19 September 2024
EMA/466892/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Opuviz

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006056/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	AE of special interest
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AS	Active substance
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thromboembolic event
BCVA	Best corrected visual acuity
BLQ	Below the limit of quantitation
BM	Bruch's membrane
BMI	Body mass index
BP	Blood pressure
CHO	Chinese hamster ovary
CI	Confidence interval
C_{max}	Maximum serum concentration
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal neovascularisation
COVID-19	Coronavirus Disease 2019
CQA	Critical quality attribute
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical study report
CST	Central subfield thickness
C_{trough}	Trough serum concentration
CV%	Coefficient variation
DA	Disc area
DDE	Drug Dictionary Enhanced
DME	Diabetic macular oedema
DNA	Deoxyribonucleic acid
DSMB	Data and safety monitoring board
eCRF	Electronic case report form
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of study
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus photography
FP	Finished product
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
icIEF	imaged capillary isoelectric focusing
IEC	Independent Ethics Committee
ILM	Internal limiting membrane
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IPC	In-process control
IPG	in-process gateway
IQRMP	Integrated Quality Risk Management Plan
IRB	Institutional Review Board
IVT	Intravitreal
IWRS	Interactive Web Response System
KST	Korea standard time
LC-ESI-MS	liquid chromatography-electrospray ionisation-mass spectrometry
Lsmean	Least Square mean
MAR	Missing-at-Random
MCB	Master cell bank
MCMC	Markov-Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MI	Multiple imputation
MNAR	Missing-not-at-Random
NAb	Neutralising antibody
NCS	Not clinically significant
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	Optical coherence tomography
PD	Protocol deviation
PDT	Photodynamic therapy
PlGF	Placental growth factor
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Process parameter
PPQ	process performance qualification
PPS	Per-Protocol Set
PT	Preferred term
QCV	Quality Control Visit
QOL	Quality of life
QTL	Quality tolerance limit

RAN	Randomised Set
RPE	Retinal pigment epithelium
RSI	Reference safety information
RVO	Retinal vein occlusion
SAE	Serious AE
SAF1	Safety Set 1
SAF2	Safety Set 2
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SI	International System of Units
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System organ class
SOP	Standard operating procedure
TEAE	Treatment-emergent AE
TRT	Total retinal thickness
TTT	Transpupillary thermotherapy
US	United States
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor A
VEGF-B	Vascular endothelial growth factor B
YAG	Yttrium Aluminium Garnet
WCB	Working cell bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Samsung Bioepis NL B.V. submitted on 6 November 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Opuviz, 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 16 December 2021.

The applicant applied for the following indication:

Opuviz is indicated for adults for the 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 diabetic macular oedema (DME)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV)*

1.2. Legal basis, dossier content

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.

The chosen reference product is:

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

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

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

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

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

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/12/797/001-002
- Bioavailability study number(s): MYL-1701P-3001

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Scientific advice

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

Date	**Reference**	**SAWP co-ordinators**
14 September 2017	EMA/CHMP/SAWP/575108/2017	*Dr. Kerstin Wickstrom and Prof. Andrea Laslop*
26 April 2019	EMA/CHMP/SAWP/227002/2019	*Dr. Kerstin Wickstrom and Prof. Andrea Laslop*

The Scientific advice pertained to the following aspects:

During the development of SB15, the Applicant sought SA from the EMA Scientific Advice Working Party (SAWP):

- In Sep 2017, an SA was received on the physicochemical, pharmaceutical and biological development, non-clinical and clinical development of SB15 [EMA/CHMP/SAWP/575108/2017, Sep 14, 2017].
- In Apr 2019, a follow-up SA was received on the proposed revised study duration of 28 weeks, tightened equivalence margin, and the approach of using a sole US-sourced reference product [EMA/CHMP/SAWP/227002/2019, Apr 26, 2019].

Scientific advice EMA/CHMP/SAWP/575108/2017 was given to the Applicant in September 2017. In the **quality section** preliminary characterisation studies to evaluate analytical similarity between SB15, EU Eylea, and US Eylea as well as the analytical similarity plan was presented: the Applicant took most of the advice given for the biosimilar development into account.

From a **clinical point of view** the following key points were addressed in listed SAs:

Health authority/date	Type of interaction	Key points regarding clinical development
EMA/ 14/SEP/2017	Scientific advice letter	• Omission of a phase I PK study • nAMD patients as study population for phase III clinical study • PEP: mean change from baseline in central subfluid thickness (CST) at Week 4 in neovascular AMD subjects • Sample size • Extrapolation of indications
EMA/ 26/APR/2019	Follow-up scientific advice letter	• Reduction of study duration to 28 weeks • Tightening of the equivalence margin to [-40 µm, 40 µm] or the mean difference of change in the central subfield thickness (CST)

In the received Scientific Advice [EMA/CHMP/SAWP/575108/2017, 14/SEP/2017] the CHMP agreed that wet AMD patients could represent a sensitive population for the biosimilarity objective, because studies with the originator showed that the treatment effect of aflibercept was largest in this population. It was advised to exclude patients with any previous systemic anti-VEGF treatment, as an impact on safety and especially immunogenicity cannot be ruled out. This was followed by the Applicant. Furthermore, immunogenicity sampling was planned for collection timepoints pre-dose at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48. Also, at any time during the visit at Week 1 and End of Study visit. This was followed with exception to timepoints at Week 1, Week 16 and Week 48. In addition, the Eylea SmPC states that no evidence of anti-drug antibodies impact on pharmacokinetics, efficacy or safety was observed. Therefore, the sampling scheme is still deemed acceptable. Furthermore, it was advised that signs of intraocular inflammation should be monitored as they may indicate an immune reaction. It was further recommended to perform subgroup analyses for ADA positive vs. ADA negative patients and to discuss any impact on efficacy and safety. This applies also to the safety profile in general, as the majority of adverse events following administration of Eylea is related to intravitreal injection procedure and is therefore comparable across indications. Overall, the advice given by the CHMP was followed.

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 56 weeks, which is considered appropriate.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Christian Gartner Co-Rapporteur: Petr Vrbata

CHMP Peer reviewer(s): N/A

The application was received by the EMA on	6 November 2023
The procedure started on	23 November 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	5 February 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	26 February 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 February 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 March 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 April 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	03 June 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 June 2024
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 September 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Opuviz on	19 September 2024

2. Scientific discussion

2.1. About the product

Opuviz (also referred to as SB15) has been developed as a biosimilar to the reference product Eylea (INN: aflibercept; EMEA/H/C/002392).

Aflibercept is in the pharmaceutical group 'ophthalmologicals / antineovascularisation agents' (ATC code: S01LA05). It 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 Opuviz are: in adults for the 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 diabetic macular oedema (DME),
- 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 - is not claimed.

2.2. Type of application and aspects on development

Similarity exercises have been performed in a stepwise approach to demonstrate the similarity between SB15 and the reference product, EU Eylea. The assessment of similarity exercises started with a comparison of the structural characteristics, physicochemical properties, and biological activities between SB15 and the reference product, which served as the foundation for biosimilar development program. Furthermore, non-clinical and clinical studies were conducted to detect any structural, functional, and clinically meaningful differences. Based on the similarity of SB15 to EU Eylea, SB15 to US Eylea, and EU Eylea to US Eylea from comparative structural, physicochemical and biological studies, and non-clinical studies, a scientific bridge between SB15, EU Eylea and US Eylea was established, which justify the relevance of the clinical data generated using US Eylea as the comparator product in the pivotal, confirmatory, clinical Phase III study (SB15-3001).

2.3. Quality aspects

2.3.1. Introduction

The finished product Opuviz (referred also as SB15) is presented as a colourless to pale yellow, sterile and preservative free solution and presented as a single-use vial containing 40 mg/mL of aflibercept for intravitreal injection.

Other ingredients are: sodium dihydrogen phosphate dihydrate, di-sodium hydrogen phosphate dihydrate, sucrose, polysorbate 20 and water for injections.

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

2.3.2. Active substance

2.3.2.1. General information

The INN name for active substance (AS) is aflibercept. The active substance aflibercept is a recombinant fusion protein consisting of human vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human IgG1 and is produced in Chinese hamster ovary (CHO) cells. The fusion protein is composed of two identical polypeptide chains (432 amino acid residues each) linked by a disulfide bond at hinge region of Fc region with a total molecular weight of approximately 97 kDa (deglycosylated). Its molecular formula without the N-glycan moiety is $C_{4330}H_{6812}N_{1168}O_{1306}S_{32}$. Each aflibercept VEGFR region contains four N-glycosylated sites and each aflibercept Fc region contains one N-glycosylated site. The total molecular weight of SB15 with the N-glycan moiety is approximately 115 kDa.

Aflibercept is a clear, colourless to pale yellow solution The apparent Isoelectric Point of the main isoform determined by imaged capillary isoelectric focusing (icIEF) is approximately 8.6. The theoretically calculated extinction coefficient (EC) of the protein is 1.152 mL $mg^{-1}cm^{-1}$. The experimentally established EC of SB15 clinical batch is 1.034 $mL{\cdot}mg^{-1}{\cdot}cm^{-1}$.

Aflibercept interferes with the biological actions of VEGF-A by tightly binding to it and preventing VEGF-A from interacting with its receptors. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration. Aflibercept can also bind to other VEGFR-1 ligands, notably PlGF. Based on this mechanism of action, the biological activity (potency) of AS was determined using cell-based assay.

2.3.2.2. Manufacture, characterisation and process controls

Details of manufacturers of the AS, master and working cell bank (MCB & WCB, name, address and responsibilities for all manufacturing sites were listed and sufficient information was provided.

The AS is manufactured and QC tested at Samsung Biologics Co., Ltd., 300, Songdo bio-daero, Yeonsu-gu, Incheon, 21987, Republic of Korea. All sites are covered by valid GMP certificates.

Description of manufacturing process and process controls

The active substance (AS) is expressed in a CHO cell line and produced in a fed-batch process. Definitions of batch and scale were provided; traceability of AS batches is ensured by a unique batch number.

Cell culture process is initiated with the thaw of cells from one WCB. The cells are concentrated by centrifugation. The centrifugate from WCB thaw is resuspended by growth medium in a shake flask. Inoculum expansion includes serial sub-cultivations in shake flasks. The following seed bioreactor steps comprise expansion of cells in steel use stainless (SUS) bioreactors. Upon transfer into the US bioreactor, cells are finally expanded and maintained under controlled conditions; nutrient feed media, glucose solution, and antifoam are

added. The culture supernatant is harvested by continuous centrifugation followed by depth filtration and subsequent 0.2 µm filtration.

The AS is purified from the clarified harvest by a combination of column chromatography steps and intermediate depth filtration, and ultrafiltration/diafiltration (UF/DF). Two orthogonal virus clearance steps, i.e. low pH treatment and filtration through a virus reduction filter, are integrated into the purification process.

The virus filtration pool is concentrated and conditioned by UF/DF (tangential flow filtration) into the final formulation buffer without polysorbate 20 (PS20). In a subsequent formulation step, 20X formulation solution is added to achieve a final SB15 formulation. The bulk active substance after formulation is filtered and dispensed into bottles within the target range of weight. The integrity of the filters pre filtration is checked. The AS containing bottles are then stored.

The description of the manufacturing process steps in the dossier is accompanied by flow charts and tables listing process and performance parameters with their classification. Exemplary chromatograms of the four chromatography steps have been presented for one PPQ batch. Regarding classification of the process parameters and the IPCs and their acceptable ranges/acceptance criteria please refer to sections below.

Chromatography resins are re-used for multiple cycles (see discussion under S.2.5 process validation).

Values for hold times and resin lifetimes (see discussion below) were included in section 3.2.S.2.4, which is acceptable. Hold times for intermediates are included in this section as CPPs. The acceptance criteria and the actual values for the maximum hold times are mentioned in section 3.2.S.2.4 and information on the used container closure system is included in section 3.2.S.6., which is acceptable.

Control of materials

Tabulated overviews of compendial and non-compendial materials used in the manufacturing process for cell culture, purification, and formulation were presented. Raw materials used, are briefly listed together with their quality standard (in-house specification, compliant with Ph. Eur.). The in-house specification for the non-compendial materials was provided. The filters, resins and membranes were listed without detailed name, type and manufacturer and are verified against the manufacturer's CoA, copies of which have been submitted. For the non-compendial media used in the cell culture process, testing for endotoxin and bioburden is foreseen. For the remaining non-compendial raw materials used in the cell culture process (sodium hydroxide, hydrochloric acid and antifoam) information on microbial control has been provided. In addition, for the cell culture media information on the qualitative composition and on agreements with suppliers to notify the MAH in case of changes to the medium has been provided upon request. The excipients, i.e. sodium phosphate, sucrose, polysorbate 20, and water for injections (active substance is fully formulated) comply with Ph. Eur.. Materials of biological origin used during the drug substance manufacturing process are listed as well. No materials of animal origin are used for MCB, WCB and AS and FP manufacturing.

The source, history and generation of the cell line has been appropriately described: The host cell line is Chinese hamster ovary cell line. The DNA fragment coding of SB15 was chemically synthesized based on the reference amino acid sequence of Eylea. The expression plasmid vectors were prepared and introduced into the host cells by transfection. The production cell line was generated by stable pool selection and single clone selection in chemically defined media.

Establishment and characterisation of a two-tiered cell bank system has been described in accordance with the ICH Q5D. Appropriate testing has been done on cell banks in line with ICH Q5A. Testing of the MCB included identify, microbiological tests (sterility, mycoplasma and bacteriostasis/fungistasis), genotypic tests (gDNA and cDNA sequencing of the product gene) and virus safety tests. Testing was performed in line with the

requirements of ICH Q5A. Genetic stability testing was performed the results show they met the acceptance criteria.

Control of critical steps and intermediates

The overall control strategy was established in accordance with ICH Q11 using an enhanced development approach. The relevant critical quality attributes have been determined using risk assessment tools. The methodology as well as the proposed classification of quality attributes in critical and non-critical attributes can be agreed. The control of the AS manufacturing process has been described. The process controls are divided into process parameters (inputs) and performance parameters (outputs). Key and critical process parameters as well as in-process gateways (IPG), critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs) have been defined. For each individual manufacturing step, process and performance parameters with their respective action ranges and/or in-process specifications are outlined. The in-process controls and their acceptance criteria/action limits are considered adequate and sufficiently described. Upon request, additional information has been provided on the specified targets for nutrient and glucose feed, analytical methods for in-process test, definition of intermediates and specification for routine testing of unprocessed bulk (UPB).

Hold and process times were included in the tables listing the process parameters for each manufacturing step; all hold times are sufficiently justified.

The AS container closure system (CCS), is a single-use bottle. A brief description of the container closure components as well as a representative technical drawing of the bottle and cap was provided. The specifications for the container closure components were also provided in the dossier.

An extractables study for the CCS has been conducted in order to determine the extractable amounts of chemical compounds which may migrate from the container into model solvents of interest. The results of the extractable study indicate that the amount of extractables was low enough to conclude that the extractables pose a very low toxicological risk to the final product. Thus, the Applicant`s conclusion that a leachable study can be omitted is agreed. Based on the extractables study results and the AS stability data presented, the CCS is suitable for the storage of the active substance.

Finally, a risk assessment on potential leachable compounds from single-use materials used during AS purification process has been conducted. The risk assessment did not identify any high-risk component which would require a process-specific leachable risk assessment.

Process validation

Process validation included a number of studies which investigated a) process performance qualification (PPQ) of both the cell culture and the purification process, b) impurity clearance to show that the intended purification process is able to reduce the impurities to acceptable levels in accordance with the pre-determined acceptance criteria, c) hold times for process intermediates, d) resin lifetime to demonstrate that the chromatography column resins are capable of maintaining acceptable performance characteristics over extensive cycling, e) shipping qualification and f) reprocessing for the virus filtration and AS final filtration to demonstrate that reprocessing has no impact on product quality.

A traditional approach was chosen to verify process performance at commercial scale. Prospective process verification encompassed manufacture of four consecutive process performance qualification (PPQ) batches at scale at the intended commercial manufacturing site Samsung Biologics (SBL) Plant 1 and according to the intended commercial process, covering all three cell culture trains. Overall, the validation criteria are acceptable and a summary on the performed PPQ including the process and performance parameters per manufacturing

step has been provided. Deviations were sufficiently described, their impact has been adequately evaluated/justified and preventive actions have been sufficiently described. All other process and performance parameters met their action ranges and in-process specifications and all PPQ batches met the drug substance specifications applicable at the time of validation and complied with the proposed commercial active substance specifications. Several limits have been changed post PPQ, which has been adequately justified. In summary, the presented process verification data demonstrate that the intended commercial manufacturing process performs consistently and delivers drug substance complying with the release specifications.

Impurity clearance was validated by using direct measurements of the impurities in process intermediates for the PPQ batches, or by using scale-down spiking models.

Physicochemical hold time studies on the different AS manufacturing steps have been done at-scale. No significant trend in the quality attributes has been observed over time. The intermediate hold times for commercial manufacturing have been established based on the validated hold times. The results from these studies demonstrate appropriate microbial control over time. Action ranges of hold times for each process intermediates held in single-use disposable bags were revised and set.

The resin lifetime study was performed at laboratory scale based on scale-down models. Scale-down models for process characterisation studies and resin lifetime studies are adequately described and validated. Based on the results, the presented data show consistent performance of the resins and would support the proposed target resin lifetimes. According to the Applicant, no carry-over was observed in the respective mock runs without sample loading and respective chromatogram overlays and tested protein concentrations have been provided.

In addition to the small-scale resin life cycle studies, the Applicant evaluates the lifetime of the resins at manufacturing scale. The protocols for evaluation of the resin lifetime at manufacturing scale have been submitted.

Shipping qualification studies in order to validate the shipping system has been performed to assure the quality of the product. Shipping qualification studies are performed in consideration of worst-case shipping conditions. The results from shipping qualification studies show shipping system with the product can maintain product temperature while maintaining product integrity during the transportation.

Validation studies for reprocessing of virus filtration (VF) were performed. Validation studies for reprocessing of the AS final filtration step were also performed. The results after reprocessing were comparable to those without reprocessing.
Reprocessing of virus filtration and final filtration has been validated. Sufficient information on the planned concurrent validation at manufacturing scale, including acceptance criteria, have been provided.

Overall the AS manufacturing process have been validated by a number of studies. It has been demonstrated that the process is capable of consistently producing active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

The development history of the AS manufacturing process has been adequately summarised including a description of the pilot-scale, clinical, PPQ and commercial scale process. Differences between pilot and clinical batches manufacturing have been adequately described. The manufacturing process and control parameters for clinical campaign were developed based on the initial process development studies (including pilot manufacturing experience). CQAs were identified based on quality attribute risk assessments which categorised the individual product quality attributes as either critical or non-critical. Generally, the described methodology

for quality attribute risk assessment is considered appropriate. Following the clinical AS production, process characterisation (PC) studies, based on the process risk assessment, were carried out for each unit operation of the AS process, employing either univariate and multivariate design of experiments (DOE) studies and using qualified scale-down models. In principle, qualification of scale-down models for the various manufacturing steps is acceptable. The design of the process characterisation studies is presented satisfactorily and appears acceptable.

Based on the outcome of the PC studies the proven acceptable ranges as well as the classification of the process parameters (PPs) were defined. Another risk assessment was performed after PC studies to establish risk mitigation and the control strategy for the PPQ process. The risk assessment appears reasonable. Minor process changes were introduced into the process prior to PPQ manufacturing process, and these changes have been adequately described and addressed.

Finally, the Applicant introduced some changes post-PPQ activities: several modifications were made to the process control strategy and process parameter classification. These changes were driven by additional manufacturing and process development. Description and justification for these changes and modifications after PPQ manufacturing was found to be adequate**.**

Two comparability studies between PPQ and clinical as well as between pilot and clinical batches were conducted using orthogonal state-of-the-art analytical procedures. Comparability assessment was performed based on the quality attributes for release test items and extended characterisation studies. The extended characterisation included physicochemical and biological assays. In addition, comparative stability studies were performed to evaluate the degradation patterns among AS batches (pilot, clinical, and PPQ active substance batches). The main differences between clinical and commercial processes were adequately described in the comparability study. Based on the provided data, and additional information (on used batches and comparability ranges), as submitted upon request, comparability between AS derived from the different process version could be demonstrated.

Characterisation

Investigation of primary structure and post translational modifications included molecular weight of deglycosylated and reduced aflibercept determined by mass spectrometry, amino acid sequence determination by liquid chromatography electrospray ionisation and mass spectrometry (LC-ESI-MS) covering 100% of the sequence. The Applicant presented the N-glycan profile of SB15 analysed by LC-ESI-MS after procainamide labeling and the quantitative amount of two groups of N-glycans by HILIC-UPLC, charged glycans and high mannose. The quantity of each charged glycan was provided. The predominant charged glycans for SB15 were identified. In addition, the specific neutral N-glycans were individually quantified and the most abundant neutral N-glycans were identified. In addition, he predominant neutral N-glycan for SB15 are also confirmed. Identity of aflibercept was assessed by peptide mapping using LC-ESI-MS. N- and C-terminal sequencing with LC-ESI-MS confirmed the presence of only one N- and one main C-terminal form (Lys-removed form).

N-glycosylation was studied by determination of the N-linked glycosylation sites using LC-ESI-MS, determination and identification of the glycan species and measurement of the relative contents of the identified N-glycans using hydrophilic interaction-ultra-performance liquid chromatography (HILIC-UPLC). The contents of total sialic acid (TSA) including N-acetylneuraminic acid (NANA) and N-glycolylneuraminic acid (NGNA) of Aflibercept were determined using high-performance liquid chromatography.

Higher order structures have been elucidated by a panel of methods including LC-ESI-MS for intra- and inter-chain disulfide bonds, free thiol (sulfhydryl) group quantification, circular dichroism (CD) spectroscopy for secondary and tertiary structures, intrinsic tryptophan fluorescence (ITF) and extrinsic fluorescence

spectroscopy for protein folding, Fourier transform infrared (FTIR) spectroscopy for evaluation of the secondary structure, differential scanning calorimetry (DSC) for conformational stability, hydrogen/deuterium exchange with mass spectrometry (H/DX-MS) for tertiary and conformational structure, sedimentation velocity analytical ultracentrifugation (SV-AUC) for relative contents of the monomer, LMW, HMWs, and fragments, as well as the MWs of the main species, and finally dynamic light scattering (DLS) to measure the size distribution of macromolecules in solution. It is agreed that the used method panel is sufficient for characterisation of the higher order structure.

Protein concentration was measured using a qualified SoloVPE spectroscopy. The theoretically calculated extinction coefficient is used for calculation of protein concentration in release specification of AS and finished product instead of the experimentally established extinction coefficient, which was adequately justified.

Biological properties were characterised by a human umbilical vein endothelial cell (HUVEC) anti-proliferation assay, a VEGF-A 165 neutralisation assay to measure the inhibitory effect of SB15 on VEGF-induced target gene expression, VEGF-A 165 binding using an enzyme linked immunosorbent assay (ELISA), VEGF-A 121 binding using an ELISA, and FcRn. VEGF-A 189 binding, PlGF-1 and PlGF-2 binding, VEGF-B 167 were also measured. The absence of ADCC and CDC was confirmed by respective assays. During the PPQ characterisation study, some additional biological properties were added. The biological characterisation is accepted**.**

Impurities

The purity and impurity profile were investigated by size exclusion high-performance liquid chromatography (SE-HPLC) and capillary electrophoresis-sodium dodecyl sulfate (CE-SDS) under reducing and non-reducing conditions. In general, the AS seems to be highly purified with only traces of product-related impurities present. LMW species by CE-SDS (reduced) are considered to be fragments from reducing reactions such as hinge region cleavage.

A brief discussion on process- and product-related impurities has been provided.

Process-related impurities include host cell protein, host cell DNA, protein A leachate, which were monitored as in-process test (IPT), or in-process measurement (IPM) during drug substance manufacturing process development. Of note, no release specification for any of the discussed process-related impurities is included in the AS specifications.

Section S.3.2 includes size variants, charge variants, deaminated and oxidated forms as product-related impurities. A detailed assessment and discussion of deaminated and oxidated forms has been included.

2.3.2.3. Specification

The release specification for the active substance includes tests for general attributes (colour, clarity, pH, osmolality), identity, quantity, biological activity, purity and impurities, microbiological safety (bacterial endotoxins and microbial enumeration) process-related impurities and N-glycan.

The proposed specifications address relevant quality attributes and the Applicant has discussed how the specifications and their acceptance criteria have been established. The acceptance criteria were tightened upon request and were established based on the combination of pilot and commercial scale AS and finished product batch release, historical and stability data, manufacturing capability and variability, analytical procedure capability and variability, developmental studies, compendial requirements, regulatory guidelines and certificates of analysis (CoA) of the reference product. The strategy how specification limits have been established is agreed.

For establishing acceptance criteria for the AS, the acceptance criteria of reference product were also considered in some test items as the acceptance criteria of reference product have been established based on sufficient clinical trials experience. In particular, the acceptance criteria for clarity, colour, and pH are based on the acceptance criteria of reference product. As mentioned above it is agreed that data from the reference product may be used for clinical justification of the specification limits of the proposed biosimilar.

Also, a justification why certain tests (for process related impurities) have not been included into the specifications was provided. Furthermore, in addition to the N-glycosylation specification limits an in-process control has been implemented. Nevertheless, the CHMP recommended the applicant to commit to re-calculate these IPC limits post-approval once a more expanded data set (e.g. after 30 AS batches) is available (REC).

Analytical methods

An overview of the analytical methods was included. The suitability of the compendial methods has been verified for their intended use. Sufficient method descriptions and satisfactory validation reports have been provided for the non-compendial, in-house methods. Method transfer reports where relevant were included.

Batch analysis

Information of AS batches including the batch size, manufacturing site and date, and use of batch was provided. Currently 7 pilot batches, 3 clinical and 4 PPQ batches have been manufactured. The batch date complied with the specifications in place at time of testing. A reported out of specification result for endotoxin in one pilot batch is considered atypical and has been adequately discussed raising no further concerns.

Reference standards

The Applicant has described the reference standards used throughout the development of SB15. Different classes of reference standards including the Research Reference Standards (RRS), the Interim Reference Standard, the Clinical Reference Standard, the Primary Reference Standard (PRS) and the Working Reference Standard (WRS) were defined.

The interim reference standard as well as the research reference standards used during the early development phase of SB15 and their characterisation/qualification have been briefly described.

An appropriately characterised in-house PRS has been prepared from clinical AS batch; it was initially established as a clinical reference standard (CRS), but as comparability of clinical and PPQ AS batches of SB15 was confirmed according to the Applicant, PRS can be considered representative of production and clinical materials. PRS was qualified against the interim reference standard IRS.

The strategy of potency assignment used for the primary reference standard is also proposed for qualification of future primary reference standards and the working reference standard to be implemented. The defined acceptance criteria are considered sufficient to avoid a potential drift in potency to future reference standards and hence is accepted.

The expiry date and storage conditions of the PRS and the stability program in place for it have been sufficiently described. Qualification of future PRS was described and is deemed acceptable. The qualification protocol of future PRS (specification and additional characterisation) is included in the dossier.

The Applicant indicated that a working reference standard will be prepared from a PPQ or commercial AS batch, but currently no WRS is available yet. A brief overview of the WRS qualification protocol is included in section 3.2.S.2.5. The new working reference standard will be qualified against currently used PRS.

2.3.2.4. Stability

The Applicant proposed a shelf-life for the AS. Currently, long-term and intermediate stability data from pilot, clinical and PPQ batches are available. In addition, stability data from the accelerated condition are available. The container used for stability studies is composed of the same material as that used for the commercial product, but only smaller in size which is acceptable.

No noteworthy changes or trends over the storage period were observed. Thus, the stability data indicate that the AS is stable and not susceptible to degradation. The clinical batches are considered representative of the commercial batches. On this basis and upon the provided long-term stability data of clinical AS batches, the proposed shelf-life claim is considered acceptable. The Applicant indicated that further stability data from the ongoing formal stability studies for PPQ batches should be submitted during the review process once they become available.

SB15 was shown to be susceptible to photo-degradation, therefore AS should be stored and shipped protected from light.

The Applicant commits to continue the formal stability testing of the primary stability batches and to place one batch per year (unless none is produced that year) on stability under approved storage conditions, following good manufacturing practice (GMP) requirements. The Applicant commits to notifying the Agency of any out of specification results during the post-approval stability studies.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The finished product (FP), also referred as SB15, is a clear, colourless to pale yellow, sterile and preservative free solution and presented as a single-use vial containing 40 mg/mL of aflibercept for intravitreal injection. Opuviz (SB15) has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Eylea, having aflibercept as the active substance. Aflibercept is a recombinant fusion protein consisting of human vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human IgG1 and is produced in Chinese hamster ovary (CHO) cells.

The chosen formulation is sufficiently supported by formulation development and formulation robustness studies. All excipients used are of compendial quality.

A risk assessment results for FP-specific quality attributes (sub-visible particulate, visible particulate, extractable volume, sterility) were provided in the dossier.

During SB15 development, the risk-based control strategy (product risk assessment as described in CTD Section 3.2.S.2.6.1) was used to define critical quality attributes, which are considered essential for safety and/or efficacy of the product. This assessment did not reveal any of the excipients used in the formulation of the AS should be considered critical for the safety and efficacy of SB15 FP. Therefore, no dedicated compatibility studies have been performed with the excipients. The stability studies on SB15 FP demonstrate the compatibility of AS with the excipients.

Process characterisation study was performed to verify product quality before/after sterile filtration, filling under the high pressure and evaluate any impact on selected product quality attributes. Results were used to develop

process parameters which were further verified during process validation. The method of sterilisation has been sufficiently justified.

Clinical FP batches and PPQ FP batches were manufactured at the same manufacturing site with some minor process changes, whereas non-clinical material was manufactured at a different site and different scale. Process changes between manufacture of non-clinical (FP pilot batch) and clinical material were sufficiently described. Comparability of non-clinical (FP pilot batch) vs clinical and clinical vs PPQ has been discussed. Comparability was evaluated by release and side-by-side characterisation testing as well as comparative stability. Respective data confirm the comparability between batches.

The container closure system of SB15 consists of a vial (Ph. Eur. compliant) with a butyl rubber stopper with Fluoropolymer coating (Ph. Eur. compliant) and a flip-off cap. Manufacturers of the primary packaging components and the information on the sterilisation are defined in the dossier. The suitability of the proposed container closure system was evaluated in extractables and leachables studies. The CHMP recommended that the Applicant should provide post-approval the results of the leachable study at the end of the shelf-life to support the final conclusion on leachable characterisation (REC).

The FP may be supplied with a 18-G × 1 ½ inch, 5-micron filter needle. A respective declaration of conformity has been provided. The compatibility of FP with dosage device was demonstrated including the capacity of the transfer filter needle to effectively remove sub-visible particles. The risk of release of silicone oil droplets from the dosage device during intravitreal injection has been sufficiently assessed.

2.3.3.2. Manufacture of the product and process controls

Manufacturers

The FP manufacturing site and its respective responsibilities are appropriately listed in the dossier. Samsung Bioepis NL B.V., Netherlands, is responsible for release and supply to the European market. All sites are covered by valid GMP certificates.

Manufacture

SB15 is manufactured according to a standard process, including AS thawing, pooling/mixing filtration, and filling/stoppering/crimping. The manufacturing process is in the main appropriately described and process parameters are sufficiently justified based on process characterisation and validation data. Proposed hold times are sufficiently justified. No reprocessing is claimed and hence, not allowed.

The process controls are divided into process parameters (inputs) and performance parameters (outputs). Process parameters are classified as key (KPP) or critical (CPP). KPP does not affect CQAs while CPP variability has an impact on CQAs. Performance parameters are classified as in-process gateways (IPGs), critical in-process gateways (CIPGs), in-process tests (IPTs), and critical in-process tests (CIPTs). Gateway tests are performed during processing and in-process tests are performed after step completion. Performance parameters have action ranges or in-process specification (IPS). The proposed control classification seems reasonable and acceptable.

Process validation

The process performance qualification was performed following a classical approach. For that purpose, three consecutive lots of SB15 FP were manufactured according to the commercial process in the commercial finished product manufacturing site. Minimum and maximum batch sizes are covered in PPQ, as well as all manufacturing process steps. All PPQ batches met the prospective acceptance criteria and in-process controls, and pre-defined specifications. Hold times were sufficiently justified based on PPQ data. In summary, PPQ

demonstrated that the manufacturing process when operated within the established parameters performs effectively and reproducibly to produce medicinal product meeting predetermined specifications and quality attributes.

Several studies were performed to demonstrated that the used 0.22 µm pore size filters are suitable for SB15 FP manufacturing. Sterile filter for Opuviz FP manufacturing was successfully validated by the manufacturer of the filter.

A bracketing approach was applied to validate aseptic filling operations. The maximum fill duration is covered by performed media fills. Shipping qualification was performed in three phases, design qualification, operational qualification, and performance qualification. Appropriate shipping validation data have been provided and worst-case shipping conditions described in the dossier.

2.3.3.3. Product specification

The release specifications for the FP include tests for appearance (clarity, colour, visible particles), general attributes (osmolality, pH, extractable volume, protein concentration), identity (VEGF binding activity, icIEF), biological activity (VEGF binding activity, VEGF neutralisation activity), purity and impurity (CE-SDS non-reduced and reduced, icIEF, SE-HPLC), and safety (endotoxin, sterility, sub-visible particulate matter).

The FP specifications were defined considering ICH Q6B guidance, Ph. Eur. monograph "Monoclonal Antibodies for Human Use", specifications of the reference medicinal product and FP manufacturing experience with several pilot scale and several commercial-scale AS batches, several pilot scale and commercial-scale FP batches. FP specifications were aligned with the AS specifications, given that the formulation of FP is equivalent to that of AS. The list of quality attributes proposed for release and stability testing is acceptable.

The release and shelf-life specifications have been sufficiently justified.

For several quality attributes separate FP release and shelf-life acceptance criteria are proposed, considering that changes are observed during FP storage. Shelf-life acceptance criteria were established by regression analysis on the stability data with pilot and clinical FP batches. Clinical justifications for the proposed limits have been provided.

The target extractable volume is justified and it was demonstrated that the proposed limit guarantees the deliverable volume of 0.05 mL with the intended administration set (syringe/needle system).

Characterisation of 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. All analysed elemental impurities were below PDE levels. Based on the presented information it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering formulation, manufacturing process including equipment/materials and container closure system 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). One

nitrosamine impurity was detected from supplier's extractables study but demonstrated that its levels will not exceed 10% of the acceptable intakes thus it is concluded that the risk of nitrosamine can be excluded.

Analytical procedures and reference standards

Appearance (colour, clarity, particulate matter), subvisible particles, osmolality, pH, extractable volume, endotoxin, and sterility methods are performed in compliance with Ph. Eur.

For in-house methods, unique method identifies are included in the list of specifications and in the respective method descriptions and method validation reports.

For compendial methods, verification reports were presented for endotoxin testing (including determination of the maximum valid dilution) and sterility testing.

The container closure integrity testing (dye ingress) is described in dossier and validation was performed according to ICH and USP guidelines, and respective data are found acceptable.

For the discussion on the reference standards, reference is made to the respective AS section.

Batch Analyses

Batch analyses data have been provided for 1 pilot FP batch (non-clinical studies, stability), three commercial scale clinical and 3 PPQ FP batches. Minimum and maximum batch sizes are sufficiently supported by process validation data. Results complied with acceptance criteria valid at time of testing for all batches. Clinical and PPQ batches also complied with commercial acceptance criteria. Furthermore, the provided batch data confirm consistency of the FP manufacturing process.

2.3.3.4. Stability of the product

The proposed shelf-life is 36 months when stored at 5 °C ± 3 °C. Stability data comprise long-term data of the three clinical FP batches (36 months data available for all three batches), which are considered representative of the commercial material. Comparability between clinical and commercial scale/PPQ batches has been sufficiently demonstrated. Representativeness of the container closure system used in stability studies has been confirmed. Furthermore, 36 months data from 1 pilot batch and 18 months data are available for the 3 PPQ batches, additionally supported the proposed shelf-life claim.

Furthermore, studies performed at the accelerated (6 months) and stress conditions (3 months) are available for the three clinical, the pilot batch, and the three PPQ batches.

While no trend in any of the quality attributes is observed at the long-term storage condition, a clear degradation trend is observed in increase in HMW and LMW with corresponding decrease in monomer and increase of acidic and basic species with corresponding decrease in main peak at accelerated conditions. At stressed conditions this trend is more pronounced together with a decrease in biological activities.

Two temperature cycling studies (i.e. a short-term temperature cycling study and a supply chain cycling study) were performed. Furthermore, the proposed possibility to store an unopened vial at room temperature was supported by stability study results using aged drug product (stored up to 36 months) that were additionally stored at room temperature condition up to 3 days.

A photostability study was performed in line with ICH Q1B. Results demonstrate that the FP is sensitive to light and must be stored protected from light. The functionality of the commercial pack in this regard has been demonstrated.

The provided post-approval stability protocol and commitment is acceptable.

In conclusion, the stability data support the shelf life of 3 years for the FP when stored at 2°C to 8°C in the original package in order to protect from light, as mentioned in the SmPC (sections 6.3 and 6.4).

2.3.3.5. Biosimilarity

A well-established biosimilarity exercise has been conducted. A three-way comparison was performed across SB15, US-sourced and EU-sourced Eylea. Comparison of US-sourced with EU-sourced Eylea is of importance as US Eylea was used as a sole comparator in the non-clinical in vivo study and the clinical Phase III study. A number of EU-sourced Eylea and US-sourced Eylea batches have been used for the similarity evaluation. The EU reference product is approved as a prefilled syringe as well as a liquid in vial presentation. For Opuviz, only a vial presentation only has been applied for.

A description of the batches including lot number, marketing site, manufacturer, expiry date, and the use within the biosimilarity assessment (establishment of the quality range, graphical comparison, side-by-side comparison) is given. The Applicant clarified that only vial presentation of the EU- and US-sourced Eylea have been used for biosimilarity evaluation.

Regarding SB15, clinical and PPQ batches have been included into the biosimilarity evaluation, in addition to the FP batches, clinical and PPQ active substance batches were included as well. The information of the batch of SB15 used in the Similarity Assessment is acceptable.

Appropriate risk assessment tools were applied to categorise quality attributes in different tiers of criticality and quality ranges based on descriptive statistics have been established. Following the establishment of similarity acceptance criteria, a side-by-side comparison of the SB15 batches with selected EU- and US-Eylea was performed, and the results derived thereof presented.

It cannot be confirmed that the applicant has considered the principles outlined in the EMA reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development EMA/CHMP/138502/2017. However, taking into account that the Applicant provided graphical and/or tabular presentations of individual analytical results as well as descriptive statistics, which enable an assessment independent of the defined quality ranges, no concerns are raised with respect to statistical data evaluation.

A summary of the of analytical similarity between SB15 finished product and Eylea is presented Table 1**.**

Table 1. Summary of the of analytical similarity between SB15 finished product and Eylea

Category	Test Item		Data Analysis Method	SB15 vs EU Eylea
Physicochemical Properties: Primary structure and post translational modification	Molecular weight		Raw data/graphical comparison	Similar
	Amino acid sequence		Raw data/graphical comparison	Similar
	Peptide mapping		Raw data/graphical comparison	Similar
	N-terminal sequence		Raw data/graphical comparison	Similar
	C-terminal sequence		Raw data/graphical comparison	Minor differences (Justified in Section 2.3.1.5)
	Oxidation		Raw data/graphical comparison	Minor differences (Justified in Section 2.3.1.6)
	Deamidation		Raw data/graphical comparison	Minor differences (Justified in Section 2.3.1.7)
	Extinction coefficient		Raw data/graphical comparison	Similar
Physicochemical Properties: Glycan profiles	N-linked glycosylation site		Raw data/graphical comparison	Similar
	N-glycan identification		Raw data/graphical comparison	Similar
	N-glycan profile	%Charged glycan	Raw data/graphical comparison	Similar
		%High mannose	Raw data/graphical comparison	Minor differences (Justified in Section 2.3.2.3)
	O-glycan identification		Raw data/graphical comparison	Similar
	Total sialic acid contents		Raw data/graphical comparison	Similar
Physicochemical Properties: Purity and Impurities	SE-HPLC	%Monomer	Quality range (Mean - 3SD)	Similar
		%HMW	Quality range (Mean + 3SD)	Similar
	CE-SDS (non-reduced)	%Main	Quality range (Mean - 3SD)	Similar
	CE-SDS (reduced)	%Main 1	Quality range (Mean ± 3SD)	Similar
		%Main 2	Quality range (Mean ± 3SD)	Similar
		%LMW	Quality range (Mean + 3SD)	Similar
Physicochemical properties: Charge heterogeneity	icIEF	pI (Main)	Quality range (Mean ± 3SD)	Similar
		%Acidic	Quality range (Mean ± 3SD)	Minor differences (Justified in Section 2.3.4.1)
		%Main	Quality range (Mean ± 3SD)	Minor differences (Justified in Section 2.3.4.1)
		%Basic	Quality range (Mean ± 3SD)	Similar

Category	Test Item		Data Analysis Method	SB15 vs EU Eylea
Physicochemical Properties: Higher order structure	Disulfide bond		Raw data/graphical comparison	Similar
	Free thiol		Raw data/graphical comparison	Minor differences (Justified in Section 2.3.5.2)
	CD		Raw data/graphical comparison	Similar
	ITF		Raw data/graphical comparison	Similar
	FTIR		Raw data/graphical comparison	Similar
	DSC		Raw data/graphical comparison	Similar
	H/DX-MS		Raw data/graphical comparison	Similar
	SEC-MALS		Raw data/graphical comparison	Similar
	SV-AUC		Raw data/graphical comparison	Minor differences (Justified in Section 2.3.5.9)
	DLS		Raw data/graphical comparison	Similar
Physicochemical Properties: Quantity	Protein concentration		Quality range (Mean ± 3SD)	Minor differences (Justified in Section 2.3.6)
Biological properties	VEGF-A 165 binding assay	%Relative binding activity	Quality range (Mean ± 2.6SD)	Similar
	HUVEC anti-proliferation assay	%Relative potency	Quality range (Mean ± 2.6SD)	Similar
	VEGF-A 165 neutralization assay	%Relative potency	Quality range (Mean ± 3SD)	Similar
	VEGF-A 121 binding assay	%Relative binding activity	Quality range (Mean ± 3SD)	Similar
	FcRn binding assay	%Relative binding activity	Quality range (Mean ± 3SD)	Similar
Additional biological properties	VEGF-A 189 binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	VEGF-A 121 neutralization assay	%Relative potency	Raw data/graphical comparison	Similar
	VEGF-A 189 neutralization assay	%Relative potency	Raw data/graphical comparison	Similar
	PlGF-1 binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	PlGF-2 binding assay	%Relative binding activity	Raw data/graphical comparison	Similar

Category	Test Item		Data Analysis Method	SB15 vs EU Eylea
	VEGF-B 167 binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	A binding specificity to VEGF-C and VEGF-D	Observation of significant binding response	Raw data/graphical comparison	Similar
	FcγRIa binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIa binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIb binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	FcγRIIIa binding assay	%Relative binding activity	Raw data/graphical comparison	Minor differences (Justified in Section 2.3.8.11)
	C1q binding assay	%Relative binding activity	Raw data/graphical comparison	Similar
	ADCC assay		Raw data/graphical comparison	Similar
	CDC assay		Raw data/graphical comparison	Similar

[a] N/A: Not applicable

Primary structure and post-translational modification have been addressed by molecular weight determination by liquid chromatography-electrospray ionisation-mass spectrometry (LC-ESI-MS), amino acid sequence by LC-ESI-MS, peptide mapping by LC-ESI-MS, N- and C-terminal sequence analysis by LC-ESI-MS, oxidation analysis by LC-ESI-MS, deamidation analysis by LC-ESI-MS and extinction coefficient analysis by size-exclusion chromatography coupled with multi angle light scattering (SEC-MALS). The molecular weight of deglycosylated and reduced SB15, US and EU Eylea were shown to be similar and equal to the theoretical value within assay variability of 0.01%. Full amino acid sequence was identified with a match of 100% sequence coverage. The data also demonstrated that the primary sequences across SB15, US and EU Eylea are identical. Peptide mapping with three different endopeptidases revealed similar chromatographic profiles across SB15, US and EU Eylea for a given endopeptidase. Only one N-terminal form (1-SDTGRPFVEMYSEIPEIIHMTEGR-24) was found in SB15, US and EU Eylea. The N-terminal sequence was similar across SB15, US and EU Eylea, and no detectable modifications were identified in the N-terminal sequence of SB15, US and EU Eylea. There were some differences in C-terminal forms compared to US and EU Eylea. However, considering Fc effector functions are not related to the biological activities of aflibercept, these differences are deemed not to have an impact on biological activities of SB15. The oxidation level was also slightly different than in US and EU Eylea. However, there was no statistically significant difference in VEGF-A 165 binding activity between SB15, US and EU Eylea. Furthermore, enrichment of oxidisation, induced by forced degradation, was shown not to have an impact on other quality attributes. Regarding deamidation the different level of deamidation in SB15 than Eylea is considered as a main cause of the difference in charge variants between SB15 and Eylea. However, no statistically significant difference in VEGF-A 165 binding activity was observed between SB15, US and EU Eylea. The determined extinction coefficient values were similar across SB15, US and EU Eylea.

Glycan profiles were characterised by N-linked glycosylation site analysis by LC-ESI-MS, N-glycan identification by procainamide labeling by LC-ESI-MS, %charged glycan & %high mannose analysis by 2-AB labeling by hydrophilic interaction-ultra-performance liquid chromatography (UPLC), and total sialic acid contents analysis by ion-exclusion HPLC. Representative MS/MS spectra of the N-glycosylation site for SB15, US and EU Eylea

are shown and indicate similar N-glycosylation sites. The N-glycan peaks identified by LC-ESI-MS for SB15, US and EU Eylea, showed an identical mass and there were no glycan species detected only in SB15, US and EU Eylea. Also, the α-galactosylated or N-glycolylneuraminic acid forms which were known to cause immunogenicity were not detected in all tested batches. Among N-glycan species of SB15, US and EU Eylea, two N-glycan groups including %Charged glycan and %High mannose were evaluated for similarity assessment. The observed differences between SB15, US and EU Eylea in %Charged glycan and %High mannose are not expected to have any impact on efficacy and safety. In relation to afucosylated glycans and galactosylated glycans between SB15, US- and EU Eylea, it is agreed with the Applicant that this minor difference in afucosylated glycans has no impact as absence of ADCC activity of SB15 and Eylea was shown. Absence of O-glycans was confirmed by intact mass and peptide mapping analysis.

Purity and impurities were evaluated by %monomer and %HMW analysis by SE-HPLC, %main analysis by capillary electrophoresis-sodium dodecyl sulfate (non-reduced), and %main 1, %main 2, and %LMW analysis by capillary electrophoresis-sodium dodecyl sulfate (reduced). SE-HPLC results indicate a slightly higher purity profile and a corresponding lower content of high molecular weight variants for the SB15 which does not jeopardise the similarity claim. The results derived from by CE-SDS (Reduced and Non-reduced) revealed no significant differences between SB and Eylea.

Charged variants were investigated by imaged capillary isoelectric focusing. All batches of SB15, US and EU Eylea have the same pI and showed similar pattern of charge variants, indicating that the net charge of SB15 and Eylea is similar. The relative contents of basic variants for all SB15 batches were within the US and EU similarity ranges. The observed differences in the relative contents of acidic variants and %Main between SB15 and Eylea were likely to be the difference in deamidation. No significant difference was observed on biological activities including VEGF-A 165 binding activity across SB15, US and EU Eylea. Thus, no impact of the differences in charge variants on the biological activities is expected. Furthermore, the applicant claims the cause is deamidation and supports this claim by CEX-fractionated (and desialylated) samples, and structure-activity analyses, which show that no acidic and main groups have indistinguishable activity.

Higher-order structure were studied and compared by disulfide bond analysis performed by LC-ESI-MS, free thiol group quantification, circular dichroism spectroscopy (far-UV and near-UV), intrinsic tryptophan fluorescence, Fourier transform infrared spectroscopy, differential scanning calorimetry, hydrogen/deuterium exchange with mass spectrometry, size-exclusion chromatography with multi angle light scattering, sedimentation velocity-analytical ultracentrifugation, dynamic light scattering, and quantity by protein concentration. In summary, the results derived from these investigations show similar secondary and higher order structures.

In general, a broad panel of standard and state-of-the-art techniques has been applied to evaluate and compare physico-chemical quality attributes of SB15 with EU- and US-sourced Eylea. Principally, structural similarity could be demonstrated between SB15 and EU-sourced Eylea, but also comparability between EU- and US-sourced Eylea was shown thus enabling the use of US-sourced Eylea as comparator in the Phase III trial. Minor differences have been sufficiently justified. At this point it should be noted that also broad set of binding and bioassays used for comparative characterisation of the biological activity do not indicate any differences there. Thus, these results further support the Applicant`s justification that the noted differences do not translate into differences in the biological activities and thus have no impact on clinical performance characteristics of SB15 when compared with Eylea.

The comparative biological characterisation included VEGF-A 165 binding using an enzyme linked immunosorbent assay (ELISA), a HUVEC anti-proliferation assay, VEGF-A 165 neutralisation assay utilising a reporter gene system, VEGF-A 121 binding using an ELISA, FcRn binding using by surface plasmon resonance

(SPR), VEGF-A 189 binding by ELISA, a VEGF-A 121 neutralisation assay, a VEGF-A 189 neutralisation assay, PlGF-1 and PlGF-2 binding by SPR, VEGF-B 167 binding by SPR, VEGF-C and VEGF-D binding assay using SPR to confirm lack of binding affinity to these VEGF variants, FcγRIa binding by ELISA, FcγRIIa, FcγRIIb, and FcγRIIIa binding, C1q binding as well as ADCC and CDC to confirm absence of any ADCC/CDC activity in SB15 and Eylea. It is agreed that that in principle a broad panel of binding and cell-based assays has been in place for evaluation of the biological properties. Also, for certain low risk biological quality attributes only a limited number of batches have been tested, this can be accepted.

In conclusion, a sound and comprehensive biosimilarity exercise has been conducted. The results derived from this exercise principally support the biosimilarity claim between SB15 and its reference medicinal product as well as the comparability between US- and EU-sourced Eylea. Observed differences have been adequately justified and are not expected to result in a different clinical performance of SB15.

2.3.3.6. Adventitious agents

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

TSE

No raw materials of animal origin were used during preparation of MCB and WCB (except CHO cells) and during the AS and FP manufacturing. Based on the information provided (and considering that any material used early in cell line development is unlikely to pose TSE risk), it is agreed that the overall risk with regard to TSE is likely minimal.

Microbial agents

The cell banks were tested for the absence of bacterial/fungal contamination and mycoplasma according to Ph. Eur. Absence of mycoplasma is routinely confirmed for the unprocessed bulk material. Bioburden and endotoxin tests are performed at multiple stages of the drug substance and drug product manufacturing processes. At the release stage, AS and FP are tested for bioburden or sterility, respectively, as well as for endotoxin content. In conclusion, the risk for microbial contamination is adequately controlled.

Adventitious viruses

Absence of viruses in cell banks was determined by a battery of tests covering a broad range of viruses.

No substances of human or animal origin are used during manufacture, and the safety of the cell substrate has been suitably demonstrated. No virus like particles were detected other than retrovirus-like particles which were identified as intracytoplasmic A and C-type particles, which are known to be present in CHO cells.

Virus clearance studies

The virus clearance capacity of the manufacturing process has been assessed in virus clearance studies using small-scale models. The design of the studies appears to be largely in line with the guidance documents ICH Q5A and CPMP/BWP/268/95. Thus, orthogonal manufacturing steps were evaluated in virus clearance studies (i.e low pH inactivation, protein A affinity chromatography, mixed mode chromatography, viral filtration) using relevant model viruses (MVM, PRV, Reo-3, X-MuLV). Tabular comparisons of the process parameters for the

manufacturing scale and small-scale process steps have been provided. The studies were conducted considering worst-case conditions. Confirmation that the qualified small-scale models described in dossier section 3.2.S.2.6 are used for the virus clearance studies has been provided. The original study reports have been provided, including sufficient information on the design of virus clearance studies (e.g. results for cytotoxicity, interference, hold controls, virus load of the different fractions tested, carry-over, age of resins, assays used to determine virus titers etc.).

A summary of virus clearance study results is presented in the dossier. The worst-case cumulative LRFs of non-enveloped viruses, MVM and Reo-3, are ≥ 10.39 and ≥ 16.94, respectively. Worst-case cumulative LRFs of enveloped viruses, PRV and X-MuLV, are ≥ 16.73 and ≥ 17.90, respectively.

Considering the worst-case retrovirus-like particle counts of the unprocessed bulk from the PPQ batches (2.50E+06 particles/mL) and the maximum dose of SB15 per patient (21.1 mL of unprocessed bulk is required; theoretical particle load 7.72 log), the safety margin to viral clearance capacity is 10.18 log10. Based on the currently available information, it can be concluded that the obtained LRF provides an acceptable safety margin regarding retrovirus-like particles.

In conclusion, the two dedicated virus clearance steps in combination with the affinity and mixed mode chromatography steps provide for an effective and robust overall clearance capacity for enveloped and non-enveloped adventitious viruses.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Opuviz has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Eylea. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A comprehensive analytical biosimilarity exercise was conducted and demonstrated that, from a quality perspective, Opuviz was shown to be highly similar to the EU reference medicinal product (Eylea). Some minor analytical differences observed have been adequately justified and are not expected have any relevant impact on the clinical performance 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.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to recalculating the in-process specification limits for galactosylated and sialylated glycan and providing the results of leachable study.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Opuviz 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.

Recommendations for future quality development have been agreed by the Applicant (see below).

In conclusion, based on the review of the data provided, the MAA for Opuviz is considered approvable from the quality point of view.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. to re-calculate the in-process specification limits for galactosylated glycan and sialylated glycan once a more expanded data set is available (e.g. after 30 AS batches).
2. to provide the results of leachable study at the end of the shelf-life (36 months at 5 ± 3°C) to support the final conclusion on leachable characterisation.

2.4. Non-clinical aspects

2.4.1. Introduction

Analytical and functional similarity between SB15 and EU/US Eylea was demonstrated in *in vitro* studies which are described and discussed in the Quality part of this report. No additional non-clinical pharmacodynamics studies, neither *in vitro* nor *in vivo*, were performed and included in Module 4 of this MAA.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro pharmacodynamic characterization studies were performed in a side-by-side comparative manner to compare the key biological activities (e.g. HUVEC anti-proliferation, VEGF-A 165 neutralization, VEGF-A 165 binding, VEGF-A 121 binding, and FcRn binding) and additional biological properties (e.g. VEGF-A 189 binding, VEGF-A 121 neutralization, VEGF-A 189 neutralization, PlGF-1 binding, PlGF-2 binding, VEFG-B 167 binding, binding specificity to VEGF-C and VEGF-D, Fcy receptors, C1q binding, ADCC, and CDC) of SB15 drug product with its comparator Eylea sourced from EU and US.

Since all *in vitro* PD studies are covered in Module 3 of this MAA, please refer to the quality section of this report.

No *in vivo* animal studies were conducted in addition to the analytical biosimilarity assessment, investigating analytical, physiochemical and functional similarity between SB15 and its referenced medicinal product (RMP) Eylea, sourced from EU and US.

2.4.3. Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with SB15 and Eylea.

TK/PK profiles of SB15 and Eylea were not assessed within the scope of the 4-week repeat-dose toxicity study in cynomolgus monkeys (number SBL327-008).

2.4.4. Toxicology

Although *in vivo* studies with SB15 were not required by the EMA, the Applicant conducted a comparative 4-week repeat dose toxicity study in Cynomolgus monkeys with SB15 and US-sourced Eylea to fulfil global requirements.

2.4.4.1. Repeat dose toxicity

The Applicant conducted a 4-week repeat dose toxicity study in Cynomolgus monkeys to evaluate and compare toxicological findings of SB15 with its reference medicinal product Eylea, sourced from US. Female Cynomolgus monkeys (4 animals/group) were assigned to 3 treatment groups (vehicle control, SB15 and US-Eylea group), receiving intravitreal injections into both eyes of either 0 or 2mg aflibercept/eye, once every two weeks for 4 weeks (total of 3 times). Animals were monitored regarding clinical signs, body weight, food consumption, electrocardiography (ECG), respiration rate, body temperature, urinalysis, hematology, blood chemistry, necropsy, organ weights, histopathology and ophthalmology examination (gross and slit-lamp examination, ocular fundus examination, intraocular pressure [IOP] and electroretinography [ERG]). Toxicity profiles of SB15 and US-Eylea were regarded as similar, with no issues identified.

The no observed adverse effect levels (NOAEL) of SB15 and Eylea (US sourced) in this study were both considered to be 2 mg/eye.

2.4.5. Ecotoxicity/environmental risk assessment

In the case of products containing proteins as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) should be provided, whereby this ERA may consist of a justification for not submitting ERA studies, e.g. that due to the nature of particular pharmaceuticals they are unlikely to result in a significant risk to the environment (EMEA/CHMP/SWP/4447/00 corr 2 issued 01 June 2006).

The Applicant provided a justification for the absence of ERA studies with Opuviz, which is deemed acceptable.

2.4.6. Discussion on non-clinical aspects

Pharmacology

A thorough *in vitro* biosimilar comparability exercise was conducted with SB15 drug product and its comparator Eylea sourced from EU and US. *In vitro* pharmacodynamic characterization studies were performed in a side-by-side comparative manner to compare the key biological activities (e.g. HUVEC anti-proliferation, VEGF-A 165 neutralization, VEGF-A 165 binding, VEGF-A 121 binding, and FcRn binding) and additional biological properties (e.g. VEGF-A 189 binding, VEGF-A 121 neutralization, VEGF-A 189 neutralization, PlGF-1 binding, PlGF-2 binding, VEFG-B 167 binding, binding specificity to VEGF-C and VEGF-D, Fcy receptor, C1q binding, ADCC, and CDC) of SB15 drug product and EU/US-Eylea.

No *in vivo* animal studies were conducted in addition to the analytical biosimilarity assessment, investigating analytical, physiochemical and functional similarity between SB15 and its referenced medicinal product (RMP)

Eylea, sourced from EU and US. This is accepted because, 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 (RMP). *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 RMP.

Pharmacokinetics

Neither stand-alone comparative pharmacokinetics studies nor separate absorption, distribution, metabolism and/or excretion studies were performed with SB15 and Eylea. TK/PK profiles of SB15 and Eylea were not assessed within the scope of the 4-week repeat-dose toxicity study in cynomolgus monkeys (number SBL327-008).

As stated in the "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA/ CHMP/ BMWP/ 403543/ 2010]: If the comparability exercise in the *in vitro* studies is considered satisfactory and no factors of concern are identified, or these factors of concern do not block direct entrance into humans, an *in vivo* animal study may not be considered necessary.

The similarity between the originator and the biosimilar product should be proven in the frame of the *in vitro* quality biocomparability testing. In contrast to *in vitro* methods, *in vivo* studies in animals are not considered informative for the similarity/comparability exercise. Due to the high variability, animal models are actually too insensitive. This conclusion concerns both pharmacokinetic comparisons and comparisons on safety.

Based on the considerations discussed above, the lack of a comparative PK study in an animal model is accepted.

Toxicology

The Applicant conducted a comparative 4-week repeat dose toxicity study in Cynomolgus monkeys with SB15 and US-sourced Eylea (study number SBL-327-008) to fulfil global requirements. No SB15 or US Eylea-related changes were noted in any treated group for assessments on clinical signs, body weight, food consumption, ophthalmology, ECG, body temperature, urinalysis, hematology, blood chemistry, necropsy, organ weights or histopathology. The tested dose 2mg/eye and the intravitreal route of administration were adequately justified based on publicly available data for Elyea. Toxicity profiles of SB15 and US-Eylea were regarded as similar, with no issues identified. The no observed adverse effect levels (NOAEL) of SB15 and US-sourced Eylea are both considered to be 2 mg/eye.

Neither single dose toxicity, genotoxicity, carcinogenicity, developmental and reproductive toxicology nor other toxicity studies were performed with SB15. No stand-alone local tolerance studies were performed with SB15 given that all the excipients used in the final commercial formulation are commonly used in currently approved biologics with the same exposure levels and same intended route of administration. This approach was endorsed by the EMA within the scope of a previous scientific advice provided in September 2017 [EMA/CHMP/SAWP/575108/2017, Sep 14, 2017], supporting the proposed strategy of the Applicant to not conduct any *in vivo* animal studies with SB15 and its RMP Eylea and is in line with 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 Rev1, Dec 2014).

Although not supported, the conduct of the 4-week repeat dose toxicity study in Cynomolgus monkeys (SBL-327-008) is accepted, as this study was performed to satisfy requirements of non-European authorities. As

there are no concerns arising from the analytical biosimilarity exercise triggering the need for further investigations, the absence of additional non-clinical *in vivo* toxicology studies conducted with SB15 is accepted and highly appreciated regarding the principles of the 3Rs (EMA/CHMP/CVMP/3Rs/677407/2015).

Environmental risk

Aflibercept is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

The applicant provided adequate rationale for not submitting a full ERA report indicating that, due to their nature, biosimilar products are unlikely to result in a significant risk to the environment. In this case, these products are broken down by naturally occurring proteolytic enzymes into smaller (inactive) polypeptides or amino acids which are either further degraded by similar pathways or reabsorbed for recycling in other molecules and pathways. There are no other intermediates that have any expected toxicity or accumulation in the environment. This is in line with the ERA guideline.

Therefore Opuviz (aflibercept by Samsung Bioepis) is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, no concern was identified which would preclude a marketing authorization application.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 2: Tabular overview of clinical studies

Table 1: Listing of Clinical Study

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Dosage Regimen	Number of Subjects	Test Subjects	Duration of Study	Study Status; Type of Report
Phase III	SB15-3001 (EudraCT No. 2019-003883-28)	CTD Section 5.3.5.1	Primary objective: To demonstrate the equivalence in efficacy of SB15 compared to US Eylea in patients with neovascular age-related macular degeneration (AMD).	Randomized, double-masked, parallel group, multicenter study Active Control/ Comparator	2 mg (0.05 mL) every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48	Randomized Set (RAN): N=449 SB15: 224 US Eylea Overall: 225 US Eylea+SB15: 111[a] US Eylea+US Eylea: 108[a] Total: 449	Patients with neovascular AMD	Patients were administered investigational product (IP) into the study eye every 4 weeks for the first 3 months (i.e., at Weeks 0, 4, and 8), followed by once every 8 weeks up to Week 48 unless they were discontinued early from the IP. The last assessment was done at Week 56.	Completed; Final CSR

[a] Based on patients who had re-randomization at Week 32, US Eylea+SB15 and US Eylea+US Eylea may not add up to US Eylea Overall.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Aflibercept is administered IVT, directly at the site of action, and its efficacy is not associated with its systemic exposure. After IVT administration, aflibercept is temporarily bioavailable in the circulation but the systemic concentrations are highly variable and too low to elicit PD effects.

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. In order to support the overall assessment of the systemic exposure of SB15 and Eylea, the PK profiles (C_{trough} and C_{max}) of SB15 and Eylea (aflibercept) were evaluated in the subgroup population in clinical Phase III study (SB15-3001). In terms of immunogenicity, the incidence of ADA and NAb to aflibercept for the Safety Set 1 (SAF 1) was assessed during the clinical Phase III study (SB15-3001).

Analytical methods

The quantitative assay was developed for the determination of aflibercept (SB15 or Eylea) in serum from patients with neovascular AMD using an electrochemiluminescence (ECL) assay of Meso Scale Discovery (MSD) platform which was successfully validated. An ECL based assay was selected to improve sensitivity compared to Enzyme-linked Immunosorbent Assay (ELISA). In this assay, all samples undergo dilution to reduce matrix interference. SB15 or Eylea in diluted samples is captured bound to the wells of a streptavidin MSD plate. Then, sulfo-Tag labeled is added to detect the captured aflibercept. Read buffer containing tripropylamine is treated and an ECL signal is produced when an electronic voltage is applied. The resulting chemiluminescence is measured in relative light units (RLU) using the MSD plate reader. The method had a lower limit of quantification (LLOQ) and an upper limit of quantification (ULOQ).

The analysis of all the samples from clinical phase III Study SB15-3001 for the quantification of aflibercept was successfully completed. Among 430 PK samples from Study SB15-3001, 430 samples had reportable value. All

samples were analyzed within the 722 days which period was fulfilled by the long-term storage stability test showing that the analyte stability in frozen matrix data for SB15 and Eylea are acceptable in human serum at –80°C.

Incurred Sample Reanalysis

To demonstrate reproducible quantitation of incurred subject samples, approximately 10% (37 ISR samples out of a total of 430 samples) of the applicable project samples were reassayed. Applicable study samples are defined as between three times the assay LLOQ and 80% of the ULOQ. The incurred sample reanalysis (ISR) values were used for comparison purposes and are included in the analytical report but not used in determining the final reported value. Incurred sample repeats were considered acceptable if the original and reassay values from two-thirds of the repeated samples had a relative percent difference of $\leq \pm$ 30%. The results of the incurred sample repeats met the acceptance criteria. The overall ISR passing rate for the project is 97.3%.

An additional method comparability test was performed to justify whether the use of SB15 as the reference standard is appropriate to measure aflibercept (SB15 and US Eylea). The comparability of bioanalytical method of SB15 PK assay was evaluated with 6 accuracy and precision runs using the calibration standards and QCs prepared from SB15 or US Eylea. The concentrations of the QCs prepared from two drugs were back-calculated using the calibration standards of each product, and the results were reported with the value of %bioanalytical bias difference (hereafter referred to as, "%BBD") to verify comparability among SB15 and US Eylea. All data from the calibration standards and QCs were acceptable according to the criteria, and %BBD at all levels were less than 10% which demonstrates their comparability. Moreover, each calibration standard curves of two comparison groups (SB15 vs US Eylea) are highly overlapped. Therefore, it is demonstrated that this validated PK assay method using SB15 as the reference standard had no differential effects on the results obtained from the SB15 and US Eylea treatment groups.

Immunogenicity

In line with recommendation of the EMA guideline [EMEA/CHMP/BMWP/14327/2006 Rev 1] and the FDA guidance "Guidance for industry, Immunogenicity testing of therapeutic protein products – developing and validating assays for anti-drug antibody detection", a multi-tiered approach for antibody assays was applied to detect ADAs in human serum. This includes a screening assay for identification of antibody positive samples, a procedure for confirming the presence of antibodies and determining antibody specificity, followed by a ligand binding assay for the assessment of the neutralizing capacity of antibodies. Following the guideline, multi-tiered approach for immunogenicity (a single bridging-ligand binding assay [SB15]: ECL-based immunoassay with MSD platform) was applied for Study SB15-3001.

Screening assay

A qualitative assay was used for the detection of ADAs against aflibercept (SB15 and Eylea) in patients with neovascular AMD in the clinical Phase III study (SB15-3001) by using a validated MSD platform. ADAs against aflibercept in human serum are detected and confirmed using a multi-tiered approach in an ECL assay. At screening assay (Tier 1), samples undergo acid dissociation to release any anti-drug antibodies complexed with aflibercept and then incubated with neutralization buffer, and bridged with master mix containing biotinylated SB15 (Biotin-SB15 [capture]) and Sulfo-Tag conjugated SB15 (sTag-SB15 [detection]).

Following the neutralization and bridging, samples are added to a blocked streptavidin MSD plate, and biotin-SB15/ADA/sTag-SB15 complexes bind to the streptavidin. In the presence of tripropylamine-containing read buffer, the Sulfo-Tag on the sTag-SB15 in the complex produces a chemiluminescent signal that is triggered when voltage is applied. Only the samples that contain antibody bound to both biotin-SB15 and sTag-SB15 will

generate an ECL signal. The resulting chemiluminescence is measured in relative light units (RLU) using the MSD Plate Reader and the resulting ECL signal is directly proportional to the amount of ADA present in the human serum.

At confirmatory assay (Tier 2), the assay is based on the use of excess unlabeled SB15 in a competitive binding format to demonstrate the specificity of the binding interactions in the antibody/labeled drug complex. Subsequently, confirmed ADA positive samples are tested whether ADAs have a neutralizing capacity (Tier 3).

In addition, the titration assay (Tier 3) follows the same procedure as done in the screening assay except that samples were serially diluted in pooled normal human serum prior to assay. The titer is determined as the highest serial dilution yielding a response greater than the assay cut point. The developed SB15 ADA assays for detection of ADA to SB15 or Eylea treatment in human serum were fully validated.

Pharmacokinetic data analysis

The collection of blood samples for PK assessment was planned in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at W0 [Day 1]).

Blood samples for pre-dose PK assessment (C_{trough}) were collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for post-dose PK assessment were collected following first IVT injection at Week 0 (samples were collected at a single time point between 24h and 72h after IVT injection of IP on Day 1) and following fifth IVT injection at Week 24 (samples were collected at 3 time points i.e., on 1 day, 2 days, and 3 days after the IVT). Blood samples for PK assessment was also collected at Week 56 (end of study [EOS] visit).

PK data were analysed only descriptively.

PK blood sampling time and serum drug concentrations of aflibercept (pre-dose, trough serum concentration [C_{trough}] and post-dose, maximum serum concentration [C_{max}]) were listed for the PK Analysis Set (PKS). PKS consists of all subjects in the SAF1 who participate in PK evaluation at PK investigational sites (PK subjects) and have at least one serum concentration data.

If the fellow eye received Eylea due to AMD during the study period after randomisation, all serum concentrations measured after treatment for the fellow eye were listed but excluded from the summary

Results

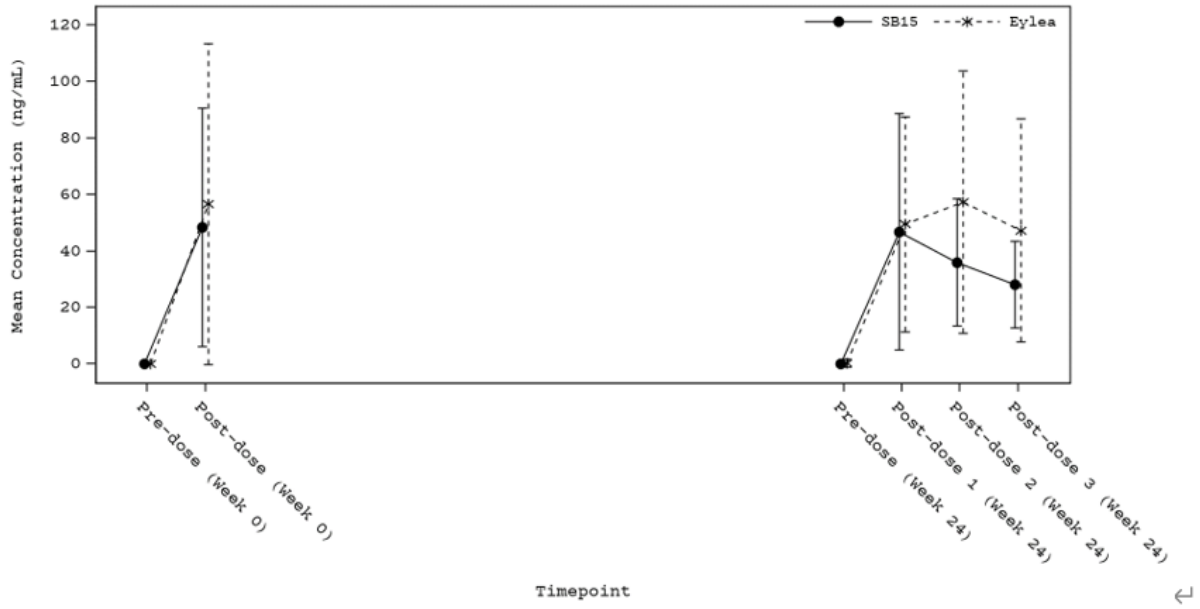
SB15-3001 was a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of SB15 compared to Eylea in subjects with neovascular AMD.

Of the 449 patients randomized, blood samples for PK assessment were collected in the Pharmacokinetic Analysis Set (PKS) (21 [9.4%] patients in the SB15 treatment group and 19 [8.4%] patients in the Eylea treatment group).

Most of the serum trough (pre-dose) concentrations were BLQ at each timepoint up to Week 56.

Through all post-dose timepoints at Week 0 and Week 24, the mean (± SD) serum concentrations for SB15 ranged from 28.058 (± 15.3292) ng/mL to 48.312 (± 42.1325) ng/mL and those for Eylea ranged from 47.255 (± 39.4663) ng/mL to 57.418 (± 46.3844) ng/mL, respectively. Through all post-dose timepoints, CV% ranged between 54.6341% and 89.3129% for SB15 and between 76.9999% and 100.1654% for Eylea.

Figure 1: Mean ± standard deviation derum concentrations profiles by treatment (Pharmacokinetic Analysis Set, Study SB15-3001)



▪ **Figure 1: → Mean ± Standard Deviation Serum Concentrations Profiles by Treatment (Pharmacokinetic Analysis Set, Study SB15-3001)**

Pre-dose = Prior to IVT injection; Post-dose = 24-72 hours after IVT injection; Post-dose 1 = 1 day after IVT injection; Post-dose 2 = 2 days after IVT injection; Post-dose 3 = 3 days after IVT injection.
Below the limit of quantitation concentrations were set to zero.
Sample not collected within sampling window was excluded in the summary.
If the fellow eye received US Eylea due to AMD during the study period after randomization, all serum concentrations measured after treatment for the fellow eye were excluded in the summary.
Source: Figure 14.2-5.1

Table 3: Summary statistics for serum concentration (ng/mL) by scheduled time and treatment Group Pharmacokinetic Analysis Set

Table 14.2-7.1 (Page 1 of 6)
Summary Statistics for Serum Concentration (ng/mL) by Scheduled Time and Treatment Group
Pharmacokinetic Analysis Set

Scheduled Time	Timepoint	Statistics	SB15 N=21	Eylea N=19
Week 0 (BL)	Prior to IVT injection	n	21	19
		Mean	0.000	0.000
		SD	0.0000	0.0000
		Median	0.000	0.000
		Min, Max	0.00, 0.00	0.00, 0.00
		CV%	NA	NA
		Geo. Mean	NA	NA
		Geo. SD	NA	NA
		Geo. CV%	NA	NA
Week 0	24-72 hr after IVT injection	n	20	17
		Mean	48.312	56.708
		SD	42.1325	56.8020
		Median	35.255	23.470
		Min, Max	0.00, 161.50	8.53, 184.50
		CV%	87.2102	100.1654
		Geo. Mean	46.642	34.255
		Geo. SD	1.8941	2.8607
		Geo. CV%	70.9810	142.0693

Scheduled Time	Timepoint	Statistics	SB15 N=21	Eylea N=19
Week 24	Prior to IVT injection	n	19	17
		Mean	0.000	0.334
		SD	0.0000	1.3752
		Median	0.000	0.000
		Min, Max	0.00, 0.00	0.00, 5.67
		CV%	NA	412.3106
		Geo. Mean	NA	5.670
		Geo. SD	NA	NA
		Geo. CV%	NA	NA
	1 day after IVT injection	n	19	17
		Mean	46.814	49.446
		SD	41.8112	38.0733
		Median	32.820	37.940
		Min, Max	0.00, 179.07	0.00, 141.32
		CV%	89.3129	76.9999
		Geo. Mean	39.063	39.654
		Geo. SD	1.9389	2.3188
		Geo. CV%	74.1753	101.4253

Scheduled Time	Timepoint	Statistics	SB15 N=21	Eylea N=19
Week 24	2 days after IVT injection	n	19	17
		Mean	35.962	57.418
		SD	22.4631	46.3844
		Median	25.570	38.210
		Min, Max	5.75, 85.93	10.48, 167.81
		CV%	62.4641	80.7843
		Geo. Mean	29.918	42.813
		Geo. SD	1.9083	2.2359
		Geo. CV%	71.9917	95.4276
	3 days after IVT injection	n	19	17
		Mean	28.058	47.255
		SD	15.3292	39.4663
		Median	21.640	33.500
		Min, Max	5.78, 68.41	10.73, 137.93
		CV%	54.6341	83.5181
		Geo. Mean	24.459	35.449
		Geo. SD	1.7404	2.1568
		Geo. CV%	59.9498	89.7416

No subject in the PKS had positive ADA result up to Week 56, therefore the impact of immunogenicity on PK cannot be assessed.

2.5.2.2. Pharmacodynamics

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

Mechanism of action

Aflibercept is understood to act as a soluble decoy receptor that binds primarily to VEGF-A and PlGF, reducing the circulating concentration of VEGF-A and PlGF available to bind their natural receptors, VEGFR-1 and VEGFR-2, which are expressed on the surface of endothelial cells. Aflibercept inhibits the receptor binding of VEGF-A and PlGF and subsequently the angiogenic downstream signal cascade and functional activities.

Immunological events

Blood samples for immunogenicity assessment were collected in all randomised subjects.

Blood samples for immunogenicity assessment were collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, Week 40, and at Week 56 (EOS visit) or ET visit.

The number and percentage of subjects with anti-drug antibody (ADA) results (i.e., positive, negative) and neutralising antibodies (NAbs) results (i.e., positive, negative) were presented by overall treatment group and visit using Safety Set 1 (SAF1). SAF1 consists of all subjects who receive at least one IP during the study period. In addition, the number and percentages of subject with ADA positive were summarised by titre and overall treatment group in each visit using SAF1. The incidence of overall ADA results (i.e., positive, negative, inconclusive) up to Week 8, Week 32, and Week 56 were presented by overall treatment group using SAF1.

Overall ADA result was defined as below:

- 'Positive' for a subject with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after pre-dose of Week 0 for subjects with negative ADA at pre-dose of Week 0, and treatment-boosted ADA indicates at least one positive result with higher titre level compared to pre-dose of Week 0 after pre-dose of Week 0 for subjects with positive ADA at pre-dose of Week 0.
- 'Negative' for a subject with negative ADA at Week 0 and without positive ADA until Week 8, Week 32, and Week 56.
- 'Inconclusive' for a subject with positive ADA at Week 0 and without positive result with higher titre level observed after pre-dose of Week 0 up to Week 8, Week 32, and Week 56.

If the fellow eye received Eylea due to AMD during the study period after randomisation, the ADA and NAb results obtained after treatment for the fellow eye were listed but excluded from the summary statistics.

Table 4: Incidence of anti-drug antibody (ADA) and neutralising antibodies (Nab) by visit and treatment group (safety set 1)

Table 12-27 Incidence of Anti-Drug Antibody (ADA) and Neutralising Antibodies (NAb) by Visit and Treatment Group (Safety Set 1)

Timepoint	Parameter	Result	SB15 N=224 n/n' (%)	Eylea Overall N=224 n/n' (%)	Eylea SB15 N=111[a] n/n' (%)	Eylea Eylea N=104[a] n/n' (%)	Total N=448 n/n' (%)
Week 0 (BL)	ADA	Positive	3/224 (1.3)	1/224 (0.4)	1/111 (0.9)	0/104 (0.0)	4/448 (0.9)
		Negative	221/224 (98.7)	223/224 (99.6)	110/111 (99.1)	104/104 (100.0)	444/448 (99.1)
	NAb	Positive	1/3 (33.3)	0/1 (0.0)	0/1 (0.0)	0/0 (-)	1/4 (25.0)
		Negative	2/3 (66.7)	1/1 (100.0)	1/1 (100.0)	0/0 (-)	3/4 (75.0)
Week 4	ADA	Positive	4/210 (1.9)	1/209 (0.5)	-	-	5/419 (1.2)
		Negative	206/210 (98.1)	208/209 (99.5)	-	-	414/419 (98.8)
	NAb	Positive	4/4 (100.0)	1/1 (100.0)	-	-	5/5 (100.0)
		Negative	0/4 (0.0)	0/1 (0.0)	-	-	0/5 (0.0)
Week 8	ADA	Positive	4/201 (2.0)	1/207 (0.5)	-	-	5/408 (1.2)
		Negative	197/201 (98.0)	206/207 (99.5)	-	-	403/408 (98.8)
	NAb	Positive	4/4 (100.0)	1/1 (100.0)	-	-	5/5 (100.0)
		Negative	0/4 (0.0)	0/1 (0.0)	-	-	0/5 (0.0)
Week 24	ADA	Positive	4/190 (2.1)	1/194 (0.5)	-	-	5/384 (1.3)
		Negative	186/190 (97.9)	193/194 (99.5)	-	-	379/384 (98.7)
	NAb	Positive	4/4 (100.0)	1/1 (100.0)	-	-	5/5 (100.0)
		Negative	0/4 (0.0)	0/1 (0.0)	-	-	0/5 (0.0)
Week 32	ADA	Positive	4/184 (2.2)	0/191 (0.0)	0/95 (0.0)	0/95 (0.0)	4/375 (1.1)
		Negative	180/184 (97.8)	191/191 (100.0)	95/95 (100.0)	95/95 (100.0)	371/375 (98.9)
	NAb	Positive	4/4 (100.0)	0/0 (-)	0/0 (-)	0/0 (-)	4/4 (100.0)
		Negative	0/4 (0.0)	0/0 (-)	0/0 (-)	0/0 (-)	0/4 (0.0)
Week 40	ADA	Positive	3/181 (1.7)	2/188 (1.1)	1/94 (1.1)	1/94 (1.1)	5/369 (1.4)
		Negative	178/181 (98.3)	186/188 (98.9)	93/ 94 (98.9)	93/ 94 (98.9)	364/369 (98.6)
	NAb	Positive	3/3 (100.0)	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)	5/5 (100.0)
		Negative	0/3 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/5 (0.0)
Week 56	ADA	Positive	4/174 (2.3)	2/182 (1.1)	1/90 (1.1)	1/92 (1.1)	6/356 (1.7)
		Negative	170/174 (97.7)	180/182 (98.9)	89/ 90 (98.9)	91/ 92 (98.9)	350/356 (98.3)
	NAb	Positive	4/4 (100.0)	2/2 (100.0)	1/1 (100.0)	1/1 (100.0)	6/6 (100.0)
		Negative	0/4 (0.0)	0/2 (0.0)	0/1 (0.0)	0/1 (0.0)	0/6 (0.0)

Treatment-induced or treatment-boosted ADA (overall ADA) up to Week 8, Week 32, and Week 56 was evaluated (Table 5).

Table 5: Incidence of overall anti-drug antibody (ADA) by visit and treatment group (safety set 1)

Table 12-28 Incidence of Overall Anti-Drug Antibody (ADA) by Visit and Treatment Group (Safety Set 1)

		SB15	Eylea			Total
Timepoint	Value	N=224 n/n' (%)	Overall N=224 n/n' (%)	SB15 N=111[a] n/n' (%)	Eylea N=104[a] n/n' (%)	N=448 n/n' (%)
Week 8 overall	Positive	2/210 (1.0)	0/209 (0.0)	-	-	2/419 (0.5)
	Negative	205/210 (97.6)	208/209 (99.5)	-	-	413/419 (98.6)
	Inconclusive	3/210 (1.4)	1/209 (0.5)	-	-	4/419 (1.0)
Week 32 overall	Positive	2/210 (1.0)	0/209 (0.0)	0/102 (0.0)	0/101 (0.0)	2/419 (0.5)
	Negative	205/210 (97.6)	208/209 (99.5)	101/102 (99.0)	101/101 (100.0)	413/419 (98.6)
	Inconclusive	3/210 (1.4)	1/209 (0.5)	1/102 (1.0)	0/101 (0.0)	4/419 (1.0)
Week 56 overall	Positive	2/210 (1.0)	1/209 (0.5)	0/102 (0.0)	1/101 (1.0)	3/419 (0.7)
	Negative	205/210 (97.6)	207/209 (99.0)	101/102 (99.0)	100/101 (99.0)	412/419 (98.3)
	Inconclusive	3/210 (1.4)	1/209 (0.5)	1/102 (1.0)	0/101 (0.0)	4/419 (1.0)

2.5.3. Discussion on clinical pharmacology

Pharmacokinetics

Methods

A PK assay for the determination of aflibercept (SB15 or Eylea) in serum from patients with neovascular AMD has been developed using an electrochemiluminescence (ECL) assay of Meso Scale Discovery (MSD) platform. A brief, but sufficient description of the PK assay is included. An ECL based assay was selected to improve sensitivity compared to an Enzyme-linked Immunosorbent Assay (ELISA) which is supported. The PK assay has been initially developed and validated for the quantification at Samsung Bioepis, but then transferred to and validated. During bioanalytical method validation the relevant validation parameters have been studied and these data indicate that the PK method is suitable for its use.

PK data analysis

No dedicated human Phase I PK studies were conducted. A demonstration of equivalence in PK between a biosimilar candidate and the reference product is an essential part of the comparability exercise. That said, in this specific IVT case, it is agreed that that it is not scientifically meaningful to predicate biosimilarity on a PK comparison of systemic exposure given the negligible and variable systemic concentrations of aflibercept

following IVT administration. To support the overall assessment of the systemic exposure of SB15 and Eylea, the PK profiles of SB15 and Eylea were evaluated in the subgroup population in clinical Phase III study (SB15-3001) to explore whether the low systemic concentrations of IVT administered SB15 and Eylea were within the same range. This approach was agreed during EMA scientific advice procedure (EMEA/H/SA/3629/1/2017/III).

Only the concentration of aflibercept was measured in the PK subset, which is deemed sufficient, as only aflibercept is expected to be the active drug.

Blood samples for PK assessment were collected at baseline, prior to IVT injection (C_{trough}) at various time points and after IVT injection around the anticipated t_{max}. As per the Eylea SmPC, C_{max} is attained within 1-3 days following IVT injection. Daily sampling around the anticipated t_{max} was performed following the fifth IVT injection at Week 24 (on 1 day, 2 days, and 3 days after the date of IVT injection). In contrast, following the first IVT injection at Week 0, samples were taken at a single time point between 24h and 72h after IVT injection. Daily sampling around the expected t_{max} after two administrations would have been preferrable to provide additional support for PK comparability. According to the Eylea SmPC, systemic concentrations of aflibercept were undetectable two weeks following dosage in almost all patients. The frequency of the PK sampling in study SB15-3001 did not allow confirmation of whether the same applies for SB15.

Of the 449 patients randomized, blood samples for PK assessment were collected in the Pharmacokinetic Analysis Set (PKS) (21 [9.4%] patients in the SB15 treatment group and 19 [8.4%] patients in the Eylea treatment group). The number of patients included in the PK analysis is deemed sufficient for determining whether there are major differences in systemic exposure between treatment arms.

Results

The demographic and baseline characteristics of the patients in the PK analysis set were well balanced between the two treatment groups. All samples at baseline were BLQ in both treatment arms. Most of the serum trough (pre-dose) conc. were BLQ at each timepoint up to Week 56 in both groups. This is considered a key observation, and is reassuring that, as for the reference treatment, serum concentrations are very limited also for the biosimilar candidate. The post-dose exposure levels at Week 0 and at Week 24 were overall within the similar range as reported in the SmPC for Eylea in nAMD patients, however only small and variable differences observed between treatment groups.

At Week 0 (24h-72h after IVT injection), serum conc. of aflibercept was somewhat higher in the SB15 group (geom.mean 46.642 ng/mL) compared to Eylea group (geom.mean 34.255), but with large variability (SD 42.1325 vs 56.8020; geo CV 87.2102% vs 100.1654%). One day after IVT injection at Week 24, serum conc. of aflibercept were similar between treatment arms (medians 32.820 ng/mL and 37.940 ng/mL; geom.means 39.063 ng/mL and 39.654 ng/mL in SB15 and Eylea groups, respectively). On Days 2 and 3 after IVT injection at Week 24, serum conc. of aflibercept were somewhat higher in the Eylea group compared to the SB15 group [on Day 2 after IVT injection at Week24: medians 25.570 ng/mL and 38.210 ng/mL, geom.means 29.918 ng/mL and 42.813 ng/mL in SB15 and Eylea group, respectively; on Day 3 after IVT injection at Week24: medians 21.640 ng/mL and 33.500 ng/mL, geom.means 24.459 ng/mL and 35.449 ng/mL in SB15 and Eylea group, respectively]. Through all post-dose timepoints, CV% ranged between 54.6341% and 89.3129% for SB15 and between 76.9999% and 100.1654% for Eylea.

The max serum conc. in the SB15 group was attained 1 day following IVT injection at Week24, after which a decline was observed. In the Eylea group the max serum concentration was attained 2 days after IVT injection at Week24.

Nonetheless, due to the limited number of patients included in the PK assessment, coupled with a further reduction in the number of measurements resulting from the exclusion of data from patients who received aflibercept treatment in the fellow eye, the large CV% (CV% from 54.6341% to 89.3129% for SB15 and from 76.9999% to 100.1654% for Eylea) at post-dose timepoints, these numerical differences should not be overinterpreted and it is concluded that there are indeed no major differences in systemic exposure between the groups. Additionally, given the overall very low systemic concentrations (ng/mL), and BLQ result for most of serum trough concentrations, these differences are not considered clinically relevant.

Pharmacodynamics

No dedicated (comparative) pharmacodynamics investigations have been performed as part of the clinical biosimilarity exercise. The applicant did not compare pharmacodynamic aspects of SB15 and Eylea. This is considered acceptable, as there are no applicable laboratory PD markers that could serve as specific surrogates for clinical efficacy and safety of aflibercept.

Immunogenicity

Methods

The development and validation of the immunogenicity assays has been appropriately described. In line with the respective guidelines a multi-tiered approach has been used. This approach includes a screening assay for identification of potential positive samples, a procedure for confirming the presence of antibodies and determining antibody specificity followed by ligand binding assays for assessment of the neutralizing capacity of antibodies and titer. The assays have been sufficiently described.

Immunogenicity analysis and results

Blood samples for immunogenicity assessment were collected in all randomised subjects at following time points: at baseline (BL), Weeks 4, 8, 24, 32, 40, and 56 (EOS visit) or ET visit.

At BL a total of 3/224 (1.3%) subjects in the SB15 group and 1/224 (0.4%) subjects in the Eylea group had a positive ADA response. One of the 3 ADA-positive subjects in the SB15 group also had neutralising antibodies at baseline.

Up to Week 56, most of the subjects were ADA negative at each timepoint. In the main period post-dose, i.e., before re-randomisation, the percentage of ADA-positive patients ranged between 1.9% (4/210) and 2.1% (4/190) in the SB15 group and it was stable at 0.5% in the Eylea group. After re-randomisation, the percentage of ADA-positive patients ranged from 1.7% (3/18) to 2.3% (4/147) in the SB15/SB15 group and was stable at 1.1% in both Eylea/SB15 and Eylea/Eylea group.

Up to Week 56, the percentage of ADA-positive patients was slightly higher in the SB15 group (max 2.3%) compared to the Eylea overall group (max 1.1%). Five subjects (2.2%) in the SB15 treatment group, 3 subjects (2.7%) in the Eylea+SB15 treatment group, and 1 subject (1.0%) in the Eylea+Eylea treatment group with positive ADA response had 1 or more instances of a positive NAb response up to Week 56.

As some patients were ADA/NAb-positive at Baseline, a more significant assessment involves the treatment-induced or treatment-boosted overall ADA up to Week 8, Week 32, and Week 56.

At Week 8, 2/210 (1%) subjects in the SB15 group and no subjects in the Eylea group had treatment-induced or treatment-boosted ADAs/NAbs. At Week 32, the numbers were the same as at Week 8. At Week 56, 2/210 (1%) subjects in the SB15 group, 1/101 (1.0%) subject in the Eylea/Eylea group and no subjects in the Eylea/SB15 group had treatment-induced or treatment-boosted ADAs/NAbs. These 2 subjects in the SB15

treatment group had treatment-induced positive ADA results at the majority of the assessments over the up to 56-week observation period with titres up to 50.

No subject in the PKS had positive ADA result up to Week 56, therefore the impact of immunogenicity on PK cannot be assessed.

The Applicant conducted a subgroup analysis for the PEP by immunogenicity. The results of the subgroup analysis by ADA result up to Week 8 cannot be assessed due to extremely small numbers of ADA positive patients up to Week 8 (2 subjects). Since the incidence of ADA through Week 56 was very low, it is not considered meaningful to request subgroup analyses at different time points.

Only one non-ocular TEAE (ankle fracture) was reported by one patient who was overall ADA positive up to Week 56 and some TEAEs were reported by patients with "inconclusive" ADA status. These TEAEs were not considered related to the treatment administered. Based on the adverse events that occurred in a small number of ADA/NAb positive patients, no concerns arise regarding the impact of immunogenicity on safety.

2.5.4. Conclusions on clinical pharmacology

The information on the used PK and immunogenicity assay is sufficient and it can be agreed that these assays are considered suitable for their use.

Pharmacokinetics:

Despite scarce PK sampling data in nAMD patients, it is concluded that no major differences in systemic exposure between SB15 and Eylea exist. Very low plasma aflibercept concentrations attest that no relevant systemic exposure exists, not only making it difficult to estimate PK parameters for PK equivalence testing between SB15 and Eylea, but also making such irrelevant from a clinical perspective.

Immunogenicity: Most of the patients of both treatment groups in the study SB15-3001 were ADA negative at each timepoint up to Week 56 and the incidence of ADAs was comparable between the two treatment groups. No subject in the PKS had positive ADA result up to Week 56, therefore the impact of immunogenicity on PK cannot be assessed. Based on the adverse events that occurred in a small number of ADA/NAb positive patients, no concerns arise regarding the impact of immunogenicity on safety.

In conclusion, the PK and immunogenicity data are considered supportive for the assessment of biosimilarity between SB15 and Eylea.

2.5.5. Clinical efficacy

2.5.5.1. Main study

SB15-3001

This was a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of SB15 compared to Eylea in subjects with neovascular AMD.

Figure 2: Study schema

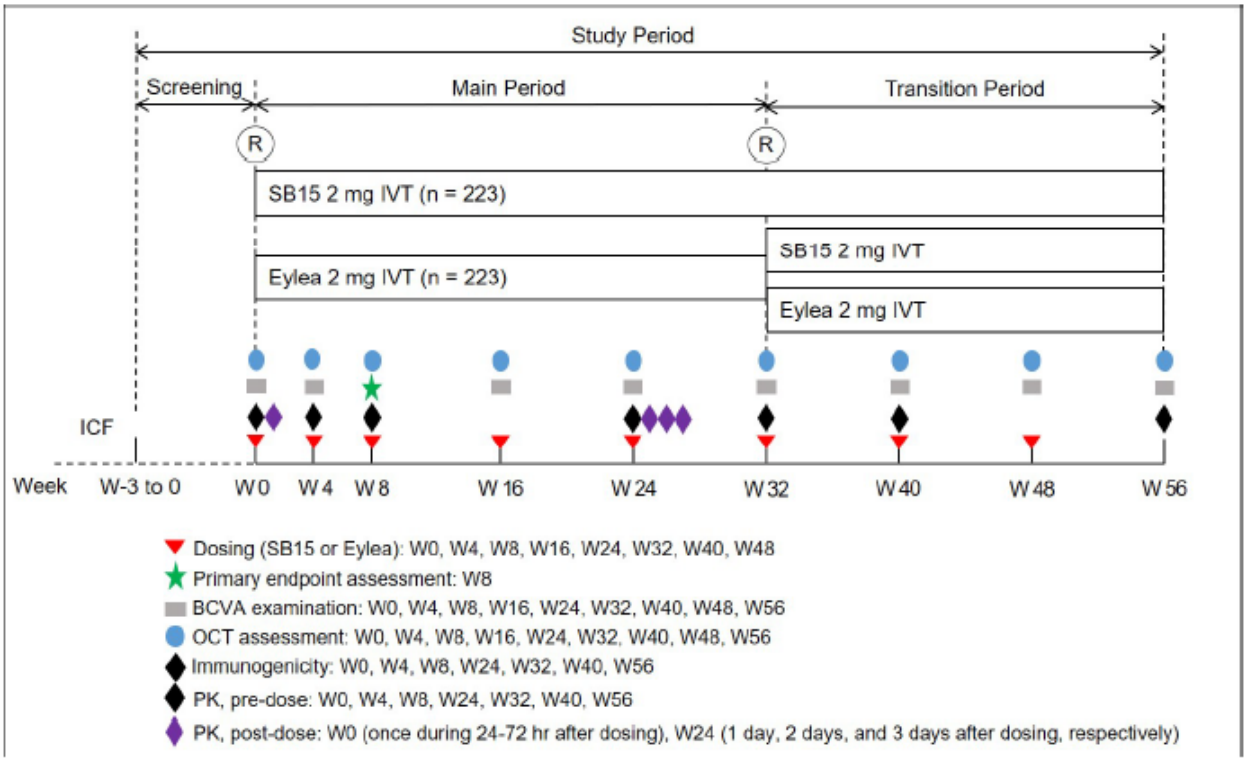


Figure 9-1 Graphical Study Design

BCVA = best corrected visual acuity; hr = hour; ICF = informed consent form; IVT = intravitreal; OCT = optical coherence tomography; PK = pharmacokinetics; R = randomisation, W = week

Methods

Subjects were randomised in a 1:1 ratio to receive either SB15 or Eylea (administered via intravitreal [IVT] injection 2 mg [0.05 mL] every 4 weeks for the first 3 consecutive visits (Weeks 0, 4, and 8), followed by 2 mg [0.05 mL] once every 8 weeks (Weeks 16, 24, 32, 40, and 48)). A total of 8 doses of IP were planned to be administered in the study.

At Week 32, subjects initially randomised to Eylea treatment group were re-randomised in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. Subjects initially randomised to SB15 continued to receive SB15 up to Week 48. The last assessments were done at Week 56, corresponding to the end of follow-up for all subjects.

Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse visual acuity (VA) was selected as the study eye. If both eyes had equal VA, the eye with clearer lens and ocular media was selected at the Investigator's discretion. If there was no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology, and subject preference were considered by the Investigator in making the selection. Subject with only one functional eye (defined as BCVA of counting finger or less on the eye with worse vision) was not allowed be enrolled, even if otherwise eligible for the study.

446 subjects were planned to be randomised. A total of 549 subjects were screened in the study of which 449 subjects were randomised.

Study Participants

The study was conducted in subjects with neovascular age-related macular degeneration (nAMD).

The study was conducted at a total of 56 investigational sites across 10 countries (Croatia, Czech Republic, Estonia, Hungary, Japan, Latvia, Poland, Republic of Korea, Russia, and United States [US]).

Key Inclusion Criteria:

1. Age ≥ 50 years at Screening

2. Treatment naïve, *active subfoveal choroidal neovascularisation (CNV) lesion secondary to AMD in the study eye

* Active CNV indicated presence of leakage and intra- or sub-retinal fluid which was confirmed by the central reading centre during Screening.

3. The area of CNV occupied at least 50% of total lesion in the study eye

4. Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars, and neovascularisation) in the study eye

5. Best corrected visual acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34, inclusive) using original series Early Treatment Diabetic Retinopathy Study (ETDRS) charts or 2702 series Number charts in the study eye at Screening and at Week 0 (Day 1) prior to randomisation

6. Non-childbearing potential female or safeguarding against pregnancy for WOCBP/their partners

Key exclusion criteria:

1. Study eye: Sub- or intra-retinal haemorrhage that comprised more than 50% of the entire lesion or presence of blood with the size of 1 DA or more involving the centre of fovea

2. Study eye: Scar, fibrosis, or atrophy involving the centre of the fovea

3. Study eye: Presence of CNV due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture, or pathologic myopia

4. Study eye: Presence of retinal pigment epithelial (RPE) tears or rips involving the macula

5. Study eye: Presence of macular hole at any stage

6. Study eye: Any concurrent macular abnormality other than AMD which could affect central vision or the efficacy of IP including but not limited to epiretinal membrane, vitreomacular traction, macular telangiectasia, retinal vascular abnormality, etc.

7. Study eye: Any concurrent ocular condition which, in the opinion of the Investigator, could either confound the interpretation of efficacy and safety of IP (e.g., ocular media opacities such as significant cataract, optic neuropathy) or require medical or surgical intervention during the study period

8. Either eye: History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy) or diabetic macular oedema (DME)

9. Study eye: Current vitreous haemorrhage

10. Either eye: Any previous IVT anti-vascular endothelial growth factor (VEGF) treatment (e.g., bevacizumab, ranibizumab, aflibercept, pegaptanib)

11. Any previous systemic anti-VEGF treatment

12. Study eye: History of treatment involving macula such as macular laser photocoagulation, photodynamic therapy (PDT), transpupillary thermotherapy (TTT), radiation therapy, or any ocular treatment for neovascular AMD

13. Any systemic treatment or therapy to treat neovascular AMD within 30 days prior to randomisation, and such treatment or therapy was not allowed during the study period.

14. Either eye: Active or suspected ocular and periocular infection at Screening or at randomisation

15. Either eye: Active intraocular inflammation including scleritis at Screening or at randomisation

16. Study eye: Uncontrolled ocular hypertension (defined as intraocular pressure [IOP] $\geq$ 25 mmHg despite treatment with anti-glaucoma medication) at Screening

17. Known allergic reactions and/or hypersensitivity to any component of Eylea or SB15

18. Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus, uncontrolled systemic hypertension (SBP $\geq$ 180 mmHg and/or DBP $\geq$ 100 mmHg on optimal medical regimen), or uncontrolled AF (resting heart rate $\geq$ 110 beats per minute) at Screening

19. Stroke, transient ischaemic attacks, or myocardial infarction within 180 days prior to randomisation

Treatments

Subjects were administered 2 mg SB15 or 2 mg Eylea IVT into the study eye every 4 weeks for the first 3 consecutive visits (Weeks 0, 4, and 8), followed by once every 8 weeks up to Week 48 (a total of 8 doses of IP) unless they were discontinued early from the IP.

Test Product, Dose and Mode of Administration, Batch Number
Test Product: SB15 (proposed aflibercept biosimilar) Solution for IVT injection **Presentation:** One vial of 0.05 mL contains 2 mg aflibercept **Mode of Administration:** IVT injection **Dose:** 2 mg (0.05 mL) every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48
Reference Product, Dose and Mode of Administration, Batch Number
Reference Product: Eylea (US sourced) Solution for IVT injection **Presentation:** One vial of 0.05 mL contains 2 mg aflibercept

Mode of Administration: IVT injection

Dose: 2 mg (0.05 mL) every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48

Prohibited concomitant therapy

The most important medications and treatments prohibited prior to randomization are enlisted in the eligibility criteria (see section 3.3.1.1.1).

Prohibited concomitant medications and treatments (from randomisation to EOS/ET visit) were following:

- IVT anti-VEGF treatment except IP (SB15 or Eylea) – study eye
- IVT anti-VEGF treatment (e.g., bevacizumab, ranibizumab, pegaptanib) except aflibercept – fellow eye. NOTE: If a subject had AMD in the fellow eye during the study period after randomisation, only Eylea (aflibercept) was allowed to treat AMD.
- Systemic anti-VEGF agents (e.g., bevacizumab, ziv-aflibercept)
- Treatment involving macula (e.g., macular laser photocoagulation, PDT, TTT, radiation therapy, or any ocular treatment for nAMD) – study eye
- Systemic treatment or therapy to treat neovascular AMD
- Intraocular or peribulbar corticosteroid injection/implant – study eye
- Any other intraocular surgery (including cataract surgery or YAG laser posterior capsulotomy) or lid surgery - study eye
- ocular IPs to treat neovascular AMD or diseases other than nAMD – study eye and fellow eye

Fellow eye treatment

The fellow eye (non-study eye) was not considered as an additional study eye. Subjects who were expected to be treated with anti-VEGF treatment on the fellow eye in the near future, especially prior to Week 8, were not to be enrolled and treatment with Eylea® for the fellow eye was to be avoided within the first 8 weeks after randomisation. If a subject had AMD in the fellow eye, the subject could receive ONLY Eylea® after Week 8 during the study period and should remain in the study.

Objectives

The **primary objective** of this study was to demonstrate the equivalence in efficacy of SB15 compared to Eylea in subjects with neovascular age-related macular degeneration (nAMD).

The null hypothesis tested for the primary efficacy analysis is that either (1) SB15 is inferior to Eylea® or (2) SB15 is superior to Eylea® based on a pre-specified equivalence margin.

Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

The **secondary objectives** were:

- To evaluate the safety of SB15 compared to Eylea®.
- To evaluate the systemic exposure of SB15 compared to Eylea® in subjects participating in PK evaluation.
- To evaluate the immunogenicity of SB15 compared to Eylea®.

No hypotheses were tested for the secondary efficacy endpoints.

Outcomes/endpoints

The primary estimand was not defined by the Applicant and has been devised by the Rapporteur based on available data.

Table 6

Population	**Patients with neovascular age-related macular degeneration (nAMD) who would not require rescue treatment or other prohibited concomitant treatments.**
Treatment condition<s>	Assignment to SB-15 in the hypothetical scenario of no discontinuation compared to assignment to US-licenced Eylea in the hypothetical scenario of no discontinuation.
Endpoint (variable)	Change from baseline in mean BCVA score at Week 8
Population-level summary	The LS mean difference in BCVA of the change from baseline between SB15 and US-Eylea
Intercurrent events and strategy to handle them	
Use of rescue treatment or other prohibited medication	Hypothetical
Withholding IP due to safety reasons	Hypothetical
Treatment discontinuation	Hypothetical/Principal Stratum (for subjects who discontinue before the first efficacy assessment following randomization and did not receive IP)
Protocol deviations	Hypothetical

Visual acuity (VA) was assessed in both the study eye and fellow eye (non-study eye) at Screening, prior to IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit.

Visual acuity was assessed using original series ETDRS charts or 2702 series Number charts at a starting distance of 4 meters, and then continue at a distance of 1 meter, if required by ETDRS protocol. Subject had to use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit. Visual acuity examiners and visual acuity lanes at investigational sites were certified to ensure consistent measurement of BCVA prior to BCVA test to subjects.

The **secondary efficacy endpoints** were:

- Change from BL in BCVA over time up to Week 32 and up to Week 56
- Proportion of subjects who lost <15 letters in BCVA compared to BL at Week 32 and Week 56 (proportion of subjects who maintained BCVA)
- Proportion of subjects who gained ≥15 letters in BCVA compared to BL at Week 32 and Week 56
- Change from BL in central subfield thickness (CST) and total retinal thickness (TRT) at Week 4, and over time up to Week 32 and up to Week 56
    - CST measured from internal limiting membrane (ILM) to RPE in 1-mm central subfield
    - TRT measured from ILM to Bruch's membrane (BM) in 1-mm central subfield
- Proportion of subjects with intra- or sub-retinal fluid on OCT at Week 32 and Week 56
- Change from BL in CNV area at Week 32 and Week 56
- Proportion of subjects with active CNV leakage at Week 32 and Week 56

Anatomical Parameters:

The average retinal thickness in the central 1-mm area in the ETDRS grid (central subfield thickness [CST] and total retinal thickness [TRT]), the presence of intra- or sub-retinal fluid and sub-RPE fluid was evaluated using optical coherence tomography (OCT) at Screening, prior to IVT injection of IP until Week 48, and at Week 56 (EOS visit) or ET visit (secondary endpoint).

The CNV area and the presence of CNV leakage were also evaluated using FP/FA at Screening and prior to IVT injection of IP at Week 32. Fundus photography (FP) / Fluorescein angiography (FA) was also performed at Week 56 (EOS visit) or ET visit (secondary endpoint).

For OCT, FP and FA images had to be sent to central reading centre.

Exploratory endpoints:

1. Proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56

   The quality of life (QOL) was assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25). NEI VFQ-25 was performed at Week 0 (Day 1) after randomisation, at Week 32 and Week 56 (EOS visit) or ET visit (exploratory endpoint).

2. Change from BL in subscale scores and composite scores of NEIVFQ-25 at Week 32 and Week 56

Sample size

With the equivalence limit of [−3 letters, 3 letters], 216 subjects per treatment group was calculated with the assumptions of the mean difference of 0.5 letters and SD of 9.0 at the overall 5% significance level, providing 80% power to reject the null hypothesis. Overall, 446 subjects (223 per treatment group) were assumed to give 216 completers per treatment group assuming a 3% loss from the randomised subjects.

Randomisation and blinding (masking)

Randomisation

A unique subject number was assigned to the subject at Screening. The subject number was used to register the subject using the Interactive Web Response System (IWRS) and the subject was then randomised (in a ratio of 1:1) to either SB15 or Eylea.

At Week 32, subjects receiving Eylea were re-randomised in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. Subjects receiving SB15 continued to receive SB15 but they also followed the randomisation procedure to maintain masking.

These randomisations occurred according to a computer-generated randomisation scheme which randomised subjects at a centre-level. If a subject was withdrawn, the randomisation number was not reused. At each study visit, the Investigator or designee contacts the IWRS and an appropriate number of codes was provided. These codes indicated which vials had been dispensed to the subject. The assigned subject number(s) and randomisation number(s) were not reused.

Blinding

The study was double-masked. Subjects, Investigators, and other site personnel remained masked to the treatment group assignment throughout the study period after randomisation. The treatment allocation remained masked throughout the study period except for staff designated for unmasking after the interim analysis (Week 32). To ensure the masking of the treatment group assignment, one carton contained only one IP vial (SB15 or Eylea). The carton and IP vial were packed and labelled in identical appearance.

Unmasking (unblinding)

Unblinding was considered only when knowledge of the treatment group to which the subject had been assigned was deemed essential for the subject's safety by the Investigator. In general, unblinding of subjects during the conduct of the clinical study was not allowed unless there were compelling medical or safety reasons to do so. Emergency unmasking was allowed to be performed by the Investigator through the Interactive Web Response System (IWRS) if deemed necessary during the study period after randomisation.

If the treatment group assigned to the subject was unblinded, the Investigator was to promptly document and explain to the Sponsor about any premature unblinding (e.g., accidental unmasking, unmasking due to a serious AE [SAE]) of the IP(s) which was administered to the subject. Pertinent information regarding the circumstances of unmasking of a subject's treatment group was to be documented in the subject's source documents. This included who performed the unmasking, the subject(s) affected, the reason for the unmasking, the date of the unmasking, and the relevant IP information. After unmasking (except unmasking for the purpose of pre-planned regulatory reporting), subjects were to be discontinued from the IP.

After all subjects completed the procedures at Week 24/32 (to be clarified, see corresponding OC), or its corresponding visit, a limited number of identified individuals of the Sponsor and/or CRO were unmasked only for the reporting purpose to regulatory agency. In addition, Coordinating Investigator was unmasked to review the main clinical study report (CSR) on behalf of Investigators. Available efficacy and safety data, PK and immunogenicity data were analysed and reported in the main CSR dated Mar 23, 2022. However, subjects, Investigators, and other site personnel remained masked throughout the whole study period.

After the last subject completed the procedures at Week 56 (end of study [EOS] visit) or the corresponding visit and database was locked, all the treatment group assignments were unmasked, and all study data were analysed and reported in this final CSR.

Statistical methods

Planned analyses

Analysis populations:

- Randomised Set (RAN) consists of all subjects who received a randomisation number at the randomisation visit.
- Full Analysis Set (FAS) consists of all randomised subjects. Following the intent-to-treat principle, subjects were analysed according to the treatment group they are assigned to at randomisation. However, subjects who did not have any efficacy assessment result after randomisation and did not receive IP during the study period were excluded from FAS.
- Per-Protocol Set (PPS) consists of all FAS subjects who had BCVA assessment result at baseline and Week 8 without any major protocol deviations (PDs) that had impact on the BCVA assessment. Major PDs that lead to exclusion from this set were pre-defined prior to unmasking the treatment group assignment for analyses.
- Safety Set 1 (SAF1) consists of all subjects who received at least one IP during the study period. Subjects were analysed according to the IP received.
- Safety Set 2 (SAF2) consists of all subjects in the SAF1 who received at least one IP after re-randomisation at Week 32. Subjects were analysed according to the IP received.
- PK Analysis Set (PKS) consists of all subjects in the SAF1 who participated in PK evaluation at PK investigational sites (PK subjects) and had at least one serum concentration data

Primary Analysis:

For the EMA submission, the primary efficacy analysis was performed for the FAS with the change from baseline in BCVA at Week 8 using an analysis of covariance model with the baseline BCVA as a covariate and region (or pooled centres) and treatment group as factors. The equivalence between the two treatment groups was to be declared if the two-sided 95% CI of the difference of LSMean of change from baseline in BCVA at Week 8 were entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The same analysis was to be performed for the PPS as a sensitivity analysis. For those subjects who drop out of the study prematurely, a multiple imputation was to be used under the missing at random assumption. The 95% CI of the difference between the two treatment groups was to be estimated for the FAS as supportive analysis.

Missing data imputation:

For the primary analysis with the FAS for BCVA, missing data were imputed for subjects who have a missing value prior to or on the primary analysis time-point. A MAR approach assumes that subjects who had missing values are similar to similar subjects who completed the study in that main treatment group.

For the components of BCVA, the missing letter were imputed by MI method with Markov-Chain Monte Carlo (MCMC)/Monotone Regression procedures. The MI method was applied as follows based on components of BCVA:

- For the intermittent missing values, the missing value was filled in using the MCMC method with multiple chains, monotone missing data imputing pattern. A total of 100 sets of imputations was performed. The seed used for these imputations was 4238 and all other multiple imputation procedures described in this SAP used this same seed as well.

The resulting 100 imputed data sets have a monotone missing pattern and were imputed using a method for monotone missingness:

- For monotone missing data, monotone regression will be used to impute missing data. The procedure was based on the 100 imputed datasets generated from the MCMC procedure and was performed by Imputation. This was based on 100 sets of imputations. The SAS® PROC MI procedure was used for the imputation.

Sensitivity analyses:

An additional sensitivity analysis using the tipping-point approach which assume Missing-not-at- Random (MNAR) will be conducted to assess the robustness of the primary analysis result.

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 SB15 and Eylea will be identified.

The analysis will be performed based on components of BCVA using a general three-step approach:

(1) Achieve monotone missing data pattern by MCMC procedure, a total of 100 sets of imputations will be performed. Impute the missing data by monotone regression, and apply delta adjustments for Week 8 total BCVA letter score, subjects with missing data have, on average, worse or better efficacy compared to those who have values. The mean difference between the (unobserved) missing values and observed values can vary independently for the different treatment groups.

(2) Each of these imputed datasets (which contains identical values of non-missing data but different values imputed for missing data) will be analysed using standard SAS procedure, e.g., PROC MIXED etc.

(3) Results from all imputed datasets are then combined together for overall inference using PROC MIANALYZE.

For BCVA change from baseline at Week 8, seven equally spaced shifts (-6 to 6 by 2) for the BCVA change from baseline for subjects with missing data will be explored.

Planned subgroup analyses

The primary efficacy variable BCVA was summarised and analysed by the following prognostic factors at baseline or immunogenicity (8-week anti-drug antibodies (ADA) result was defined as an overall ADA result up to Week 8, refer to Section 8.6) results for exploratory purpose:

- Summary of change from baseline in BCVA by overall ADA result up to Week 8 for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by overall ADA result up to Week 8 for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by lesion type (Occult, Predominantly Classic, and Minimally Classic) at baseline for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by total lesion area (≤4DA vs. >4DA) at baseline for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by country for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by BCVA baseline (<50 letter score vs. ≥ 50 letter score) for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by Age group (<75 years vs. ≥75 years) for FAS

- Subgroup analysis of change from baseline in BCVA at Week 8 by Iris Color Group in Study Eye (Light Color and Dark Color) for FAS

In addition, forest plot will be used to display the difference of LSMean of change from baseline in BCVA at Week 8 between main treatment groups, with 95% CI and 90% CI respectively by predefined subgroups above, for each subgroup level, a covariance model with baseline BCVA as a covariate (except for subgroup factor BCVA baseline analyses), country and treatment as fixed factors will be used to construct the difference of LSMean and CI.

Error probabilities, adjustment for multiplicity and interim analyses

No multiple comparison adjustments for type I error was used.

Changes from protocol-specified analyses

A number of changes were implemented between SAP versions before finalization on Dec. 14, 2021. Amendment 1 dated May 10, 2022 added additional clarifications regarding treatment groups and missing data imputation.

Results

Participant flow

Figure 3: Participant flow

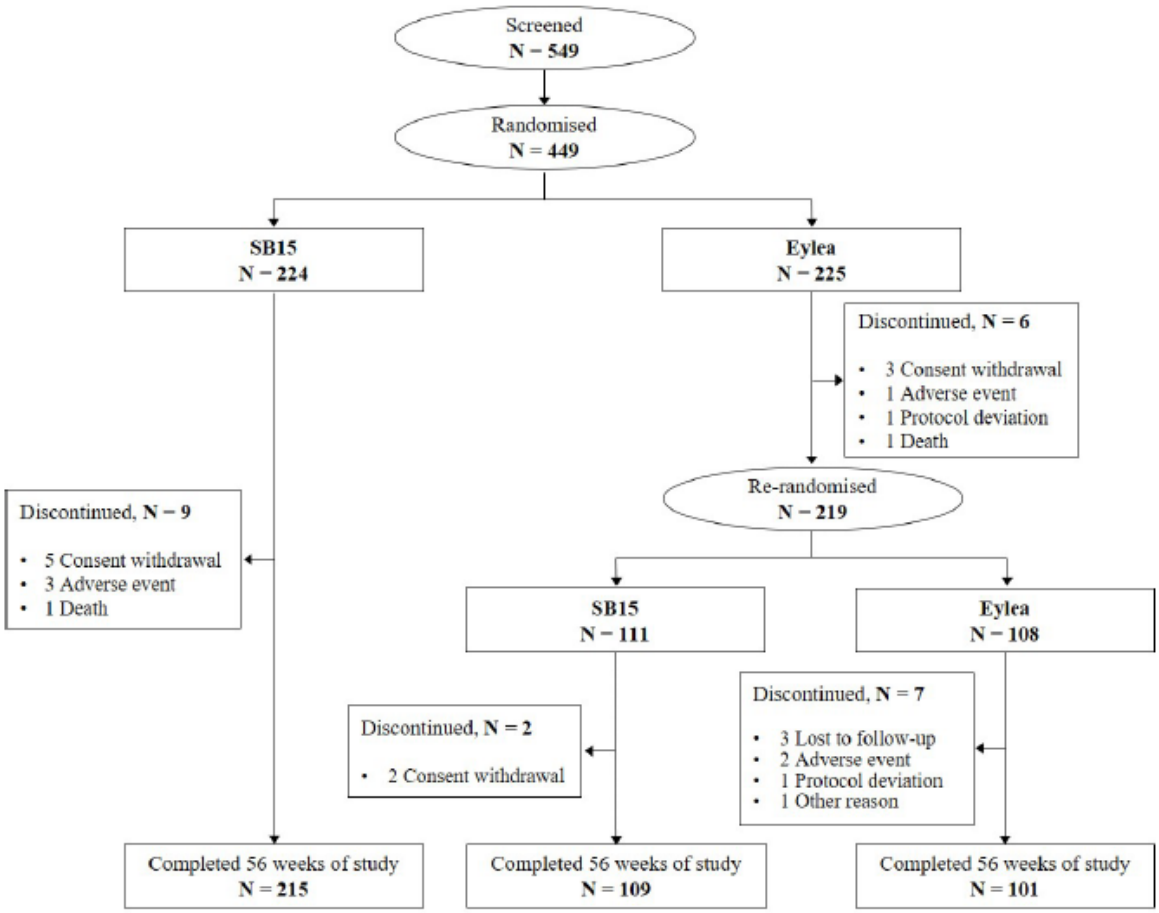


Figure 10-1 Subject Disposition
Source: Table 14.1-1.1

First Subject Signed Informed Consent: Jun 23, 2020; Last Subject's Week 56 Visit: Mar 16, 2022

Of the 449 subjects who were randomised, 438 (97.6%) subjects completed 32 weeks of the study (main period) and 425 (97.0%) subjects completed 56 weeks of the study (EOS). Prior to Week 32, 11 (2.4%) subjects discontinued treatment with the IP. The most common reason for discontinuation from IP before Week 32 was consent withdrawal by subject (8 [1.8%] subjects). After transition at Week 32 to the end of treatment at Week 48, 11 (2.5%) subjects discontinued treatment with the IP. The most common reasons for discontinuation from IP after transition at Week 32 to the end of treatment at Week 48 were AEs and lost to follow-up (3 [0.7%] subjects each). After the end of treatment to the end of study at Week 56, 2 (0.5%) subjects discontinued from the study, both of which were due to AEs.

Table 7: Subject disposition by treatment group (enrolled set)

Table 10-1 Subject Disposition by Treatment Group (Enrolled Set)

Number (%) of subjects	SB15	Eylea			Total
	n (%)	Overall n (%)	SB15 n (%)	Eylea n (%)	n (%)
Screened	-	-	-	-	549
Screening failures	-	-	-	-	100
Reasons for screening failures					
Does not meet eligibility criteria	-	-	-	-	83 (83.0)
Consent withdrawal	-	-	-	-	15 (15.0)
Lost to follow-up	-	-	-	-	0 (0.0)
Other	-	-	-	-	2 (2.0)
Randomised at Week 0[a]	224 (100.0)	225 (100.0)	-	-	449 (100.0)
Completed at Week 8[a]	223 (99.6)	224 (99.6)	-	-	447 (99.6)
Subject discontinuation from IP before Week 8[a]	1 (0.4)	1 (0.4)	-	-	2 (0.4)
Main reasons for IP discontinuation					
Adverse event	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Consent withdrawal by subject	1 (0.4)	1 (0.4)	-	-	2 (0.4)
Lost to follow-up	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Death	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Protocol Deviation	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Disease progression/Lack of efficacy according to Investigator decision	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Other	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Subject discontinuation from IP before Week 8 related to COVID-19[a,c]	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Completed at Week 32[a]	219 (97.8)	219 (97.3)	-	-	438 (97.6)
Subject discontinuation from IP before Week 32[a]	5 (2.2)	6 (2.7)	-	-	11 (2.4)
Main reasons for IP discontinuation					
Adverse event	0 (0.0)	1 (0.4)	-	-	1 (0.2)
Consent withdrawal by subject	5 (2.2)	3 (1.3)	-	-	8 (1.8)
Lost to follow-up	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Death	0 (0.0)	1 (0.4)	-	-	1 (0.2)
Protocol deviation	0 (0.0)	1 (0.4)	-	-	1 (0.2)
Disease progression/Lack of efficacy according to Investigator decision	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Other	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Subject discontinuation from IP before Week 32 related to COVID-19[a,c]	0 (0.0)	0 (0.0)	-	-	0 (0.0)
Randomised at Week 32[b]	219 (100.0)	219 (100.0)	111 (100.0)	108 (100.0)	438 (100.0)

Number (%) of subjects	SB15	Eylea			Total
	n (%)	Overall n (%)	SB15 n (%)	Eylea n (%)	n (%)
Completed end of treatment at Week 48[b]	215 (98.2)	212 (96.8)	109 (98.2)	103 (95.4)	427 (97.5)
Subject discontinuation from IP after transition at Week 32 up to end of treatment at Week 48[b]	4 (1.8)	7 (3.2)	2 (1.8)	5 (4.6)	11 (2.5)
Main reasons for IP discontinuation					
Adverse event	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Consent withdrawal by subject	0 (0.0)	2 (0.9)	2 (1.8)	0 (0.0)	2 (0.5)
Lost to follow-up	0 (0.0)	3 (1.4)	0 (0.0)	3 (2.8)	3 (0.7)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Protocol deviation	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.2)
Disease progression/Lack of efficacy according to Investigator decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.9)	1 (0.2)
Subject discontinuation from IP after transition at Week 32 up to end of treatment at Week 48 related to COVID-19[b,c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Completed end of study at Week 56[b]	215 (98.2)	210 (95.9)	109 (98.2)	101 (93.5)	425 (97.0)
Subject discontinuation after the end of the treatment up to end of study at Week 56[b]	0 (0.0)	2 (0.9)	0 (0.0)	2 (1.9)	2 (0.5)
Main reasons for discontinuation					
Adverse event (including COVID-19 disease)	0 (0.0)	2 (0.9)	0 (0.0)	2 (1.9)	2 (0.5)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject refusal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject refusal due to COVID-19 risk	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative due to COVID-19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

COVID-19 = Coronavirus Disease 2019; IP = investigational product; n = number of subjects

Percentages of screening failure reasons were based on number of screening failures.

a Percentages were based on the number of randomised subjects at Week 0.

b Percentages were based on the number of randomised subjects at Week 32.

c 'Related to COVID-19' was assessed by Investigator's decision and associated with the main reason for discontinuation.

Source: Table 14.1-1.1

Conduct of the study

Protocol amendments

Only country specific amendments were made pertinent to Japan and Korea which are not considered relevant for the European MA.

Protocol deviations

A total of 192 (42.8%) subjects had PDs and 93 (20.7%) subjects had at least 1 major PD. Major PDs were defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments. The most common major PDs that led to exclusion from PPS were related to study procedures in 12 (2.7%) subjects, followed by violations of inclusion criteria in 3 (0.7%) subjects (Table 10-2).

Up to Week 56, 1 (0.2%) subject had missed a study visit due to subject refusal due to COVID-19 risk.

Seven (1.6%) subjects had visit window deviation related to COVID-19; 2 (0.4%) subjects due to AE of COVID-19 infection, 1 (0.2%) subject refusal due to COVID-19 risk, and 4 (0.9%) subjects for administrative reason due to COVID-19 (Listing 16.2.1-1.2). During the study, the impact on compliance of study visit from the COVID-19 pandemic was low.

Table 8: Summary of protocol deviation by main treatment group (randomised set)

Table 10-2 Summary of Protocol Deviation by Main Treatment Group (Randomised Set)

	SB15 N=224	Eylea N=225	Total N=449
Number (%) of subjects	n (%)	n (%)	n (%)
Any protocol deviation	87 (38.8)	105 (46.7)	192 (42.8)
With at least one major protocol deviation	39 (17.4)	54 (24.0)	93 (20.7)
- Excluded from Per-Protocol Set	6 (2.7)	11 (4.9)	17 (3.8)
Study procedure	5 (2.2)	7 (3.1)	12 (2.7)
Inclusion criteria	0 (0.0)	3 (1.3)	3 (0.7)
Concomitant medication criteria	0 (0.0)	1 (0.4)	1 (0.2)
Exclusion criteria	1 (0.4)	0 (0.0)	1 (0.2)
Withdrawal criteria	0 (0.0)	1 (0.4)	1 (0.2)
- Others	35 (15.6)	47 (20.9)	82 (18.3)
Study procedure	30 (13.4)	36 (16.0)	66 (14.7)
IP compliance	3 (1.3)	11 (4.9)	14 (3.1)
Exclusion criteria	2 (0.9)	2 (0.9)	4 (0.9)
Concomitant medication criteria	1 (0.4)	2 (0.9)	3 (0.7)
With at least one minor protocol deviation	68 (30.4)	81 (36.0)	149 (33.2)
Study procedure	68 (30.4)	80 (35.6)	148 (33.0)
IP compliance	0 (0.0)	1 (0.4)	1 (0.2)

IP = investigational product; N = number of subjects in the Randomised Set; n = number of subjects with protocol deviation
Percentages are based on the number of subjects in the Randomised Set.
Others: Major protocol deviations not excluded from Per-Protocol Set.
Source: Table 14.1-1.4

Table 9: Summary of visit not done and window deviation by treatment group (randomised set)

Table 14.1-1.3 (Page 1 of 4)
Summary of Visit Not Done and Window Deviation by Treatment Group
Randomised Set

Timepoint	Category	SB15 N=224 n (%)	Eylea Overall N=225 n (%)	Eylea SB15 N=111* n (%)	Eylea Eylea N=108* n (%)	Total N=449 n (%)
Week 4	Reason for visit not done	0 (0.0)	1 (0.4)			1 (0.2)
	Adverse event (including COVID-19 disease)	0 (0.0)	1 (0.4)			1 (0.2)
	Subject refusal due to COVID-19 risk	0 (0.0)	0 (0.0)			0 (0.0)
	Administrative due to COVID-19	0 (0.0)	0 (0.0)			0 (0.0)
	Other	0 (0.0)	0 (0.0)			0 (0.0)
	Reason for visit window deviation	4 (1.8)	3 (1.3)			7 (1.6)
	Adverse event (including COVID-19 disease)	2 (0.9)	0 (0.0)			2 (0.4)
	Subject refusal due to COVID-19 risk	0 (0.0)	0 (0.0)			0 (0.0)
	Administrative due to COVID-19	0 (0.0)	2 (0.9)			2 (0.4)
	Other	2 (0.9)	1 (0.4)			3 (0.7)
Week 8	Reason for visit not done	0 (0.0)	0 (0.0)			0 (0.0)
	Adverse event (including COVID-19 disease)	0 (0.0)	0 (0.0)			0 (0.0)
	Subject refusal due to COVID-19 risk	0 (0.0)	0 (0.0)			0 (0.0)
	Administrative due to COVID-19	0 (0.0)	0 (0.0)			0 (0.0)
	Other	0 (0.0)	0 (0.0)			0 (0.0)
	Reason for visit window deviation	3 (1.3)	2 (0.9)			5 (1.1)
	Adverse event (including COVID-19 disease)	3 (1.3)	0 (0.0)			3 (0.7)
	Subject refusal due to COVID-19 risk	0 (0.0)	1 (0.4)			1 (0.2)
	Administrative due to COVID-19	0 (0.0)	0 (0.0)			0 (0.0)
	Other	0 (0.0)	1 (0.4)			1 (0.2)

Baseline data

Overall, the mean age was 74.0 years (range: 50-96 years) and the majority of subjects were white (76.2%). A slightly higher proportion of females (55.7%) vs males (44.3%) participated in the study. The mean body mass index (BMI) was 27.22 kg/m^2 (range: 16.9-45.8 kg/m^2). Most patients were European (61.7%). The baseline demographic characteristics were comparable across the treatment groups. The mean baseline BCA was 59.2 (median 62.0). The majority of patients in both groups had ≥50 letter score at baseline (overall 82.2%).

The majority of patients in the study had occult lesion type (56.8%), with slightly higher percentage of patients in SB15 group (61.6%) compared to Eylea group (52.0%). The mean time since diagnosis of nAMD in the study eye was 0.227 years. The man IOP was 15.1 mmHg. More than half of patients (57.9%) had cataract in the study eye at baseline. Most of the baseline characteristics were comparable across treatment arms. However, there was a statistically significant difference between treatment arms in the mean central subfield thickness (353.275 mcm and 382.296 mcm in SB15 and Eylea group, respectively, p= 0.0053) and in the mean proportion of patients with intra-retinal fluid (47.8% and 60.4% in SB15 and Eylea group, respectively, p = 0.0070) at baseline. A post-hoc analysis of IVT aflibercept injection for nAMD patients, the treatment effect of aflibercept (i.e. on the changes in central retinal thickness [CRT] at Week 52) was found to be correlated with baseline CRT levels; the thicker the CRT at baseline, the greater the magnitude of the changes in CRT (see Outcomes and estimation). Ocular and non-ocular (especially with regard to the vascular disorders) medical and surgical history was balanced across treatment arms. No concerns arise from the prior or concomitant medications. No subject received prohibited medications during any study period.

Numbers analysed

Table 10: Number (%) of subjects in the analysis sets by treatment group (randomised set)

Table 11-1 Number (%) of Subjects in the Analysis Sets by Treatment Group (Randomised Set)

	SB15	Eylea			Total
		Overall	SB15	Eylea	
Number (%) of subjects	N=224 n (%)	N=225 n (%)	N=111[a] n (%)	N=108[a] n (%)	N=449 n (%)
Randomised Set	224 (100.0)	225 (100.0)	111 (100.0)	108 (100.0)	449 (100.0)
Full Analysis Set	224 (100.0)	224 (99.6)	111 (100.0)	108 (100.0)	448 (99.8)
Per-Protocol Set	215 (96.0)	214 (95.1)	104 (93.7)	106 (98.1)	429 (95.5)
Safety Set 1	224 (100.0)	224 (99.6)	111 (100.0)	104 (96.3)	448 (99.8)
Safety Set 2	219 (97.8)	215 (95.6)	111 (100.0)	104 (96.3)	434 (96.7)
Pharmacokinetic Analysis Set	21 (9.4)	19 (8.4)	-	-	40 (8.9)

N = number of subjects in the Randomised Set; n = number of subjects

[a] Based on subjects who had re-randomisation at Week 32, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Percentages were based on the number of subjects in the Randomised Set.

Source: Table 14.1-2.1

Outcomes and estimation

Primary efficacy analysis

The primary efficacy analysis was performed for the FAS with the change from baseline in BCVA at Week 8 (Table 11). The sensitivity analysis and subgroup analysis were performed for change from baseline in BCVA at Week 8.

Table 11: Primary analysis of change from baseline in BCVA at week 8 (full analysis set)

Table 11-6 Primary Analysis of Change from Baseline in BCVA at Week 8 (Full Analysis Set)

Timepoint	Treatment	n	LSM (SE)	Difference (SB15 – Eylea)		
				LSM (SE)	90% CI	95% CI
Week 8	SB15 (N=224)	224	6.7 (0.56)	0.1 (0.71)	[−1.1, 1.2]	[−1.3, 1.4]
	Eylea (N=224)	224	6.6 (0.57)			

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; LSM = least square mean; MAR = Missing-at-Random; MI = multiple imputation; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at Week 8; SE = standard error

Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and country and treatment as fixed factors.

BCVA letter scores at 4 meter and 1 meter were imputed by MI method with the assumption of monotone missing pattern and regression method under the MAR.

Source: Table 14.2-2.1

Sensitivity analyses

To explore the robustness of the change from baseline in BCVA at Week 8 for the FAS, the change from baseline in BCVA at Week 8 and its 95% CI were analysed and calculated for the FAS (Table 12) and PPS (Table 13) based on the available cases.

Sensitivity Analysis in the FAS

Table 12: Sensitivity analysis of change from baseline in BCVA based on available case at week 8 (full analysis set)

Table 11-7 Sensitivity Analysis of Change from Baseline in BCVA Based on Available Case at Week 8 (Full Analysis Set)

Timepoint	Treatment	n	LSM (SE)	Difference (SB15 – Eylea)		
				LSM (SE)	90% CI	95% CI
Week 8	SB15 (N=224)	223	6.7 (0.56)	0.1 (0.71)	[−1.1, 1.2]	[−1.3, 1.5]
	Eylea (N=224)	224	6.6 (0.57)			

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; LSM = least square mean; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at Week 8; SE = standard error

Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and country and treatment as fixed factors.

BCVA letter scores with missing value were not imputed, available case was used for analysis.

Source: Table 14.2-2.2

Sensitivity Analysis in the PPS

Table 13: Sensitivity analysis of change from baseline in BCVA based on available case at week 8 (per protocol set)

Table 11-8 Sensitivity Analysis of Change from Baseline in BCVA Based on Available Case at Week 8 (Per-Protocol Set)

Timepoint	Treatment	n	LSM (SE)	Difference (SB15 – Eylea)		
				LSM (SE)	90% CI	95% CI
Week 8	SB15 (N=215)	215	6.6 (0.57)	−0.2 (0.73)	[−1.4, 1.0]	[−1.6, 1.2]
	Eylea (N=214)	214	6.8 (0.58)			

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; LSM = least square mean; N = number of subjects in the Per-Protocol Set; n = total number of subjects with available data at Week 8; SE = standard error

Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and country and treatment as fixed factors.

Source: Table 14.2-2.3

Secondary endpoints

1. Change from Baseline in BCVA Over Time up to Week 32 and up to Week 56 (Figure 4, Table 14)

Figure 4: Mean change from baseline through week 56 in BCVA (full analysis set)

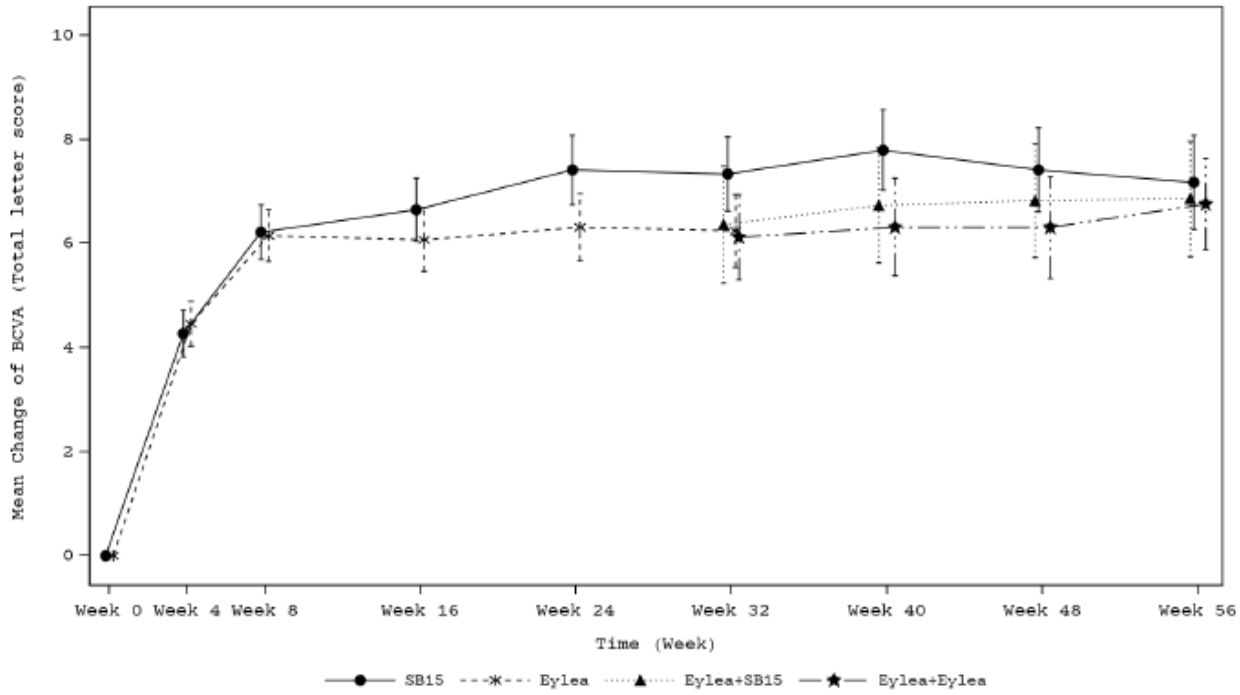


Figure 11-1 Mean Change from Baseline Through Week 56 in BCVA (Full Analysis Set)

BCVA = best corrected visual acuity (total letter score)

The symbol and error bar represented mean and standard error at each timepoint.

Source: Figure 14.2-1.1

Table 14: Analysis of change from baseline in BCVA at week 32 and week 56 (full analysis set)

Table 11-9 Analysis of Change from Baseline in BCVA at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n	LSM (SE)	Difference (A – B)		
				LSM (SE)	90% CI	95% CI
Available Case						
Week 32	SB15 [N=224] (A)	219	7.6 (0.78)	1.1 (1.00)	[−0.5, 2.8]	[−0.8, 3.1]
	Eylea [N=224] (B)	216	6.5 (0.80)			
Week 56	SB15[a] [N=224] (A)	216	7.4 (0.93)	0.4 (1.45)	[−2.0, 2.8]	[−2.5, 3.2]
	Eylea[a] [N=113] (B)	101	7.0 (1.29)			
	Eylea+SB15[b] [N=111] (A)	109	7.9 (1.13)	0.0 (1.42)	[−2.3, 2.4]	[−2.8, 2.8]
	Eylea+Eylea[b] [N=108] (B)	101	7.8 (1.15)			
	SB15[a] [N=224] (A)	216	7.6 (0.89)	0.4 (1.15)	[−1.5, 2.3]	[−1.8, 2.7]
	Eylea overall [N=224] (B)	210	7.2 (0.92)			
MI Assuming MAR						
Week 32	SB15 [N=224] (A)	224	7.6 (0.78)	1.3 (0.99)	[−0.3, 3.0]	[−0.6, 3.3]
	Eylea [N=224] (B)	224	6.3 (0.79)			
Week 56	SB15[a] [N=224] (A)	224	7.3 (0.91)	0.9 (1.39)	[−1.4, 3.2]	[−1.8, 3.6]
	Eylea[a] [N=113] (B)	113	6.4 (1.24)			
	Eylea+SB15[b] [N=111] (A)	111	7.9 (1.11)	0.4 (1.40)	[−1.9, 2.7]	[−2.3, 3.2]
	Eylea+Eylea[b] [N=108] (B)	108	7.5 (1.13)			
	SB15[a] [N=224] (A)	224	7.5 (0.88)	0.7 (1.12)	[−1.2, 2.5]	[−1.5, 2.9]
	Eylea overall [N=224] (B)	224	6.8 (0.90)			

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; FAS = full analysis set; LSM = least square mean; MAR = Missing-at-Random; MI = multiple imputation; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at each timepoint; SE = standard error

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32 among the FAS, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and country and treatment as fixed factors. LSM is adjusted mean of each treatment after adjusting covariates from the model based on data of treatments A and B.

2. Proportion of Subjects Who Lost < 15 Letters in BCVA Compared to BL at W32 and W56 (Table 15)

Table 15: Analysis of proportion of subjects who lost fewer than 15 letter in BCVA compared to the baseline at week 32 and week 56 (full analysis set)

Table 11-10 Analysis of Proportion of Subjects who Lost Fewer than 15 Letters in BCVA Compared to Baseline at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n'	n	(%)	Adjusted Risk Difference (A – B)	
					Estimate	95% CI
Week 32	SB15 (N=224) (A)	219	214	(97.7)	1.0	[−2.04, 4.10]
	Eylea (N=224) (B)	216	209	(96.8)		
Week 56	SB15[a] [N=224] (A)	216	207	(95.8)	−2.4	[−6.18, 1.40]
	Eylea[a] [N=113] (B)	101	99	(98.0)		
	Eylea+SB15[b] [N=111] (A)	109	105	(96.3)	−1.8	[−6.32, 2.63]
	Eylea+Eylea[b] [N=108] (B)	101	99	(98.0)		
	SB15[a] [N=224] (A)	216	207	(95.8)	−1.3	[−4.81, 2.21]
	Eylea overall [N=224] (B)	210	204	(97.1)		

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; CMH = Cochran-Mantel-Haenszel

N = number of subjects in the Full Analysis Set; n' = number of subjects with available assessment results at each timepoint; n = number of subjects having change from baseline in BCVA less than 15 letters loss

Percentages were based on n'.

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32 among the FAS, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

The adjusted risk difference and its 95% CI were analysed by a stratified CMH test with country as a factor.

Source: Table 14.2-4.2

3. Proportion of Subjects Who Gained ≥15 Letters in BCVA Compared to BL at W32 and W56

Table 16: Analysis of proportion of subjects who gained 15 letters or more in BCVA compared to baseline at week 32 and week 56 (full analysis set)

Table 11-11 Analysis of Proportion of Subjects who Gained 15 Letters or More in BCVA Compared to Baseline at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n'	n	(%)	Adjusted Risk Difference (A – B)	
					Estimate	95% CI
Week 32	SB15 (N=224) (A)	219	48	(21.9)	3.3	[−4.20, 10.83]
	Eylea (N=224) (B)	216	40	(18.5)		
Week 56	SB15[a] [N=224] (A)	216	57	(26.4)	8.2	[−1.38, 17.86]
	Eylea[a] [N=113] (B)	101	18	(17.8)		
	Eylea+SB15[b] [N=111] (A)	109	25	(22.9)	4.8	[−6.07, 15.73]
	Eylea+Eylea[b] [N=108] (B)	101	18	(17.8)		
	SB15[a] [N=224] (A)	216	57	(26.4)	5.7	[−2.28, 13.74]
	Eylea overall [N=224] (B)	210	43	(20.5)		

BCVA = best corrected visual acuity (total letter score); CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the Full Analysis Set; n' = number of subjects with available assessment results at each timepoint; n = number of subjects having change from baseline in BCVA equal to or greater than 15 letters gain

Percentages were based on n'.

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32 among the FAS, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

The adjusted risk difference and its 95% CI were analysed by a stratified CMH test with country as a factor.

Source: Table 14.2-4.3

4. Change from Baseline in Central Subfield Thickness (CST) and Total Retinal Thickness (TRT) at Week 4, Week 32 and up to Week 56

Figure 5: Mean change from baseline through week 56 in CST (full analysis set)

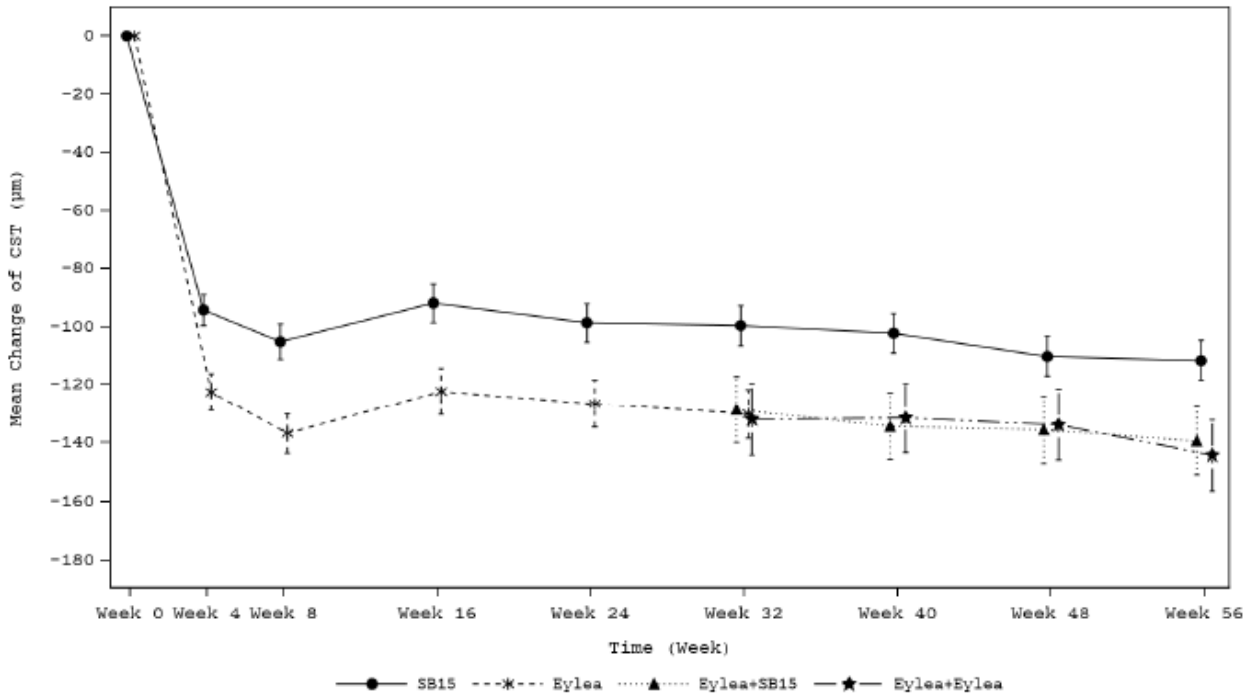


Figure 11-4 Mean Change from Baseline through Week 56 in CST (Full Analysis Set)

CST = central subfield thickness (µm).

The symbol and error bar represented mean and standard error at each timepoint.

Source: Figure 14.2-2.1

Figure 6: Mean change from baseline through week 56 in TRT (full analysis set)

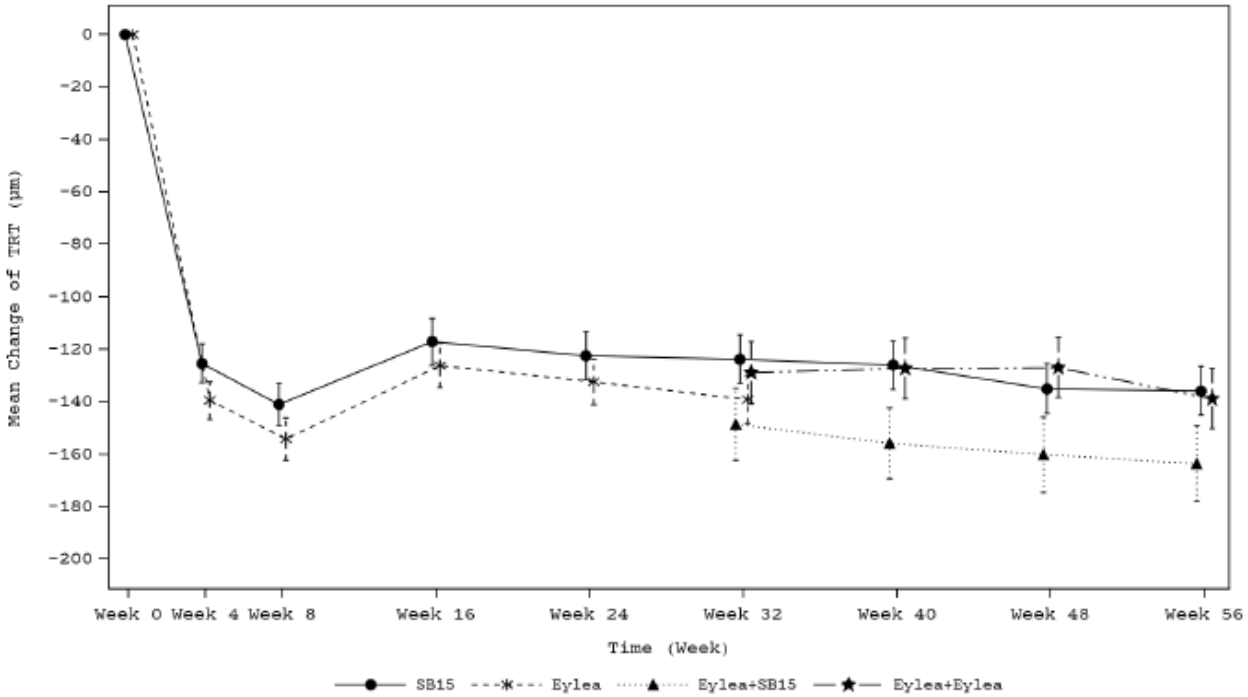


Figure 11-5 Mean Change from Baseline through Week 56 in TRT (Full Analysis Set)

TRT = total retinal thickness (μm)

The symbol and error bar represented mean and standard error at each timepoint.

Source: Figure 14.2-3.4

NB: Tables 17 to Table 19 presented below show results based on analysis of covariance model with the baseline CST as a covariate (see Ancillary analyses for details)

Table 17: Analysis from change from baseline is CST and TRT at week 4 (full analysis set)

Table 11-12 Analysis of Change from Baseline in CST and TRT at Week 4 (Full Analysis Set)

Timepoint	Parameter	Treatment	n	LSM (SE)	Difference (A – B)		
					LSM (SE)	90% CI	95% CI
Week 4	CST	SB15 [N=224] (A)	220	−101.763 (4.2619)	11.140 (5.4549)	[2.148, 20.132]	[0.418, 21.861]
		Eylea [N=224] (B)	220	−112.903 (4.3344)			
	TRT	SB15 [N=224] (A)	219	−128.227 (5.4352)	4.638 (6.9236)	[−6.775, 16.052]	[−8.970, 18.247]
		Eylea [N=224] (B)	219	−132.866 (5.5044)			

CST = central subfield thickness (µm); CI = confidence interval; LSM = least square mean; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at each timepoint; SE = standard error; TRT = total retinal thickness (µm)

Inferential statistics were based on analysis of covariance model with the baseline CST/TRT as a covariate and country and treatment as fixed factors.

Missing values were not imputed, available case was used for analysis.

Source: Table 14.2-4.4 and Table 14.2-4.5

Table 18: Analysis of change from baseline to CST and TRT at week 32 (final analysis set)

Table 11-13 Analysis of Change from Baseline in CST and TRT at Week 32 (Full Analysis Set)

Timepoint	Parameter	Treatment	n	LSM (SE)	Difference (A – B)		
					LSM (SE)	90% CI	95% CI
Week 32	CST	SB15 [N=224] (A)	216	−110.915 (4.7329)	5.246 (6.1182)	[−4.840, 15.332]	[−6.780, 17.273]
		Eylea [N=224] (B)	213	−116.162 (4.8756)			
	TRT	SB15 [N=224] (A)	216	−127.919 (7.3476)	4.499 (9.4462)	[−11.073, 20.071]	[−14.069, 23.067]
		Eylea [N=224] (B)	212	−132.418 (7.5420)			

CST = central subfield thickness (µm); CI = confidence interval; LSM = least square mean; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at each timepoint; SE = standard error; TRT = total retinal thickness (µm)

Inferential statistics were based on analysis of covariance model with the baseline CST/TRT as a covariate and country and treatment as fixed factors.

Missing values were not imputed, available case was used for analysis.

Source: Table 14.2-4.4 and Table 14.2-4.5

Table 19: Analysis of change from baseline in CST and TRT at week 56 (final analysis set)

Table 11-14 Analysis of Change from Baseline in CST and TRT at Week 56 (Full Analysis Set)

Timepoint	Parameter	Treatment	n	LSM (SE)	Difference (A – B)		
					LSM (SE)	90% CI	95% CI
Week 56	CST	SB15[a] [N=224] (A)	215	−119.221 (4.3570)	7.421 (6.8774)	[−3.926, 18.768]	[−6.113, 20.955]
		Eylea[a] [N=113] (B)	99	−126.642 (6.1504)			
		Eylea+SB15[b] [N=111] (A)	109	−136.400 (6.1521)	7.259 (7.8192)	[−5.664, 20.181]	[−8.162, 22.679]
		Eylea+Eylea[b] [N=108] (B)	99	−143.659 (6.3803)			
		SB15[a] [N=224] (A)	215	−123.301 (4.2099)	4.205 (5.4683)	[−4.810, 13.220]	[−6.544, 14.954]
		Eylea overall [N=224] (B)	208	−127.506 (4.3714)			
	TRT	SB15[a] [N=224] (A)	215	−132.376 (7.1928)	3.876 (11.2931)	[−14.757, 22.508]	[−18.348, 26.099]
		Eylea[a] [N=113] (B)	98	−136.251 (10.1017)			
		Eylea+SB15[b] [N=111] (A)	109	−151.070 (9.6794)	−1.701 (12.3964)	[−22.188, 18.787]	[−26.149, 22.748]
		Eylea+Eylea[b] [N=108] (B)	98	−149.369 (10.0951)			
		SB15[a] [N=224] (A)	215	−137.765 (6.9826)	4.872 (9.0190)	[−9.997, 19.740]	[−12.857, 22.601]
		Eylea overall [N=224] (B)	207	−142.637 (7.2225)			

CST = central subfield thickness (µm); CI = confidence interval; LSM = least square mean; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at each timepoint; SE = standard error; TRT = total retinal thickness (µm)

4. Proportion of Subjects with Intra- or Sub-Retinal Fluid on optical coherence tomography (OCT) at Week 32 and Week 56

Table 20: Summary of proportion of subjects with intra- or sub-retinal fluid by visit and treatment group (full analysis set)

Table 11-15 Summary of Proportion of Subjects with Intra- or Sub-retinal Fluid by Visit and Treatment Group (Full Analysis Set)

Timepoint	SB15 N=224 n/n' (%)	Eylea			Total N=448 n/n' (%)
		Overall N=224 n/n' (%)	SB15 N=448 n/n' (%)	Eylea N=108[a] n/n' (%)	
Week 0 (BL)	219/224 (97.8)	222/224 (99.1)	110/111 (99.1)	107/108 (99.1)	441/448 (98.4)
Week 4	144/223 (64.6)	143/223 (64.1)	-	-	287/446 (64.3)
Week 8	113/222 (50.9)	101/223 (45.3)	-	-	214/445 (48.1)
Week 16	140/223 (62.8)	143/220 (65.0)	-	-	283/443 (63.9)
Week 24	129/220 (58.6)	128/219 (58.4)	-	-	257/439 (58.5)
Week 32	128/219 (58.4)	120/215 (55.8)	58/111 (52.3)	62/104 (59.6)	248/434 (57.1)
Week 40	121/219 (55.3)	115/214 (53.7)	55/110 (50.0)	60/104 (57.7)	236/433 (54.5)
Week 48	105/218 (48.2)	107/213 (50.2)	49/109 (45.0)	58/104 (55.8)	212/431 (49.2)
Week 56	102/216 (47.2)	97/210 (46.2)	48/109 (44.0)	49/101 (48.5)	199/426 (46.7)

BL = baseline; n = number of subjects with at least one of intra or sub retinal fluid is 'Yes' at each timepoint; n': number of subjects with available assessment results at each timepoint.

Percentages were based on n'.

[a] Based on subjects who had re-randomisation at Week 32 among the full analysis set, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Source: Table 14.2-3.3

Table 21: Analysis of proportion of subjects with intra- or sub-retinal fluid on OCT at week 32 and week 56 (full analysis set)

Table 11-16 Analysis of Proportion of Subjects with Intra- or Sub-Retinal Fluid on OCT at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n'	n	(%)	Adjusted Risk Difference (A – B)	
					Estimate	95% CI
Week 32	SB15 (N=224) (A)	219	128	(58.4)	2.6	[−6.62, 11.84]
	Eylea (N=224) (B)	215	120	(55.8)		
Week 56	SB15[a] [N=224] (A)	216	102	(47.2)	−1.5	[−13.25, 10.19]
	Eylea[a] [N=113] (B)	101	49	(48.5)		
	Eylea+SB15[b] [N=111] (A)	109	48	(44.0)	−3.8	[−17.20, 9.68]
	Eylea+Eylea[b] [N=108] (B)	101	49	(48.5)		
	SB15[a] [N=224] (A)	216	102	(47.2)	0.7	[−8.71, 10.03]
	Eylea overall [N=224] (B)	210	97	(46.2)		

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; N = number of subjects in the Full Analysis Set; n = number of subjects with at least one of intra or sub retinal fluid is 'Yes' at each timepoint; n': number of subjects with available assessment results at each timepoint; OCT = optical coherence tomography

Percentages were based on n'.

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

The adjusted risk difference and its 95% CI were analysed by a stratified CMH test with country as a factor.

Source: Table 14.2-4.6

5. Change from Baseline in Choroidal Neovascularisation (CNV) Area at Week 32 and Week 56

Table 22: Analysis of change from baseline in area of CNV at week 32 and week 56 (full analysis set)

Table 11-17 Analysis of Change from Baseline in Area of CNV at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n	LSM (SE)	Difference (A – B)		
				LSM (SE)	90% CI	95% CI
Week 32	SB15 [N=224] (A)	208	−0.99578 (0.22540)	−0.61310 (0.28919)	[−1.08988, −0.13633]	[−1.18162, −0.04459]
	Eylea [N=224] (B)	208	−0.38268 (0.22931)			
Week 56	SB15[a] [N=224] (A)	208	−1.25935 (0.28078)	−0.16554 (0.44231)	[−0.89539, 0.56430]	[−1.03605, 0.70496]
	Eylea[a] [N=113] (B)	98	−1.09380 (0.39232)			
	Eylea+SB15[b] [N=111] (A)	104	−0.67639 (0.41536)	0.57787 (0.52653)	[−0.29243, 1.44817]	[−0.46072, 1.61646]
	Eylea+Eylea[b] [N=108] (B)	98	−1.25426 (0.42312)			
	SB15[a] [N=224] (A)	208	−1.26557 (0.27499)	−0.38619 (0.35756)	[−0.97570, 0.20332]	[−1.08914, 0.31675]
	Eylea overall [N=224] (B)	202	−0.87937 (0.28484)			

CI = confidence interval; CNV = choroidal neovascularisation (area of CNV = mm^2); LSM = least square mean; N = number of subjects in the Full Analysis Set; n = total number of subjects with available data at each timepoint; SE = standard error

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Inferential statistics were based on analysis of covariance model with the baseline CNV Area as a covariate and country and treatment as fixed factors.

Missing values were not imputed, available case was used for analysis.

Source: Table 14.2-4.7

6. Proportion of Subjects with Active CNV Leakage at Week 32 and Week 56

Table 23: Analysis of proportion of subjects with active CNV leakage at week 32 and week 56 (full analysis set)

Table 11-18 Analysis of Proportion of Subjects with active CNV leakage at Week 32 and Week 56 (Full Analysis Set)

Timepoint	Treatment	n'	n	(%)	Adjusted Risk Difference (A – B)	
					Estimate	95% CI
Week 32	SB15 (N=224) (A)	212	187	(88.2)	−3.5	[−9.00, 2.07]
	Eylea (N=224) (B)	210	192	(91.4)		
Week 56	SB15[a] [N=224] (A)	212	165	(77.8)	−2.1	[−11.51, 7.27]
	Eylea[a] [N=113] (B)	98	78	(79.6)		
	Eylea+SB15[b] [N=111] (A)	106	89	(84.0)	4.6	[−5.67, 14.81]
	Eylea+Eylea[b] [N=108] (B)	98	78	(79.6)		
	SB15[a] [N=224] (A)	212	165	(77.8)	−4.2	[−11.60, 3.30]
	Eylea overall [N=224] (B)	204	167	(81.9)		

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CNV = choroidal neovascularisation; N = number of subjects in the Full Analysis Set; n' = number of subjects with available assessment results at each timepoint; n = number of subjects with active CNV leakage

Percentages were based on n'.

[a] SB15 (SB15/SB15+SB15) and Eylea (Eylea/Eylea+Eylea) include subjects (SB15, Eylea) who were randomised to SB15 or Eylea respectively and discontinued from IP before transition at Week 32.

[b] Based on subjects who had re-randomisation at Week 32, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

The adjusted risk difference and its 95% CI were analysed by a stratified CMH test with country as a factor.

Source: Table 14.2-4.8

Exploratory efficacy endpoints

1. Proportion of Subjects with Sub-RPE Fluid on OCT at Week 32 and Week 56

Table 24: Summary of proportion of subjects with sub-RPE fluid by visit and treatment group (full analysis set)

Table 11-19 Summary of Proportion of Subjects with Sub-RPE Fluid by Visit and Treatment Group (Full Analysis Set)

Timepoint	SB15 N=224 n/n' (%)	Eylea			Total N=448 n/n' (%)
		Overall N=224 n/n' (%)	SB15 N=111[a] n/n' (%)	Eylea N=108[a] n/n' (%)	
Week 0 (BL)	106/224 (47.3)	106/224 (47.3)	49/111 (44.1)	54/108 (50.0)	212/448 (47.3)
Week 4	69/223 (30.9)	72/223 (32.3)	-	-	141/446 (31.6)
Week 8	63/222 (28.4)	55/223 (24.7)	-	-	118/445 (26.5)
Week 16	81/223 (36.3)	87/220 (39.5)	-	-	168/443 (37.9)
Week 24	69/220 (31.4)	73/219 (33.3)	-	-	142/439 (32.3)
Week 32	68/219 (31.1)	64/215 (29.8)	29/111 (26.1)	35/104 (33.7)	132/434 (30.4)
Week 40	55/218 (25.2)	62/214 (29.0)	33/110 (30.0)	29/104 (27.9)	117/432 (27.1)
Week 48	55/218 (25.2)	63/213 (29.6)	35/109 (32.1)	28/104 (26.9)	118/431 (27.4)
Week 56	52/216 (24.1)	55/210 (26.2)	30/109 (27.5)	25/101 (24.8)	107/426 (25.1)

BL = baseline; N = number of subjects in the Full Analysis Set; n = number of subjects with sub-RPE Fluid on OCT at each timepoint; n' = number of subjects with available assessment results at each timepoint; OCT = optical coherence tomography; RPE = retinal pigment epithelium

Percentages were based on n'.

[a] Based on subjects who had re-randomisation at Week 32 among the full analysis set, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Source: Table 14.2-5.1

2. Change from Baseline in Subscale Scores and Composite Score of NEI VFQ-25 at W32 and W56

Table 25: Summary statistics for NEI VFQ-25 composite score (full analysis set)

Table 11-20 Summary Statistics for NEI VFQ-25 Composite Score (Full Analysis Set)

Timepoint	SB15 N=224		Eylea Overall N=224		Eylea SB15 N=111[a]		Eylea Eylea N=108[a]		Total N=448	
Statistics	Value	Change	Value	Change	Value	Change	Value	Change	Value	Change
Week 0 (BL)										
n	180	-	194	-	92	-	97	-	374	-
Mean	79.55	-	75.35	-	76.84	-	74.56	-	77.37	-
SD	14.093	-	15.907	-	15.143	-	16.232	-	15.188	-
Median	83.79	-	76.95	-	78.33	-	75.88	-	80.59	-
Min	37.8	-	28.4	-	32.2	-	32.5	-	28.4	-
Max	97.6	-	97.4	-	97.4	-	96.9	-	97.6	-
Week 32										
n	174	174	188	188	92	92	95	95	362	362
Mean	82.52	2.94	78.43	2.72	79.68	2.83	77.25	2.67	80.40	2.83
SD	14.349	10.416	14.979	11.192	13.893	11.099	16.016	11.383	14.802	10.812
Median	87.92	1.89	80.44	1.35	81.88	0.88	80.34	1.89	84.29	1.76
Min	36.1	−28.3	34.8	−39.2	35.5	−23.2	34.8	−39.2	34.8	−39.2
Max	100.0	34.2	98.5	33.7	98.0	33.7	98.5	30.5	100.0	34.2
Week 56										
n	175	175	182	182	90	90	92	92	357	357
Mean	83.81	4.14	80.14	4.50	81.50	4.90	78.82	4.11	81.94	4.33
SD	13.433	12.274	15.016	12.944	14.132	13.371	15.798	12.574	14.360	12.603
Median	87.95	2.84	83.19	2.84	83.60	2.34	82.91	3.45	85.87	2.84
Min	30.6	−42.5	28.5	−40.9	43.7	−28.7	28.5	−40.9	28.5	−42.5
Max	98.2	43.7	100.0	44.5	100.0	44.5	97.6	31.1	100.0	44.5

BL = baseline; Change = Value – Baseline; N = number of subjects in the Full Analysis Set; n = number of subjects; NEI VFQ-25 = National Eye Institute 25-Item Visual Function Questionnaire

Composite Score was summarised without subjects who received Eylea in the fellow eye due to AMD.

[a] Based on subjects who had re-randomisation at Week 32 among the full analysis set, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Source: Table 14.2-6.2

Ancillary analyses

Pre-defined subgroup analyses

Table 26: Subgroup analysis of change from baseline in BCVA at week 8 by overall ADA result up to week 8 (full analysis set)

Table 14.2-2.5 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Overall ADA Result up to Week 8
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
Positive	SB15 (N=2)	2	-1.0 (0.00)	NA	NA	NA
	Eylea (N=0)	0	NA			
Negative	SB15 (N=205)	205	6.9 (0.58)	0.1 (0.73)	[-1.1, 1.3]	[-1.4, 1.5]
	Eylea (N=208)	208	6.9 (0.58)			
Inconclusive	SB15 (N=3)	3	NA	NA	NA	NA
	Eylea (N=1)	1	NA			

Table 27: Subgroup analysis of change from baseline in BCVA at week 8 by lesion type at baseline (full analysis set)

Table 14.2-2.6 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Lesion Type at Baseline
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
Predominantly Classic	SB15 (N=41)	41	8.8 (1.56)	3.5 (1.94)	[0.3, 6.8]	[-0.3, 7.4]
	Eylea (N=46)	46	5.3 (1.57)			
Minimally Classic	SB15 (N=40)	40	7.0 (1.33)	-0.5 (1.60)	[-3.2, 2.1]	[-3.7, 2.6]
	Eylea (N=56)	56	7.5 (1.18)			
Occult	SB15 (N=138)	138	6.2 (0.69)	0.1 (0.92)	[-1.4, 1.7]	[-1.7, 1.9]
	Eylea (N=117)	117	6.1 (0.76)			

Table 28: Subgroup analysis of change from baseline in BCVA at week 8 by total lesion area at baseline (full analysis set)

Table 14.2-2.7 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Total Lesion Area at Baseline
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
≤ 4DA	SB15 (N=81)	81	8.8 (0.85)	0.8 (1.06)	[-0.9, 2.6]	[-1.3, 2.9]
	Eylea (N=88)	88	7.9 (0.82)			
> 4DA	SB15 (N=143)	143	5.7 (0.73)	-0.1 (0.94)	[-1.6, 1.5]	[-1.9, 1.8]
	Eylea (N=136)	136	5.7 (0.77)			

Table 29: Subgroup analysis of change from baseline in BCVA at week 8 by country (full analysis set)

Table 14.2-2.8 (Page 1 of 2)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Country
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
Croatia	SB15 (N=10)	10	6.0 (2.17)	0.3 (3.00)	[-4.9, 5.5]	[-6.0, 6.6]
	Eylea (N=11)	11	5.8 (2.07)			
Czech Republic	SB15 (N=31)	31	8.1 (1.28)	0.0 (1.82)	[-3.0, 3.1]	[-3.6, 3.7]
	Eylea (N=30)	30	8.0 (1.30)			
Estonia	SB15 (N=7)	7	5.0 (3.66)	-5.0 (5.72)	[-15.5, 5.5]	[-17.9, 7.9]
	Eylea (N=5)	5	10.0 (4.34)			
Hungary	SB15 (N=43)	43	6.7 (1.21)	2.6 (1.72)	[-0.3, 5.5]	[-0.8, 6.0]
	Eylea (N=42)	42	4.1 (1.22)			
Japan	SB15 (N=12)	12	7.4 (2.14)	-0.8 (3.31)	[-6.5, 5.0]	[-7.7, 6.2]
	Eylea (N=9)	9	8.2 (2.48)			
Korea	SB15 (N=40)	40	4.7 (1.20)	-3.1 (1.67)	[-5.9, -0.4]	[-6.4, 0.2]
	Eylea (N=42)	42	7.8 (1.16)			
Latvia	SB15 (N=11)	11	9.4 (2.21)	-0.9 (3.07)	[-6.2, 4.4]	[-7.3, 5.5]
	Eylea (N=12)	12	10.3 (2.11)			
Poland	SB15 (N=36)	36	4.2 (1.23)	0.9 (1.72)	[-1.9, 3.8]	[-2.5, 4.4]
	Eylea (N=38)	38	3.3 (1.20)			
Russia	SB15 (N=20)	20	6.5 (1.89)	1.4 (2.65)	[-3.1, 5.8]	[-4.0, 6.7]
	Eylea (N=21)	21	5.1 (1.84)			
United States	SB15 (N=14)	14	7.5 (1.85)	1.3 (2.62)	[-3.2, 5.7]	[-4.1, 6.7]
	Eylea (N=14)	14	6.2 (1.85)			

Table 30: Subgroup analysis of change from baseline in BCVA at week 8 by BCVA group at baseline (full analysis set)

Table 14.2-2.9 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by BCVA Group at Baseline
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
< 50 letter score	SB15 (N=36)	36	7.2 (1.77)	-0.7 (2.38)	[-4.7, 3.2]	[-5.5, 4.0]
	Eylea (N=43)	43	8.0 (1.78)			
≥ 50 letter score	SB15 (N=188)	188	6.6 (0.57)	0.2 (0.73)	[-1.0, 1.4]	[-1.2, 1.6]
	Eylea (N=181)	181	6.4 (0.58)			

Table 31: Subgroup analysis of change from baseline in BCVA at week 8 by age group at baseline (full analysis set)

Table 14.2-2.10 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Age Group at Baseline
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
< 75 years	SB15 (N=111)	111	8.4 (0.84)	1.2 (1.02)	[-0.5, 2.9]	[-0.8, 3.2]
	Eylea (N=116)	116	7.2 (0.85)			
≥ 75 years	SB15 (N=113)	113	4.8 (0.78)	-1.0 (0.99)	[-2.6, 0.7]	[-2.9, 1.0]
	Eylea (N=108)	108	5.7 (0.79)			

Table 32: Subgroup analysis of change from baseline in BCVA at week 8 by iris colour group in study eye (full analysis set)

Table 14.2-2.11 (Page 1 of 1)
Subgroup Analysis of Change from Baseline in BCVA at Week 8 by Iris Color Group in Study Eye
Full Analysis Set

				Difference (SB15 - Eylea)		
Category	Treatment	n	LSM (SE)	LSM (SE)	90% CI	95% CI
Light Color	SB15 (N=129)	129	7.0 (0.75)	0.7 (0.96)	[-0.9, 2.3]	[-1.2, 2.6]
	Eylea (N=131)	131	6.3 (0.75)			
Dark Color	SB15 (N=94)	94	5.5 (1.25)	-0.3 (1.08)	[-2.1, 1.4]	[-2.5, 1.8]
	Eylea (N=91)	91	5.8 (1.26)			

Ad hoc important subgroup analyses

Figure 7: Mean change from baseline through week 56 in CST (full analysis set)

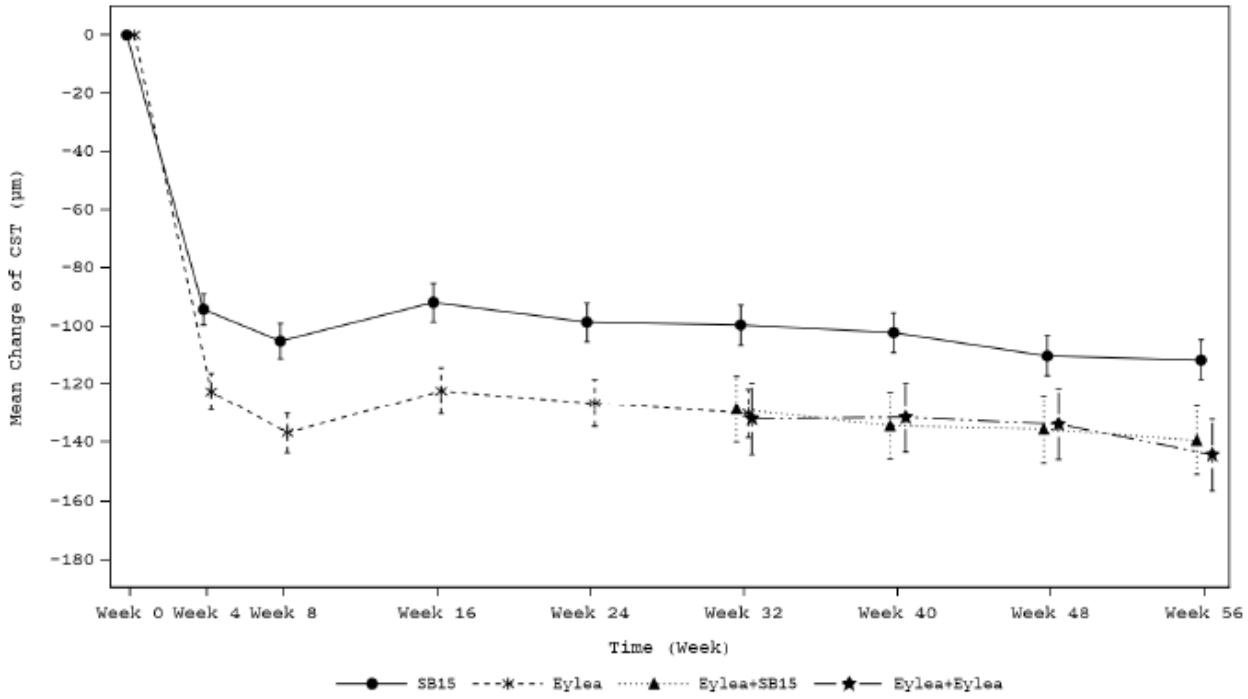


Figure 11-4 Mean Change from Baseline through Week 56 in CST (Full Analysis Set)

CST = central subfield thickness (µm).
The symbol and error bar represented mean and standard error at each timepoint.
Source: Figure 14.2-2.1

As shown in the above figure, a consistent absolute difference of 30 µm or more was observed between the two treatment groups over time up to Week 56, which is presumably due to the noted difference in baseline CST between the two treatment groups (353.275 µm in the SB15 treatment group and 382.296 µm in the Eylea treatment group; p-value = 0.0053). Of note, in a post-hoc analysis of IVT aflibercept injection for neovascular AMD patients, the treatment effect of aflibercept (i.e. on the changes in central retinal thickness

[CRT] at Week 52) in neovascular AMD patients was found to be correlated with baseline CRT levels; the thicker the CRT at baseline, the greater the magnitude of the changes in CRT [Ho et al., 2018].

Thus, an ad-hoc analysis result of LSmean change from baseline in CST over time up to Week 56 is provided herein (Table 15), also as a graphical representation (Figure 2), to which an ANCOVA model was applied using 'baseline CST' as a covariate and 'country' and 'treatment' as fixed factors.

Figure 8: LSmean change from baseline through week 56 in CST (full analysis set, study SB-3001) (*Ad-hoc* analysis)

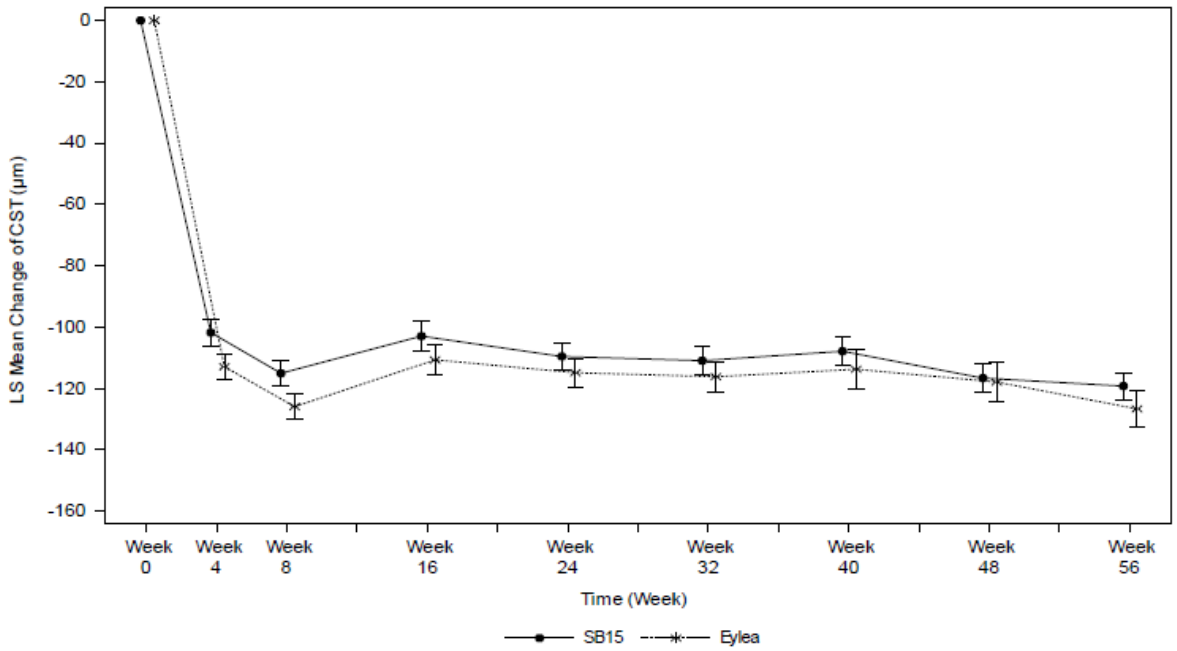


Figure 4: LSmean Change from Baseline Through Week 56 in CST (Full Analysis Set, Study SB15-3001) (*Ad-hoc* Analysis)

CST = central subfield thickness (µm); LSmean = least square mean
Inferential statistics were based on analysis of covariance model with the baseline CST as a covariate and country and treatment as fixed factors. LS Mean is adjusted mean of each treatment after adjusting covariates from the model based on data of treatments.
The symbol and error bar represented LSmean and standard error at each timepoint.
Missing value were not imputed, available case was used for analysis.
Source: Section 2.7.3, Figure 4

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 33: Summary of efficacy for trial SB15-3001

Title: A Phase III Randomised, Double-masked, Parallel Group, Multicenter Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB15 (Proposed Aflibercept Biosimilar) and Eylea in Subjects with Neovascular Age-related Macular Degeneration		
Study identifier	SB15-3001 (protocol number), 2019-003883-28 (EudraCT number)	
Design	Randomized, double-masked, parallel, multicenter clinical study The study was composed of two distinct periods (main, transition periods). A total of 449 patients with neovascular age-related macular degeneration were first randomized in a 1:1 ratio to receive either SB15 2 mg (N = 224) or Eylea 2 mg (N = 225) via intravitreal (IVT) injections (every 4 weeks for first 3 months followed by once every 8 weeks). At Week 32, patients in the Eylea treatment group were randomized again in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. In the 8-week treatment cycle, investigational products (IPs) (SB15 or Eylea) were administered up to Week 48. patients receiving SB15 continued to receive SB15 up to Week 48, but they also followed the randomization procedure to maintain masking.	
	Duration of treatment:	56 weeks (duration of treatment) Last investigational product (IP; SB15 or Eylea) injection was at Week 48 and last assessment was done at Week 56.
Hypothesis	Equivalence	
Treatment Group	SB15 (N = 224 randomized)	Patients were randomized to receive SB15 via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months [i.e., at Weeks 0, 4, and 8], followed by 2 mg [0.05 mL] once every 8 weeks). At Week 32, patients receiving SB15 continued to receive SB15 up to Week 48, but they also followed the randomization procedure to maintain masking.
	Eylea Overall (N = 225 randomized)	Patients were randomized to receive Eylea via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months [i.e., at Weeks 0, 4, and 8], followed by 2 mg [0.05 mL] once every 8 weeks). At Week 32, patients in the Eylea treatment group were randomized again in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. In the 8-week treatment cycle, investigational products (IPs) (SB15 or Eylea) were administered up to Week 48.
	Eylea+SB15 (N = 111 randomized)	Patients were randomized to receive Eylea via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months [i.e., at Weeks 0, 4, and 8], followed by 2 mg [0.05 mL] once every 8 weeks). At Week 32, patients in the Eylea treatment group were randomized again in a 1:1 ratio to be transitioned to SB15 treatment. In the 8-week treatment cycle, SB15 was administered up to Week 48.
	Eylea+Eylea (N = 108 randomized)	Patients were randomized to receive Eylea via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months [i.e., at Weeks 0, 4, and 8], followed by 2 mg [0.05 mL] once every 8 weeks). At Week 32, patients in the Eylea treatment group were randomized again in a 1:1 ratio to continue on Eylea. In the 8-week treatment cycle, Eylea was administered up to Week 48.
Endpoints and definitions	Primary endpoint	Change from baseline in Best Corrected Visual Acuity (BCVA) at Week 8.
Database lock	May 12, 2022	
Results and Analysis		

Analysis description	**Primary Analysis**		
Analysis population and timepoint description	Full Analysis Set (FAS): FAS consists of all randomized patients. Following the intent to treat principle, patients were analyzed according to the treatment group they were assigned to at randomization. However, patients who did not have any efficacy assessment result after randomization and did not receive IP during the study period were excluded from the FAS. **Week 8**		
Descriptive statistics, estimate variability, effect estimate per comparison	Treatment group	SB15	Eylea
	Number of patients (n)	224	224
	Method: Multiple Imputation assuming Missing-at-Random LSMeans (Standard Error [SE]) of change from baseline in BCVA at Week 8	6.7 (0.56)	6.6 (0.57)
	LSMean difference (SB15 – Eylea) [95% CI]	0.1 [–1.3, 1.4]	
Analysis description	**Sensitivity Analysis of Primary Efficacy Variable**		
Analysis population and timepoint description	Full Analysis Set **Week 8**		
Descriptive statistics, estimate variability, effect estimate per comparison	Treatment group	SB15	Eylea
	Number of patients (n)	223	224
	Method: based on available case LSMeans (SE) of change from baseline in BCVA at Week 8	6.7 (0.56)	6.6 (0.57)
	LSMean difference (SB15 – Eylea) [95% CI]	0.1 [–1.3, 1.5]	
Analysis population and timepoint description	Per-protocol Set (PPS): PPS consists of all FAS patients who had BCVA assessment result at baseline and Week 8 without any major protocol deviations (PDs) that had impact on the BCVA assessment. Major PDs that led to exclusion from this set were pre-defined prior to unmasking the treatment group assignment for analyses. Patients meeting any of following criteria were excluded from the PPS as well although it is not captured as a PD: – Patients missed any of IP injection at Week 0 or Week 4 – IP injection (± 7 days) at Week 4 is out of visit window **Week 8**		
Descriptive statistics, estimate	Treatment group	SB15	Eylea
	Number of patients (n)	215	214

variability, effect estimate per comparison	Method: based on available case LSMeans (SE) of change from baseline in BCVA at Week 8	6.6 (0.57)	6.8 (0.58)
	LSMean difference (SB15 – Eylea) [95% CI]	–0.2 [–1.6, 1.2]	

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant conducted a single pivotal phase III study in patients with neovascular age-related macular degeneration (nAMD) (SB15-3001). SB15-3001 was a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of SB15 compared to US-Eylea in subjects with neovascular AMD. A single Phase III study is considered acceptable for the proposed biosimilar candidate.

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). nAMD and DME are likely the most sensitive indications as compared to RVO, and CNV to detect possibly existing differences between the treatments. An evaluation in patients with RVO is not appropriate due to the rather large rate of spontaneous improvements. Patients with CNV secondary to myopia might need very few injections and are also not considered appropriate. Furthermore, studies with the originator showed that the treatment effect of aflibercept was largest in patients with nAMD (comparison against placebo).

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

Only treatment-naïve patients were included in the study. 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 to the reference product in terms of efficacy and safety. Treatment-experienced patients may have reached the plateau in terms of maximal gain in visual acuity and may maintain their visual acuity with less frequent dosing, which makes them a less sensitive population. From a safety view, the assessment of immunogenicity and adverse event profile may also be compromised.

The inclusion criterion for BCVA was between 20/40 and 20/200 (letter score of 73 to 34, inclusive). The upper limit (20/40) gives room for a 15 letter gain in visual acuity (ceiling effect if subjects with higher visual acuity were to be included). The lower limit (20/200) corresponds to the WHO-defined level of legal blindness) and can be accepted. The eligibility criteria are overall acceptable.

Intervention: Subjects were administered 2 mg SB15 or 2 mg Eylea IVT into the study eye every 4 weeks for the first 3 consecutive visits (Weeks 0, 4, and 8), followed by once every 8 weeks up to Week 48. A total of 8

doses of IP were planned to be administered in the study. The dose administered is in line with posology approved for Eylea.

Comparator: The US-licenced Eylea was used as the comparator in the Phase 3 Study -3001. Although a reference medicinal product authorised in the EEA is generally preferred, the use of an US-licenced reference product may be accepted provided that the analytical similarity between US-Eylea, EU-Eylea, and SB-15 has been demonstrated.

The **duration of treatment** was 48 weeks, last assessments were made at Week 56. 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. Also, this allows assessing safety data for the period of approximately one year, which is deemed acceptable. The follow up duration was in line with recommendations given by the EMA during a scientific advice procedure (EMEA/H/SA/3629/1/FU/1/2019/III).

The **methods** used **for the primary** (visual acuity) **and secondary efficacy assessments** (central subfield thickness and total retinal thickness, the presence of intra- or sub-retinal fluid and sub-RPE fluid, CNV area and the presence of CNV leakage) represent standard used for respective assessments and are considered adequate.

Randomisation: Subjects were randomised in a 1:1 ratio to receive either SB15 or Eylea. At Week 32, subjects initially randomised to Eylea treatment group were re-randomised in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. Subjects initially randomised to SB15 continued to receive SB15 up to Week 48. The last assessments were done at Week 56, corresponding to the end of follow-up for all subjects. Randomization was stratified by centre and corresponding analyses adjusted by country which is considered adequate. 446 subjects were planned to be randomised. A total of 549 subjects were screened in the study of which 449 subjects were randomised.

Blinding: The study was conducted in a double-blind manner. At the time of the primary efficacy analysis a limited number of identified individuals were unmasked to conduct the corresponding analysis. In principle this is considered acceptable. The primary analysis was performed once all subjects had their Week 32 assessment completed. This was changed from an original plan covering only 24 weeks during the trial. Conflicting statements between SAP and Protocol regarding the timing of the primary analysis were due to a failure to update the Protocol in response to the change. No substantial impact on the statistical analysis is expected. Clarification by the Applicant confirms that the SAP was finalised before the study was unblinded. Subsequent updates do not include substantial changes that would impact the statistical analysis.

Overall, the study design is considered adequate to establish similarity between SB15 and the reference product Eylea.

Objectives, endpoints and estimands

The primary objective of this study was to demonstrate the equivalence in efficacy of SB15 compared to Eylea in subjects with neovascular age-related macular degeneration (nAMD). Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

Primary endpoint: Change from baseline in BCVA at Week 8 – change from BL is a continuous endpoint which can detect improvement or deterioration in the disease status and is considered to be a sensitive endpoint to detect differences between the biosimilar candidate and the reference product.

Timing of the primary analysis: Week 8 – based on pivotal studies with Eylea in nAMD subjects the efficacy plateau was reached approximately at Week 12 or Week 16. The sensitivity to detect differences between treatments is higher prior to reaching the plateau i.e., at the ascending part of the time/response curve. Therefore, Week 8 is considered an adequate time point for the primary analysis. Nonetheless, a similar response is expected at other time points to confirm similarity of two treatments.

Estimand: The protocol did not define an explicit estimand. Based on the inclusion criteria, analysis populations, missing data handling and primary analysis method, the implicit estimand of Study SB15-3001 was derived above. The corresponding estimand targets a treatment effect in a population and timepoint following treatment initiation that is considered sensitive to detect potential differences in clinical efficacy between biosimilar products. Potential intercurrent events were not defined prospectively, however, exclusion criteria, handling of protocol deviations and corresponding imputation of resulting missing data imply a hypothetical strategy, which (especially given the limited number of affected subjects) is considered acceptable. Subjects without any efficacy assessment following the randomization and who did not receive IP were excluded from the FAS, which implies an improper method targeting a principal stratum estimand. Again, considering the limited number of affected subjects, this is not considered of concern. In summary the estimand targeted by the study is considered acceptable to permit a conclusion on clinical biosimilarity.

The **secondary efficacy endpoints** comprised Change from BL in BCVA over time up to Week 32 and up to Week 56, Proportion of subjects who lost <15 letters in BCVA compared to BL at Week 32 and Week 56, Proportion of subjects who gained ≥15 letters in BCVA compared to BL at Week 32 and Week 56, Change from BL in central subfield thickness (CST) and total retinal thickness (TRT) at Week 4, and over time up to Week 32 and up to Week 56, Proportion of subjects with intra- or sub-retinal fluid on OCT at Week 32 and Week 56, Change from BL in CNV area at Week 32 and Week 56 and Proportion of subjects with active CNV leakage at Week 32 and Week 56.

Statistical methods for estimation and sensitivity analysis

Definition of analysis sets is by and large acceptable. Subjects who did not have a post-randomization efficacy assessment and who did not receive IP were excluded from the FAS. In principle this may result in challenges when interpreting the results, however, given the limited number of affected subjects, this is not considered of concern.

Demonstration of clinical similarity was based on the two-sided 95% confidence interval for the between group difference in mean change from baseline BCVA at Week 8. Corresponding estimates were obtained using ANCOVA adjusted for baseline BCVA and region (or pooled centres). The FAS was the primary analysis population. Missing values were imputed using a multiple imputation procedure assuming values missing at random. A corresponding analysis using the PPS as analysis set was performed as a sensitivity analysis.

In principle the primary analysis strategy is considered adequate.

Imputation of missing data using MI can be acceptable if the corresponding missing at random assumptions is plausible. Corresponding tipping point analyses are not considered conservative as it appears that treatment groups were treated equally (i.e. the same shift in BCVA outcomes was added/subtracted from missing subjects of either group). Considering the very limited amount of data missing from the primary analysis, however, the potential impact on the main conclusions is expected to be limited and no concern is raised.

Analyses planned to evaluate biosimilarity in prespecified subgroups are considered adequate.

The sample size was determined to provide 80% power to demonstrate biosimilarity based on the two-side 95% confidence interval for the between group difference in mean change from baseline BCVA at Week 8. Corresponding calculations can be reproduced and the underlying assumptions appear acceptable.

The main conclusion regarding clinical similarity was based on the two-sided 95% confidence interval for the between group difference in mean change from baseline BCVA at Week 8. This is in line with established requirements for the demonstration of biosimilarity and considered adequate. Analyses of secondary endpoints and subgroup analyses were not controlled for multiplicity. This is considered acceptable as no corresponding secondary claims are intended.

A number of changes to the preplanned analyses were implemented across versions of the SAP prior to finalization on Dec. 14, 2021. The exact extent of these changes and their potential impact on the primary analysis is difficult to assess, as no prior versions of the SAP were submitted with the Dossier. Please refer to the concern regarding time of first unblinding above for further details.

Study conduct: The study completion rate was overall high and comparable between treatment arms. Of the 449 subjects who were randomised, 438 (97.6%) subjects completed 32 weeks of the study (main period) and 425 (97.0%) subjects completed 56 weeks of the study (EOS). Prior to Week 32, 11 (2.4%) subjects discontinued treatment with the IP. The most common reason for discontinuation from IP before Week 32 was consent withdrawal by subject (8 [1.8%] subjects). After transition at Week 32 to the end of treatment at Week 48, 11 (2.5%) subjects discontinued treatment with the IP. The most common reasons for discontinuation from IP after transition at Week 32 to the end of treatment at Week 48 were AEs and lost to follow-up (3 [0.7%] subjects each). After the end of treatment to the end of study at Week 56, 2 (0.5%) subjects discontinued from the study, both of which were due to AEs. Up to Week 8 i.e., timing of the primary analysis, only 2 patients (1 in each treatment arm) discontinued the IP (consent withdrawal by subject).

A total of 192 (42.8%) subjects had protocol deviations (PDs) and 93 (20.7%) subjects had at least 1 major PD. The number of patients who had at least one major protocol deviation was higher in Eylea group (24%) in comparison with SB15 (17.4%). The percentage of patients with major PDs who were excluded from the PPS was generally low (17/93 subjects (3.8%)). The most common major PDs that led to exclusion from PPS were related to study procedures in 12 (2.7%) subjects, followed by violations of inclusion criteria in 3 (0.7%) subjects. There were slightly more subjects in the Eylea group who were excluded from the PPS due to major PD (11 subjects (4.9%)) compared to the SB15 group (6 subjects (2.7), however the individual reasons for exclusion were overall comparable between the treatment arms.

The proportion of patients with major PD due to IP compliance was overall low [14 subjects (3.1%)], however, an imbalance between the groups is noted [3 subjects (1.3%) versus 11 subjects (4.9%), in the SB15 and Eylea groups, respectively]. While in principle an imbalance in PD due to IP compliance in favour of the IP could make the IP appear more efficacious, given the overall limited number of affected patients, the impact on the secondary efficacy and safety endpoints in considered small. In the majority of these subjects (12/14) IP injection was NOT administered at any one of visits throughout the study.

The primary analysis was done at Week; the post-dose visits were done at Weeks 4 and 8. One patient in the Eylea group and no patients in the SB15 group did not have a Week 4 visit, due to an AE. The percentage of patients with time window deviations at Week 4 was overall low and comparable between the treatment arms (4 patients (1.8%) and 3 patients (1.3% in the Eylea arm, respectively). The reasons for time window deviations were also comparable between treatment arms.

At Week 8 no patient in either arm missed the visit. The percentage of patients with Week 8 window deviation was generally low and comparable between treatment arms (3 subjects (1.3% and 2 subject (0.9%) in SB15 and Eylea arm, respectively). The study conduct appears overall acceptable.

Of the 449 subjects randomised, 448 (99.8%) subjects were included in the FAS (primary analysis population) and 429 (95.5%) subjects were included in the PPS (analysis set used in a sensitivity analysis). One subject was incorrectly randomised and did not receive the IP.

Efficacy data and additional analyses

Primary efficacy analysis: The LS mean observed for change from baseline in BCVA at Week 8 was similar in both treatment groups (6.7 letters and 6.6 letters in SB15 and Eylea group, respectively). The LSmean difference in BCVA of the change from baseline between SB15 and Eylea at Week 8 was 0.1 letters (95% CI of [−1.3, 1.4]), and was completely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The **sensitivity analyses** of the primary efficacy endpoint supported the robustness of the equivalence between SB15 and Eylea in terms of the primary efficacy endpoint. The results of sensitivity analysis performed on available case in the FAS revealed that the treatment difference in LSmean between SB15 and Eylea (0.1 letters) was similar to the results from the primary analysis (0.1 letters). The LSmean difference of SB15 and Eylea had a 95% CI of [−1.3, 1.5], which was completely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The results of sensitivity analysis performed on available case in the PPS revealed that the treatment difference in LSmean between SB15 and Eylea (−0.2 letters) was similar to the results from the primary analysis (0.1 letters). The LSmean difference of SB15 and Eylea had a 95% CI of [−1.6, 1.2], which was completely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. Based on the above, the equivalence between SB15 and US-Eylea has been demonstrated for the primary endpoint, change from baseline in BCVA at Week 8.

Secondary efficacy endpoints

Change from BL in BCVA over time: At Week 32, the LSmean difference of the changes from BL in BCVA between SB15 and Eylea was 1.3 letters (95% CI of [−0.6, 3.3]) for the FAS based on the analysis using the MI method assuming MAR; and 1.1 letters (95% CI [−0.8, 3.1]) for the FAS based on available cases (missing values were not imputed). After Week 32 (re-randomisation), the main comparison of interest is that between patients in SB15 arm (SB15/SB15) and patients who remained in the Eylea arm (Eylea/Eylea). At Week 56, the LSmean difference between SB15 and Eylea was 0.9 letters (95% CI [-1.8, 3.6]) for the FAS based on the analysis using the MI method assuming MAR; and 0.4 letters (95% CI [−2.5, 3.2]), for the FAS based on available cases. Until Week 8 (primary analysis) treatments were nearly identical with regard to the primary endpoint change from baseline in BCVA. However, thereafter the difference between treatments notably increased, albeit still in the range of similarity margins. The results of the PPS analysis are overall consistent with those for the FAS.

Proportion of Subjects Who Lost <15 Letters in BCVA Compared to BL at W32 and W56: The proportion of subjects who lost <15 letters in BCVA compared to BL at Week 32 and Week 56 was comparable between the 2 treatment groups.

Proportion of subjects who gained ≥15 letters in BCVA compared to BL at W32 and W56: The proportion of subjects who gained ≥15 letters in BCVA compared to BL at Week 32 was slightly higher in the SB15 group (SB15: 21.9% [48/219 subjects]; Eylea: 18.5% [40/216 subjects]). Similarly, the proportion of subjects who gained ≥15 letters in BCVA compared to BL at Week 56 was higher in the SB15 group (SB15: 26.4% [57/216 subjects] vs Eylea: 17.8% [18/101 subjects]. suggesting that SB15 was better.

Change from Baseline (BL) in central subfluid thickness (CST) at Weeks 4, 32 and 56: The change in CST from BL at Week 4 was initially proposed by the Applicant in a request for a scientific advice (EMEA/H/SA/3629/1/2017/III), which was in principle found acceptable with a critical remark regarding the lack of a clear definition of CST. Based on available data for Eylea, the most sensitive time point to detect potential differences between SB15 and Eylea in CST is at Week 4, in the steep part of the curve before the efficacy plateau is reached. An equivalence margin of [−40 µm, 40 µm] was deemed acceptable for not being clinically relevant (EMEA/H/SA/3629/1/FU/1/2019/III). Although the primary endpoint has been changed compared to the SA, the change in CST is still considered a relevant endpoint. CST was defined as the mean retinal thickness from internal limiting membrane (ILM) to retinal pigment epithelial (RPE) measured within the 1-mm-circle centered on fovea (not single center point measurements)

A decrease from baseline in CST was observed in both treatment groups at all time points. At Week 4, a somewhat larger decrease was observed in the Eylea group (SB15: −101.763 µm; Eylea: −112.903 µm). The LSmean difference of the change from baseline between SB15 and Eylea at Week 4 was 11.140 µm (95% CI [0.418, 21.861]), which is within the margin proposed by the Applicant during a request for SA (i.e., [−40 µm, 40 µm]). These results pertain to the FAS based on available cases (missing values were not imputed). Additional analyses for change in CTS at Week 4 for (1) FAS based on the analysis using the MI method assuming MAR and (2) PPS were consistent with the originally reported result performed for the FAS. The change from baseline in CST at Week 32 and Week 56 were comparable between groups. In summary, a decrease from baseline in CTS was observed in both treatment groups at all time points and was similar between SB15 and Eylea over time.

Change from Baseline (BL) in total retinal thickness (TRT) at Week 4, Week 32 and up to Week 56: A decrease from BL was also observed for TRT in both treatment groups at all time points and was similar between SB15 and Eylea.

Proportion of Subjects with Intra- or Sub-Retinal Fluid on OCT at Week 32 and Week 56: A decrease in the proportion of subjects with intra- or sub-retinal fluid from baseline was noted in both groups at Week 32 and Week 56. In the SB15 group, the proportion of subjects with Intra- or Sub-Retinal Fluid on OCT decreased from 97.8% [219/224 subjects] at BL to 58.4% [128/219 subjects] at Week 32 and further decreased to 47.2% [102/216 subjects] at Week 56. In the Eylea/(Eylea+Eylea) group the proportion of subjects with Intra- or Sub-Retinal Fluid on OCT decreased from 99.1% [222/224 subjects] at BL to 55.8% [120/215 subjects] at Week 32 and further decreased to 48.5% [49/101 subjects] at Week 56. There were no major differences between treatments.

Change from Baseline in Choroidal Neovascularisation (CNV) Area at Week 32 and Week 56: At Week 32, the CNV area decreased compared to the baseline, and a further decrease was observed at Week 56 in both treatment groups. However, the decrease was higher in the SB15 group compared to the Eylea group at both time points. The LSmean observed for the change from baseline in CNV area at Week 32 for the FAS was −0.99578 mm^2 for the SB15 group and −0.38268 mm^2 for the Eylea group. The LSmean observed for the change from baseline in CNV area at Week 56 for the FAS was −1.25935 mm^2 for the SB15 group and −1.09380 mm^2 for the Eylea group. These differences were not reflected in clinically relevant differences between treatments in terms of BCVA, which represent a functional parameter.

Proportion of Subjects with Active CNV Leakage at Week 32 and Week 56: At Baseline, all patients in both groups had active CNV leakage. The proportion of patients with active CNV leakage decreased by Week 32 (88.2% and 91.4% in the SB15 and Eylea group, respectively) and further decreased by Week 56 (77.8% and 79.6% in the SB15 and Eylea group, respectively). The Proportion of Subjects with Active CNV Leakage at Week 32 and Week 56 was similar between treatments.

Subgroup analyses: The subgroup analysis by lesion type revealed some difference between treatments in for the predominantly classic CNV (8.8 letters (41 subjects) vs 5.3 letters (46 subjects) in the SB15 and Eylea group, respectively. The LSmean difference was 3.5 letters with (95% CI of [−0.3, 7.4]), which can at least in part be explained by the differences in baseline characteristics between groups.

Subgroup Analysis of Change from BL in CST at Week 4 by Baseline CST (< 350 µm, ≥ 350 µm): A much larger improvement in CST was observed in patients with baseline CST of ≥ 350 cm (−152.510 µm and −168.743 µm in the SB15 and Eylea group) compared to patients with baseline CST of <350 µm (−51.336 µm and −55.272 µm in the SB15 and Eylea group) in both treatment groups. In patients with baseline CST of <350 µm, the change from BL in CST at Week 4 for the FAS was similar between treatments (3.936 µm (95% CI [−6.119, 13.991]). In patients with baseline CST of ≥ 350 µm, a larger change from BL was observed in the Eylea group compared to the SB15 group (−152.510 µm and −168.743 µm in the SB15 and Eylea group, respectively). In this subgroup, the LSmean difference of the change from baseline in CST between SB15 and Eylea at Week 4 was 16.233 µm (95% CI [−3.330, 35.796]). Although in the latter group there was a notable difference between treatments, the CI was within the range considered by the CHMP during SA as not clinically relevant. However, it is critically noted that, by not limiting the inclusion criterion to CST of ≥ 350 µm as recommended by the CHMP, the heterogeneity of the study population is increased. As this was a secondary endpoint, this is not considered a major concern.

2.5.7. Conclusions on the clinical efficacy

From the efficacy perspective, the clinical data indicate similarity between the proposed biosimilar SB15 and the reference product US-Eylea.

2.5.8. Clinical safety

The safety of SB15 was evaluated in a phase III randomised, double-masked, parallel group, multicentre study SB15-3001.

The purpose of study SB15-3001 was to compare the efficacy, safety, pharmacokinetic, and immunogenicity of SB15 with the reference product Eylea in subjects with neovascular age-related macular degeneration.

In study SB15-3001, safety assessments consisted of collecting all AEs, SAEs, including their severity and relationship to study treatment or study procedure. Safety assessments also included the regular monitoring of haematology, blood chemistry, and urinalysis. Safety assessments additionally included immunogenicity testing, assessments of vital signs, and physical condition. Furthermore, an ophthalmic examination consisting of slit-lamp examination, IOP measurement, and indirect ophthalmoscopy was performed. Development of binding and neutralizing antidrug antibodies (ADAs) up to Week 56 was assessed as well.

The schedule showing the timing of the assessments for the efficacy and safety endpoints and other study activities is provided in Table 34 below.

Table 34: Schedule of activities

Table 9-3 Schedule of Activities

Procedures	Study Period									
W: Week	**Screening[25]**	**W0**	**W4**	**W8**	**W16**	**W24**	**W32**	**W40**	**W48 EOT[26]**	**W56 EOS[27]/ET[28]**
D: Day (± Visit Window)	**D−21 to D−1**	**D1**	**D29 (± 7)**	**D57 (± 7)**	**D113 (± 7)**	**D169 (± 7)**	**D225 (± 7)**	**D281 (± 7)**	**D337 (± 7)**	**D393 (± 7)**
V: Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Written informed consent[1]	X									
Inclusion/exclusion criteria	X	X								
Demographic data[2]	X									
Medical/ophthalmic history	X									
Physical examination[3]	X									X
Randomisation[4]		X					X[5]			
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
BCVA examination[7]	X	X[8]	X	X[9] (Primary)	X	X	X	X	X	X
OCT[10]	X	X	X	X	X	X	X	X	X	X
FP/FA[11]	X						X			X
Indirect ophthalmoscopy[12] (pre- and post-dose)	X	X	X	X	X	X	X	X	X	X
Slit lamp examination[13]	X	X	X	X	X	X	X	X	X	X
IOP[14] (pre- and post-dose)	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[15]		X					X			X
Clinical laboratory test[16]	X			X			X	X		X
Blood sampling for immunogenicity[17]		X	X	X		X	X	X		X
Blood sampling for PK[18]		X	X	X		X	X	X		X[19]
W: Week	**Screening[25]**	**W0**	**W4**	**W8**	**W16**	**W24**	**W32**	**W40**	**W48 EOT[26]**	**W56 EOS[27]/ET[28]**
D: Day (± Visit Window)	**D−21 to D−1**	**D1**	**D29 (± 7)**	**D57 (± 7)**	**D113 (± 7)**	**D169 (± 7)**	**D225 (± 7)**	**D281 (± 7)**	**D337 (± 7)**	**D393 (± 7)**
V: Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Pregnancy test[20]	X	X	X	X	X	X	X	X	X	X
IP injection[21]		X[22]	X	X	X	X	X	X	X	
AE monitoring[23]	Continuously									
Prior or concomitant medication or therapy[24]	Continuously									

AE = adverse event; BCVA = best corrected visual acuity; EOS = end of study; EOT = end of treatment; ET = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; FP = fundus photography; IP = investigational product; IOP = Intraocular pressure; IVT = intravitreal; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OCT = optical coherence tomography; PK = pharmacokinetics; SAE = serious adverse event

1. Written informed consent was obtained from the subject prior to any study related procedures.
2. Demographic data included the date of birth (year of birth was required), gender, race, and ethnicity.
3. Physical examination was performed at Screening and Week 56 (EOS visit) or ET visit. Body weight was measured and recorded at Screening and Week 56 (EOS visit) or ET visit, whereas height was measured and recorded only at Screening.
4. All subjects' eligibility was confirmed by the central reading centre and the Investigator prior to randomisation.
5. At Week 32, subjects in the Eylea treatment group were randomised in a 1:1 ratio to either continue on Eylea treatment or be transitioned to SB15 treatment. Subjects receiving SB15 continued to receive SB15 up to Week 48, but they also followed the randomisation procedure in order to maintain masking.
6. Vital signs included blood pressure (BP), pulse rate, and body temperature. Vital signs were assessed at Screening, prior to IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit.
7. Visual acuity was assessed in both the study eye and fellow (non-study) eye at Screening, prior to IVT injection of IP at each visit until Week 48, and during the final visit at Week 56 (EOS visit) or ET visit. Subject used either original series ETDRS chart or 2702 series Number chart (at a starting distance of 4 meters) consistently from Screening to Week 56 (EOS visit) or ET visit. Visual acuity testing was performed before dilation of pupils and other ophthalmic procedures including FA/FP and OCT assessment. A decrease in visual acuity of ≥ 15 letters from the last assessment of VA was reported as AEs/SAEs as appropriate. If there was a decrease in visual acuity of ≥ 30 letters from the last assessment of visual acuity or if there was a decrease in visual acuity to the level of light perception or worse, it was reported as SAE.
8. The Investigator confirmed that the subject could read between 73 letters and 34 letters, inclusive, in the study eye using original series ETDRS chart or 2702 series Number chart at Week 0 (Day1) prior to randomisation.
9. Visit at Week 8 was the most critical as this was the visit scheduled for the primary endpoint assessment. Thus, every effort was made to adhere to the visit schedule for the subjects.

10. OCT was performed on both eyes at Screening and those images taken from both eyes were sent to the central reading centre. OCT was performed on the study eye prior to IVT injection of IP at each visit until Week 48 and at Week 56 (EOS visit) or ET visit. OCT images taken from the study eye were sent to the central reading centre. Only OCT devices certified by the central reading centre were allowed to be used in this study. If one or more OCT devices were certified in an investigational site, a subject used the same OCT system from the same manufacture consistently from Screening to Week 56 (EOS visit) or ET visit.
11. FP/FA was performed on both eyes at Screening and those images taken from both eyes were sent to the central reading centre. FP/FA was also performed on the study eye prior to IVT injection of IP at Week 32 and at Week 56 (EOS visit) or ET visit. Those images taken from the study eye at Week 32 and Week 56 (EOS visit) or ET visit were sent to the central reading centre. Only FP/FA devices certified by the central reading centre were allowed to be used in this study. If one or more FP/FA devices were certified in an investigational site, a subject used the same FP/FA system from the same manufacture consistently from Screening to Week 56 (EOS visit) or ET visit.
12. Indirect ophthalmoscopy using a standard way (i.e., usually using a head-mounted light source and a 20-30 D lens) was performed on the study eye at Screening, prior to IVT injection of IP and 0-15 minutes after IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit.
13. Slit lamp examination was performed on both the study eye and fellow eye (non-study eye) at Screening and prior to IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit.
14. IOP was measured using Goldmann applanation tonometry. The same method of IOP measurement was used in each subject from Screening to Week 56 (EOS visit) or ET visit. IOP was measured on the study eye at Screening, prior to each IVT injection of IP and 30-60 minutes after IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit. If IOP was measured prior to OCT and FP/FA, IOP was carefully measured not to cause corneal erosion, which could affect the quality of OCT/FP/FA images.
15. NEI VFQ-25 was performed at Week 0 (Day 1) after randomisation. Subsequently, NEI VFQ-25 was performed before dilation of pupils at Week 32 and at Week 56 (EOS visit) or ET visit.
16. Blood and urine samples for clinical laboratory test were collected at Screening, prior to IVT injection of IP at Week 8, Week 32, Week 40, and at Week 56 (EOS visit) or ET visit. Urine samples were collected before performing FA to avoid interference with fluorescein in urinalysis.
    - Haematology: Haemoglobin, haematocrit, platelet count, and white blood cell count (total and differential)
    - Chemistry: Sodium, potassium, creatinine, glucose, calcium, phosphorus, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase
    - Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, and urobilinogen
17. Blood samples for immunogenicity assessment were collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40, and at Week 56 (EOS visit) or ET visit.
18. Blood samples for PK assessment were collected only in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1]). Blood samples for pre-dose PK assessment were collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for post-dose PK assessment were collected once between 24 hours and 72 hours after IVT injection of IP at Week 0 (Day 1) and on 1 day, 2 days and 3 days after the date of IVT injection of IP at Week 24 (total 3 times of PK sample collection for 3 consecutive days). Blood samples for PK assessment were also collected at Week 56 (EOS visit).
19. Blood samples for PK assessment were not allowed to be collected at ET visit.
20. Only for women of childbearing potential, a serum pregnancy was performed at Screening. A pregnancy test (on serum or urine at the Investigator's discretion) was repeated and a negative result had to be obtained prior to each IVT injection of IP after randomisation.
21. Subjects were administered SB15 or Eylea 2 mg (0.05 mL) via IVT injection into the study eye every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48. Dosing visits were allowed within ± 7 days of the scheduled dosing visit date (except Week 0 [Day 1], visit window not allowed).
22. The first IVT injection of IP was performed on the same day of randomisation.
23. Ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs were recorded after the written informed consent was obtained from the subject until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).
24. Any medications, including prescription drugs, non-prescription drugs or any therapy received locally (in the study eye and/or fellow eye) or systemically within 180 days prior to Screening were recorded until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).
25. If the subject was not randomised within 21 days after signing the informed consent form, the subject was screen failed. Once a subject was screen failed for one eye, he or she was not allowed to be re-screened for the same eye. Screening for the other eye was allowed within the Screening period.
26. EOT visit was defined as the visit for the last scheduled IVT injection of SB15 or Eylea. The Sponsor did not provide IP (SB15 or Eylea) to subjects after they completed the EOT visit.
27. EOS visit was defined as Week 56, corresponding to 8 weeks (± 7 days) after the last scheduled IVT injection of SB15 or Eylea.
28. ET visit was recommended to be performed at 8 weeks (± 7 days) after the last IVT injection of SB15 or Eylea. When this schedule was not available (e.g., due to subject not available), the ET visit was still performed as soon as available and no later than Week 56 from the first IVT injection of IP. If ET visit occurred before 7 weeks after the last IVT injection of IP, a follow-up visit or telephone interview was conducted at 8 weeks (± 7 days) after the last IVT injection of IP to collect adverse events and related concomitant medications.

Source: SB15-3001 CSR Body, pg. 43ff.

AEs were coded using MedDRA version 23.0.

2.5.8.1. Patient exposure

Table 35: Patient exposure (up to study completion date of 16-03-2022.

	Patients enrolled[a]	Patients exposed*	Patients exposed to the proposed dose range[b]	Patients with long term** safety data
Blinded studies (placebo-controlled)	N/A	N/A	N/A	N/A
Blinded studies (active -controlled)	Total: N=449 SB15: N=224 Eylea: N=225	Total: N=448 SB15: N=224 Eylea: N=224	Total: N=438 SB15: N=219 Eylea: N=219	Total: N=425 SB15: N=215 Eylea: N=210
Open studies	N/A	N/A	N/A	N/A
Post marketing	N/A	N/A	N/A	N/A

	Patients enrolled[a]	Patients exposed*	Patients exposed to the proposed dose range[b]	Patients with long term** safety data
Compassionate use	N/A	N/A	N/A	N/A

* Received at least 1 dose of active treatment.
** In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure. Subjects completed at Week 56 (end of study).
[a] Subjects randomized at Week 0.
[b] Subjects completed at Week 32 (end of main period).

Source: SB15-3001 CSR Body, 10.1 Disposition of Subjects, pg. 71 and 12.1 Extent of Exposure, pg. 108

Overall Extent of Exposure

In Study SB15-3001, patients with neovascular AMD were randomly allocated to the SB15 treatment group or US Eylea treatment group in a 1:1 ratio to receive either SB15 or US Eylea (administered via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months [i.e., at Weeks 0, 4, and 8], followed by 2 mg [0.05 mL] once every 8 weeks).

A total of 449 subjects were randomly allocated to the SB15 or Eylea treatment groups and 448 (99.8%) subjects received at least 1 injection of SB15 or Eylea. Overall, 438 (97.6%) subjects (SB15: 219 [97.8%] subjects; Eylea: 219 [97.3%] subjects) completed study procedures at Week 32. A total of 425 (97.0%) subjects (SB15: 215 [98.2%] subjects; Eylea overall: 210 [95.9%] subjects; Eylea+SB15: 109 [98.2%] subjects; Eylea+Eylea: 101 [93.5%] subjects) completed the end of study at Week 56. The mean duration of exposure up to Week 32 was 221.7 days (SB15: 221.7 days; Eylea: 221.8 days). The mean duration of exposure up to Week 56 was 383.8 days (SB15: 385.5 days; Eylea overall: 382.2 days; Eylea+SB15: 390.9 days; Eylea+Eylea: 391.8 days) (see also SB15-3001 CSR Body, Table 12-1, pg. 108f.).

Safety Analysis Set

The Safety Set 1 (SAF 1) consisted of all patients who received at least one investigational product (IP) during the study period. The Safety Set 2 (SAF 2) consists of all patients in the SAF1 who received at least one IP after re-randomization at Week 32. As a result, of the 449 patients randomized, a total of 448 (99.8%) patients were included in the SAF 1 and 434 (96.7%) patients were included in the SAF 2.

2.5.8.2. Adverse events

Overview of TEAEs in the Main Period

An overview of AEs or TEAEs by number of subjects concerned, frequency and number of events was provided for the main period in Table 36 below.

Table 36: Summary of adverse events in the screening and main period (safety set 1, study SB15-3001)

Table 13: Summary of Adverse Events in the Screening and Main Period (Safety Set 1, Study SB15-3001)

	SB15 N = 224			US Eylea N = 224			Total N = 448		
Number of Patients Experiencing	**n**	**(%)**	**E**	**n**	**(%)**	**E**	**n**	**(%)**	**E**
No AEs	**114**	**50.9**	**0**	**119**	**53.1**	**0**	**233**	**52.0**	**0**
AEs	**110**	**49.1**	**182**	**105**	**46.9**	**207**	**215**	**48.0**	**389**
Pre-treatment AEs (Pre-AEs)	**6**	**2.7**	**7**	**12**	**5.4**	**14**	**18**	**4.0**	**21**
TEAEs	**108**	**48.2**	**175**	**99**	**44.2**	**193**	**207**	**46.2**	**368**
TEAE severity									
Mild	73	32.6	127	64	28.6	144	137	30.6	271
Moderate	26	11.6	36	28	12.5	40	54	12.1	76
Severe	9	4.0	12	7	3.1	9	16	3.6	21
Drug causality									
Related	3	1.3	3	2	0.9	2	5	1.1	5
Not related	105	46.9	172	97	43.3	191	202	45.1	363
IVT injection causality									
Related	11	4.9	12	3	1.3	3	14	3.1	15
Not related	97	43.3	163	96	42.9	190	193	43.1	353
Ocular TEAEs in the study eye	**41**	**18.3**	**46**	**28**	**12.5**	**33**	**69**	**15.4**	**79**
Ocular TEAE severity (study eye)									
Mild	31	13.8	3.5	17	7.6	22	48	10.7	57
Moderate	9	4.0	10	11	4.9	11	20	4.5	21
Severe	1	0.4	1	0	0.0	0	1	0.2	1
Drug causality (study eye)									
Related	3	1.3	3	1	0.4	1	4	0.9	4
Not related	38	17.0	43	27	12.1	32	65	14.5	75
IVT injection causality (study eye)									
Related	11	4.9	11	3	1.3	3	14	3.1	14
Not related	30	13.4	35	25	11.2	30	55	12.3	65
Ocular TEAEs in the fellow eye	**18**	**8.0**	**19**	**20**	**8.9**	**23**	**38**	**8.5**	**42**
Ocular TEAE severity (fellow eye)									
Mild	12	5.4	13	14	6.3	17	26	5.8	30
Moderate	6	2.7	6	6	2.7	6	12	2.7	12
Severe	0	0.0	0	0	0.0	0	0	0.0	0
Drug causality (fellow eye)									
Related	0	0.0	0	0	0.0	0	0	0.0	0
Not related	18	8.0	19	20	8.9	23	38	8.5	42
IVT injection causality (fellow eye)									
Related	0	0.0	0	0	0.0	0	0	0.0	0
Not related	18	8.0	19	20	8.9	23	38	8.5	42
Non-ocular TEAEs	**74**	**33.0**	**110**	**68**	**30.4**	**137**	**142**	**31.7**	**247**
Non-ocular TEAE severity									
Mild	53	23.7	79	45	20.1	105	98	21.9	184

Moderate	13	5.8	20	16	7.1	23	29	6.5	43
Severe	8	3.6	11	7	3.1	9	15	3.3	20
Drug causality									
Related	0	0.0	0	1	0.4	1	1	0.2	1
Not related	74	33.0	110	67	29.9	136	141	31.5	246
IVT injection causality									
Related	1	0.4	1	0	0.0	0	1	0.2	1
Not related	73	32.6	109	68	30.4	137	141	31.5	246
AESI	**11**	**4.9**	**11**	**6**	**2.7**	**6**	**17**	**3.8**	**17**
Ocular AESI category (study eye)	3	1.3	3	2	0.9	2	5	1.1	5
Category 1	0	0.0	0	0	0.0	0	0	0.0	0
Category 2	0	0.0	0	0	0.0	0	0	0.0	0
Category 3	0	0.0	0	0	0.0	0	0	0.0	0
Category 4	0	0.0	0	1	0.4	1	1	0.2	1
Category 5	0	0.0	0	0	0.0	0	0	0.0	0
Category 6	1	0.4	1	0	0.0	0	1	0.2	1
Category 7	2	0.9	2	1	0.4	1	3	0.7	3
Non-ocular AESI category	8	3.6	8	4	1.8	4	12	2.7	12
Category 8	5	2.2	5	2	0.9	2	7	1.6	7
Category 9	3	1.3	3	2	0.9	2	5	1.1	5
Intraocular inflammation TEAEs	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**1**	**0.2**	**1**
Intraocular inflammation TEAEs in the study eye	0	0.0	0	1	0.4	1	1	0.2	1
Intraocular inflammation TEAEs in the fellow eye	0	0.0	0	0	0.0	0	0	0.0	0
TEAEs leading to IP discontinuation	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**1**	**0.2**	**1**
Ocular TEAEs leading to IP discontinuation in the study eye	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Ocular TEAEs leading to IP discontinuation in the fellow eye	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Non-ocular TEAEs leading to IP discontinuation	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**1**	**0.2**	**1**
SAEs	**12**	**5.4**	**15**	**15**	**6.7**	**17**	**27**	**6.0**	**32**
Drug causality									

Related	0	0.0	0	1	0.4	1	1	0.2	1
Not related	12	5.4	15	14	6.3	16	26	5.8	31
IVT injection causality									
Related	1	0.4	1	0	0.0	0	1	0.2	1
Not related	11	4.9	14	15	6.7	17	26	5.8	31
Serious TEAEs	**12**	**5.4**	**15**	**15**	**6.7**	**17**	**27**	**6.0**	**32**
Drug causality									
Related	0	0.0	0	1	0.4	1	1	0.2	1
Not related	12	5.4	15	14	6.3	16	26	5.8	31
IVT injection causality									
Related	1	0.4	1	0	0.0	0	1	0.2	1
Not related	12	5.4	15	14	6.3	16	26	5.8	31
Ocular serious TEAEs in the study eye	**3**	**1.3**	**3**	**1**	**0.4**	**1**	**4**	**0.9**	**4**
Ocular serious TEAEs in the fellow eye	**1**	**0.4**	**1**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Non-ocular serious TEAEs	**8**	**3.6**	**11**	**14**	**6.3**	**16**	**22**	**4.9**	**27**
TEAEs leading to death	**0**	**0.0**	**0**	**1**	**0.4**	**1**	**1**	**0.2**	**1**

AE = adverse event; AESI = adverse event of special interest; E = frequency of events; IP = investigational product; IOP = intraocular pressure; IVT = intravitreal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 1; n = number of patients with events; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
Percentages were based on the number of patients in the Safety Set 1.
If a patient had multiple events with different severity (or causality), then the patient was counted only once at the worst severity (or worst causality, i.e., related) for the number of patients (n).
AESI Category
Category 1: New onset pre-injection IOP of ≥ 25 mmHg
Category 2: Post-injection IOP ≥ 35 mmHg
Category 3: Any case of intraocular infection (suspected infection) such as endophthalmitis
Category 4: Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis
Category 5: Iatrogenic traumatic cataract
Category 6: Retinal pigment epithelial tear
Category 7: Subretinal hemorrhage with the size of 1 DA or more involving the center of the fovea, or if the size of the hemorrhage is ≥ 50% of the total lesion area
Category 8: Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischemic events
Category 9: Non-ocular hemorrhage.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Table 12-3

Source: Summary of Clinical Safety, section 2.1.1.2.1.2. TEAEs in the Main Period (SAF 1), pg. 43ff.

A summary of **ocular TEAEs in the study eye** by SOC and PT that have been reported for >1% of subjects in any treatment group was provided in the following table.

Table 37: Ocular treatment-emergent adverse events in study eye by system organ class and preferred term (>1% in any treatment group) in the main period (safety set 1, study SB15-3001)

Table 15: Ocular Treatment-emergent Adverse Events in Study Eye by System Organ Class and Preferred Term (> 1% in Any Treatment Group) in the Main Period (Safety Set 1, Study SB15-3001)

System Organ Class	SB15 N = 224			US Eylea N = 224			Total N = 448		
Preferred Term	n	%	E	n	%	E	n	%	E
Any ocular TEAEs in the study eye	**41**	**18.3**	**46**	**28**	**12.5**	**33**	**69**	**15.4**	**79**
Eye disorders	**36**	**16.1**	**41**	**23**	**10.3**	**25**	**59**	**13.2**	**66**
Visual acuity reduced	8	3.6	8	5	2.2	5	13	2.9	13
Conjunctival haemorrhage	9	4.0	9	3	1.3	3	12	2.7	12
Neovascular age-related macular degeneration	2	0.9	2	3	1.3	4	5	1.1	6
Retinal haemorrhage	3	1.3	3	2	0.9	2	5	1.1	5
Cataract	0	0.0	0	3	1.3	3	3	0.7	3
Eye pain	3	1.3	3	0	0.0	0	3	0.7	3
Posterior capsule opacification	3	1.3	3	0	0.0	0	3	0.7	3
General disorders and administration site conditions	**2**	**0.9**	**2**	**3**	**1.3**	**3**	**5**	**1.1**	**5**
Disease progression	2	0.9	2	3	1.3	3	5	1.1	5
Infections and infestations	**3**	**1.3**	**3**	**3**	**1.3**	**4**	**6**	**1.3**	**7**
Conjunctivitis	2	0.9	2	3	1.3	3	5	1.1	5

E = frequency of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 1; n = number of patients with event; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
Percentages were based on number of patients in the Safety Set 1.
System Organ Classes were presented alphabetically; Preferred Terms were sorted within each System Organ Class in descending order of patient frequency of total treatment group. If the frequency of the Preferred Terms were tied, the Preferred Terms were ordered alphabetically.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Table 12-8, Table 14.3.1-2.2.1

Source: Summary of Clinical Safety, section 2.1.1.2.1.2. TEAEs in the Main Period (SAF 1), pg. 48f.

Additionally, the Applicant provided an assessment of the reported BCVA data analysed by the proportion of patients with ≥15 letters decreased compared to the previous visit in the study eye along with the statistical difference between treatment groups (Table 38) .

Table 38: Analysis of difference in proportion of patients with having at least one experience of 15 or more letter loss compared to previous visit in the study eye in the main period (full analysis set, study SB15-3001) (*Ad-hoc* analysis)

Table 1: Analysis of Difference in Proportion of Patients with Having at Least One Experience of 15 or More Letter Loss Compared to Previous Visit in the Study Eye in the Main Period (Full Analysis Set, Study SB15-3001) (*Ad-hoc* Analysis)

Treatment	n'	n	%	Adjusted Risk Difference (A-B)	
				Estimate	95% CI
SB15 (N = 224) (A)	224	13	5.8	0.8	[−3.38, 4.96]
Eylea (N = 224) (B)	224	11	4.9		

BCVA = Best corrected visual acuity (total letter score); CI = confidence interval; N = number of patients having change from previous visit in BCVA with 15 or more letter loss; n' = number of patients with available assessment results.
Percentages were based on n'.
The adjusted risk difference and its 95% CI were analyzed by a stratified Cochran-Mantel-Haenszel (CMH) test with country as a factor.
Source: Section 5.3.5.1, Final CSR, Study SB15-3001, Listing 16.2.6-1.1

The Applicant has also provided the following tabular overview including severity, investigational product (IP) or intravitreal (IVT) procedure-relatedness and outcome of each case of 'visual acuity reduced' and 'conjunctival haemorrhage' reported in the study eye during the main period (Table 39).

Table 39: Details of "visual acuity reduced" and "conjunctival haemorrhage" reported in the study eye during the main period (safety set 1, study SB15-3001)

Table 2: Details of 'Visual Acuity Reduced' and 'Conjunctival Haemorrhage' Reported in the Study Eye during the Main Period (Safety Set 1, Study SB15-3001)

SOC/PT	Patient No.	Treatment Group	Start Date/Day[a] End Date/Day[a]	Severity	IP or IVT Relatedness	Action Taken to IP	Action Taken to Treat AE	Outcome	AESI	SAE
Eye disorders/ Visual acuity reduced	[redacted]	SB15	[redacted]	Moderate	Not related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	Not related	No action	No action	Recovered/ Resolved	No	No
		SB15		Moderate	Not related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	Not related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	Not related	No action	N/A	Not recovered/ Not resolved	No	No
		SB15		Mild	Not related	No action	N/A	Recovered/ Resolved with sequelae	No	No
		SB15		Moderate	Not related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Moderate	Not related	No action	N/A	Recovered/ Resolved with sequelae	No	No
		Eylea		Mild	Not related	No action	N/A	Unknown	No	No
		Eylea		Mild	Not related	No action	N/A	Recovered/ Resolved	No	No
		Eylea		Moderate	Not related	No action	Other[b]	Recovered/ Resolved	No	No
	[redacted]	Eylea	[redacted]	Mild	Not related	No action	N/A	Recovered/ Resolved	No	No
		Eylea		Moderate	Not related	No action	Other[b]	Recovered/ Resolved	No	No
Eye disorders/ Conjunctival haemorrhage		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IP- and IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Moderate	Not related	No action	N/A	Recovered/ Resolved	No	No
		SB15		Mild	Not related	No action	N/A	Recovered/ Resolved	No	No
		Eylea		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		Eylea		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No
		Eylea		Mild	IVT injection-related	No action	N/A	Recovered/ Resolved	No	No

AESI = adverse event of special interest; IP = investigational product; IVT = intravitreal; No. = number; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class
[a] Study Day = (date of event - first IP dosing date) + 1 if the date of the event is on or after the first IP dosing date or Study Day = (date of event - first IP dosing date) if the date of the event is prior to the first IP dosing date.
[b] AE was treated with study IP.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Listing 16.2.7-1.1

AESI = adverse event of special interest; IP = investigational product; IVT = intravitreal; No. = number; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class
[a] Study Day = (date of event - first IP dosing date) + 1 if the date of the event is on or after the first IP dosing date or Study Day = (date of event - first IP dosing date) if the date of the event is prior to the first IP dosing date.
[b] AE was treated with study IP.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Listing 16.2.7-1.1

A total of 18 (8.0%) subjects in the SB15 arm and 20 (8.9%) subjects in the US Eylea arm reported at least one **ocular TEAE in the fellow eye**. None of the ocular TEAEs in the fellow eye were related to either the IP or the IVT injection procedure in the main period.

A summary of **non-ocular TEAEs** by SOC and PT that have been reported for >2% of subjects in any treatment group was provided in the following table.

Table 40: Non-ocular treatment-emergent adverse effects in study eye by system organ class and preferred term (>2% in any treatment group) in the main period (safety set 1, study SB15-3001)

Table 16: Non-ocular Treatment-emergent Adverse Events in Study Eye by System Organ Class and Preferred Term (> 2% in Any Treatment Group) in the Main Period (Safety Set 1, Study SB15-3001)

System Organ Class	SB15 N = 224			US Eylea N = 224			Total N = 448		
Preferred Term	n	%	E	n	%	E	n	%	E
Any non-ocular TEAE	**74**	**33.0**	**110**	**68**	**30.4**	**137**	**142**	**31.7**	**247**
Infections and infestations	**20**	**8.9**	**23**	**18**	**8.0**	**22**	**38**	**8.5**	**45**
Nasopharyngitis	5	2.2	5	2	0.9	3	7	1.6	8
Vascular disorders	**11**	**4.9**	**12**	**4**	**1.8**	**4**	**15**	**3.3**	**16**
Hypertension	6	2.7	6	1	0.4	1	7	1.6	7

E = frequency of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 1; n = number of patients with event; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
Percentages were based on number of patients in the Safety Set 1.
System Organ Classes were presented alphabetically; Preferred Terms were sorted within each System Organ Class in descending order of patient frequency of total treatment group. If the frequency of the Preferred Terms were tied, the Preferred Terms were ordered alphabetically.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Table 12-9, Table 14.3.1-2.4.1

Source: Summary of Clinical Safety, section 2.1.1.2.1.2. TEAEs in the Main Period (SAF 1), pg. 50

Overview of TEAEs in the Transition Period

An overview of AEs or TEAEs by number of subjects concerned, frequency and number of events was provided for the transition period in the following table.

Table 41: Summary of all adverse events in the transition period (safety set 2, study SB15-3001)

Table 17: Summary of All Adverse Events in the Transition Period (Safety Set 2, Study SB15-3001)

Number of Patients Experiencing	SB15+SB15 N = 219			US Eylea Overall N = 215			US Eylea SB15 N = 111			US Eylea US Eylea N = 104			Total N = 434		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
No AEs	**139**	**63.5**	**0**	**145**	**67.4**	**0**	**72**	**64.9**	**0**	**73**	**70.2**	**0**	**284**	**65.4**	**0**
AEs	**80**	**36.5**	**140**	**70**	**32.6**	**142**	**39**	**35.1**	**94**	**31**	**29.8**	**48**	**150**	**34.6**	**282**
TEAEs	**80**	**36.5**	**140**	**70**	**32.6**	**142**	**39**	**35.1**	**94**	**31**	**29.8**	**48**	**150**	**34.6**	**282**
TEAE severity															
Mild	49	22.4	92	38	17.7	93	23	20.7	63	15	14.4	30	87	20.0	185
Moderate	26	11.9	42	23	10.7	37	12	10.8	24	11	10.6	13	49	11.3	79
Severe	5	2.3	6	9	4.2	12	4	3.6	7	5	4.8	5	14	3.2	18
Drug causality															
Related	2	0.9	2	1	0.5	1	1	0.9	1	0	0.0	0	3	0.7	3
Not related	78	35.6	138	69	32.1	141	38	34.2	93	31	29.8	48	147	33.9	279
IVT injection causality															
Related	0	0.0	0	1	0.5	1	1	0.9	1	0	0.0	0	1	0.2	1
Not related	80	36.5	140	69	32.1	141	38	34.2	93	31	29.8	48	149	34.3	281
Ocular TEAEs in the study eye	**20**	**9.1**	**22**	**15**	**7.0**	**19**	**12**	**10.8**	**14**	**3**	**2.9**	**5**	**35**	**8.1**	**41**
Ocular TEAE severity (study eye)															
Mild	13	5.9	14	12	5.6	16	12	10.8	14	0	0.0	2	25	5.8	30
Moderate	6	2.7	7	2	0.9	2	0	0.0	0	2	1.9	2	8	1.8	9
Severe	1	0.5	1	1	0.5	1	0	0.0	0	1	1.0	1	2	0.5	2
Drug causality (study eye)															
Related	2	0.9	2	1	0.5	1	1	0.9	1	0	0.0	0	3	0.7	3
Not related	18	8.2	20	14	6.5	18	11	9.9	13	3	2.9	5	32	7.4	38
IVT injection causality (study eye)															
Related	0	0.0	0	1	0.5	1	1	0.9	1	0	0.0	0	1	0.2	1
Not related	20	9.1	22	14	6.5	18	11	9.9	13	3	2.9	5	34	7.8	40
Ocular TEAEs in the fellow eye	**22**	**10.0**	**23**	**19**	**8.8**	**22**	**15**	**13.5**	**18**	**4**	**3.8**	**4**	**41**	**9.4**	**45**
Ocular TEAE severity (fellow eye)															
Mild	15	6.8	16	11	5.1	12	8	7.2	9	3	2.9	3	26	6.0	28
Moderate	7	3.2	7	7	3.3	9	6	5.4	8	1	1.0	1	14	3.2	16
Severe	0	0.0	0	1	0.5	1	1	0.9	1	0	0.0	0	1	0.2	1
Drug causality (fellow eye)															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	22	10.0	23	19	8.8	22	15	13.5	18	4	3.8	4	41	9.4	45
IVT injection causality (fellow eye)															

Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	22	10.0	23	19	8.8	22	15	13.5	18	4	3.8	4	41	9.4	45
Non-ocular TEAEs	**55**	**25.1**	**95**	**49**	**22.8**	**101**	**25**	**22.5**	**62**	**24**	**23.1**	**39**	**104**	**24.0**	**196**
Non-ocular TEAE severity															
Mild	35	16.0	62	27	12.6	65	15	13.5	40	12	11.5	25	62	14.3	127
Moderate	16	7.3	28	15	7.0	26	7	6.3	16	8	7.7	10	31	7.1	54
Severe	4	1.8	5	7	3.3	10	3	2.7	6	4	3.8	4	11	2.5	15
Drug causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	55	25.1	95	49	22.8	101	25	22.5	62	24	23.1	39	104	24.0	196
IVT injection causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	55	25.1	95	49	22.8	101	25	22.5	62	24	23.1	39	104	24.0	196
AESI	**5**	**2.3**	**5**	**3**	**1.4**	**3**	**0**	**0.0**	**0**	**3**	**2.9**	**3**	**8**	**1.8**	**8**
Ocular AESI category (study eye)	3	1.4	3	1	0.5	1	0	0.0	0	1	1.0	1	4	0.9	4
Category 1	2	0.9	2	0	0.0	0	0	0.0	0	0	0.0	0	2	0.5	2
Category 2	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Category 3	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Category 4	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Category 5	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Category 6	1	0.5	1	0	0.0	0	0	0.0	0	0	0.0	0	1	0.2	1
Category 7	0	0.0	0	1	0.5	1	0	0.0	0	1	1.0	1	1	0.2	1
Non-ocular AESI category	2	0.9	2	2	0.9	2	0	0.0	0	2	1.9	2	4	0.9	4
Category 8	2	0.9	2	2	0.9	2	0	0.0	0	2	1.9	2	4	0.9	4
Category 9	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Intraocular inflammation TEAEs	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**
Intraocular inflammation TEAEs in the study eye	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Intraocular inflammation TEAEs in the fellow eye	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
TEAEs leading to IP discontinuation	**3**	**1.4**	**6**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**3**	**0.7**	**6**
Ocular TEAEs leading to IP discontinuation in the study eye	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**

Ocular TEAEs leading to IP discontinuation in the fellow eye	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
Non-ocular TEAEs leading to IP discontinuation	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**0**	**0.0**	**0**	**1**	**0.2**	**1**
SAEs	**11**	**5.0**	**12**	**12**	**5.6**	**16**	**6**	**5.4**	**10**	**6**	**5.8**	**6**	**23**	**5.3**	**28**
Drug causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	11	5.0	12	12	5.6	16	6	5.4	10	6	5.8	6	23	5.3	28
IVT injection causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	11	5.0	12	12	5.6	16	6	5.4	10	6	5.8	6	23	5.3	28
Serious TEAEs	**11**	**5.0**	**12**	**12**	**5.6**	**16**	**6**	**5.4**	**10**	**6**	**5.8**	**6**	**23**	**5.3**	**28**
Drug causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	11	5.0	12	12	5.6	16	6	5.4	10	6	5.8	6	23	5.3	28
IVT injection causality															
Related	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0	0	0.0	0
Not related	11	5.0	12	12	5.6	16	6	5.4	10	6	5.8	6	23	5.3	28
Ocular serious TEAEs in the study eye	**1**	**0.5**	**1**	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**1**	**1.0**	**1**	**2**	**0.5**	**2**
Ocular serious TEAEs in the fellow eye	**1**	**0.5**	**1**	**1**	**0.5**	**1**	**1**	**0.9**	**1**	**0**	**0.0**	**0**	**2**	**0.5**	**2**
Non-ocular serious TEAEs	**9**	**4.1**	**10**	**11**	**5.1**	**14**	**6**	**5.4**	**9**	**5**	**4.8**	**5**	**20**	**4.6**	**24**
TEAEs leading to death	**1**	**0.5**	**1**	**1**	**0.5**	**1**	**0**	**0.0**	**0**	**1**	**1.0**	**1**	**2**	**0.5**	**2**

AE = adverse event; AESI = adverse event of special interest; E = frequency of events; IP = investigational product; IOP = intraocular pressure; IVT = intravitreal; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 2; n = number of patients with event; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
Percentages were based on number of patients in the Safety Set 2.
If a patient had multiple events with different severity (or causality), then the patient was counted only once at the worst severity (or worst causality, i.e., related) for the number of patient (n).
AESI Category
Category 1: New onset pre-injection IOP of ≥ 25 mmHg
Category 2: Post-injection IOP ≥ 35 mmHg
Category 3: Any case of intraocular infection (suspected infection) such as endophthalmitis
Category 4: Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis
Category 5: Iatrogenic traumatic cataract
Category 6: Retinal pigment epithelial tear
Category 7: Subretinal hemorrhage with the size of 1 DA or more involving the center of the fovea, or if the size of the hemorrhage is ≥ 50% of the total lesion area
Category 8: Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischemic events
Category 9: Non-ocular hemorrhage.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Table 14.3.1-1.2

Source: Summary of Clinical Safety, section 2.1.1.2.1.3. TEAEs in the Transition Period (SAF 2), pg. 52ff.

A summary of **ocular TEAEs in the study eye** by SOC and PT that have been reported for >1% of subjects in any treatment group was provided in the following table.

Table 42: Ocular treatment-emergent adverse events in the study eye by system organ class and preferred term (>1% in any treatment group) in the transition period (safety set 2, study SB15-3001)

Table 19: Ocular Treatment-emergent Adverse Events in the Study Eye by System Organ Class and Preferred Term (> 1% in Any Treatment Group) in the Transition Period (Safety Set 2, Study SB15-3001)

System Organ Class	SB15+SB15 N = 219			US Eylea Overall N = 215			US Eylea SB15 N = 111			US Eylea US Eylea N = 104			Total N = 434		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any ocular TEAE in the study eye	20	9.1	22	15	7.0	19	12	10.8	14	3	2.9	5	35	8.1	41
Eye disorders	19	8.7	21	13	6.0	16	10	9.0	11	3	2.9	5	32	7.4	37
Cataract	4	1.8	4	2	0.9	2	1	0.9	1	1	1.0	1	6	1.4	6
Visual acuity reduced	4	1.8	4	2	0.9	2	1	0.9	1	1	1.0	1	6	1.4	6
Posterior capsule opacification	0	0.0	0	2	0.9	2	2	1.8	2	0	0.0	0	2	0.5	2
Xerophthalmia	0	0.0	0	2	0.9	2	2	1.8	2	0	0.0	0	2	0.5	2

E = frequency of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 2; n = number of patients with event; TEAE = treatment-emergent adverse event
Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.
Percentages were based on number of patients in the Safety Set 2.
System Organ Classes were presented alphabetically; Preferred Terms were sorted within each System Organ Class in descending order of patient frequency of total treatment group.
If the frequency of the Preferred Terms were tied, the Preferred Terms were ordered alphabetically.
Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Table 12-10, Table 14.3.1-2.2.2

Source: Summary of Clinical Safety, section 2.1.1.2.1.3. TEAEs in the Transition Period (SAF 2), pg. 61

A total of 41 (9.4%) subjects [22 (10.0%) subjects in the SB15+SB15 arm, 15 (13.5%) subjects in the Eylea+SB15, and 4 (3.8%) subjects in the Eylea+Eylea arm) reported at least one **ocular TEAE in the fellow eye**. In terms of severity, 26 (6.0%) subjects (SB15+SB15: 15 [6.8%] subjects; Eylea overall: 11 [5.1%] subjects; Eylea+SB15: 8 [7.2%] subjects; Eylea+Eylea: 3 [2.9%] subjects) had mild ocular TEAEs in the fellow eye, and 14 (3.2%) subjects (SB15+SB15: 7 [3.2%] subjects; Eylea overall: 7 [3.3%] subjects; Eylea+SB15: 6 [5.4%] subjects; Eylea+Eylea: 1 [1.0%] subject) had moderate ocular TEAEs in the fellow eye. Severe ocular TEAE of visual acuity reduced in the fellow eye was reported in 1 (0.2%) subject (Eylea overall: 1 [0.5%] subject; Eylea+SB15: 1 [0.9%] subject). None of the ocular TEAEs in the fellow eye were considered related to either the IP or the IVT injection procedure in the main period.

A total of 55 (25.1%) subjects in the SB15+SB15 arm, 25 (22.5%) subjects in the Eylea+SB15 arm and 24 (23.1%) in the Eylea+Eylea arm reported at least one **non-ocular TEAE**.

The most frequently reported TEAEs by **SOC** included infections and infestations reported by 28 (6.5%) subjects [17 (7.8%) subjects in the SB15+SB15 arm, 3 (2.7%) subjects in the Eylea+SB15 arm and 8 (7.7%) subjects in the Eylea+Eylea arm]; investigations reported by 20 (4.6%) subjects [11 (5.0%) subjects in the SB15+SB15 arm, 6 (5.4%) subjects in the Eylea+SB15 arm and 3 (2.9%) subjects in the Eylea+Eylea arm]; musculoskeletal and connective tissue disorders reported by 14 (3.2%) subjects [8 (3.7%) subjects in the SB15+SB15 arm, 5 (4.5%) subjects in the Eylea+SB15 arm and 1 (1.0%) subject in the Eylea+Eylea arm]; and gastrointestinal disorders reported by 12 (2.8%) subjects [(4 (1.8%) subjects in the SB15+SB15 arm, 2 (1.9%) subjects in the Eylea+Eylea arm and 6 (5.4%) subjects in the Eylea+SB15 arm)].

The most frequently reported non-ocular TEAEs by **PT** were hypertension reported by 6 (1.4%) subjects [1 (0.5%) subjects in the SB15+SB15 arm, 3 (2.7%) subjects in the Eylea+SB15 arm and 2 (1.9%) subject in the Eylea+Eylea arm]; anemia reported by 4 (0.9%) subjects [1 (0.5%) subjects in the SB15+SB15 arm, 2 (1.8%) subjects in the Eylea+SB15 arm and 1 (1.0%) subject in the Eylea+Eylea arm]; urinary tract infection reported by 4 (0.9%) subjects [3 (1.4%) subjects in the SB15+SB15 arm, none in the Eylea+SB15 arm and 1

(1.0%) subject in the Eylea+Eylea arm]; blood creatinine increased reported by 4 (0.9%) subjects [2 (0.9%) subjects in the SB15+SB15 arm, none in the Eylea+SB15 arm and 2 (1.9%) subjects in the Eylea+Eylea arm]; and osteoarthritis reported by 4 (0.9%) subjects [2 (0.9%) subjects in the SB15+SB15 arm, 2 (1.8%) in the Eylea+SB15 arm and none in the Eylea+Eylea arm].

Adverse events related to study treatment or study procedure

Main Period

Study drug related ocular TEAEs in the study eye included eye disorders reported by 3 (1.3%) subjects in the SB15 arm and 1 (0.4%) subject in the US Eylea arm. Reported ocular TEAEs in the study eye by PT were conjunctival haemorrhage reported by 1 (0.4%) subject in the SB15 arm; iridocyclitis reported by 1 (0.4%) subject in the US Eylea arm; and retinal pigment epithelial tear reported by 1 (0.4%) subject in the SB15 arm.

Study drug related non-ocular TEAEs included nervous system disorders (PT: ischaemic stroke) reported by 1 (0.4%) subject in the US Eylea arm.

IVT injection related ocular TEAEs in the study eye included eye disorders reported by 14 (3.1%) subjects [11 (4.9%) in the SB15 arm and 3 (1.3%) in the US Eylea arm]. Reported ocular TEAEs in the study eye by PT were conjunctival haemorrhage reported by 10 (2.2%) subjects [7 (3.1) in the SB15 arm and 3 (1.3%) in the US Eylea arm]; eye pain; conjunctival suffusion; retinal vascular disorder; and vitreous floaters each reported by 1 (0.4%) subject in the SB15 arm.

None of the **ocular TEAEs in the fellow eye** were considered related to either the study drugs or the IVT injection procedure in the main period.

One **non-ocular TEAE** (PT: headache) reported by 1 (0.4%) subject in the SB15 arm was considered related to IVT injection.

Transition Period

Study drug related ocular TEAEs in the study eye included eye disorders reported by 3 (0.7%) subjects [2 (0.9%) in the SB15+SB15 arm and 1 (0.9) in the Eylea+SB15 arm]. Reported ocular TEAEs in the study eye by PT were abnormal sensation in eye; and glaucoma each reported by 1 (0.5%) subject in the SB15+SB15 arm; and vitreous floaters reported by 1 (0.9%) subject in the Eylea+SB15 arm.

IVT injection related ocular TEAEs in the study eye included eye disorders (PT: vitreous floaters) reported by 1 (0.9%) subject in the Eylea+SB15 arm.

None of the **ocular TEAEs in the fellow eye** were considered related to either the IP or the IVT injection procedure in the transition period.

None of the **non-ocular TEAEs** were considered related to either the IP or the IVT injection procedure in the transition period.

2.5.8.3. Serious adverse event/deaths/other significant events

Adverse events of special interest

Adverse events of special interest (AESI) were collected using 9 categories.

Ocular AESI categories in the study eye

- Category 1: New onset pre-injection IOP of ≥ 25 mmHg
- Category 2: Post-injection IOP ≥ 35 mmHg
- Category 3: Any case of intraocular infection (suspected infection) such as endophthalmitis
- Category 4: Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis
- Category 5: Iatrogenic traumatic cataract
- Category 6: RPE tear
- Category 7: Subretinal hemorrhage with the size of 1 DA or more involving the center of the fovea, or if the size of the hemorrhage is ≥ 50% of the total lesion area

Non-ocular AESI categories

- Category 8: Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischemic events
- Category 9: Non-ocular hemorrhage

Of the reported AESIs in the transition period, the events of glaucoma and intraocular pressure increased belong to **category 1**. Both events were mild in intensity. One mild event (PT: glaucoma) reported in the SB15+SB15 arm was considered related to study drug.

Of the reported AESIs in the main period, the moderate event of iridocyclitis belonged to **category 4**. According to the CSR this event was reported in the Eylea arm in the main period. According to Listing 14.3.2-1.3, this event was reported in the Eylea+SB15 arm of the transition period. The event was considered moderate in severity. One moderate event (PT: iridocyclitis) reported in the Eylea+SB15 arm was considered related to study drug.

The event of retinal pigment epithelial tear belonged to **category 6**. According to the CSR, these two AESIs reported in 2 subjects (1 [0.4%] subject in the SB15 arm in the main period and 1 [0.5%] subject in the SB15+SB15 arm in the transition period) (SB15-3001 CSR Body, pg. 154). According to Listing 14.3.2-1.3, both events were reported in the SB15+SB15 arm. One event was mild and one moderate in severity. One moderate event (PT: retinal pigment epithelial tear) reported in the SB15+SB15 arm was considered related to study drug.

The events of retinal haemorrhage belonged to **category 7**. According to the CSR, four AESIs (PT: retinal haemorrhage) reported in 4 subjects (2 [0.9%] subjects in the SB15 arm in the main period, 1 [0.4%] subject in the Eylea arm in the main period, and 1 [1.0%] subject in the Eylea+Eylea arm in the transition period). According to Listing 14.3.2-1.3, the events have been reported by 2 subjects in the SB15+SB15 arm and 2 subjects in the Eylea+Eylea arm in the transition period. One event in the SB15+SB15 arm and one event in the Eylea+Eylea arm were considered severe, 1 event in the SB15+SB15 arm was considered moderate and one event in the Eylea+Eylea arm was considered mild in severity.

According to the CSR, 11 AESIs of **category 8** were reported in total 10 subjects (1 subject in the SB15+SB15 treatment group had AESI in the main period and the transition period, respectively; 4 subjects in the SB15 treatment group in the main period; 2 subjects in the Eylea treatment group in the main period; 1 subject in the SB15+SB15 treatment group in the transition period; 2 subjects in the Eylea+Eylea treatment group in the

transition period) (SB15-3001 CSR Body, pg. 154f.). According to Listing 14.3.2-1.3, seven events were reported in 6 subjects in the SB15+SB15 arm, 2 events were reported by 2 subjects in the Eylea arm and 2 events were reported by 2 subjects in the Eylea+Eylea arm (SB15-3001 CSR Body, pg. 2365ff.). 3 events reported by 2 subjects in the SB15+SB15 arm were considered severe (PT: transient ischaemic attack, angina unstable; acute myocardial infarction). Also, the events reported in the Eylea arm and the Eylea+Eylea arm were considered severe (PT: ischaemic stroke, renal artery stenosis, cerebrovascular accident, ischaemic stroke). The remaining events were considered mild or moderate in severity. The reported PTs belonging to category 8 were transient ischaemic attack, cerebral infarction, angina unstable, lacunar infarction, peripheral arterial occlusive disease, ischaemic stroke and renal artery stenosis. One severe event (PT: ischaemic stroke) reported in the Eylea arm was considered related to study drug.

According to the CSR, 5 AESIs of **category 9** were reported by 5 subjects (3 subjects in the SB15 treatment group in the main period; 2 subjects in the Eylea treatment group in the screening and main periods) (SB15-3001 CSR Body, pg. 155). According to Listing 14.3.2-1.3, 1 event was reported by 1 subject in the SB15 arm; 2 events were reported by 2 subjects in the SB15+SB15 arm; 1 event was reported by 1 subject in the Eylea+Eylea arm; and 1 event was reported by 1 subject in the Eylea+SB15 arm (SB15-3001 CSR Body, pg. 2365ff.). The event reported in the SB15 arm was considered severe (PT: duodenal ulcer haemorrhage), the other events were considered mild in severity. Vessel puncture site haematoma, duodenal ulcer haemorrhage, haematuria and epistaxis belonged to category 9.

With Day 120 responses the Applicant provided a table (Table 43) presenting AESIs by category, SOC and PT in the overall period to allocate the respective patients in line with the respective listing to clarify allocation of AESIs to the respective treatment groups.

Table 43: Adverse events of special interest (AESI) by AESI category, system organ class and preferred term in overall period (safety set 1, study SB15-3001) (*Ad-hoc* analysis)

Table 1: Adverse Events of Special Interest (AESI) by AESI Category, System Organ Class and Preferred Term in Overall Period (Safety Set 1, Study SB15-3001) (*Ad-hoc* Analysis)

AESI Category System Organ Class Preferred Term	SB15 N = 224			US Eylea Overall N = 224			US Eylea SB15 N = 111			US Eylea US Eylea N = 104			Total N = 448		
	n	%	E	n	%	E	n	%	E	n	%	E	n	%	E
Any AESI of Category 1	2	(0.9)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.4)	2
Eye disorders	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Glaucoma	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Investigations	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Intraocular pressure increased	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Any AESI of Category 4	0	(0.0)	0	1	(0.4)	1	1	(0.9)	1	0	(0.0)	0	1	(0.2)	1
Eye disorders	0	(0.0)	0	1	(0.4)	1	1	(0.9)	1	0	(0.0)	0	1	(0.2)	1
Iridocyclitis	0	(0.0)	0	1	(0.4)	1	1	(0.9)	1	0	(0.0)	0	1	(0.2)	1
Any AESI of Category 6	2	(0.9)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.4)	2
Eye disorders	2	(0.9)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.4)	2
Retinal pigment epithelial tear	2	(0.9)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.4)	2
Any AESI of Category 7	2	(0.9)	2	2	(0.9)	2	0	(0.0)	0	2	(1.9)	2	4	(0.9)	4
Eye disorders	2	(0.9)	2	2	(0.9)	2	0	(0.0)	0	2	(1.9)	2	4	(0.9)	4
Retinal haemorrhage	2	(0.9)	2	2	(0.9)	2	0	(0.0)	0	2	(1.9)	2	4	(0.9)	4
Any AESI of Category 8	6	(2.7)	7	4	(1.8)	4	0	(0.0)	0	2	(1.9)	2	10	(2.2)	11
Cardiac disorders	1	(0.4)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	2
Acute myocardial infarction	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Angina unstable	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Nervous system disorders	4	(1.8)	4	3	(1.3)	3	0	(0.0)	0	2	(1.9)	2	7	(1.6)	7
Cerebral infarction	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Cerebrovascular accident	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0	1	(1.0)	1	1	(0.2)	1
Ischaemic stroke	0	(0.0)	0	2	(0.9)	2	0	(0.0)	0	1	(1.0)	1	2	(0.4)	2
Lacunar infarction	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Transient ischaemic attack	2	(0.9)	2	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	2	(0.4)	2
Renal and urinary disorders	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Renal artery stenosis	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Vascular disorders	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Peripheral arterial occlusive disease	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Any AESI of Category 9	3	(1.3)	3	2	(0.9)	2	1	(0.9)	1	1	(1.0)	1	5	(1.1)	5
Renal and urinary disorders	1	(0.4)	1	1	(0.4)	1	1	(0.9)	1	0	(0.0)	0	2	(0.4)	2
Haematuria	1	(0.4)	1	1	(0.4)	1	1	(0.9)	1	0	(0.0)	0	2	(0.4)	2
Gastrointestinal disorders	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Duodenal ulcer haemorrhage	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
General disorders and administration site conditions	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0	1	(1.0)	1	1	(0.2)	1
Vessel puncture site haematoma	0	(0.0)	0	1	(0.4)	1	0	(0.0)	0	1	(1.0)	1	1	(0.2)	1
Respiratory, thoracic and mediastinal disorders	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1
Epistaxis	1	(0.4)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(0.2)	1

AESI = adverse event of special interest; E = frequency of events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the Safety Set 1; n = number of patients with event

Adverse events were coded to System Organ Class and Preferred Term using MedDRA coding dictionary version 23.0.

Category of AESI: 1=New onset pre-injection IOP of ≥ 25 mmHg; 2=Post-injection IOP ≥ 35 mmHg; 3=Any case of intraocular infection (suspected infection) such as endophthalmitis; 4=Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis; 5=Iatrogenic traumatic cataract; 6=Retinal pigment epithelial tear; 7=Subretinal haemorrhage with the size of 1 DA or more involving the centre of the fovea, or if the size of the haemorrhage is ≥ 50% of the total lesion area; 8=Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischaemic events; 9=Non-ocular haemorrhage.

Percentages were based on number of patients in the Safety Set 1.

System Organ Classes were presented alphabetically; Preferred Terms were sorted within each System Organ Class in descending order of patient frequency of total treatment group.

If the frequency of the Preferred Terms were tied, the Preferred Terms were ordered alphabetically.

Source: Section 5.3.5.1 Final CSR, Study SB15-3001, Listing 14.3.2-1.3

Intraocular inflammation

TEAEs of **intraocular inflammation in the study eye** by SOC and PT reported in the main period were provided in the following table.

Table 44: Treatment-emergent adverse events for intraocular inflammation in study eye by system organ class and preferred term in main period (safety set 1)

Table 14.3.1-9.1.1 (Page 1 of 1)
Treatment-Emergent Adverse Events for Intraocular Inflammation in Study Eye
by System Organ Class and Preferred Term in Main Period
Safety Set 1

System organ class Preferred term	SB15 N=224 n (%) E	Eylea N=224 n (%) E	Total N=448 n (%) E
Any TEAE for intraocular inflammation in the study eye	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Eye disorders	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Iridocyclitis	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1

Source: Listing 16.2.7-1.1
- Adverse events were coded to system organ class and preferred term using MedDRA coding dictionary version 23.0.
- TEAE: treatment-emergent adverse event; n: number of subjects with event; E: frequency of events.
- Percentages were based on the number of subjects in the Safety Set 1.
- System organ classes were presented alphabetically; preferred terms were sorted within each system organ class in descending order of subject frequency of Total treatment group. If the frequency of the preferred terms were tied, the preferred terms were ordered alphabetically.

Source: SB15-3001 CSR Body, pg. 2309

No TEAE of intraocular inflammation in the study eye was reported in the transition period.

The TEAEs of intraocular inflammation in the study eye (PT: iridocyclitis) was considered moderate in severity and related to study drug.

Serious adverse events

Main Period

In the main period, overall, 12 (5.4%) subjects reported serious TEAEs in the SB15 arm and 15 (6.7%) subjects reported serious TEAEs in the US Eylea arm.

Ocular serious TEAEs in the study eye have been reported in 3 (1.3%) subjects in the SB15 arm vs. 1 (0.4%) subject in the Eylea arm. Most frequently reported ocular serious TEAEs in the study eye in the main period by SOC were eye disorders reported by (2 (0.9%) subjects in the SB15 arm and none in the US Eylea arm. By PT, one event of retinal haemorrhage and retinal vascular disorder was reported by 1 (0.4%) subject in the SB15 arm. **Ocular serious TEAEs in the fellow eye** were reported by 1 (0.4%) subject in the SB15 arm. This was one moderate event of general disorders and administration site conditions (PT: disease progression). **Non-ocular serious TEAEs** have been reported by 8 (3.6%) subjects in the SB15 arm and 14 (6.3%) subjects in the US Eylea arm. Most frequently reported were neoplasms benign, malignant and unspecified (incl. cysts and polyps) reported by 3 (1.3%) subjects in the SB15 arm and 6 (2.7%) subjects in the US Eylea arm.

None of the **ocular serious TEAEs in the study eye** that have been reported in the main period were considered related to the IMP. One of the ocular serious TEAEs in the study eye reported by 1 (0.4%) subject in the SB15 arm (SOC: eye disorders; PT: retinal vascular disorder) was considered related to the IVT injection procedure.

None of the **ocular serious TEAEs in the fellow eye** were considered related to the study drug or IVT injection procedure.

One of the **serious non-ocular TEAEs** reported by 1 (0.2%) subject in the US Eylea arm of nervous system disorders (PT: ischaemic stroke) was considered related to the study drug. None of the non-ocular serious TEAEs was considered related to the IVT injection procedure.

Transition Period

In the transition period, overall, 11 (5.0%) subjects reported serious TEAEs in the SB15+SB15 arm; 6 (5.8%) subjects in the Eylea+Eylea arm and 6 (5.4%) subjects in the Eylea+SB15 arm).

Ocular serious TEAEs in the study eye have been reported by 1 (0.5%) subject in the SB15+SB15 arm vs. 1 (1.0%) subject in the Eylea+Eylea arm (none in the Eylea+SB15 arm). Both events belonged to the SOC eye disorders. By PT, these were 1 severe event of vitreous haemorrhage in the SB15+SB15 arm and 1 event of retinal haemorrhage in the Eylea+Eylea arm. **Ocular serious TEAEs in the fellow eye** have been reported by 1 (0.5%) subject in the SB15+SB15 arm vs. none in the Eylea+Eylea arm (1 (0.9%) subject in the Eylea+SB15 arm). Both events belonged to the SOC eye disorders. By PT, these were 1 moderate event of nAMD in the SB15+SB15 arm and 1 event of visual acuity reduced in the Eylea+SB15 arm. **Non-ocular serious TEAEs** have been reported by 9 (4.1%) subjects in the SB15+SB15 arm vs. 5 (4.8%) subjects in the Eylea+Eylea arm (6 (5.4%) subjects in the Eylea+SB15 arm). Most frequently reported non-ocular serious TEAEs by SOC belonged to neoplasms benign, malignant and unspecified (incl. cysts and polyps) (PT: adenocarcinoma gastric, benign neoplasm of bladder, colon cancer metastatic and neuroendocrine carcinoma metastatic); cardiac disorders (PT: acute myocardial infarction, cardiac failure and cardiac failure acute); and musculoskeletal and connective tissue disorders (PT: osteoarthritis and intervertebral disc protrusion).

None of the **ocular serious TEAEs in the study eye** that have been reported in the transition period were considered related to the study drug or the IVT injection procedure.

None of the **ocular serious TEAEs in the fellow eye** that have been reported in the transition period were considered related to the study drug or the IVT injection procedure.

None of the **non-ocular serious TEAEs** that have been reported in the transition period were considered related to the study drug or the IVT injection procedure.

Deaths

Three subjects died during study SB15-3001. In the main period, 1 death was reported for 1 (0.4%) subject in the US Eylea arm (SOC: vascular disorder, PT: circulatory collapse). In the transition period, 1 death was reported for 1 (0.5%) subject in the SB15+SB15 arm (SOC: general disorders and administration site conditions, PT: death). One death was reported for 1 (1.0%) subject in the Eylea+Eylea arm (SOC: nervous system disorders, PT: cerebrovascular accident). None of these events leading to death were considered related to study drug. In addition, subject dying from sudden death, was screen-failed and did not receive any IP injections. All the causes of death were of non-ocular nature. None of the reported deaths were considered related to the study drug.

2.5.8.4. Laboratory findings

Hematology, chemistry, and urinalysis assessments were performed at Screening, Week 8, Week 32, Week 40, and Week 56 (EOS)/early termination (ET) visit.

Changes in mean values from baseline for **hematology parameters** (hemoglobin, hematocrit, platelets, leukocytes, neutrophils, lymphocytes, monocytes, basophils, and eosinophils) were comparable across the treatment groups (see also SB15-3001 CSR Body, Table 14.3-2.1, pg. 1240ff. and Table 14.3-2.5, pg. 1305ff.). Majority of patients had values in the normal range at baseline and remained normal. Shifts from baseline reported as TEAEs have been presented in Table 14.3.1-2.1.1 (main period) or Table 14.3.1-2.1.2 (transition period) of the CSR (SB15-3001 CSR Body, pg. 1457ff. or pg. 1475ff. respectively). None of them were considered as SAE.

Table 45: Excerpt of Table 14.3.1-2.1.1 - Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Main Period (Created by the Clinical Assessor)

System organ class Preferred term	SB15 N=224 n (%) E	Eylea N=224 n (%) E	Total N=448 n (%) E
Any TEAE	108 (48.2) 175	99 (44.2) 193	207 (46.2) 368
Blood and lymphatic system disorders	2 (0.9) 2	1 (0.4) 1	3 (0.7) 3
Anaemia	2 (0.9) 2	1 (0.4) 1	3 (0.7) 3
Investigations	2 (0.9) 2	7 (3.1) 9	9 (2.0) 11
Blood pressure increased	0 (0.0) 0	4 (1.8) 4	4 (0.9) 4
Blood alkaline phosphatase increased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Blood creatinine increased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Blood glucose increased	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1
Blood potassium increased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Eosinophil count increased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Lipase increased	0 (0.0) 0	1 (0.4) 1	1 (0.2) 1
Transaminases increased	1 (0.4) 1	0 (0.0) 0	1 (0.2) 1

Source: Listing 16.2.7-1.1
- Adverse events were coded to system organ class and preferred term using MedDRA coding dictionary version 23.0.
- TEAE: treatment-emergent adverse event; n: number of subjects with event; E: frequency of events.
- Percentages were based on the number of subjects in the Safety Set 1.
- System organ classes were presented alphabetically; preferred terms were sorted within each system organ class in descending order of subject frequency of Total treatment group. If the frequency of the preferred terms were tied, the preferred terms were ordered alphabetically.

Source: SB15-3001 CSR Body, pg. 1457ff.

Table 46: Excerpt of Table 14.3.1-2.1.2 - Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Transition Period (Created by the Clinical Assessor)

System organ class Preferred term	SB15+SB15 N=219 n (%) E	Eylea Overall N=215 n (%) E	Eylea SB15 N=111 n (%) E	Eylea Eylea N=104 n (%) E	Total N=434 n (%) E
Any TEAE	80 (36.5) 140	70 (32.6) 142	39 (35.1) 94	31 (29.8) 48	150 (34.6) 282
Blood and lymphatic system disorders	2 (0.9) 2	5 (2.3) 5	4 (3.6) 4	1 (1.0) 1	7 (1.6) 7
Anaemia	1 (0.5) 1	3 (1.4) 3	2 (1.8) 2	1 (1.0) 1	4 (0.9) 4
Iron deficiency anaemia	0 (0.0) 0	1 (0.5) 1	1 (0.9) 1	0 (0.0) 0	1 (0.2) 1
Leukopenia	0 (0.0) 0	1 (0.5) 1	1 (0.9) 1	0 (0.0) 0	1 (0.2) 1
Microcytic anaemia	1 (0.5) 1	0 (0.0) 0	0 (0.0) 0	0 (0.0) 0	1 (0.2) 1
Investigations	12 (5.5) 13	9 (4.2) 14	6 (5.4) 7	3 (2.9) 7	21 (4.8) 27
Blood creatinine increased	2 (0.9) 2	2 (0.9) 2	0 (0.0) 0	2 (1.9) 2	4 (0.9) 4
Blood alkaline phosphatase increased	1 (0.5) 1	2 (0.9) 2	0 (0.0) 0	2 (1.9) 2	3 (0.7) 3
Glucose urine present	1 (0.5) 1	2 (0.9) 2	1 (0.9) 1	1 (1.0) 1	3 (0.7) 3

Blood lactate dehydrogenase increased	1	(	0.5)	1	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	2	(	0.5)	2
Blood pressure increased	1	(	0.5)	1	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	2	(	0.5)	2
Haemoglobin decreased	1	(	0.5)	1	1	(	0.5)	1	0	(	0.0)	0	1	(	1.0)	1	2	(	0.5)	2
Urine analysis abnormal	1	(	0.5)	1	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	2	(	0.5)	2
Alanine aminotransferase increased	1	(	0.5)	1	0	(	0.0)	0	0	(	0.0)	0	0	(	0.0)	0	1	(	0.2)	1
Blood glucose increased	0	(	0.0)	0	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	1	(	0.2)	1
Blood potassium increased	1	(	0.5)	1	0	(	0.0)	0	0	(	0.0)	0	0	(	0.0)	0	1	(	0.2)	1
Haematocrit increased	0	(	0.0)	0	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	1	(	0.2)	1
Helicobacter test positive	1	(	0.5)	1	0	(	0.0)	0	0	(	0.0)	0	0	(	0.0)	0	1	(	0.2)	1
Intraocular pressure increased	1	(	0.5)	1	0	(	0.0)	0	0	(	0.0)	0	0	(	0.0)	0	1	(	0.2)	1
Lymphocyte count decreased	0	(	0.0)	0	1	(	0.5)	1	0	(	0.0)	0	1	(	1.0)	1	1	(	0.2)	1
Weight decreased	1	(	0.5)	1	0	(	0.0)	0	0	(	0.0)	0	0	(	0.0)	0	1	(	0.2)	1
White blood cells urine positive	0	(	0.0)	0	1	(	0.5)	1	1	(	0.9)	1	0	(	0.0)	0	1	(	0.2)	1

Source: Listing 16.2.7-1.1
- Adverse events were coded to system organ class and preferred term using MedDRA coding dictionary version 23.0.
- TEAE: treatment-emergent adverse event; n: number of subjects with event; E: frequency of events.
- Percentages were based on the number of subjects in the Safety Set 2.
- System organ classes were presented alphabetically; preferred terms were sorted within each system organ class in descending order of subject frequency of Total treatment group. If the frequency of the preferred terms were tied, the preferred terms were ordered alphabetically.

Source: SB15-3001 CSR Body, pg. 1475ff.

Changes in mean values from baseline for **chemistry parameters** (sodium, potassium, creatinine, glucose, calcium, phosphate, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase) were comparable between the treatment groups (see also SB15-3001 CSR Body, Table 14.3-2.2, pg. 1268ff. and Table 14.3-2.6, pg. 1347ff.). Majority of patients had values in the normal range at baseline and remained normal. Shifts from baseline reported as TEAEs have been presented in Table 14.3.1-2.1.1 (main period) or Table 14.3.1-2.1.2 (transition period) of the CSR (SB15-3001 CSR Body, pg. 1457ff. or pg. 1475ff. respectively). See excerpts of Tables 14.3.1-2.1.1 and 14.3.1-2.1.2 above. None of them were considered as SAE.

The proportion of subjects with each result (normal, abnormal not clinically significant (NCS), and abnormal clinically significant (CS)) for **urinanalysis** were presented in Table 47 [Table 14.3-2.3 of the CSR (SB15-3001 CSR Body, pg. 1292)].

Table 47: Summary of urinalysis assessment (safety set 1)

Table 14.3-2.3 (Page 1 of 1)
Summary of Urinalysis Assessment
Safety Set 1

		SB15	Eylea			Total
			Overall	SB15	Eylea	
		N=224	N=224	N=111*	N=104*	N=448
Timepoint	Result	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)	n/n' (%)
Screening (BL)	Normal	166/224 (74.1)	164/222 (73.9)	78/110 (70.9)	82/104 (78.8)	330/446 (74.0)
	Abnormal,ncs	58/224 (25.9)	57/222 (25.7)	31/110 (28.2)	22/104 (21.2)	115/446 (25.8)
	Abnormal,cs	0/224 (0.0)	1/222 (0.5)	1/110 (0.9)	0/104 (0.0)	1/446 (0.2)
Week 8	Normal	174/221 (78.7)	178/221 (80.5)			352/442 (79.6)
	Abnormal,ncs	46/221 (20.8)	42/221 (19.0)			88/442 (19.9)
	Abnormal,cs	1/221 (0.5)	1/221 (0.5)			2/442 (0.5)
Week 32	Normal	163/214 (76.2)	174/215 (80.9)	88/110 (80.0)	86/103 (83.5)	337/429 (78.6)
	Abnormal,ncs	48/214 (22.4)	40/215 (18.6)	21/110 (19.1)	17/103 (16.5)	88/429 (20.5)
	Abnormal,cs	3/214 (1.4)	1/215 (0.5)	1/110 (0.9)	0/103 (0.0)	4/429 (0.9)
Week 40	Normal	172/218 (78.9)	175/214 (81.8)	90/110 (81.8)	84/103 (81.6)	347/432 (80.3)
	Abnormal,ncs	45/218 (20.6)	36/214 (16.8)	17/110 (15.5)	19/103 (18.4)	81/432 (18.8)
	Abnormal,cs	1/218 (0.5)	3/214 (1.4)	3/110 (2.7)	0/103 (0.0)	4/432 (0.9)
Week 56	Normal	188/218 (86.2)	172/209 (82.3)	86/108 (79.6)	86/101 (85.1)	360/427 (84.3)
	Abnormal,ncs	29/218 (13.3)	35/209 (16.7)	21/108 (19.4)	14/101 (13.9)	64/427 (15.0)
	Abnormal,cs	1/218 (0.5)	2/209 (1.0)	1/108 (0.9)	1/101 (1.0)	3/427 (0.7)

Source: Listing 16.2.8-1.4
- BL: baseline; ncs: not clinically significant; cs: clinically significant.
- n': number of subjects with available assessment results at each visit; n: number of subjects in the specific category at each visit.
- Percentages were based on n'.
- * based on subjects in Safety Set 2, Eylea+SB15 and Eylea+Eylea may not add up to Eylea Overall.

Source: SB15-3001 CSR Body, pg. 1292

According to the Applicant relevant AEs reported in subjects with abnormal urinalysis findings included cystitis, cystitis bacterial, leukocyturia, glucose urine present, urinary tract infection, urine analysis abnormal, and white blood cells urine positive. A tabular overview was not provided.

Overall, when compared with baseline the mean changes in **vital signs** (systolic and diastolic BP, pulse rate, and body temperature) were comparable between the treatment groups (systolic blood pressure, diastolic blood pressure, pulse rate, body temperature). Up to Week 56, 3 (0.7%) subjects (Eylea+SB15: 1 [0.9%] subject; Eylea+Eylea: 2 [1.9%] subjects) had clinically significant high systolic blood pressure and 8 (1.8%) subjects (SB15: 2 [0.9%] subjects; Eylea+SB15: 3 [2.7%] subjects; Eylea+Eylea: 3 [2.9%] subjects) had clinically significant high diastolic blood pressure.

The **intraocular pressure** measured was comparable across the treatment groups at each timepoint in the Screening and main period, transition period, and overall period.

No positive **pregnancy** test was reported. There were no subjects with **cells and flare in the anterior chamber** of the study eye and the fellow eye in any treatment groups. None of the **vitreous haze** assessments were deemed clinically significant.

2.5.8.5. Discontinuation due to adverse events

One event of chronic myelomonocytic leukaemia reported by 1 (0.2%) subject in the Eylea arm leading to IP discontinuation was considered severe but not related to study drug. One event of vitreous haemorrhage reported by 1 (0.5%) subject in the SB15+SB15 arm was considered severe but not related to study drug. One event of retinal tear reported by the same subject as the event of vitreous haemorrhage in the SB15+SB15

arm was considered moderate but not related to study drug. The remaining 4 events reported by 3 (1.4%) subjects were considered mild and not related to study drug.

2.5.8.6. Post marketing experience

Not applicable.

2.5.9. Discussion on clinical safety

Safety data collection

The main safety data submitted by the Applicant in support of the marketing authorisation of SB15 (proposed similar biological medicinal product to Eylea) is based on one phase III study (SB15-3001), a randomized, double-masked, parallel group, multicenter study. This is considered appropriate.

Patient exposure

A total of 438 (97,6%) patients completed 32 weeks of the study (main period). After transition at week 32, the Eylea treatment group were randomised in 1:1 ratio again. The study was completed by 425 (97.0%) subjects and the last assessment was done after 56 weeks, which is adequate and in line with the ICH E1 guideline. Up to the final study completion date (56-week analysis) a total of 448 (99.8%) nAMD patients have received at least one dose of IMP (SB15) or RMP (US Eylea) (224 subjects each). The number of IP doses administered and duration of exposure to study drug were comparable across the treatment groups.

Adverse events

Main Period

In the main period, overall incidence for TEAEs was slightly higher in the SB15 arm vs. US Eylea arm (108 (48.2%) subjects vs. 99 (44.2%) subjects). **Ocular TEAEs in the study eye** have been reported in a higher proportion of the SB15 arm vs. US Eylea arm (41 (18.3%) subjects vs. 28 (12.5%) subjects). Most frequent **ocular TEAEs in the study eye** were reported by 36 (16.1%) subjects in the SB15 arm vs. 23 (10.3%) subjects in the US Eylea arm. Similar was observed for the most frequent PTs visual acuity reduced (SB15 vs. US Eylea: 8 (3.6%) subjects vs. 5 (2.2%) subjects) or conjunctival haemorrhage (SB15 vs. US Eylea: 9 (4.0%) subjects vs. 3 (1.3%) subjects).

Transition Period

In the transition period, overall incidence for TEAEs was higher in the SB15+SB15 arm vs. Eylea+Eylea arm (80 (36.5%) subjects vs. 31 (29.8%) subjects; Eylea+SB15: 39 (35.1%) subjects). **Ocular TEAEs in the study eye** have been reported in a higher proportion in the SB15+SB15 arm vs. Eylea+Eylea arm (20 (9.1%) subjects vs. 3 (2.9%) subjects; Eylea+SB15:12 (10.8%) subjects). **Ocular TEAEs in the study eye** were mostly of SOC eye disorders (SB15+SB15: 19 (8.7%) subjects; Eylea+Eylea: 3 (2.9%) subjects, Eylea+SB15: 10 (9.0%) subjects).

The overall incidence for **ocular TEAEs in the fellow eye** was higher in the SB15+SB15 arm vs. the Eylea+Eylea arm (22 (10.0%) subjects vs. 4 (3.8%) subjects; Eylea+SB15: 15 (13.5%) subjects.

With the Day 121 responses the Applicant addressed observed imbalances in frequencies of ocular TEAEs in the study eye. The Applicant provided an assessment of the reported BCVA data analysed by the proportion of patients with ≥15 letters decreased compared to the previous visit in the study eye along with the statistical

difference between treatment groups. Results showed no significant difference between groups. Also, TEAEs of 'visual acuity reduced' were of mild or moderate severity, none of them was considered related to IP or IVT and most cases resolved/recovered. TEAEs of 'conjunctival haemorrhage' were mostly considered related to IVT. However, they were mostly mild in severity and recovered/resolved. Incidence was within the reported range of 24.2% of Eylea in aflibercept-treated patients as reported by Clark et al. for the VIBRANT study [Clark et al., 2016]. In addition, frequency was comparable with incidence rates as presented in the initial and current Eylea EPARs [Eylea EPAR, 2012; Eylea EPAR, 2024]. Significance of imbalances in frequencies of ocular TEAEs for the study eye, therefore, is considered sufficiently discussed for the main period.

Ocular TEAEs in the study eye have also been reported in a higher proportion in the SB15+SB15 arm vs. Eylea+Eylea arm (20 (9.1%) subjects vs. 3 (2.9%) subjects; Eylea+SB15:12 (10.8%) subjects) in the transition period. However, this imbalance has not been addressed by the Applicant. Nevertheless, following the Applicants reasoning of ocular TEAEs in the study eye in the main period, similar arguments are true for the transition period: The majority of reported TEAEs in the transition period were non-ocular. Most frequent ocular TEAEs in the study eye were of the SOC 'eye disorders'. Most frequent PTs were 'cataract' and 'visual acuity reduced'. Both were reported in comparable frequencies for all treatment arms. All events of 'cataract' and 'visual acuity reduced' were of mild or moderate severity, none were considered related to study drug or IVT injection procedure. Only one event of 'visual acuity reduced' was considered serious. Therefore, no further safety concern is raised in this regard.

Incidence of non-ocular TEAEs was overall comparable between study arms.

Main vs. Transition Period

SB15 vs. SB15+SB15

Overall, more TEAEs have been reported in the main period vs. transition period for subjects receiving IMP only (SB15 vs. SB15+SB15: 108 (48.2%) subjects vs. 80 (36.5%) subjects). **Ocular TEAEs in the study eye** have been reported in a higher proportion in the main period vs. transition period (SB15 vs. SB15+SB15: 41 (18.3%) subjects vs. 20 (9.1%) subjects). Most frequent **ocular TEAEs in the study eye** were eye disorders (SB15 vs. SB15+SB15: 36 (16.1%) subjects vs. 19 (8.7%) subjects). Notable differences have been reported for the most frequently reported PTs visual acuity reduced and conjunctival haemorrhage.

Also, **non-ocular TEAEs** have been reported in a higher proportion in the main period vs. transition period (SB15 vs. SB15+ SB15: 74 (33.0%) subjects vs. 55 (25.1%) subjects). Notable imbalances have been reported for the most frequently reported non-ocular TEAEs by **SOC** gastrointestinal disorders, vascular disorders, nervous system disorders, and investigations. This was also observed, regarding one of the most frequently reported **PTs** hypertension.

Eylea vs. Eylea+Eylea

Overall, more TEAEs have been reported in the main period vs. transition period for subjects receiving RMP only (Eylea vs. Eylea+Eylea: 99 (44.2%) vs. 31 (29.8%) subjects). **Ocular TEAEs in the study eye** have been reported in a notably higher proportion in the main period vs. transition period (Eylea vs. Eylea+Eylea: 28 (12.5%) subjects vs. 3 (2.9%) subjects). Notable differences have also been reported for the most frequent **ocular TEAEs in the study eye** in the Eylea arm vs. Eylea+Eylea arm by SOC were eye disorders. Nevertheless, the disproportion in ocular TEAEs in the study eye reported for the main vs. transition period is not considered significant, as the same pattern (higher frequencies reported for the main period) is observed for patients receiving SB15 only as well as for patients receiving US Eylea only in comparable numbers.

Ocular TEAEs in the fellow eye have been reported in higher frequency in the Eylea vs. Eylea+Eylea arm (20 (8.9%) subjects vs. 4 (3.8%) subjects). **Non-ocular TEAEs** have been reported in 68 (30.4%) subjects in the Eylea arm vs. 24 (23.1%) subjects in the Eylea+Eylea arm. Among the most frequent non-ocular TEAEs by **SOC**, musculoskeletal and connective tissue disorders were notably more frequently reported in Eylea vs. Eylea+Eylea.

In general, differences in frequencies between main and transition period for non-ocular TEAEs showed the same pattern for patients receiving SB15 only as well as for patients receiving US Eylea only. Therefore, these overall imbalances are not considered relevant. However, notable differences for SOCs vascular disorders and investigations, were reported for patients in the SB15 vs. SB15+SB15 treatment group. Considering, that according to the SmPC of the RMP Eylea, systemic adverse events including arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition.

With the Day 121 responses the Applicant showed that frequencies of the most prominent PT 'hypertension' of SOC 'vascular disorders' were relatively low compared to literature data (VIEW1 and VIEW2 studies) [Heier et al., 2012]. Also, none of the TEAEs of hypertension were considered related to IP. Incidence rates for low or high diastolic blood pressure were shown to be comparable between treatment periods (SB15 vs. SB15+SB15). No case of low or high systolic blood pressure has been reported in the SB15 treatment group and the mean changes in blood pressure (both SBP and DBP) were comparable between the SB15 and SB15+SB15 treatment. Therefore, no further safety concern arises regarding the imbalances observed for SOC 'vascular disorders' of study SB15-3001.

SOC 'investigations' has been reported in lower frequency for SB15 vs. SB15+SB15 group (0.9% vs. 5.0%). However, it is true that PTs have only been reported by 1 or 2 patients respectively. Also, none of the PTs were considered drug or IVT injection related. Therefore, no further safety concern arises regarding SOC 'investigations'.

Incidence of ATEs in study SB15-3001 (AESIs category 8) was comparable to literature data [Heier et al., 2012]. The Applicant expects the risk of systemic adverse events from VEGF inhibition to be minimal, considering the low incidence of ATE observed in study SB15-3001. With regard to numbers presented in the Applicant's response and in the Eylea EPAR, this conclusion can be followed.

ADRs

During the main period **study drug related ocular TEAEs in the study eye** have been reported by a slightly higher proportion in the SB15 arm vs. US Eylea arm (3 (1.3%) subjects vs. 1 (0.4%) subject). The occurrence of study drug related ocular TEAE has been slightly higher in the study eye than in the reference treatment eye (fellow eye). This disproportion is not considered significant, especially when the drug causality has been evaluated as related only in 3 cases in the IMP arm (conjunctival haemorrhage, macular hole, retinal pigment epithelial tear) and 1 case in the RMP arm (iridocyclitis). On the other hand, **IVT injection related ocular TEAEs in the study eye** have been reported by a notably higher proportion in the SB15 arm vs. US Eylea arm (11 (4.9%) subjects vs. 3 (1.3%) subjects).

The occurrence of ocular TEAE in the fellow eye or the occurrence of non-ocular TEAEs were comparable, also in terms of causality or severity of reported TEAEs.

During the transition period no notable difference in study drug related ocular TEAEs in the study eye have been reported between treatment groups. The occurrence of ocular TEAE in the study eye has been slightly higher than in the reference treatment eye. However, this disproportion is not considered significant, especially

because the drug causality has only been evaluated as related in 2 cases in the SB15+SB15 arm (abnormal sensation in eye, glaucoma) and 1 case in the Eylea+SB15 arm (vitreous floaters). None of the ocular TEAEs in the fellow eye or non-ocular TEAEs were considered related to study drug or IVT injection procedure. Frequency and nature of TEAEs was in line with known undesirable effects of Eylea [Eylea SmPC, 2024]. Therefore, this is considered acceptable.

Main vs. Transition Period

Ocular TEAEs in the study eye related to IVT injection were clearly higher in the main period (SB15 vs. SB15+SB15: 11 (4.9%) subjects vs. none; Eylea vs. Eylea+Eylea: 3 (1.3%) subjects vs. none).

With Day 120 responses the Applicant argued that most IVT injection procedure related ocular TEAEs in the study eye of the main period of study SB15-3001 were due to conjunctival haemorrhage. Relation of this TEAE to the insertion/removal of the needle into/from the vitreous humor is plausible.

This does not explain the imbalance between the two treatment arms or between treatment periods. However, all events of 'conjunctival haemorrhage' were mild in severity, did not require any treatment, and were resolved/recovered without intervention. Furthermore, incidence rate was not only below frequencies reported in literature, but also as presented in the Eylea EPAR [Clark et al., 2016; Eylea EPAR, 2012; Eylea EPAR, 2024].

Also, according to the Applicant, no difference in the IVT injection procedure between the clinical study sites is expected. The presented "SB15-3001 study's pharmacy manual" recommends that the principal investigator follows the same IVT injection procedure as intended for Eylea. The manual contains a link to the current Eylea SmPC. Therefore, recommendations regarding the IVT injection procedure included in the manual are considered acceptable.

In summary, no further concerns for clinical safety are raised concerning IVT injection related ocular TEAEs in the study eye.

Ocular TEAEs in the fellow eye and **non-ocular TEAEs** were comparable in their frequencies between periods. Nature of reported TEAEs was reasonably connected to treatment and, overall, in line with the known undesirable effects of Eylea [Eylea SmPC, 2024]. This is considered acceptable.

AESIs

The following AESIs were considered related to drug treatment: glaucoma (cat1, SB15+SB15 arm), iridocyclitis (cat4, Eylea+SB15 arm), retinal pigment epithelial tear (cat6, SB15+SB15 arm) and ischaemic stroke (cat8, Eylea arm). Occurrence of these AESIs is expected and in line with the section 4.8 of the Eylea SmPC.

Nevertheless, initially there have been inconsistencies in the categorization of AESI events. Narrative of the Applicant in the CSR is not consistent with the respective Listing (14.3.2-1.3). This was observed for events of category 4, 6, 7, 8 and 9.

However, with D121 responses, the Applicant clarified that data presented in Listing 14.3.2-1.3 depicts the correct allocation of AESIs to the respective treatment groups. A table giving an overview of the allocation was provided by the Applicant. This is acknowledged.

Most events were reported for the SB15+SB15 arm (Transition period). However, most events were of mild or moderate severity, and did recover/resolve. Furthermore, as already stated in the D120 OV, occurrence of AESIs considered related to study drug (glaucoma (cat1, SB15+SB15 arm), iridocyclitis (cat4, Eylea+SB15 arm), retinal pigment epithelial tear (cat6, SB15+SB15 arm) and ischaemic stroke (cat8, Eylea arm) is expected and in line with the section 4.8 of the Eylea SmPC.

Therefore, no further safety concerns arise regarding the allocation of AESIs.

Serious TEAEs

Main Period

In the main period, overall incidence for TEAEs was comparable between SB15 and US Eylea arm. **Ocular serious TEAEs in the study eye** have been reported for a slightly higher proportion of subjects in the SB15 arm vs. US Eylea arm (3 (1.3%) subjects vs. 1 (0.4%) subject). Most frequently reported SOC was eye disorders. **Ocular serious TEAEs in the fellow eye** were reported by 1 (0.4%) subject in the SB15 arm (PT: disease progression). **Non-ocular serious TEAEs** have been reported in comparable frequencies for both treatment arms (PT: neoplasms benign, malignant and unspecified (incl. cysts and polyps).

Transition Period

In the transition period, overall incidence for TEAEs was comparable between SB15+SB15 arm, Eylea+Eylea arm and Eylea+SB15 arm. Two events of **ocular serious TEAEs in the study eye** have been reported (SB15+SB15: 1 (0.5%) subject; Eylea+Eylea: 1 (1.0%) subject; Eylea+SB15: none). (SOC: eye disorders; PT - SB15+SB15: vitreous haemorrhage; Eylea+Eylea: retinal haemorrhage). Two events of **ocular serious TEAEs in the fellow eye** have been reported (SB15+SB15: 1 (0.5%) subject; Eylea+Eylea: none; Eylea+SB15: 1 (0.9%) subject) (SOC: eye disorders; PT: SB15+SB15: nAMD; Eylea+SB15: visual acuity reduced). **Non-ocular serious TEAEs** have been reported in comparable frequencies (SOCs: neoplasms benign, malignant and unspecified (incl. cysts and polyps); cardiac disorders; and musculoskeletal and connective tissue disorders). Regarding frequency and nature, TEAEs were in line with known undesirable effects of Eylea [Eylea SmPC, 2024; Eylea EPAR, 2012]. This is considered acceptable.

1 (0.4%) subject in the Eylea arm reported a study drug related non-ocular serious TEAE (SOC: nervous system disorders; PT: ischaemic stroke). According to approved product information of Eylea, arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following intravitreal use of VEGF inhibitors. Therefore, TEAEs like stroke or myocardial infarction cannot be excluded. 1 (0.4%) subject in the SB15 arm reported IVT injection related ocular serious TEAEs in the study eye (SOC: eye disorders; PT: retinal vascular disorder). The occurrence of TEAEs connected with the IVT injection procedure are expected.

No safety concerns are raised regarding the occurrence of the serious TEAEs.

Laboratory and other findings

Haematology, chemistry, and urinalysis assessments were performed at Screening, Week 8, Week 32, Week 40, and Week 56 (end of study)/early termination visit. Changes in mean values from baseline for **haematology parameters**, **chemistry parameters** and **vital signs** were comparable between the treatment groups.

Haematology:

11 subjects had clinically significant abnormalities in haematology parameters in the main and transition periods (1 subject in the SB15 treatment group and 1 subject in the Eylea treatment group in the main period; 4 subjects in the SB15+SB15 treatment group, 3 subjects in the Eylea+SB15 treatment group, and 2 subjects in the Eylea+Eylea treatment group in the transition period). According to the Listing 16.2.7-1.1 Adverse Events (Safety Set 1),module 5.3.5.1 – Appendices (table 16.2.7-1.1), relevant AEs reported in subjects with abnormal

haematology parameters in the screening and main period and transition period included anaemia (SB15+SB15 – 3x not related; Eylea+SB15 - 4x not related,1x Eylea arm not related), chronic myelomonocytic leukaemia (1x Eylea arm only - not related), haematocrit increased (Eylea+SB15 – 1x not related), haematology test abnormal (1x Eylea arm only - not related), haemoglobin decreased (SB15+SB15 - 1x not related, 1x Eylea arm not related), lymphocyte count decreased (1x Eylea arm only - not related), and microcytic anaemia (SB15+SB15 – 1x not related). No observed AEs were considered related to SB15, this is acknowledged without any additional comment.

Chemistry:

A total of 15 subjects had clinically significant abnormalities in chemistry parameters in the main and transition periods (1 subject in the SB15 treatment group and 2 subjects in the Eylea treatment group in the main period; 4 subjects in the SB15+SB15 treatment group, 5 subjects in the Eylea+SB15 treatment group and 2 subjects in the Eylea+Eylea treatment group in the transition period; 1 subject who had clinically significant abnormalities in chemistry parameters in both main and transition periods in the Eylea+Eylea treatment group). Relevant AEs reported in subjects with abnormal chemistry parameters in the screening and main period and transition periods included alanine aminotransferase increased (1x SB15+SB15 not related,1x Eylea+SB15 not related), blood alkaline phosphatase increased (1x SB15+SB15 not related, 3x Eylea arms not related), blood creatinine increased (4x SB15 +SB15 not related, 4x Eylea arms not related), blood glucose increased (1x SB15+SB15 not related, 2x Eylea+SB1 not related), blood lactate dehydrogenase increased (1x SB15 +SB15 not related, 1x Eylea+SB15 not related), blood potassium increased (1x SB15 +SB15 not related, 1x Eylea+SB15 not related), blood test abnormal (1x Eylea arm only, not related), chronic kidney disease (1x Eylea+SB15 not related, 2x Eylea arms not related), and transaminases increased (1x SB15 +SB15 not related). No observed AEs were considered related to SB15, this is acknowledged without any additional comment.

Urinalysis assessment:

10 subjects had clinically significant abnormalities in urinalysis parameters in the main and transition periods (1 subject in the SB15 treatment group in the main period; 5 subjects in the SB15+SB15 treatment group, 2 subjects in the Eylea+SB15 treatment group, 1 subject in the Eylea+Eylea treatment group in the transition period; 1 subject who had clinically significant urinalysis parameters in both main and transition periods in the Eylea+SB15 treatment group). Relevant AEs reported in subjects with abnormal urinalysis findings included cystitis (5x SB15+SB15 – not related, 1x Eylea arm - not related), cystitis bacterial (2x SB15+SB15 - not related), leukocyturia (1x SB15+SB15 - not related), glucose urine present (1x SB15+SB15 - not related, 1x Eylea+SB15 - not related, 1x Eylea arm - not related), urinary tract infection (3x SB15+SB15 - not related, 2x Eylea arms - not related), urine analysis abnormal (1x SB15+SB15 - not related, 1x Eylea+SB15 - not related) and white blood cells urine positive (1x Eylea+SB15 - not related). No observed AEs were considered related to SB15, this is acknowledged without any additional comment.

Vital signs:

The Applicant states that when compared with baseline the mean changes in vital signs (systolic and diastolic BP, pulse rate, and body temperature) were comparable between the treatment groups with no apparent trend in any of the parameters. This is endorsed.

A total of 21 subjects had clinically significant abnormal vital signs (3 subjects in the SB15 treatment group and 6 subjects in the Eylea treatment group in the main period; 5 subjects in the SB15+SB15 treatment group, 1 subject in the Eylea+SB15 treatment group, and 1 subject in the in the Eylea+Eylea treatment group in the transition period; 2 subjects who had clinically significant abnormal vital signs in both main and transition

periods in the SB15+SB15 treatment group; 1 subject who had clinically significant abnormal vital signs in both main and transition periods in the Eylea+Eylea treatment group; 2 subjects who had clinically significant abnormal vital signs in both main and transition periods in the Eylea+SB15 treatment group). Clinically significant abnormal vital signs included blood pressure increased (SB15+SB15 - 1x not related, Eylea+SB15 - 3x not related, Eylea arms - 3x not related) and hypertension (SB15+SB15 – 7x not related, Eylea+SB15 - 3x not related, Eylea arm - 3x not related). No observed clinically significant changes in vital signs were considered related to SB15, this is acknowledged without any additional comment.

The Applicant stated that abnormalities in pulse rate and temperature were reported in a minimal number of subjects.

No safety concerns are raised regarding the observed changes in laboratory findings.

Intraocular pressure (IOP) was measured on the study eye at Screening, prior to IVT injection of IP and 30-60 minutes after IVT injection of IP at each visit until Week 48, and at Week 56 (EOS visit) or ET visit. The IOP measured was comparable across the treatment groups at each timepoint in the Screening and main period, transition period, and overall period. Mean post-injection IOP remained below 17.4 mmHg in both groups until the data cutoff date. This is acknowledged. No safety concerns are raised regarding the observed changes in intraocular pressure.

Slit Lamp Examination:

No subjects with cells and flare in the anterior chamber of the study eye and the fellow eye in any treatment groups were observed.

2.5.10. Conclusions on the clinical safety

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. The overall safety profile of SB15 is in line with known adverse events of the RMP Eylea [Eylea SmPC, 2024]. Some events were reported more frequently in the SB15 arm, while others were more frequent in the Eylea arm. Biosimilarity is supported from a safety perspective.

2.6. Risk Management Plan

Identified and potential risks.

The safety concerns in the RMP for a biosimilar product OPUVIZ are aligned with the safety concerns for the reference product EYLEA, taking into account findings from the comparative study SB15-3001 and potential unique characteristics of the OPUVIZ medicinal product.

2.6.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 48: 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 risk	Medication errors Off-label use and misuse Embryo-foetotoxicity
Missing information	None

2.6.2. Pharmacovigilance plan

Routine pharmacovigilance (PV) activities beyond ADRs reporting and signal detection include specific adverse reaction (ADR) follow-up (FU) questionnaires to collect data to further characterise and/or closely monitor any suspected intraocular infection and intraocular inflammation to deepen the understanding of this risk associated with aflibercept.

These forms aim to collect detailed information about the patient, concerned medicinal product, patient's history, relevant laboratory findings (bacteriology, serology, biopsy), clinical presentation of the event, and information on the treatment.

There are no on-going or planned additional PV studies/activities in the PV Plan for Opuviz (Aflibercept). This is acceptable.

2.6.3. Risk minimisation measures

The target audience of the RMM are healthcare professionals specialised in intravitreal injections of anti-VEGF treatments as well as the patients to be treated.

Table 49: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimisation SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Patients should be monitored a week following injection per the SmPC section 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up questionnaire Additional pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay per the SmPC section 4.2 and 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	None
Intraocular inflammation	Routine risk minimisation SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Patients should be monitored a week following injection per the SmPC section 4.4. Patients should be instructed to report any symptoms of intraocular inflammation per the SmPC section 4.4. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection Targeted follow-up questionnaire Additional pharmacovigilance activities None
Transient intraocular pressure increase	Routine risk minimisation SmPC sections 4.2, 4.4, 4.8, and 4.9	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL sections 2 and 4 Patients should be monitored immediately following the injection per the SmPC section 4.2. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	None <u>Additional pharmacovigilance activities</u> None
Retinal pigment epithelial tears	<u>Routine risk minimisation</u> SmPC sections 4.4 and 4.8 PL sections 2 and 4 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections <u>Additional risk minimisation</u> Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u> None <u>Additional pharmacovigilance activities</u> None
Cataract (especially of traumatic origin)	<u>Routine risk minimisation</u> SmPC sections 4.2, 4.4, and 4.8 PL sections 2, 3, and 4 Subject to restricted medical prescription	<u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection</u> None <u>Additional pharmacovigilance activities</u>

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	None
Medication errors	Routine risk minimisation SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None
Off-label use and misuse	Routine risk minimisation SmPC sections 4.1, 4.2, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	
Embryo-foetotoxicity	Routine risk minimisation SmPC sections 4.4, 4.6, and 5.3 PL section 2 Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept as per the SmPC section 4.4 and 4.6. Subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections Additional risk minimisation Educational materials: • Prescriber's guide and video • Patient's guide (including its audio version) for RVO (branch and central), CNV (myopic), DME, and wet AMD	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection None Additional pharmacovigilance activities None

AMD = age-related macular degeneration; CNV = choroidal neovascularisation; DME = diabetic macular oedema; PL = Package Leaflet; RVO = retinal vein occlusion; SmPC = Summary of Product Characteristics.

Additional risk minimisation measures

The Applicant proposed additional risk minimisation measures (RMM) in line with the reference product EYLEA. Besides routine RMM (SmPC and patient leaflet - PL), educational materials (prescriber's guide and patient guide, the latter including an audio version) are deemed necessary for the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelium tears, and cataract (especially of traumatic origin), as well as for the important potential risks of medication errors, off-label use and misuse, and embryo-fetotoxicity. These materials cover the indications of wet AMD, myopic CNV, DME branch or central RVO.

The physician information pack should contain the following elements:

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

Of note, the physician information should focus on:

- Techniques for the intravitreal injection, including use of a 30G needle, and angle of injection
- The fact that the vial is for single use only
- The need to expel excess volume of the syringe before injecting OPUVIZ 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 to use effective contraception while pregnant women should not use Opuviz

The patient information pack should include an information guide (and its audio version), with the following key elements:

- PL
- Who should be treated with Opuviz
- How to prepare for Opuviz treatment
- What are the steps following treatment with Opuviz
- 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

2.6.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Opuviz (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

Opuviz (also referred to as SB15) has been developed as a biosimilar to the reference product Eylea.

The reference product Eylea is authorised in 4 presentations: Eylea 40 mg/mL solution for injection in pre-filled syringe, Eylea 40 mg/mL solution for injection in a vial and Eylea 114.3 mg/ml solution for injection. The approved indications differ for respective presentations as follows:

- Eylea 40 mg/mL solution for injection in pre-filled syringe: nAMD, branch RVO or central RVO, DME, myopic CNV in adults. This presentation has an additional indication in preterm infants which is not authorised for other presentation: for the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.
- Eylea 40 mg/mL solution for injection in a vial: nAMD, branch RVO or central RVO, DME, myopic CNV in adults
- Eylea 114.3 mg/ml solution for injection: nAMD and DME in adults

The Applicant applied only for one presentation, i.e. Eylea 40 mg/mL solution for injection in a vial and claims corresponding indications i.e., nAMD, branch RVO or central RVO, DME, myopic CNV in adults.

The administration route (intravitreal), posology, and the claimed indications are identical to the reference product Eylea 40 mg/mL solution for injection in a vial.

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

A well-established biosimilarity exercise has been conducted. A three-way comparison was performed across SB15, US-sourced and EU-sourced Eylea at the quality level. Comparison of US-sourced with EU-sourced Eylea is of importance as US Eylea was used as a sole comparator in the non-clinical in vivo study and the clinical Phase III study. Up to EU-sourced Eylea and US-sourced Eylea batches have been used for the similarity evaluation. The EU reference product is approved as a prefilled syringe as well as a liquid in vial presentation. Regarding the biosimilar candidate SB15, clinical and PPQ drug product batches have been included into the biosimilarity evaluation, in addition to the drug product clinical and PPQ drug substance batch were included as well.

The clinical development comprised one pivotal phase III clinical study (SB15-3001), a randomised, double-masked, parallel group, multicentre study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB15 and Eylea, administered intravitreally, in subjects with neovascular age-related macular degeneration.

The design of the clinical study has been partly discussed in a CHMP Scientific Advice [EMA/CHMP/SAWP/575108/2017, 14/SEP/2017] and a Follow-up Advice [EMA/CHMP/SAWP/227002/2019, Apr 26, 2019], which were mostly followed by the Applicant. Notably, the primary endpoint that was discussed during SA procedures has not been followed. Nonetheless, the eventually employed PEP is deemed acceptable.

This study is completed with the data study completion-date of 16/MAR/2022 (56-week analysis).

3.2. Results supporting biosimilarity

Quality

In general, a broad panel of standard and state-of-the-art techniques has been applied to evaluate and compare physico-chemical quality attributes of SB15 with EU- and US-sourced Eylea. Structural similarity could be demonstrated between SB15 and EU-sourced Eylea, but also comparability between EU- and US-sourced Eylea was shown thus enabling the use of US-sourced Eylea as comparator in the Phase III trial. Minor differences have been sufficiently justified. At this point it should be noted that also broad set of binding and bioassays used for comparative characterisation of the biological activity do not indicate any differences there. Thus,

these results further support the Applicant`s justification that the noted differences do not translate into differences in the biological activities and thus have no impact on clinical performance characteristics of SB15 when compared with Eylea. It is also agreed that in principle a broad panel of binding and cell-based assays has been in place for evaluation of the biological properties. For certain low risk biological quality attributes only a limited number of batches have been tested, which can be accepted. The available results from the biological characterisation do not indicate any significant differences and thus further support the similarity claim. Finally, the Applicant has provided the results from comparative stress stability studies. These short-term studies have been carried out to compare degradation pathways and kinetics between clinical SB15, EU-, and US-Eylea. In summary, the presented results indicate a similar degradation between clinical SB15, EU-, and US-Eylea. Some remaining uncertainties raised at Day120 could be ruled out with the submission of additional data and information on the analytical methods.

Non-clinical

Analytical and functional similarity between SB15 and EU/US Eylea was demonstrated in *in vitro* studies which are described and discussed in the Quality Assessment Report (please refer to Module 3). No additional non-clinical pharmacodynamics studies, neither *in vitro* nor *in vivo*, were performed and included in Module 4 of this MAA.

Although not supported, the conduct of the 4-week repeat dose toxicity study in Cynomolgus monkeys (SBL-327-008) is accepted, as this study was performed to satisfy requirements of non-European authorities. As there are no concerns arising from the analytical biosimilarity exercise triggering the need for further investigations, the absence of additional non-clinical *in vivo* toxicology studies conducted with SB15 is accepted and highly appreciated regarding the principles of the 3Rs (EMA/CHMP/CVMP/3Rs/677407/2015).

From a non-clinical point of view, no concern was identified which would argue against a marketing authorization application. Please refer to the Quality assessment report for discussion and conclusion on the biosimilar comparability exercise.

Clinical

Pharmacokinetics

Assessment of systemic aflibercept levels conducted in a subset of 40 patients in the pivotal clinical study SB15-3001 revealed no major differences in systemic exposure between SB15 and Eylea. Most of the serum trough (pre-dose) conc. were BLQ at each timepoint up to Week 56 in both treatment groups. The post-dose exposure levels at Week 0 and at Week 24 were overall very low, as expected after an IVT injection, and within the similar range for both products and in the range reported in the SmPC for Eylea in nAMD patients.

Immunogenicity

The percentage of ADA-positive patients from the first IP administration through Week 56 was generally low in both treatment arms and ranged between 1.7% and 2.3% in the SB15 group and between 0.5% and 1.1% for the Eylea overall treatment group. All patients who were ADA positive also had neutralising antibodies. Although the percentage of ADA/Nab-positive patients was slightly higher with SB15 compared to Eylea across all timepoints up to Week 56 and overall, the number of patients with treatment-induced or treatment-boosted ADAs was similar between treatments.

Efficacy

The clinical Phase III study (SB15-3001) demonstrated equivalence in efficacy of the proposed biosimilar SB15 and the reference product, Eylea in patients with neovascular AMD, in both the primary and secondary endpoints, as follows:

- The LSmean observed for change from baseline in BCVA at Week 8 was equivalent for the SB15 and Eylea treatment groups in the FAS (MI-MAR). The LSmean difference in BCVA of the change from baseline between the SB15 and Eylea treatment groups at Week 8 was 0.1 letters (95% CI [−1.3, 1.4], and was completely contained within the pre-defined and accepted equivalence margin of [−3 letters, 3 letters].
- The results of sensitivity analyses performed on the FAS (available case, imputation method: MI-MNAR) and on the PPS were similar to the results from primary analysis and were both completely contained within the pre-defined equivalence margin:
    - FAS MI-MNAR: treatment difference in LSmean between SB15 and Eylea was 0.1 letters (95% CI of [−1.3, 1.5]);
    - PPS: the treatment difference in LSmean between SB15 and Eylea was −0.2 letters (95% CI of [−1.6, 1.2]).
- Secondary efficacy endpoints (e.g., change from baseline in BCVA, proportion of patients who lost fewer than 15 letters in BCVA, proportion of patients who gained 15 letters or more in BCVA, change from baseline in CST and TRT, proportion of patients with intra or sub retinal fluid on OCT, change from baseline in CNV area, and proportion of patients with active CNV leakage) were overall comparable between the SB15 and Eylea treatment groups

Safety

Up to the study completion date of 16/MAR/2022 (56-week analysis) a total of 448 (99.8%) nAMD patients have received at least one dose of SB15 or US Eylea (224 subjects each). The number of IP doses administered and duration of exposure to study drug were comparable across the treatment groups. A total of 425 (97.0%) subjects (SB15 overall: 215 [98.2%] subjects; Eylea overall: 210 [95.9%] subjects; Eylea+SB15: 109 [98.2%] subjects; Eylea+Eylea: 101 [93.5%] subjects) completed the end of study at Week 56. Therefore, no relevant differences in the exposure to study treatment between the two treatment groups were observed.

Incidence for ocular TEAEs in the fellow eye was comparable between both study arms in the main period. The overall incidence for non-ocular TEAEs throughout the study was comparable between study arms.

Throughout the study, most TEAEs reported were mild or moderate in severity across all treatment groups.

Most of reported TEAEs were known undesirable effects of Eylea (SmPC), e.g., visual acuity reduced and conjunctival haemorrhage were among the most frequently observed adverse reactions. Therefore, occurrence of these TEAEs is not surprising.

No study drug related ocular TEAEs in the fellow eye have been considered related to study drug or IVT injection during throughout the study. None of the non-ocular TEAEs were considered related to either the IMP or the IVT injection procedure in the transition period. In general, their frequency and nature of TEAEs is reasonable and in line with the SmPC of the RMP Eylea [Eylea SmPC, 2024]. Frequency for ocular TEAEs in the study eye related to study drug were comparable between periods. Ocular TEAEs in the fellow eye and non-ocular TEAEs were comparable in their frequencies between periods.

All the events leading to death were considered not related to the study drug or study procedure, all patients had prior/concomitant co-morbidities and the causes of most of the deaths are consistent with the age of the study population.

None of the events leading to study discontinuation were considered related to study drug.

Changes in mean values from baseline for haematology parameters, chemistry parameters, urinalysis and vital signs were comparable between the treatment groups.

3.3. Uncertainties and limitations about biosimilarity

Clinical

Pharmacokinetics

Some differences were observed between treatment groups in aflibercept systemic concentrations, but with large variability (CV% ranged between 54.6341% and 89.3129% for SB15 and between 76.9999% and 100.1654% for Eylea). Some differences were also observed in time when the max concentration following IVT was attained, i.e., after 1 day in the SB15 group (after which a decline was observed) vs. after 2 days in the Eylea group. Due to the limited number of patients included in the PK assessment, coupled with large CV% at post-dose timepoints, these numerical differences should not be overinterpreted. Generally speaking, very low plasma aflibercept concentrations make the estimation of PK parameters difficult.

According to the Eylea SmPC, systemic concentrations of aflibercept were undetectable two weeks following dosage in almost all patients. The frequency of the PK sampling in study SB15-3001 did not allow confirmation of whether the same applies for SB15.

Only the concentration of aflibercept was measured in the PK subset. Given that only bound aflibercept has been demonstrated to accumulate in plasma, the measurement of total aflibercept would have offered additional support for PK comparability.

Immunogenicity

No subject in the PKS had positive ADA result up to Week 56, therefore, based on presented data, there seems to be no impact of immunogenicity on PK. Similarly, due to overall low incidence of ADAs, the impact of immunogenicity on efficacy and safety is very limited.

Safety

Overall incidence for TEAEs was higher in the SB15 treatment group (main period – SB15: 108 (48.2%) subjects vs. US Eylea: 99 (44.2%) subjects reported TEAEs; transition period: SB15+SB15: 80 (36.5%) subjects vs. Eylea+Eylea: 31 (29.8%) subjects; Eylea+SB15: 39 (35.1%) subjects).

Ocular TEAEs in the study eye have been reported in a higher proportion of the SB15 arm vs. US Eylea arm in the main period or the SB15+SB15 arm vs. Eylea+Eylea arm in the transition period.

The overall incidence for ocular TEAEs in the fellow eye was higher in the SB15+SB15 arm vs. the Eylea+Eylea arm in the transition period.

Observed imbalances are not considered significant, because only a minority of reported TEAEs was considered related to IMP.

3.4. Discussion on biosimilarity

Quality

In conclusion, a sound and comprehensive biosimilarity exercise has been conducted. The results derived from this exercise principally support the biosimilarity claim between SB15 and its RMP as well as the comparability between US- and EU-sourced Eylea. Observed differences have been adequately justified and are not expected to result in a different clinical performance of SB15. A few minor concerns could be solved and thus remaining uncertainties ruled out.

Non-clinical

From a non-clinical point of view, no concern was identified which would argue against a marketing authorization application. Please refer to the Quality assessment report for discussion and conclusion on the biosimilar comparability exercise.

Clinical

Based on scarce PK sampling data in nAMD patients, there are no major differences in systemic exposure between SB15 and Eylea. Very low plasma aflibercept concentrations attest that no relevant systemic exposure exists. While making it difficult to estimate PK parameters for PK equivalence testing between SB15 and Eylea, this also makes such conclusions irrelevant from a clinical perspective.

Most of the patients of both treatment groups in the study SB15-3001 were ADA negative at each timepoint up to Week 56. Both products had very low and comparable immunogenicity. For this reason, no impact of immunogenicity on PK, efficacy and safety could be reliably assessed.

The PK and immunogenicity data are considered supportive of biosimilarity between SB15 and Eylea.

The pivotal clinical study SB15-3001 was adequately designed to demonstrate clinical equivalence between SB15-3001 and Eylea, both in terms of efficacy and safety. The selected study population, consisting of patients with nAMD as well as primary and secondary efficacy endpoints are deemed appropriate for this biosimilarity exercise.

The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined and accepted equivalence margin of +/- 3.0 letters. Biosimilarity in terms of efficacy was further supported by secondary endpoints.

The overall **safety profile** of SB15 is in line with known adverse events of Eylea (SmPC). Some events were reported more frequently in the SB15 arm, while others were more frequent in the Eylea arm. Most observed imbalances are not considered significant (based, e.g., on the assessed relatedness).

Overall, the clinical data suggest similarity between Opuviz (SB15) and Eylea regarding efficacy and safety, as well as PK.

3.5. Extrapolation of safety and efficacy

In the EU, the reference product Eylea is approved in adults for the treatment of nAMD, RVO, DME and myopic CNV in adults. The clinical development program for the proposed biosimilar SB15 comprised a single pivotal phase III study (SB15-3001) to compare Eylea and SB15 regarding efficacy, safety, pharmacokinetics (in a subset of patients) and immunogenicity in the treatment of subjects with nAMD.

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, DME, myopic CNV in adults), based on the common mechanism of action across all indications and comparable PK, safety, and immunogenicity profiles of aflibercept (Eylea) across the approved indications. The pathogenesis of all approved indications involves angiogenesis mediated by the members of the VEGF family of angiogenic factors, and the mechanism of action of aflibercept in nAMD is considered representative of the mechanism of action of aflibercept in all other approved indications for Eylea.

As highlighted in CHMP Scientific Advice procedures (EMA/CHMP/SAWP/233863/2018 and EMA/CHMP/SAWP/347653/2019), "the four diseases share a common pathophysiology. Since the receptor and mechanism of action of aflibercept are the same in the different ophthalmological indications and since aflibercept is delivered at its site of action, robust evidence of comparability of the test and reference products in pharmaceutical quality and a well-conducted trial in a sensitive patient population should allow extrapolation to all other indications of Eylea."

3.6. Additional considerations

Some process modifications between the clinical and the PPQ and final commercial substance manufacturing process have been implemented. To address these late modifications a sound and comprehensive comparability analysis of clinical versus PPQ material as well as adequate description and justification for minor changes after PPQ manufacturing, prior to commercial SB15 manufacturing, has been conducted confirming a comparable quality profile.

It seems that the Applicant did not consider in advance (i.e. prior to setting of similarity criteria) the relevance of a difference regarding its impact on clinical performance and the operating characteristics of the chosen comparability/similarity criteria. Principally, as discussed in the revised version (21 July 2021) of the EMA reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development EMA/CHMP/138502/2017, a more elaborated justification addressing definition of a general "similarity condition" and subsequently a specific corresponding "similarity criterion", the underlying data distribution, the operating characteristics of the similarity criterion etc. would be expected. Regarding the underlying data distribution, it seems that for most of the attributes the data are normally distributed and are not impacted by few extreme results. Taking into account that the Applicant provided graphical and/or tabular presentations of individual analytical results as well as descriptive statistics, which enable an assessment independent of the defined quality ranges, no concerns are raised with respect to statistical data evaluation.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Opuviz 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 Opuviz is favourable in the following indication(s):

Opuviz is indicated for adults for the 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 diabetic macular oedema (DME)
- visual impairment due to myopic choroidal neovascularisation (myopic CNV)

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

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Opuviz. 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 Opuviz is marketed, ophthalmological clinics where Opuviz is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- 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 30G needle, and angle of injection
- The vial is for single use only
- The need to expel excess volume of the syringe before injecting Opuviz 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 Opuviz

The patient information pack of the educational material for the adult population 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 Opuviz
- How to prepare for Opuviz treatment
- What are the steps following treatment with Opuviz
- 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 Opuviz.