	0.8	0.79	[-0.5; 2.1] Table 14.2.4.3	[-0.8; 2.4] Table 14.2.5.3	yes
ANCOVA, FAS Multiple imputation for all patients excluded from the PPS	0.8	0.79	[-0.5; 2.2] Table 14.2.4.4	[-0.7; 2.4] Table 14.2.5.4	yes
MMRM, FAS Data up to Week 24 while on treatment	This analysis was not performed. Less than 10 patients had BCVA values until Week 24 that were assessed after discontinuation of treatment. Table 14.2.4.5 and Table 14.2.5.5				
Method, set, data	**LS mean difference [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 excluding assessments after missed injections	0.9	0.77	[-0.4; 2.2] Table 14.2.4.6	[-0.6; 2.4] Table 14.2.5.6	yes
MMRM, FAS Data up to Week 24 excluding assessments after major protocol deviations	0.8	0.78	[-0.5; 2.1] Table 14.2.4.7	[-0.8; 2.3] Table 14.2.5.7	yes
MMRM, FAS Data up to Week 24 excluding assessments directly after specific protocol deviations with impact on BCVA	Analysis not performed due to low number of relevant protocol deviations. Table 14.2.4.8 and Table 14.2.5.8				

ANCOVA = analysis of covariance, BCVA = best corrected visual acuity, CI = confidence interval (based on normal approximation), ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, PPS = per protocol set, SE = standard error of LS mean

[1] Difference calculated as FYB203 – Eylea

Source: directly in the table

Secondary endpoints

Change in Foveal Centre Point Retinal Thickness From Baseline to Week 4

This endpoint (Table 15) was tested in a confirmatory way as key secondary endpoint for the EU-specific analysis only, for the US analysis all secondary endpoints were weighted equally and analysed without formal hypothesis testing.

Table 15: Comparison of change in foveal centre retinal thickness (µm) from baseline to week 4 including data up to week 24 (EU analysis, FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 95.2% CI
Week 4 (V2)						
FYB203	215	206	9	-171.4	10.32	[-191.9; -150.9]
Eylea	218	210	8	-166.9	10.39	[-187.5; -146.3]
Difference: FYB203 - Eylea				**-4.5**	**10.03**	**[-24.4; 15.4]**

CI = confidence interval, FAS = full analysis set, FCP = foveal center point, LS = least squares, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, MMRM = Mixed Model Repeated Measures, SE = standard error of the LS mean, V = Visit

The 2-sided 95.2% CI was based on normal approximation.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 4 assessments were considered if they have at least 1 post-Baseline FCP value until Week 24.

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

Source: Table 14.1.4.1, Table 14.2.6.1.1.1

To account for missing values in a different way, MI followed by an ANCOVA was performed on the FAS and the PPS and served as a sensitivity analysis.

In the PPS, the estimated LS mean difference of -7.5 µm (95.2% CI: [-28.2 µm; 13.1 µm]) between the treatments was similar to the FAS.

In the FAS, the ANCOVA including MI showed a similar estimated LS mean difference between the 2 treatments of -7.1 µm (95.0% CI: [-27.3 µm; 13.1 µm]).

Change in Foveal Central Subfield Retinal Thickness From Baseline to Week 4

Table 16: Comparison of change in fcs retinal thickness (µm) from baseline to week 4 including data up to week 24 (FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 95.0% CI
Week 4 (V2)						
FYB203	215	212	3	-163.5	9.55	[-182.3; -144.7]
Eylea	218	215	3	-157.4	9.63	[-176.3; -138.4]
Difference: FYB203 - Eylea				**-6.2**	**9.22**	**[-24.3; 12.0]**

CI = confidence interval, FAS = full analysis set, FCS = foveal central subfields, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error of the LS mean, V = Visit

The 2-sided 95.2% CI was based on normal approximation.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 4 assessments were considered if they have at least 1 post-Baseline FCS value until Week 24.

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

Source: Table 14.1.4.1, Table 14.2.6.4.1.1

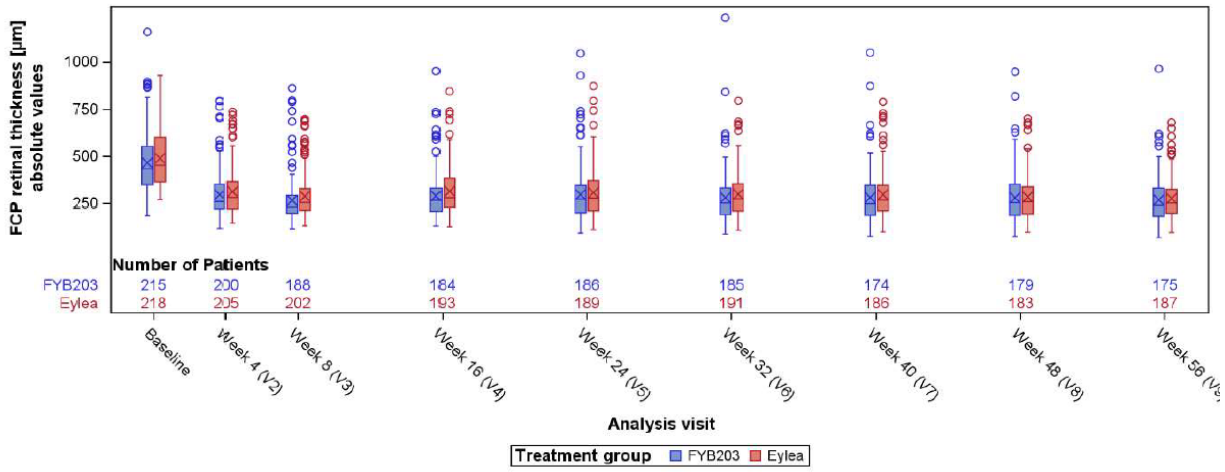
In the PPS, the estimated LS mean difference of -6.2 µm (95.0% CI: [-24.9 µm; 12.4 µm]) between the treatments was similar to the FAS.

In the FAS, the ANCOVA including MI showed a similar estimated LS mean difference between the 2 treatments of -5.9 µm (95.0% CI: [-24.1 µm; 12.4 µm]).

Changes in Foveal Centre Point and Foveal Central Subfield Retinal Thickness From Baseline to Week 24, Week 40 and Week 56

Foveal Centre Point Retinal Thickness

Figure 11-3 shows the absolute FCP retinal thickness by treatment group until Week 56 in the FAS. The 2 treatment groups showed similar FCP retinal thickness measurements at Baseline and at each post-Baseline visit. In the FAS, the overall Baseline median (IQR) FCP retinal thickness was 440.0 (354.0 - 574.0) µm. At Week 24, the median (IQR) reduced to 274.0 (208.0 - 358.0) µm. The reduction sustained throughout the study, resulting in an overall median (IQR) of 261.5 (200.5 - 346.0) µm at Week 40 and a median (IQR) of 248.0 (191.0 - 328.0) µm at Week 56.



Legend below next figure.
Source: Figure 14.2.6.3.4.1

Figure 4: Absolute FCP retinal thickness (µm) from baseline to week 56 (FAS, N=433)

Table 17: Comparison of change in FCP retinal thickness (µm) from baseline to week 24, week 40 and week 56 (FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 95.0% CI
Week 24 (V5), including data up to Week 24						
FYB203	215	206	9	-172.1	11.87	[-195.4; -148.7]
Eylea	218	210	8	-163.8	11.91	[-187.2; -140.4]
Difference: FYB203 - Eylea				**-8.2**	**12.98**	**[-33.7; 17.3]**
Week 40 (V7), including data up to Week 56						
FYB203	215	206	9	-193.6	11.35	[-215.9; -171.3]
Eylea	218	213	5	-185.7	11.32	[-208.0; -163.5]
Difference: FYB203 - Eylea				**-7.9**	**12.37**	**[-32.2; 16.4]**
Week 56 (V9), including data up to Week 56						
FYB203	215	206	9	-207.9	10.84	[-229.2; -186.7]
Eylea	218	213	5	-202.7	10.81	[-224.0; -181.5]
Difference: FYB203 - Eylea				**-5.2**	**11.41**	**[-27.7; 17.2]**

CI = confidence interval, FAS = full analysis set, FCP = foveal center point, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error of the LS mean, V = Visit

The 2-sided 95.0% CI was based on normal approximation.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 24/Week 40/Week 56 assessments were considered if they had at least 1 post-Baseline FCP value until Week 24/Week 56/Week 56.

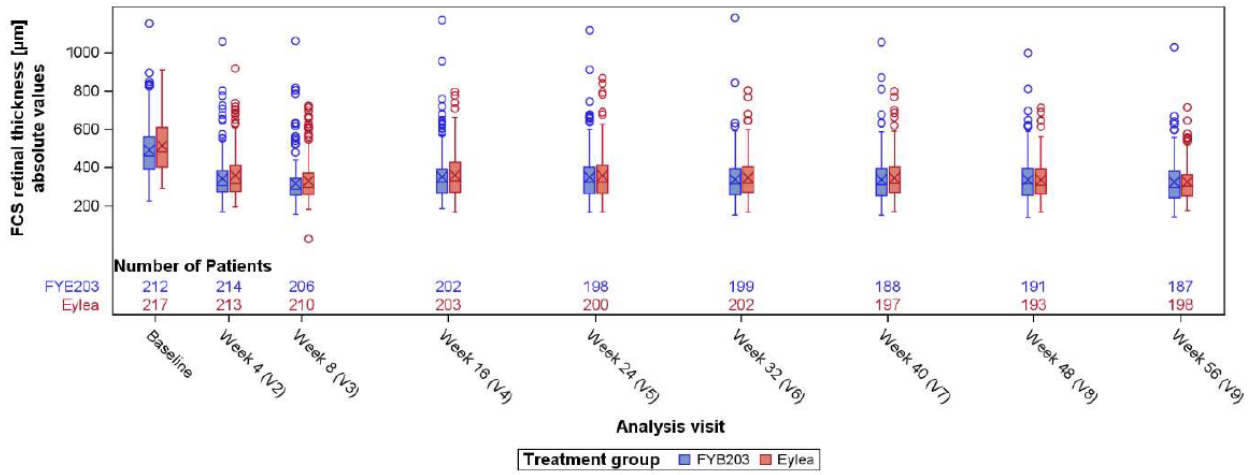
[b] Estimates are adjusted for Baseline FCP, region (Japan vs. Rest of world), treatment, visit, treatment-visit-interaction and Baseline-visit-interaction.

Source: Table 14.1.4.1, Table 14.2.6.3.8.1 (Week 24), Table 14.2.6.3.9.1 (Week 40), Table 14.2.6.3.10.1 (Week 56)

In the PPS, the estimated LS mean differences between the 2 treatment groups of -12.5 µm (95.0% CI: [-39.1 µm; 14.0 µm]) at Week 24, -11.4 µm (95.0% CI: [-36.2 µm; 13.4 µm]) at Week 40 and -9.1 µm (95.0% CI: [-32.3 µm; 14.0 µm]) at Week 56 were similar to the FAS.

Foveal Central Subfield Retinal Thickness

Figure 11-5 shows the absolute FCS retinal thickness by treatment group until Week 56 in the FAS. The 2 treatment groups showed similar FCS retinal thickness measurements at Baseline and at each post-Baseline visit. In the FAS, the overall Baseline median (IQR) FCS retinal thickness was 472.0 (398.0 – 585.0) µm. At Week 24, the median (IQR) reduced to 323.0 (266.0 – 409.0) µm. The reduction was sustained throughout the study, resulting in an overall median (IQR) of 316.0 (262.0 – 399.0) µm at Week 40 and a median (IQR) of 303.0 (250.0 – 373.0) µm at Week 56.



Legend below next figure.
Source: Figure 14.2.6.4.4.1

Figure 5: Absolute FCS retinal thickness (µm) from baseline to week 56 (FAS, N=433)

Table 18: Comparison of change in FCS retinal thickness (µm) from baseline to week 24, week 40 and week 56 (FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 95.0% CI
Week 24 (V5), including data up to Week 24						
FYB203	215	212	3	-159.3	10.73	[-180.3; -138.2]
Eylea	218	215	3	-153.0	10.77	[-174.1; -131.8]
Difference: FYB203 - Eylea				**-6.3**	**11.49**	**[-28.9; 16.3]**
Week 40 (V7), including data up to Week 56						
FYB203	215	212	3	-180.7	10.23	[-200.8; -160.6]
Eylea	218	215	3	-176.9	10.24	[-197.0; -156.7]
Difference: FYB203 - Eylea				**-3.8**	**10.99**	**[-25.4; 17.8]**
Week 24 (V5), including data up to Week 56						
FYB203	215	212	3	-192.9	9.80	[-212.2; -173.7]
Eylea	218	215	3	-192.3	9.80	[-211.6; -173.1]
Difference: FYB203 - Eylea				**-0.6**	**10.16**	**[-20.6; 19.4]**

CI = confidence interval, FAS = full analysis set, FCS = foveal central subfield, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error of the LS mean, V = Visit

The 2-sided 95.0% CI was based on normal approximation.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 24/Week40/Week 56 assessments were considered if they had at least 1 post-Baseline FCS value until Week 24/Week 56/Week 56.

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

Source: Table 14.1.4.1, Table 14.2.6.4.8.1 (Week 24), Table 14.2.6.4.9.1 (Week 40), Table 14.2.6.4.10.1 (Week 56)

In the PPS, the estimated LS mean differences between the 2 treatment groups of -8.3 µm (95.0% CI: [-31.7 µm; 15.2 µm]) at Week 24, -5.4 µm (95.0% CI: [-27.4 µm; 16.6 µm]) at Week 40 and -2.8 µm (95.0% CI: [-23.4 µm; 17.7 µm]) at Week 56 were similar to the FAS.

Change in BCVA From Baseline to Week 24, Week 40 and Week 56

Table 19: Comparison of change in BCVA (ETDRS Letters) from baseline to week 24, week 40 and week 56 (FAS, N=433)

Week (Visit) Treatment group Difference	N	MMRM LS estimation n[a]	nmiss[a]	LS mean[b]	SE[b]	2-sided 95.0% CI
Week 24 (V5), , including data up to Week 24						
FYB203	215	215	0	6.5	0.82	[4.9; 8.1]
Eylea	218	218	0	6.2	0.82	[4.6; 7.8]
Difference: FYB203 - Eylea				**0.3**	**0.93**	**[-1.5; 2.2]**
Week 40 (V7), including data up to Week 56						
FYB203	215	215	0	7.7	0.87	[5.9; 9.4]
Eylea	218	218	0	6.3	0.87	[4.6; 8.0]
Difference: FYB203 - Eylea				**1.4**	**1.02**	**[-0.6; 3.4]**
Week 56 (V9), including data up to Week 56						
FYB203	215	215	0	7.5	0.92	[5.7; 9.3]
Eylea	218	218	0	6.2	0.91	[4.4; 8.0]
Difference: FYB203 - Eylea				**1.3**	**1.09**	**[-0.9; 3.5]**

BCVA = best corrected visual acuity, CI = confidence interval, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error, V = Visit

The 2-sided 95.0% CI was based on normal approximation.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 24/Week 40/Week 56 assessments were considered if they have at least 1 post-Baseline BCVA value until Week 24/Week 56/Week 56.

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

Source: Table 14.1.4.1, Table 14.2.6.2.12.1 (Week 24), Table 14.2.6.2.13.1 (Week 40), Table 14.2.6.2.14.1 (Week 56)

In the PPS, the estimated LS mean differences between the 2 treatment groups of 0.1 ETDRS letter (95.0% CI: [-1.8; 2.0]) at Week 24, 1.0 ETDRS letter (95.0% CI: [-1.0; 3.0]) at Week 40 and 0.9 ETDRS letter (95.0% CI: [-1.3; 3.1]) at Week 56 were similar to the FAS.

Gain or Loss of Best Corrected Visual Acuity by ≥ 5, 10 and 15 ETDRS Letters From Baseline to Week 24, Week 40 and Week 56

Table 20 summarises the proportion of patients with specific categories of gains or losses in BCVA from Baseline to Week 24, Week 40 and Week 56.

At Week 24, the proportion of patients who gained or lost 5 to 9, 10 to 14, or more than 15 ETDRS letters compared to Baseline were comparable between the FYB203 and Eylea groups. Overall, approximately 20% of patients gained 15 or more ETDRS letters, 10 to 14 ETDRS letters or 5 to 9 ETDRS letters, each. No relevant change in BCVA, i.e. gain or loss up to 4 ETDRS letters, was experienced by 27.2% of patients. A total of 10.7% of patients lost at least 5 letters.

At Week 40, 23.3%, 21.2% and 19.7% of the patients overall gained 15 or more, 10 to 14, or 5 to 9 ETDRS letters, respectively. No relevant change in BCVA, i.e. gain or loss up to 4 ETDRS letters, was

experienced by 20.4% of patients treated with FYB203 and 26.0% of patients treated with Eylea. A total of 12.6% of patients lost at least 5 letters.

At Week 56, 27.7% of patients in the FYB203 group and 24.4% of patients in the Eylea group gained BCVA by 15 or more ETDRS letters. Furthermore, 22.9% of patients in the FYB203 group and 17.9% of patients in the Eylea group gained BCVA by 10 to 14 ETDRS letters. 18.1% of patients in the FYB203 group and 19.4% of patients in the Eylea group gained 5 to 9 ETDRS letters. No relevant change in BCVA, i.e. gain or loss up to 4 ETDRS letters, was experienced by 22.4% of patients. A total of 12.5% of patients lost at least 5 letters. Similar percentages were observed between the 2 treatment groups.

Table 20: Proportion of patients gaining or losing <5, 5 to 9, 10 to 14, or ≥15 ETDRS letters from baseline to week 24, week 40 and week 56 (FAS, N=433)

		FYB203 (N=215)		Eylea (N=218)		Total (N=433)	
BCVA change from Baseline		**n**	**(%)**	**N**	**(%)**	**n**	**(%)**
Week 24							
≥ 15 letters	(gain 15 or more)	45	(22.4)	38	(18.7)	83	(20.5)
≥ 10 and < 15 letters	(gain 10–14)	41	(20.4)	39	(19.2)	80	(19.8)
≥ 5 and < 10 letters	(gain 5–9)	41	(20.4)	47	(23.2)	88	(21.8)
> -5 and < 5 letters	(gain or loss up to 4)	52	(25.9)	58	(28.6)	110	(27.2)
> -10 and ≤ -5 letters	(loss 5–9)	12	(6.0)	13	(6.4)	25	(6.2)
> -15 and ≤ -10 letters	(loss 10–14)	6	(3.0)	2	(1.0)	8	(2.0)
≤ -15 letters	(loss 15 or more)	4	(2.0)	6	(3.0)	10	(2.5)
Missing		14		15		29	
Week 40							
≥ 15 letters	(gain 15 or more)	48	(25.1)	43	(21.5)	91	(23.3)
≥ 10 and < 15 letters	(gain 10–14)	44	(23.0)	39	(19.5)	83	(21.2)
≥ 5 and < 10 letters	(gain 5–9)	39	(20.4)	38	(19.0)	77	(19.7)
> -5 and < 5 letters	(gain or loss up to 4)	39	(20.4)	52	(26.0)	91	(23.3)
> -10 and ≤ -5 letters	(loss 5–9)	14	(7.3)	21	(10.5)	35	(9.0)
> -15 and ≤ -10 letters	(loss 10–14)	3	(1.6)	2	(1.0)	5	(1.3)
≤ -15 letters	(loss 15 or more)	4	(2.1)	5	(2.5)	9	(2.3)
Missing		24		18		42	
Week 56							
≥ 15 letters	(gain 15 or more)	52	(27.7)	49	(24.4)	101	(26.0)
≥ 10 and < 15 letters	(gain 10–14)	43	(22.9)	36	(17.9)	79	(20.3)
≥ 5 and < 10 letters	(gain 5–9)	34	(18.1)	39	(19.4)	73	(18.8)
> -5 and < 5 letters	(gain or loss up to 4)	39	(20.7)	48	(23.9)	87	(22.4)
> -10 and ≤ -5 letters	(loss 5–9)	12	(6.4)	13	(6.5)	25	(6.4)
> -15 and ≤ -10 letters	(loss 10–14)	6	(3.2)	7	(3.5)	13	(3.3)
≤ -15 letters	(loss 15 or more)	2	(1.1)	9	(4.5)	11	(2.8)
Missing		27		17		44	

BCVA = best corrected visual acuity, ETDRS = early treatment diabetic retinopathy study, FAS = full analysis set, N = total number of patients in the treatment group and analysis set, n = number of non-missing assessments

Source: Table 14.2.6.2.6.1 (Week 24), Table 14.2.6.2.8.1 (Week 40), Table 14.2.6.2.10.1 (Week 56). See also bar plots Figure 14.2.6.2.7.1 for Week 24 FAS, Figure 14.2.6.2.7.2 for Week 24 PPS, Figure 14.2.6.2.9.1 for Week 40 FAS, Figure 14.2.6.2.9.2 for Week 40 PPS, Figure 14.2.6.2.11.1 for Week 56 FAS and Figure 14.2.6.2.11.2 for Week 56 PPS

Fluid-Free Macula at Each Visit

Table 21summarises the number and proportion of patients who had absence of disease activity (fluid-free macula) by analysis visit. At Baseline, no patient had a fluid-free macula. The highest proportion of patients with fluid-free macula was observed at Week 8, with 56.7% in the FYB203 group and 54.3% in the Eylea group. Afterwards, with the extension of the dosing intervals from 4 to 8 weeks, it reduced to 34.5% in the FYB203 group and 35.8% in the Eylea group at Week 16. Until Week 56, it increased again to 42.2% in the FYB203 group and 50.5% in the Eylea group.

Table 21: Summary of patients with fluid-free macula by analysis visit (FAS, N=433)

Week	Fluid-free macula	FYB203 (N=215) N	(%)	Eylea (N=218) n	(%)	Total (N=433) n	(%)	Difference FYB203 - Eylea % diff.	95.0% CI
Baseline	Yes	0/214	(0.0)	0/217	(0.0)	0/431	(0.0)	n.c.	n.c.
Week 4	Yes	85/215	(39.5)	87/214	(40.7)	172/429	(40.1)	-1.12%	[-10.36%;8.14%]
Week 8	Yes	118/208	(56.7)	114/210	(54.3)	232/418	(55.5)	2.45%	[-7.07%;11.92%]
Week 16	Yes	70/203	(34.5)	73/204	(35.8)	143/407	(35.1)	-1.30%	[-10.55%;7.97%]
Week 24	Yes	71/198	(35.9)	65/200	(32.5)	136/398	(34.2)	3.36%	[-5.96%;12.64%]
Week 32	Yes	69/199	(34.7)	81/202	(40.1)	150/401	(37.4)	-5.43%	[-14.81%;4.06%]
Week 40	Yes	73/188	(38.8)	86/197	(43.7)	159/385	(41.3)	-4.83%	[-14.57%;5.02%]
Week 48	Yes	76/191	(39.8)	86/193	(44.6)	162/384	(42.2)	-4.77%	[-14.56%;5.11%]
Week 56	Yes	79/187	(42.2)	100/198	(50.5)	179/385	(46.5)	-8.26%	[-18.07%;1.72%]

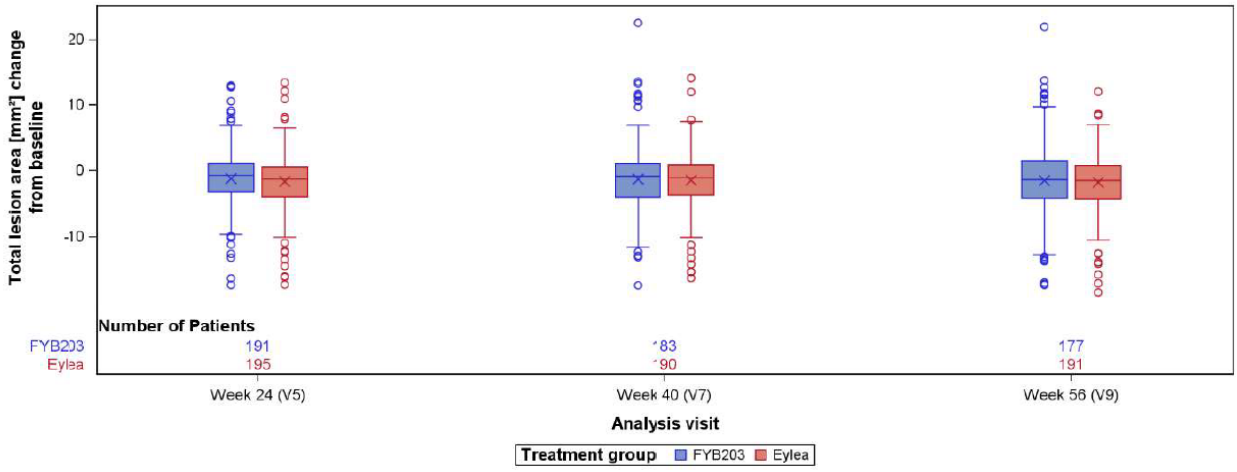
CI = confidence interval, FAS = full analysis set, N = total number of patients in the treatment group and analysis set, n = number of non-missing assessments, n.c. = not calculable

Source: Table 14.2.6.6.1.1. See also bar plots Figure 14.2.6.6.3.1 for FAS and Figure 14.2.6.6.3.2 for PPS

Changes in Total Lesion Area to Week 24, Week 40 and Week 56

The 2 treatment groups showed similar total lesion area measurements at Baseline (assessed at Screening) and at each following visit. In the FAS, the overall Baseline median (IQR) lesion area was 8.6 (4.8 – 13.2) mm^2. At Week 24, it decreased to 6.8 (3.9 – 11.0) mm^2. The reduction was sustained throughout the study, resulting in an overall lesion area of 6.5 (3.7 – 11.0) mm^2 at Week 40 and 6.1 (3.3 – 11.0) mm^2 at Week 56.

Figure 6 shows the changes from Baseline total lesion area (assessed at Screening) by treatment group until Week 56. Overall in the FAS, a similar reduction from Baseline was observed throughout the study, with a median (IQR) change of -1.1 (-3.8 – 0.7) mm^2 at Week 24, -1.1 (-3.9 – 0.9) mm^2 at Week 40 and -1.5 (-4.3 – 1.0) mm^2 at Week 56.



FAS = full analysis set, IQR = inter quartile range: 1st quartile–3rd quartile, V = visit

Boxplot markers: x = arithmetic mean, line = median, lower box boundary = 1st quartile, upper box boundary = 3rd quartile, o = outlier (below 1.5*IQR), upper whisker = maximum value below upper fence, lower whisker = minimum value above lower fence, upper fence = 1.5 times the IQR above the 3* quartile, lower fence = 1.5 times the IQR below the 1st quartile

Source: Figure 14.2.6.5.6.1

Figure 6: Changes from screening in total lesion (mm²) at week 24, week 40 and week 56 (FAS, N=433)

Table 22: Comparison of change in total lesion area (mm²) from screening to week 24, week 40 and week 56 (FAS, N=433)

		ANCOVA/MMRM LS estimation				
Week (Visit) Treatment group **Difference**	**N**	**n[a]**	**nmiss[a]**	**LS mean[b]**	**SE[b]**	**2-sided 95.0% CI**
Week 24 (V5)						
FYB203	215	191	24	-1.1	0.44	[-2.0; -0.2]
Eylea	218	195	23	-1.4	0.44	[-2.3; -0.6]
Difference: FYB203 - Eylea				**0.3**	**0.42**	**[-0.5; 1.2]**
Week 40 (V7), including data up to Week 56						
FYB203	215	204	11	-0.9	0.45	[-1.8; 0.0]
Eylea	218	206	12	-1.2	0.45	[-2.0; -0.3]
Difference: FYB203 - Eylea				**0.2**	**0.47**	**[-0.7; 1.1]**
Week 56 (V9), including data up to Week 56						
FYB203	215	204	11	-1.4	0.47	[-2.3; -0.4]
Eylea	218	206	12	-1.5	0.46	[-2.4; -0.6]
Difference: FYB203 - Eylea				**0.1**	**0.49**	**[-0.8; 1.1]**

ANCOVA = analysis of covariance, CI = confidence interval, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, N = total number of patients in the treatment group and analysis set, n/nmiss = number of non-missing/missing assessments, SE = standard error of the LS mean, V = Visit

The 2-sided 95.0% CI was based on normal approximation.

Note: There were no values for the change in total lesion area before Week 24, therefore the MMRM results are identical to an ANCOVA.

[a] For the calculation of LS means based on the MMRM, all patients with missing and non-missing Week 40/Week 56 assessments were considered if they have at least 1 post-Baseline total lesion area value until Week 56/Week 56.

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

Source: Table 14.1.4.1, Table 14.2.6.5.1.1 (Week 24), Table 14.2.6.5.8.1 (Week 40), Table 14.2.6.5.9.1 (Week 56)

In the PPS, the estimated LS mean differences between the 2 treatments of +0.2 mm² ([95.0% CI: -0.6; 1.1]) at Week 24, +0.1 mm² ([95.0% CI: -0.9; 1.0]) at Week 40 and +0.1 mm² ([95.0% CI: -0.9; 1.1]) at Week 56 were similar to the FAS.

The ANCOVA including MI using the FAS showed a similar LS mean difference between the 2 treatments at Week 24: +0.4 (95.0% CI: -0.4; 1.2) mm².

Change in Vision-Related Functioning and Well-Being (NEI VFQ-25) From Baseline to Week 24, Week 40 and Week 56

The absolute values and changes from Baseline in the NEI VFQ-25 subscales are presented for the FAS and PPS in section below and summarised in Table 26. As for the composite score, the subscales scores also showed a stable general health and functioning in the context of visual disability. There were no relevant differences between the 2 treatment groups. Single patients showed changes in both directions in the 2 treatment groups in composite as well as in subscale scores.

Table 23: Mean and median NEI VFQ-25 vision-targeted composite and subscale scores at baseline and change from baseline at week 24, week 40 and week 56 (FAS, N=433)

NEI VFQ-25 vision-targeted composite and subscale scores		FYB203 (N=215) Mean (SD); Median	Eylea (N=218) Mean (SD); Median	Total (N=433) Mean (SD); Median
Composite score	Baseline	74.8 (16.91); 79.0	77.4 (15.84); 83.0	76.1 (16.41); 80.0
	ΔV5/W24	3.8 (11.06); 3.0	1.8 (10.97); 1.0	2.8 (11.05); 2.0
	ΔV7/W40	4.0 (11.25); 3.0	2.4 (13.00); 2.0	3.1 (12.19); 2.0
	ΔV9/W56	3.8 (12.22); 4.0	1.7 (12.46); 2.0	2.8 (12.37); 3.0
Subscale scores				
General health	Baseline	42.7 (19.53); 50.0	42.8 (18.65); 50.0	42.7 (19.07); 50.0
	ΔV5/W24	0.3 (18.63); 0.0	-1.2 (16.50); 0.0	-0.5 (17.58); 0.0
	ΔV7/W40	1.2 (19.69); 0.0	-1.0 (18.56); 0.0	0.1 (19.12); 0.0
	ΔV9/W56	2.5 (21.14); 0.0	-1.5 (19.47); 0.0	0.4 (20.37); 0.0
General vision	Baseline	58.0 (15.76); 60.0	59.6 (15.59); 60.0	58.8 (15.68); 60.0
	ΔV5/W24	4.3 (16.92); 0.0	4.6 (17.02); 0.0	4.4 (16.95); 0.0
	ΔV7/W40	5.1 (16.62); 0.0	5.3 (17.19); 0.0	5.2 (16.89); 0.0
	ΔV9/W56	5.6 (16.98); 0.0	4.3 (16.36); 0.0	4.9 (16.65); 0.0
Ocular pain	Baseline	80.2 (21.61); 88.0	82.2 (20.41); 88.0	81.2 (21.02); 88.0
	ΔV5/W24	2.7 (18.02); 0.0	1.0 (19.84); 0.0	1.8 (18.96); 0.0
	ΔV7/W40	5.1 (19.58); 0.0	0.3 (21.19); 0.0	2.6 (20.54); 0.0
	ΔV9/W56	3.9 (20.92); 0.0	1.9 (20.66); 0.0	2.8 (20.78); 0.0
Near activities	Baseline	66.6 (20.92); 67.0	70.2 (21.10); 75.0	68.4 (21.06); 67.0
	ΔV5/W24	5.4 (19.79); 0.0	3.7 (18.26); 0.0	4.5 (19.03); 0.0
	ΔV7/W40	6.5 (17.65); 0.0	3.9 (19.72); 4.0	5.2 (18.77); 0.0
	ΔV9/W56	6.1 (19.81); 8.0	3.4 (19.88); 0.0	4.7 (19.87); 8.0
Distance activities	Baseline	76.4 (21.50); 83.0	79.1 (20.03); 83.0	77.7 (20.79); 83.0
	ΔV5/W24	2.5 (18.46); 0.0	1.0 (15.93); 0.0	1.8 (17.23); 0.0
	ΔV7/W40	3.7 (15.64); 0.0	0.8 (17.24); 0.0	2.2 (16.52); 0.0
	ΔV9/W56	2.9 (16.50); 0.0	0.3 (16.13); 0.0	1.6 (16.34); 0.0
Social functioning	Baseline	88.4 (18.15); 100.0	89.0 (17.27); 100.0	88.7 (17.69); 100.0
	ΔV5/W24	2.3 (16.01); 0.0	1.2 (13.93); 0.0	1.7 (14.99); 0.0
	ΔV7/W40	0.6 (15.49); 0.0	0.6 (17.40); 0.0	0.6 (16.48); 0.0
	ΔV9/W56	0.9 (15.20); 0.0	0.4 (14.68); 0.0	0.7 (14.92); 0.0

Mental health	Baseline	64.0 (24.13); 69.0	68.5 (22.77); 75.0	66.2 (23.54); 75.0
	ΔV5/W24	7.7 (20.46); 6.0	3.2 (19.71); 6.0	5.4 (20.19); 6.0
	ΔV7/W40	6.7 (20.83); 6.0	6.4 (19.46); 6.0	6.5 (20.11); 6.0
	ΔV9/W56	7.1 (20.92); 6.0	4.9 (20.51); 6.0	6.0 (20.71); 6.0
Role difficulties	Baseline	64.1 (29.15); 63.0	70.4 (27.54); 75.0	67.3 (28.49); 75.0
	ΔV5/W24	5.4 (27.26); 0.0	1.1 (22.92); 0.0	3.2 (25.21); 0.0
	ΔV7/W40	5.2 (26.31); 0.0	1.5 (24.64); 0.0	3.3 (25.48); 0.0
	ΔV9/W56	5.6 (27.08); 0.0	0.7 (25.64); 0.0	3.0 (26.42); 0.0
Dependency	Baseline	81.8 (24.80); 92.0	85.6 (22.95); 100.0	83.8 (23.92); 100.0
	ΔV5/W24	3.3 (20.68); 0.0	0.7 (16.72); 0.0	2.0 (18.80); 0.0
	ΔV7/W40	2.8 (17.40); 0.0	2.8 (19.68); 0.0	2.8 (18.60); 0.0
	ΔV9/W56	2.4 (19.05); 0.0	1.1 (19.58); 0.0	1.7 (19.31); 0.0
Driving	Baseline	68.6 (31.96); 75.0	72.2 (30.85); 83.0	70.4 (31.36); 83.0
	ΔV5/W24	2.2 (15.94); 0.0	1.0 (18.55); 0.0	1.6 (17.29); 0.0
	ΔV7/W40	1.8 (22.26); 0.0	1.4 (21.84); 0.0	1.6 (21.98); 0.0
	ΔV9/W56	4.0 (25.05); 0.0	-0.0 (21.87); 0.0	2.0 (23.49); 0.0
Color vision	Baseline	91.5 (17.85); 100.0	92.3 (14.47); 100.0	91.9 (16.22); 100.0
	ΔV5/W24	0.8 (15.87); 0.0	0.1 (15.18); 0.0	0.4 (15.51); 0.0
	ΔV7/W40	0.0 (14.97); 0.0	0.5 (14.97); 0.0	0.3 (14.95); 0.0
	ΔV9/W56	1.1 (17.36); 0.0	-0.4 (14.93); 0.0	0.3 (16.14); 0.0
Peripheral vision	Baseline	80.8 (21.91); 75.0	82.0 (20.50); 75.0	81.4 (21.20); 75.0
	ΔV5/W24	3.8 (19.74); 0.0	0.9 (19.70); 0.0	2.3 (19.75); 0.0
	ΔV7/W40	4.8 (21.04); 0.0	0.0 (21.56); 0.0	2.3 (21.41); 0.0
	ΔV9/W56	3.4 (20.01); 0.0	-0.6 (19.48); 0.0	1.3 (19.82); 0.0

Δ = difference, FAS = full analysis set, N = total number of patients in the treatment group and analysis set, NEI VFQ-25 = National Eye Institute Visual Function Questionnaire 25, SD = standard deviation, V = visit, W = week

Source: Table 14.2.6.7.1.1, Table section 14.2.6.7.4

Figure 7 shows the absolute values of the composite score by treatment group at Baseline, Week 24, Week 40 and Week 56. The NEI VFQ-25 composite scores were similar at each visit for the 2 treatment groups. In the FAS, the overall Baseline median (IQR) composite score was 80.0 (67.0 – 89.0) score points, 84.0 (70.0 – 92.0) score points at Week 24, 83.0 (71.0 – 91.0) score points at Week 40 and 83.0 (70.0 – 92.0) score points at Week 56.

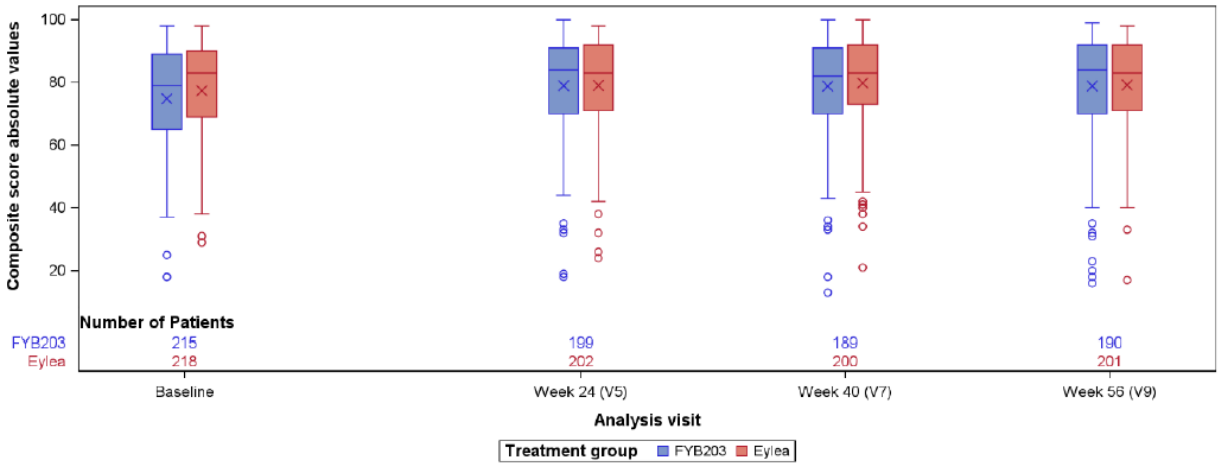


Figure 7: Absolute values of the composite NEI VFQ-25 score at baseline, week 24, week 40 and week 56 (FAS, N=433)

Pre-defined subgroup analyses

Table 24: Subgroup analyses of the primary efficacy endpoints (US and EU Analyses, FAS, N=433)

Comparison of treatments at Week 8 MMRM estimated LS mean Δ (FYB203–Eylea)						
Subgroup by Category (N)		Δ	2-sided CIs, Source		Δ	2-sided CIs, Source
Gender	Female (N=248)	0.2	90.4% CI: [-1.5; 1.9] Table 14.2.7.1.1 95.2% CI: [-1.8; 2.2] Table 14.2.7.2.1	Male (N=185)	1.7	90.4% CI: [-0.2; 3.7] Table 14.2.7.1.2 95.2% CI: [-0.5; 4.0] Table 14.2.7.2.2
Ancillary chart use	Yes (N=20)	-1.7	90.4% CI: [-5.5; 2.1] Table 14.2.8.1.1 95.2% CI: [-6.3; 2.9] Table 14.2.8.2.1	No (N=411)	1.2	90.4% CI: [-0.1; 2.5] Table 14.2.8.1.2 95.2% CI: [-0.4; 2.8] Table 14.2.8.2.2
ADA status	Positive (N=6)	n.c.	Table 14.2.9.1.1 Table 14.2.9.2.1	Negative (N=404)	0.9	90.4% CI: [-0.4; 2.2] Table 14.2.9.1.2 95.2% CI: [-0.7; 2.5] Table 14.2.9.2.2
Total lesion area	< 9 mm² (N=228)	0.6	90.4% CI: [-1.2; 2.3] Table 14.2.10.1.1 95.2% CI: [-1.5; 2.6] Table 14.2.10.2.1	≥ 9 mm² (N=205)	1.1	90.4% CI: [-0.7; 3.0] Table 14.2.10.1.2 95.2%CI: [-1.0; 3.3] Table 14.2.10.2.2
Lesion type	Type 1 MNV (N=143)	1.0	90.4% CI: [-1.0; 3.0] Table 14.2.11.1.1 95.2% CI: [-1.4; 3.4] Table 14.2.11.2.1	Type 2 MNV (N=100)	2.3	90.4% CI: [-0.8; 5.4] Table 14.2.11.1.2 95.2% CI: [-1.4; 6.0] Table 14.2.11.2.2
	Mixed Type 1 and Type 2 MNV (N=150)	1.1	90.4% CI: [-1.0; 3.2] Table 14.2.11.1.3 95.2% CI: [-1.4; 3.6] Table 14.2.11.2.3	Type 3 MNV (N=38)	-1.5	90.4% CI: [-5.7; 2.8] Table 14.2.11.1.4 95.2% CI: [-6.6; 3.7] Table 14.2.11.2.4
Injection syringe use	Original syringe by Sponsor (N=418)	0.9	90.4% CI: [-0.4; 2.2] Table 14.2.12.1.1 95.2% CI: [-0.7; 2.4] Table 14.2.12.2.1	Other syringes (N=15)	3.3	90.4%CI: [-3.2; 9.8] Table 14.2.12.1.2 95.2% CI: [-4.6; 11.2] Table 14.2.12.2.2
Region	Japan (N=33)	-0.5	90.4% CI: [-5.2; 4.1] Table 14.2.13.1.1 95.2% CI: [-6.1; 5.0] Table 14.2.13.2.1	ROW (N=400)	1.1	90.4% CI: [-0.2; 2.4] Table 14.2.13.1.2 95.2%CI: [-0.5; 2.7] Table 14.2.13.2.2

Δ = difference, ADA = anti-drug antibody, CI = confidence interval, FAS = full analysis set, LS = least squares, MMRM = Mixed Model Repeated Measures, MNV = macular neovascularization, N = total number of patients in the analysis set (and subgroup), n.c. = not calculable, ROW = rest of world

Source: directly in the table

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the biosimilarity assessment (see later sections).

Table 25: Summary of efficacy for trial FYB203-03-01

Title: A Phase 3 Randomized, Double-masked, Multicenter Study to Compare the Efficacy and Safety of the Proposed Aflibercept FYB203 Biosimilar in Comparison to Eylea® in Patients with Neovascular Age-Related Macular Degeneration (MAGELLAN-AMD)			
Study identifier	FYB203-03-01 (protocol number), 2019-003923-39 (EudraCT number)		
Design	Parallel, randomised, active-controlled, double-masked, multi-centre study. Subjects were randomised 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 subject.		
	Duration of treatment:	56 weeks (duration of treatment) Last investigational product (IP; FYB203 or Eylea) injection was at Week 48 and last assessment was done at Week 56.	
Hypothesis	Equivalence		
Treatments groups	FYB203 (215)	215 subjects started treatment with FYB203, a total of 196 subjects in the FYB203 group completed the study until Week 56	
	Eylea (218)	218 subjects started treatment with Eylea, a total of 206 subjects in the Eylea group completed the study until Week 56	
Endpoints and definitions	Primary endpoint	Change from baseline in Best Corrected Visual Acuity (BCVA) by ETDRS letters at Week 8.	
Database lock	10-Aug-2023		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Patients with nAMD who were randomised to receive either FYB203 or Eylea and who received at least 1 dose of investigational medicinal product, i.e., the FAS. Absolute change from Baseline to Week 8 in BCVA by ETDRS letters: $CHG_{BCVA,Week\ 8} = BCVA_{Week\ 8} - BCVA_{Base}$, using analysis visits.		
Descriptive statistics and estimate variability	Treatment group	FYB203	Eylea
	Number of subjects	215	218
	Mixed model repeated measurements (MMRM) LSMeans (Standard Error [SE]) of percent change from baseline in BCVA at Week 8	6.6 (0.73)	5. 6 (0.73)
	LSMean difference (FYB203 – Eylea) [95.2% CI]	1.0 [-0.6; 2.5]	

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical study

The applicant conducted a single pivotal phase III study in patients with neovascular age-related macular degeneration (nAMD). The study was not aimed at establishing efficacy per se since efficacy in the respective therapeutic indications has already been established for the reference product Eylea. Instead, the study aimed at demonstrating similarity with respect to efficacy between the biosimilar candidate and the reference product. Study FYB203-03-01 was a randomised, double-masked, parallel group, multicentre study to evaluate the clinical efficacy, safety, and immunogenicity of FYB203 compared to EU-approved Eylea. The Applicant conducted a single pivotal phase III study in patients with neovascular age-related macular degeneration (nAMD) (FYB203-03-01).

The applicant claims the same indications as those approved for the respective presentation of the reference product Eylea (nAMD, branch RVO or central RVO, DME, myopic CNV). The receptor and mechanism of action of aflibercept are the same across different ophthalmological indications approved for the reference product and aflibercept is directly delivered at its site of action. Since nAMD patients are generally considered a sensitive population for assessing similarity in clinical efficacy (see section 3) of aflibercept, it is agreed that, if similarity is demonstrated in nAMD patients, the findings can be extrapolated to other indications approved for Eylea (CRVO/BRVO, DME and myopic CNV).

The study was conducted in subjects with neovascular age-related macular degeneration (nAMD). Studies with the originator showed that the treatment effect of aflibercept was largest in patients with nAMD. There are no data that evaluates the treatment effect of Eylea vs. sham in patients with nAMD. However, in MARINA (and ANCHOR) where Lucentis (ranibizumab) was evaluated, it was shown that, on average, sham-treated patients lost around 10 letters of BCVA over 12 months whereas the treated arm gained 7 letters. In the VIEW studies where Eylea was evaluated compared to ranibizumab in a very similar nAMD population, subjects gained on average around 7 letters. By imputing natural disease history data from sham-treated subjects in MARINA, the overall treatment effect would thus translate into close to 20 letters in BCVA.

In addition, if left untreated, neovascular AMD shows homogeneous disease progressions with only few confounding factors, resulting in severe visual impairment. The selected patient population is considered relevant and sufficiently sensitive for the detection of potential differences between FYB203 and the reference product. Furthermore, the mechanism of action of Eylea is the same across all approved indications and the safety profile is similar among populations. The administered dose is in line with the posology approved for Eylea. The duration of treatment was 48 weeks, last assessments were made at Week 56. This is considered acceptable for the assessment of biosimilarity.

The inclusion and exclusion criteria are acceptable. Only treatment-naïve patients were included in the study. The recruitment of patients with a BCVA between 20/40 and 20/200 is endorsed, as it allows for quantification of changes in BCVA regarding improvement as well as potential worsening. Furthermore, the CHMP recommended lowering the cut-off of total area of whole lesion to ≤ 9 disc areas, which was acknowledged. In addition, patients with fibrosis > 50% of the total lesion in the study eye and patients with spherical equivalent of the refractive error in the study eye demonstrating more than 6 dioptres of myopia were excluded. Therefore, the criteria are in line with the scientific advice.

Subjects were randomised in a ratio of 1:1 to either FYB203 or Eylea (administered via intravitreal injection 2 mg every 4 weeks for the first 3 months, followed by 2 mg once every 8 weeks). The EU-licenced Eylea was used as the comparator in the Phase 3 Study which is endorsed. Randomisation was stratified by country (Japan, rest of world) and participation in PK sub-study (yes, no). Patients were

centrally assigned to study treatment by interactive web response system. Randomisation method is acceptable.

Due to differences in the products presentation, the FYB203 and Eylea EU were administered by an unmasked IVT administrator who was responsible for the study injections only. The unmasked study site personnel could also perform the post-dose safety check or tonometry, according to the clinical practice of the study site. The treatment each subject received was only disclosed to the unmasked IVT administrator but not to other study site staff, patient, sponsor, or study vendors. This is acceptable.

The methods used for the primary (Best Corrected Visual Acuity) and secondary efficacy assessments (Ophthalmological Examination, Colour Fundus Photography and Fluorescein Angiography, Spectral Domain Optical Coherence Tomography and NEI VFQ-25) represent standard used for respective assessments and are considered adequate.

Overall, the study design of Phase III study FYB203-03-01 is considered adequate to establish similarity between FYB203 and the reference product Eylea.

Objectives, endpoints and estimands

The primary objective of the study was to demonstrate similar efficacy of FYB203 and Eylea EU in terms of BCVA. The primary endpoint was mean change from baseline in BCVA score using ETDRS testing charts at Week 8. Given that the maximum improvement of BCVA appeared to be reached starting at 12 weeks in VIEW 1 and VIEW 2 pivotal aflibercept studies, 8 weeks is considered a sensitive time-point to detect any differences between FYB203 and Eylea in terms of BCVA change from baseline. Therefore, the primary endpoint 'change in BCVA by ETDRS letters between Week 8 and baseline' is considered an appropriate primary endpoint for the assessment of biosimilarity. Treatment policy strategy to handle intercurrent events in the analysis of primary endpoint is acceptable as well.

The proposed equivalence range for the mean difference in the primary endpoint for the wet AMD population of ± 3.5 letters is considered conservative enough to establish the clinical equivalence between FYB203 and Eylea and is therefore endorsed.

The applicant performed the main analysis of primary efficacy endpoint for assessing equivalence between a biosimilar and an innovator product based on the full analysis set, i.e., those patients who received at least 1 injection of study medication in the study eye. The corresponding analysis of the primary efficacy endpoint, the change in BCVA by ETDRS letters from baseline to Week 8 on per protocol set was also performed.

Secondary endpoints evaluated the change in BCVA by ETDRS letters; foveal (centre point and central subfield) thickness at different time points and over time; the proportion of subjects who gained or lost ≥5, 10, or 15 ETDRS letters compared to baseline; percentage of subjects with fluid-free macula; change in lesion size compared to baseline; PK, ADAs analyses; and quality of life assessment. The secondary endpoints are adequately defined to further support biosimilarity assessment and the maintenance of efficacy over time and are supported.

Statistical methods for estimation and sensitivity analysis

Main analysis model for primary efficacy endpoint, i.e., linear mixed-effects model (MMRM) with fixed effects of BCVA at baseline, region, visit, treatment, baseline by visit interaction and treatment by visit interaction is acceptable. Covariance structure within patient is modelled by unstructured covariance matrix and Kenward-Roger approximation of degrees of freedom for testing of fixed effects in MMRM. Such MMRM can be considered as acceptable.

Basic sample size calculation of 400 patients for "EU analysis" is acceptable. Actual number of patients considered for study was 434 randomised patients.

Masked sample size review (MSSR) was performed after first 200 treated patients who completed study Week 8 (Visit 3) as there was some uncertainty about assumed value of standard deviation (SD) for primary efficacy endpoint, i.e., 9 letters, which was used for sample size calculation. Based on estimated common SD after first 200 treated patients, final sample size could be increased up to 800 patients from original number of 400 patients. However, as estimate of common SD for primary efficacy endpoint was 8.14 letters which was less than 9 letters, original number of 400 patients was retained.

According to section 7.4.3. Recommendations based on the masked sample size review in document 16.1.9. Documentation of Statistical Methods, common SD estimated after first 200 treated patients for key secondary efficacy endpoint for "EU analysis" could also influence value of final sample size which could be up to 800 patients. Assumed value of SD for sample size calculation was 135 µm. However, as estimate of common SD for key secondary efficacy endpoint for "EU analysis" was 110.11 µm (see Sample size re-assessment in Statistical Methods), original number of 400 patients was retained.

As MSSR was planned to be performed after 200 patients, the applicant performed a simulations prior to study initiation to assess impact of MSSR on potential inflation of overall type 1 error probability (OT1EP). Results of simulations indicated inflation of OT1EP and 95.2% confidence interval (CI) had to be used for assessment of equivalence in "EU analysis" instead of nominal 95% CI.

The applicant provided missing Appendix I to the SAP which described the methodology applied as well as the results of the simulations for both the EMA and the FDA specific analyses.

It was pointed out by the assessor that simulations may not exhaust all possible scenarios and analytical calculation of OT1EP should be performed to verify that 95.2% CI is reasonable. The applicant stated that MSSR after 200 subjects did not inflate OT1EP as original sample size of 400 patients was retained. Moreover, the applicant stated that although OT1EP can be calculated analytically (see Friede and Kieser (2003): Blinded sample size reassessment in non-inferiority and equivalence) such calculation needed numerical method and result could be imprecise. Instead, tipping point analysis was performed by the applicant with respect to both primary endpoint and key secondary endpoint for full analysis set and for per protocol set, respectively, in "EU analysis". This calculation searched for maximum value of confidence level (CL) which led to equivalence across both endpoints and in both analysis sets considered for these endpoints. Such maximum value of CL was 99.90%. Consequently, 99.90% CI can be considered as sufficient CL to cover possible OT1EP inflation due to MSSR. Hence, issue with MSSR is resolved.

Two **protocol amendments** were made. Amendment 1 was issued before screening of subjects started. The second amendment was issued after study initiation. The changes were clearly described and no influence on study results is expected since occurred prior to study unmasking. There was also change in the planned subgroup analysis relevant for this application - only the regions Japan versus ROW were used, since the differences between study population in Japan versus the other countries was regarded as more important than possible differences between countries. Numerically, the originally planned analysis by country was not recommended due to the very small number of patients in 1 country. This is acceptable.

Study conduct: The study completion rate was high (more than 91%), with slightly more subjects in Elyea arm in comparison with FYB203 arm. Up to Week 8, which was when the primary analysis was evaluated, 3 patients from FYB203 group and 2 patients from Eylea treatment group discontinued the IP. The primary reason for the subject's discontinuation before week 8 is not clear but given the low number of patients who discontinued before Week 8, the impact is considered negligible and the issue will not be further pursued.

Classification of the protocol deviation as a major or minor was not prespecified in the study protocol. All protocol deviations for all treated patients were reviewed during the Blind Data Review Meeting before

database lock and unmasking for the originally planned US analysis with data up to Week 24 in order to allocate all patients into the different analysis sets. Major Protocol deviations were defined as a deviation, which should impact the BCVA assessment until Week 8.

A total of 367 (84.8%) patients had at least 1 minor protocol deviation and 27 patients (6.2%) had at least 1 major protocol deviation, which led to the exclusion from the PPS. The percentage of patients with any protocol deviation was comparable between treatment arms. The most common major protocol deviations that led to exclusion from PPS were BCVA schedule deviations with comparable occurrence between treatment groups.

The proportion of patients with major protocol deviation due to study treatment incompliance was low and well comparable between the groups [2 subjects in both groups]. Visit schedule deviation at week 8 (V3 – when assessment of the primary endpoint was performed) occurred in 1 subject (0.5%) in FYB203 group and 2 subjects (0.9%) in Eylea group. Covid19 related V3 visit schedule deviation occurred only in 1 subject from FYB203 group. Deviations from the protocol were clearly described and do not raise any concerns.

Since the classification of the protocol deviation was not prespecified in the study protocol, demonstration of the robustness of the primary analysis of both FAS and PPS is of particular importance.

Of the 434 subjects randomised, 433 (99.8%) subjects were included in the FAS (primary analysis population) and 406 (93.8%) subjects were included in the PPS (analysis set used in a sensitivity analysis). One subject randomised to the Eylea group in FAS did not receive the IP. In addition, there were two subjects (1 in each study groups) who received wrong IMPs. Therefore, SAF and FAS are not identical. In the FAS, patients were analysed according to their randomisation, while in the SAF they were analysed according to the treatment currently received. Number of patients excluded from the PPS was comparable between treatment groups.

Overall, the mean age of the patients included in the study was 73.5 years (range: 68-79 years). The majority of subjects were white (91.9%). There was a higher proportion of females (57.3%) compared to males (42.7%) participated in the study. The baseline demographic characteristics were comparable across the treatment groups.

Most of the patients were diagnosed 30 days before randomisation (median value), however, for 60 patients this information is missing. The median time since first diagnosis of nAMD was 32.0 days in the FYB203 group and 29.0 days in the Eylea group. The mean BCVA score [ETDRS letters] at baseline was 57.9 letters (median 60 letters) and well balanced across treatment groups.

The lesion type (in most subjects Type 1 MNV, type 2 NV or mixed type 1 and type 2 MNV), total lesion area (mean value at screening 9.6 mm^2 (5.84)) and IOP (mean 15.3 mmHg) was comparable across treatment arms. Baseline (V1) FCP and FCS retinal thickness were slightly thicker in the Eylea group (mean 448.5 µm and 484.0 µm, respectively) vs FYB203 group (465.9 µm and 493.5 µm, respectively).

Both treatment arms were similar regarding medical history, prior medications and treatments, as well as concomitant medications. Almost half of patients (49.9%) had cataract in the study eye at baseline (48.4% and 51.4 % in FYB203 and Eylea treatment groups, respectively). In the fellow eye, dry age-related macular degeneration occurred overall, in 267 (62.7%) patients and cataract in 50.8 %. Neovascular age-related macular degeneration was diagnosed in 33 patients (7.6%) (17 (7.9%) and 16 (7.3%) in FYB203 and Eylea treatment groups, respectively) at baseline. Fellow eye treatment with Eylea was not permitted during the first eight weeks of the study to exclude any potential impact on the efficacy evaluation at Week 8 and no injections were performed prior to the Week 8 assessments. Overall, the number of patients who needed fellow eye treatment was low and similar between groups (FYB203: 19

(8.8%); Eylea: 20 (9.2%)). Fellow eye treatment was to be separated by at least 14 days from study eye treatment such that treatments could not have been mixed up.

A tabulated summary of intercurrent events until week 8 was provided. No other pre-defined intercurrent event was observed during this time period, except for treatment discontinuation prior to week 8. The number of subjects discontinuing treatment prior to week 8 was comparable between treatment arms thus does not represent a risk for biosimilarity assessment. During the first 24 weeks, vitrectomy was performed on the study eye in one subject from FYB203 group and laser therapy was performed in one subject in the Eylea group. These therapies may have affected the primary efficacy endpoint and were prohibited during the study period but were not classified as a major deviation. The reason why this was not classified as a major protocol deviation is unclear. However, as only 2 patients were affected by this (1 in each arm) the impact on study results is considered negligible. Therefore, the issue is not further pursued.

Efficacy data and additional analyses

Primary efficacy analysis

The least squares (LS) mean observed for change from baseline in BCVA at Week 8 was similar in both treatment groups, i.e., 6.6 letters and 5.6 letters in FYB203 and Eylea group, respectively, based on patients from full analysis set (FAS). The LS mean difference in BCVA of the change from baseline between FYB203 and Eylea at Week 8 was 1.0 letter with 95.2% confidence interval (CI) of [−0.6 letter; 2.5 letters] and was completely contained within the pre-defined equivalence range (ER) of [−3.5 letters, 3.5 letters].

The sensitivity analyses for the primary endpoint were performed using linear mixed effects model (MMRM) and analysis of covariance (ANCOVA) model. Impact of missing data in FAS on study results was investigated by ANCOVA model. Impact of different structure of FAS on study results was investigated by MMRM. The results of these sensitivity analyses for the primary efficacy endpoint supported the robustness of the equivalence between FYB203 and Eylea based on FAS.

Further, tipping point analysis for the primary efficacy endpoint was performed to investigate whether missing at random (MAR) assumption underlying the use of MMRM was reasonable for missing data in the FAS. Missing data were imputed by missing not at random mechanism and shifted by certain range of values. Due to high value of shift either for FYB203 or Eylea or both the MAR assumption was reasonable and MMRM could be used.

The number of patients with missing assessments was overall low and comparable between treatment groups (6 and 5 in the FYB203 and Eylea group, respectively), indicating that the performed tipping analyses will likely not be much different from the primary analysis. The smallest tipping point that would lead to a conclusion of lower efficacy of FYB203 compared to Eylea was a shift of 0 in the Eylea group and a shift of -79 letters in the FYB203 group. The likelihood that all these patients would have much worse changes than the observed minimum changes is regarded as very low.

Finally, supplemental analyses for primary endpoint using MMRM restricted to the PPS, to modified FAS, or using different approaches for handling of intercurrent events were performed. These supplemental analyses led to equivalence as 95.2% CIs were fully within ER [−3.5 letters, 3.5 letters] for each considered supplemental analysis.

The analysis of the primary efficacy endpoint, the change in BCVA by ETDRS letters from baseline to Week 8 on per protocol set (PPS) was performed. For PPS, 95.2% confidence interval (CI) for difference between FYB203 and Eylea is (-0.8 letter, 2.4 letters) and this CI fully lies within equivalence range (ER)

which is (-3.5 letters, 3.5 letters). Thus, results based both on PPS and FAS are consistent and support the similarity of the products.

Secondary efficacy endpoints

Change in foveal centre point retinal thickness and foveal central subfield retinal thickness

Change in foveal centre point retinal thickness in the study eye from baseline to Week 4 based on the FAS and PPS was considered as a key secondary endpoint. The estimated LS mean change in FCP retinal thickness from baseline to Week 4 was -171.4 µm in patients treated with FYB203 and -166.9 µm in patients treated with Eylea. The estimated LS mean difference between the treatment groups was -4.5 µm (95.2% CI: [-24.4 µm; 15.4 µm]) and completely contained in the pre-defined equivalence range of [-45.0 µm; 45.0 µm]. In the PPS, the estimated LS mean difference of -7.5 µm (95.2% CI: [-28.2 µm; 13.1 µm]) between the treatments was similar to the FAS.

The difference between treatments increased at later time points as compared to the difference observed at Week 4, as follows: (-8.2 µm (95.0% CI: [-33.7 µm; 17.3 µm]) at Week 24; -7.9 µm (95.0% CI: [-32.2 µm; 16.4 µm]) at Week 40 and -5.2 µm (95.0% CI: [-27.7 µm; 17.2 µm]) at Week 56); however, it was still contained within the acceptance range.

The estimated LS mean change in FCS retinal thickness from baseline to Week 4 was -163.5 µm in patients treated with FYB203 and -157.4 µm in patients treated with Eylea. The estimated LS mean difference between the treatments was -6.2 µm (95.0% CI: [-24.3 µm; 12.0 µm]). In the PPS, the estimated LS mean difference of -6.2 µm (95.0% CI: [-24.9 µm; 12.4 µm]) between the treatments was similar to the FAS.

The difference between treatments at later time points was similar or smaller to the one observed at Week 4. The estimated LS mean differences between the two treatment groups were -6.3 µm (95.0% CI: [-28.9 µm; 16.3 µm]) at Week 24, -3.8 µm (95.0% CI: [-25.4 µm; 17.8 µm]) at Week 40 and -0.6 µm (95.0% CI: [-20.6 µm; 19.4 µm]) at Week 56. Similar to change in FCP retinal thickness, change FCS retinal thickness slightly worse performance of FYB203 compared to Eylea, however still within the pre-specified margins.

In summary, a decrease from baseline in foveal centre point and foveal central subfield retinal thickness was observed in both treatment groups at all time points. No significant differences between treatments were noted.

Change in BCVA From Baseline to Week 24, Week 40 and Week 56

In the FAS, increase in ETDRS letters from Baseline was observed throughout the study, with a median (IQR) increase of 8.0 (0.0 - 13.0) ETDRS letters at Week 24, 8.0 (1.0 - 14.0) ETDRS letters at Week 40 and 8.0 (0.0 15.0) ETDRS letters at Week 56.

The estimated LS mean differences in BCVA between the 2 treatment groups were 0.3 ETDRS letter (95.0% CI: [-1.5; 2.2]) at Week 24, 1.4 ETDRS letters (95.0% CI: [-0.6; 3.4]) at Week 40 and 1.3 ETDRS letters (95.0% CI: [-0.9; 3.5]) at Week 56.

The proportion of patients who gained or lost ≥ 5, 10 and 15 ETDRS letters

The proportion of patients who gained or lost ≥ 5, 10 and 15 ETDRS letters was comparable between the 2 treatment groups at all time points. The number of patients who gained more than 15 letters was slightly higher in FYB203 group (22.4%, 25.1% and 27.7% of at week 24, 40 and 56, respectively) compared to Eylea group (18.7%, 21.5% and 24.4% of at week 24, 40 and 56, respectively).

The proportion of subjects who lost 15 or more letters in BCVA compared to baseline at Week 56 was slightly lower in the FYB203 (FYB203: 1.1% [2 subjects] vs Eylea: 4.5% [9 subjects].

Fluid-Free Macula at Each Visit

No patient had a fluid-free macula at baseline. The highest proportion of patients with fluid-free macula was observed at Week 8 (56.7% in the FYB203 group and 54.3% in the Eylea group). A reduction in the proportion of subjects with a fluid-free macula occurred after week 8, according to the applicant, as a result of the extension in dosing intervals. After that, the proportion of patients increased again to 42.2% in the FYB203 group and 50.5% in the Eylea group. No statistically difference between treatment groups was observed.

Change in total lesion area

The ANCOVA/MMRM was used to analyse the change in total lesion area from Baseline to Week 24, Week 40 and Week 56 on the FAS. The estimated LS mean changes of total lesion area from Screening until Week 56 were similar between the 2 treatment groups. At Week 24, the estimated LS mean change in total lesion area was -1.1 mm² in patients treated with FYB203 and -1.4 mm² in patients treated with Eylea. At Week 40, it was -0.9 mm² in patients treated with FYB203 and -1.2 mm² in patients treated with Eylea. At Week 56, it was -1.4 mm² in patients treated with FYB203 and -1.5 mm² letters in patients treated with Eylea. The estimated LS mean differences between the 2 treatment groups were +0.3 mm² (95.0% CI: [-0.5; 1.2]) at Week 24, +0.2 mm² (95.0% CI: [-0.7; 1.1]) at Week 40 and +0.1 mm² (95.0% CI: [-0.8; 1.1]) at Week 56.

Change from Baseline in vision-related functioning and well-being measured by NEI VFQ-25 in patients treated with FYB203 or Eylea was highly variable. No statistical comparison between groups was made.

No substantial difference between treatment groups were observed.

The **subgroup analysis** revealed in some cases inequivalence for difference between treatments with respect to primary efficacy endpoint if corresponding 95.2% confidence interval (CI) was compared to equivalence range [-3.5 letters, 3.5 letters].

This was revealed in case of the males (the LS mean difference was 1.7 letters with 95.2% CI of [−0.5 letter, 4.0 letters]) where upper limit of 95.2% CI was higher than 3.5 letters. Further, this was revealed in case of certain lesion types. More specifically, Type 2 MNV (the LS mean difference was 2.3 letters with 95.2% CI of [−1.4 letter, 6.0 letters]) where upper limit of 95.2% CI was higher than 3.5 letters, Mixed Type 1 and Type 2 MNV (the LS mean difference was 1.1 letters with 95.2% CI of [−1.4 letter, 3.6 letters]) where upper limit of 95.2% CI was higher than 3.5 letters and Type 3 MNV (the LS mean difference was -1.5 letters with 95.2% CI of [−6.6 letters, 3.7 letters]) where lower limit of 95.2% CI was less than -3.5 letters.

However, number of subjects in individual subgroups may not lead to sufficient statistical power (at least 80%) to conclude equivalence with respect to range [-3.5 letters, 3.5 letters] as study was not planned for subgroup analyses. In this case it was sufficient that point estimates for treatment difference for individual subgroups were fully within equivalence range [-3.5 letters, 3.5 letters].

The results of the subgroup analysis by ADA result up to Week 8 were not assessed due to extremely small numbers of ADA positive patients up to Week 8 (6 patients only).

The subgroup analysis by ancillary chart use, injection syringe use and region also revealed some differences. However, due to the unequal size of the groups, no firm conclusion could be drawn from the results.

2.5.7. Conclusions on the clinical efficacy

The clinical data indicate similarity between the proposed biosimilar Ahzantive and the reference product Eylea EU.

2.5.8. Clinical safety

The clinical safety assessment of FYB203-03-01 (further referred as FYB203 – proposed aflibercept biosimilar) is based on one phase III parallel-group, 1:1 randomised, double-masked, multicentre completed study (MAGELLAN-AMD). The study compares the efficacy and safety of the FYB203 biosimilar with EU Eylea in patients with neovascular Age-Related Macular Degeneration (AMD).

Table 26: Evaluation and visit schedule

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8	V9 (EOS/ Early Termination)
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												

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V3a	V4	V5	V6	V7	V8	V9 (EOS/ Early Termination)
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.

[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)

2.5.8.1. Patient exposure

Table 27: Patient exposure (cut off)

	Patients enrolled[a]	Patients exposed[b]	Patients exposed to the proposed dose range[c]	Patients with long term[d] safety data
Blinded studies (placebo-controlled)	N/A	N/A	N/A	N/A
Blinded studies (active -controlled)	Total: N= 434 FYB203: N= 215 Eylea: N= 219	Total: N= 433 FYB203: N= 215 Eylea: N= 218	Total: N= 382 FYB203: N= 183 Eylea: N= 199	Total: N= 402 FYB203: N= 196 Eylea: N=206
Open studies	N/A	N/A	N/A	N/A
Post marketing	N/A	N/A	N/A	N/A
Compassionate use	N/A	N/A	N/A	N/A

[a] Patients randomised at Week 0.
[b] Received at least 1 dose of active treatment.
[c] Patients who received all 8 scheduled injections until Week 56.
[d] In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure. In this case, patients completed study until Week 56.

Patients with newly diagnosed neovascular age-related macular degeneration (AMD) were randomly allocated to two treatment groups in a 1:1 ratio – one arm received test product FYB203 and one arm received reference product Eylea (Table 7).

Overall, 712 patients were screened and enrolled (including 7 re-screened patients) in 77 in 9 countries. In total, 434 patients were randomised to receive the FYB203 treatment (215 patients) or Eylea treatment (219 patients). After consent withdrawal by 1 patient, 433 patients started the treatment (FYB203 – 215 patients; Eylea – 218 patients). These patients formed the FAS (full analysis set) and the SAF (safety analysis set).

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. The study was completed at Week 56.

A total of 196 (91.2%) patients in the FYB203 group and 206 (94.1%) patients in the Eylea group completed the study until Week 56, which is acceptable. The provided safety database is considered sufficient to assess the comparability of common and very common adverse events. However, it is too small to inform on less frequently occurring adverse events.

Until Week 56, 183 patients (85.1%) in the FYB203 group and 199 patients (91.3%) in the Eylea group received all 8 scheduled injections (88.2% in total).

Up to Week 56, 19 (8.8%) patients in the FYB203 group and 12 (5.5%) patients in the Eylea group discontinued the study prematurely. In the **FYB203 group**, 5 patients experienced AEs, 4 patients died, 3 patients withdrew consent, 1 patient was lost to follow-up, 1 patient had a protocol violation and 5 patients discontinued due to other reasons. In the **Eylea group**, 7 patients withdrew consent, 2 patients discontinued following physician decision, 1 patient died, 1 patient was lost to follow-up and 1 patient discontinued due to other reasons.

There were 27 (6.2%) patients with major protocol deviations leading to the exclusion from the PPS (per protocol set), resulting in a PPS of 201 patients treated with FYB203 and 205 patients treated with Eylea.

The PKS (plasma concentration analysis set) consisted of 31 patients treated with FYB203 and 26 patients treated with Eylea. Three patients were excluded from the 60 recruited patients due to positive total aflibercept concentration at Baseline.

The mean (SD) treatment duration was 323.1 (58.97) days and the mean (SD) study duration was 398.7 (53.03) days. In general, the treatment and study duration were well balanced between both treatment groups and no relevant differences were observed.

2.5.8.2. Adverse events

Overview of TEAEs

An overview of all TEAE sub-categories occurring during the course of the study until Week 56 is presented in Table 28depicting the number of events and the number and percentage of patients corresponding to each sub-category.

Overall, there were no clinically relevant differences in TEAEs between the 2 treatment groups until Week 56: 498 events were reported in 165 (76.7%) patients treated with FYB203 versus 536 events in 158 (72.5%) patients treated with Eylea.

Overall, the SAE occurrences until Week 56 were comparable in the 2 treatment groups: 38 events in 19 (8.8%) patients treated with FYB203 and 40 events in 28 (12.8%) patients treated with Eylea. The SAEs were mostly systemic and rarely local.

Table 28: Overview of treatment-emergency adverse events (SAF, N=433)

TEAE category	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
TEAEs	165	(76.7)	498	158	(72.5)	536	323	(74.6)	1034
Local (study eye)	67	(31.2)	125	75	(34.4)	157	142	(32.8)	282
Local (fellow eye)	45	(20.9)	53	48	(22.0)	58	93	(21.5)	111
Systemic	124	(57.7)	320	113	(51.8)	321	237	(54.7)	641
Serious TEAEs (SAEs)	19	(8.8)	38	28	(12.8)	40	47	(10.9)	78
Local (study eye)	2	(0.9)	3	2	(0.9)	2	4	(0.9)	5
Local (fellow eye)	0	(0.0)	0	3	(1.4)	3	3	(0.7)	3
Systemic	17	(7.9)	35	23	(10.6)	35	40	(9.2)	70
Fatal TEAEs	4	(1.9)	8	1	(0.5)	1	5	(1.2)	9
Nonfatal SAEs	18	(8.4)	30	27	(12.4)	39	45	(10.4)	69
Severe TEAEs	10	(4.7)	23	15	(6.9)	20	25	(5.8)	43
Local (study eye)	2	(0.9)	3	0	(0.0)	0	2	(0.5)	3
Local (fellow eye)	0	(0.0)	0	4	(1.8)	4	4	(0.9)	4
Systemic	8	(3.7)	20	11	(5.0)	16	19	(4.4)	36
Related TEAEs to study treatment	20	(9.3)	34	16	(7.3)	32	36	(8.3)	66
Related serious TEAEs	2	(0.9)	3	0	(0.0)	0	2	(0.5)	3
Related severe TEAEs	3	(1.4)	4	0	(0.0)	0	3	(0.7)	4
Related TEAEs to IVT injection procedure	28	(13.0)	55	37	(17.0)	93	65	(15.0)	148
TEAEs leading to withdrawal of study treatment	10	(4.7)	18	2	(0.9)	2	12	(2.8)	20
TEAE leading to discontinuation of study	9	(4.2)	16	1	(0.5)	1	10	(2.3)	17
AESIs	6	(2.8)	10	7	(3.2)	12	13	(3.0)	22

Ev = number of TEAEs of specified adverse event type, IVT = intravitreal, N = total number of patients, n = number of patients with at least 1 adverse event of specified adverse event type, SAE = serious adverse event, SAF = safety analysis set, TEAE = treatment-emergent adverse event, AESI = Adverse event of special interest

Treatment-emergent adverse events (TEAEs) which were observed in at least 2% of the patients are displayed in Table 29 by System Organ Class (SOC) and Preferred Term (PT). The assessment includes all ocular and non-ocular, local and systemic TEAEs in ≥2.0% of patients.

Table 29: Frequency of treatment emergency adverse events in ≥ 2.0% of patients in either of the treatment groups (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 haemorrhage	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
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

Ev = number of TEAEs of specified adverse event type, MedDRA = medical dictionary for regulatory activities, N = total number of patients, n = number of patients with at least 1 AE of specified AE type, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Source: Table 14.3.2.2.2

Overall, there were no clinically relevant differences in TEAEs between the two treatment groups until Week 56: 498 events were reported in 165 (76.7%) patients treated with FYB203 versus 536 events in 158 (72.5%) patients treated with Eylea. The most commonly affected SOCs in both treatment groups in at least 2.0% of patients in the SAF were Eye disorders (see below for more details) and Infections and infestations (COVID-19). Slight imbalances in frequencies of TEAEs by SOC or PT have been reported (e.g., for PT conjunctival haemorrhage (FYB203 vs. Eylea: 5 (2.3%) subjects vs. 14 (6.4%) subjects). However, also considering relationship to study treatment and/or procedure, no safety concerns are

raised based on these imbalances. There were no clinically relevant differences between both treatment groups. No new or unknown TEAEs for the class of drug were identified.

Table 30: Frequency of treatment-emergency adverse events by maximum intensity (SAF, N-433)

Maximum Intensity	FYB203 N=215		Eylea N=218		Total N=433	
	n	(%)	N	(%)	n	(%)
Any TEAE	165	(76.7)	158	(72.5)	323	(74.6)
Mild	96	(44.7)	85	(39.0)	181	(41.8)
Moderate	59	(27.4)	58	(26.6)	117	(27.0)
Severe	10	(4.7)	15	(6.9)	25	(5.8)

N = total number of patients in analysis set, n = number of patients with at least 1 adverse event in corresponding class, SAF = safety analysis set, TEAE = treatment-emergent adverse event,
Source: Table 14.3.2.2.5

The SOC Eye disorders included total 7 events in 6 (1.4%) patients (Table 34 below). In the FYB203 group, PT Iridocyclitis was recorded in 1 (0.5%) patient, PT Retinal pigment epithelial tear was recorded in 1 (0.5%) patient and PT Uveitis was recorded in 1 (0.5%) patient. All 3 PTs were observed in the study eye and were probably related to study treatment. PT Iridocyclitis and PT Uveitis were listed as SAEs. Additionally, PT Cerebrovascular accident under SOC Nervous system disorders was reported as possibly related to study treatment. In the Eylea group, PT Neovascular age-related macular degeneration was reported for 2 (0.9%) patients, PT Glaucoma was reported for 1 (0.5%) patient and PT Macular degeneration in 1 (0.5%) patient. All 3 PTs were observed in the fellow eye and were unrelated to study treatment. The PT Neovascular age-related macular degeneration in the fellow eye was listed as an SAE.

Other severe TEAEs until Week 56 were reported in the SOC Infections and infestations:4 (1.9%) patients treated with FYB203 and 1 (0.5%) patient treated with Eylea; SOC Neoplasms benign, malignant and unspecified: 3 (1.4%) patients treated with FYB203 and 2 (0.9%) patients treated with Eylea; SOC Cardiac disorders: 1 (0.5%) patient treated with FYB203 and 2 (0.9%) patients treated with Eylea; SOC Nervous system disorders: 1 (0.5%) patient treated with FYB203 and 2 (0.9%) patients treated Eylea. PTs under other SOCs occurred mostly in single patients in either of the 2 treatment groups.

Table 31: Frequency of severe treatment-emergent adverse events (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
Severe TEAEs									
Any	10	(4.7)	23	15	(6.9)	20	25	(5.8)	43
Eye disorders, overall	2	(0.9)	3	4	(1.8)	4	6	(1.4)	7
Neovascular age-related macular degeneration	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Glaucoma	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Iridocyclitis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Macular degeneration	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal pigment epithelial tear	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Uveitis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Infections and infestations, overall	4	(1.9)	7	1	(0.5)	1	5	(1.2)	8
COVID-19	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Appendicitis	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
COVID-19 pneumonia	1	(0.5)	1	0	(0.0)	0	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
Toxic shock syndrome	1	(0.5)	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	3	(1.4)	3	2	(0.9)	3	5	(1.2)	6
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

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
Adenocarcinoma of colon	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Gallbladder cancer	0	(0.0)	0	1	(0.5)	2	1	(0.2)	2
Oesophageal carcinoma stage 0	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Cardiac disorders, overall	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3
Cardiac failure	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Angina pectoris	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Nervous system disorders, overall	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3
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
Transient ischaemic attack	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Musculoskeletal and connective tissue disorders, overall	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Back pain	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Rheumatoid arthritis	0	(0.0)	0	1	(0.5)	1	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
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
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
Hepatobiliary disorders, overall	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Gallbladder disorder	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Injury, poisoning and procedural complications, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Radius fracture	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Metabolism and nutrition disorders, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Diabetic metabolic decompensation	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
Surgical and medical procedures, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Chemotherapy	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Vascular disorders, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Aortic aneurysm	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 adverse event in corresponding class, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Source: Table 14.3.2.2.11

Table 32: Frequency of treatment-emergent adverse events related to study treatment (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
Related TEAEs [1]									
Any	20	(9.3)	34	16	(7.3)	32	36	(8.3)	66
Eye disorders, overall	15	(7.0)	23	11	(5.0)	15	26	(6.0)	38
Neovascular age-related macular degeneration	6	(2.8)	7	3	(1.4)	4	9	(2.1)	11
Retinal pigment epithelial tear	3	(1.4)	3	1	(0.5)	1	4	(0.9)	4
Eye pain	3	(1.4)	3	0	(0.0)	0	3	(0.7)	3
Iritis	1	(0.5)	1	2	(0.9)	3	3	(0.7)	4
Vitritis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Conjunctival haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Iridocyclitis	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Lacrimation increased	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Macular degeneration	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal depigmentation	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal disorder	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Scleral haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Subretinal fibrosis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Subretinal fluid	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Uveitis	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Vitreous floaters	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Investigations, overall	1	(0.5)	2	6	(2.8)	14	7	(1.6)	16
Intraocular pressure increased	1	(0.5)	2	5	(2.3)	12	6	(1.4)	14
Blood alkaline phosphatase increased	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Gamma-glutamyltransferase increased	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Nervous system disorders, overall	3	(1.4)	4	0	(0.0)	0	3	(0.7)	4
Headache	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Cerebrovascular accident	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Somnolence	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Vascular disorders, overall	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Hypertension	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Blood and lymphatic system disorders, overall	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Anaemia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Ear and labyrinth disorders, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Deafness neurosensory	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
General disorders and administration site conditions, overall	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Asthenia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Infections and infestations, overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Conjunctivitis	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Injury, poisoning and procedural complications, overall	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Intraocular injection complication	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2

A total of 36 (8.3%) patients experienced 66 TEAEs related to the study treatment. The occurrences of related TEAEs were similar in both treatment groups: 34 events in 20 (9.3%) patients treated with FYB203 and 32 events in 16 (7.3%) patients treated with Eylea.

Table 33: Frequency of treatment-emergent adverse events related to study procedure (IVT injection) (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 Related TEAEs[1]	28	(13.0)	55	37	(17.0)	93	65	(15.0)	148
Eye disorders, overall	23	(10.7)	38	31	(14.2)	59	54	(12.5)	97
Conjunctival haemorrhage	4	(1.9)	4	14	(6.4)	24	18	(4.2)	28
Eye pain	4	(1.9)	4	5	(2.3)	8	9	(2.1)	12
Vision blurred	5	(2.3)	5	0	(0.0)	0	5	(1.2)	5
Neovascular age-related macular degeneration	2	(0.9)	3	2	(0.9)	3	4	(0.9)	6
Iritis	1	(0.5)	1	2	(0.9)	3	3	(0.7)	4
Punctate keratitis	1	(0.5)	1	2	(0.9)	4	3	(0.7)	5
Swelling of eyelid	0	(0.0)	0	3	(1.4)	4	3	(0.7)	4
Vitreous floaters	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Conjunctival hyperaemia	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Iridocyclitis	1	(0.5)	2	1	(0.5)	1	2	(0.5)	3
Lacrimation increased	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Photophobia	1	(0.5)	1	1	(0.5)	3	2	(0.5)	4
Visual impairment	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Vitritis	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Cataract subcapsular	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Conjunctival suffusion	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Eye irritation	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Foreign body sensation in eyes	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Macular hole	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Ocular hypertension	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Photopsia	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
Scleral haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Uveitis	1	(0.5)	2	0	(0.0)	0	1	(0.2)	2
Vitreous detachment	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Investigations, overall	6	(2.8)	8	8	(3.7)	22	14	(3.2)	30
Intraocular pressure increased	6	(2.8)	8	8	(3.7)	22	14	(3.2)	30
General disorders and administration site conditions, overall	1	(0.5)	3	4	(1.8)	4	5	(1.2)	7
Sensation of foreign body	0	(0.0)	0	3	(1.4)	3	3	(0.7)	3
Injection site pain	1	(0.5)	3	1	(0.5)	1	2	(0.5)	4
Nervous system disorders, overall	3	(1.4)	3	2	(0.9)	4	5	(1.2)	7
Headache	2	(0.9)	2	2	(0.9)	4	4	(0.9)	6
Somnolence	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Injury, poisoning and procedural complications, overall	1	(0.5)	2	2	(0.9)	2	3	(0.7)	4
Intraocular injection complication	1	(0.5)	2	2	(0.9)	2	3	(0.7)	4
Infections and infestations, overall	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Conjunctivitis	0	(0.0)	0	2	(0.9)	2	2	(0.5)	2
Musculoskeletal and connective tissue disorders, overall	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Pain in extremity	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1

Ev = number of adverse events of 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 adverse event in corresponding class, SAF = safety analysis set, TEAE = treatment-emergent adverse event

[1] Related TEAEs are all TEAEs which are "probably" or "possibly" related to study procedure or relationship is unknown or missing

Source: Table 14.3.2.2.31

The number and percentage of patients with TEAEs related to the study procedure until Week 56 were similar in both treatment groups, with 55 events in 28 (13.0%) patients treated with FYB203 versus 93 events in 37 (17.0%) patients treated with Eylea.

Most frequently, the TEAEs with a relation to study procedure belonged to the SOC Eye disorders. The most frequently reported PT was Conjunctival haemorrhage: 4 events in 4 (1.9%) patients treated with FYB203 versus 24 events in 14 (6.4%) patients treated with Eylea. All cases of conjunctival haemorrhage in the study eye were considered probably related to study procedure. All events were of mild severity and recovered/resolved. Therefore, no issues are raised. The second most frequently reported PT was

Eye pain: 4 events in 4 (1.9%) patients treated with FYB203 and 8 events in 5 (2.3%) patients treated with Eylea. Other PTs under the SOC Eye disorders occurred mostly in single patients.

A notable PT related to study procedure was IOP increased, which was recorded with 8 events in 6 (2.8%) FYB203 treated patients versus 22 events in 8 (3.7%) patients treated with Eylea.

Table 34: frequency of local (ocular, study eye) treatment-emergent adverse events in ≥ 1.0% of patients in either of the treatment groups (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 local (ocular) TEAE in study eye	67	(31.2)	125	75	(34.4)	157	142	(32.8)	282
Eye disorders, overall	60	(27.9)	103	66	(30.3)	116	126	(29.1)	219
Conjunctival haemorrhage	4	(1.9)	4	14	(6.4)	24	18	(4.2)	28
Cataract	8	(3.7)	9	7	(3.2)	7	15	(3.5)	16
Neovascular age-related macular degeneration	7	(3.3)	9	7	(3.2)	9	14	(3.2)	18
Eye pain	6	(2.8)	6	6	(2.8)	9	12	(2.8)	15
Visual acuity reduced	7	(3.3)	7	4	(1.8)	4	11	(2.5)	11
Vision blurred	6	(2.8)	6	3	(1.4)	3	9	(2.1)	9
Visual impairment	3	(1.4)	3	5	(2.3)	5	8	(1.8)	8
Retinal pigment epithelial tear	4	(1.9)	4	2	(0.9)	2	6	(1.4)	6
Retinal haemorrhage	3	(1.4)	3	2	(0.9)	2	5	(1.2)	5
Iritis	1	(0.5)	1	3	(1.4)	4	4	(0.9)	5
Macular fibrosis	3	(1.4)	3	1	(0.5)	1	4	(0.9)	4
Swelling of eyelid	0	(0.0)	0	4	(1.8)	5	4	(0.9)	5
Vitreous detachment	3	(1.4)	3	1	(0.5)	1	4	(0.9)	4
Vitreous floaters	3	(1.4)	3	1	(0.5)	1	4	(0.9)	4
Photopsia	3	(1.4)	3	0	(0.0)	0	3	(0.7)	3
Subretinal fluid	3	(1.4)	3	0	(0.0)	0	3	(0.7)	3
Vitreoretinal traction syndrome	3	(1.4)	3	0	(0.0)	0	3	(0.7)	3
Investigations, overall	7	(3.3)	9	9	(4.1)	25	16	(3.7)	34
Intraocular pressure increased	7	(3.3)	9	9	(4.1)	25	16	(3.7)	34
Infections and infestations, overall	5	(2.3)	6	7	(3.2)	7	12	(2.8)	13
Conjunctivitis	5	(2.3)	6	6	(2.8)	6	11	(2.5)	12
Injury, poisoning and procedural complications, overall	3	(1.4)	4	3	(1.4)	3	6	(1.4)	7
General disorders and administration site conditions, overall	1	(0.5)	3	4	(1.8)	4	5	(1.2)	7
Sensation of foreign body	0	(0.0)	0	3	(1.4)	3	3	(0.7)	3

Ev = number of TEAEs of specified AE type, MedDRA = medical dictionary for regulatory activities, N = total number of patients, n = number of patients with at least 1 adverse event of specified AE type, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Source: Table 14.3.2.2.15

For local TEAEs (ocular, study eye) until Week 56, the event numbers were comparable with FYB203 and Eylea treatment. Also, they were in line with known undesirable effects of Eylea [Eylea SmPC, 2024; Elyea EPAR, 2024]. 125 events occurred in 67 (31.2%) patients treated with FYB203 versus 157 events in 75 (34.4%) patients treated with Eylea. The most frequent PT under the SOC Eye disorders was Conjunctival haemorrhage with 4 events in 4 (1.9%) patients with FYB203 versus 24 events in 14 (6.4%) patients with Eylea. Other notable PTs included PT Cataract with 9 events in 8 (3.7%) patients with FYB203 versus 7 events in 7 (3.2%) patients with Eylea and PT Neovascular age-related macular degeneration with 9 events in 7 (3.3%) patients with FYB203 versus 9 events in 7 (3.2%) patients with Eylea. The events of Neovascular age-related macular degeneration in the study eye were mild or moderate and majority of the outcomes were recorded as resolved and unrelated to study procedure or study treatment. The most frequent PT under the SOC Investigations was IOP increased occurring with 9 events in 7 (3.3%) patients with FYB203 versus 25 events in 9 (4.1%) patients with Eylea.

Table 35: Frequency of local (ocular, fellow eye) treatment-emergent adverse events (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 local (ocular) TEAE in fellow eye	45	(20.9)	53	48	(22.0)	58	93	(21.5)	111
Eye disorders, overall	40	(18.6)	46	45	(20.6)	55	85	(19.6)	101
Neovascular age-related macular degeneration	22	(10.2)	22	24	(11.0)	26	46	(10.6)	48
Cataract	7	(3.3)	7	4	(1.8)	4	11	(2.5)	11
Visual acuity reduced	2	(0.9)	2	2	(0.9)	2	4	(0.9)	4
Age-related macular degeneration	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Chalazion	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Choroidal neovascularization	1	(0.5)	1	2	(0.9)	2	3	(0.7)	3
Cataract cortical	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Cataract nuclear	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Dry eye	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Eye pruritus	1	(0.5)	1	1	(0.5)	1	2	(0.5)	2
Keratitis	2	(0.9)	2	0	(0.0)	0	2	(0.5)	2
Blepharitis	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Blepharitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Conjunctival haemorrhage	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Conjunctival suffusion	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Conjunctivitis allergic	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Detachment of macular retinal pigment epithelium	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Glaucoma	0	(0.0)	0	1	(0.5)	2	1	(0.2)	2
Lacrimation increased	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Lens dislocation	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Macular degeneration	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Photopsia	1	(0.5)	1	0	(0.0)	0	1	(0.2)	1
Retinal degeneration	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal depigmentation	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Retinal pigment epithelial tear	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Vision blurred	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Vitreous floaters	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Vitreous haemorrhage	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Infections and infestations, overall	5	(2.3)	5	1	(0.5)	1	6	(1.4)	6
Conjunctivitis	5	(2.3)	5	0	(0.0)	0	5	(1.2)	5
Conjunctivitis bacterial	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Investigations, overall	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Intraocular pressure increased	2	(0.9)	2	1	(0.5)	1	3	(0.7)	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps), overall	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1
Fibroma	0	(0.0)	0	1	(0.5)	1	1	(0.2)	1

Ev = number of TEAEs of specified adverse events type, MedDRA = medical dictionary for regulatory activities, N = total number of patients, n = number of patients with at least 1 adverse event of specified adverse event type, SAF = safety analysis set, TEAE = treatment-emergent adverse event

Source: Table 14.3.2.2.20

For local TEAEs (ocular, fellow eye) until Week 56, the occurrences were similar in the two treatment groups: 53 events in 45 (20.9%) patients with FYB203 and 58 events in 48 (22.0%) patients with Eylea. The most frequent PT that occurred in the fellow eye was Neovascular age-related macular degeneration: in total, 48 events in 46 (10.6%) patients. The occurrences were similar between the groups: 22 events in 22 (10.2%) patients from the FYB203 group and 26 events in 24 (11.0%) patients from the Eylea treatment group. A slight imbalance in frequencies has been reported for the PT conjunctivitis for FYB203 vs. Eylea (5 (2.3%) subjects vs. none). Nevertheless, reported events of conjunctivitis in the fellow eye were of mild or moderate severity. All events did recover/resolve. Incidence was low and none of the cases reported were considered related either to study treatment or study procedure. Therefore, no safety concerns are raised regarding this imbalance.

Of note, the fellow eye could be treated with Eylea, which was allowed after Visit 3 and was to be timely separated by at least 14 days from study eye treatment. The TEAEs in the fellow eyes were mild or moderate in nature and started after Visit 3. The outcomes were recorded as ongoing (not recovered/not resolved) at the time of the study completion. The TEAEs in the fellow eyes were judged as unrelated to the study procedure or treatment in the study eye.

2.5.8.3. Serious adverse event/deaths/other significant events

AESI

The following AEs were classified as Adverse Events of Special Interest (AESIs):

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

Table 36: Treatment-emergent adverse events of special interest (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

Source: Table 14.3.2.2.28

A total of 13 (3.0%) patients reported AESIs until Week 56: 10 events in 6 (2.8%) patients treated with FYB203 and 12 events in 7 (3.2%) patients treated with Eylea.

Regarding local AESIs, the most frequent TEAEs belonged to the SOC Eye disorders and were classified as ocular inflammatory AESIs: a total of 13 events in 8 (1.8%) patients were reported. Frequently reported PTs were Iridocyclitis, Iritis, Vitritis and Uveitis. These events occurred in the study eye.

Of the PTs, Iritis with 5 events (in one patient treated with FYB203 and in three patients treated with Eylea) was reported as possibly related to the study treatment in 4 of these cases. PT Iridocyclitis with 4 events (in two patients treated with FYB203 and one patient treated with Eylea) was reported as probably related to the study treatment for 2 events or unrelated to the study treatment for the other 2 events.

PT Vitritis with 2 events (in one patient treated with FYB203 and in one patient treated with Eylea) was reported as possibly related to the study treatment. PT Uveitis with 2 events (in 1 patient treated with FYB203) was reported as possibly related to the study treatment (1 event) and probably related to the study treatment (1 event).

AESIs grouped under the SOC Investigations included the PT IOP increased: Two events in one (0.5%) patient treated with FYB203 where one event affected the study eye and one event affected the fellow eye. The events were reported as unrelated to the study procedure or study treatment and the outcome was recorded as resolved. Both events were moderate in severity. PT IOP increased was observed with 5 events in 3 (1.4%) patients treated with Eylea where all 5 events affected the study eye. Three of the events were reported as possibly/probably related to study treatment and the outcome was recorded as resolved. The events were mild or moderate in severity.

The frequency of AESIs reported for both treatment arms was comparable. With exception to one moderate ocular AESI of the fellow eye reported by one patient of the FYB203 arm (PT: IOP increased), ocular AESIs were reported for the study eye. Most ocular AESIs were of mild or moderate severity. One severe event of iridocyclitis and one severe event of uveitis, were both reported by one patient in the FYB203 arm. Non-ocular AESIs were reported as one mild event of ischaemic stroke by one patient in the Eylea arm and one severe event of cerebrovascular accident reported by one patient in the FYB203 arm. All AESIs recovered/resolved (with sequelae). Type and frequency of AESIs is in line with Eylea SmPC and/or EPAR [2024]. This is considered acceptable. Most of the AESIs reported were considered probably or possibly related to study procedure or study treatment. All related AESIs recovered/resolved (with sequelae). Reported AESIs were all in line with the Eylea SmPC/EPAR. Most events were of mild or moderate severity. Therefore, no safety concerns are raised regarding the occurrence of AESIs related to study procedure or study treatment.

SAEs

Table 37: Overview of serious systemic treatment-emergent adverse events (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 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	(0.5)	1	0	(0.0)	0	1	(0.2)	1

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
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
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
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

System Organ Class Preferred Term (MedDRA 23.0 Mixed)	FYB203 N=215			Eylea N=218			Total N=433		
	n	(%)	Ev	n	(%)	Ev	n	(%)	Ev
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 = 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

Source: Table 14.3.2.2.26

The most frequently recorded SOC was Infections and infestations with a total of 15 (3.5%) patients: 13 events in 8 (3.7%) patients treated with FYB203 and 8 events in 7 (3.2%) patients treated with Eylea. The most frequently reported PT under SOC Infections and infestations was COVID-19: 4 events in 4 (1.9%) patients treated with FYB203 and 1 event in 1 (0.5%) patient treated with Eylea.

Other systemic SAEs were recorded more than once in the following SOCs, but with PTs occurring in mostly single patients only: Neoplasms benign, malignant and unspecified (incl. cysts and polyps) in 8 (1.8%) patients; Cardiac disorders in 6 (1.4%) patients; Gastrointestinal disorders in 6 (1.4%) patients; Nervous system disorders in 5 (1.2%) patients; Musculoskeletal and connective tissue disorders in 4 (0.9%) patients; Injury, poisoning and procedural complications in 3 (0.7%) patients; Metabolism and nutrition disorders in 3 (0.7%) patients; Hepatobiliary disorders in 2 (0.5%) patients; Respiratory, thoracic and mediastinal disorders in 2 (0.5%) patients; and Vascular disorders in 2 (0.5%) patients.

All systemic SAEs reported until Week 56 were unrelated to study procedure or to study treatment except for 1 event (Cerebrovascular accident, patient treated with FYB203: possibly related to treatment).

Table 38: Serious treatment-emergent adverse events affecting eye (local) per patient

Patient	Age / Sex	MedDRA PT / (Start day–Stop day)	Eye Affected	AESI / Severity	Related to Study Procedure / Study Treatment	Outcome
Treatment Group: FYB203						
	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						
	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 16.2.7.3, Listing 16.2.4.1

Overall, the nonfatal SAE occurrences until Week 56 were comparable in the 2 treatment groups: 38 events in 19 (8.8%) patients treated with FYB203 and 40 events in 28 (12.8%) patients treated with Eylea. The SAEs were mostly systemic and rarely local.

For the study eye, local SAEs until Week 56 were observed in a total of 4 patients: 2 patients in the FYB203 group (PT Iridocyclitis, PT Uveitis and PT Rhegmatogenous retinal detachment) and 2 patients in the Eylea group (PT Visual impairment and PT Corneal dystrophy, both unrelated to study treatment or study procedure). The Investigator judged PT Iridocyclitis and PT Uveitis as probably related to study treatment and to study procedure. PT Rhegmatogenous retinal detachment was judged as possibly related to study procedure but unrelated to study treatment. Local SAEs in the study eyes were resolved or resolved with sequelae. The SAE Rhegmatogenous retinal detachment led to study discontinuation and study treatment withdrawal in one patient. Additionally, PT Iridocyclitis and PT Uveitis in one patient were considered as a TEAE of special interest.

For the fellow eye, local SAEs until Week 56 were observed in 3 patients (PTs Neovascular age-related macular degeneration, Retinal degeneration and Glaucoma). PT Neovascular age-related macular degeneration resolved or resolved with sequelae while the other 2 PTs were not resolved. Local SAEs in the fellow eyes were unrelated to study treatment or study procedure.

Deaths

All fatal outcomes were considered as unrelated to study treatment or study procedure.

Table 39: Occurrence of death by patient during treatment

Patient	Age / Sex	MedDRA PT / (Start day–Stop / Death day)	AESI/ Severity/ Serious	Related to Study Procedure / Study Treatment	Outcome
Treatment Group: Eylea					
	69 / Male	Cardiac failure/ (Day 41–Day 41)	No/Severe/ Yes	Unrelated / unlikely to be related	Fatal
Treatment Group: FYB203					
	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	Toxic shock syndrome/ (Day 273–Day 274)	No/Severe/ Yes	Unrelated / unrelated	Fatal
		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, PT = preferred term

Source: Listing 16.2.7.10, Listing 16.2.4.1

2.5.8.4. Discontinuation due to adverse events

Overall, 18 events in 10 (4,7%) patients treated with FYB203 and 2 events in 2 patients (0,9%) treated with Eylea led to discontinuation of treatment.

The TEAEs leading to study treatment withdrawal were the same as TEAEs leading to study discontinuation, except for 3 single events – overall, 16 events in 9 patients (4,2%) vs. 1 event in 1 patient (0,5%) led to completely discontinuation of the study.

FYB203 - The local (ocular) TEAEs leading to discontinuation in the FYB203 group included macular hole, rhegmatogenous retinal detachment and subretinal fluid while the rest were systemic TEAEs (cardiac failure, COVID-19, COVID-19, pneumonia, toxic shock syndrome, acute myeloid leukaemia, oesophageal carcinoma stage 0, aspiration, pulmonary fibrosis, abdominal adhesions, ileus and cerebrovascular accident).

Eylea - The TEAEs leading to discontinuation in the Eylea group were cardiac failure (fatal) and eye disorder (not related).

None of the TEAEs occurred in more than 1 patient except for cardiac failure reported by a total of 3 (0.7%) patients and COVID-19 reported by a total of 2 (0.5%) patients.

Most events reported in the FYB203 arm were not related to study procedure or treatment (12/18 events). None of the events reported in the Eylea arm were considered related to study treatment or procedure.

TEAEs leading to study treatment withdrawal or to discontinuation of the study judged as possibly/probably related to the study treatment or to study procedure are described below:

Macular hole (moderate event) was reported by one patient treated with FYB203 and was judged as possibly related to study procedure but unlikely to be related to study treatment and the outcome was recorded as not recovered or not resolved. The reported TEAE led to withdrawal of study treatment, however, the study was completed on day 393.

Rhegmatogenous retinal detachment led to premature study discontinuation in one patient (3 moderate events) and was recorded as an SAE. The Investigator suspected the TEAE as possibly related to the study procedure and unrelated to the study treatment. The treatment discontinued after 1 administration on day 1 and the study discontinued on day 37.

Subretinal fluid (moderate event) was reported by one patient treated with FYB203 a was judged as probably related to study treatment. The outcome was recorded as not recovered/not resolved. The study treatment was discontinued on day 225 and the study on day 267.

Cerebrovascular accident (stroke) occurred in one patient treated with FYB203 was judged as possibly related to study treatment. The TEAE cerebrovascular accident was considered as severe and the outcome was resolved with sequelae. The treatment was discontinued on day 169 (5^{th} IVT injection) and the study on day 221.

In the terms of severity, in the FYB203 arm, 12 TEAEs leading to study treatment withdrawal or study discontinuation were considered as severe and 6 as moderate. In the Eylea arm, 1 TEAE was considered as severe, 1 as mild.

2.5.8.5. Laboratory findings

The applicant states that the results of clinical safety laboratory evaluation, vital signs and physical examination did not indicate any relevant differences between the 2 treatment groups. Furthermore, the results from other safety assessments resulting from ophthalmological examinations and tonometry were also well balanced between the 2 treatment groups and no relevant safety-related differences were identified.

Regarding haematology, the mean and median changes during the study until Week 56 were minimal. No clinically relevant differences between the treatment groups have been observed in any haematology parameter throughout the study. Clinically significant abnormal values for clinical chemistry were slightly more prominent in the FYB203 vs. Eylea treatment group up to Week 40 (V7) and comparable at Week 56 (V9). Clinically significant abnormal urinalysis values were comparable between treatment groups throughout the study. Also, no clinically relevant differences between the treatment groups have been observed for the patients' coagulation profile. In general, no substantial differences were observed regarding vital signs, or physical examination parameters between the treatment groups during the study.

Full data regarding to laboratory evaluation, vital signs and physical examination is to be found in module 5.

In the SOC investigations, 16 treatment-related events in 7 (1.6%) patients were observed overall. The most frequently reported treatment-related PT was IOP increased with a total of 14 events in 6 (1.4%) patients: 2 events in 1 (0.5%) patient treated with FYB203 and 12 events in 5 (2.3%) patients treated with Eylea. A total of 30 events in 14 (3.2%) patients were reported as being related to study procedure indicating that increase in IOP was judged as either related to study treatment or to study procedure.

The incidence of IOP in Eylea arm is slightly higher than in the FYB203 arm (FYB203 vs. Eylea: 8 (3.7%) vs. 9 (4.1%) patients), this is acceptable. According to Eylea SmPC, the frequency for Intraocular pressure increase is determined as common (≥1/100 to <1/10). Increase in IOP was classified as an AESI for 1 patient from the FYB203 group and 3 patients from the Eylea group.

One patient experienced one moderate episode in the study eye and the fellow eye each. Both events recovered and were not considered related to study procedure or treatment. The patient completed the study without any treatment interruption.

One patient had 3 moderate episodes of IOP increased in the study eye. All episodes did recover/resolve. Two episodes were considered related to study procedure and/or treatment. The patient completed the study.

One patient experienced one moderate episode of IOP increased in the study eye. The event resolved on the same day. The episode was considered related to study procedure and treatment. The patient completed the study without any treatment interruption.

One patient experienced one mild episode of IOP increased in the study eye. The event resolved on the same day. The episode was considered related to study procedure and treatment. The patient completed the study.

2.5.8.6. In vitro biomarker test for patient selection for safety

Not applicable

2.5.8.7. Safety in special populations

Not applicable

2.5.8.8. Immunological events

See *Immunogenicity* in section 2.5.3

2.5.8.9. Safety related to drug-drug interactions and other interactions

Not applicable

2.5.8.10. Post marketing experience

Not applicable

2.5.9. Discussion on clinical safety

No Summary of clinical safety was provided by the applicant (document contained only reference to the specific section of the Clinical study report). This is not fully in accordance with the ICH Topic M4E. The safety assessment is based on data provided in the Clinical overview and Clinical study report.

Data collection:

The clinical safety assessment of FYB203 is based on one phase III parallel-group, 1:1 randomised, double-masked, multicentre completed study (MAGELLAN-AMD). The study compares the efficacy and safety of the FYB203 biosimilar with EU Eylea in patients with neovascular Age-Related Macular

Degeneration (AMD). According to the CHMP advice, it was agreed that a naive nAMD population is a sensitive and reasonable patient population to assess clinical biosimilarity between Eylea and FYB203.

Patient exposure:

A total of 433 patients have received at least one dose of test product FYB203 or reference product Eylea. The patients were randomised in ratio 1:1 approximately (215/218 patients) in two comparable arms.

A total of 196 (91.2%) patients in the FYB203 group and 206 (94.1%) patients in the Eylea group completed the study until Week 56.

A total of 183 patients (85.1%) in the FYB203 group and 199 patients (91.3%) in the Eylea group completed the treatment – they received all 8 scheduled injections.

The exposure to study treatment between these two arms seems to be comparable, there are no relevant differences.

The last assessment was done after 56 weeks. The mean (SD) treatment duration was 323.1 (58.97) days and the mean (SD) study duration was 398.7 (53.03) days.

In general, the treatment and study duration were well balanced between both treatment groups and no relevant differences were observed.

Adverse events:

TEAEs

Overall incidence for TEAEs was slightly higher in the FYB203 arm vs. Eylea arm (76.7 % vs 72.5 %). Incidence of ocular TEAEs in study eye were slightly lower in FYB203 arm vs Eylea arm (31.2 % vs 34.4 %) and also in fellow eye (20.9 % vs 22.0%).

Systemic TEAEs were observed in FYB203 arm (57.7 %) with higher incidence compared to Eylea arm (51.8 %). Incidence of serious TEAEs is lower in FYB203 arm compared to Eylea arm (7.9 % vs 10.6 %) as well as the incidence of severe TEAEs (3.7 % vs 5.0 %). Regarding PTs, incidences have been higher for the FYB203 arm vs. Eylea arm regarding nasopharyngitis (10 (4.7%) vs. 6 (2.8%) subjects); Coronavirus infection (6 (2.8%) vs. 1 (0.5%) subjects); and osteoarthritis (10 (4.7%) vs. 1 (0.5%) subjects). With exception to one event of severe coronavirus infection reported for one patient in the FYB203 arm, whose outcome is unknown, all these events were of mild or moderate severity, considered not or unlikely related to study procedure or treatment and recovered/resolved. Therefore, no safety concerns are raised regarding this imbalance.

Based on Eylea SmPC, systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. This information is provided in the PI of the reference medicinal product Eylea and also in the proposed PI (sections 4.4 and 4.8). According to the information provided in the section related to SAE, all systemic SAEs reported until Week 56 were unrelated to study procedure or to study treatment except for 1 event (Cerebrovascular accident, patient treated with FYB203: possibly related to treatment, see section AESI for more details). Given the FYB203 related systemic TEAEs, the following were reported within the study -related to study treatment (FYB203) - headache, cerebrovascular accident, somnolence, hypertension, anaemia, asthenia; related to study procedure (FYB203) – headache, somnolence, pain in extremity. For more details, please see the section TEAEs by relationship below.

Based on the size of the patients included in clinical study, such a study can generally not well inform on the rare (and less frequent) AEs. Nevertheless, the provided safety database is considered sufficient to

assess the comparability of common (≥1/100 to <1/10) and very common (≥1/10) adverse events. This is considered acceptable for biosimilar medicinal product.

The most frequently reported TEAEs were under the SOCs Eye disorders and SOC Infections and infestations. The number of events for TEAEs under the SOC Eye disorders was lower in the FYB203 group - 149 events/ 84 patients (39.1%) than in Eylea group -171 events/ 95 patients (43.6%).

The most **frequently** reported PTs under the SOCs Eye disorders were neovascular age-related macular degeneration (13.0 % FYB203 vs 12.8 % Eylea), cataract (5.1 % FYB203 vs 4.6 % Eylea) and conjunctival haemorrhage (2.3 % FYB203 vs 6.4 % Eylea). The observed PTs are in accordance with the known safety profile of aflibercept (proposed indication - neovascular AMD**;** cataract and conjunctival haemorrhage are listed ADRs). No clinically significant disbalances were noted.

The number of events for TEAEs under the SOC Infections and infestations was slightly higher in the FYB203 - (27.0 %) than in Eylea group (25.2 %). The most frequently reported PTs under the SOCs Infections and infestations were Covid-19 (8.8 % FYB203 vs 8.3 % Eylea), Nasopharyngitis (4.7 % FYB203 vs 2.8 % Eylea) and Conjunctivitis (2.8 % FYB203 vs 2.8 % Eylea). No clinically significant disbalances were noted.

Higher disbalances in observed PT osteoarthritis (4.7 % FYB203 vs 0.5 % Eylea) and PT hypertension (7.0 %, 15 patients FYB203 vs 4.1 %, 9 patients Eylea) and SOC Gastrointestinal disorders (10.2 % vs 6.9 %) were noted. It is acknowledged that hypertension was assessed as related to study treatment only in 1 patient in each group but considering the fact that a systemic VEGF inhibition is described to cause dose-related increases in systolic and diastolic blood pressure and since none of these risks is listed in Eylea and also in proposed PI, the applicant is asked to discuss the proposed disbalances further. The applicant provided additional data on the higher incidence of medical history of gastrointestinal disorders in the study - 17.2% in the FYB203 group (37 of 215 patients) and 14.7% in the Eylea group (32 of 218 patients) and also on incidence of a pre-existing and ongoing hypertension -72.1% in the FYB203 group (155 patients) and 70.6% in the Eylea group (154 patients). Moreover, the provided details did not show any observed trends. Thus, the issue has been considered sufficiently justified and solved.

Except the requested discussion on osteoarthritis and hypertension and GIT disorders, both arms are considered to be comparable, and no safety concern has been identified.

According to the **intensity** of reported TEAEs, both arms (FYB203 and Eylea) are considered comparable. The majority of TEAEs were mild (44.7 % FYB203 vs 39.0 % Eylea) or moderate (27.4 % FYB203 vs 26.6 % Eylea) intensity. Severe TEAEs were observed in lower incidence in FYB203 arm (10 patients/4.7 % vs 15 patients/6.9 %).

Severe TEAEs were most frequently observed in SOC Eye disorders (6 patients in total), Infection and infestations (5 patients in total) and Neoplasms benign, malignant and unspecified incl. cysts and polyps (5 patients in total). No PT was reported more than 2 times. In FYB203, PT with severe intensity were iridocyclitis, retinal pigment epithelial tear and uveitis. All 3 PTs were observed in the study eye and were probably related to study treatment. All 3 PT are listed in the Eylea and proposed SmPC.

Additionally, PT Cerebrovascular accident under SOC Nervous system disorders was reported as possibly related to study treatment. Please see above section AESI for further details.

TEAE was considered to be related to the study treatment if the Investigator had judged the relationship as "probably related" or "possibly related" or if the relationship to study treatment was missing or unknown.

Incidence of related TEAEs to the treatment were slightly higher in FYB203 arm compared to Eylea (9.3 % vs 7.3 %). The most frequently reported related TEAEs were from SOC Eye disorders (26 patients in total - FYB203 15 patients vs Eylea 11 patients) and Investigations (7 patients in total- FYB203 1 patient vs Eylea 6 patients). Majority of related PTs occurred with similar frequencies in both treatment groups and/or mostly in single patients.

Incidence of **related** TEAEs to the IVT injection were slightly lower in FYB203 arm compared to Eylea (13.0 % vs 17.0 %). The most frequently reported related TEAEs were from SOC Eye disorders (54 patients - FYB203 23 patients vs Eylea 31 patients) and Investigations (14 patients in total- FYB203 6 patients vs Eylea 8 patients). Majority of related PTs occurred with similar frequencies in both treatment groups and/or mostly in single patients. PT conjunctival haemorrhage was observed with higher frequency in Eylea arm (6.4 % vs 1.9 % in FYB203 arm). PT Vision blurred was observed in slightly higher frequency in FYB203 arm (2.3 % vs 0 %). A notable PT related to study procedure was IOP increased: 8 events in 6 (2.8%) patients with FYB203 versus 22 events in 8 (3.7%) patients treated with Eylea. Increased intraocular pressure, vision blurred and conjunctival haemorrhage are listed ADRs with frequency common or very common, which corresponds with observed TEAEs.

No clinical difference between reported related TEAEs arms or discrepancies from known safety profile of aflibercept were noted.

Ocular TEAE in study eye were observed with lower incidence in FYB203 arm (31.2 % vs 34.4 % in Eylea arm). The most frequently reported related TEAEs were from SOC Eye disorders (126 patients in total - FYB203 60 patients vs Eylea 66 patients) and Investigations (16 patients in total - FYB203 7 patients vs Eylea 9 patients). The most frequently reported PTs were conjunctival haemorrhages, cataract, neovascular AMD, eye pain, visual acuity reduced, visual blurred and increased intraocular pressure. These PTs correspond with known safety profile of aflibercept.

Ocular TEAEs in fellow eye were observed with lower incidence in FYB203 arm (20.9 % vs 22.0 % in Eylea arm). The most frequently reported related TEAEs were from SOC Eye disorders (85 patients in total - FYB203 40 patients vs Eylea 45 patients) and Investigations (6 patients in total - FYB203 5 patients vs Eylea 1 patient). The most frequently reported PTs were neovascular AMD, cataract, visual acuity reduced, AMD and conjunctivitis. The observed TEAEs are considered comparable between both arms.

ADRs:

TEAEs

TEAEs related to study treatment were reported in a total of 36 (8.3%) patients. The occurrence of related TEAEs was similar in both treatment groups: 34 events in 20 (9.3%) patients treated with FYB203 and 32 events in 16 (7.3%) patients treated with Eylea.

The most frequently reported TEAEs related to study treatment in FYB203 arm were: Neovascular age-related macular degeneration (6), Retinal pigment epithelial tear (3), Eye pain (3). The most frequently reported TEAEs related to study treatment in Eylea arm were: Intraocular pressure increased (5) and Neovascular age-related macular degeneration (3). Other PT were reported once or two times.

The most frequently reported TEAEs related to study procedure in FYB203 arm were: Intraocular pressure increased (6), Vision blurred (5), Conjunctival haemorrhage (4), Eye pain (4). The most frequently reported TEAEs related to study treatment in Eylea arm were: Conjunctival haemorrhage (14), Intraocular pressure increased (8), Eye pain (5), Swelling of eyelid (3) and Sensation of foreign body (3). Other PT were reported once or two times.

Given the FYB203 related systemic TEAEs, the following were reported within the study:

- related to study treatment (FYB203 arm) – headache 2 patients, cerebrovascular accident 1, somnolence 1, hypertension 1, anaemia 1, asthenia 1

- related to study procedure (FYB203 arm) – headache 2, somnolence 1, pain in extremity 1

No clinical difference between reported related TEAEs arms or discrepancies from known safety profile of aflibercept were noted.

Ocular SAEs

Frequencies of ocular serious TEAEs in the study eye have been comparable between treatment groups.

Two patients in FYB203 arm with coded ocular SAEs were assessed as related to study procedure and study treatment. One patient (iridocyclitis- probably related and uveitis – possibly related) and one patient (rhegmatogenous retinal detachment -possible related to study procedure). All coded SAEs affected study eye. Ocular SAEs in Eylea arm occurred in 5 patients (2 in study eye and 3 in fellow eye) and none of reported events was assessed as related. (For further detail please see table 10-12).

Systemic SAEs

All systemic SAEs reported until Week 56 were unrelated to study procedure or to study treatment except for 1 event (Cerebrovascular accident, patient treated with FYB203: possibly related to treatment).

AESI

A total of 13 (3.0%) patients reported AESIs until Week 56. 10 events in 6 (2.8%) patients treated with FYB203 and 12 events in 7 (3.2%) patients treated with Eylea. 3 patients treated with FYB203 had coded events as related to treatment/study procedure (patient – 63 yo female experienced mild vitritis – possibly related, patient – 77 yo female experienced mild iritis – possibly related and patient with iridocyclitis- probably related and uveitis – possibly related).

Deaths

None of the 5 patients treated with aflibercept with fatal outcome was assessed as related to the study procedure or study treatment.

Discontinuation

Only 2 reported TEAEs leading to study discontinuation were judged as possibly/probably related to the study treatment - subretinal fluid, reported by one patient and cerebrovascular accident (stroke), reported by one patient. Both TEAEs were observed in the FYB203 arm. Further 2 TEAEs leading to study discontinuation observed in FYB203 arm were judged as possibly related to the study procedure (one patient – macular hole, one patient - rhegmatogenous retinal detachment).

The reported ADRs in FYB203 are considered comparable with reported ADR in reference medicinal product (Eylea) arm. TEAEs related to study treatment were reported in slightly lower incidence than in Eylea arm. The observed ADRs are considered in accordance with known safety profile of aflibercept. Observed incidences of all reported ADRs do not significantly differ between both arms and are considered in line with the provided frequencies stated in proposed Product Information (PI). No safety concern is raised regarding the reported and assessed ADRs.

The provided data is considered relevant and support the proposed product information. The proposed ADRs (in accordance with reference medicinal product Eylea) are considered justified.

SAEs

Three serious TEAEs considered related to study treatment have been reported by 2 (0.9%) patients in the FYB203 arm vs. none in the Eylea arm.

Ocular SAEs – 2 patients in FYB203 arm experienced ocular SAEs.

78 y/o male patient experienced severe iridocyclitis and uveitis in study eye on days 237-252 (considered to be AESI). SAEs were assessed as probable related to study procedure and also study treatment. These risks are listed in Product Information. Outcome is described as resolved with sequelae (decreased visual acuity). 65 y/o male patient experienced moderate rhegmatogenous retinal detachment in study eye on days 44-51. SAE was assessed as possibly related to study procedure but unrelated to study treatment. SAE recovered due to surgery, but still needed follow-up observation and medicine. This SAE led to discontinuation of study. This risk is described in section 4.4 of SmPC and retinal detachment is listed in section 4.8 of SmPC. In Eylea arm 5 ocular SAEs were reported (all assessed as not related). Coded SAEs were neovascular age related macular degeneration, visual impairment, corneal dystrophy, retinal degeneration and glaucoma. With exception to the event of uveitis, all events recovered/resolved (with sequelae).

Systemic SAEs incidence is slightly lower in FYB203 arm than in Eyla arm (7.9% vs 10.6%). The most frequently were reported SAEs in SOC Infections and Infestations (FYB203 3.7 % vs Eylea 3.2 %). All systemic SAEs reported until Week 56 were unrelated to study procedure or to study treatment except for 1 event (Cerebrovascular accident, patient treated with FYB203: possibly related to treatment, see section AESI for more details). Additional PTs occur in mostly single patients only. Both arms are considered comparable. Most systemic serious TEAEs were of moderate or severe severity. Overall, reported SAEs were in line with known undesirable effects of Eylea [Eylea SmPC and EPAR, 2024]. This is considered acceptable. Therefore, no safety concerns are raised regarding the occurrence of the serious TEAEs.

According to the theoretical risk that non-ocular haemorrhages and arterial thromboembolic events may relate to VEGF inhibition, increased focus was given to all SAEs from SOC Cardiac disorders (2 patients, 2 cardiac failures in FYB203 arm) and SOC Nervous system disorders (1 case of cerebrovascular accident in FYB203 arm) and SOC Vascular disorders (no SAEs in FYB203 arm). No safety concern was raised regarding the systemic SAEs.

AESI

A total of 13 (3.0%) patients reported AESIs until Week 56. 10 events in 6 (2.8%) patients treated with FYB203 and 12 events in 7 (3.2%) patients treated with Eylea. The most frequent AESI belonged to the SOC Eye disorders and were classified as ocular inflammatory AESIs in study eye (4 patients in FYB203 arm vs 4 patients in Eylea arm). The coded PTs were iritis, iridocyclitis, vitritis and uveitis. All PTs are listed in product information with frequency uncommon (rare for vitritis), this corresponds with known safety profile of aflibercept. Further, intraocular pressure increased and cerebrovascular accident were reported in 1 patient each in FYB203 arm compared to 3 patients with increased intraocular pressure and 1 patient with ischaemic stroke in Eylea arm. Below are provided summaries of patients with coded AESI in FYB203 arm.

Patient – 73 yo male experienced mild iridocyclitis in a study eye on day 56 (duration 24 days). The drug was interrupted and medication was given. Outcome is coded as resolved (day 79) and causality unrelated. The patient completed study. Patient – 63 yo female experienced mild vitritis in a study eye on day 227 (duration 57 days). Dose was not changed and no treatment was given. Outcome is coded as recovered with possible causality. Patient completed study.

Patient – 77 y/o female experienced mild iritis in study eye on day 113 (duration 15 days). Dose was not changed and treatment was given. Outcome is coded as recovered with possible causality. Patient completed study.

Patient – 81 y/o female experienced intraocular pressure increased (26mmHg) with moderate severity in study and also in fellow eye on day 109 (duration 5 days). Dose was not changed and treatment was given. Outcome is coded as recovered with unrelated causality.

Patient – 84 y/o male (with history of hypertension, coronary artery disease, hypercholesterolaemia, atrial fibrillation and carotid artery stenosis) experienced severe cerebrovascular accident on days 201 (duration 23 days). Drug was withdrawn and treatment was given. Outcome is coded as recovered with sequelae (slight paresis of the left limbs). Causality is coded as unrelated to study procedure but possibly related to study treatment.

Patient – 78 y/o male experienced severe/mild uveitis (on day 237, duration 16 days and on day 253, duration 85 days) and moderate/severe iridocyclitis (on day 228, duration 9 days and on day 237, duration 16 days). Drug was interrupted and adequate treatment was given. Outcome is coded as recovered with sequelae (panuveitis, decreased visual acuity). Causality is coded as probably related. The patient completed study.

The applicant provided brief information on the fact that the subgroup of 15 patients received injections with different syringes than the original ones provided by the Sponsor and total of 5 (33.3%) patients in this group experienced ocular inflammatory AESIs (according to the CSR – 2 patients in FYB203 experienced 1 iritis and 1 vitritis and 3 patients in Eylea arm experienced iritis (2) and vitritis (1). The other subgroup of 418 patients received injections with the original syringes provided by the Sponsor and an ocular inflammatory AESI was observed in 3 (0.7%) patients. The applicant was asked for thorough discussion of the evident difference between observed higher incidence of ocular inflammatory AESIs with different syringes (reasons for usage of different syringes, characterisation of their differences and discussion on causation of such a difference in incidence in AESI - 1/3 of patients with different syringe suffered from ocular inflammatory). The provided reason for the usage of different syringes with observed higher incidence of ocular inflammatory AESIs was justified by the deviation of the single site. The deviation was caused by the preference of the single site due to the smaller size of the injection syringe allowing for easier handling and not blocking the injector's visual field to the cornea during the injection. The main differences in the devices and procedure at site 14008 included the use of two siliconised syringes instead of one, different syringe material and additional handling steps. According to the provided tables, filter needles were identical, differences were in the usage of sterile syringes - syringe n.1 - polycarbonate vs polypropylene, luer slip instead of luer lock, syringe n.2 (only in the 14008 site) – polypropylene + different needle design (staked-in) with same dimensions. The applicant discussed the causation of such difference and explained it by the possible increased particulate matter release from the siliconised devices or by potential bending or dulling of the injection needle (from insertion into the tip of the transfer syringe). The applicant's justification is acknowledged and as the issues was caused by the deviation of the single site. The concern is not further pursued.

Ocular TEAEs in the study eye have been reported in higher frequency in the FYB203 arm vs. Eylea arm for subjects injected with "other syringes" (7 (100.0%) subjects reported 25 events vs. 7 (87.5%) subjects reported 47 events). While eye disorders were more frequent in the FYB203 arm (7 (100.0%) subjects/19 events vs. 7 (87.5%) subjects/24 events), investigations were reported in higher frequency in the Eylea group. Only PT for the latter reported was IOP increased (3 (42.9%) subjects/4 events vs. 5 (62.5%) subjects/18 events). In comparison, frequencies of reported ocular TEAEs in the study eye for the subgroup "original syringes" were comparable to the overall data as discussed above. The low number of subjects in the subgroup "other syringes" may hamper interpretability of data presented.

To address the notable imbalances in the number of events for IOP increased, as shown for the "other syringes" subgroup vs. "original syringes", the applicant provided a summary of the number of events and patients by treatment group and eye affected by increased IOP. Also, a table of tonometry results for the "IOP increased"-TEAEs in the study eye has been presented, categorised by syringe used,

treatment group and patient. All events of "IOP increased" for patients in the Eylea group receiving treatment via "other syringes" were of mild or moderate severity and did recover/resolve or were recovering/resolving.

Furthermore, it was reported that all 15 patients receiving injections with "other syringes" than provided by the sponsor were treated at this same site. Major differences of the medical devices and application procedure used at this one site vs. devices provided by the sponsor were:

- use of a separate transfer syringe in addition to the injection syringe
- syringe material ("other syringes" vs. "provided by sponsor"): polypropylene vs. polycarbonate
- connections and dimensions of the needles ("other syringes" vs. "provided by sponsor"): staked-in needle (30G x ½", 0.3 mm x 12.7 mm) vs. Luer-lock needle (30G x ½", 0.3 mm x 13 mm)

Dimensions of the listed filter needles and injection needles are, nevertheless, in line with the recommendations given in the product information of the originator [Eylea SmPC, 2024]: a 18 G, 5-micron filter needle is provided together with the vial. A 30 G x ½ inch injection needle and a 1-ml sterile, Luer-lock syringe are recommended for the intravitreal injection procedure.

However, application procedure as recommended in the Eylea SmPC has not been followed for the use of the "other syringes". The vials were emptied using a separate Luer-slip transfer syringe. After removing the filter needle, the plunger was moved up and down several times to expel air bubbles. This was followed by inserting the staked-in needle of the injection syringe in the Luer-slip tip of the transfer syringe to withdraw the contents. Remaining steps were in accordance with the Eylea SmPC. The applicant hypothesises that the cumulative agitation from the additional plunger movements, could have increased particulate matter release from the siliconised devices or may have resulted in bending or dulling of the injection needle. This is plausible.

These discrepancies have affected only a small number of study participants. Also, all events of IOP increased in the "other syringe" subgroup were of moderate or mild severity and did resolve/recover or were resolving/recovering. Furthermore, recommended syringe and needles for the application procedure listed in the Ahzantive SmPC as well as the description of the application procedure itself are in line with the originator. Therefore, in summary, the concern regarding the imbalances in the number of events for IOP increased reported for the "other syringes" subgroup is considered resolved.

The applicant justified the selection of the AESI by the collaboration between the applicant and the CROs. The selection of AESIs was based on the applicant's and CRO's earlier experience with ranibizumab biosimilars taking into account the EMA SmPC and FDA Prescribing information and considering the listed AESIs as typical for both aflibercept and ranibizumab products.

TEAEs leading to discontinuation

Overall, 18 events in 10 (4,7%) patients treated with FYB203 and 2 events in 2 patients (0,9%) treated with Eylea led to discontinuation of treatment. 16 events in 9 patients (4,2%) in the FYB203 arm vs. 1 event in 1 patient (0,5%) the Eylea arm led to completely discontinuation of the study.

As possibly/probably related to study treatment were judged following TEAEs:

Subretinal fluid was reported by one patient treated with FYB203 a was judged as probably related to study treatment. The outcome was recorded as not recovered/not resolved. The study treatment was discontinued on day 225 and the study on day 267.

Cerebrovascular accident (stroke) occurred in one patient treated with FYB203 was judged as possibly related to study treatment. The TEAE cerebrovascular accident was considered as severe and the

outcome was resolved with sequelae. The treatment was discontinued on day 169 (5th IVT injection) and the study on day 221.

As possibly related to study procedure were judged following TEAEs observed in the FYB203 arm:

Macular hole was reported by one patient treated with FYB203 and was judged as possibly related to study procedure but unlikely to be related to study treatment and the outcome was recorded as not recovered or not resolved. The reported TEAE led to withdrawal of study treatment, however, the study was completed on day 393.

Rhegmatogenous retinal detachment led to premature study discontinuation in one patient (3 events) and was recorded as an SAE. The Investigator suspected the TEAE as possibly related to the study procedure and unrelated to the study treatment. The treatment discontinued after 1 administration on day 1 and the study discontinued on day 37.

In term of severity, in the FYB203 arm, 12 TEAEs were considered as severe (7 of them were fatal, 3 were not recovered/not resolved and 2 resolved with sequelae) and in the Eylea arm, 1 TEAE was considered as severe (fatal).The incidence of severe TEAEs leading to discontinuation is higher in the FYB203 arm (12 TEAEs vs. 1 TEAE), however, the overall incidence of severe TEAEs observed in both arms is comparable (23 TEAEs vs 20 TEAEs). Only one severe TEAE cerebrovascular accident (stroke) reported in one patient was assessed as possibly related to study treatment FYB203 and none to study treatment Eylea.

Most events considered related to study procedure or treatment were of moderate severity and in line with the Eylea SmPC/EPAR [2024] or reasonably connected to the application procedure.

The incidence of TEAEs leading to withdrawal of study treatment (4,7% vs.0,9%) or to complete discontinuation of study (4,2% vs. 0,5%) is higher in the FYB203 arm.

The discussion regarding the imbalance between the incidence of TEAEs leading to discontinuation of the treatment, resp. to discontinuation of the study has been provided.

Deaths

In total 7 deaths were reported within the study. 2 patients did not receive any treatment product (screening period), 1 patient died when treated with Eylea (cardiac failure, day 41 of treatment, assessed as unrelated). 4 patients died when treated with FYB203.

One patient (86 y/o female) died due to pulmonary fibrosis and cardiac failure on Day 325. Death was assessed as not related to FYB203. The patient was several times hospitalised, had positive microbiology sampling for pseudomonas, decreased kidney function values, breathing difficulties and was treated with antibiotics and oxygen therapy.

One patient (70 y/o male) died due to COVID-19/pneumonia and heart failure on Day 265. Death was assessed as not related to FYB203.

One patient (72 y/o male) died due to toxic shock syndrome caused by ileus on day 274. Death was assessed as not related to FYB203. One patient (77 y/o male) died due to acute myeloid leukaemia on day 270. Concomitantly patient suffered from coronavirus infection and kidney failure. Death was assessed as not related to FYB203.

All causes of death were of non-ocular nature. The narratives for all patients have been provided by the applicant. All patients had prior/concomitant co-morbidities and the causes of most of the deaths are consistent with the age of the study population. None of the reported deaths were considered related to the study drug. No safety concerns are raised from reported fatal cases.

Immunogenicity

The percentage of ADA-positive patients from the first IP administration through Week 56 was generally low in both treatment arms and ranged between 1.0% and 2.7% in the FYB203 group and between 0.5% and 1.5% for the Eylea overall treatment group. 2 patients at week 40 and 3 patients at week 56 had Nab positive in FYB203 arm and no patient with positive Nab was observed in Eylea arm. The percentage of ADA patients was slightly higher with FYB203 compared to Eylea across all timepoints up to Week 56 and the number of patients with treatment-induced ADA is also slightly higher in FYB203 arm - 4 patients vs 2 patients in Eylea arm. No treatment-boosted ADAs were observed between treatments. Based on the provided data and due to overall low incidence of ADAs, the impact of immunogenicity on safety is very limited and no concerns arise regarding the impact of immunogenicity on safety. Information on the risk of immunogenicity is described in sections 4.4 and 4.8 of SmPC in line with the reference medicinal product.

Laboratory and other findings

In the SOC Investigations, 16 treatment-related events in 7 (1.6%) patients were observed overall. The most frequently reported treatment-related PT was IOP increased with a total of 14 events in 6 (1.4%) patients: 2 events in 1 (0.5%) patient treated with FYB203 and 12 events in 5 (2.3%) patients treated with Eylea. A total of 30 events in 14 (3.2%) patients were reported as being related to study procedure indicating that increase in IOP was judged as either related to study treatment or to study procedure.

No safety concerns are raised regarding the observed changes in laboratory findings. Full data regarding to laboratory evaluation, vital signs and physical examination is to be found in module 5, however, some summary or broad discussion from the applicant is missing. No summary of clinical safety was provided and even in the clinical overview such a discussion is not to be found.

A thorough discussion regarding to abnormalities in haematology, chemical and urinalysis parameters, their clinical significance and their relationship to the drug treatment has been provided. The summary of the laboratory parameters, vital signs and other monitored parameters has been also provided No safety concerns have been identified regarding the observed changes in laboratory and other findings.

including increased PT IOP.

2.5.10. Conclusions on the clinical safety

The overall safety profile of FYB203 is in line with known adverse events of the reference medicinal product Eylea [SmPC 2024]. No safety concerns (regarding assessed AEs, clinically meaningful differences in laboratory findings and immunogenicity) were seen compared to reference medicinal product. Overall, FYB203 and Eylea demonstrated comparable safety profiles. Biosimilarity is supported from a safety perspective.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelia tears • Cataract (especially of traumatic origin)
Important potential risks	• Medication errors • Off-label use and misuse • Embryo-fetotoxicity
Missing information	• None

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Table 40: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2,3 and 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures : Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see Annex 4.1) Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet sections 2,3 and 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see Annex 4.1) Additional pharmacovigilance activities: None
Transient intraocular pressure increase	Routine risk minimisation measures: SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	
Retinal pigment epithelial tears	Routine risk minimisation measures: SmPC sections 4.4, and 4.8 Package Leaflet sections 2 and 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin)	Routine risk minimisation measures: SmPC sections 4.2, 4.4, and 4.8 Package Leaflet sections 2, 3 and 4 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on identified and potential risks (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	
Medication errors	Routine risk minimisation measures: SmPC sections 4.2, 4.9, and 4.6 Package Leaflet sections 1 and 3 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None
Off-label use and misuse	Routine risk minimisation measures: SmPC sections 4.1. 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	
Embryo-fetotoxicity	Routine risk minimisation measures: SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2 Other routine risk minimisation measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Ahzantive must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimisation measures: Educational programme: Beyond routine minimisation activities, additional measures are currently needed to raise patients' and physicians' awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video; patient guide "Your guide to Ahzantive", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Not applicable. Additional pharmacovigilance activities: None

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Eylea 40 mg/mL solution for injection in a vial. The bridging report submitted by the applicant has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ahzantive (aflibercept) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Ahzantive (also referred to as FYB203) 40 mg/mL solution for injection in a vial has been developed as a biosimilar to the reference product Eylea.

The reference product Eylea is authorised in 3 presentations: Eylea 40 mg/mL solution for injection in pre-filled syringe, Eylea 40 mg/mL solution for injection in a vial and Eylea 114.3 mg/ml solution for injection. The approved Eylea indications differ for respective presentations as follows:

- Eylea 40 mg/mL solution for injection in pre-filled syringe: nAMD, branch RVO or central RVO, DME, myopic CNV in adults. This presentation has an additional indication in preterm infants which is not authorised for other presentation: the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

- Eylea 40 mg/mL solution for injection in a vial: nAMD, branch RVO or central RVO, DME, myopic CNV in adults
- Eylea 114.3 mg/ml solution for injection: nAMD and DME in adults.

The applicant applied only for one presentation, i.e. Ahzantive 40 mg/mL solution for injection in a vial.

The administration route (intravitreal), posology, and the claimed indications of Ahzantive 40 mg/mL solution for injection in a vial are identical to the reference product Eylea 40 mg/mL solution for injection in a vial. The treatment of retinopathy of prematurity (ROP) with zone I (stage1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease of ROP in preterm infants, approved for Eylea 40 mg/mL solution for injection in pre-filled syringe, has not been claimed.

In this case, not claiming the full range of indications approved for Eylea, is deemed acceptable, considering the unavailability of respective pre-filled syringe presentation for which an additional indication is approved and distinct Summary of Product Characteristics for these.

A comprehensive analytical exercise was performed to evaluate Ahzantive (FYB203) similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics. Analysis covered primary and higher order structure, product related substances and impurities, variants related to cysteine chemistry, charge, isoaspartate formation, glycosylation, or molecular size, and DP related attributes. Functional activity was compared by a large panel of binding assays and cell-based biological assays covering the mode of action for the targeted indications as well as Fc-related functions. In addition to initial characterisation study, comparative forced degradation study and stability study under accelerated and stress conditions were performed and study results provide supportive information with regard to totality of evidence.

The in vitro comparability data was provided in quality part of the dossier. The in vitro data support the similarity of FYB203 to the reference products EU-Eylea.

A repeat-dose toxicology study was performed for the proposed aflibercept biosimilar FYB203 manufactured using process I to evaluate the toxicological effects of repeated IVT injections of FYB203 in comparison with EU-approved Eylea over a 5-week period in albino NZW rabbits. The overall ocular and systemic toxicological properties of FYB203 were similar to those of EU–approved Eylea. The FYB203 alternative formulation, as well as differences in quality attributes (specifically degree of sialylation), were shown not to impact the safety profile of FYB203.

The clinical development comprised one pivotal phase III clinical study (FYB203-03-01), a parallel-group, randomised, active-controlled, double-masked, multi-centre study to demonstrate therapeutic equivalence of FYB203 to Eylea and to compare the safety and immunogenicity in subjects with neovascular age-related macular degeneration (nAMD).

The design of the clinical study has been partly discussed in a CHMP Scientific Advice [EMA/CHMP/SAWP/398725/2019].

3.2. Results supporting biosimilarity

For most quality attributes including multiple attributes covering the mechanism of action and other functional activities, FYB203 was demonstrated to be highly similar to the reference products EU-Eylea. Results for comprehensive analytical exercise of FYB203 and EU-Eylea reference medicinal product generally support similarity with regard to primary and higher order structure and functional characterisation. Profile of product related variants (charged and size variants, N-glycosylation variants) is considered qualitatively comparable and no new variants were identified for FYB203 however, differences were observed in relative content of the individual variants. Size variants (HMW, LMW) and

various oxidation/deamidation forms were found generally lower for FYB203 which does not preclude similarity conclusion. Force degradation studies revealed similar degradation pathways and comparative accelerated/stress stability showed similar degradation trends and rates in tested quality attributes. Characterisation of potency by orthogonal analytical methods confirmed similarity. Generally comparable results were also found for additional functional characterisation regarding FcRn and FcgR binding properties, affinity to VEGF-B, VEGF-C, VEGF-D, PlGF-1, PlGF-2, Galectin-1 and absence of the Fc-mediated effector functions tested by relevant bioassays. The observed differences in glycosylation variants and minor analytical differences have been adequately justified regarding their impact on potency of the product.

No dedicated human PK study was conducted, instead the comparability was evaluated in supportive PK analysis in the subset of patients enrolled in phase III study FYB203-03-01. A total of 57 patients were included in the PK subgroup (31 in FYB203 and 26 in Eylea group) and the post-dose plasma levels were evaluated at Week 0 and at Week 8 after IVT injection. The levels of free aflibercept were in the similar range as previously reported.

The systemic exposure was low and there were no significant differences between FYB203 and Eylea treatment groups.

The percentage of ADA-positive patients from the first IP administration through Week 56 was generally low in both treatment arms and ranged between 1.0% and 2.7% in the FYB203 group and between 0.5% and 1.5% for the Eylea overall treatment group. There were 2 patients at week 40 and 3 patients at week 56 who were Nab positive in FYB203 arm and no patient with positive Nab was observed in Eylea arm. The percentage of ADA-positive patients was slightly higher with FYB203 compared to Eylea across all timepoints up to Week 56 and the number of patients with treatment-induced ADA was also slightly higher in FYB203 arm - 4 patients vs 2 patients in Eylea arm. No treatment-boosted ADAs were observed in either treatment group. Based on the provided data and due to overall low incidence of ADAs, the impact of immunogenicity on efficacy and safety is very limited and no concerns arise regarding the impact of immunogenicity on efficacy and safety.

Primary endpoint: The least squares (LS) mean observed for change from baseline in BCVA at Week 8 was similar in both treatment groups, i.e., 6.6 letters and 5.6 letters in FYB203 and Eylea group, respectively in the FAS. The LS mean difference in BCVA of the change from baseline between FYB203 and Eylea at Week 8 was 1.0 letter with 95.2% confidence interval (CI) of [−0.6 letter; 2.5 letters] and was completely contained within the pre-defined equivalence range (ER) of [−3.5 letters, 3.5 letters].

The sensitivity analyses for the primary endpoint were performed using linear mixed effects model (MMRM) and analysis of covariance (ANCOVA) model and results of these analyses for the primary efficacy endpoint supported the robustness of the equivalence between FYB203 and Eylea based on FAS.

Secondary endpoints: (e.g., change in BCVA by ETDRS letters; foveal (centre point and central subfield) thickness at different time points and over time; the proportion of subjects who gained or lost ≥5, 10, or 15 ETDRS letters compared to baseline; percentage of subjects with fluid-free macula; change in lesion size compared to baseline and quality of life assessment) were overall comparable between the FYB203 and Eylea treatment groups.

A total of 433 nAMD patients (215 patients in FYB203 arm vs. 218 patients Eylea arm) have received at least one dose of study treatment.

A total of 196 (91.2%) patients in the FYB203 group and 206 (94.1%) patients in the Eylea group completed the study until Week 56. Until Week 56, 183 patients (85.1%) in the FYB203 group and 199 patients (91.3%) in the Eylea group received all 8 scheduled injections (88.2% in total). The mean

(SD) treatment duration was 323.1 (58.97) days and the mean (SD) study duration was 398.7 (53.03) days.

The number of scheduled IVT injections and the duration of exposure to one of the study treatments were comparable between both treatment groups.

Overall, the incidence of TEAEs was slightly higher in the FYB203 arm vs. Eylea arm (76.7 % vs 72.5 %). Incidence of ocular TEAEs in study eye were slightly lower in FYB203 arm vs Eylea arm (31.2 % vs 34.4 %) and also in fellow eye (20.9 % vs 22.0%). Systemic TEAEs were observed in FYB203 arm (57.7 %) with higher incidence compared to Eylea arm (51.8 %). Incidence of serious TEAEs is lower in FYB203 arm compared to Eylea arm (7.9 % vs 10.6 %) as well as the incidence of severe TEAEs (3.7 % vs 5.0 %).

According to the intensity of reported TEAEs, both arms (FYB203 and Eylea) are considered comparable. The majority of TEAEs were mild (44.7 % FYB203 vs 39.0 % Eylea) or moderate (27.4 % FYB203 vs 26.6 % Eylea) intensity. Severe TEAEs were observed in lower incidence in FYB203 arm (10 patients/4.7 % vs 15 patients/6.9 %).

Incidence of TEAEs related to the treatment were slightly higher in FYB203 arm compared to Eylea (9.3 % vs 7.3 %). The most frequently reported related TEAEs were from SOC Eye disorders and Investigations. Majority of related PTs occurred with similar frequencies in both treatment groups and/or mostly in single patients.

Incidence of TEAEs related to the study procedure were slightly lower in FYB203 arm compared to Eylea (13.0 % vs 17.0 %). The most frequently reported related TEAEs were from SOC Eye disorders and Investigations.

Overall, the SAEs occurrences (excluding deaths) until Week 56 are comparable in the 2 treatment groups: 30 events in 18 (8.4%) patients treated with FYB203 and 39 events in 27 (12.4%) patients treated with Eylea. All systemic SAEs reported until Week 56 were unrelated to study procedure or to study treatment except for 1 event treated with FYB203.

A total of 13 (3.0%) patients reported AESIs until Week 56. 10 events in 6 (2.8%) patients treated with FYB203 and 12 events in 7 (3.2%) patients treated with Eylea. The most frequent AESI belonged to the SOC Eye disorders and were classified as ocular inflammatory AESIs in study eye (4 patients in FYB203 arm vs 4 patients in Eylea arm).

TEAEs cerebrovascular accident and subretinal fluid leading to discontinuation of the study treatment were judged as possibly/probably related to study treatment.

All the events leading to death were considered not related to the study drug or study procedure.

The overall safety profile of FYB203 is in line with known adverse events of the reference medicinal product Eylea [Eylea SmPC, 2024]. Overall, FYB203 and Eylea demonstrated comparable safety profiles.

3.3. Uncertainties and limitations about biosimilarity

The differences between FYB203 and EU-Eylea reference medicinal product have been identified in N-glycosylation profile with regard to overall fucosylation, galactosylation, mannosylation and sialylation content. Primarily differences in sialylation content contributed to different relative content and distribution of charged variants. It was demonstrated that observed differences in N-glycosylation profile do not impact the primary or secondary mechanism of action of aflibercept. Potential impact of differences in N-glycosylation profile to pharmacokinetic properties is not expected in regard to the intravitreal application which is supported by scientifically sound discussion. Additional sporadic findings

of results outside of the quality ranges of the EU-Eylea product for various quality attributes in initial characterisation study do not preclude the similarity conclusion. All residual uncertainty with regard to demonstration of analytical similarity has been sufficiently resolved.

A repeat-dose toxicology study was performed with the aflibercept biosimilar FYB203 to evaluate the toxicological effects of repeated IVT injections of FYB203 in comparison with EU-approved Eylea over a 5-week period in albino NZW rabbits. However, nonclinical *in vivo* data in the context of a biosimilar development are regarded of supportive value only and no conclusions on similarity can be drawn due to general lack of sensitivity of *in vivo* (animal) models regarding biosimilarity assessment.

There were minor differences in aflibercept plasma levels between the treatment arms, at Week 0, the plasma concentrations of aflibercept were slightly higher in the FYB203 group (GM 21.667 ng/mL) compared to Eylea group (GM 14.235 ng/mL), but with large variability (CV 58.9% vs 119.3%).

The percentage of ADA-positive patients was slightly higher with FYB203 compared to Eylea across all timepoints up to Week 56 and the number of patients with treatment-induced ADA was also slightly higher in FYB203 arm - 4 patients vs 2 patients in Eylea arm.

No subject in the PK subset had positive ADA result so the impact of ADA on pharmacokinetics cannot be assessed. Also due to overall low incidence of ADAs, the impact of immunogenicity on efficacy and safety is very limited but no concerns arise in this context.

A simulation study had been conducted prior to the initiation of the study to assess the impact of a masked sample size review (MSSR) on possible inflation of overall type 1 error probability. Results of simulations suggested a necessary adjustment of alpha to 2.4% for all EU-specific statistical analyses which corresponded to consideration of two-sided 95.2% confidence interval (CI) instead of nominal 95% CI. It was pointed out by the assessor that simulation may not exhaust all possible scenarios and analytical calculation of OT1EP should be performed to justify that the 95.2% CI was appropriate. Despite existence of analytical solution for evaluation of OT1EP inflation in case of equivalence trials (see Friede and Kieser (2003): Blinded sample size reassessment in non-inferiority and equivalence), the applicant found analytical calculation imprecise. Instead, the applicant performed tipping point analysis which searched for maximum confidence level (CL) when equivalence would still be concluded across primary endpoint and key secondary endpoint and both for full analysis set and per protocol set considered for these endpoints. Maximum value of CL is 99.90%. Consequently, 99.90% CI can be considered as sufficient to cover possible OT1EP inflation due to MSSR. Hence issue with MSSR is resolved.

The safety database is considered sufficient to assess the comparability regarding common (≥1/100 to <1/10) and very common (≥1/10) adverse events. However, it is too small to inform on less frequently occurring adverse events.

3.4. Discussion on biosimilarity

A comprehensive analytical exercise was performed to evaluate FYB203 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics. In addition to initial characterisation study, comparative forced degradation study and stability study under accelerated and stress conditions were performed and study results provide supportive information with regard to totality of evidence.

Overall, the differences between FYB203 and EU-Eylea reference medicinal product have been identified in N-glycosylation profile with regard to overall fucosylation, galactosylation, mannosylation and sialylation content. Also, lower levels of oxidation and deamidation was observed in FYB203. These findings contributed to different relative content and distribution of charged variants and lower FcγRIIIA affinity. Nonetheless, it has been justified that this heterogeneity does not significantly impact the

primary or secondary mechanism of action of aflibercept as generally robust functional characterisation supports the similarity between FYB203 and EU-Eylea. Also, it is concluded that observed differences presumably do not have impact on safety and immunogenicity of the FYB203. Potential impact of differences in N-glycosylation profile to pharmacokinetic properties is not expected in regard to the intravitreal application which is supported by scientifically sound discussion. Available non-clinical data for all tested FYB203 batches showed a high degree of similarity to treatment with Eylea in the relevant ocular matrices (vitreous humor, aqueous humor, retina/choroid tissue) which further support this conclusion. All residual uncertainty with regard to demonstration of analytical similarity has been sufficiently resolved. FYB203 is considered similar to EU-Eylea in relevant physical and chemical attributes and functional characteristics and identified differences in quality profile are not expected to affect clinical performance.

Based on the PK data in subset of patients with nAMD there were no significant differences in systemic exposure between FYB203 and Eylea treatment groups identified.

The incidence of ADA-positive patients from the first IP administration through Week 56 was generally low and comparable in both treatment arms.

The PK and immunogenicity data are considered supportive of biosimilarity between FYB203 and Eylea.

The pivotal clinical study FYB203-03-01 was adequately designed to demonstrate clinical equivalence between FYB203 and Eylea on both with respect to efficacy and safety. The selected study population, consisting of patients with nAMD as well as primary and secondary efficacy endpoints are deemed appropriate for this biosimilarity exercise.

The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined equivalence range of +/- 3.5 letters both for PPS and FAS and demonstrated equivalent efficacy in the primary endpoint.

The overall safety profile of FYB203 is in line with known adverse events of Eylea (SmPC). Only few disbalances were observed within the study (PTs Hypertension, Osteoarthritis, SOC Gastrointestinal Disorders) and in higher incidence of observed TEAEs leading to withdrawal of study treatment or to complete discontinuation of study in the FYB203 arm. These imbalances were discussed by the applicant. The provided justification is considered adequate and the overall safety biosimilarity is considered comparable between both arms. No differences in expected adverse events in each indication of use in adult patient population is expected.

3.5. Extrapolation of safety and efficacy

In the EU, the reference product Eylea is approved in adults for the treatment of nAMD, RVO, DME and myopic CNV in adults. The clinical development programme for the proposed biosimilar FYB203 comprised a single pivotal phase III study (FYB203-03-01) to investigate Eylea and FYB203 regarding efficacy, safety, pharmacokinetics (in a subset of patients) and immunogenicity in the treatment of subjects with nAMD.

The applicant claimed the same indication as approved for the respective presentation of the reference product, Eylea 40 mg/mL solution for injection in a vial (nAMD, branch RVO or central RVO, DME, myopic CNV in adults), based on the common mechanism of action across all indications and comparable PK, safety, and immunogenicity profiles of aflibercept (Eylea) across the approved indications. The pathogenesis of all approved indications involves angiogenesis mediated by the members of the VEGF family of angiogenic factors, and the mechanism of action of aflibercept in nAMD is considered representative of the mechanism of action of aflibercept in all other approved indications for Eylea.

Thus, the justification presented to allow extrapolation from nAMD to all approved indications of Eylea in adults is considered adequate.

Clinical comparability of the overall safety profile of FYB203 with Eylea has been shown. Safety profile is in line with known adverse events of the reference medicinal product Eylea [Eylea SmPC, 2024]. Biosimilarity is supported from a safety perspective.

3.6. Additional considerations

Most neovascular and VEGF dependent retina diseases including particularly AMD are diseases seen in adults. Therefore, the potential for off-label use in the paediatric population is expected to be very limited due to the nature of paediatric ophthalmic diseases. Aflibercept may be also used to treat some cases of retinopathy of prematurity (ROP). Compared to the reference medicinal product Eylea (40 mg/mL solution for injection in pre-filled syringe), Ahzantive (40 mg/mL solution for injection in a vial) is not proposed to be approved for preterm infants for the treatment of ROP. Risk of off-label use and misuse is considered to be important potential risk in the risk management plan (RMP); thus it is expected to be routinely monitored. The number of such cases is considered very low and their care is provided by paediatric ophthalmologists who are tertiary care-based and experienced in the care of these infants. An educational programme is proposed to be performed as an additional risk minimisation measure to raise patients' awareness on identified and potential risks.

Intentional misuse, as such, is difficult to prevent because of the user's deliberate decision to deviate from the provided instructions. However, intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections.

No safety additional comments on the potential for misuse and off label use have been raised.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ahzantive is considered biosimilar to Eylea.

Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ahzantive is favourable in the following indication(s):

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product

Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH has agreed to provide EU Educational Material for Ahzantive.

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreements with the National Competent Authorities in each Member State where Ahzantive is marketed, ophthalmological clinics where Ahzantive is expected to be used for the treatment of adult patients are provided with an updated physician information pack containing the following elements:

- Physician information booklet
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- Confirmation that the vial is for single use in adults only
- The need to expel excess volume of the syringe before injecting Ahzantive to avoid overdose
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Ahzantive

The patient information pack of the educational material includes a patient information guide "Your

guide to Ahzantive" and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Ahzantive
- How to prepare for Ahzantive treatment
- What are the steps following treatment with Ahzantive
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear, and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Ahzantive