30 January 2025
EMA/60973/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Skojoy

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006551/0000

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	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AMD	age-related macular degeneration
AS	active substance
ASM	Amgen Singapore Manufacturing
BCVA	best corrected visual acuity
BI	biological indicator
BLE	break-loose/extrusion
CDC	complement-dependent cytotoxicity
CCIT	container closure integrity test
CCS	container closure system
CD	circular dichroism
CHO	Chinese hamster ovary (cells)
CNV	choroidal neovascularization
COP	cyclin olefin polymer
CPP	critical process parameter
CQA	critical quality attribute
CRT	controlled room temperature
CSR	clinical study report
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
CVD	chorioretinal vascular disease
DLS	dynamic light scattering
DSC	differential scanning calorimetry
DME	diabetic macular edema
DR	diabetic retinopathy
EAC	equivalence acceptance criterion
ECL	electrochemiluminescence
EMA	European Medicines Agency
EOI	event of interest
EOP	end of production (cells)
EOS	end of study
ES	externally sterilized
ESI	electrospray ionization
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FACS	fluorescence-activated cell sorting
FAS	full analysis set
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FDA	Food and Drug Administration
FP	finished product
FTIR	Fourier transform infrared spectroscopy
GMP	good manufacturing practices

HCP	host-cell protein
HIAC	high accuracy light obscuration particle counting
HMW	high molecular weight
HUVEC	human umbilical vein endothelial cells
ICH	International Council for Harmonisation
IOP	intraocular pressure
IPC	in-process control
IPCD	internal process challenge device
IVT	intravitreal
LC-MS	liquid chromatography mass spectrometry
LC-MS/MS	liquid chromatography tandem mass spectrometry
LOQ	limit of quantification
LS	least squares
MAA	marketing authorization application
MALDI-TOF	matrix assisted laser desorption ionization- time of flight
MCB	master cell bank
MFI	microflow imaging
MMV	murine minute virus
MOA	mechanism of action
MS	mass spectrometry
NANA	N-acetylneuraminic acid
NGNA	N-glycolylneuraminic acid
OOS	out-of-specification
PACMP	post-approval change management plan
PC	process characterisation
PD	pharmacodynamic
PDE	permitted daily exposure
PDL	population doubling level
PEG	polyethylene glycol
PFS	prefilled syringe
pI	isoelectric point
PlGF	placental growth factor
PlGF-1	placental growth factor-1
PlGF-2	placental growth factor-2
PK	pharmacokinetic
PP	process parameter
PQA	product quality attribute
PRV	Pseudorabies Virus
PS80	polysorbate 80
PV	process validation
PVDF	polyvinylidene fluoride
Reo-3	Reovirus type 3
RefMP	reference medicinal product
ROP	retinopathy of prematurity
RP	reference product
RS	reference standard
RVO	retinal vein occlusion
SAL	sterilization assurance level

SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SmPC	Summary of Product Characteristics
SOC	system organ class
SPR	surface plasmon resonance
SV-AUC	sedimentation velocity analytical ultracentrifugation
TEM	transmission electron microscopy
TSE	transmissible spongiform encephalopathy
US	United States
USP	United States Pharmacopoeia
USPI	United States Prescribing Information
UV	ultraviolet
VCD	viable cell density
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor type A
VEGFR	vascular endothelial growth factor receptor
VEGFR-1	vascular endothelial growth factor (VEGF) receptor-1
VEGFR-2	vascular endothelial growth factor (VEGF) receptor-2
WCB	working cell bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Technology (Ireland) Unlimited Company submitted on 8 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Skojoy, 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 26 April 2023.

The applicant applied for the following indication:

Skojoy 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 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 product.

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 Pavblu 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 comparability tests and studies have been conducted:

- 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

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.

1.1. 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
14 December 2017	EMEA/H/SA/3701/1/2017/III	*Mr Christian Gartner, Dr Walter Janssens and Dr Marion Haberkamp*
28 March 2019	EMEA/H/SA/3701/1/FU/1/2019/III	*Mr Christian Gartner and Dr Kerstin Wickström*
23 July 2020	EMEA/H/SA/3701/1/FU/2/2020/II	*Dr Sheila Killalea and Mr Nicolas Beix*
10 December 2020	EMEA/H/SA/3701/2/2020/III	*Dr Elena Wolff-Holz and Prof Andrea Laslop*

The applicant received scientific advice on the development of aflibercept (ABP 938) as a biosimilar from the CHMP on 14/12/2017 (EMEA/H/SA/3701/1/2017/III). The Scientific Advice pertained to the following aspects of development:

Quality: analytical similarity assessment plan, quality attributes and assays, between aflibercept (EU) and aflibercept (US)

Nonclinical: non-clinical programme to demonstrate similarity

Clinical: requirement for a comparative systemic PK study, features of the confirmatory clinical study (Protocol 20170542), patient population, endpoints and assessments, study duration, statistical analyses, sample size and margin, primary analysis submission at week 24, long-term safety and immunogenicity data submission

Multidisciplinary: scientific bridge between aflibercept (US) and aflibercept (EU) based on analytical and non-clinical pharmacology similarity assessments, development programme supporting approval for all approved aflibercept indications of the reference product.

The applicant received scientific advice on the development of aflibercept (ABP 938) as a biosimilar from the CHMP on 28/03/2019, (EMEA/H/SA/3701/1/FU/1/2019/III). The scientific advice pertained to the following aspects of development.

Quality: analytical similarity testing plan,

Clinical: Appropriateness of the proposed features of the clinical similarity study for demonstrating similar efficacy, safety, and immunogenicity between ABP 938 and aflibercept, proposed endpoints and timing of assessments, statistical analyses, including sample size and margin, PK assessments of Cmax in a subset of subjects

Multidisciplinary: the ABP 938 PFS in the initial MAA and need for additional clinical data with the PFS presentation

The applicant received Scientific Advice on the development of Aflibercept (ABP 938) as a biosimilar from the CHMP on 23/07/2020, (EMA/H/SA/3701/1/FU/2/2020/II). The Scientific Advice pertained to the following aspects of development.

Clinical: Modification to the immunogenicity testing strategy for Study 20170542.

The applicant received Scientific Advice on the development of Aflibercept (ABP938), a biosimilar to Eylea, from the CHMP on 10/12/2020 (EMEA/H/SA/3701/2/2020/III). The Scientific Advice pertained to the following multi-disciplinary quality, pre-clinical and clinical aspects of development:

The use of frequentist and Bayesian models to inform the development of the clinical similarity study.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Daniela Philadelphy Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	8 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 May 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 May 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 September 2024

The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 October 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	7 November 2024
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 November 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	7 January 2025
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	15 January 2025
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 Skojoy on	30 January 2025

2. Scientific discussion

2.1. About the product

Skojoy (ABP 938) has been developed as a biosimilar to the reference product Eylea (INN: aflibercept).

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 ABP 938 are in adults for treatment of

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

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

During development of ABP 938, the applicant sought scientific advice (SA) from the EMA Scientific Advice Working Party (SAWP).

2.3. Quality aspects

2.3.1. Introduction

Skojoy has been developed as a similar biological medicinal product to the reference medicinal product, Eylea. The active substance aflibercept (INN) is a recombinant fusion protein consisting of human vascular endothelial growth factor (VEGF) receptor-1 (VEGFR-1) domain 2 and VEGF receptor-2 (VEGFR-2) extracellular domain 3 fused to the Fc portion of human IgG1. ABP 938 is produced in Chinese hamster ovary (CHO) cells.

The finished product is presented as a solution for intravitreal injection containing 40 mg/mL aflibercept as active substance.

Other ingredients are: sucrose, α,α-trehalose dihydrate , polysorbate 80 and water for injections.

The product is available in the following two presentations, where the finished product has the same formulation:

- a Type I glass vial with an elastomeric rubber stopper and aluminium seal with flip-off cap

and as

- a cyclic olefin polymer (COP) Luer-lock pre-filled syringe (PFS) marked with a dosing line, with an elastomeric rubber plunger stopper, elastomeric rubber tip cap and polypropylene rigid shield.

A notified body opinion is provided for the pre-filled syringe medical device.

2.3.2. Active substance

2.3.2.1. General information

The INN of the active substance (AS) is aflibercept and the laboratory name, which is used throughout the dossier, is ABP 938. Aflibercept 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 fragment crystallizable (Fc) portion of human IgG1 and is produced in recombinant Chinese hamster ovary (CHO) cells.

The active substance is a human recombinant fusion protein that acts as a soluble decoy receptor that specifically binds vascular endothelial growth factor type A (VEGF-A) and placental growth factor (PlGF) and inhibits their binding and subsequent activation of VEGF receptor 1 (VEGFR-1) and VEGF receptor 2 (VEGFR-2).

The active substance contains a total of 864 amino acids. Each polypeptide chain contains 432 amino acids. The dimeric glycoprotein has a protein molecular weight of approximately 97 kDa and a total molecular weight of approximately 114 kDa including glycosylation at asparagines in positions 36, 68, 123, 196 and 282. The molecular formula for the predominant form without glycosylation is

$C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$. The extinction coefficient determined experimentally is 1.26 mL mg^{-1} cm^{-1} at 280 nm and the isoelectric point is 7.0.

2.3.2.2. Manufacture, process controls and characterisation

Manufacturers

The active substance is manufactured by Amgen Singapore Manufacturing Pte Ltd (ASM) in Singapore.

Manufacturing authorisations/GMP certificates have been provided for all the facilities. Overall, the information provided in this section is sufficient.

Description of manufacturing process and process controls

The active substance of ABP 938 (aflibercept), is manufactured in Chinese hamster ovary (CHO) cells. Briefly, one working cell bank (WCB) is expanded in several steps in shake flasks, culture bags and in a bioreactor. The bioreactor is harvested and clarified, and subsequently the active substance is purified by chromatography steps. Virus clearance steps are performed and pools concentrated and diluted to the final protein concentration. After filtration, the active substance is stored until used for finished product (FP) preparation.

The information provided on the batch size and definition is considered acceptable. Traceability of active substance batches is ensured by unique batch codes. Sufficient details on the batch numbering system are provided. The manufacturing process is sufficiently well described with process parameters provided and in-process controls (IPCs) in place, with acceptable ranges/acceptance criteria/action limits defined. Bioburden is controlled. An integrated control strategy of the active substance manufacturing process is in place and considered sufficiently justified.

A description of the container closure system (CCS) has been provided, including the identity of materials of construction of each primary packaging component, and their specifications. A representative certificate of conformance is included. Suitability and protection of the CCS has been confirmed by testing according to relevant pharmacopeial monographs, stability, and integrity testing. A summary of extractables/leachables study has been provided. All leachables (inorganic and organic) were considered not of toxicologic concern.

Overall, sufficient information on the container closure system (CCS) has been provided.

Control of materials

Raw materials

Raw materials used for active substance manufacturing are listed with their respective quality standard (compliant with Ph. Eur., USP/NF, in-house specification) and their intended use. No human or animal derived materials are used in the manufacture of the active substance. Acceptable in-house specifications are provided for the non-compendial raw materials. The filters, membranes and disposable containers used in the manufacturing process are described. In-house specifications are provided for all chromatography resins. The composition of the cell culture media and feeds at each cell culture step is described.

Overall, sufficient information on raw materials used in the active substance manufacturing process has been submitted.

Cell Substrate

The construction of the expression plasmid and its genetic elements is described in sufficient detail. The information provided on origin and generation of the cell substrate is satisfactory.

A two-tiered cell bank system is used. The master cell bank (MCB) and working cell bank (WCB) preparation processes were described in sufficient detail. The strategy for providing a continued supply of cells from cell banks includes only the establishment of a future WCB since the MCB inventory is considered sufficient to support future production of new WCBs. The criteria for qualification of new WCB was presented and it is found acceptable. MCB and WCB storage stability is monitored. Characterization of the cell banks included an adequate demonstration the genetic stability and integration site stability. The genetic stability for ABP 938 production has been assessed.

In conclusion, the characterisation of the cell banks mostly demonstrates identity, purity, suitability, and genetic stability. For further discussion regarding adventitious agents, please refer to Adventitious agents safety evaluation.

Control of critical steps and intermediates

Sufficiently justified action or rejection limits were established for all critical IPCs. Results for process validation lots manufactured at the commercial site and scale have demonstrated robust removal of process-related impurities in the commercial process. A critical IPC with action and rejection limits for HCP is proposed to ensure control in the final active substance; the action limit was tightened during the procedure.

Overall, a comprehensive microbial control strategy was established for bioburden, endotoxin, and mycoplasma. Analytical methods for safety related critical IPCs are adequately described and justified. The bioburden and bacterial endotoxin methods are provided. The adventitious virus testing of unprocessed bulk is performed.

Process consistency IPCs have been established for the upstream and downstream steps of the manufacturing process.

Overall, acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical and non-critical operational parameters and in-process tests. Actions taken if limits are exceeded are specified and sufficiently justified.

Process validation

Process performance qualification (PPQ) batches were manufactured at the intended commercial manufacturing site Amgen Singapore Manufacturing (ASM). Overall, the validation criteria are acceptable and sufficient validation data has been provided. Deviations were adequately described and evaluated/justified and had no product quality or validation impact. Upon request some IPC limits were tightened.

Hold times validation

Hold times for in-process pools have been validated under consideration of physicochemical stability and microbial control. Microbial studies were conducted at the commercial scale. The proposed hold times are sufficiently justified.

Resin and membrane reuse and cleaning

Resin lifetimes and potential carry-over have been investigated in small-scale studies and will be verified at scale. Re-usability of the ultrafiltration/diafiltration membrane has been evaluated during process characterization and will be verified at commercial scale.

Impurity clearance

Clearance of process-related impurities is sufficiently validated at commercial scale. Results showed that these impurities are cleared to acceptable levels.

Shipping validation

Shipping qualification studies to validate the shipping system have been performed to assure the quality of the product. Adequate shipping qualification reports on the performed shipping validation were provided.

Reprocessing

Reprocessing is proposed; this is sufficiently justified based on data from process validation.

In conclusion, the presented process validation data demonstrate that the intended commercial manufacturing process performs consistently under commercial operating conditions.

Manufacturing process development

The applicant followed an enhanced development approach using existing product and process knowledge, development and manufacturing experience, risk ranking and filtering, and process characterisation studies to develop a control strategy as outlined in ICH Q11 and EMA/CHMP/BWP/187338/2014.

The outcome of a quality attribute risk assessment to categorize individual product quality attributes as either critical or non-critical was presented and the impact of the manufacturing process on quality attributes was evaluated. The methodology as well as the proposed classification of quality attributes in critical and non-critical attributes is agreed.

Comparability assessment

The manufacturing history for all sites is presented and flow charts summarising the changes of the ABP 938 active substance upstream and downstream process between the different process versions have been provided; the implemented changes are sufficiently justified.

Comparability studies were performed based on batch analysis release testing and characterization studies. In general, based on the provided data, comparability between active substance materials derived from the different process versions was sufficiently demonstrated.

Characterisation

The ABP 938 active substance was 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 consisting of human VEGFR-1 domain 2 and VEGFR-2 extracellular domain 3 fused to the Fc portion of human IgG1a. Characterisation results describing primary structure, post-translational modifications, product variants, higher order structure, general characteristics and biological functions and activities were provided.

Process-related impurities include host cell proteins (HCP), DNA, raw materials and process reagents. Process validation data show that the commercial manufacturing process can clear process-related impurities to acceptable safety levels.

Control of mycoplasma and adventitious viruses is assessed in section Adventitious Agents Safety Evaluation.

In conclusion, the information provided on characterisation is considered sufficient.

2.3.2.3. Specification

The active substance specification covers general tests (appearance), identity, purity, product- and process-specific impurities, glycosylation profile, potency and adventitious agents (bioburden), bacterial endotoxins (Ph. Eur.).

During the evaluation procedure the applicant was requested to justify the absence of certain specification attributes and to tighten specification acceptance criteria. The methods used are either Ph.Eur. or in-house methods for which unique in-house method numbers are listed. The references to Ph. Eur. chapters are also included.

Of note, potency assays, are used for potency control. This is sufficiently justified.

In the context of the overall control strategy, the active substance specification is considered acceptable. The proposed specification acceptance limits are sufficiently justified.

Analytical methods

The analytical procedures used to test active substance for release and/or for stability have been adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines demonstrating that they are suitable for active substance control testing.

Batch analysis

Batch analysis data is presented for all lots for active substance ABP 938 used during development and for active substance manufactured at commercial scale at the commercial manufacturing facility (ASM). All presented results were within the active substance specifications in place at the time of manufacture. The results demonstrate consistency of the manufacturing process.

Reference materials

In line with ICH Q6B, a two-tiered reference standard system comprised of a primary reference standard and a working reference standard calibrated against the primary standard has been established. The primary reference standard will be used to qualify new primary and working reference standards whereas the working reference standard is used for both active substance and finished product release and stability testing.

A brief history of the reference standard is given. The representativeness of the primary standard for clinical and commercial material is confirmed.

A protocol for qualification of future primary and working reference standards is provided and considered acceptable. The potency of future reference standards will be evaluated against the potency of the primary reference standard.

2.3.2.4. Stability

A shelf-life for the active substance when stored at the recommended long-term storage temperature is proposed.

The stability data confirm that active substance can be considered stable as no trends or outliers were identified. The stability studies were generally according to ICH Q5C.

The stability study samples are stored in containers that can be considered representative for the commercial CCS. Generally, the stability testing for evaluation of the shelf-life included relevant quality attributes that have been shown to be stability indicating. Container closure integrity although not part of the long-term stability program was confirmed by a microbial aerosol challenge test.

In addition to the long-term stability studies, stability of the active substance has been studied under accelerated and stress conditions.

Photostability is discussed within the finished product section and is considered acceptable.

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

Any confirmed out of trend results of a post-approval stability protocol study will be investigated, as appropriate, to determine potential impact to active substance stored under real-time storage conditions. If an impact to product quality is confirmed, the outcome of the investigation will be reported to the Agency. Taking into account that no significant changes under the long-term storage conditions are expected (and were not observed during the supporting, primary, and production lot stability studies), and that a more extensive post-marketing stability protocol for both finished product presentations is in place, the proposed strategy for the post-marketing stability confirmation of active substance is accepted.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and pharmaceutical development

The ABP 938 finished product (FP) has been developed as a similar product to the approved product Eylea and has the same route of administration, dosage form and strength as the reference product.

ABP 938 finished product is supplied in two presentations: a single use vial containing 40 mg/ml aflibercept, to allow a deliverable volume of 0.05 ml of solution, containing 2 mg of aflibercept; and a PFS with the same aflibercept concentration as the vial and a fill volume, to allow for an injection of 50 µL of solution containing 2 mg of aflibercept.

Both presentations are clear to opalescent and colorless to slightly yellow, sterile, preservative free solutions intended for intravitreal administration.

ABP 938 is formulated at 40 mg/mL in sucrose, α,α-trehalose dihydrate, PS80 at pH 6.2.

The vial's container closure system consists of an ISO 2R Type I glass vial, elastomeric stopper, and aluminium seal with flip-off cap. The primary container closure system for the PFS consists of a cyclic olefin polymer (COP) luer-lock syringe (silicone oil free, 0.5 mL), with an integrated rubber tip cap, plunger-stopper and a dose mark (printed ink dose line). Syringe barrel, plunger stopper and tip cap comply with Ph. Eur.

The description and composition of the vial and PFS presentations are sufficiently detailed. No overages or overfills are used for either finished product presentation. The appropriateness of the container closure system is discussed and accepted.

Composition of the finished product

Active substance is supplied at a target concentration 40 mg/mL in the final formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Formulation development

The presented data from formulation robustness studies show that the intended formulation is robust and provides adequate stability of the finished product.

Physicochemical and biological properties

Physicochemical and biological properties of ABP 938 have been sufficiently addressed.

Manufacturing process development

Th finished product has been developed in two presentations: a vial and a PFS. The changes in the manufacturing process are adequately described and evaluated and respective comparability studies have been performed to support these manufacturing process changes. In addition, lot history has been provided, including the lots used in the clinical study.

A process design approach has been used to develop the finished product manufacturing process for the vial and PFS presentations. This is based on prior knowledge, data of reference product and other protein manufacturing processes experience, ABP 938 process development studies and the results of process risk assessments. The finished product manufacturing process is controlled by process parameters, IPCs, release specifications, and periodic testing controls of the active substance and finished product (e.g. validation, comparability and stability). The control strategy is based on knowledge of product quality attributes (PQAs), quality risk management used to identify potential risks to patients and a subset of PQAs identified as critical quality attributes (CQA).

Comprehensive process characterization studies have been conducted to evaluate the robustness of the finished product manufacturing process. These studies demonstrate that the finished product manufacturing process is under control and can deliver the required product quality and process consistency when operated within acceptable ranges.

Sufficient information was provided on extractables and leachables assessment.

Comparability

The vial manufacturing process was transferred to the commercial manufacturing site. A summary of the comparison between the two processes was provided. Minor changes to accommodate facility fit and scale differences were implemented and sufficiently justified. The set of analytical procedures applied to investigate analytical comparability is deemed adequate to detect changes in relevant quality attributes.

In general, based on the provided data, comparability is considered demonstrated. Therefore, this approach is acceptable.

A comparability study between vial and PFS presentation has been presented. Based on all the results it is agreed that comparability between vial and PFS presentation has been sufficiently demonstrated.

Changes during the sterilization process development are supported by analytical comparability studies.

Container closure system

The primary container closure systems are

- an ISO 2R Type I glass vial with elastomeric stopper or

- a 0.5 mL COP luer-lock syringe with a rubber tip cap and a rubber plunger-stopper. The syringe barrel has a printed ink dose mark to allow delivery of 0.05 mL.

The primary packaging components for the vial presentation consist of a glass vial, a rubber stopper, and an aluminium seal with a flip-off cap.

Certificates from the supplier were provided and the container closure system has been demonstrated to be compatible with ABP 938 vial finished product over the proposed shelf life.

Glass vials are washed and depyrogenated using dry heat. Details are listed, including details on the dry heat depyrogenation process and are in accordance with the Guideline on the sterilisation of medicinal products.

The stopper and vial both comply with Ph. Eur. and USP requirements. Vial and stopper were evaluated in an extractable study and extractables were considered not of toxicological concern. A leachable study was performed, indicating no toxicological risk. Primary packaging materials coming into contact with the finished product are of Ph. Eur. quality.

The description for the CCS is given in sufficient detail. The suppliers are listed. Drawings and specifications are provided for each component of the CCS and include critical dimensions. The PFS and plunger stopper are provided sterilized by the sterilization process that has been developed and validated, which is acceptable. Certificates of compliance have been provided.

The suitability of the container closure systems for product storage and transportation was adequately demonstrated by stability data. Protection from light by secondary packaging was adequately shown.

No substance of safety concern is leaking into the finished product as indicated by results of leachables and extractables testing. Targeted organic extractables were monitored through leachables testing and were below the safety evaluation threshold. All organic extractables from ink and adhesive migration studies were considered of no toxicologic concern. Elemental impurities were evaluated in line with ICH Q3D.

Overall, the development of the container closure systems is considered adequately described and compatibility between the finished product and the proposed container closure systems is sufficiently demonstrated.

A Notified Body Opinion for the prefilled syringe, on the conformity of the integral device part with the relevant general safety and performance requirements set out in Annex I of the EU Medicinal Device Regulation (2017/745), has been provided.

2.3.3.2. Manufacture of the product and process controls

All sites are confirmed to be compliant with the relevant GMP guidelines.

During the procedure, a major objection was raised regarding the applicability of the US-EU Mutual Recognition Agreement (MRA) for batch release testing, as the manufacturing of the active substance was performed outside the EEA. In response, the applicant has transferred the batch release testing to a site in the EEA, and the major objection was considered resolved.

Batch size

Minimum and maximum batch sizes for the vial and PFS presentations have been described.

Sufficient information has been provided to cover the minimum and maximum batch size through various studies in addition to the process validation.

Description of the manufacturing process and process controls

The manufacturing process of ABP 938 consists of active substance formulation sterile filtration, and aseptic filling followed by inspection and packaging.

Prefilled syringes undergo assembly external surface sterilization before final packaging. The process is adequately described, and process parameters are sufficiently justified based on process characterization and validation data. Process flow diagrams of the finished product manufacturing processes and descriptions for each step, including in-process testing, are provided.

Process parameters are sufficiently justified based on process characterization and validation data.

Hold times are sufficiently justified with validated hold-time studies or with process design studies.

The batch numbering system has been sufficiently described.

No reprocessing or reworking steps are defined for either presentation.

Control of critical steps and intermediates

The manufacturing process controls are sufficiently described. Performance indicators are used to evaluate process performance. A subset of performance indicators is designated as in-process controls, which are controlled in routine manufacturing by defined action or control limits which are sufficiently justified.

Process parameters and their limits are described. No process intermediate storage steps have been defined the finished product manufacturing process.

Process validation

Process validation studies were conducted for each presentation following a classical approach.

The process validation covered all finished product manufacturing process steps and, in addition, hold times validation, media fill validation, sterile filter validation, cleaning validation and shipping qualification. All acceptance criteria for process parameters were met or and a summary of deviations that occurred during process validation, including sufficient assessment of those deviations, has been provided.

The external sterilization process has been validated. In conclusion, the manufacturing processes for both vial and PFS presentations have been validated. It has been demonstrated that the manufacturing processes are capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

2.3.3.3. Product specification

Specifications for the vial presentation are described and for the PFS presentation. Specifications were set considering ICH Q6B guidance and Ph. Eur. monograph “Monoclonal Antibodies for Human Use” #2031. The specifications were defined using development, clinical and commercial lots. The finished product release specifications for vial and PFS include tests for appearance (colour and clarity), testing of identity, testing of purity and other impurities, testing of potency, quantity, contaminants (endotoxin and sterility) and general tests. A parameter and analytical procedure (including validation) for testing for syringe functionality has been included. Batch release testing has been adequately justified.

During the evaluation procedure the applicant was requested to justify the absence of certain specification attributes and to tighten some specification acceptance criteria.

Analytical methods

The analytical methods used have been adequately described and non-compendial methods appropriately validated to demonstrate their suitability for their intended use, according to ICH guidelines.

With regards to the bacterial endotoxins test, the efforts and plans to develop and implement an endotoxin assay based on recombinant Factor C (instead of animal lysate) in the foreseeable future has been described upon request and is acknowledged.

Batch analysis

Batch analyses data was provided for PFS batches, sterilized PFS and batches of the vial presentation. Results complied with acceptance criteria valid at time of testing for all batches.
In general, the provided batch data confirm manufacturing process consistency for both presentations.

Reference materials

The reference standards are the same as those used for testing of the active substance. Reference is made to the corresponding active substance section.

Characterisation of impurities

There are no further impurities in the finished product compared to those already discussed for the active substance.

Nitrosamines

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 no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Elemental impurities

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment and the presented batch data it can be concluded that the overall risk as regards elemental impurities is negligible and it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

2.3.3.4. Stability of the product

Based on available stability data, the shelf-life for the finished product (both vial and PFS presentations) of 36 months (3 years) for storage at 2°C to 8°C with storage for a single period of up to 3 days at a maximum of 30°C, as stated in the SmPC, are acceptable.

For the vial presentation, the proposed shelf-life is based on stability data for storage at the intended condition. In addition, accelerated stability data and stress stability data was provided for all batches. Supportive data from development batches is considered applicable, since comparability between development, clinical and commercial scale/PPQ batches was sufficiently demonstrated.

For the PFS presentation, the proposed shelf-life is based on long-term stability data. The number and selection of batches included in the stability studies is acceptable. Sufficient data demonstrating that polysorbate levels remain stable over the proposed shelf life of the finished product have been provided upon request. Data on syringe functionality over the shelf life are provided and considered sufficient. Other attributes that are potentially impacted by the container closure were evaluated.

The stability studies were in line with ICH Q5C and the container closure systems used for stability studies are identical to those proposed for commercial distribution.

Shelf-life specifications consist of a subset of release specifications. Acceptance criteria for shelf life/stability testing, where different from release, have been detailed. The shelf life/stability acceptance limits are adequate, and justifications are provided.

For the recommended storage condition, all samples met acceptance criteria.

Accelerated conditions were evaluated at and stressed storage conditions. Forced degradation studies were performed to evaluate degradation pathways in comparison to the reference medicinal product (RefMP) and results were provided.

In addition, stability studies were performed on representative batches to evaluate conditions that may be experienced during transportation, storage, handling, and use, including photostability studies, temperature cycling and transportation studies. Results from photostability studies, which were conducted according to ICH Q1B, demonstrated that the finished product is sensitive to light and that secondary packaging protects ABP 938 adequately from photodegradation for both presentations.

The scope of quality attributes foreseen to be tested during post-approval stability studies, as included in the presented post-approval stability protocol, is limited but acceptable as the stability studies on the primary batches tested a wide range of relevant parameters.

The provided post-approval stability protocol and commitment are acceptable. The set of post-approval stability testing is very limited. However, for evaluation of shelf-life, a more comprehensive stability set was provided. If any changes are implemented to the manufacturing process, the stability protocol will be re-evaluated.

Overall, the finished product stability specifications are considered acceptable.

2.3.3.5. Post approval change management protocol(s)

The applicant appropriately presented the planned process changes for active substance in sufficient detail and the expected impact of those changes was discussed. Appropriate justifications or supportive studies were conducted. The submitted PACMP was considered acceptable.

The applicant submitted a PACMP for routine product release of product. The change will apply to the ABP 938 finished product PFS only. No changes will be introduced to the active substance or the ABP 938 finished product vial. The applicant appropriately presented the planned changes in sufficient detail and the expected impact of those changes was discussed. Appropriate justifications or supportive studies were conducted. The submitted PACMP was considered acceptable.

2.3.3.6. Adventitious agents

Multiple measures are implemented to ensure product safety with regard to non-viral and viral adventitious agents. The measures include evaluation and testing of raw materials, testing of cell banks and process intermediates for microbial and viral contaminants, testing of microbial attributes as in-process controls and release testing, implementation and validation of virus clearance steps, and steps contributing to virus reduction.

Sterility of ABP 938 finished product is ensured by bioburden reduction filtration, sterile filtration, aseptic processing, and integrity of the container closure system. The measures set to ensure microbiological safety of the FP are considered sufficient.

Non-viral adventitious agents

MCB, WCB and EOPCB were tested for the absence of bacterial, fungal and mycoplasma contamination according to Ph. Eur. 2.6.1 and 2.6.7. Tests for bioburden and endotoxin are performed at multiple steps during the manufacturing process for active substance and finished product. No animal-derived raw-materials were used in MCB and WCB manufacturing or during active substance and finished product manufacturing. The only animal derived raw material used in the development of ABP 938 is the CHO-derived cell line, which was tested and shown to be free of adventitious agents. Unprocessed bulk was tested for the absence of mycoplasma and bacterial contamination. In conclusion, the risk for microbial contamination is adequately controlled and the risk with regard to transmissible spongiform encephalopathy (TSE) is minimal.

Adventitious viruses

Cell banks were tested with numerous assays. The host cell line used in the generation of MCB was tested for the presence of bovine and porcine viruses and corresponding certificates of analysis were provided.

Unprocessed bulk testing encompasses mycoplasma, adventitious virus, and bioburden testing. Results of testing were provided and they were all negative. A high-level description of used *in vitro* viral assay was provided.

In conclusion, testing of cell banks and unprocessed bulk was performed according to the ICH Q5A guideline. No adventitious viruses were detected except for A- and C-type retrovirus-like particles. The reports for all viral testing are provided. Control of adventitious viruses is considered acceptable.

Virus clearance studies

The virus clearance capacity of the manufacturing process was assessed with virus clearance studies using small scale models of the respective large-scale manufacturing process steps. The design of the studies is in line with guideline ICH Q5A. Tabular comparisons of the process parameters for the manufacturing scale and the small-scale process steps were provided. Details on small scale models are adequately described and deemed representative for the large-scale process. For the chromatography steps, a potential impact of resin aging on virus clearance and potential carry-over of viruses was investigated.

Different process steps were evaluated in studies using model viruses. The selected panel of viruses represents a broad range of virus types with different physicochemical characteristics and is appropriate for this type of product and the production system. It is agreed that the chosen viruses represent relevant models that could potentially contaminate the active substance. The set of model viruses is acceptable. Reports of the virus validation studies were provided.

A summary of virus clearance study results is presented in the dossier. Considering the worst-case retrovirus-like particle counts of the unprocessed bulk from active substance batches per dose, it is concluded that the obtained log-reduction values provide an acceptable safety margin regarding retrovirus-like particles.

In conclusion, the steps provide for an effective and robust overall clearance capacity for adventitious viruses. The risk of potential contamination and transmission of bacterial, viral or TSE agents is acceptably low.

2.3.3.7. GMO

Not applicable.

2.3.3.8. Biosimilarity

In general, a very comprehensive and scientifically sound biosimilarity assessment has been conducted. Since both aflibercept EU-sourced reference product and US-sourced comparator product (Eylea) have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product, based on 3 pairwise analytical comparisons, has been established. This strategy is accepted and in line with the EMA guidance CHMP/437/04 Rev 1 which outlines that it may be possible for an Applicant to compare the biosimilar in certain clinical studies with a non-EEA authorised comparator which will need to be authorised by a regulatory authority with similar scientific and regulatory standards as EMA (e.g. ICH countries) and provided that an acceptable bridge based on structural and functional data to the EEA-authorised reference product has been established.

ABP 938 has been developed as vial and as pre-filled syringe presentation, similar to the reference product presentations. The applicant outlined that the main parts of the biosimilarity evaluation were conducted with the vial presentation whereas for the pre-filled syringe presentation a targeted analytical similarity assessment focusing on the finished product specific attributes was conducted.

ABP 938 active substance lots, including development lots, all lots used in clinical studies, and process validation lots, were represented in the primary comparative analytical similarity assessment. For attributes specific to the finished product (e.g., volume), ABP 938 vial finished product lots were assessed. PFS finished product lots, including development, clinical, and process validation lots, were represented in the targeted analytical similarity assessment. It is agreed that sufficient batches from both the proposed biosimilar and the reference product were included to enable a robust and reliable similarity assessment.

For establishment of the similarity ranges, a quality range approach was used for quantitative comparison. In addition, ABP 938 was also evaluated against the reference product min-max ranges for further similarity assessment. If any individual value exceeded the quality range (or min-max range), the magnitude and the criticality of the observed differences were discussed and justified. For attributes/activities that have the potential to impact clinical outcomes and where the data are best evaluated based on method capability and/or product knowledge, an expectation approach was employed to assess similarity.

In general, a broad panel of orthogonal standard and state-of-the-art methods has been applied for biosimilarity evaluation, reflecting relevant physiochemical and biological quality attributes of Aflibercept.

The provided results support the biosimilarity claim. For most of the quality attributes similarity was demonstrated. Observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance of the product. A more detailed discussion on primary structure, product-related substances and impurities, higher order structure, general properties, biological activity, degradation studies and the assessment for the pre-filled syringe is given below.

Similarity of the primary structure was confirmed by a set of orthogonal methods. Protein sequence and disulfide linkage patterns were assessed by intact molecular mass analysis by MALDI-TOF-MS, reduced and deglycosylated molecular mass analysis by ESI-TOF-MS, and reduced and non-reduced peptide maps by LC-MS. Minor differences in the N-and C-terminal variants are not considered to have any impact on clinical efficacy and safety.

The glycan map results demonstrate that ABP 938 has similar levels compared to aflibercept (US) and aflibercept (EU). Slight differences in the N-glycosylation pattern could be justified by demonstration of similar levels of biological activities associated with the full Mode of Action (MOA).

Finally, the characterisation of the primary structure included the comparison of experimentally derived extinction coefficients, determination of the isoelectric point (pI) by capillary isoelectric focusing and identity testing via ELISA.

Similarity of purity, product related variants and impurities was evaluated by SE-UHPLC, rCE-SDS, and nrCE-SDS. Charge variants were assessed by cIEF. Characterisation of the charged variants by cIEF shows a wider variability for the proposed biosimilar in comparison to reference/comparator product. SE-UHPLC showed slightly higher levels of HMW variants with a concomitant lower main peak for the US comparator and EU reference product. Likewise, rCE-SDS indicated an improved purity profile for the proposed biosimilar.

Similarity assessment of the higher order structures was done by FTIR spectroscopy for the secondary structure, near-UV CD spectroscopy for the tertiary structure and DSC for thermal stability. Submicron particles were assessed by dynamic light scattering (DLS) while aggregates were characterized by SV-AUC. Molar masses of size variants were evaluated by SE-HPLC-LS. A comprehensive analysis of subvisible particles was done during development, The results from studies including ABP 938, aflibercept (EU), and aflibercept (US) demonstrate ABP 938 to have low levels of subvisible particles and to be of an appropriate quality for intravitreal administration. In the overall manufacturing and quality control strategy, subvisible particles are tested as part of the finished product specifications for the ABP 938 vial and PFS presentations. The results from testing during development show consistently low levels of subvisible particles in ABP 938 and demonstrate that the manufacturing process of ABP 938 provides sufficient control of this attribute. In the finished product lot release and stability testing for both vial and PFS presentations, all ABP 938 finished product lots remain within specification acceptance criteria that meet the compendial standards described in USP <789> Particulate Matter in Ophthalmic Solutions for drug product and the Ph. Eur. 2.9.19 Particulate Contamination: Sub-visible particles.

Similarity assessment of the general properties of finished product in the vial presentation included the evaluation of protein concentration and volume. Additionally, all ABP 938 results are within the established specification. Minor differences regarding the volume are not considered clinically meaningful because the full contents of the vial are extracted, and the excess quantity is expelled from the syringe allowing the 0.05 mL label volume to be measured using the graduations of the syringe. Taking these arguments into account the applicant`s conclusion that these differences are not considered to be clinically meaningful is agreed. Consequently, similarity/comparability between all three product groups for the general attributes could be demonstrated.

Biological activity was evaluated by a broad set of cell-based in vitro and binding assays. The VEGF-A165 isoform was primarily used to assess function activities associated with the MOA for ABP 938, aflibercept (US), and aflibercept (EU) in the inhibition of VEGF-A165-mediated HUVEC proliferation assay, the VEGF-A165/VEGFR-2 signalling inhibition in HUVEC assay, the VEGF-A165/VEGFR-2 signalling inhibition assay in HEK293 cells, and the VEGF-A165/VEGFR-2 inhibition of binding by luminescence proximity assay. The results from these MOA-relevant assays demonstrate that ABP 938, aflibercept (US), and aflibercept (EU) have similar biological activity. Regarding other VEGF-A isoforms VEGF-A165 and VEGF-A189 as the long forms and VEGF-A111 and VEGF-A121 as the short forms were used to evaluate binding kinetics and affinity by SPR of ABP 938, aflibercept (US), and aflibercept (EU) in a side-by-side analysis. Binding specificity against VEGF-C and VEGF-D was assessed for ABP 938, aflibercept (US), and aflibercept (EU) in a side-by-side analysis using SPR demonstrating that ABP 938, aflibercept (US), and aflibercept (EU) are similar in having no binding to VEGF-C and VEGF-D.

PlGF-1 and/or PlGF-2 were used to assess functional activities associated with the mode of action for ABP 938, aflibercept (US), and aflibercept (EU) in the PlGF-1/VEGFR-1 dimerization inhibition assay in U2OS cells, the PlGF-2/VEGFR-1 dimerization inhibition assay in U2OS cells, the PlGF-1 inhibition of binding by luminescence proximity assay, the PlGF-1 binding assay, and the PlGF-2 binding assay, and the PlGF-1 and PlGF-2 binding kinetics and affinity by SPR. As binding to galectin-1 may play a role in pathological events in eye disease, Galectin-1 binding was evaluated in the galectin-1 binding assay by SPR. VEGF-B167 was used to evaluate binding activities in the VEGF-B167 binding by ELISA, while VEGF-B186 was used to assess binding kinetics and affinity by SPR for ABP 938, aflibercept (US), and aflibercept (EU) in a side-by-side analysis.

Fc domain-mediated binding activities and the combined VEGFR/Fc-mediated functions were compared for ABP 938 and aflibercept. Fc-mediated binding to FcRn, C1q, and the Fc y receptors (FcyRIa, FcyRIIa-131H, FcyRIIb, FcyRIIIa-158V, and FcyRIIIb) were evaluated as part of the comprehensive similarity assessment. The biological functions of aflibercept are primarily mediated through the VEGFR domains, and the Fc domain of the molecule does not induce effector function as the VEGF protein family members exist as predominantly soluble proteins. The lack of effector function for ABP 938 and aflibercept was confirmed using the antibody-dependent cellular cytotoxicity (ADCC), the antibody-dependent cellular phagocytosis (ADCP), and the complement-dependent cytotoxicity (CDC) cell-based assays. In summary despite some noted differences the results of biological characterisation demonstrate a similar biological activity of ABP 938, aflibercept (US), and aflibercept (EU).

The targeted analytical similarity exercise included an evaluation of quality attributes which are specific to the PFS presentation. Product strength, total extractable volume, and deliverable dose volume were evaluated for ABP 938 PFS, aflibercept (US) PFS, and aflibercept (EU) PFS lots. A few minor outliers were not considered to be clinically meaningful. In summary similarity/comparability between all three product groups for product strength, total extractable volume, and deliverable dose volume could be demonstrated.

To further strengthen the similarity claim, thermal stability and degradation studies at accelerated C, stressed, and forced degradation conditions (thermal stability and photostability under UV light exposure) have been performed to compare degradation kinetics and pathways between ABP 938 finished product, US comparator and EU reference product. These studies have been accurately designed and performed. In summary, the results from these studies further support the similarity/comparability between all three product groups.

In summary, the results of the biosimilarity exercise support the similarity claim. In addition, comparability of US sourced comparator with EU sourced reference product was demonstrated. The results are summarized in Table 1.

Table 1. Analytical Similarity Assessment Approach for Attributes/Activities

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Quantity	Protein concentration	UV absorbance	Results for ABP 938 were within the quality and min-max ranges for the EU reference and US comparator products.
	Volume	Gravimetry	
Quantity (targeted similarity	Protein concentration	UV absorbance	Results for ABP 938 were within the quality ranges for the EU reference and US comparator products and slightly exceeded the min-max ranges for

Molecular parameter	Attribute	Methods for control and characterization	Key findings
assessment for the PFS presentation)			both. The differences are minor and not considered clinically meaningful.
	Volume	Gravimetry	Results for ABP 938 were within the quality ranges for the EU reference and US comparator products and slightly exceeded the min-max range for the EU reference product. The difference is minor and not considered clinically meaningful because the full contents of the vial are extracted, and the excess quantity is expelled from the syringe allowing the 0.05 mL label volume to be measured using the graduations of the syringe.
	Deliverable dose volume	Procedure as described in the product label	Results for ABP 938 were within the quality and min-max ranges for the EU reference and US comparator products.
Primary structure and post-translational modifications, including glycosylation (N-glycosylation)	Intact molecular mass and profile	MALDI-TOF MS	ABP 938 molecular mass within ± 100 ppm of theoretical mass; same results for the US comparator and EU reference products. MALDI-TOF profiles visually similar between ABP 938 and the US comparator and EU reference products.
	Reduced and deglycosylated molecular mass and profile	ESI-TOF MS	ABP 938 molecular mass within ± 100 ppm of theoretical mass; same results for the US comparator and EU reference products. ESI-TOF MS profiles visually similar between ABP 938 and the US comparator and EU reference products.
	Reduced peptide map	LC-MS/MS	Amino acid sequence and peptide masses identical between ABP 938 and the US comparator and EU reference products. Peptide map profile visually similar between ABP 938 and the US comparator and EU reference products. Minor differences were observed in post-translational modifications which are not considered clinically meaningful.
	Non-reduced peptide map	LC-MS	For assessment of the disulfide structure, the observed masses were within ± 5 ppm of theoretical mass for ABP 938 and the US comparator and EU reference products. The peptide maps were similar for the three products.
	Free sulfhydryl content	Peptide mapping	Similar results for ABP 938 and the US comparator and EU reference products.
	N-glycans	HILIC N-glycan map	All ABP 938 batches were generally within the EU reference and US comparator quality and min-max ranges. Minor numerical differences were observed These differences are not considered clinically meaningful as similar levels of biological activities associated with the MOA were demonstrated
	High mannose N-glycans	HILIC N-glycan map	The range for ABP 938 exceeded the quality ranges and min-max ranges for EU reference and

Molecular parameter	Attribute	Methods for control and characterization	Key findings
			US comparator products. These differences are not considered clinically meaningful.
	N-glycan profile	HILIC N-glycan map	N-glycan profiles visually similar between ABP 938 and the US comparator and EU reference products.
	Site-specific N-glycan occupancy	Reduced and deglycosylated peptide map	The minor differences in site occupancy are not considered clinically meaningful as similar levels of biological activities associated with the MOA were demonstrated.
	Glycan structure	Reduced peptide map	Lower levels for ABP 938 when compared to EU reference and US comparator products. These differences are considered minor and not clinically meaningful.
	Extinction coefficient	Amino acid analysis	Results for ABP 938 within ±10% of the results for the EU reference and US comparator products.
	Isoelectric point and cIEF profile	cIEF	The isoelectric point of ABP 938 was similar to the EU reference and US comparator and the cIEF profiles were visually similar.
	Identity	ELISA	Results were similar for ABP 938 and the EU reference and US comparator products.
Higher Order structure and biophysical properties	FTIR spectrum	FTIR spectroscopy	The FTIR spectra when compared were similar for ABP 938 and the EU reference and US comparator products. The profiles were visually similar.
	Near UV CD spectrum	CD spectroscopy	The near UV CD spectra when compared for ABP 938 and the EU reference and US comparator products. The profiles were visually similar.
	Thermal stability	DSC	the DSC profiles were visually similar.
	Submicron particles	DLS	The DLS results were visually similar.
	Size distribution	SV-AUC	HMW species were at levels for ABP 938 and the EU reference and the US comparator products. Size distribution profiles were visually similar
	Molar mass	SE HPLC-LS	The results were comparable for the EU reference and US comparator products. The SE-HPLC-LS profiles were visually similar.
Particles - subvisible	Particles/mL (subvisible particles)	HIAC	The results show that levels of subvisible particles in this size range are consistently low and comparable between ABP 938 and the EU reference and US comparator products. All results met the acceptance criteria of USP<789> *Particulate Matter in Ophtalmic Solutions* and PhEur 2.9.19 *Particulate Contamination: Sub-visible particles*
	Subvisible particles	MFI	For all particle size ranges, ABP 938 had similarly low particle counts compared to aflibercept (US) and aflibercept (EU). These levels are higher than for the HIAC method, which can be understood by differences in sensitivity between the methods. The particle counts for the size ranges described in PhEur 2.9.19 meet the most stringent pharmacopoeial criteria and, overall, the results

Molecular parameter	Attribute	Methods for control and characterization	Key findings
			demonstrate a quality that is appropriate for intravitreal administration.
Purity and Impurities (product related substances and impurities, including charge variants)	Size variants	SE-UHPLC	The SE-UHPLC chromatograms were visually similar for ABP 938, EU reference and US comparator. The range of percentage of the main peak for ABP 938 was higher than the quality and min-max ranges for the EU reference and US comparator products. The range of percentage of HMW species for ABP 938 was lower than the quality and min-max ranges for the EU reference and US comparator products. These results indicate a higher purity of ABP 938 in terms of size variants when compared to the EU reference and US comparator products.
	Size variants	rCE-SDS	The range of percentage for ABP 938 was lower than the quality and min-max ranges for the EU reference and US comparator products. The range of percentage for ABP 938 was higher than the quality and min-max ranges for the EU reference and US comparator products. The percentage range for ABP 938 slightly exceeded the quality and min-max ranges for the EU reference and US comparator products. These slightly lower levels which do not impact the conclusion on biosimilarity. These results taken together indicate a higher purity of ABP 938 in terms of size variants when compared to the EU reference and US comparator products.
	Size variants	nrCE-SDS	The nrCE-SDS profiles were visually similar when compared between ABP 938 and the EU reference and US comparator products. The range of percentages for ABP 938 exceeded the quality and min-max ranges for the EU reference and US comparator products. The percentage range in ABP 938 exceeded the quality and min-max ranges for the EU reference and US comparator products. These results taken together indicate a higher purity of ABP 938 in terms of size variants when compared to the EU reference and US comparator products.
	Charge variants	cIEF	The cIEF profiles were visually similar when compared between ABP 938 and the EU reference and US comparator products. Minor differences were observed for the quality and min-max ranges for the EU reference and US comparator products. These differences are not considered clinically meaningful as similar levels of biological activities associated with the MOA were demonstrated.
Thermal stability and degradation – accelerated stability at 30 °C	Size variants, charge variants, and biological activity (VEGF-A/VEGFR-2 inhibition of binding)	SE-UHPLC, rCE-SDS, cIEF, cell-based assay (luminescence proximity assay)	The results were compared. Minor differences were observed between ABP 938 and the EU reference and US comparator products.

Molecular parameter	Attribute	Methods for control and characterization	Key findings
Thermal stability and degradation – stressed stability at 40 °C	Size variants, charge variants, and biological activity (VEGF-A/VEGFR-2 inhibition of binding)	SE-UHPLC, rCE-SDS, cIEF, cell-based assay (luminescence proximity assay)	The results were compared. For the physico-chemical methods, minor differences in degradation behaviour were observed between ABP 938 and the EU reference and US comparator products. The results met the similarity assessment criteria for VEGF-A/VEGFR-2 inhibition of binding.
Thermal stability and degradation – forced degradation at 45 °C	Size variants, charge variants, reduced peptide map, and biological activity (inhibition of VEGF-A-mediated HUVEC proliferation, VEGF-A/VEGFR-2 inhibition of binding, PlGF-1/VEGFR-1 dimerization inhibition in U2OS cells)	SE-UHPLC, rCE-SDS, cIEF, LC-MS/MS, cell-based assays	The results were qualitatively compared and met the similarity assessment criteria for size variants by rCE-SDS, charge variants by cIEF, inhibition of VEGF-A-mediated HUVEC proliferation, VEGF-A/VEGFR-2 inhibition of binding and PlGF-1/VEGFR-1 dimerization inhibition in U2OS cells. Minor differences were observed between ABP 938 and the EU reference and US comparator products for the size variants by SE-UHPLC and in the reduced peptide map by LC-MS/MS
Thermal stability and degradation – photostability at 25 °C)	Size variants, charge variants, reduced peptide map, and biological activity (inhibition of VEGF-A-mediated HUVEC proliferation, VEGF-A/VEGFR-2 inhibition of binding, PlGF-1/VEGFR-1 dimerization inhibition in U2OS cells)	SE-UHPLC, rCE-SDS, nrCE-SDS, cIEF, LC-MS/MS, cell-based assays	The results were qualitatively compared and met the similarity assessment criteria for charge variants by cIEF. Minor differences were observed between ABP 938 and the EU reference and US comparator products for the remaining quality attributes.
Biological Properties	Inhibition of VEGF-A-mediated HUVEC proliferation	Cell-based assay	All ABP 938 batches were within the EU reference and US comparator quality and min-max ranges for inhibition of VEGF-A- mediated HUVEC proliferation, inhibition of VEGF-A/VEGFR-2 signalling in HUVEC and HEK293 cells, and VEGF-A/VEGFR-2 inhibition of binding, demonstrating comparable biological activity. Minor numerical differences due to method variability were observed for VEGF-A/VEGFR-2 signalling inhibition in HUVEC (for min-max range, ABP 938 vs EU and US vs EU), VEGF-A/VEGFR-2 signalling inhibition in HEK293 cells, and VEGF-A/VEGFR-2 inhibition of binding (for min-max range, ABP 938 vs EU and US vs EU). These differences are not considered clinically meaningful
	VEGF-A/VEGFR-2 signalling inhibition in HUVEC	Cell-based assay	
	VEGF-A/VEGFR-2 signalling inhibition in HEK293 cells	Cell-based assay	
	VEGF-A/VEGFR-2 inhibition of binding	Cell-based assay (luminescence proximity assay)	
	VEGF-A isoforms binding kinetics and affinity	SPR	Similar binding kinetics and affinity between ABP 938 and the EU reference and US comparator products
	Specificity against VEGF-C and VEGF-D	SPR	Similar lack of binding between ABP 938 and the EU reference and US comparator products
	PlGF-1/VEGFR-1 dimerization	Cell-based assay	All ABP 938 batches were within the EU reference and US comparator quality and min-max ranges

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	inhibition in U2OS cells		for inhibition of PlGF-1/VEGFR-1 and PlGF-2/VEGFR-1 dimerization in U2OS cells, demonstrating comparable biological activity. Minor numerical differences due to method variability were observed for both tests (for min-max ranges, ABP 938 vs US and ABP 938 vs EU). These differences are not considered clinically meaningful.
	PlGF-2/VEGFR-1 dimerization inhibition in U2OS cells	Cell-based assay	
	PlGF-1/VEGFR-1 inhibition of binding	Cell-based assay (luminescence proximity assay)	The range for ABP 938 batches exceeded the EU reference and US comparator quality and min-max ranges for PlGF-1/VEGFR-1 inhibition of binding and PlGF-1 binding by SPR. Results for the EU reference and US comparator products were similar to each other. It is considered that these minor differences do not impact the conclusion of comparable biological activity.
	PlGF-1 binding	SPR	
	PlGF-2 binding	SPR	All ABP 938 batches were within the EU reference and US comparator quality and min-max ranges for PlGF-2 binding, demonstrating comparable biological activity. Minor numerical differences due to method variability were observed for both tests. These differences are not considered clinically meaningful.
	PlGF-1 binding kinetics and affinity	SPR	Similar binding kinetics and affinity were measured for PlGF-1 and PlGF-2 binding.
	PlGF-2 binding kinetics and affinity	SPR	
	Galectin-1 binding	SPR	The range for ABP 938 batches were within the ranges for the EU reference and slightly exceeded the range for the US comparator. The numerical differences are considered minor and not clinically meaningful.
	VEGF-B_{167} binding	ELISA	All ABP 938 batches were within the EU reference and US comparator ranges. Minor numerical differences due to method variability were observed which are not considered clinically meaningful.
	VEGF-B isoform binding kinetics and affinity	SPR	Similar binding kinetics and affinity between ABP 938 and the EU reference and US comparator products
	FcRn binding	SPR	Slightly lower binding of ABP 938 to FcRn when compared to EU reference and US comparator. This is considered a minor difference that is not clinically meaningful and does not impact the conclusion on biosimilarity.
	C1q binding	ELISA	Slightly lower levels of binding to C1q for ABP 938 when compared to EU reference and US comparator. This difference is not considered clinically meaningful.

Molecular parameter	Attribute	Methods for control and characterization	Key findings
	FcγRIa binding	SPR	Similar binding kinetics and affinity between ABP 938 and the EU reference and US comparator products
	FcγRIIa-131H binding	SPR	Slightly lower levels of binding to FcγRIIa-131H, FcγRIIb, FcγRIIIa and FcγRIIIb binding for ABP 938 when compared to EU reference and US comparator.
	FcγRIIb binding	SPR	
	FcγRIIIa binding	SPR	
	FcγRIIIb binding	SPR	
	ADCC activity in PBMC and SKOV3 cells	Cell-based assay	Similar lack of ADCC, ADCP and CDC activity for ABP 938 when compared to EU reference and US comparator.
	ADCP activity in PBMC ($CD14^+$) and SKOV3 cells	Cell-based assay	
	CDC activity in SKOV3 cells with rabbit serum	Cell-based assay	

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The finished product has been developed as vial and PFS presentations, similar to the reference product presentations.

During the procedure, a major objection was raised regarding the applicability of the US-EU MRA for batch release testing site, as the manufacturing of the active substance was performed outside the EEA. In response, the applicant has transferred the batch release testing site to a site in the EEA, and the major objection was considered resolved.

A comprehensive and scientifically-sound biosimilarity assessment has been conducted. The results of the biosimilarity exercise support the claim of similarity of ABP 938 with the EU reference product Eylea. Observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance (safety and efficacy) of the product.

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.

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. Recommendation(s) for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Analytical and functional similarity between ABP 938 and Eylea (EU- and US-aflibercept) was demonstrated in *in vitro* studies which are described and discussed in the Quality Assessment (please refer to Section 2.3).

A comparative ocular distribution study performed in male New Zealand white rabbits (study SR-01382) and a comparative one-month intravitreal toxicology study in female cynomolgus monkeys (study 119678), including toxicokinetic evaluation, were performed and submitted in non-clinical dossier part of this MAA.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

A thorough *in vitro* biosimilar comparability exercise was conducted with ABP 938 and EU- and US-aflibercept and was submitted in quality dossier part of this MAA.

2.4.3. Pharmacokinetics

To investigate the suitability of Alexa fluor 488-conjugated Aflibercept (EU) and ABP 938 used in the IVT ocular distribution study in rabbits (Study SR-01382), a supporting exploratory study (R20190077) was conducted to compare test material pre-and post-conjugation in important attributes as protein concentration, degree of labelling, biological activity, higher order structure, subvisible particles and aggregates, impurities, excipient content and endotoxin levels. Acceptance criteria of important attributes were met or slight differences justified appropriately. Results indicate that fluorophore-conjugated products remained comparable to pre-conjugated drug products in important attributes.

In study SR-01382, ocular distribution of ABP 938 and EU-aflibercept was investigated in male New Zealand white rabbits following a single intravitreal injection of ABP 938 or EU-aflibercept, conjugated with a fluorophore (AF488). Fluorescence was measured with an Occumetrics Fluorotron Master fluorophotometer (Fluorotron) using the vitreous scan optic. A pilot phase 1 part of this study was conducted to determine the most appropriate study conditions for the definitive phase 2 part of this study. In the latter, male New Zealand White rabbits (n = 3/group) received single 1 mg/eye (25 µL/eye) IVT injections of ABP 938 or EU-aflibercept into both eyes. Fluorophotometry was performed predose, 6 and 24 hours postdose and on study days 3, 5, 8, 10, 12, 15 and 24. Exposures of ABP 938 or EU-aflibercept in vitreous humor and aqueous humor were similar, whereat T_{max} values were noticed to be higher in EU-Aflibercept treated rabbits, but still within 2-fold, as defined assessment criteria for similarity in this study. Additionally, ophthalmic examinations (e.g slit-lamp biomicroscopy and indirect ophthalmoscope) were performed and revealed mild to moderate conjunctival hyperemia in ABP 938 and EU-aflibercept treated rabbits and mild chemosis in ABP 938 treated animals.

The applicant submitted a GLP-compliant 1-month intravitreal toxicology study in female Cynomolgus monkeys (study 119678) including toxicokinetic evaluation of ABP 938 in comparison to EU-aflibercept. A validated electrochemiluminescent method (ECL) was used to determine ABP 938 and aflibercept (EU) concentrations in the serum samples. Concentrations of ABP 938 and EU-aflibercept in serum were comparable (within 2-fold), but slightly higher for EU-aflibercept after the first dose. Mean vitreous fluid concentrations of ABP 938 and EU-aflibercept appeared to be comparable as well, with higher values observed for ABP 938 for both eyes.

2.4.4. Toxicology

2.4.4.1. Repeat dose toxicity

In study 119678, animals (4 females/group) were treated intravitreally with either control (sterile saline), 1mg/eye of ABP 938 or EU-aflibercept (both eyes) at day 1 and day 29 and monitored regarding mortality, clinical observations, body weights, ophthalmic observations (indirect ophthalmoscopy and slit-lamp biomicroscopy), intraocular pressure measurements, full-field electroretinography, and clinical and anatomic pathology. A mild increase in vitreous cells (0.5 to 1+) was noticed in all treatment groups, whereas a transient mild increase in aqueous cells (0.5+) was only observed in ABP 938 and Eylea® treated animals (one eye each), however, considered procedure-related rather than test-article related as well. White vitreous floater with multifocal small clear spheres were observed near the dosing site in ABP 938 and Eylea® treated animals and related to silicone droplets used as a lubricate in syringes. Subconjunctival hemorrhage was noticed only transiently in one eye of an ABP 938 treated female and not considered test article- but procedure-related. No ABP 938- or Eylea®- related effects in intraocular pressure (IOP) and electroretinography (ERG) measurements were noted. Significant decreases in B-wave amplitudes (week 5) observed in ABP 938 and Eylea® treated animals were considered due to an increase in B-wave amplitudes in the saline control group. An asymmetric response in ERG amplitude was only noticed for one female animal treated with Eylea®. The toxicity profiles of ABP 938 and Eylea® were regarded similar and the NOAEL for ABP 938 was determined to be greater than 1 mg/eye.

2.4.4.2. Other toxicity studies

The applicant provided a scientific justification for impurity levels and a discussion on the safety of formulation excipients in ABP 938.

Overall, a conservative approach, determining a safety evaluation threshold below the QT of 0.15% of drug substance in ICH Q3A(R2) (2006) and the QT of 1.0% of drug product in ICH Q3B(R2) (2006), was used, if no even lower compound specific IVT PDE was derived internally.

Regarding process reagents, the amount of one reagent was above the safety evaluation threshold but considered qualified due to available published data found in literature, even higher levels in an approved IV drug product and the 1-month repeat-dose toxicity study conducted with ABP 938 in Cynomolgus monkeys (study 119678).

One leachable, was above the safety evaluation threshold and needed safety evaluation, even though it was not detected in the ABP 938 drug product vial system. Therefore, a IVT PDE was established for PEG, representing an at least 12-fold safety margin.

Sterilant residuals were found to be below the current IVT PDEs and even below the safety evaluation threshold.

The two excipients in ABP 938, α,α-trehalose dihydrate and polysorbate 80, which are not included in the RefMP Eylea, are well-known compendial excipients and approved in other IVT drug products at even higher dose levels (Lucentis® [ranibizumab] or Beovu® [brolucizumab], respectively.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant provided a valid justification for the absence of an Environmental Risk Assessment, which is deemed acceptable and in line with the EMA Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2 issued 2006), where it is stated, that in the case of medicinal products comprised of naturally occurring substances (e.g. vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates and lipids) as active substance, the ERA may consist of a justification for not submitting ERA studies and such a justification could be, for example, that due to the physico-chemical nature of the active substance these products are unlikely to pose a risk to the environment. Alternatively, based on the environmental fate and/or common presence in the environment, these products are unlikely to alter the concentration or distribution of the substance in the environment.

2.4.6. Discussion on non-clinical aspects

Pharmacology

Overall, the applicant conducted a comprehensive comparative analytical similarity assessment including a series of primary pharmacodynamic *in vitro* studies. Please refer to the Quality assessment for more detailed information.

Primary pharmacology assessment was not the subject of any in vivo research. Further, it was justified that ABP 938 did not require secondary pharmacology, pharmacodynamic drug-drug interaction, or safety pharmacology studies because the proposed biosimilar would not benefit from the nonclinical information obtained from these experiments. The overall strategy is adequate as well as the omission of *in vivo* studies. As outlined in the EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1; 2014) and the EMA Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev 1), a stepwise approach is recommended for evaluation of the biosimilarity of drug product (DP) and the EU-licenced referenced medicinal product (RefMP). *In vitro* assays may be considered as paramount for the non-clinical biosimilar comparability exercise since they are often more specific and sensitive in detecting differences between the biosimilar and the RefMP.

Pharmacokinetics

The applicant conducted extensive *in vivo* research to study PK, TK and toxicity profile of ABP 938 despite the scientific advice EMA/CHMP/SAWP/796258/2017 recommending omission of such studies due to lack of sensitivity when extrapolating to human PK and safety. To evaluate the similarity of ABP 938 and aflibercept (EU) with respect to serum toxicokinetics (TK) and ocular distribution the applicant conducted a comparative 1-month IVT toxicology study in cynomolgus monkeys (Study 119678), a non-terminal comparative IVT ocular distribution study in New Zealand White rabbits (Study SR-01382), and a supporting exploratory *in vitro* study characterizing the fluorophore-conjugated products used in the rabbit ocular distribution study (Study R20190077). In rabbits and monkeys a comparable exposure (Cmax and AUC0-inf) in vitreous and aqueous humors were demonstrated for ABP 938 and aflibercept. Ophthalmic examinations (slit-lamp biomicroscopy and indirect ophthalmoscope) in rabbits revealed mild to moderate conjunctival hyperemia in ABP 938 and EU-aflibercept treated rabbits and

mild chemosis in ABP 938 treated animals. In female cynomolgus monkeys ABP 938 and aflibercept were administered by 1 mg/eye twice (Study Days 1 and 29) via intravitreal injection (study 119678) and exposures were comparable (within approximately 2-fold) in serum by AUC (168 or 672 hours) and Cmax. ABP 938 and aflibercept treated animals also displayed comparable mean vitreous fluid concentrations.

Toxicology

Although the choice of cynomolgus was definitely not supported and strongly recommended to be replaced by another species, with further focus on the biosimilar candidate only (follow-up scientific advice in March 2019, EMA/CHMP/SAWP/180668/2019), the applicant conducted a GLP-compliant comparative one-month intravitreal toxicology study in female cynomolgus monkeys (study 119678) with ABP 938 and EU-aflibercept to distinguish between differences in toxicity profiles due to different formulations. A low number of animals was used which needs to be taken into account when extrapolating study results to clinical situation. The 1 mg/eye dose was chosen to provide an HED of 2 mg/eye to patients adjusting for vitreous volume differences between monkeys (2.0 mL) and humans (4.0 mL). A mild increase in cells in the vitreous was observed at comparable frequencies in all three groups, and a single transient instance of mildly increased cells in the aqueous humor was observed in one eye administered ABP 938 and in one eye administered Eylea. Safety profiles of the biosimilar and the RefMP are regarded as similar in the merit of provided data. A NOAEL of 1mg/eye could be determined for ABP 938.

Neither single dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicology, local tolerance nor other toxicity studies were performed with ABP 938, which is accepted and adequate for a biosimilar drug product application.

The applicant's justifications on impurity levels and formulation excipients in ABP 938 are accepted. After request, the applicant provided a thorough discussion on safety factors used for the PDE calculation. Nonclinical and quality documentation of the ABP 938 marketing authorisation application were updated accordingly.

Environmental risk

Aflibercept is already used in existing marketed products (Eylea) and no significant increase in environmental exposure is anticipated based on justification.

Therefore Skojoy (Aflibercept of Amgen Technology (Ireland) Unlimited Company) is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Not applicable.

2.4.7. Conclusion on the non-clinical aspects

In the context of provided non-clinical data on pharmacokinetics, toxicokinetics and safety, the biosimilar and the RefMP are regarded as similar. No major concern was identified which would argue against a marketing authorization application and concerns were properly addressed and resolved by the applicant. Please refer to the Quality assessment report for discussion and conclusion on the biosimilar comparability exercise.

2.5. Clinical aspects

ABP 938 has been developed as a proposed biosimilar to Eylea (aflibercept). 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 IgG1. Aflibercept 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 clinical evidence supporting the similarity of ABP 938 to Eylea (aflibercept) includes a completed randomized, double-masked, active-controlled comparative clinical study in subjects with neovascular (wet) AMD (Study 20170542); and a completed open-label, 2-arm, randomized, multi-site PFS clinical usability study investigating whether the ABP 938 PFS can be used effectively and safely by retina specialists in adult subjects with various chorioretinal vascular diseases (CVDs), including neovascular (wet) AMD, DME, macular edema following RVO, or diabetic retinopathy (DR) (Study 20210034).

2.5.1. Introduction

GCP aspects

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

- Tabular overview of clinical studies

Type of Study	Study Identifier Protocol No.	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	Number of Subjects Randomized/ Number of Subjects Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Study Duration[b]	Study Status; Type of Report/Location
Study Reports of Controlled Clinical Studies Pertinent to Claimed Indications								
Comparative clinical study	20170542	Primary: Efficacy of ABP 938 compared to aflibercept (EU) Secondary: Safety and immunogenicity of ABP 938 compared to aflibercept (EU)	Randomized, multicenter, double-masked, active-controlled study	ABP 938, aflibercept (EU); 2 mg IVT injection on day 1, wk 4, and wk 8; At wk 16, subjects receiving ABP 938 to continue ABP 938, subjects receiving aflibercept (EU) re-randomized to continue aflibercept (EU) or switch to ABP 938, 2mg IVT injection every 8 wks from wk 16 until wk 48	579/576[a]	• Men and women ≥ 50 yrs old • Subjects with neovascular (wet) AMD in the study eye • Active, treatment naïve subfoveal CNV lesions secondary to neovascular (wet) AMD • BCVA between 73 and 34 letters, inclusive, in the study eye using ETDRS testing	52 weeks	Complete; CSR/Module 5.3.5.1 (20170542)

Type of Study	Study Identifier Protocol No.	Study Objectives	Study Design and Type of Control	Test Products; Dosage Regimens; Route of Administration	Number of Subjects Randomized/ Number of Subjects Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects and Key Entry Criteria	Study Duration[b]	Study Status; Type of Report/Location
Other Study Reports and Related Information								
PFS clinical usability study	20210034	Primary: Ability of retina specialists to successfully administer, via an IVT injection, a 2 mg dose of ABP 938, using the ABP 938 PFS, compared to a 2 mg dose of aflibercept using the aflibercept (US) PFS. Secondary: Safety of ABP 938 PFS compared to aflibercept (US) PFS	Randomized, multicenter, open-label, 2-arm study	ABP 938, aflibercept (US); 2 mg IVT injection using a PFS, single dose	49/48	• Adult men and women ≥ 18 years of age with various CVDs, including neovascular (wet) AMD, DME, macular edema following RVO, or DR	28 days	Complete; CSR/Module 5.3.5.4 (20210034)

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CSR = clinical study report; CVD = chorioretinal vascular disease; DME = diabetic macular edema; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; GCP = Good Clinical Practice; IVT = intravitreal; PFS = prefilled syringe; US = United States; wk = week; RVO = retinal vein occlusion

a Safety analysis set does not include data from site 54221006. Three subjects were excluded from all analysis sets due to major GCP violations (see Section 8.7.6 of the Study 20170542 CSR).

b Does not include screening period

A clinical Phase I PK study was not conducted since it was considered not meaningful to determine the biosimilarity based on the low level of aflibercept in serum following IVT administration.

The clinical development program to support the similarity of ABP 938 to Eylea comprises one Phase III therapeutic similarity study conducted in patients with (wet) AMD (Study 20170542). Comparative PK evaluation was a secondary objective in this study.

2.5.2. Clinical pharmacology

A separate clinical Phase 1 PK study was not conducted, since it was considered not meaningful to determine the biosimilarity based on the low level of aflibercept in serum following IVT administration.

The clinical development program to support the similarity of ABP 938 to Eylea comprises one Phase III therapeutic similarity study conducted in patients with (wet) AMD (Study 20170542, see Table 1 above). Comparative PK evaluation was a secondary objective in this study.

The clinical study 20170542 provided supportive PK data (plasma concentration following 1st and 3th IVT injections) in accordance with the EMA guideline: Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010), Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1).

No specific studies dedicated to human PD have been performed for aflibercept and the PD data was derived from in vitro, animal, and human efficacy studies (Eylea EPAR, 2012). No validated PD markers considered relevant to predicting efficacy of aflibercept in (wet) AMD patients exist. Therefore, no PD markers were included in the clinical study with ABP 938.

2.5.2.1. Pharmacokinetics

Bioequivalence

Study 20170542

Design and methods of the study are described in detail in the Section on Clinical Efficacy.

PK sampling and data analysis

Pharmacokinetic (PK) samples were obtained during Main Study Period of Study 20170542, where patients were administered either 2 mg/0.05 mL ABP 938 or EU-Eylea IVT injection using a single-dose vial every 4 weeks for the first 3 doses, then every 8 weeks from week 16 until week 48.

A total of 49 subjects were enrolled in the PK substudy. Overall, 44 (89.8%) of the subjects enrolled in the PK substudy were included in the PK analysis set.The collection of blood samples for PK assessment was done in 44 subjects participating in PK evaluation (18 subjects in the ABP 938 treatment group and 26 subjects in the aflibercept treatment group). Blood samples for PK assessment (Ctrough) were predose (within 60 minutes before day 1 dose) and postdose (24 hours after day 1 dose) and postdose at week 8.

The PK analysis set consists of all subjects enrolled in the PK substudy who received at least 1 dose of investigational product between day 1 and week 8 (inclusive) and who have at least 1 reported serum concentration of ABP 938 or aflibercept (EU); based on actual treatment the subject received in the study eye. If it was anticipated that the fellow eye would need to be treated prior to the week 8 postdose PK sample, then the subject was not to be enrolled into the PK substudy. If the need for treating the fellow eye was identified at the week 8 visit, then the fellow eye was treated after the week 8 postdose PK sample had been drawn for those subjects included in the PK substudy.

PK data were analysed only descriptively.

Results

A summary of the unbound (free) drug concentrations following IVT administration of ABP 938 or aflibercept (EU) for subjects in the PK analysis set are provided in Table 2.

Table 2: Summary of Pharmacokinetic Concentrations (ng/mL) (PK Analysis Set)

Visit Statistic	ABP 938 (N = 18)	Aflibercept (EU) (N = 26)
Baseline		
n	16	22
Mean (SD)	0.00 (0.00)	0.00 (0.00)
Median	0.00	0.00
Minimum, maximum	0.0, 0.0	0.0, 0.0
Day 1 postdose		
n	16	22
Mean (SD)	33.28 (38.225)	58.41 (50.011)
Median	24.95	37.30
Minimum, maximum	0.0, 139.0	0.0, 220.0
m	10	21
GeoMean	44.98	46.75
GeoCV (%)	65.5	85.6
Geometric LS mean	52.90	51.97
Ratio of geometric LS means (ABP 938/Aflibercept [EU])	1.0179	
90% CI for ratio of geometric LS means	(0.6342, 1.6337)	
Week 8 postdose		
n	15	23
Mean (SD)	58.03 (53.111)	75.83 (36.743)
Median	35.60	74.10
Minimum, maximum	0.0, 192.0	25.4, 173.0
m	14	23
GeoMean	47.37	67.44
GeoCV (%)	84.5	54.3
Geometric LS mean	47.68	66.55
Ratio of geometric LS means (ABP 938/Aflibercept [EU])	0.7165	
90% CI for ratio of geometric LS means	(0.4926, 1.0421)	

BCVA = best corrected visual acuity; EU = European Union; GeoCV = geometric coefficient of variation; GeoMean = geometric mean; LS = least squares; m = number of subjects with a non-zero concentration; n = number of subjects with non-missing values; PK = pharmacokinetics

Note: Lower limit of quantification was < 15.0 ng/mL. Pharmacokinetic concentrations below the lower limit of quantification were assigned a value of 0 and were excluded from the calculations of GeoMean, GeoCV, geometric LS mean, geometric mean ratio, and 90% CI (calculated only if m ≥ 5). The geometric LS mean, ratio of geometric LS means, and 90% CI were estimated based on ANCOVA model adjusted for the actual stratification factors of geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters). Postdose samples were collected approximately 24 hours after the day 1 dose, with an allowable window of: -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose). PK sample collection window 1 day after week 8 dose: -6 hours to +24 hours (ie, 18 hours to 48 hours after week 8 dose).

The median free drug serum concentrations at day 1 postdose for the ABP 938 and aflibercept (EU) treatment groups were 24.95 ng/mL and 37.30 ng/mL, respectively. The median free drug serum concentrations at week 8 postdose for the ABP 938 and aflibercept (EU) treatment groups were 35.60 ng/mL and 74.10 ng/mL, respectively. These concentrations are consistent with the mean Cmax of free aflibercept reported for patients with neovascular (wet) AMD, RVO, and DME following IVT administration of Eylea (aflibercept). Although the median and geometric mean free drug concentrations at day 1 postdose and week 8 postdose were higher for the aflibercept (EU) treatment group compared to the ABP 938 treatment group.

No formal PK parameters such as Cmax or AUC were assessed. Normally, a complete PK profile would be preferred, including determination of Cmax as one of the most relevant PK endpoints. However, based on the observed results, no issue is made, please see below. In general, results show low systemic exposure of unbound (free) drug concentrations following IVT administration of aflibercept (EU) in this subject population and are below the concentration required to half-maximally bind systemic VEGF (2.91 μg/mL) for a pharmacologically relevant reduction in endogenous systemic VEGF. Furthermore, in alignment with EMA advice, standard PK parameters (ie, area under the concentration-time curve and maximum observed concentration [Cmax]) were not necessarily considered evaluable.

2.5.2.2. Pharmacodynamics

Mechanism of action

Aflibercept exerts its therapeutic effects by binding to Vascular Endothelial Growth Factor A (VEGF-A) and placental growth factor (PlGF) thereby inhibiting the binding and activation of these cognate VEGF receptors. VEGF-A and PlGF are members of the VEGF family of angiogenic factors that can act as mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF acts via two receptor tyrosine kinases; Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1) and Vascular Endothelial Growth Factor Receptor 2 (VEGFR-2), present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Activation of these receptors by VEGF-A can result in neovascularization and excessive vascular permeability.

Aflibercept acts as a soluble protein decoy for VEGFRs (VEGFR-1 and VEGFR-2) present on the surface of endothelial cells in the retina. Aflibercept preferentially binds to VEGF-A and PlGF with a much greater affinity than its natural angiogenic competitors (VEGFR-1 and VEGFR-2). Through this mechanism, aflibercept prevents ligand-induced dimerization of VEGFR-2, preventing downstream activation of the intracellular tyrosine kinase domains from inhibiting pathologic angiogenesis. Aflibercept exerts its inhibitory effects on VEGFRs preventing endothelial proliferation, vascular permeability, and neovascularization.

Based on the totality of the published literature and in line with prior CHMP reviews of Eylea, the binding to VEGF-A and PlGF is considered to be the principal MoA of aflibercept for all the indications for which Eylea is approved.

Immunological events

Immunogenicity was evaluated based on the safety analysis set defined as all subjects who received at least 1 dose of investigational product, with treatment assignment based on actual treatment received; used for analysis of safety and immunogenicity endpoints. In this study 20170542, blood samples for ADA analysis were collected prior to dosing on day 1/week 0 (baseline), and weeks 8, 16, 24, 40, and 52/EOS. All available samples were screened for binding ADAs.

Table 3: Antidrug Antibody Results – Entire Study (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

Variable	ABP 938/ ABP 938 (N = 273)	Aflibercept (EU)/ ABP 938 (N = 133)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Subjects with an on-study result through week 52[a]	273	133	136
Developing antibody incidence [n (%)]			
Binding antibody positive post-baseline with a negative or no result at baseline	4 (1.5)	3 (2.3)	0 (0.0)
Subjects with a result at baseline	269	129	136
Pre-existing antibody incidence, n (%)			
Binding antibody positive at or before baseline	9 (3.3)	2 (1.6)	5 (3.7)
Subjects with a post-baseline result through week 8	264	129	131
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	1 (0.4)	3 (2.3)	0 (0.0)
Subjects with a post-baseline result through week 16	273	132	136
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	1 (0.4)	3 (2.3)	0 (0.0)
Subjects with a post-baseline result through week 24	273	133	136
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	4 (1.5)	3 (2.3)	0 (0.0)

Variable	ABP 938/ ABP 938 (N = 273)	Aflibercept (EU)/ ABP 938 (N = 133)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Subjects with a post-baseline result through week 40	273	133	136
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	4 (1.5)	3 (2.3)	0 (0.0)
Subjects with a post-baseline result through week 52	273	133	136
Developing antibody incidence, n (%)			
Binding antibody positive post-baseline with a negative or no result at baseline	4 (1.5)	3 (2.3)	0 (0.0)
Transient[b]	2 (0.7)	2 (1.5)	0 (0.0)

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CSR = clinical study report; EU = European Union
Note: Baseline was defined as the last non-missing assessment taken prior to the first dose of study investigational product. Percentages were calculated using the corresponding category count as the denominator.
[a] Subjects considered on-study after signing informed consent
[b] Negative result at the subject's last time point tested within the study period

A low incidence of binding ADAs was observed in all treatment groups over the entire study. Since the binding ADA positive rate was low for both ABP 938 and aflibercept (EU) in Study 20170542, ADAs are not expected to impact ABP 938 efficacy or safety at the clinical dose.

Treatment-emergent ADAs were rare, of low magnitude (titers ≤ 30), and often transient. Similar levels of binding ADAs were seen between the ABP 938 and aflibercept (EU) treatment groups and were consistent with those reported for Eylea (aflibercept) in neovascular (wet) AMD, RVO, and DME studies. Results support a demonstration of similar immunogenicity of ABP 938 to Eylea (aflibercept).

2.5.3. Discussion on clinical pharmacology

Analytical methods

PK assay: Validation of an MSD-ECL method for the quantitation of ABP 938 or Eylea® (Aflibercept) in human serum (#153135).

A PK assay for the determination of ABP 938 or Eylea in human serum using an MSD-ECL method has been developed and validated. The PK assay was initially qualified to demonstrate analytical comparability of ABP 938 and Eylea and to justify the use of ABP 938 as a calibrator for a single standard curve. All reagents, matrices and antibodies and used lot numbers are well described. The assay was validated for its accuracy/precision, selectivity and matrix effects, interference and specificity, dilutional linearity, hook effect, and stability.

All validation parameters were within pre-specified acceptance criteria. No matrix-related interference was observed, lipemia and haemolysis did not have any effect on quantification. Dilutional linearity was demonstrated for 100.000 ng/ml diluted at 20-, 200- and 2000-fold. No hook effect was detected. Bench-top stability was confirmed for 26 hours at RT and long-term stability demonstrated for 729 days at -20°C and -80°C.

The reference standard used for clinical study 20170542 was the same as used for method validation (i.e. 0010473693). Incurred sample reanalysis within study 20170542 confirmed suitability of the assay (13.2% samples re-tested, 100% of samples met the pre-specified criteria). QC performance was within acceptance criteria. All samples were analysed within the demonstrated long-term stability.

Taken together, presented assay for determination of aflibercept in human serum was well described and established. It is considered valid for its intended use. Performance of the assay during clinical study 20170542 is found acceptable.

Immunogenicity assays: Validation of an MSD-ECL Method for the detection of Anti-ABP 938 or Anti-Eylea (Aflibercept) Antibodies in human serum (ICDIM 448).

The applicant has adopted a three-tiered MSD-ECL method to screen, confirm and quantify aflibercept specific antibodies in human serum.

All critical reagents, drugs, and antibodies and used lot numbers were well described. Surrogate anti-ABP 938 EE3.1 rat monoclonal antibody supplied by Amgen was used for positive control preparation. Pools were prepared by spiking anti-ABP 938 antibodies into the screened negative control pool. The assay was validated for its precision, selectivity, sensitivity, drug tolerance, target interference, cross-reactivity, prozone effect and stability. Intra- and inter-assay precision were below 18.8%. Sensitivity was determined as < 1.00 ng/mL. Cut points for the screening and confirmation assay were estimated in 50 individual drug-naïve human serum samples with no detectable ADA activity. For confirmatory cut-point, human sera were spiked with an excess of drug prior to analysis. The complete statistical reports were included into the validation report. The suitability of the validated screening cut point was evaluated by determining the number and percentage of screening assay false positives in the study (according to Devanarayan et al., 2017). The screening assay false positive rate in baseline samples was determined to be 27/556 (4.9%), indicating that the validated cut points were suitable for use in the study (the FPR should be ideally between 2 and 11 % according to Shankar et al.).

Antigenic equivalence to Eylea was demonstrated, and the absence of a prozone effect was confirmed for antibody levels up to 20.000 ng/mL rat monoclonal anti-ABP 938 antibodies. The assay was tolerant to haemolytic and lipemic samples and to VEGF levels up to 10 ng/ml. Benchtop (24 hours at RT) and freeze/thaw (6 F/T cycles) stability of serum samples was confirmed.

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.

As agreed by FDA and EMA, neutralizing activity against ABP 938 and Eylea was not assessed in study 20170542 due to low incidence of binding ADAs and neutralizing ADAs reported for Eylea.

Pharmacokinetics

During EMA Scientific Advice (EMEA/ H/SA/3701/1/FU/1/2019/III) it was agreed that biosimilarity conclusions could not be based on a PK comparison of systemic exposure, considering the low and variable systemic concentrations of aflibercept after IVT administration. Consequently, no formal bioequivalence testing was conducted. Instead, supportive PK analyses were conducted in a subset of patients enrolled in the Phase 3 study 20170542, to explore whether the low systemic concentrations of IVT administered ABP 938 and Eylea were within the same range. A total of 49 subjects with nAMD were enrolled into the PK sub-study and comprised 8.5% of all randomised patients (N=579). A total of 44 subjects (18 subjects in the ABP 938 group and 26 subjects in the Eylea group) were included in the PK analysis set, which is an acceptable number for this purpose. Five subjects were excluded from the PK analysis due to a missing reported concentration of either drug. The timepoints for blood sample collection were also in line with the EMA advice and therefore endorsed.

In the PK substudy within Study 20170542, serum samples for PK analysis were obtained predose (within 60 minutes before day 1 dose) and postdose (approximately 24 hours after day 1 dose) and postdose at week 8 (approximately 24 hours after week 8 dose). The allowable time window for sampling was 18 hours to 48 hours from dosing. Only unbound (free) drug concentration in plasma was assessed.

All baseline serum concentrations were below the lower limit of quantification in both treatment arms. Post-dose concentrations were higher for Eylea compared to ABP 938. At day 1, the median post-dose concentrations of free aflibercept were 24.95 ng/mL for the ABP 938 and 37.30 ng/mL for Eylea; geometric mean concentration was also higher for Eylea (46.75 ng/mL) compared to ABP 938 (44.98 ng/mL). The median post-dose concentrations at week 8 were 35.60 ng/mL for ABP 938 and 74.10 ng/mL for Eylea; geometric mean concentrations for ABP 938 and Eylea were 47.37 ng/mL and 67.44 ng/mL, respectively. The reported serum concentrations were generally very low for both treatments and consistent with the range of Cmax published for the reference medicinal product Eylea. Large coefficient of variation (CV%) was reported for both treatments through all post-dose timepoints. For ABP 938, CV% ranged between 65.5% and 84.5% and for Eylea, the range of CV% was between 54.3% and 85.6%. Although the reported serum concentrations were higher for Eylea compared to ABP 938, these observed differences are not considered clinically relevant due to the large CV% and generally very low post-dose concentrations for both treatments.

No formal PK parameters such as Cmax or AUC were assessed. Normally, a complete PK profile would be preferred as Cmax is one of the most relevant PK endpoints, and in this specific case it is important to rule out that intravitreal application would lead to systemic aflibercept levels that could have an unwanted pharmacological effect. The observed differences in free drug concentration between groups could result from differences in Tmax, which can only be controlled when PK samples are taken at multiple timepoints after administration. Apart from not establishing Cmax, a wide time window was allowed for sampling, which further hampers a proper comparison of results between groups.

Nevertheless, the results point at low systemic exposure of unbound (free) drug concentrations following IVT administration of ABP 938 or aflibercept (EU) in patients with (wet) AMD. Measured drug levels are below the concentration required to half-maximally bind systemic VEGF (2.91 μg/mL) for a pharmacologically relevant reduction in endogenous systemic VEGF. Based on the results of median free drug concentration an unwanted impact on safety caused by the biosimilar can be ruled out, thus no concern is raised despite the methodological deficiencies of the PK assessment.

Pharmacodynamics

No dedicated comparative pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise and they are not considered necessary.

Immunological events

Immunogenicity of ABP 938 was evaluated in (wet) AMD patients as a part of the main Phase III Study 20170542 using the state-of-the-art and validated assays. Blood samples for immunogenicity assessment were collected prior to intravitreal injection of investigational product at Week 0 (Day 1), Week 8, Week 16, Week 24, Week 40 and at Week 52 (EOS visit).

The occurrence of ADAs was low over the entirety of the study period and the observed ADA responses were comparable between the two treatments.

As the number of ADA positive patients was very limited, the impact of immunogenicity on PK, efficacy or safety could not be assessed. However, due to the low incidences of ADA there is no concern for immunological events caused by ABP 938.

2.5.4. Conclusions on clinical pharmacology

As expected, the observed systemic aflibercept concentrations in patients were generally low and comparable with the mean Cmax of free aflibercept reported for patients with neovascular (wet) AMD, RVO, and DME following IVT administration of Eylea (aflibercept).

However, no formal PK parameters such as Cmax or AUC were assessed. Normally, a complete PK profile would be preferred as Cmax is one of the most relevant PK endpoints, and in this specific case it is important to rule out that intravitreal application would lead to systemic aflibercept levels that could have an unwanted pharmacological effect. Nevertheless, the results point at low systemic exposure of unbound (free) drug concentrations following IVT administration of ABP 938 or aflibercept (EU) in patients with (wet) AMD. Based on the results of median free drug concentration an unwanted major difference of the biosimilar can be ruled out. The PK and immunogenicity results are considered supportive for biosimilarity.

2.5.5. Clinical efficacy

2.5.5.1. Dose response studies

Not applicable

2.5.5.2. Main study

Study 20170542: A Randomized, Double-masked, Phase 3 Study of ABP 938 Efficacy and Safety Compared to Aflibercept (Eylea®) in Subjects with Neovascular Age-related Macular Degeneration

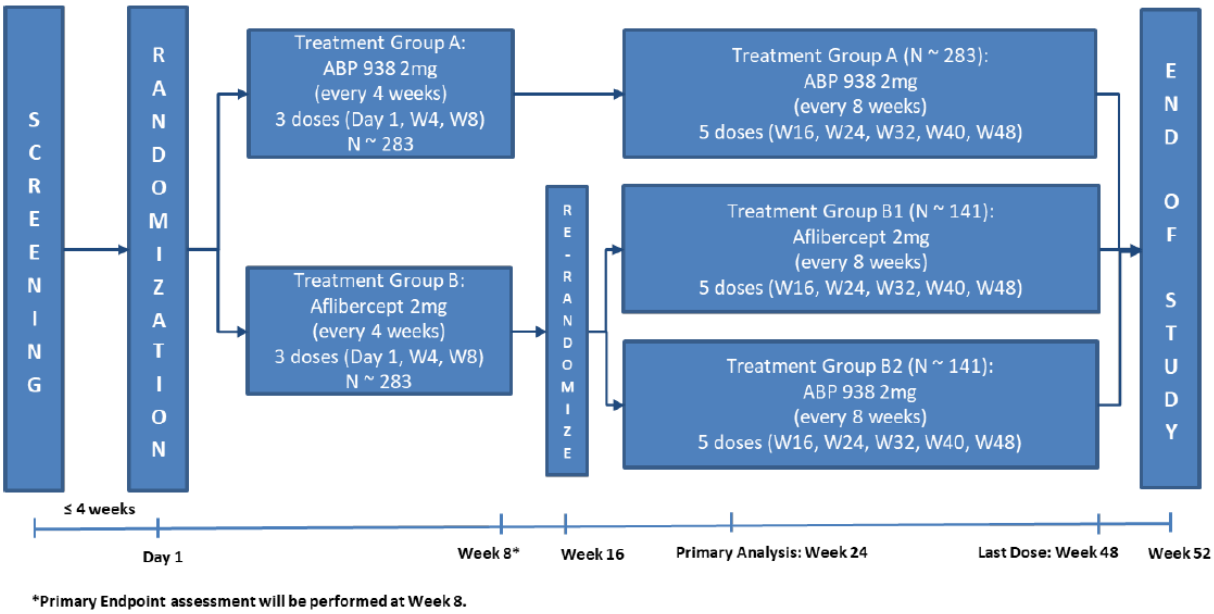
Methods

The comparative clinical Study 20170542 was a phase 3, randomized, double-masked, active-controlled study in adult subjects with neovascular (wet) AMD. The primary objective of the study was to assess the efficacy of ABP 938 compared to aflibercept (EU); the secondary objective was to assess the safety and immunogenicity of ABP 938 compared to aflibercept (EU). Eligible subjects were randomized in a masked 1:1 ratio to receive 2 mg (0.05 mL) of either ABP 938 (Treatment Group A) or aflibercept (EU) (Treatment Group B) administered by IVT injection every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, and week 8). Randomization was stratified by geographic region (East Asia, Europe, North America) and disease severity (BCVA <64 letters vs ≥64 letters).

At week 8, subjects were assessed for the primary endpoint (BCVA change from baseline as measured by ETDRS). Subjects were then re-randomized at week 16 in a masked fashion such that:

- subjects initially randomized to ABP 938 (Treatment Group A) continued to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48
- subjects initially randomized to aflibercept (EU) (Treatment Group B) were re-randomized in a 1:1 ratio to either continue on aflibercept (EU) (Treatment Group B1) or transition to ABP 938 (Treatment Group B2) by IVT injection every 8 weeks from week 16 until week 48

Re-randomization was stratified using the same factors as the initial randomization.



*Primary Endpoint assessment will be performed at Week 8.

Subjects who were unable to complete the week 16 visit within the visit window were not re-randomized, were discontinued from the study, and were asked to return to complete an end of study (EOS) visit within 28 days from determining that the subject would discontinue from the study. An EOS visit was conducted at week 52 for subjects that completed the study.

The treatment of the fellow eye was allowed (except in Czech Republic, Israel, and Japan) starting at baseline (day 1) if needed. Subjects who also had the fellow eye treated received the same investigational product received in the study eye. Subjects needing fellow eye treatment at day 1 or week 4 followed the same dosing schedule of the study eye (every 4 weeks ±3 days). Those subjects needing fellow eye treatment at weeks 8, 16, 24, 32, 40, and 48 followed the same dosing schedule of the study eye (every 8 weeks ±5 days).

Approximately 32 subjects were to be enrolled into the pharmacokinetic (PK) substudy. These subjects were to have a PK sample collected predose (within 60 minutes before day 1 dose) and postdose (approximately 24 hours after day 1 dose), with an allowable window -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose) and postdose at week 8 (approximately 24 hours after week 8 dose), with an allowable time window of -6 hours to +24 hours (ie, 18 hours to 48 hours postdose).

The dose of ABP 938 and aflibercept (EU) and frequency of dosing used in Study 20170542 (ie, 2 mg IVT injection every 4 weeks for the first 12 weeks, followed by 2 mg IVT injection every 8 weeks) were selected based on the product labeling for Eylea (aflibercept) for treatment of patients.

Study participants

The study was conducted at 102 centers in Canada, Czech Republic, Estonia, Germany, Hong Kong, Hungary, Israel, Italy, Japan, South Korea, Latvia, Lithuania, Poland, Slovakia, Spain, and the US.

Eligible subjects were men and women ≥50 years old with neovascular (wet) AMD in the study eye.

Both eyes were assessed at the screening visit for eligibility, and only 1 eye was selected from each subject as the study eye. If both eyes met the eligibility criteria, the study eye was the one with the worse BCVA.

Eligible subjects met the following key criteria:

- men or women ≥50 years old

- subjects were diagnosed with neovascular (wet) AMD in the study eye
- active, treatment naïve subfoveal choroidal neovascularization (CNV) lesions secondary to neovascular (wet) AMD including juxtafoveal lesions that affect the fovea as confirmed with spectral domain optical coherence tomography, fluorescein angiography, and/or fundus photography in the study eye
- BCVA between 73 and 34 letters, inclusive, in the study eye using ETDRS testing
- Central retinal thickness of >270 µm in the study eye as measured by the machine calculated average thickness in the ETDRS central 1 mm subfield (CST) by SD-OCT at screening (confirmed by central imaging vendor before randomization)

Subjects were excluded from participation if they had a total lesion size >12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) in the study eye; had active CNV area (classic plus occult components) that is <50% of the total lesion area in the study eye; or had scar, fibrosis, or atrophy involving the center of the fovea in the study eye. Subjects were excluded from participation if they were pregnant, breastfeeding, or planning to become pregnant. Sexually active subjects and their partners who were of childbearing potential were excluded if they were unwilling to use adequate contraception while on study and for 3 months after the last dose of study drug.

Washouts and Nonpermitted Treatments:

- Any prior ocular or systemic treatment, including another investigational product or surgery for neovascular (wet) AMD (including anti-vascular endothelial growth factor [VEGF] therapy) in the study eye, except dietary supplements or vitamins
- Any ocular or systemic treatment including another investigational product or surgery for neovascular (wet) AMD (including anti-VEGF therapy) in the fellow eye, within 30 days before randomization, except dietary supplements or vitamins
- Prior systemic anti-VEGF treatment as follows:
    a) Investigational or approved anti-VEGF therapy systemically within 3 months before randomization
    b) Aflibercept, ziv-aflibercept, or a biosimilar of aflibercept/ziv-aflibercept systemically at any time
- Any IVT therapy, including adrenocorticotropic hormone, in the study or fellow eye, or intramuscular or intravenous corticosteroids within 4 weeks before randomization. The use of long-acting steroids, either systemically or intraocularly, in the 3 months before randomization
- Currently receiving treatment with another investigational device or study drug, or less than 30 days or 5 half-lives (whichever is longer) since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded

Approximately 566 subjects (including at least 30 subjects from East Asia) were planned to be enrolled. Enrollment in the study completed with 579 total subjects enrolled and randomized.

Treatments

The Investigational Product was ABP 938 and the Reference Product was Aflibercept (EU) (Eylea®).

ABP 938 was manufactured by Amgen and packaged by Parexel North American Distribution Center. ABP 938 was supplied as a sterile, single-dose, preservative-free solution for IVT injection in a vial containing 40 mg/mL ABP 938.

Eylea (aflibercept [EU]) was sourced from the EU. Aflibercept (EU) was supplied as a sterile, single-dose, preservative-free solution for IVT injection in a vial containing 40 mg/mL aflibercept.

Investigational product was administered via IVT injection by the investigator (or qualified designee).

The dose and frequency of dosing were chosen based on the product labeling for aflibercept (EU) for treatment of patients with neovascular (wet) AMD (Eylea SmPC, 2023).

Subjects were initially randomized to 1 of 2 treatment groups to receive a dose of either ABP 938 or aflibercept (EU), as follows:

- Treatment Group A: ABP 938, IVT injection, 2 mg (0.05 mL) administered every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, and week 8)
- Treatment Group B: Aflibercept (EU), IVT injection, 2 mg (0.05 mL) administered every 4 weeks for the first 3 doses (ie, baseline/day 1, week 4, and week 8)

At week 8, subjects were assessed for the primary endpoint (BCVA change from baseline as measured by ETDRS). Subjects were then re-randomized at week 16 in a masked fashion such that:

- subjects initially randomized to ABP 938 (Treatment Group A) continued to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48
- subjects initially randomized to aflibercept (EU) (Treatment Group B) were re-randomized in a 1:1 ratio to either continue on aflibercept (EU) (Treatment Group B1) or transition to ABP 938 (Treatment Group B2) by IVT injection every 8 weeks from week 16 until week 48

Investigational product (ABP 938 or aflibercept [EU]) was to be administered after all other procedures were completed for each visit (except for postdose slit-lamp examination and postdose intraocular pressure [IOP]), ensuring that the study eye was administered first, then the fellow eye.

Dose modifications were not permitted during this study. However, investigational product dose(s) were to be withheld if clinically necessary, in accordance with the current product labeling for Eylea (eg, in case of rhegmatogenous retinal detachment, stage 3 or 4 macular hole, a subretinal hemorrhage involving the center of the fovea, or other reason per the product labeling).

If any scheduled dose of investigational product was delayed from the scheduled visit, subsequent doses were to be administered according to the original schedule (ie, at the planned timepoint relative to first dose) for investigational product doses.

Treatment of the fellow eye was allowed (except in Czech Republic, Israel, and Japan) starting at baseline (day 1) if needed. Subjects who also had the fellow eye treated received the same investigational product received in the study eye. Subjects needing fellow eye treatment at day 1 or week 4 followed the same dosing schedule of the study eye (every 4 weeks ±3 days). Those subjects needing fellow eye treatment at weeks 8, 16, 24, 32, 40, and 48 followed the same dosing schedule of the study eye (every 8 weeks ±5 days).

Prior neovascular (wet) AMD therapies that were taken/used 1 month before randomization and prior non-neovascular (wet) AMD therapies that were taken/used from 28 days before randomization were collected.

Any concomitant medications or treatments deemed necessary to provide adequate supportive care except those listed below were allowed and recorded.

Any nonstudy intraocular treatments, including macular photocoagulation or photodynamic therapy, long-acting intramuscular or intravenous corticosteroids were prohibited. Nonstudy aflibercept and ziv-aflibercept and any nonstudy intraocular or systemic anti-VEGF therapy were prohibited. Any experimental (biological or nonbiological) therapy (within or outside of a clinical study), except for the study drug, for subjects were prohibited. Subjects requiring these treatments were to discontinue study treatment.

Any other treatment (not explicitly excluded) considered necessary for the subject's welfare was allowed at the discretion of the investigator and recorded.

Study assessments

Efficacy assessments

The primary efficacy endpoint was the change from baseline in BCVA as measured by ETDRS letter score at week 8. The primary estimand was the difference in change from baseline in BCVA at week 8 between the ABP 938 group and the aflibercept (EU) group in subjects with neovascular (wet) AMD who are randomized, regardless of missing or discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8. Secondary endpoints for this study are listed further below.

Visual acuity is the measure of the ability of the eye to distinguish shapes and the details of objects at a given distance. To assess changes in visual acuity, the ETDRS chart is widely used (Schmetterer et al, 2023). The ETDRS chart presents a series of 5 letters of equal difficulty on each row with standardized spacing between letters and rows, for a total of 14 lines (70 letters). ETDRS letters score can be calculated when 20 or more letters are read correctly at 4 m; the visual acuity letter score is equal to the total number of letters read correctly at 4 m plus 30. If less than 20 letters are read correctly at 4 m, the visual acuity letter score is equal to the total number of letters read correctly at 4 m (number of letters recorded on line 1), plus the total number of letters read correctly at 1 m in the first 6 lines (Canadian Agency for Drugs and Technologies in Health, 2015).

Measurements of CNV area provide morphological insight into the pharmacodynamic (PD) effects at the target site for neovascular (wet) AMD. To visualize CNV and assess change from baseline in CNV area, fluorescein angiography was used. Fluorescein angiography is a technique used to examine the retina and provides information about vascular leakage and pooling (de Carlo et al, 2015).

Central subfield thickness (CST) is known to be a fast reacting variable that shows reproducible PD responses to anti-VEGF treatments. In conjunction with optical coherence tomography and the use of blinded independent review of images, central subfield thickness is considered an objective and accurate anatomical parameter of PD response in patients with neovascular (wet) AMD. Central subfield thickness was defined as the average thickness in the ETDRS central 1 mm diameter subfield (the central subfield) and was measured by SD-OCT, a technique that provides a cross-sectional view of the retina.

Fundus photography was used to evaluate vascular and structural changes in the eye by capturing images of posterior pole of eye (fundus) at screening, week 8, 16, 24, and 52 (EOS). The central and peripheral retina, optic disc and macula were examined.

PK assessments are described further above.

Antidrug Antibody Assessment

Incidence of antidrug antibodies (ADAs) was identified as a secondary endpoint for this study. Blood samples for ADA assessments were collected at time points specified below.

Table 4: Schedule of Activities

	Screening	Baseline	Week (± 3 days)		Week (± 5 days)					End of Study[j] (± 5 days)
		day 1 (week 0)	4	8	16[l]	24	32	40	48	52
Clinical Assessments										
Informed Consent	X									
Medical/treatment history	X									
Physical examination	X			X						X
Height and weight	X									
Vital signs	X	X		X	X					X
ECG	X									
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events	X[a]	X	X	X	X	X	X	X	X	X
Treatment										
Randomization		X			X					
ABP 938/aflibercept (EU)[b]		X	X	X	X	X	X	X	X	
Disease Assessment										
Indirect ophthalmoscopy[c,d]	X	X	X	X	X	X	X	X	X	X
Slit-lamp[d,e]	X	X	X	X	X	X	X	X	X	X
IOP[d,f]	X	X	X	X	X	X	X	X	X	X
BCVA using ETDRS chart	X	X	X	X	X	X	X	X	X	X
Fluorescein angiography	X			X	X	X				X
Fundus Photography	X			X	X	X				X
Spectral domain optical coherence tomography	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments										
Serum chemistry	X	X		X	X					X
Hematology	X	X		X	X					X
PT, aPTT, and INR	X									
PK samples (substudy subjects only)[g]		X[h]		X[i]						
Anti-drug antibodies[j]		X		X	X	X		X		X
Urinalysis	X	X		X	X					X
Pregnancy[k]	X	X								

ADA = antidrug antibody; BCVA = best corrected visual acuity; ECG = electrocardiogram; EOS = end of study; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; INR = international normalized ratio; IOP = intraocular pressure; PK = pharmacokinetics; PT = prothrombin time; aPTT = activated partial thromboplastin time

[a] Only serious adverse events were reported during the screening period.

[b] ABP 938/aflibercept (EU) were administered after all other procedures were completed for each visit (except for postdose slit-lamp examination and postdose IOP), ensuring that the study eye was administered first, then the fellow eye. If the subject presented with an infection at the dosing visit(s), the administration of investigational product was allowed to be delayed (up to 3 days for weeks 4 and 8, and up to 5 days for doses thereafter). In the case of delayed or missed dose for any reason, subsequent doses were administered according to the original schedule (ie, at the planned timepoint relative to first dose).

[c] Examination of the retina of the study eye was performed with pupil dilation. Predose on treatment days.

[d] Procedure was performed for the fellow eye on the day of investigational product administration to the fellow eye, including the EOS visit (if the fellow eye was dosed).

[e] Predose (on the day of injection) and postdose (within 60 minutes) slit-lamp examination was performed with pupil dilation on treatment days. Single, postdilation examination on other days.

[f] IOP was measured predose (on the day of injection) and postinjection (at minimum 15 minutes and no longer than 60 minutes) on treatment days. Single examination on other days.

[g] For subjects who consented for the PK substudy only: approximately 32 subjects who consented for the PK sub study were to have PK samples collected at the timepoints noted. If it was anticipated that the fellow eye needed to be treated prior to the week 8 postdose PK sample, then the subject was not enrolled into the PK substudy. If an enrolled PK substudy subject developed a need for treatment of the fellow eye prior to the week 8 postdose PK sample, no further PK samples were collected. If the need for treating the fellow eye was identified at the week 8 visit, then the fellow eye was treated after the week 8 postdose PK sample had been drawn for those subjects included in the PK substudy.

[h] This measurement was taken predose (within 60 minutes before day 1 dose) and postdose (approximately 24 hours after the day 1 dose), with an allowable window of: -6 hours to +24 hours (ie, 18 hours to 48 hours after day 1 dose).

[i] PK sample collection window 1 day after week 8 dose: -6 hours to +24 hours (ie, 18 hours to 48 hours after week 8 dose). Details were provided in an Investigator Laboratory Manual.

[j] ADA samples were taken within 3 hours prior to administration of investigational product into either eye at the study visits noted in schedule above. Details were provided in an Investigator Laboratory Manual.

[k] Required for females of childbearing potential. Serum pregnancy test was done at screening by the central laboratory. A urine pregnancy test was performed locally. Additional local urine pregnancy tests were done as per local requirements as needed.

[l] Subjects who were unable to complete the week 16 visit within the visit window were not re-randomized and were discontinued from the study. For subjects who discontinued from the study or terminated from the study early, all the end of study procedures scheduled for week 52 were performed within 28 days from determining that the subject discontinued from the study.

Objectives

The primary objective of Study 20170542 was to assess the efficacy of ABP 938 compared to aflibercept (EU).

Outcomes/endpoints

The primary efficacy endpoint is change from baseline in BCVA as measured by ETDRS letter score at week 8. The primary endpoint is considered a highly sensitive clinical outcome measure for detecting any potential clinically meaningful differences between ABP 938 and Eylea (aflibercept). Visual acuity is the measure of the ability of the eye to distinguish shapes and the details of objects at a given distance.

To assess changes in visual acuity, the ETDRS chart is widely used (Schmetterer et al, 2023). The ETDRS chart presents a series of 5 letters of equal difficulty on each row with standardized spacing between letters and rows, for a total of 14 lines (70 letters). ETDRS letters score can be calculated when 20 or more letters are read correctly at 4 m; the visual acuity letter score is equal to the total number of letters read correctly at 4 m plus 30. If less than 20 letters are read correctly at 4 m, the visual acuity letter score is equal to the total number of letters read correctly at 4 m (number of letters recorded on line 1), plus the total number of letters read correctly at 1 m in the first 6 lines (Canadian Agency for Drugs and Technologies in Health, 2015).

The timing of the primary endpoint at week 8 was selected based on FDA and EMA feedback. Published studies have shown that repeated monthly IVT dosing of Eylea (aflibercept) over 8 weeks demonstrated significant reductions in retinal thickness and improvements in visual acuity (Brown et al, 2011; Heier et al, 2012).

Table 5: Estimands for primary objective

Population	Subjects with neovascular (wet) AMD, who were randomized.
Treatment condition<s>	Assignment to ABP938 or aflibercept, regardless of missing or discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8.
Endpoint (variable)	Change from baseline in best corrected visual acuity (BCVA) as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letter score at week 8.
Population-level summary	Difference in mean change from baseline at week 8 of BCVA between ABP 938 and aflibercept (EU) arms.
Intercurrent events and strategy to handle them	
Missing BCVA at Week 8 (0/1)	Treatment policy
Outside of Visit Window (5/3)	Treatment policy
Discontinuation for Adverse Event (1/1)	Treatment policy
Death (0/1)	Treatment policy
Consent Withdrawn (2/1)	Treatment policy
PI Decision (1/0)	Treatment policy
Use of prohibited medication (1/2)	Treatment policy

The primary estimand of this study was the difference in change from baseline in BCVA at week 8 between the ABP 938 group and the aflibercept (EU) group in subjects with neovascular (wet) AMD who were randomized, regardless of missing or discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8. The intercurrent events were handled using a treatment policy strategy. The value of BCVA at week 8 (if observed) was used regardless of whether an intercurrent event occurred. A missing BCVA value at week 8 was assumed to be missing completely at random for the primary analysis for the primary estimand based on observed data using the full analysis set (FAS).

The secondary endpoints were proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline; change from baseline in BCVA as measured by ETDRS letter score over the study duration; proportion of subjects who gained at least 10 letters of vision at week 8 and proportion of subjects who gained at least 15 letters of vision at week 52 as compared to baseline; and change from baseline in CNV area as measured by FA and CST as measured by SD-OCT over the study duration.

Exploratory efficacy endpoints included proportion of subjects who maintained vision at each visit and proportion of subjects who gained ≥10 letters and ≥15 letters at each visit.

Sample size

Approximately 566 subjects (including at least 30 East Asian subjects) were to be randomized in a 1:1 ratio initially to receive ABP 938 (Treatment Group A) or aflibercept (Treatment Group B). The total sample size will provide > 90% power to demonstrate equivalence at a 2-sided significance level of 0.025 with an equivalence margin of (-3.9, 3.9) (global) on the primary efficacy endpoint BCVA change from baseline at week 8, assuming a true mean difference of 0 in the primary endpoint between the 2 groups, a standard deviation of 12.5 letters, and a 2% dropout by week 8. In addition, the number of East Asian subjects (i.e., at least 30) was chosen to enable an assessment of the treatment difference within East Asian subjects with reasonable accuracy and precision, while ensuring the study recruitment is feasible and can be completed in a timely manner.

Randomisation and blinding (masking)

Randomization was performed through a centralized IXRS. Eligible subjects were assigned to ABP 938 or aflibercept (EU) in a 1:1 ratio. Each subject received a unique randomization number when he/she was assigned treatment. Subjects were allocated to treatment according to the randomization code. The randomization was stratified by geographic region (East Asia, Europe, North America) and disease severity (baseline BCVA <64 letters vs ≥64 letters).

At week 8, subjects were assessed for the primary endpoint (BCVA change from baseline). Subjects were then re-randomized at week 16 in a masked fashion such that:

- subjects initially randomized to ABP 938 (Treatment Group A) continued to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48
- subjects initially randomized to aflibercept (EU) (Treatment Group B) were re-randomized in a 1:1 ratio to either continue on aflibercept (EU) (Treatment Group B1) or transition to ABP 938 (Treatment Group B2) by IVT injection every 8 weeks from week 16 until week 48

Re-randomization was stratified using the same factors as the initial randomization. Each subject received a second randomization number when he/she was re-randomized.

Masking

The study was double-masked. ABP 938 and aflibercept (EU) were coded and labeled in a manner that protected masking. The investigators, study personnel (with the exception of the randomization statistician, unmasked statistician, and unmasked programmers), and the study subjects were masked to treatment allocation.

All personnel involved with the analysis of the study remained masked until database lock and identification of protocol deviations for the primary analysis. Personnel unmasked for the primary analysis were not further involved in the management of the study.

Unmasking

Unmasking was only to be allowed in the case of an emergency, when knowledge of the treatment was essential for the clinical management of the subject.

Statistical methods

Analysis Sets:

- Full Analysis Set (FAS) includes all randomized subjects. Subjects were analyzed according to randomized treatment (regardless of actual treatment received). This analysis set was the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for all secondary efficacy endpoints.

- The Safety Analysis Set includes all subjects who received at least one dose of investigational product. Subjects were analyzed according to actual treatment received. This analysis set was used for summaries of safety data as well as immunogenicity data.

- The Per protocol (PP) Analysis Set includes all subjects in the FAS who completed dosing at day 1 and week 4 and completed BCVA assessment at week 8 without experiencing an important protocol deviation that may have affected their evaluation for the primary endpoint of the study. Important protocol deviations that could affect the primary endpoint were defined and agreed upon before unmasking for the primary and final analysis; based on actual treatment the subject received in the study eye; used for sensitivity analysis of the primary and key secondary efficacy endpoints.

- The PK Analysis Set includes all subjects enrolled in the PK substudy who received at least one dose of IP between day 1 and week 8 (inclusive) and had at least 1 reported serum concentration of ABP 938 or aflibercept. The analysis set was analyzed according to actual treatment the subject received in the study eye.

Primary Analysis:

For the MA submission the primary efficacy analysis was based on change from baseline analysis of BCVA at week 8 using ANCOVA model with treatment, region and baseline BCVA measurement as covariates. The primary analysis was performed using the full analysis set (FAS) based on randomised treatment and observed data. If the 2-sided 95% CI of mean change from baseline at week 8 of BCVA between ABP 938 and aflibercept arms were within the prespecified global equivalence margin (-3.9, 3.9), then it was to be declared that ABP 938 and aflibercept is clinically similar per global criteria.

Sensitivity analyses:
To assess the robustness of the primary analysis result, the ANCOVA analysis described above was repeated using the PP analysis set based on observed cases and using FAS analysis set based on last observation carried Forward (LOCF) imputation.

A repeated-measures analysis for day 1 through week 8 period based on FAS analysis set was performed as a sensitivity analysis assuming the data are missing at random (MAR). Besides the stratification factor of region, the baseline BCVA value, visit, treatment, and treatment-by-visit interaction were included in the model, with visit as a categorical variable. The point estimate of the mean difference in change from baseline in BCVA at week 8 between ABP 938 and aflibercept and its corresponding 2-sided 90% and 95% confidence intervals was obtained.

Tipping point analyses were performed using FAS to explore the sensitivity of results to violations in assumptions about the missing data (i.e., to various missing not-at-random assumptions). Assumptions (tipping point) under which the 90% CI or 95% CI no longer rules out unacceptable differences in efficacy as determined by BCVA change from baseline at week 8 between ABP 938 and aflibercept will be identified. In this analysis, all the observed data was included as non-missing, regardless of adherence to treatment or use of prohibited medication.

Results

Participant flow and numbers analysed

Overall, 579 subjects (290 subjects in the ABP 938 treatment group and 289 subjects in the aflibercept [EU] treatment group) were randomized. Two subjects randomized to the ABP 938 treatment group and 1 subject randomized to the aflibercept (EU) treatment group were excluded from all analysis sets due to major Good Clinical Practice violations from a single study site. Thus, a total of 576 subjects in the FAS were randomized.

All randomized subjects were treated with investigational product in the study eye. Overall, 565 (98.1%) of the 576 subjects who were initially randomized had completed investigational product dosing in the study eye at week 8. Further details on product disposition through Week 16 are listed in the following table.

Table 6: Study and Investigational Product Disposition Through Week 16 (Full Analysis Set)

Variable	ABP 938 (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)	Total (N = 576) n (%)
Subjects randomized	288 (100)	288 (100)	576 (100)
Subjects treated with IP in study eye	288 (100)	288 (100)	576 (100)
Completed IP in study eye[a]	284 (98.6)	281 (97.6)	565 (98.1)
Discontinued IP in study eye[b]	11 (3.8)	11 (3.8)	22 (3.8)
Adverse event	0 (0.0)	1 (0.3)	1 (0.2)
Lost to follow-up	2 (0.7)	0 (0.0)	2 (0.3)
Death	0 (0.0)	1 (0.3)	1 (0.2)
Subject request	1 (0.3)	0 (0.0)	1 (0.2)
Protocol violation	1 (0.3)	2 (0.7)	3 (0.5)
Protocol specified criteria	6 (2.1)	7 (2.4)	13 (2.3)
Other	1 (0.3)	0 (0.0)	1 (0.2)
Discontinued IP in study eye due to COVID-19 related reasons	0 (0.0)	1 (0.3)	1 (0.2)
Death	0 (0.0)	1 (0.3)	1 (0.2)
Subjects treated with IP in fellow eye (N1)	18 (6.3)	16 (5.6)	34 (5.9)
Discontinued IP in fellow eye[b,c]	0 (0.0)	1 (6.3)	1 (2.9)
Protocol specified criteria	0 (0.0)	1 (6.3)	1 (2.9)

Discontinued IP in fellow eye due to COVID-19 related reasons[c]	0 (0.0)	0 (0.0)	0 (0.0)
Completed through week 16[d]	273 (94.8)	270 (93.8)	543 (94.3)
Discontinued study prior to re-randomization[b]	15 (5.2)	18 (6.3)	33 (5.7)
Adverse event	1 (0.3)	2 (0.7)	3 (0.5)
Death	0 (0.0)	2 (0.7)	2 (0.3)
Consent withdrawn	3 (1.0)	3 (1.0)	6 (1.0)
Physician decision	1 (0.3)	1 (0.3)	2 (0.3)
Lost to follow up	2 (0.7)	0 (0.0)	2 (0.3)
Protocol violation	1 (0.3)	2 (0.7)	3 (0.5)
Protocol specified criteria	6 (2.1)	7 (2.4)	13 (2.3)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Discontinued study prior to re-randomization due to COVID-19 related reasons	0 (0.0)	2 (0.7)	2 (0.3)
Death	0 (0.0)	2 (0.7)	2 (0.3)

CSR = clinical study report; EU = European Union; IP = investigational product

[a] Completed IP in study eye includes subjects who completed IP dosing in study eye at week 8

[b] Includes subjects who discontinued IP/study due to COVID-19 related reasons and non-COVID-19 related reasons. Subjects who discontinued IP prior to or on week 16 are included in the summary of IP discontinuation. Subjects who had week 8 treatment dosage but discontinued IP prior to week 16 are included.

[c] Percentage was calculated using the count (N1) as the denominator.

[d] Subject was considered completed through week 16 period if re-randomized

Source: Modified from Table 14-1.2 of the Study CSR

Of the 543 subjects who were re-randomized at week 16, 273 (50.3%) were initially randomized to ABP 938 and continued to receive ABP 938 (ABP 938/ABP 938 treatment group); 134 (24.7%) subjects were initially randomized to aflibercept (EU) and were re-randomized to transition to ABP 938 (aflibercept [EU]/ABP 938 treatment group); and 136 (25.0%) subjects were initially randomized to aflibercept (EU) and continued on aflibercept (EU) (aflibercept [EU]/aflibercept [EU] treatment group).

Overall, 542 (99.8%) re-randomized subjects were treated with investigational product in the study eye (273 [100%] subjects in the ABP 938/ABP 938 treatment group, 133 [99.3%] subjects in the aflibercept [EU]/ABP 938 treatment group, and 136 [100%] subjects in the aflibercept [EU]/aflibercept [EU] treatment group). A total of 500 (92.1%) of the 543 subjects who were re-randomized had completed investigational product dosing in the study eye at week 48. A total of 43 (7.9%) subjects discontinued investigational product in the study eye.

Further details on product disposition post Week 16 are listed in the following table.

Table 7: Study and Investigational Product Disposition Post Week 16 (Study 20170542 Full Analysis Set - Re-randomized)

Variable	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 134) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)	Total (N = 543) n (%)
Subjects re-randomized at week 16	273 (100)	134 (100)	136 (100)	543 (100)
Subjects treated with IP in study eye	273 (100)	133 (99.3)	136 (100)	542 (99.8)
Completed IP in study eye[a]	249 (91.2)	124 (92.5)	127 (93.4)	500 (92.1)
Discontinued IP in study eye[b]	24 (8.8)	10 (7.5)	9 (6.6)	43 (7.9)
Adverse event	8 (2.9)	1 (0.7)	5 (3.7)	14 (2.6)

Lost to follow-up	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.4)
Death	2 (0.7)	2 (1.5)	0 (0.0)	4 (0.7)
Subject request	4 (1.5)	6 (4.5)	2 (1.5)	12 (2.2)
Physician decision	3 (1.1)	1 (0.7)	1 (0.7)	5 (0.9)
Requirement for alternative therapy	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Requirement for alternative dosing schedule	3 (1.1)	0 (0.0)	1 (0.7)	4 (0.7)
Other	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Discontinued IP in study eye due to COVID-19 related reasons	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects treated with IP in fellow eye (N1)	42 (15.4)	21 (15.7)	17 (12.5)	80 (14.7)
Discontinued IP in fellow eye[b,c]	16 (38.1)	6 (28.6)	4 (23.5)	26 (32.5)
Adverse event	0 (0.0)	1 (4.8)	0 (0.0)	1 (1.3)
Death	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.3)
Subject request	3 (7.1)	3 (14.3)	0 (0.0)	6 (7.5)
Physician decision	11 (26.2)	2 (9.5)	3 (17.6)	16 (20.0)
Requirement for alternative therapy	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.3)
Requirement for alternative dosing schedule	0 (0.0)	0 (0.0)	1 (5.9)	1 (1.3)
Discontinued IP in fellow eye due to COVID-19 related reasons[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed study	251 (91.9)	123 (91.8)	125 (91.9)	499 (91.9)
Discontinued study[b]	22 (8.1)	11 (8.2)	11 (8.1)	44 (8.1)
Adverse event	7 (2.6)	1 (0.7)	5 (3.7)	13 (2.4)
Death	2 (0.7)	2 (1.5)	0 (0.0)	4 (0.7)
Consent withdrawn	4 (1.5)	6 (4.5)	3 (2.2)	13 (2.4)
Physician decision	3 (1.1)	1 (0.7)	1 (0.7)	5 (0.9)
Lost to follow-up	2 (0.7)	0 (0.0)	1 (0.7)	3 (0.6)
Requirement for alternative therapy	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)
Requirement for alternative dosing schedule	2 (0.7)	0 (0.0)	1 (0.7)	3 (0.6)
Other	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.4)
Discontinued study due to COVID-19 related reasons	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

CSR = clinical study report; EU = European Union; IP = investigational product

[a] Completed IP in study eye includes subjects who completed IP dosing in study eye at week 48.

[b] Includes subjects who discontinued IP/study due to COVID-19 related reasons and non-COVID-19 related reasons.

[c] Percentage was calculated using the count (N1) as the denominator.

Source: Modified from Table 14-1.3 of the CSR

Conduct of the study

The study began in June 2020, which included the period during which the COVID-19 pandemic was occurring globally. Contingency measures were implemented to manage study conduct during the

COVID-19 pandemic. These measures included COVID-19 related precautions and procedures (including SARS-CoV-2 testing/screening).

Changes in the conduct of the study that were implemented by protocol amendment(s) are described in the study protocol. Substantial changes in the conduct of the study are described below.

Table 8: Protocol Amendment Summary Table

Amendment	Major Changes
Original Protocol 05 August 2019	Not applicable
Amendment 1 18 October 2019	• Section 4.1 – Inclusion Criteria was updated. • Section 4.2 – Exclusion Criteria was updated. • Section 5.2.4 – Fundus photography was added as an efficacy assessment.
Amendment 2 23 March 2021	• Section 1.1.2 – Non-Amgen Investigational Product (Aflibercept) was updated to include additional adverse events reflected in the warnings and precautions section of the product labeling. • Section 1.3 – Benefit/Risk Assessment was updated to include a COVID-19 risk assessment. • Section 2 – Study Objective and Endpoints, 1 of the secondary efficacy endpoints was updated. • Section 3.1 – Study Design was updated to include information on the PK substudy and treatment of the fellow eye. • Section 4.1 – Inclusion Criteria was updated. • Section 4.2 – Exclusion Criteria was updated. • Section 5.5 – Antidrug Antibodies was updated. • Section 6.5 – Treatment of the Fellow Eye was updated. • Section 6.6.1 – A new section, Coronavirus Disease 2019 Considerations was included.
Amendment 3 16 May 2022	• Section 2 – Study Objectives, Endpoints, and Estimand was updated to include the information of primary estimand. • Section 8.5.1 – Primary Endpoint/Estimand was updated to include the analysis of primary estimand.

PK = pharmacokinetic

Baseline data

Demographic and baseline physical characteristics (height and weight) for subjects in the FAS are provided below. In subjects in the FAS, 322 (55.9%) were female, 498 (86.5%) were white, and 556 (96.5%) were not Hispanic or Latino. The mean (SD) age was 76.0 (7.93) years with a range of 51 to 95 years; 49 (8.5%) subjects were younger than 65 years of age.

Table 9: Demographic and Baseline Physical Characteristics by Initial Randomization (Full Analysis Set)

Characteristic	ABP 938 (N = 288)	Aflibercept (EU) (N = 288)	Total (N = 576)
Age (years)			
n	288	288	576
Mean (SD)	76.0 (7.93)	76.0 (7.95)	76.0 (7.93)
Median	76.0	77.0	76.0

Min, Max	51, 95	52, 94	51, 95
Age group, n (%)			
< 65 years	23 (8.0)	26 (9.0)	49 (8.5)
≥ 65 years	265 (92.0)	262 (91.0)	527 (91.5)
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	36 (12.5)	39 (13.5)	75 (13.0)
Japanese	8 (2.8)	17 (5.9)	25 (4.3)
Other	28 (9.7)	22 (7.6)	50 (8.7)
Black or African American	1 (0.3)	1 (0.3)	2 (0.3)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	1 (0.3)	0 (0.0)	1 (0.2)
White, Native Hawaiian or other Pacific Islander	1 (0.3)	0 (0.0)	1 (0.2)
White	250 (86.8)	248 (86.1)	498 (86.5)
Not allowed to collect	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Sex, n (%)			
Female	151 (52.4)	171 (59.4)	322 (55.9)
Male	137 (47.6)	117 (40.6)	254 (44.1)
Ethnicity, n (%)			
Hispanic or Latino	6 (2.1)	13 (4.5)	19 (3.3)
Not Hispanic or Latino	281 (97.6)	275 (95.5)	556 (96.5)
Not allowed to collect	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	1 (0.3)	0 (0.0)	1 (0.2)
Height (cm)			
n	288	288	576
Mean (SD)	166.3 (10.25)	164.4 (10.16)	165.3 (10.24)
Median	165.0	164.0	165.0
Min, Max	135, 196	122, 193	122, 196
Weight (kg)			
n	288	288	576
Mean (SD)	75.8 (16.03)	73.2 (15.02)	74.5 (15.60)
Median	74.0	72.0	73.0
Min, Max	34, 128	41, 120	34, 128
BMI (kg/m^2)			
n	288	288	576

Mean (SD)	27.3 (4.81)	27.1 (5.01)	27.2 (4.91)
Median	27.0	26.5	26.8
Min, Max	17, 45	17, 50	17, 50
Geographic region, n (%)			
East Asian	36 (12.5)	38 (13.2)	74 (12.8)
Europe	151 (52.4)	152 (52.8)	303 (52.6)
North America	101 (35.1)	98 (34.0)	199 (34.5)

BMI = body mass index; CSR = clinical study report; EU = European Union; max = maximum; min = minimum
Source: Table 4 from Module 2.7.3

Baseline neovascular (wet) AMD characteristics for subjects in the FAS by initial randomization are provided below. In subjects overall, the mean (SD) duration of disease was 7.04 (22.206) weeks. The overall mean (SD) BCVA ETDRS letter score at study baseline was 58.2 (11.24).

Table 10: Baseline Disease Characteristics by Initial Randomization (Full Analysis Set)

Characteristic	ABP 938 (N = 288)	Aflibercept (EU) (N = 288)	Total (N = 576)
Duration of disease (weeks)[a]			
n	288	288	576
Mean (SD)	7.40 (26.909)	6.69 (16.235)	7.04 (22.206)
Median	3.50	3.14	3.29
Min, Max	1.0, 374.3	0.6, 195.6	0.6, 374.3
Baseline BCVA group			
< 64 letters	168 (58.3)	168 (58.3)	336 (58.3)
≥ 64 letters	120 (41.7)	120 (41.7)	240 (41.7)
BCVA ETDRS letter score			
n	288	288	576
Mean (SD)	58.9 (10.68)	57.6 (11.74)	58.2 (11.24)
Median	60.0	60.0	60.0
Min, Max	34, 73	24, 73	24, 73
CNV area size (mm^2)			
n	288	288	576
Mean (SD)	8.508 (5.6621)	9.343 (5.2270)	8.926 (5.4602)
Median	7.448	8.440	7.845
Min, Max	0.19, 29.80	0.36, 22.66	0.19, 29.80
CST (μm)			
n	288	288	576
Mean (SD)	438.4 (129.05)	448.8 (128.12)	443.6 (128.58)
Median	402.5	433.0	418.0
Min, Max	243, 1040	226, 1155	226, 1155

AMD = age-related macular degeneration; BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CSR = clinical study report; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union

[a] The disease duration is the number of weeks from the date of diagnosis of neovascular (wet) AMD to the date of randomization.

Source: Table 5 from Module 2.7.3

Medical history is listed in the original tables in the CSR but has not been summarized.

Outcomes and estimation

Primary Analysis of the Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline in BCVA as measured by ETDRS letter score at week 8. The primary estimand was the difference in change from baseline in BCVA at week 8 between the ABP 938 group and the aflibercept (EU) group in subjects with neovascular (wet) AMD who are randomized, regardless of missing or discontinuing investigational product administration to the study eye, or use of additional medications for AMD in the study eye prior to observing BCVA at week 8.

At week 8, the observed mean (SD) change from baseline in BCVA as measured by ETDRS letter score was 6.4 (8.18) in the ABP 938 treatment group and 6.5 (8.97) in the aflibercept (EU) treatment group. The point estimate of the least squares mean difference in change from baseline in BCVA as measured by ETDRS letter score at week 8 between the treatment groups was 0.1 with a 2-sided 95% CI of (-1.3, 1.5). The 95% CI was within the prespecified similarity margin of (-3.9, 3.9) and supports the demonstration of no clinically meaningful differences between ABP 938 and aflibercept (EU).

Table 11: Analysis of Change From Baseline in BCVA at Week 8 (as Observed) (Study 20170542 Full Analysis Set)

	ABP 938 (N = 288)		Aflibercept (EU) (N = 288)	
Visit Statistic	BCVA	Change From Baseline	BCVA	Change From Baseline
Week 8				
n	279	279	281	281
Mean (SD)	65.4 (12.36)	6.4 (8.18)	64.2 (13.09)	6.5 (8.97)
95% CI of mean	(63.9, 66.9)	(5.4, 7.4)	(62.7, 65.7)	(5.4, 7.5)
Difference between means[a]		0.1		
95% CI[a]		(-1.3, 1.5)		

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union

[a] Estimated using ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates

Source: Modified from Table 14-4.1.1 of the Study 20170542 CSR

Sensitivity Analyses of the Primary Efficacy Endpoint

Results of sensitivity analyses of the primary efficacy endpoint of change from baseline in BCVA as measured by ETDRS letter score at week 8 are summarized below. Results from sensitivity analyses were consistent with results from the primary efficacy analysis.

Table 12: Sensitivity Analysis of Change From Baseline in BCVA at Week 8

	ABP 938		Aflibercept (EU)	
Population Statistic	BCVA	Change From Baseline	BCVA	Change From Baseline
PP analysis set, as observed: ANCOVA, n/N	265/265	265/265	265/265	265/265
Mean (SD)	65.4 (12.43)	6.4 (8.31)	64.5 (13.21)	6.7 (8.96)
Difference (ABP 938 – aflibercept [EU]) between means of change from baseline[a]		-0.1		
90% CI[a]		(-1.3, 1.1)		
95% CI[a]		(-1.6, 1.4)		
FAS with LOCF: ANCOVA, n/N	288/288	288/288	288/288	288/288
Mean (SD)	65.2 (12.39)	6.3 (8.22)	64.0 (13.12)	6.5 (9.02)
Difference (ABP 938 – aflibercept [EU]) between means of change from baseline[a]		0.0		
90% CI[a]		(-1.2, 1.2)		
95% CI[a]		(-1.4, 1.4)		
FAS, repeated measures mixed model, n/N		279/288		281/288
LS Mean (SE)		6.4 (0.51)		6.4 (0.51)
Difference (ABP 938 – aflibercept [EU]) between LS means of change from baseline[b]		0.0		
90% CI[b]		(-1.1, 1.1)		
95% CI[b]		(-1.3, 1.3)		
FAS: stepwise selected covariates, n/N		279/288		281/288
Mean (SD)		6.4 (8.18)		6.5 (8.97)
Difference (ABP 938 – aflibercept [EU]) between means[c]		0.1		
90% CI[c]		(-1.1, 1.3)		
95% CI[c]		(-1.3, 1.5)		

BCVA = best corrected visual acuity; BMI = body mass index; CNV = choroidal neovascularization; CSR = clinical study report; CST = central subfield thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; FAS = full analysis set; LOCF = last observation carried forward; LS = least squares; PP = per-protocol; SE = standard error

[a] Estimated using ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates.

[b] Estimated using a repeated measures Mixed model including the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA, (treatment, visit, and treatment-by-visit interaction in the model, with visit as a categorical variable. A compound symmetry covariance structure was used.

[c] Estimated using a final ANCOVA model adjusted for the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA. A general linear model for the mean difference in change from baseline in BVCA at week 8 was fit using proc GLM with stepwise selection of the following covariates: age, age category, race, sex, ethnicity, height, weight, BMI, duration of disease, BCVA ETDRS letter score, CNV area size, CST, and fellow eye treated prior to week 8. A covariate withp-value <0.25 entered the model and a covariate with a p-value <0.1 stayed in the model. The stratification factor of geographic region and baseline BCVA value were forced into the model.

Source: Modified from Table 14-4.1.2, Table 14-4.1.3, Table 14-4.1.4, and Table 14-4.1.5

A tipping point analysis was conducted to explore the sensitivity of the primary efficacy analysis to violations in assumptions about the missing data (ie, to various missing not-at-random assumptions). The table below displays the estimated mean difference and 95% CIs between the ABP 938 treatment group and the aflibercept (EU) treatment group for change from baseline in BCVA at week 8, with varying assumptions regarding differences in each treatment group between outcomes in subjects with missing change from baseline in BCVA at week 8 data and outcomes in subjects with data. The 95% CIs for all assumptions were within the margin of (-3.9, 3.9) and were consistent with the results from the primary efficacy analysis.

Secondary Efficacy Endpoints

Secondary efficacy endpoint data are discussed through week 16 and over the entire study through the EOS in the sections below. When discussing treatment comparisons for time points prior to re-randomization (week 16 included), treatment groups are identified by initial randomization; when discussing treatment comparison for time points after re-randomization, treatment groups are identified by initial randomization/re-randomization.

Proportion of Subjects who Maintained Vision at Week 52

Table 13: Analysis of Proportion of Subjects Who Maintained Vision at Week 52 (as Observed) (Full Analysis Set - Re-randomized)

Visit Statistic	ABP 938/ ABP 938 (N = 273)	Aflibercept (EU)/ ABP 938 (N = 134)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Week 52			
Subjects who maintained vision, n/N1 (%)	240/251 (95.6)	118/123 (95.9)	122/125 (97.6)
95% CI for proportion	(93.1, 98.2)	(92.5, 99.4)	(94.9, 100.0)
Risk difference (%)[a]	-2.1	-1.7	
90% CI for risk difference (%)[a]	(-5.2, 2.2)	(-6.2, 2.8)	
95% CI for risk difference (%)[a]	(-5.9, 3.4)	(-7.4, 4.0)	

BCVA = best corrected visual acuity; CSR = clinical study report; ETDRS = Early Treatment Diabetic Retinopathy Study; EU = European Union; n = the number of subjects meeting the criteria at week 52; N1 = the number of subjects having available data at week 52.

Note: A subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score, assessed on the study eyes, compared to baseline.

Note: The risk differences for subjects who maintained vision and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU)/ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters)

Source: CSR Table 10-4

Change From Baseline in BCVA Over Study Duration Through Week 16

Results for the analyses of change from baseline in BCVA as measured by ETDRS letter score at weeks 4, 8, and 16 for the FAS with observed data are summarized below.

Table 14: Analysis of Change From Baseline in BCVA by Visit – Through Week 16 (as Observed) (Full Analysis Set)

	AFP 938 (N = 288)		Aflibercept (EU) (N = 288)	
Visit Statistic	BCVA	Change From Baseline	BCVA	Change From Baseline
Baseline				
n	288		288	
Mean (SD)	58.9 (10.68)		57.6 (11.74)	
Week 4				
n	285	285	282	282
Mean (SD)	63.8 (11.07)	5.0 (6.53)	62.0 (12.82)	4.5 (8.17)
Difference between means[a]		0.65		
90% CI[a]		(-0.4, 1.6)		
95% CI[a]		(-0.5, 1.8)		
Week 8				
n	279	279	281	281
Mean (SD)	65.4 (12.36)	6.4 (8.18)	64.2 (13.09)	6.5 (8.97)
Difference between means[a]		0.11		
90% CI[a]		(-1.1, 1.3)		
95% CI[a]		(-1.3, 1.5)		
Week 16				
n	281	281	277	277
Mean (SD)	65.8 (12.52)	6.8 (8.61)	64.6 (13.04)	7.2 (9.26)
Difference between means[a]		-0.17		
90% CI[a]		(-1.4, 1.1)		
95% CI[a]		(-1.6, 1.3)		

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union

[a] Estimated using ANCOVA model with treatment, the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA as covariates

Source: CSR Table 10-5

Change From Baseline in BCVA Over Study Duration Over the Entire Study

Results for the analyses of change from baseline in BCVA as measured by ETDRS letter score are summarized over the entire study for re-randomized subjects in the FAS with observed data.

Table 15: Analysis of Change From Baseline in BCVA by Visit – Entire Study (as Observed) (Full Analysis Set - Re-randomized)

	ABP 938/ABP 938 (N = 273)		Aflibercept (EU)/ ABP 938 (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
Visit Statistic	BCVA	Change From Baseline	BCVA	Change From Baseline	BCVA	Change From Baseline
Baseline						
n	273		134		136	
Mean (SD)	59.0 (10.74)		57.8 (11.53)		57.2 (11.76)	
Week 4						
n	272	272	131	131	136	136
Mean (SD)	64.0 (11.11)	5.0 (6.57)	61.6 (13.16)	3.8 (8.19)	62.6 (12.22)	5.4 (8.35)
Difference between means[a]		-0.08		-1.50		
90% CI[a]		(-1.3, 1.2)		(-3.0, 0.0)		
95% CI[a]		(-1.6, 1.4)		(-3.2, 0.3)		
Week 8						
n	270	270	133	133	134	134
Mean (SD)	65.6 (12.29)	6.5 (8.10)	63.5 (13.28)	5.6 (8.86)	64.9 (12.89)	7.6 (9.30)
Difference between means[a]		-0.82		-1.94		
90% CI[a]		(-2.3, 0.7)		(-3.6, -0.2)		
95% CI[a]		(-2.6, 0.9)		(-4.0, 0.1)		
Week 16						
n	273	273	134	134	136	136
Mean (SD)	65.8 (12.59)	6.8 (8.69)	64.9 (13.14)	7.1 (9.32)	64.7 (12.87)	7.5 (9.31)
Difference between means[a]		-0.35		-0.30		
90% CI[a]		(-1.9, 1.2)		(-2.1, 1.5)		
95% CI[a]		(-2.2, 1.5)		(-2.4, 1.8)		
Week 24						
n	267	267	130	130	136	136
Mean (SD)	66.4 (13.09)	7.2 (9.63)	65.1 (13.72)	7.0 (10.12)	64.3 (13.96)	7.1 (9.30)
Difference between means[a]		0.39		0.04		
90% CI[a]		(-1.3, 2.1)		(-1.9, 2.0)		

95% CI[a]		(-1.6, 2.4)		(-2.3, 2.3)		
Week 32						
n	263	263	131	131	132	132
Mean (SD)	66.0 (13.73)	7.1 (11.00)	64.7 (14.56)	6.6 (11.11)	66.0 (12.32)	8.7 (9.21)
Difference between means[a]		-1.29		-1.90		
90% CI[a]		(-3.1, 0.5)		(-4.0, 0.2)		
95% CI[a]		(-3.5, 0.9)		(-4.4, 0.6)		
Week 40						
n	258	258	125	125	130	130
Mean (SD)	66.2 (13.94)	7.3 (11.00)	66.3 (13.17)	7.9 (10.08)	65.6 (13.24)	8.1 (11.00)
Difference between means[a]		-0.48		0.01		
90% CI[a]		(-2.3, 1.4)		(-2.2, 2.2)		
95% CI[a]		(-2.7, 1.7)		(-2.6, 2.6)		
Week 48						
n	251	251	123	123	126	126
Mean (SD)	66.3 (14.47)	7.2 (11.51)	66.0 (14.13)	8.1 (10.74)	66.4 (12.71)	8.7 (10.84)
Difference between means[a]		-1.21		-0.60		
90% CI[a]		(-3.2, 0.8)		(-2.9, 1.7)		
95% CI[a]		(-3.5, 1.1)		(-3.3, 2.1)		
Week 52						
n	251	251	123	123	125	125
Mean (SD)	66.6 (14.51)	7.6 (11.60)	66.2 (13.99)	8.0 (11.14)	67.0 (12.68)	9.4 (10.18)
Difference between means[a]		-1.47		-1.22		
90% CI[a]		(-3.4, 0.5)		(-3.5, 1.1)		
95% CI[a]		(-3.8, 0.9)		(-3.9, 1.5)		

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union

Note: The differences between means of change from baseline and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU)/ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using ANCOVA model with treatment and the stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA as covariates

Source: CSR Table 10-6

Proportion of Subjects who Gained ≥10 Letters at Week 8

Table 16: Analysis of Proportion of Subjects Who Gained **≥10** Letters From Baseline at Week 8 (as Observed) (Full Analysis Set)

Visit Statistic	ABP 938 (N = 288)	Aflibercept (EU) (N = 288)
Week 8		
Subjects who gained ≥ 10 letters from baseline, n/N1 (%)	82/279 (29.4)	92/281 (32.7)
95% CI for proportion	(24.1, 34.7)	(27.3, 38.2)
Risk difference (ABP 938 – aflibercept [EU]) (%)[a]	-3.4	
90% CI for risk difference (%)[a]	(-9.8, 3.1)	
95% CI for risk difference (%)[a]	(-11.0, 4.3)	

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union; n = the number of subjects meeting the criteria at week 8; N1 = the number of subjects having available data at week 8

[a] Estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters)

Source: Module 2.7.3 Table 12

Proportion of Subjects who Gained ≥15 Letters at Week 52

Table 17: Analysis of Proportion of Subjects Who Gained ⩾15 Letters From Baseline at Week 52 (as Observed) (Full Analysis Set - Re-randomized)

Visit Statistic	ABP 938/ ABP 938 (N = 273)	Aflibercept (EU)/ ABP 938 (N = 134)	Aflibercept (EU)/ Aflibercept (EU) (N = 136)
Week 52			
Subjects who gained ≥ 15 letters from baseline, n/N1 (%)	61/251 (24.3)	30/123 (24.4)	37/125 (29.6)
95% CI for proportion	(19.0, 29.6)	(16.8, 32.0)	(21.6, 37.6)
Risk difference (%)[a]	-5.3	-5.2	
90% CI for risk difference (%)[a]	(-13.6, 2.5)	(-14.4, 4.2)	
95% CI for risk difference (%)[a]	(-15.2, 4.0)	(-16.1, 6.0)	

BCVA = best corrected visual acuity; CSR = clinical study report; EU = European Union; n = the number of subjects meeting the criteria at week 52; N1 = the number of subjects having available data at week 52.

Note: The risk differences for subjects who gained ≥ 15 letters from baseline and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU)/ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using the stratified Newcombe confidence limits (with Mantel-Haenszel weights) adjusting for stratification factors geographic region (East Asia, Europe, North America) and baseline BCVA (BCVA < 64 letters, BCVA ≥ 64 letters)

Source: Module 2.7.3 Table 13

Change From Baseline in CNV Area Size

Results for the analyses of change from baseline in CNV area size as measured by FA at weeks 8 and 16 for the FAS with observed data are summarized below.

Table 18: Analysis of Change From Baseline in CNV Area Size by Visit – Through Week 16 (as Observed) (Full Analysis Set)

	AEP 938 (N = 288)		Aflibercept (EU) (N = 288)	
Visit Statistic	CNV Area Size (mm^2)	Change From Baseline	CNV Area Size (mm^2)	Change From Baseline
Baseline				
n	288		288	
Mean (SD)	8.508 (5.6621)		9.343 (5.2270)	
Week 8				
n	263	263	271	271
Mean (SD)	3.660 (4.3213)	-4.863 (5.1719)	3.976 (4.5295)	-5.371 (4.9836)
Difference between means[a]		-0.003		
90% CI[a]		(-0.552, 0.545)		
95% CI[a]		(-0.657, 0.650)		
Week 16				
n	251	251	252	252
Mean (SD)	4.389 (5.1224)	-4.002 (5.3484)	4.398 (5.0479)	-4.947 (5.1489)
Difference between means[a]		0.414		
90% CI[a]		(-0.229, 1.056)		
95% CI[a]		(-0.353, 1.180)		

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CSR = clinical study report; EU = European Union

[a] Estimated using ANCOVA model with treatment, baseline CNV measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates

Source: Module 2.7.3 Table 14

Results for the analyses of change from baseline in CNV area size as measured by FA over the entire study for re-randomized subjects in the FAS with observed data are summarized below.

Table 19: Analysis of Change From Baseline in CNV Area Size by Visit – Entire Study (as Observed) (Full Analysis Set – Re-randomized)

	ABP 938/ABP 938 (N = 273)		Aflibercept (EU)/ ABP 938 (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
Visit Statistic	CNV Area Size (mm^2)	Change From Baseline	CNV Area Size (mm^2)	Change From Baseline	CNV Area Size (mm^2)	Change From Baseline
Baseline						
n	273		134		136	
Mean (SD)	8.550 (5.7413)		9.167 (5.3255)		9.490 (5.0549)	
Week 8						
n	255	255	130	130	127	127
Mean (SD)	3.601 (4.3070)	-4.962 (5.1604)	4.004 (4.9665)	-5.169 (4.6943)	4.028 (4.1565)	-5.479 (5.1023)
Difference between means[a]		-0.048		0.105		
90% CI[a]		(-0.734, 0.638)		(-0.682, 0.891)		
95% CI[a]		(-0.866, 0.770)		(-0.833, 1.042)		
Week 16						
n	245	245	125	125	121	121
Mean (SD)	4.261 (5.1050)	-4.089 (5.3668)	4.492 (5.3074)	-4.751 (4.8814)	4.373 (4.8033)	-5.174 (5.2280)
Difference between means[a]		0.431		0.245		
90% CI[a]		(-0.367, 1.229)		(-0.667, 1.158)		
95% CI[a]		(-0.521, 1.383)		(-0.842, 1.333)		
Week 24						
n	242	242	118	118	119	119
Mean (SD)	4.072 (4.7763)	-4.323 (5.5972)	4.069 (5.4950)	-5.121 (5.2776)	4.335 (4.8535)	-5.308 (5.6238)
Difference between means[a]		0.197		-0.116		
90% CI[a]		(-0.625, 1.019)		(-1.065, 0.834)		
95% CI[a]		-0.783, 1.177)		(-1.248, 1.017)		
Week 52						

n	234	234	114	114	119	119
Mean (SD)	2.185 (3.7203)	-6.276 (6.2690)	2.764 (4.8173)	-6.434 (5.2445)	2.237 (3.6345)	-7.280 (5.8262)
Difference between means[a]		0.156		0.647		
90% CI[a]		(-0.561, 0.872)		(-0.186, 1.479)		
95% CI[a]		(-0.699, 1.010)		(-0.346, 1.639)		

BCVA = best corrected visual acuity; CNV = choroidal neovascularization; CSR = clinical study report; EU = European Union;

Note: The differences between means of change from baseline and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU) /ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using ANCOVA model with treatment, baseline CNV measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates

Source: Module 2.7.3 Table 15

Change From Baseline in CST Over Study Duration

Results for the analyses of change from baseline in CST as measured by SD-OCT at weeks 4, 8, and 16 for the FAS with observed data are summarized below.

Table 20: Analysis of Change From Baseline in CST by Visit – Through Week 16 (as Observed) (Full Analysis Set)

	A3P 938 (N = 288)		Aflibercept (EU) (N = 288)	
Visit Statistic	CST (μm)	Change From Baseline	CST (μm)	Change From Baseline
Baseline				
n	288		288	
Mean (SD)	438.4 (129.05)		448.8 (128.12)	
Week 4				
n	283	283	282	282
Mean (SD)	302.2 (79.74)	-136.0 (109.32)	302.6 (80.32)	-145.8 (105.64)
Difference between means[a]		3.0		
90% CI[a]		(-6.3, 12.3)		
95% CI[a]		(-8.1, 14.1)		
Week 8				
n	278	278	280	280
Mean (SD)	290.2 (81.47)	-145.7 (106.47)	289.3 (77.16)	-156.5 (113.62)
Difference between means[a]		3.9		
90% CI[a]		(-5.7, 13.6)		
95% CI[a]		(-7.6, 15.5)		

Week 16				
n	281	281	276	276
Mean (SD)	314.7 (102.13)	-122.7 (124.73)	313.1 (90.99)	-135.5 (112.48)
Difference between means[a]		5.4		
90% CI[a]		(-6.4, 17.3)		
95% CI[a]		(-8.6, 19.5)		

BCVA = best corrected visual acuity; CSR = clinical study report; CST = central subfield thickness; EU = European Union

[a] Estimated using ANCOVA model with treatment, baseline CST measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates

Source: Module 2.7.3 Table 16

Results for the analyses of change from baseline in CST as measured by SD-OCT over the entire study for re-randomized subjects in the FAS with observed data are summarized below.

Table 21: Analysis of Change From Baseline in CST by Visit – Entire Study (as Observed) (Full Analysis Set – Re-randomized)

	ABP 938/ABP 938 (N = 273)		Aflibercept (EU)/ ABP 938 (N = 134)		Aflibercept (EU)/ Aflibercept (EU) (N = 136)	
Visit Statistic	CST (µm)	Change From Baseline	CST (µm)	Change From Baseline	CST (µm)	Change From Baseline
Baseline						
n	273		134		136	
Mean (SD)	439.4 (130.35)		458.8 (127.12)		440.3 (126.90)	
Week 4						
n	270	270	131	131	136	136
Mean (SD)	303.2 (81.16)	-136.5 (108.91)	310.5 (87.97)	-149.7 (107.01)	297.3 (74.54)	-143.1 (107.32)
Difference between means[a]		6.2		6.3		
90% CI[a]		(-5.6, 17.9)		(-7.4, 20.0)		
95% CI[a]		(-7.9, 20.2)		(-10.1, 22.7)		
Week 8						
n	269	269	132	132	134	134
Mean (SD)	290.9 (82.60)	-145.9 (106.24)	291.7 (78.45)	-167.4 (118.52)	289.1 (78.48)	-146.3 (110.39)
Difference between means[a]		1.3		-5.1		
90% CI[a]		(-11.0, 13.5)		(-19.3, 9.1)		
95% CI[a]		(-13.3,		(-22.1,		

		15.9)		11.9)		
Week 16						
n	273	273	134	134	135	135
Mean (SD)	314.1 (102.79)	-125.2 (124.81)	315.6 (93.53)	-143.2 (121.93)	312.1 (89.88)	-127.3 (103.35)
Difference between means[a]		1.9		-3.8		
90% CI[a]		(-12.9, 16.6)		(-20.9, 13.3)		
95% CI[a]		(-15.7, 19.4)		(-24.2, 16.5)		
Week 24						
n	265	265	128	128	133	133
Mean (SD)	308.7 (96.69)	-130.8 (125.63)	310.4 (89.55)	-151.2 (118.21)	308.9 (88.18)	-131.7 (102.98)
Difference between means[a]		0.1		-6.0		
90% CI[a]		(-14.1, 14.4)		(-22.6, 10.6)		
95% CI[a]		(-16.9, 17.1)		(-25.8, 13.8)		
Week 32						
n	262	262	131	131	132	132
Mean (SD)	303.0 (94.48)	-133.2 (122.93)	304.7 (84.97)	-154.8 (114.22)	305.2 (87.02)	-134.1 (116.02)
Difference between means[a]		-1.2		-7.0		
90% CI[a]		(-15.3, 12.9)		(-23.3, 9.3)		
95% CI[a]		(-18.1, 15.6)		(-26.5, 12.5)		
Week 40						
n	257	257	124	124	130	130
Mean (SD)	300.6 (90.40)	-132.3 (113.25)	302.4 (78.49)	-155.7 (119.95)	301.7 (91.16)	-135.6 (119.07)
Difference between means[a]		0.2		-6.5		
90% CI[a]		(-13.7, 14.1)		(-22.8, 9.8)		
95% CI[a]		(-16.4, 16.8)		(-25.9, 12.9)		
Week 48						
n	251	251	123	123	125	125
Mean (SD)	299.8 (94.71)	-132.3 (124.15)	299.7 (79.60)	-157.8 (121.23)	293.8 (80.58)	-141.1 (112.29)
Difference between means[a]		7.0		-0.5		
90% CI[a]		(-7.4,		(-17.3,		

		21.4)		16.2)		
95% CI[a]		(-10.2, 24.2)		(-20.5, 19.5)		
Week 52						
n	250	250	123	123	125	125
Mean (SD)	274.2 (64.35)	-157.1 (114.25)	280.3 (68.53)	-177.4 (122.22)	272.8 (65.06)	-159.1 (108.82)
Difference between means[a]		1.6		2.3		
90% CI[a]		(-9.3, 12.5)		(-10.5, 15.0)		
95% CI[a]		(-11.4, 14.7)		(-12.9, 17.4)		

BCVA = best corrected visual acuity; CST = central subfield thickness; CSR = clinical study report; EU = European Union

Note: The differences between means of change from baseline and the corresponding CIs in the ABP 938/ABP 938 and aflibercept (EU)/ABP 938 columns are for ABP 938/ABP 938 minus aflibercept (EU)/aflibercept (EU) and aflibercept (EU)/ABP 938 minus aflibercept (EU)/aflibercept (EU), respectively.

[a] Estimated using ANCOVA model with treatment, baseline CST measurement and the stratification factors geographic region (East Asia, Europe, North America) and baseline BVCA (BCVA < 64 letters, BCVA ≥ 64 letters) as covariates.

Source: Module 2.7.3 Table 17

Exploratory efficacy endpoints

The proportion of subjects who maintained vision was similar across the treatment groups at each visit through week 16 and post week 16.

The proportion of subjects who gained ≥10 letters was in general similar across the treatment groups at each visit through week 16 and post week 16.

The proportion of subjects who gained ≥15 letters was similar across the treatment groups at each visit through week 16 and post week 16.

Ancillary analyses

Subgroup analyses of the primary efficacy endpoint of change from baseline in BCVA as measured by ETDRS letter score at week 8 were conducted for the following subgroups: geographic region (East Asia, Europe, North America), disease severity (baseline BCVA <64 letters vs ≥64 letters), age (<65 years vs ≥65 years), race (white vs non-white), sex, and subjects with fellow eye treated prior to week 8 (yes vs no). The 95% and 90% CIs of difference in mean change from baseline in BCVA as measured by ETDRS letter score at week 8 across subgroups were provided. In general, results for all subgroups were consistent with results from the primary efficacy analysis.

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 22: Summary of efficacy for trial 20170542

Title: A Randomized, Double-masked, Phase 3 Study of ABP 938 Efficacy and Safety Compared to Aflibercept (Eylea®) in Subjects with Neovascular Age-related Macular Degeneration			
Study identifier	20170542 (protocol number), 2019-002503-17 (EudraCT Number)		
Design	Phase 3, randomized, double-masked, active-controlled, parallel, multicenter study Eligible subjects were randomized in a masked 1:1 ratio to receive 2 mg of either ABP 938 or aflibercept (EU) by IVT injection every 4 weeks for the first 3 doses. Subjects in the control arm were re-randomized at week 16 in a 1:1 ratio to either continue on aflibercept (EU) or transition to ABP 938		
	Duration of main phase: Duration of Run-in/screening phase: Duration of Extension phase:	52 weeks 4 weeks not applicable	
Hypothesis	Equivalence		
Treatment groups in the Main Study Period	ABP 938 (N=290 randomized)	ABP 938, IVT injection, 2 mg (0.05 mL) administered every 4 weeks for the first 3 doses (i.e., day 1, week 4, and week 8) followed by ABP 938 by IVT injection every 8 weeks from week 16 until week 48	
	Eylea (Aflibercept EU) (N=289 randomized)	Aflibercept (EU), IVT injection, 2 mg (0.05 mL) administered every 4 weeks for the first 3 doses (i.e., day 1, week 4, and week 8) Subjects were re-randomized at week 16 in a 1:1 ratio to either continue on aflibercept (EU) or transition to ABP 938 by IVT injection every 8 weeks from week 16 until week 48	
Endpoints and definitions	Primary endpoint	Change from baseline in Best Corrected Visual Acuity as measured by ETDRS letter score at week 8	
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Full Analysis Set (FAS): FAS includes all randomized subjects. Subjects were analyzed according to randomized treatment (regardless of actual treatment received). This analysis set was the primary set used for analyses/summaries of the primary efficacy endpoint, as well as for all secondary efficacy endpoints. Week 8		
Descriptive statistics and estimate variability	Treatment group	ABP 938	Eylea (Aflibercept EU)
	Number of subjects	288	288
	Mean (SD) of change from baseline in BCVA at Week 8	6.4 (8.18)	6.5 (8.97)

Title: A Randomized, Double-masked, Phase 3 Study of ABP 938 Efficacy and Safety Compared to Aflibercept (Eylea®) in Subjects with Neovascular Age-related Macular Degeneration			
Study identifier	20170542 (protocol number), 2019-002503-17 (EudraCT Number)		
	Mean difference (ABP 938 – Eylea) [95% CI] using ANCOVA model adjusted for stratification factors	0.1 [-1.3, 1.5]	
Analysis description	Sensitivity analysis of the Primary Efficacy Endpoint		
Analysis population and time point description	Per-Protocol (PP) set The PP set includes all subjects in the FAS who completed dosing at day 1 and week 4 and completed BCVA assessment at week 8 without experiencing an important protocol deviation that may have affected their evaluation for the primary endpoint of the study. Week 8		
Descriptive statistics and estimate variability	Treatment group	ABP 938	Eylea (Aflibercept EU)
	Number of subjects	265	265
	Means (SD) of change from baseline in BCVA at Week 8	6.4 (8.31)	6.7 (8.96)
	Mean difference (ABP 938 – Eylea) [95% CI] using ANCOVA model adjusted for stratification factors	-0.1 [-1.6, 1.4]	
Analysis description	Sensitivity analysis of Primary Efficacy Variable		
Analysis population and time point description	FAS with last observation carried forward Week 8		
Descriptive statistics and estimate variability	Treatment group	ABP 938	Eylea (Aflibercept EU)
	Number of subjects	288	288
	Means (SD) of change from baseline in BCVA at Week 8	6.3 (8.22)	6.5 (9.02)
	Mean difference (ABP 938 – Eylea) [95% CI] using ANCOVA model adjusted for stratification factors	0.0 [-1.4, 1.4]	
Analysis description	Sensitivity analysis of Primary Efficacy Variable		

Title: A Randomized, Double-masked, Phase 3 Study of ABP 938 Efficacy and Safety Compared to Aflibercept (Eylea®) in Subjects with Neovascular Age-related Macular Degeneration			
Study identifier	20170542 (protocol number), 2019-002503-17 (EudraCT Number)		
Analysis population and time point description	FAS, repeated measures mixed model Week 8		
Descriptive statistics and estimate variability	Treatment group	ABP 938	Eylea (Aflibercept EU)
	Number of subjects	279	281
	LS Mean (SE) of change from baseline in BCVA at Week 8	6.4 (0.51)	6.4 (0.51)
	Difference (ABP 938 – aflibercept [EU]) between LS means	0.0 [-1.3, 1.3]	

Clinical studies in special populations

Not applicable.

In vitro biomarker test for patient selection for efficacy

Not applicable.

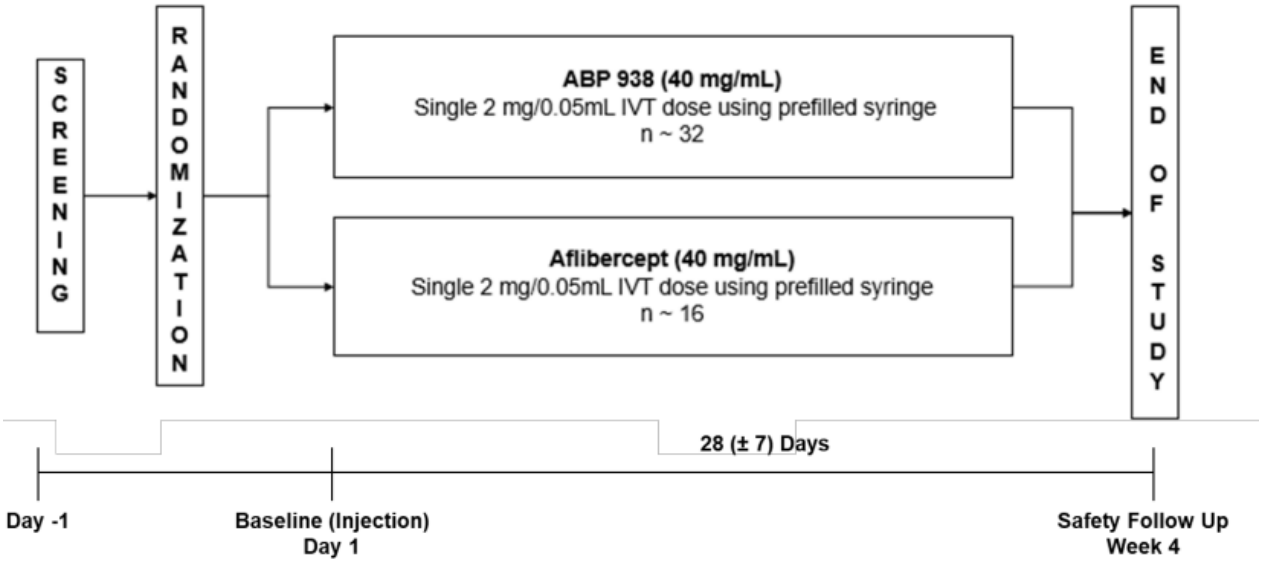
Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Supportive study

Study 20210034 was an open-label, 2-arm, randomized, multi-site study within the US in adult subjects with chorioretinal vascular disease (CVD). Subjects were randomized in a ratio of 2:1 to receive either a single IVT injection of ABP 938 in a PFS or a single injection of aflibercept (US) in a PFS (33 subjects in the ABP 938 PFS treatment group and of 16 subjects in the aflibercept (US) PFS treatment group). The study consisted of a screening visit (day -1), a baseline visit (day 1), and an end-of-study (EOS) visit (day 28 ± 7 days).

Figure 8-1. Study Schema for Protocol 20210034



The purpose of the usability study (Study 20210034) is to investigate whether the ABP 938 PFS can be used effectively and safely by retina specialists to administer a 2 mg dose of ABP 938 when descriptively compared to the US-licensed Eylea (aflibercept) (hereafter referred to as aflibercept [US]) PFS. Further objective was to assess the safety of ABP 938 administered to subjects with various CVDs via an IVT injection, using the ABP 938 PFS compared to aflibercept (US) administered using the aflibercept (US) PFS.

The following usability endpoints were assessed:

- Proportion of IVT injections successfully administered to subjects with various CVDs by retina specialists, utilizing the ABP 938 PFS or aflibercept (US) PFS
- Incidence of ocular adverse events and serious adverse events in the study eye until the EOS visit (day 28 visit)
- Incidence of non-ocular serious adverse events until the EOS visit (day 28 visit)

Successful injections were defined by the following response recorded by the investigator (ie, retina specialist) in the Investigational Product Administration eCRF for each subject.

Did the prefilled syringe allow safe and effective administration of the prescribed dose? (Yes/No)

A total of 47 (95.9%) subjects completed the study (32 [97.0%] subjects in the ABP 938 PFS treatment group and 15 [93.8%] subjects in the aflibercept [US] PFS treatment group), and 2 (4.1%) subjects discontinued the study (1 [3.0%] and 1 [6.3%] subjects, respectively). Reasons for discontinuation from the study included consent withdrawn (subject in the ABP 938 PFS treatment group) and lost to follow-up (subject in the aflibercept [US] PFS treatment group). No subjects discontinued the study due to COVID-19-related reasons, and no subjects discontinued the study due to adverse events.

All IVT injections were successfully administered; estimated success rates (95% CI) were 100.0% (89.1,100.0) in the ABP 938 PFS treatment group and 100.0% (79.4,100.0) in the aflibercept (US) PFS treatment group. Observed success rates for the 4 individual retina specialists were the same between the 2 treatment groups.

2.5.6. Discussion on clinical efficacy

The applicant conducted a pivotal phase III study in patients with neovascular age-related macular degeneration (nAMD) (Study 20170542). 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 (and safety) between the biosimilar candidate and the reference product. This is considered acceptable to evaluate comparative efficacy of the biosimilar candidate and the reference product.

In addition to the comparative clinical study, a PFS clinical usability study (Study 20210034) was conducted.

Study design

The comparative efficacy and safety study 20170542 was a phase 3, randomized, double-masked, active-controlled study in adult subjects with neovascular (wet) AMD.

Study population: The study was conducted in subjects with neovascular age-related macular degeneration (nAMD). Neovascular AMD is one of the approved indications of Eylea in the EU. Other approved indications include visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME), and visual impairment due to myopic choroidal neovascularisation (myopic CNV). Neovascular AMD (nAMD) and DME are likely the most sensitive indications as compared to RVO, and CNV to detect any differences between the treatments. Furthermore, studies with the originator showed that the treatment effect of aflibercept was largest in patients with nAMD (comparison against placebo). Thus, the nAMD is considered an appropriate indication to assess comparison between the test and reference product in terms of clinical efficacy.

Only treatment-naïve patients were to be included in the study, as recommended during the scientific advice procedures. A treatment-naïve nAMD population in which a significant effect on visual acuity is anticipated is regarded a sensitive and reasonable patient population to assess clinical biosimilarity, as well as safety of the biosimilar to the reference product. Treatment-experienced patients may have reached the plateau in terms of maximal gain in visual acuity and may well maintain their visual acuity with less frequent dosing, which makes them a less sensitive population.

The inclusion criterion for BCVA was a letter score of 73 to 34, inclusive (corresponding to a Snellen equivalent 20/40 – 20/200). The lower BCVA limit of 20/200 represents the limit of legal blindness, below which high variability in EDTRS is reported, while the upper limit leaves room for a 15-letter improvement in visual acuity. These limits are considered adequate for the primary efficacy endpoint.

As pointed out during the scientific advice procedures, a higher gain in visual acuity was detected in patients with smaller baseline lesion area across studies with Lucentis (HARBOR, ANCHOR, and MARINA), thus it was recommended to set the lesion size cutoff at 9 disc areas (DA) in order to achieve a more sensitive study population than with a cutoff at 12 DA. Similarly, a higher CRT at baseline leaves more room for improvement, thus a cutoff at 300 µm is considered more sensitive than the lower cutoff at 270 µm. This had been agreed by the applicant and incorporated into the initial Study Protocol. However, with Protocol Amendment 2, the applicant altered these criteria to the less sensitive levels >12 DA and >270 µm CST. Therefore, the applicant was requested to provide an evaluation of the primary efficacy endpoint separately for patients enrolled before and after Protocol Amendment 2 came into effect (see further below).

Subjects with prior systemic aflibercept or ziv-aflibercept therapy at any time were not eligible for the study. Subjects on another anti-VEGF therapy systemically 3 months or more before randomization were eligible. This is acceptable.

Subjects were not eligible for the study if they had any prior ocular or systemic treatment, including another investigational product or surgery for neovascular (wet) AMD in the study eye (except dietary supplements or vitamins), or any ocular or systemic treatment including another investigational product or surgery for neovascular (wet) AMD in the fellow eye within 30 days before randomization (except dietary supplements or vitamins). Previously, it was recommended to include a completely treatment-naïve patient population; according to the eligibility criteria, however, patients could be enrolled if they had previous treatment with aflibercept in the fellow eye more than 30 days ago.

The number of subjects that received aflibercept as a prior medication for treatment of the fellow eye before the first dose of investigational product was low and balanced between treatment groups (3 [1.0%] subjects in the ABP 938 treatment group and 3 [1.0%] subjects in the aflibercept [EU] treatment group). One of the 6 subjects received aflibercept treatment in the fellow eye prior to randomisation and at the time of the first dose of investigational product. As non-study aflibercept treatment during the study was prohibited per protocol, this subject was excluded from the per-protocol analysis set. Of the 6 subjects who received prior aflibercept treatment in the fellow eye, all subjects tested negative for binding ADA at baseline, and 1 subject (randomised in the aflibercept [EU]/ABP 938 treatment group) tested positive for the development of binding ADAs at week 8. This subject had a transient response, testing negative for binding ADA at all timepoints tested beyond week 8. Thus, the impact of prior aflibercept treatment on the comparative immunogenicity assessment is considered negligible.

Randomization and blinding: Initially subjects were randomized in a 1:1 ratio to either ABP938 or aflibercept. Randomization was stratified by age and baseline BCVA (dichotomized <64 letters, vs. ≥ 64 letters). This is considered acceptable. At week 16 subjects in the aflibercept group were re-randomized to either receive ABP938 or aflibercept in a 1:1 ratio, applying the same stratification factors as initially. This was implemented to obtain evidence for switching between products, which is not strictly necessary in Europe, but can be accepted. Methods to ensure blinding of relevant study personnel are considered acceptable.

Trial intervention: EU-sourced Eylea (“Aflibercept EU”) was used as the comparator which is preferred over reference medicinal products not authorized in the EEA. The dose administered is in line with posology approved for Eylea and considered adequate for the comparative efficacy evaluation. Treatment duration was 48 weeks, last assessments were conducted at Week 52. The duration of the study is considered adequate to assess whether the initially observed similarity in clinical efficacy is maintained for at least 1 year. For an authorisation in the EU and from a strict regulatory point of view, only subjects in the ABP 938 arm and those subjects in the Eylea arm who remain on their originally assigned treatment are relevant. Data after switching are not considered informative for the biosimilarity assessment and interchangeability is not of pivotal interest for a marketing authorization in the EU. It is however acknowledged that this procedure is required for the submission in other regions and that a sufficiently large number of patients (>>100) continued treatment with the reference product throughout the study.

Study assessments: The methods used for the primary (best corrected visual acuity) and secondary efficacy assessments (SD-OCT, fundus photography and fluorescein angiography) represent standards used for the respective assessments and are considered acceptable.

Objectives, endpoints and estimand

The protocol defined primary estimand – following a treatment policy strategy - is not in line with “ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials (EMA/CHMP/ICH/436221/2017)”, which for the demonstration of biosimilarity suggests an estimand that prioritises sensitivity to detect differences between treatments. Furthermore, it is unclear to what extent the applied analysis strategy and handling of subjects with

intercurrent events (esp. use of prohibited medication) does indeed follow a treatment policy strategy as subjects with intercurrent events were treated as missing. In this regard discrepancies in the handling of subjects with intercurrent events and missing outcomes are noted and need to be clarified (see below).

The applicant has provided sensitivity analyses based on the PP as well as a tipping point analysis evaluating the robustness of the primary analysis results with respect to deviations from an assumption of data missing at random. The latter can be interpreted as a conservative type of hypothetical strategy and therefore may appropriately address concerns with respect to the less-than-ideal choice of primary estimand.

The primary endpoint “change from baseline in BCVA as measured by ETDRS letter score at week 8” is considered appropriate. Change from baseline in BCVA is a continuous endpoint which can detect improvement or deterioration in the disease status and is considered a sensitive endpoint to detect differences between the biosimilar candidate and the reference product.

From the VIEW1 and VIEW2 studies conducted with the originator, i.e. studies with the patient population to be evaluated for similarity, it is evident that the efficacy plateau is essentially reached after 12-16 weeks. The selected time point for the efficacy comparison at week 8, on the other hand, lies in the ascending part of the response curve and is therefore considered sufficiently sensitive to detect any differences between treatments.

The applicant prespecified a similarity margin of (-3.9, 3.9) letters for the primary endpoint. This follows scientific advice received, where it was pointed out that ideally an equivalence margin around 3, but below 4 letters was most suitable for the purpose of efficacy comparison at the selected time point. The applicant was also advised to provide a clinical justification for the selected margin at the time of MAA submission. Such justification has not been provided. However, as the actual results fall well within the prespecified margin and the minimum requirement based on previous SA was followed, no concern is raised.

The following secondary efficacy endpoints were selected and are deemed appropriate to provide supportive data for comparative efficacy and pharmacodynamics assessment:

- proportion of subjects who maintained vision at week 52, where a subject was classified as maintaining vision if he/she lost fewer than 15 letters in ETDRS letter score compared to baseline
- change from baseline in BCVA as measured by ETDRS letter score over the study duration
- proportion of subjects who gained at least 10 letters of vision at week 8 and proportion of subjects who gained at least 15 letters of vision at week 52 as compared to baseline
- change from baseline in CNV area as measured by fluorescein angiography (FA) and central subfield thickness (CST) as measured by spectral domain optical coherence tomography (SD-OCT) over the study duration

No estimands are explicitly defined for the secondary objectives. However, based on corresponding analysis a strategy similar to the primary estimand has been employed. Similar concerns regarding the sensitivity of a treatment policy strategy to detect potential clinical differences between treatments do apply. However, considering the limited number of subjects with intercurrent events, good alignment between analyses based on FAS and PP, no concern is raised.

Statistical methods

Statistical methods are in general acceptable. Sample size calculations can be reproduced and appear plausible. Use of an ANCOVA model to estimate the difference of mean change from baseline, stratified

for BCVA at baseline and Region can be considered appropriate. Planned sensitivity analyses (esp. tipping point analysis) are considered suitable to evaluate the robustness of the prespecified primary analyses and address concerns raised with respect to a potential lack of sensitivity of the primary estimand following a treatment policy strategy. Nevertheless, some concerns regarding handling of prohibited medication require clarification (see above).

Sub-group analyses were pre-planned for important stratification factors. Corresponding analyses were included for exploratory reasons and not to address confirmatory claims. This is acceptable.

Results

Participant flow and protocol deviations

The study was initiated in June 2020. The final Study Protocol Version 4 dates from 14-JUL-2023. The applicant provided a summary of the protocol amendments for each new version. Changes introduced in Protocol Amendment 1 (Version 2.0) are not considered to have impacted the study outcome as it was dated 18 October 2019 before the study was initiated (first subject was enrolled on 22 June 2020). Protocol Amendment 2 (Version 3.0) included updates to Section 2 Study Objective and Endpoints to clarify that change from baseline in CNV area (secondary efficacy endpoint) was to be measured by FA. Further, eligibility criteria with a potential impact on the sensitivity of the study population were updated with Amendment 2. In addition, regarding the change to allow treatment of the fellow eye at baseline (day 1) if needed, the result of subgroup analysis for subjects who did not receive fellow eye treatment prior to week 8 (278 subjects in ABP 938 and 280 in Aflibercept groups) was consistent with the result of the primary efficacy analysis and the number of subjects treated with the investigational product in the fellow eye prior to week 8 was low and balanced between treatment groups (10 and 8 subjects respectively in ABP 938 and Aflibercept groups).

Notably, the IP washout period for the fellow eye was updated from within 6 months to within 30 days. This is effectively undermining the underlying idea of no ongoing fellow-eye treatment, since it does not exclude patients on regular aflibercept treatment, where the recommended treatment posology is one injection per month for three consecutive doses followed by a treatment interval of two months.

A total of 1037 subjects were screened for the study, of which 579 subjects (55.8%) were randomised. The details relating to screening failure of these subjects were provided by the applicant. Overall, 565/576 (98.1%) subjects (284/288 and 281/288 in the test and reference group, respectively) completed treatment through week 8 for the primary efficacy analysis. 543/576 (94.3%) subjects (273/288 and 270/288 in the test and reference group, respectively) completed treatment through week 16 and were re-randomized as planned. In total, 338 (58.7%) subjects were enrolled before, and 238 (41.3%) subjects were enrolled after Protocol Amendment 2 came into effect. The numbers of subjects (%) enrolled before and after Protocol Amendment 2 were comparable between groups: 58.0% and 42.0% in the ABP 938 group compared to 59.4% and 40.6% in the reference group.

In general, subject disposition and study completion/discontinuation were comparable between treatment groups throughout the study, i.e., pre- and post-rerandomization and do not give rise to concern.

In 5 cases prohibited medications were used for the treatment of non-ocular indications and initiated after the BCVA assessment at week 8. Therefore, handling of subjects who required prohibited medications is not of concern in the primary analysis. The rest of intercurrent events were set as missing values and tipping point analyses treating them as MNAR to test deviations from the assumption of data missing at random appropriately addressed this concern.

Baseline data

Overall, demographic and baseline physical characteristics as well as baseline disease characteristics were sufficiently similar between the test and reference group. Values for CNV and CST were slightly higher in the reference group, rendering the setting more conservative as they leave more room for improvement in the reference group. Thus, no concern is raised. However, as discussed above, criteria for eligibility could have been more stringent to render the study population more sensitive for detection of differences between treatments.

Medical history is listed in the original tables in the CSR but has not been summarized. According to Table 14-2.3, imbalances are noted in the numbers of subjects between groups with a history of eye disorders (232/288 in the ABP 938 group compared to 207/288 in the reference group), including dry AMD, cataract, wet AMD and vitreous detachment. Such disease history could potentially influence the baseline disease characteristics and thus bias the study results. However, as specified above, baseline BCVA data (both, BCVA group and ETDRS letter score) were balanced between groups, thus no concern is raised.

Primary efficacy analysis

In the FAS, the observed mean (SD) change from baseline in BCVA at week 8 was similar between the ABP 938 and the aflibercept (EU) treatment group, as measured by ETDRS letter score (6.4 (8.18) and 6.5 (8.97) letters, respectively). The point estimate of the least squares mean difference between the treatment groups was 0.1 with a 2-sided 95% CI of (-1.3, 1.5). The 95% CI was entirely within the prespecified similarity margin of (-3.9, 3.9). Therefore, the primary objective of the study was met.

The following sensitivity analyses were performed to assess the robustness of the primary efficacy analysis result. The ANCOVA analysis was repeated using the per-protocol (PP) analysis set based on observed cases and using the FAS based on last observation carried forward imputation. In the PP set, the point estimate of the least squares mean difference between the treatment groups was -0.1 with a 2-sided 95% CI of (-1.6, 1.4) and in the FAS LOCF set, the point estimate of the least squares mean difference between the treatment groups was 0.0 with a 2-sided 95% CI of (-1.4, 1.4). In addition, a mixed model repeated-measures analysis for day 1 through week 8 based on the FAS was performed. In this model, the point estimate of the least squares mean difference between the treatment groups was 0.0 with a 2-sided 95% CI of (-1.3, 1.3). Further, an analysis using the FAS was done to explore the impact of other baseline covariates on BCVA change from baseline to week 8 in addition to the stratification factor of region and baseline BCVA value. In this analysis, the point estimate of the least squares mean difference between the treatment groups was 0.1 with a 2-sided 95% CI of (-1.3, 1.5). In addition, tipping point analyses were performed using the FAS to explore the sensitivity of the primary analysis results to violations in assumptions about missing data. The 95% CIs for all assumptions were within the pre-defined similarity margin of (-3.9, 3.9).

The applicant was requested to provide an evaluation of the primary efficacy endpoint separately for patients enrolled before and after Protocol Amendment 2 came into effect, since important eligibility criteria with a potential impact on the sensitivity of the patient population were revised with this amendment. The point estimates of the least squares mean difference in change from baseline in BCVA and the corresponding 95% confidence intervals were -0.1 (-2.0, 1.8) for the subgroup of subjects enrolled before Protocol Amendment 2 and 0.3 (-1.8, 2.3) for the subgroup of subjects enrolled after Protocol Amendment 2. The results for both subgroups were comparable and completely within the predefined similarity margin of (-3.9, 3.9) for the primary efficacy endpoint. Thus, the results of this subgroup analysis were consistent with results from the primary analysis of the primary efficacy endpoint based on the full analysis set (FAS).

In summary, all sensitivity analyses support the findings of the primary efficacy analysis.

Secondary efficacy endpoints

As for the primary assessment at week 8, change from baseline in BCVA was also similar between the two treatment groups at weeks 4 and 16 with a difference between means estimated using ANCOVA model with treatment, the stratification factors geographic region and baseline BVCA as covariates of 0.65 and -0.17, respectively. The respective 95% CIs were (-0.5, 1.8) and (-1.6, 1.3).

After Week 16 (re-randomisation), the main comparison of interest is that between patients in the ABP 938 arm (ABP 938/ABP 938) and patients who remained in the Eylea arm (Aflibercept/Aflibercept). From week 32 through week 52, mean values in change from baseline are lower in the ABP 938 group compared to the reference group. This trend is also noticed in the Aflibercept/ABP 938 group, for which mean values fall in between those of the other 2 groups. However, SD values are relatively large and differences between means are generally less than 2 letters, thus the numerical differences are not considered clinically relevant.

Results for the following endpoints were similar across the treatment groups: proportion of subjects who maintained vision at week 52; proportion of subjects who gained ≥10 letters at week 8; proportion of subjects who gained ≥15 letters at week 52.

Change From Baseline in CNV Area Size

Throughout the study, mean change from baseline in CNV area size was numerically lower in the ABP 938 group compared to the reference group. Mean (SD) values were -4.863 (5.1719) mm^2 and -5.371 (4.9836) mm^2 at week 8 and -4.002 (5.3484) mm^2 and -4.947 (5.1489) mm^2 at week 16 for ABP 938 and reference treatment, respectively. After rerandomization, mean (SD) values were -4.323 (5.5972) mm^2 and -5.308 (5.6238) mm^2 at week 24 and -6.276 (6.2690) mm^2 and -7.280 (5.8262) mm^2 at week 52 for the ABP 938/ABP 938 and Aflibercept/Aflibercept arm, respectively. Notably, the absolute baseline level of CNV area size was lower in the ABP 938 group (8.508 (5.6621) mm^2) compared to the reference group (9.343 (5.2270) mm^2), thus leaving more room for improvement in the reference group. The absolute values for CNV area size were similar across both treatments at the respective time points throughout the study.

Change From Baseline in CST

The results of change from baseline in CST as measured by SD-OCT at weeks 4, 8, and 16 were numerically lower in the ABP 938 group compared to the reference group. Mean (SD) values were -136.0 (109.32) µm and -145.8 (105.64) µm at week 4, -145.7 (106.47) µm and -156.5 (113.62) µm at week 8, and -122.7 (124.73) µm and -135.5 (112.48) µm at week 16 for the ABP 938 group and the reference group, respectively. This may at least partially be due to the slightly lower baseline CST in the ABP 938 arm compared to the reference arm (438.4 and 448.8 µm, respectively). Absolute CST values were similar across both treatments at the respective time points. From week 24 through 52, both, absolute CST values and change from baseline values were similar between the ABP 938/ABP 938 and Aflibercept/Aflibercept arms.

Overall, the analyses of the primary and secondary efficacy endpoints support the notion of similarity between ABP 938 and the reference product Eylea (aflibercept EU).

Usability

The ability of healthcare professionals to follow the instructions for use to successfully prepare and administer the IVT injection to patients was evaluated in a usability study (Study 20210034). Design and objective of the study are considered adequate. The results demonstrate that intravitreal administration can be achieved successfully and there is no difference between ABP 938 and the reference PFS product.

2.5.7. Conclusions on the clinical efficacy

The results of the efficacy evaluation provide the notion of biosimilarity between the biosimilar candidate ABP 938 and the reference product Eylea.

2.5.8. Clinical safety

The safety information is based on one main clinical Study 20170542 in adult subjects with neovascular (wet) age-related macular degeneration (AMD) and a usability Study (20210034) in subjects with various chorioretinal vascular diseases (CVDs). The Main Study Period data were collected up to Week 52. At week 8, subjects were assessed for the primary efficacy endpoint (BCVA change from baseline as measured by ETDRS letter score). Subjects were then re-randomized at week 16 in a masked fashion such that:

• subjects initially randomized to ABP 938 (Treatment Group A) continued to receive ABP 938 by IVT injection every 8 weeks from week 16 until week 48

• subjects initially randomized to aflibercept (EU) (Treatment Group B) were re-randomized in a 1:1 ratio to either continue on aflibercept (EU) (Treatment Group B1) or transition to ABP 938 (Treatment Group B2) by IVT injection every 8 weeks from week 16 until week 48.

The Safety Set for Main Study Period consists of all subjects who received at least 1 dose of investigational product, with treatment assignment based on actual treatment received; used for analysis of safety and immunogenicity endpoints.

2.5.8.1. Patient exposure

In Study 20170542, 288 subjects in the safety analysis set received ABP 938 and 288 subjects received aflibercept (EU) through week 16. Post week 16, 273 subjects in the ABP 938/ABP 938 treatment group received ABP 938, 133 subjects in the aflibercept (EU)/ABP 938 treatment group received ABP 938, and 136 subjects in the aflibercept (EU)/aflibercept (EU) treatment group received aflibercept (EU). In Study 20210034, 32 subjects received ABP 938, and 16 subjects received aflibercept (US). A total of 624 subjects received any amount of ABP 938 or Eylea (aflibercept). Of the 624 subjects who received investigational product, 453 subjects received ABP 938.

A total of 576 subjects (288 subjects in the ABP 938 treatment group and 288 subjects in the aflibercept [EU] treatment group) were treated with investigational product in the study eye and were included in the safety analysis set.

Figure 1: Overall Extent of Exposure to Investigational Product (All Clinical Studies)

Study Type / Study Number	Number of Subjects Receiving ABP 938 or Aflibercept RP		
	ABP 938	Aflibercept (EU)	Aflibercept (US)
Comparative clinical study in subjects with neovascular (wet) AMD			
Study 20170542	421[a]	288	0
PFS clinical usability study in subjects with various CVDs			
Study 20210034	32	0	16
All clinical studies			
Total	453[a]	288	16

AMD = age-related macular degeneration; CSR = clinical study report; CVD = chorioretinal vascular disease; EU = European Union; PFS = prefilled syringe; RP = reference product; US = United States
Note: Only aflibercept (EU) was used in Study 20170542, and only aflibercept (US) was used in Study 20210034.
[a] A total of 133 of the 288 subjects who were initially randomized to aflibercept (EU) were re-randomized to transition to ABP 938 at week 16.

The safety profile of Eylea is well-established and the available safety database of 453 patients treated for up to 52 weeks with ABP 938, is considered sufficient for the general evaluation of safety and immunogenicity of ABP 938 in comparison to the reference product.

2.5.8.2. Adverse events

The following table fives an overview of treatment-emergent AEs (TEAES) in Study 20170542.

Figure 2: Overall Summary of Adverse Events – Entire Study (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

Adverse Event Category	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Any adverse event	181 (66.3)	89 (66.9)	81 (59.6)
Any grade ≥ 3 adverse event	27 (9.9)	15 (11.3)	15 (11.0)
Any fatal adverse event	2 (0.7)	2 (1.5)	0 (0.0)
Any serious adverse event	27 (9.9)	17 (12.8)	11 (8.1)
Any adverse event leading to discontinuation of IP/study	9 (3.3)	3 (2.3)	5 (3.7)
Any EOI	14 (5.1)	8 (6.0)	2 (1.5)
Any adverse event leading to interruption of IP[a]	29 (10.6)	11 (8.3)	7 (5.1)

CSR = clinical study report; EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

In Study 20170542, adverse events were reported by 181 (66.3%) subjects in the ABP 938/ABP 938 treatment group, 89 (66.9%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 81 (59.6%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group. Most adverse events over the entire study were CTCAE grade 1 or 2 in severity. Grade ≥ 3 adverse events were reported in 27

(9.9%) subjects in the ABP 938/ABP 938 treatment group, 15 (11.3%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 15 (11.0%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group.

Study Eye

Table 23: Overall summary of ocular adverse events in Study Eye – Entire Study (Study20170542 Safety Analysis Set – Re-randomzied and treated in Study Eye)

Adverse Event Category	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Any ocular adverse event	85 (31.1)	43 (32.3)	37 (27.2)
Any grade ≥ 3 adverse event	1 (0.4)	1 (0.8)	3 (2.2)
Any serious adverse event	0 (0.0)	0 (0.0)	2 (1.5)
Any adverse event leading to discontinuation of IP/study	2 (0.7)	0 (0.0)	3 (2.2)
Any EOI	5 (1.8)	4 (3.0)	1 (0.7)
Any adverse event leading to interruption of IP[a]	4 (1.5)	0 (0.0)	2 (1.5)

CSR = clinical study report; EOI = event of interest; EU = European Union; IP = investigational product
Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.
[a] Drug Interrupted was used for temporary modification of the dosing schedule.

In Study 20170542, ocular adverse events in the study eye were reported by 85 (31.1%) subjects in the ABP 938/ABP 938 treatment group, 43 (32.3%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 37 (27.2%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group.

Usability Study 20210034

Table 24: Overall Summary of Adverse Events (Study 20210034 Safety Analysis Set)

	ABP 938 PFS (N = 32) n (%)	Aflibercept (US) PFS (N = 16) n (%)
Any ocular adverse event in the study eye	3 (9.4)	0
Any non-ocular adverse event	4 (12.5)	2 (12.5)
Any ocular serious adverse event in the study eye	0	0
Any non-ocular serious adverse event	0	0
Any grade ≥ 3 adverse event	0	0
Any fatal adverse event	0	0
Any COVID-19 adverse event[a]	0	0
Any adverse event leading to discontinuation of study	0	0
Any investigational product related adverse event	0	0
Any study procedure related adverse event	1 (3.1)	0
Any device related adverse event	0	0
Any adverse event of interest	0	0

CSR = clinical study report; eCRF = electronic case report form; MedDRA = Medical Dictionary for Regulatory Activities; PFS = prefilled syringe; US = United States

Note: Only treatment-emergent adverse events were summarized by actual treatment received. For each category, subjects were included only once, even if they experienced multiple adverse events in that category.

[a] Adverse event data collected on the Adverse Events eCRF was used to identify COVID-19 adverse events using the COVID-19 Standardized MedDRA Query narrow search strategy.

In Study 20210034, ocular adverse events in the study eye were reported in 3 (9.4%) subjects in the ABP 938 PFS treatment group and 0 subjects in the aflibercept (US) PFS treatment group. Non-ocular adverse events were reported in 4 (12.5%) subjects in the ABP 938 PFS treatment group and 2 (12.5%) subjects in the aflibercept (US) PFS treatment group. All adverse events (ocular in the study eye and non-ocular) were CTCAE grade 1 or 2 in severity; there were no grade ≥ 3 adverse events reported during the study.

Serious Adverse Events Post week 16

Post week 16, 47 (8.7%) subjects experienced serious adverse events comprising 22 (8.1%) subjects in the ABP 938/ABP 938 treatment group, 14 (10.5%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 11 (8.1%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group. While the number of subjects reporting a serious adverse event of cerebrovascular accident was numerically higher post week 16 in the ABP 938/ABP 938 treatment group and the aflibercept (EU)/ABP 938 treatment group (2 [0.7%] subjects and 3 [2.3%] subjects, respectively) compared to the aflibercept (EU)/aflibercept (EU) treatment group (0 [0.0%] subjects), the number of subjects reporting these events was low and the incidence of these events was within the range for incidence of arterial thromboembolic events reported for Eylea (aflibercept) (Heier et al, 2012). Notably, all of these subjects had at least 1 major cardiovascular risk factor (ie, high blood pressure, hypercholesterolemia, older age, and prior history of cardiovascular disease). There were no notable differences in the incidence of serious adverse events by preferred term or SOC between the treatment groups post

week 16. There were no new safety signals observed or new patterns of serious adverse events reported.

Table 25: Serious Adverse Events by System Organ Class and Preferred Term Post Week 16 (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Number of subjects reporting serious treatment-emergent adverse events	22 (8.1)	14 (10.5)	11 (8.1)
Injury, poisoning and procedural complications	6 (2.2)	2 (1.5)	1 (0.7)
Femur fracture	3 (1.1)	0 (0.0)	0 (0.0)
Femoral neck fracture	2 (0.7)	0 (0.0)	0 (0.0)
Hip fracture	1 (0.4)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	1 (0.7)
Contusion	0 (0.0)	1 (0.8)	0 (0.0)
Fall	0 (0.0)	1 (0.8)	0 (0.0)
Rib fracture	0 (0.0)	1 (0.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2)	3 (2.3)	1 (0.7)
Colon cancer	1 (0.4)	0 (0.0)	0 (0.0)
Invasive ductal breast carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Prostate cancer	1 (0.4)	0 (0.0)	0 (0.0)
Small cell lung cancer	1 (0.4)	0 (0.0)	0 (0.0)
Transitional cell cancer of the renal pelvis and ureter	1 (0.4)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Basal cell carcinoma	0 (0.0)	1 (0.8)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.7)
Plasma cell myeloma	0 (0.0)	1 (0.8)	0 (0.0)
Squamous cell carcinoma of the tongue	0 (0.0)	1 (0.8)	0 (0.0)
Nervous system disorders	4 (1.5)	3 (2.3)	0 (0.0)
Cerebrovascular accident	2 (0.7)	3 (2.3)	0 (0.0)
Sciatica	1 (0.4)	0 (0.0)	0 (0.0)
Syncope	1 (0.4)	0 (0.0)	0 (0.0)
Infections and infestations	3 (1.1)	2 (1.5)	1 (0.7)
COVID-19	2 (0.7)	0 (0.0)	0 (0.0)
Diverticulitis	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.4)	1 (0.8)	0 (0.0)
Appendicitis	0 (0.0)	1 (0.8)	0 (0.0)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Arthropod-borne disease	0 (0.0)	0 (0.0)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	0 (0.0)	1 (0.7)
Epistaxis	1 (0.4)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	1 (0.7)
Endocrine disorders	1 (0.4)	0 (0.0)	0 (0.0)
Adrenal hematoma	1 (0.4)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.4)	0 (0.0)	3 (2.2)
Retinal detachment	1 (0.4)	0 (0.0)	0 (0.0)
Retinal hemorrhage	0 (0.0)	0 (0.0)	1 (0.7)
Visual acuity reduced	0 (0.0)	0 (0.0)	1 (0.7)
Visual impairment	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	1 (0.4)	0 (0.0)	1 (0.7)
Pneumatosis intestinalis	1 (0.4)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	1 (0.7)
Renal and urinary disorders	1 (0.4)	0 (0.0)	0 (0.0)
Renal failure	1 (0.4)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Benign prostatic hyperplasia	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	2 (1.5)	1 (0.7)
Acute myocardial infarction	0 (0.0)	1 (0.8)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.7)
Cardiac failure congestive	0 (0.0)	1 (0.8)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.7)
Cholangitis acute	0 (0.0)	0 (0.0)	1 (0.7)
Investigations	0 (0.0)	1 (0.8)	0 (0.0)
Heart rate decreased	0 (0.0)	1 (0.8)	0 (0.0)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Metabolism and nutrition disorders	0 (0.0)	1 (0.8)	0 (0.0)
Dehydration	0 (0.0)	1 (0.8)	0 (0.0)
Hypokalemia	0 (0.0)	1 (0.8)	0 (0.0)
Hyponatremia	0 (0.0)	1 (0.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.7)
Hemarthrosis	0 (0.0)	0 (0.0)	1 (0.7)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 25.1 Only treatment-emergent adverse events were summarized. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.

Adverse drug reactions

Through week 16, 2 (0.7%) subjects in the ABP 938 treatment group and 0 (0.0%) subjects in the aflibercept (EU) treatment group experienced a retinal detachment EOI. Subjects in the ABP 938 treatment group experienced retinal detachment EOIs of grade 1 or grade 2 retinal tear.

Table 26: Treatment emergent retinal detachment events by preferred Term through week 16 (Study 20170542 Safety analysis set)

Preferred Term	ABP 938 (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Number of subjects reporting any retinal detachment events[a]	2 (0.7)	0 (0.0)
Retinal tear	2 (0.7)	0 (0.0)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan
Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

IThrough week 16, 2 (0.7%) subjects in the ABP 938 treatment group and 2 (0.7%) subjects in the aflibercept (EU) treatment group experienced increase in IOP EOIs.

Table 27: treatment emergent increase in intraocular Pressure by preferred term trough week 16 (Study 20170542 Safety analysis set)

Preferred Term	ABP 938 (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Number of subjects reporting any increase in intraocular pressure events[a]	2 (0.7)	2 (0.7)
Intraocular pressure increased	1 (0.3)	0 (0.0)
Normal tension glaucoma	1 (0.3)	0 (0.0)
Ocular hypertension	0 (0.0)	2 (0.7)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan

Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Post week 16, 1 (0.4%) subject in the ABP 938/ABP 938 treatment group, 0 (0.0%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 1 (0.7%) subject in the aflibercept (EU)/aflibercept (EU) treatment group experienced a retinal detachment EOI.

Table 28: Treatment Emergent Retinal Detachment Events by Preferred Term Post Week 16 (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Number of subjects reporting any retinal detachment events[a]	1 (0.4)	0 (0.0)	1 (0.7)
Retinal detachment	1 (0.4)	0 (0.0)	0 (0.0)
Retinal tear	0 (0.0)	0 (0.0)	1 (0.7)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan

Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Increase in IOP EOIs post week 16 of the study for re-randomized and treated subjects are presented by preferred term in Table 45. Post week 16, 5 (1.8%) subjects in the ABP 938/ABP 938 treatment group, 4 (3.0%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 0 (0.0%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group experienced increase in IOP EOIs.

Table 29: Treatment Emergent Increase in Intraocular Pressure Events by Preferred Term Post Week 16 (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Number of subjects reporting any increase in intraocular pressure events[a]	5 (1.8)	4 (3.0)	0 (0.0)
Intraocular pressure increased	3 (1.1)	2 (1.5)	0 (0.0)
Ocular hypertension	2 (0.7)	2 (1.5)	0 (0.0)
Open angle glaucoma	0 (0.0)	1 (0.8)	0 (0.0)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan

Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

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There were no EOIs reported during the study.

2.5.8.3. Serious adverse event/deaths/other significant events

Arterial thromboembolic events (ATEs) and TEAEs related to IVT injection procedure were considered AESIs by considering Eylea's safety profile and were closely monitored.

- ATEs: ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause) according to the Antiplatelet Trialists' Collaboration. The PTs for ATE analysis were reviewed and determined in a masked manner before the database lock and the final determination for the PTs was specified in the statistical analysis plan (SAP). All captured ATEs and suspicious fatal cases were medically reviewed and classified as potential ATEs.

All AEs related to the IVT injection procedure including but not limited to the following: endophthalmitis, increases in IOP, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. AEs considered by the investigator to be related to the IVT injection procedure were included in the safety analysis.

Through week 16, 2 (0.7%) subjects in the ABP 938 treatment group and 1 (0.3%) subject in the aflibercept (EU) treatment group experienced thromboembolic EOIs. In the ABP 938 treatment group, 1 subject experienced a thromboembolic EOI of grade 1 myocardial infarction, and 1 subject experienced grade 1 superficial vein thrombosis. In the aflibercept (EU) treatment group, 1 subject experienced the thromboembolic EOI of grade 4 pulmonary embolism.

Table 30: Treatment Emergent Thromboembolic Events by Preferred Term Through Week 16 (Study 20170542 Safety Analysis Set)

Preferred Term	ABP 938 (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Number of subjects reporting any thromboembolic events[a]	2 (0.7)	1 (0.3)
Myocardial infarction	1 (0.3)	0 (0.0)
Superficial vein thrombosis	1 (0.3)	0 (0.0)
Pulmonary embolism	0 (0.0)	1 (0.3)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan

Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

Post week 16, 4 (1.5%) subjects in the ABP 938/ABP 938 treatment group, 4 (3.0%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 1 (0.7%) subject in the aflibercept (EU)/aflibercept (EU) treatment group experienced thromboembolic EOIs.

Table 31: Treatment Emergent Thromboembolic Events by Preferred Term Post Week 16 (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Number of subjects reporting any thromboembolic events[a]	4 (1.5)	4 (3.0)	1 (0.7)
Cerebrovascular accident	2 (0.7)	3 (2.3)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)	0 (0.0)
Retinal vein thrombosis	1 (0.4)	0 (0.0)	0 (0.0)
Acute myocardial infarction	0 (0.0)	1 (0.8)	0 (0.0)
Hemiparesis	0 (0.0)	1 (0.8)	0 (0.0)
Peripheral arterial occlusive disease	0 (0.0)	1 (0.8)	0 (0.0)
Thrombophlebitis	0 (0.0)	0 (0.0)	1 (0.7)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities; SAP = Statistical Analysis Plan

Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each preferred term, subjects were included only once, even if they experienced multiple events in that preferred term.

There were no EOIs reported during the usability study 20210034.

Overall, the frequency of TEAEs was comparable between the groups in both time periods, trough week 16 and after re-randomization post week 16. This is acceptable. Regarding the frequency and nature, TEAEs were in line with the Eylea RefMP.

Deaths

A total of 6 (1.0%) subjects experienced fatal adverse events.

Through week 16, 2 (0.3%) subjects in the safety analysis set experienced a fatal adverse event. In the ABP 938 treatment group, no fatal adverse events were reported. In the aflibercept (EU) treatment group, 2 subjects experienced a fatal adverse event. Both events were considered not related to investigational product or study by the investigator.

Post week 16, 4 (0.7%) subjects in the safety analysis set who were treated post re-randomization experienced a fatal adverse event. In the ABP 938/ABP 938 treatment group, 1 (0.4%) subject and in the aflibercept (EU)/ABP 938 treatment group, 1 (0.8%) subject (experienced a fatal adverse event and 1 (0.8%) subject experienced a fatal adverse event. Both events were considered not related to investigational product or study by the investigator. In the aflibercept (EU)/aflibercept (EU) treatment group, no fatal adverse events were reported.

No subjects experienced fatal (grade 5) adverse events in the Usability study 20210034.

Other Serious adverse Events

Through week 16, 15 (2.6%) subjects experienced serious adverse events comprising 6 (2.1%) subjects in the ABP 938 treatment group and 9 (3.1%) subjects in the aflibercept (EU) treatment group. Through week 16, 0 (0.0%) subjects in the ABP 938 treatment group and 3 (20.0%) subjects in the aflibercept (EU) treatment group experienced a serious adverse event. There were no new safety signals observed or new pattern of serious adverse events reported.

Table 32: Serious Adverse Events by System Organ Class and Preferred Term Through Week 16 (Study 20170542 Safety Analysis Set)

System Organ Class Preferred Term	ABP 938 (N = 288) n (%)	Aflibercept (EU) (N = 288) n (%)
Number of subjects reporting serious treatment-emergent adverse events	6 (2.1)	9 (3.1)
Renal and urinary disorders	2 (0.7)	0 (0.0)
Bladder neck obstruction	1 (0.3)	0 (0.0)
Hematuria	1 (0.3)	0 (0.0)
Cardiac disorders	1 (0.3)	1 (0.3)
Ventricular tachycardia	1 (0.3)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (0.3)
Infections and infestations	1 (0.3)	3 (1.0)
Urinary tract infection	1 (0.3)	0 (0.0)
COVID-19	0 (0.0)	2 (0.7)
Pneumonia	0 (0.0)	1 (0.3)
Injury, poisoning and procedural complications	1 (0.3)	0 (0.0)
Femur fracture	1 (0.3)	0 (0.0)
Radius fracture	1 (0.3)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	2 (0.7)
Rosai-Dorfman syndrome	1 (0.3)	0 (0.0)
Basal cell carcinoma	0 (0.0)	1 (0.3)
Colon cancer	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)
Pulmonary embolism	0 (0.0)	1 (0.3)
Vascular disorders	0 (0.0)	2 (0.7)
Peripheral artery stenosis	0 (0.0)	1 (0.3)
Subclavian artery stenosis	0 (0.0)	1 (0.3)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 25.1. Only treatment-emergent adverse events were summarized. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.

Study Eye

No serious ocular adverse events in the study eye through week 16 were reported.

Fellow Eye

A serious ocular adverse event in the fellow eye through week 16 was reported for 1 (6.3%) subject in the aflibercept (EU) treatment group.

Post week 16, 47 (8.7%) subjects experienced serious adverse events comprising 22 (8.1%) subjects in the ABP 938/ABP 938 treatment group, 14 (10.5%) subjects in the aflibercept (EU)/ABP 938 treatment

group, and 11 (8.1%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group. Notably, all of these subjects had at least 1 major cardiovascular risk factor (ie, high blood pressure, hypercholesterolemia, older age, and prior history of cardiovascular disease There were no notable differences in the incidence of serious adverse events by preferred term or SOC between the treatment groups post week 16. There were no new safety signals observed or new patterns of serious adverse events reported.

Serious Adverse Events Post week 16

Post week 16, 47 (8.7%) subjects experienced serious adverse events comprising 22 (8.1%) subjects in the ABP 938/ABP 938 treatment group, 14 (10.5%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 11 (8.1%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group. While the number of subjects reporting a serious adverse event of cerebrovascular accident was numerically higher post week 16 in the ABP 938/ABP 938 treatment group and the aflibercept (EU)/ABP 938 treatment group (2 [0.7%] subjects and 3 [2.3%] subjects, respectively) compared to the aflibercept (EU)/aflibercept (EU) treatment group (0 [0.0%] subjects), the number of subjects reporting these events was low and the incidence of these events was within the range for incidence of arterial thromboembolic events reported for Eylea (aflibercept) (Heier et al, 2012). Notably, all of these subjects had at least 1 major cardiovascular risk factor (ie, high blood pressure, hypercholesterolemia, older age, and prior history of cardiovascular disease). Post week 16, 1 (5.6%) subject in the ABP 938/ABP 938 treatment group, 1 (16.7%) subject in the aflibercept (EU)/ABP 938 treatment group, and 0 (0.0%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group experienced a serious adverse event.There were no notable differences in the incidence of serious adverse events by preferred term or SOC between the treatment groups post week 16. There were no new safety signals observed or new patterns of serious adverse events reported.

Table 33: Serious Adverse Events by System Organ Class and Preferred Term Post Week 16 (Study 20170542 Safety Analysis Set – Re-randomized and Treated)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Number of subjects reporting serious treatment-emergent adverse events	22 (8.1)	14 (10.5)	11 (8.1)
Injury, poisoning and procedural complications	6 (2.2)	2 (1.5)	1 (0.7)
Femur fracture	3 (1.1)	0 (0.0)	0 (0.0)
Femoral neck fracture	2 (0.7)	0 (0.0)	0 (0.0)
Hip fracture	1 (0.4)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	1 (0.7)
Contusion	0 (0.0)	1 (0.8)	0 (0.0)
Fall	0 (0.0)	1 (0.8)	0 (0.0)
Rib fracture	0 (0.0)	1 (0.8)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (2.2)	3 (2.3)	1 (0.7)
Colon cancer	1 (0.4)	0 (0.0)	0 (0.0)
Invasive ductal breast carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Invasive lobular breast carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Prostate cancer	1 (0.4)	0 (0.0)	0 (0.0)
Small cell lung cancer	1 (0.4)	0 (0.0)	0 (0.0)
Transitional cell cancer of the renal pelvis and ureter	1 (0.4)	0 (0.0)	0 (0.0)
Transitional cell carcinoma	1 (0.4)	0 (0.0)	0 (0.0)
Basal cell carcinoma	0 (0.0)	1 (0.8)	0 (0.0)
Lung neoplasm malignant	0 (0.0)	0 (0.0)	1 (0.7)
Plasma cell myeloma	0 (0.0)	1 (0.8)	0 (0.0)
Squamous cell carcinoma of the tongue	0 (0.0)	1 (0.8)	0 (0.0)
Nervous system disorders	4 (1.5)	3 (2.3)	0 (0.0)
Cerebrovascular accident	2 (0.7)	3 (2.3)	0 (0.0)
Sciatica	1 (0.4)	0 (0.0)	0 (0.0)
Syncope	1 (0.4)	0 (0.0)	0 (0.0)
Infections and infestations	3 (1.1)	2 (1.5)	1 (0.7)
COVID-19	2 (0.7)	0 (0.0)	0 (0.0)
Diverticulitis	1 (0.4)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.4)	1 (0.8)	0 (0.0)
Appendicitis	0 (0.0)	1 (0.8)	0 (0.0)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Arthropod-borne disease	0 (0.0)	0 (0.0)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	2 (0.7)	0 (0.0)	1 (0.7)
Epistaxis	1 (0.4)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (0.4)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	1 (0.7)
Endocrine disorders	1 (0.4)	0 (0.0)	0 (0.0)
Adrenal hematoma	1 (0.4)	0 (0.0)	0 (0.0)
Eye disorders	1 (0.4)	0 (0.0)	3 (2.2)
Retinal detachment	1 (0.4)	0 (0.0)	0 (0.0)
Retinal hemorrhage	0 (0.0)	0 (0.0)	1 (0.7)
Visual acuity reduced	0 (0.0)	0 (0.0)	1 (0.7)
Visual impairment	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	1 (0.4)	0 (0.0)	1 (0.7)
Pneumatosis intestinalis	1 (0.4)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	1 (0.7)
Renal and urinary disorders	1 (0.4)	0 (0.0)	0 (0.0)
Renal failure	1 (0.4)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (0.4)	0 (0.0)	0 (0.0)
Benign prostatic hyperplasia	1 (0.4)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	2 (1.5)	1 (0.7)
Acute myocardial infarction	0 (0.0)	1 (0.8)	0 (0.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.7)
Cardiac failure congestive	0 (0.0)	1 (0.8)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.7)
Cholangitis acute	0 (0.0)	0 (0.0)	1 (0.7)
Investigations	0 (0.0)	1 (0.8)	0 (0.0)
Heart rate decreased	0 (0.0)	1 (0.8)	0 (0.0)

System Organ Class Preferred Term	ABP 938/ ABP 938 (N = 273) n (%)	Aflibercept (EU)/ ABP 938 (N = 133) n (%)	Aflibercept (EU)/ Aflibercept (EU) (N = 136) n (%)
Metabolism and nutrition disorders	0 (0.0)	1 (0.8)	0 (0.0)
Dehydration	0 (0.0)	1 (0.8)	0 (0.0)
Hypokalemia	0 (0.0)	1 (0.8)	0 (0.0)
Hyponatremia	0 (0.0)	1 (0.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.7)
Hemarthrosis	0 (0.0)	0 (0.0)	1 (0.7)

CSR = clinical study report; EU = European Union; MedDRA = Medical Dictionary for Regulatory Activities
Note: Adverse events were coded using MedDRA version 25.1 Only treatment-emergent adverse events were summarized. For each system organ class and preferred term, subjects were included only once, even if they experienced multiple events in that system organ class or preferred term.

Study Eye

Two subjects in the aflibercept (EU)/aflibercept (EU) treatment group experienced serious ocular adverse events in the study eye through week 16. Serious ocular adverse events included grade 3 retinal hemorrhage and grade 3 visual acuity reduced.

Fellow Eye

No serious ocular adverse events in the fellow eye post week 16 were reported.

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There were no serious adverse events (ocular in the study eye or non-ocular) reported during the study.

2.5.8.4. Laboratory findings

Overall, no clinically important changes in laboratory values were observed post-baseline in the completed comparative clinical study (Study 20170542).

Hematology Laboratory Results

There were no notable differences between the re-randomized treatment groups in median changes from baseline for hematology values over the entire study.

Chemistry Laboratory results

There were no notable differences between the re-randomized treatment groups in median changes from baseline for chemistry laboratory results values over the entire study.

Urinalysis Results

There were no notable differences between the re-randomized treatment groups in median changes from baseline for urinalysis values over the entire study.

Best-Corrected Visual Acuity

There were no notable differences between treatment groups were observed.

Intraocular Pressure

There were no notable differences between treatment groups were observed.

Slit-lamp Biomicroscopy Results

There were no notable differences between treatment groups were observed.

Indirect Opthlmoscopy Results

There were no notable differences between treatment groups were observed.

Spectral domain optical Coherence Tomography

There were no notable differences between treatment groups were observed.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not available.

2.5.8.6. Safety in special populations

Not applicable.

2.5.8.7. Immunological events

Please see the dedicated section in this report for evaluation of immunological events.

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

Not applicable.

2.5.8.9. Discontinuation due to adverse events

Through week 16, 1 (0.3%) subject in the ABP 938 treatment group and 4 (1.4%) subjects in the aflibercept (EU) treatment group discontinued investigational product or discontinued the study due to an adverse event. In the aflibercept (EU) treatment group, 2 (0.7%) subjects discontinued investigational product or study, 1 (0.3%) subject discontinued, and 1 (0.3%) subject discontinued.

Eye Level

Through week 16, 1 (0.3%) subject in the ABP 938 treatment group and 0 (0.0%) subjects in the aflibercept (EU) treatment group discontinued investigational product or discontinued the study due to an ocular adverse event.

Fellow Eye

Through week 16, no ocular adverse events in the fellow eye leading to discontinuation from investigational product or discontinuation from the study were reported. Post week 16, 9 (3.3%) subjects in the ABP 938/ABP 938 treatment group, 3 (2.3%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 5 (3.7%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group discontinued investigational product or discontinued the study due to an adverse event.

There were no differences in percentages between the treatment groups leading to discontinuation of the study drug presented in the tables in the CSR of the applicant. Therefore, no concerns regarding biosimilarity arise.

2.5.8.10. Post marketing experience

Not available.

2.5.9. Discussion on clinical safety

The safety assessment of the aflibercept biosimilar candidate ABP 938 was conducted by taking into account the known safety profile of the reference product Eylea (aflibercept (EU)). This is line with the overall concept of comparable safety evaluation for a similar biological medicinal product and thus acceptable.

The clinical safety assessment of ABP 938 is based on one phase 3 study (Study 20170542), a randomized, active-controlled, double-masked study to compare efficacy and safety of ABP9 938 in comparison with Eylea in patients with neovascular (wet) AMD.

The Safety Analysis Set is defined as all randomly assigned patients who received at least 1 full or partial dose of study drug in Study Period. Patients were analyzed based on the treatment actually received.

Vital signs, ophthalmologic examinations and adverse events were assessed at every visit of the study, and laboratory tests, physical examination and immunogenicity were assessed less frequently, but throughout the study duration of 52 weeks, which is considered appropriate.

The total safety database for ABP 938 in this application consists of 453 patients with various CVDs (421 (wet) AMD)) who were exposed to ABP 938 or aflibercept (EU) at a dose of 2 mg per IVT injection every 4 weeks for 3 doses, and then every 8 weeks from week 16 until week 48. After that, subjects were re-randomized at week 16 in a masked fashion. Subjects initially randomized to ABP 938 continued to receive ABP 938 an subjects initially randomized to aflibercept (EU) were re-randomized in a 1:1 ratio to either continue on aflibercept or transition to ABP 938 by IVT injection every 8 weeks from week 16 until week 48.

The safety profile of Eylea is well established and the safety database of 421 patients treated for up to 52 weeks with ABP 938 is considered sufficient for the general evaluation of safety and immunogenicity of CT-P42 in comparison to the reference product.

The overall number [proportion] of patients who experienced at least 1 TEAE in Study 20170542 was 181 [66.3%], 89 [66.9%] and 81 [59.6%] patients in the ABP 938/ABP 938, the Aflibercept (EU)/ABP 938 and Aflibercept (EU)/Aflibercept (EU) groups.

The number [proportion] of patients who experienced at least 1 ocular TEAE in the study eye was 85 [31.1%], 43 [32.3%] and 37 [27.2%] patients in the APB 398/ABP 938, the Aflibercept (EU)/ABP 938 and Aflibercept (EU)/Aflibercept (EU) groups, respectively. The most frequently reported ocular TEAE in the study eye was conjunctival hemorrhage in the entire study (12 [4.4%] vs 13 [9.8%] and 8 [5.9%] patients, respectively).

The number [proportion] of patients who experienced at least 1 ocular TEAE in the fellow eye was 5 [27.8%], 3 [30.0%] and 1 [33.3%] patients in the ABP 938, the Aflibercept/ABP 938 and Aflibercept/Aflibercept groups, respectively.

There were no significant differences in frequency of ocular adverse events by treatment groups.

Other Serious adverse Events

Through week 16, 15 (2.6%) subjects experienced serious adverse events comprising 6 (2.1%) subjects in the ABP 938 treatment group and 9 (3.1%) subjects in the aflibercept (EU) treatment group. There were no notable differences in the incidence of serious adverse events by preferred term or SOC between the treatment groups through week 16. There were no new safety signals observed or new pattern of serious adverse events reported. No serious ocular adverse events in the study eye through week 16 were reported.

A serious ocular adverse event in the fellow eye through week 16 was reported for 1 subject in the aflibercept (EU) treatment group. The serious ocular adverse event was grade 3 visual impairment.

Post week 16, 47 (8.7%) subjects experienced serious adverse events comprising 22 (8.1%) subjects in the ABP 938/ABP 938 treatment group, 14 (10.5%) subjects in the aflibercept (EU)/ABP 938 treatment group, and 11 (8.1%) subjects in the aflibercept (EU)/aflibercept (EU) treatment group. There were no notable differences in the incidence of serious adverse events by preferred term or SOC between the treatment groups post week 16. There were no new safety signals observed or new patterns of serious adverse events reported.

Post week 16 two subjects in the aflibercept (EU)/aflibercept (EU) treatment group experienced serious ocular adverse events in the study eye which included grade 3 retinal haemorrhage and grade 3 visual acuity reduced. This is in accordance with the approved product information of Eylea. No serious ocular adverse events in the fellow eye post week 16 were reported.

From other serious TEAEs Peripheral artery stenosis (Left common femoral artery stenosis (>50%)) Grade 2 was reported in one subject (ID 54223001001) which was considered related to the study drug. Patient was assigned to Aflibercept-ABP 938 treatment group. The stenosis was of thromboembolic origin and may be related to systemic VEGF inhibition as described in the approved product information of Eylea. The subject had a history of hypertension, myocardial infarction, carotid endarterectomy, bundle branch block, and diabetes mellitus which could be considered as confounding factors in the case assessment. No safety concerns are raised.

Adverse events of interest

The EOIs prespecified for Study 20170542 included endophthalmitis, retinal detachment, increase in IOP, and thromboembolic events. The number of subjects reporting a thromboembolic EOI of cerebrovascular accident was numerically higher post week 16 in the ABP 938/ABP 938 treatment group and the aflibercept (EU)/ABP 938 treatment group (2 [0.7%] subjects and 3 [2.3%] subjects, respectively) compared to the aflibercept (EU)/aflibercept (EU) treatment group (0 [0.0%] subjects). All of these subjects had at least 1 major cardiovascular risk factor. According to the approved product information of Eylea, the arterial thromboembolic events may be related to systemic VEGF inhibition. Thus, the observed events in Study 20170542 are not considered unexpected serious adverse reactions. Overall, the incidence of these events was within the range for incidence of arterial thromboembolic events reported for Eylea (aflibercept). No safety concerns are raised regarding the occurrence of EOIs related to study procedure or study treatment.

Deaths

Six patients died during the study. All causes of deaths were of non-ocular nature and were considered as not related to the treatment. No safety concerns are raised regarding the events leading to death.

Discontinuations

As all events occurred in single subjects and as there were no differences in percentages between the treatment groups leading to discontinuation of the study drug presented in the tables in the CSR of the applicant, these findings are not considered to impact the overall assessment of clinical similarity between ABP 938 and the reference product.

Overall, no clinically important changes in laboratory values were observed post-baseline in the completed comparative clinical study (Study 20170542). Changes in mean values from baseline for haematology parameters, chemistry parameters, urinalysis and vital signs were comparable between the treatment groups.

Immunogenicity

Immunological events are discussed in the section on clinical pharmacology.
The incidence of TEAE related to clinical chemistry and haematology laboratory parameters was overall low and comparable between groups. The same holds true for vital signs and related parameters.

PFS Clinical Usability Study – Study 20210034

In Study 20210034, ocular adverse events in the study eye were reported in 3/32 (9.4%) subjects in the ABP 938 PFS treatment group and 0/16 subjects in the aflibercept (US) PFS treatment group. Ocular adverse events reported in the 3 subjects in the ABP 938 PFS treatment group included grade 1 eye pain, grade 1 halo vision, grade 1 visual impairment, and grade 1 vitreous detachment. Non-ocular adverse events were reported in 4/32 (12.5%) subjects in the ABP 938 PFS treatment group and 2/16 (12.5%) subjects in the aflibercept (US) PFS treatment group. All adverse events were CTCAE grade 1 or 2 in severity. There were no adverse events leading to study discontinuation. There were no serious adverse events. Even though the number of ocular adverse events reported in the ABP 938 PFS treatment group was higher compared to the aflibercept (US) PFS treatment group, the number of these events was low and fell within the expected range for incidence and severity as described for Eylea. Therefore, no safety concerns are raised.

2.5.10. Conclusions on the clinical safety

Overall, the safety profile established in the ABP 938 clinical development program is consistent with the known safety profile of Eylea. Duration and number of subjects in performed clinical study is generally considered appropriate. No safety concerns (regarding assessed AEs, clinically meaningful differences in laboratory findings and immunogenicity) were seen compared to reference medicinal product.

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 epithelial 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 34: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Endophthalmitis (likely infectious origin)	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing reports suspicious for endophthalmitis and intraocular inflammation • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Intraocular inflammation	Routine risk minimization measures: • SmPC Sections 4.2, 4.3, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing reports suspicious for endophthalmitis and intraocular inflammation • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Transient intraocular pressure increase	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, 4.8, and 4.9 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific questionnaire to be used for any postmarketing report regarding intraocular pressure increase following the use of the PAVBLU pre-filled syringe • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Retinal pigment epithelial tears	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Cataract (especially of traumatic origin)	Routine risk minimization measures: • SmPC Sections 4.2, 4.4, and 4.8 • PL Sections 2, 3, and 4 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Medication errors	Routine risk minimization measures: • SmPC Section 4.2, 4.9, and 6.6 • PL Sections 1 and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise physicians' awareness on medication error (prescriber guide and video; patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks (continued)		
Off-label use and misuse	Routine risk minimization measures: • SmPC Sections 4.1, 4.3, 4.4, and 4.6 • PL Sections 1, 2, and 3 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients' and physicians' awareness on off-label use (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Embryo-fetotoxicity	Routine risk minimization measures: • SmPC Sections 4.4, 4.6, and 5.3 • PL Section 2 • Medicinal product subject to restricted medical prescription. PAVBLU must only be administered by a qualified physician experienced in administering IVT injections. Additional risk minimization measures: • Educational program: Beyond routine minimization 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 childbearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and patient guide "Your guide to PAVBLU," and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • For traceability purposes, brand name and batch number of the product received by the patient will be recorded wherever possible. Additional pharmacovigilance activities: • None
Missing Information		
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, Skojoy (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

The proposed indications for Skojoy are based on those approved for Eylea (aflibercept). Eylea (aflibercept) is currently approved in the EU to treat patients with the following conditions:

- neovascular (wet) age-related macular degeneration (AMD)
- visual impairment due to macular edema secondary to retinal vein occlusion (RVO) (branch RVO or central RVO)
- visual impairment due to diabetic macular edema (DME)
- visual impairment due to myopic choroidal neovascularization (CNV)

- retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or aggressive posterior-ROP disease

Amgen is seeking approval of Skojoy as a biosimilar product to Eylea (aflibercept) for the neovascular (wet) AMD, visual impairment due to macular edema secondary to RVO (branch RVO or central RVO), and visual impairment due to myopic CNV indications. The DME indication is not sought for Skojoy.

Amgen did not develop a paediatric dosing device to be used in combination with the prefilled syringe (PFS) for intravitreal (IVT) administration to preterm infants; thus, the ROP indication is not currently being sought.

Quality aspects

In general, a very comprehensive and sound biosimilarity assessment has been conducted. Since both, EU-sourced reference product and US-sourced comparator product, have been used in the comparative clinical trials, a scientific bridge between EU-sourced reference product and US-sourced comparator product, based on 3 pairwise analytical comparisons (Biosimilar vs EU RMP, Biosimilar vs US comparator, and EU RefMP vs US comparator) has been established. ABP 938 has been developed as vial and as pre-filled syringe presentation similar to the reference product presentations. The main parts of the biosimilarity evaluation have been conducted with the vial presentation whereas for the pre-filled syringe presentation a targeted analytical similarity assessment focusing on the drug product specific attributes related to product strength (i.e., protein concentration and volume) was conducted. A broad panel of orthogonal standard and sophisticated state-of-the-art methods has been applied for biosimilarity evaluation to address primary structure, product-related substances and impurities, higher order structure, general properties, biological activity, degradation studies and the targeted similarity assessment for the pre-filled syringe. Methods were fully qualified/validated, and the reference product which has a different formulation was qualified as a sample type (or inferred with appropriate justification) in each method.

Non-clinical aspects

A thorough *in vitro* biosimilar comparability exercise, including functional similarity between ABP 938 and EU-/US-aflibercept, was conducted and submitted in the Quality part of the dossier of this MAA.

Clinical aspects

The clinical evidence supporting the similarity of ABP 938 to Eylea (aflibercept) derives from a completed randomized, double-masked, active-controlled comparative clinical study in subjects with neovascular (wet) AMD (Study 20170542).

A clinical Phase I PK study was not conducted since it was considered not meaningful to determine the biosimilarity based on the low level of aflibercept in serum following IVT administration. Instead, comparative PK evaluation was included as a secondary objective in the phase 3 study.

3.2. Results supporting biosimilarity

Quality

In principle, the provided results support the biosimilarity claim. For most of the quality attributes similarity was demonstrated, observed differences in certain quality attributes are minor and could be sufficiently justified to have no impact on the clinical performance of the product.

Clinical

In Study 20170542, the primary endpoint “change from baseline in BCVA using the ETDRS chart at Week 8” is considered to be a sensitive endpoint to detect differences between the biosimilar candidate and the reference product and thus appropriate for this comparative clinical evaluation. Equivalence between the main treatment groups was to be declared if the 95% CI of the difference was entirely contained within the pre-defined equivalence margin of (-3.9, 3.9) letters.

In the FAS, the observed LS mean change for BCVA at week 8 was similar between the ABP 938 and Eylea groups (6.4 letters and 6.5 letters respectively). The point estimate of the least squares mean difference between the treatment groups was 0.1 with a 2-sided 95% CI of (-1.3, 1.5), which was entirely within the prespecified equivalence margin.

In the PP set, the observed LS mean change for BCVA at week 8 was similar between the ABP 938 and Eylea groups (6.4 letters and 6.7 letters respectively). The 95% CI of (-1.6, 1.4) for the treatment difference was entirely within the prespecified equivalence margin.

Sensitivity analyses were performed to assess the robustness of the primary efficacy analysis result. The ANCOVA analysis was repeated using the FAS based on last observation carried forward imputation. A mixed model repeated-measures analysis for day 1 through week 8 based on the FAS was performed as well as an analysis using the FAS was done to explore the impact of other baseline covariates on BCVA change from baseline to week 8 in addition to the stratification factor of region and baseline BCVA value. In addition, tipping point analyses were performed using the FAS to explore the sensitivity of the primary analysis results to violations in assumptions about missing data. All sensitivity analyses support the findings of the primary efficacy analysis.

Overall, the primary analysis supports biosimilarity between ABP 938 and Eylea.

The secondary analyses (mean changes in BCVA over the study duration, proportion of subjects who maintained vision at week 52, proportion of patients who gained ≥10 letters at week 8, proportion of subjects who gained ≥15 letters at week 52, change from baseline in CNV area and central subfield thickness were also similar between treatments.

Overall, the safety and immunogenicity profile established in the ABP 938 clinical development programme is consistent with the known safety profile of Eylea. There were no significant differences in frequency of either ADA formation, adverse events, drug related adverse events, deaths and discontinuation by treatment groups.

3.3. Uncertainties and limitations about biosimilarity

Quality

No uncertainties about biosimilarity remain.

Clinical

As agreed in the scientific advice procedures, no formal bioequivalence testing was conducted for PK parameters considering the low and variable systemic concentrations of aflibercept after IVT administration. Instead, supportive PK analyses were conducted in a subset of patients enrolled in the Phase 3 study to explore whether the systemic concentrations of IVT administered ABP 938 and Eylea were within the same range.

The applicant did not evaluate formal PK parameters such as Cmax or AUC. Instead, systemic free drug concentration was evaluated at baseline and at one single time point after the first dose and at one time point after the week 8 dose.

The median post-dose free drug concentrations at week 8 were 35.60 ng/mL for ABP 938 and 74.10 ng/mL for Eylea; geometric mean concentrations for ABP 938 and Eylea were 47.37 ng/mL and 67.44 ng/mL, respectively. The observed differences in free drug concentration between groups could result from differences in Tmax, which can only be controlled when PK samples are taken at multiple timepoints after administration. Apart from not establishing Cmax, a wide time window was allowed for sampling, which further hampers a proper comparison of results between groups.

It is not known if there was any subject with positive ADA result in the pharmacokinetic data set. Due to the limited number of ADA positive patients, the impact of immunogenicity on pharmacokinetics as well as clinical efficacy or safety cannot be evaluated.

3.4. Discussion on biosimilarity

From a qualitative perspective, the results derived from a robust and well-designed biosimilarity exercise principally support the similarity claim. In addition, comparability of US sourced comparator with EU sourced reference product could be demonstrated. However, a few minor concerns leave some uncertainties open and need to be solved before a final agreement on demonstrated biosimilarity can be given.

From a clinical perspective, only sparse PK data were provided and no formal PK parameters were established to compare systemic aflibercept concentrations between treatments. Nevertheless, the results point at low systemic exposure of unbound (free) drug concentrations following IVT administration of ABP 938 or aflibercept (EU) in patients with (wet) AMD. Measured drug levels are below the concentration required for a pharmacologically relevant reduction in endogenous systemic VEGF. Thus, based on the results of median free drug concentration an unwanted impact on safety caused by the biosimilar can be ruled out.

The pivotal clinical study was adequately designed to demonstrate clinical equivalence between ABP 938 and the reference product Eylea, both in terms of efficacy and safety. The selected study population, consisting of patients with wet AMD, as well as primary and secondary efficacy endpoints are in principle deemed appropriate for this biosimilarity exercise. However, uncertainty pertains to the sensitivity of the study population based on the altered eligibility criteria and to concomitant medication.

The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined equivalence margin of +/- 3.9 letters. Biosimilarity in terms of efficacy was further confirmed by secondary endpoints.

Incidences of adverse events were overall comparable between the two treatments and the safety risks identified in the ABP 938 clinical development programme are overall consistent with the known safety profile of Eylea.

3.5. Extrapolation of safety and efficacy

The applicant claims the same indications as approved for the respective presentation of the reference product, Eylea 40 mg/mL solution for injection (nAMD, branch RVO or central RVO, myopic CNV in adults) except for the DME and ROP indication. The applicant provided a comprehensive scientific discussion for extrapolation across indications, taking into account aflibercept's mechanism of action, PK and PD, toxicities, immunogenicity and efficacy in each condition of use. This information is briefly summarised below.

The mechanism of action in each condition of use is a key component of the scientific justification for extrapolation. Aflibercept acts by binding VEGF-A and PlGF and thereby inhibiting the binding and

activation of VEGFR-1 and VEGFR-2. Eylea (aflibercept) prescribing information and published scientific literature support the conclusion that neovascular (wet) AMD, macular edema secondary to RVO (branch RVO or central RVO), DME, and myopic CNV share common molecular mechanisms of VEGF-A and PlGF-mediated pathologies, although the exact contribution of these mechanisms across indications is uncertain.

ABP 938 has been shown to be similar to aflibercept (US and EU) in comprehensive analytical and functional similarity assessments. These data demonstrate that the biological activity and potency of ABP 938 have a high degree of similarity to aflibercept reference product and provide additional evidence that the mechanism of action of the two products, the binding of VEGF-A and PlGF and thereby inhibiting the binding and activation of VEGFR-1 and VEGFR-2, is the same. Thus, it has been demonstrated that ABP 938 and Eylea (aflibercept) are similar in their ability to induce these activities.

Eylea (aflibercept) prescribing information provides detailed information regarding PK and PD profiles of Eylea (aflibercept) across the approved indications. Across the approved adult indications for which licensure is sought, low systemic exposure of unbound concentrations of aflibercept was observed following IVT administration of Eylea (aflibercept). With regards to the PD effects, decreases in retinal thickness were observed in patients treated with Eylea (aflibercept) across the approved indications, and decreases in CNV lesion size were observed in patients with neovascular (wet) AMD and patients with myopic CNV treated with Eylea (aflibercept).

Results from the PK substudy in Study 20170542 confirmed low systemic exposure of unbound (free) drug concentrations following IVT administration of ABP 938 or aflibercept (EU) in subjects with neovascular (wet) AMD. Results in Study 20170542 also support a demonstration of PD similarity of ABP 938 to Eylea (aflibercept) based on the anatomic endpoints of change from baseline in CST and CNV area size over the study duration.

Eylea (aflibercept) prescribing information provides detailed information regarding the safety profile of Eylea (aflibercept) across the approved indications. The safety profile of Eylea (aflibercept) is generally consistent across the adult indications, for which licensure is sought, and the corresponding dosing regimens.

In the comparative clinical study in subjects with neovascular (wet) AMD (Study 20170542) and in the PFS clinical usability study in subjects with various CVDs (Study 20210034), the safety profile of ABP 938 was found to be similar to that of Eylea (aflibercept). The size of the safety database from the clinical study in the neovascular (wet) AMD therapeutic indication is considered adequate to inform the toxicities anticipated with ABP 938 for all indications of use. Based on publicly available scientific data supporting a consistent and comparable safety profile of Eylea (aflibercept) across the approved adult indications for which licensure is sought, as well as the similar safety profiles for ABP 938 and Eylea (aflibercept) as demonstrated in subjects with neovascular (wet) AMD and subjects with various CVDs, it is expected that the safety profile of ABP 938 will be similar to that of Eylea (aflibercept) and support the scientific justification for extrapolation across the conditions of use for which licensure is sought.

Further, results from Study 20170542 support a demonstration of similar immunogenicity of ABP 938 to Eylea (aflibercept). Based on publicly available scientific data supporting similar antibody responses across the adult indications, as well as the immunogenicity data from the ABP 938 comparative clinical study in subjects with neovascular (wet) AMD, the immunogenicity profile of ABP 938 supports the scientific justification for extrapolation across the conditions of use for which licensure is sought.

With respect to efficacy, improvements in visual acuity were generally observed patients with neovascular (wet) AMD, macular edema secondary to RVO (branch RVO or central RVO), and DME, and myopic CNV following IVT administration of Eylea (aflibercept).

In the comparative clinical study in subjects with neovascular (wet) AMD (Study 20170542), similarity in clinical efficacy was established between ABP 938 and aflibercept (EU) based on the primary efficacy endpoint of change from baseline in BCVA at week 8. Based on publicly available scientific data supporting an improvement of visual acuity in patients treated with Eylea (aflibercept) across the approved adult indications for which licensure is sought, as well as the similar efficacy profiles for ABP 938 and Eylea (aflibercept) as demonstrated in subjects with neovascular (wet) AMD, it is expected that the efficacy profile of ABP 938 will be similar to that of Eylea (aflibercept) and support the scientific justification for extrapolation across the conditions of use for which licensure is sought.

Taken together, the justification presented by the applicant to allow extrapolation from wet AMD to all approved indications of Eylea in adults that are sought in this application is considered adequate, provided that all outstanding issues regarding biosimilarity are resolved.

3.6. Additional considerations

None.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Skojoy 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 Skojoy 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 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 agrees to provide EU educational material for Skojoy. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Skojoy is marketed, ophthalmological clinics where Skojoy is expected to be used are provided with a physician information pack containing the following elements:

- Physician information guide
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

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 and the pre-filled syringe are for single use only
- The need to expel excess volume of the syringe before injecting Skojoy 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 Skojoy

The patient information pack of the educational material includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet
- Who should be treated with Pavblu
- How to prepare for Pavblu treatment
- What are the steps following treatment with Pavblu
- 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 Pavblu.