19 September 2024
EMA/466863/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Afqlir

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006150/0000

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
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
BCVA	Best-corrected visual acuity
BLQ	Below the limit of quantification
CF	Color Fundus
CI	Confidence interval
CNV	Choroidal neovascularization
COVID-19	Corona virus disease 2019
CRC	Central reading center
CRO	Contract research organization
CSFT	Central subfield thickness
CSR	Clinical study report
CV	Coefficient of variation
DME	Diabetic macular edema
eCRF	Electronic case report form
EOS	End of study
ETDRS	Early treatment diabetic retinopathy study
Eylea EU	EU-authorized Eylea®; the registered trademark sign "®" will be omitted from all following instances of Eylea EU in the document
Eylea US	US-licensed Eylea®; the registered trademark sign "®" will be omitted from all following instances of Eylea US in the document
FA	Fluorescein angiography
FAS	Full Analysis Set
FPR	False positive rate
FSH	Follicle-stimulating hormone
GMR	Geometric mean ratio
IAS	Immunogenicity Analysis Set
ICF	Informed consent form
IEC	Independent Ethics Committee
IOP	Intraocular pressure

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISI	Integrated summary of immunogenicity
IVT	Intravitreal(ly)
LISY	Liquid in (prefilled) syringe
LIVI	Liquid in (single-use) vial
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS mean	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-model repeated measures
NAb	Neutralizing antibody
nAMD	Neovascular age-related macular degeneration
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PlGF	Placental growth factor
PP	Per-protocol
PPS	Per-protocol Set
PT	Preferred term
QTL	Quality Tolerance Limit
RAS	Randomized set
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical analysis plan
SARS-Cov-2	Severe acute respiratory syndrome coronavirus type 2
SD	Standard deviation
SD-OCT	Spectral-domain optical coherence tomography
SE	Standard error
SmPC	Summary of product characteristics
SOC	System organ class
SOK583	Sandoz' aflibercept biosimilar product to Eylea®; the registered trademark sign "®" will be omitted from all following instances of Eylea in the document

SOP	Standard operating procedure
Study 301	Short key for Study CSOK583A12301
Study 303	Short key for Study CSOK583A12303
Study 304	Short key for Study CSOK583A12304
TEAE	Treatment-emergent adverse event
SUSAR	Suspected Unexpected Serious Adverse Reaction
USPI	United States prescribing information
VEGF	Vascular endothelial growth factor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sandoz GmbH submitted on 23 August 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Afqlir, 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 23 June 2022.

The applicant applied for the following indication:

Afqlir 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
26 April 2018	EMEA/H/SA/3782/1/2018/III	*Kerstin Wickström, Christian Gartner*
27 June 2019	EMEA/H/SA/3782/1/FU/1/2019/III	*Kerstin Wickström, Christian Gartner*
22 April 2022	EMA/SA/0000077752	*Kerstin Wickström, Andrea Laslop*
15 December 2022	EMA/SA/0000109005	*Larissa Higgins, Linda Trauffler*

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

- analytical similarity to reference product, batch selection, representativeness of drug product, comparability of EU and US reference product, comparability between presentations, human factors data.
- need for non-clinical in vivo studies.
- waiver of PK study in healthy volunteers and clinical program focussed on PD (central retinal thickness) endpoint, design of confirmatory clinical efficacy and safety study, appropriateness of the validated bioanalytical assays.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Antonio Gomez-Outes Co-Rapporteur: Hjalti Kristinsson

The application was received by the EMA on	23 August 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	20 December 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 January 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 December 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 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 Afqlir on	19 September 2024

2. Scientific discussion

2.1. About the product

Afqlir (also referred to as SOK583) has been developed as a biosimilar to Eylea (INN: aflibercept; EMEA/H/C/002392).

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

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin G1. It acts as a soluble decoy

receptor that binds VEGF-A, VEGF-B and PlGF, and thereby inhibits the binding and activation of their cognate VEGF receptors.

The claimed therapeutic indications for Afqlir 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 pre-filled syringe - is not claimed.

The recommended dose of Eylea for the treatment of ROP is a single intravitreal (IVT) injection of 0.4 mg aflibercept, equivalent to 0.01 mL. For the administration of this dose, a dedicated paediatric dosing device (PICLEO) was developed by Bayer AG to be used in combination with the pre-filled syringe, as no available alternative low-volume syringe or device was considered appropriate for the administration of the 0.01 mL of aflibercept solution 40 mg/mL for IVT injection.

2.2. Quality aspects

2.3. Introduction

Introduction

The finished product, also referred to as drug product (DP), is presented as solution for injection, for intravitreal use, containing 40 mg/mL of aflibercept as active substance (AS), also referred to as drug substance (DS).

Other ingredients are: polysorbate 20 (E 432), L-histidine, L-histidine monohydrochloride monohydrate, trehalose dihydrate, sodium hydroxide and hydrochloric acid (for pH adjustment) and water for injections.

The product is available in two presentations:

- Solution in pre-filled syringe (type I glass) marked with a dosing line, with a plunger stopper (elastomeric rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber);
- Solution in a vial (type I glass) with a stopper (elastomeric rubber), and an 18 G filter needle. Each vial contains an extractable volume of at least 0.240 mL.

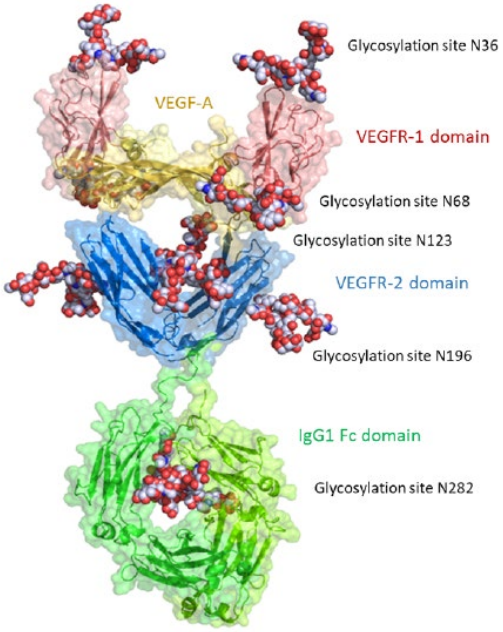
Active substance - aflibercept

General information

The international non-proprietary name (INN) for the DS is aflibercept; the laboratory code, used throughout the document, is SOK583.

SOK583 is a fusion protein consisting of portions of human vascular endothelial growth factor receptors 1 (VEGFR-1) and 2 (VEGFR-2), and the Fc portion of IgG1 (Figure 1-1). This dimeric glycoprotein is composed of two identical chains (431 amino acids each), which are N-glycosylated at asparagine residues N36, N68, N123, N196 and N282: two in both, the Ig domain 2 of human VEGFR-1 and Ig domain 3 of human VEGFR-2, and one in the constant Fc region of human IgG1. Its structure is given in Figure 1.

Figure 1: Crystal structure of aflibercept molecule with bound VEGF-A



SOK583 is designed to bind, and therefore trap, vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor-B (VEGF-B), and placental growth factor (PlGF), thereby preventing angiogenesis and neovascularisation.

General properties and structure of SOK583 have been overall adequately described, and AS nomenclature has been defined.

Manufacture, process controls and characterisation

The manufacturing site responsible for manufacturing of SOK583 DS is Boehringer Ingelheim Fremont Inc., California, USA.

Description of manufacturing process and process controls

The SOK583 DS manufacturing process has been adequately described. For manufacture of SOK583, protein production in a fed-batch process followed by a series of chromatography purification steps is conducted, with additional steps for virus removal or inactivation.-Flow diagrams for the upstream and downstream processes are included in the dossier.

The main steps are as follows: the cell culture process begins with the thaw of the WCB, and the culture is then propagated through the series of shake flasks . Cells are further expanded, and production phase is ultimately performed in a bioreactor. After harvesting, the cell culture harvest is clarified before being stored. The upstream manufacturing process is considered to be overall adequately described, and the different steps from WCB vial thawing to culture harvest are depicted.

The downstream manufacturing process involves a series of steps typical for purification of monoclonal antibodies and related products. It consists of three chromatography steps (capture chromatography, multimodal chromatography, and cation-exchange chromatography) and two dedicated orthogonal viral clearance steps (virus inactivation by acid treatment and virus filtration). For final formulation, ultrafiltration and diafiltration are conducted. The different steps are overall well described.

The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for each step. The active substance manufacturing process is considered acceptable.

For chromatography resins, the resin type, cycle lifetime, cleaning and storage protocols have been provided.

Conditions for shipping have been defined.

Control of materials

The raw materials for the upstream and downstream process are described. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented and are considered appropriate. Single use materials (e.g. bags and filters) and their material of construction are defined. No raw materials of animal or human origin are used.

The development of the parental cell line is indicated.

The source, history and generation of the cell substrate is sufficiently described and, in general, follows the recommendations of ICH Q5B and ICH Q5D.

A two-tier cell bank system has been used. The protocol for the generation and expansion of the cell banks is included. These are acceptable. A protocol for implementation of new WCBs is provided and is acceptable. Future WCBs will be tested and released according to the specifications of WCBs. Characterisation of the cell banks has been carried out in line with ICH Q5D. The MCB, WCB and PPCB were tested for adventitious agents in line with ICH Q5A (assessed in Module 3.A.2) and the requirements are included in the specifications.

Control of critical steps and intermediates

A detailed overview of IPCs of output parameters employed during manufacture of SOK583 is provided, and process indicators have been classified according to their criticality. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Process validation

Process validation was executed on the basis of the results obtained during process characterisation studies. Transport qualification was performed.

Most of the analytical methods used in validation studies are the same as those used for DS release; for the remaining analytical methods, information on the qualification status has been provided. The SOK583 active substance manufacturing process has been validated adequately.

Manufacturing process development

As the basis of the process development, CQAs were identified; an overview of critical quality attributes monitored in SOK583 active substance manufacturing is given. In addition to process

development activities, process characterisation studies were performed to define the process parameter criticality and establish pre-validation acceptable ranges. Small-scale models were developed and qualified for being used in process characterisation and validation activities.

Based on the outcomes of development and validation activities, a control strategy for the active substance was established to ensure that it is suitable for the manufacturing of the DP.

Manufacturing process development focused on the design of a suitable commercial manufacturing process. Early development experiments were conducted at laboratory scale, and pilot scale experiments were later performed to better define the manufacturing process.

Process characterisation studies were conducted to define the process parameter criticality and their acceptable ranges. For characterisation studies, small-scale models (SSMs) were used when applicable.

Resin reuse studies at small-scale were performed. Protein carryover, resin integrity and cleaning efficiency were also tested. Impurity spiking studies were also conducted using SSMs.

Characterisation

S.3.1. Elucidation of structure and other characteristics

A comprehensive characterisation assessment is performed.

Descriptions of the analytical methods used for characterisation are provided. SOK583A1 DS has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure. The analytical results are consistent with the proposed structure.

Furthermore, heterogeneity of the active substance was adequately characterised by analysing of the size and charge variants.

Biological characterisation indicates that it has the ability to bind to the target and to the Fc Receptor as expected. In summary, the characterisation is considered appropriate for this type of molecule.

Container closure system

A detailed narrative description and technical drawing is provided. A suppliers' declarations of conformity is available in the dossier. ***Specification***

The release specification panel proposed for SOK583 DS includes testing of appearance and description (color, clarity, pH), testing of identity testing of purity, testing of product-derived impurities, testing of residual HCP, protein content, potency and microbiological contamination (endotoxins and bioburden). The proposed testing panel for DS release is considered adequate. The proposed DS specification set is based on product/process characterisation, release and stability results of representative DS batches, CQA assessment, QTPP, historically observed range of the reference product, analytical method capabilities, control strategy, prior knowledge and currently recognized standards. Statistical analyses have been conducted to establish the proposed DS specification limits. The applicant has tightened the limits for some of the requested tests and commits to revise the DS specifications when additional batch data are available (REC1).

Analytical methods

The analytical methods used for DS release have been described. Compendial methods are performed according to the Ph. Eur., including detection of bacterial endotoxins, bioburden count, assessment of

clarity, testing of the degree of coloration and pH determination. The compendial method used to detect bacterial endotoxins was verified.

The procedures, reagents, equipment, system set up, evaluation of the data and acceptance criteria for the non-compendial analytical methods are described in the dossier, the methods have been adequately validated.
In conclusion, the DS specification panel for release and stability are considered adequate. The acceptance limits for some of the tests will be revised when more data are available.

Batch analysis

Analyses results are provided for AS batches manufactured during development. All analyses results met the specifications acceptance criteria.

Reference materials

The quality of SOK583 DS and DP is monitored by a two-tier reference standard approach with primary reference standard and working reference standard.

Stability

Real time, real condition stability data on three full scale registration stability batches manufactured at full scale under long term (≤ -60° C) for up to 36 months, and accelerated conditions (5° ± 3° C) for up to 6 months and stress (25 ± 2° C / 60 ± 5% RH) storage conditions for up to 6 months have been performed for SOK583 DS batches manufactured at BIFI. All batches are considered as fully representative for the final process. Stability DS material is stored in small containers which are identical to the large containers used in production regarding material quality and container closure system.

The specification proposed for DS stability includes testing of color, clarity, pH, purity, product related impurities, protein content and relative potency. The specifications for stability are considered adequate.
Stability testing protocols have been included.

No trends were observed during long-term stability studies, and consistency in results is observed among batches.

A freeze/thaw study and a photostability study have been also performed.

The proposed shelf-life is considered acceptable.

Sandoz commits to complete the ongoing stability studies according to the stability testing programs.

Finished medicinal product

SOK583 is a biosimilar of Eylea. Two presentations of the reference medicinal product (RMP) have been authorized: 40 mg/mL in vial and 40 mg/mL in pre-filled syringe (PFS). The same presentations have been developed for SOK583 (LIVI and LISY, respectively).

SOK583 40 mg/mL in vial, also referred to as LIVI, was developed in parallel to 40 mg/mL in pre-filled syringe, also referred to as LISY. All excipients, listed in the Introduction section of the Quality aspects, are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no excipients of human or animal origin, or novel excipients used for formulation of SOK583 DP. The excipients are contained within DPs previously approved for intravitreal injection.

Finished medicinal product (SOK583 in vial; LIVI)

Description of the product and pharmaceutical development

SOK583 DP 40 mg/mL (2 mg/0.05 mL) liquid in vial (LIVI) as a sterile single-use, preservative-free, colorless to slightly brownish-yellow solution for intravitreal injection. The vial contains an overfill that allows the withdraw of the labelled amount, no overage is proposed.

SOK583 LIVI finished product (DP) and its composition are appropriately described. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no excipients of human or animal origin, or novel excipients used for formulation of SOK583 DP. The excipients are contained within DPs previously approved for intravitreal injection. CoAs are provided.

The QTTP was established based on the RMP Eylea. A risk assessment was used to determine the CQAs related to the formulation and the DP manufacturing process, and a summary is provided. The control strategy comprises product understanding, process understanding, and commercial controls. Further, the control strategy of each CQA was also defined.

LISVIis produced using standard manufacturing steps, including DS thawing, dissolving of excipients, compounding, sterile filtration and aseptic filling in vials. Characterisation of the manufacturing steps was conducted by evaluating the impact of different conditions for process parameters on product QAs. The operations of SOK583 LIVI manufacturing process were evaluated at both lab and commercial scale, and acceptable ranges (ARs) of the process parameters were derived thereof. Parameters of all manufacturing steps were studied in characterisation studies and ARs were defined based on the knowledge gained during the manufacture of at small and at large scale batches.

The primary container closure system of SOK583 DP consists of a vial (type I glass) with a stopper (elastomeric rubber). The glass vial and stopper comply with Ph. Eur.

The vial containing SOK583 DP is co-packaged with a filter needle (18G)a CE-marked off-the shelf device, which is provided sterile in an individually sealed blister by the supplier. A declaration of conformity with the MDD, dated November 2021, together with the Manufacturer’s Declaration of Certificate Validity in alignment with Medical device regulations 2017/745 (MDR) transitional provisions, have been provided

The compatibility of the product with process materials was evaluated.

The container closure system (CCS) was studied at the development stage and several studies were carried out to establish the suitability of the chosen CCSThe microbiological control of DP manufacture is achieved by 1) Container closure integrity testing (CCIT) and 2) Control of microbiological hold times of SOK583 DP manufacture. Those strategies are considered adequate.

Data were requested from several studies performed in the pharmaceutical development stage. The applicant has now provided the results of these studies.

Manufacture of the product and process controls

SOK583 Liquid in vial (LIVI) is produced using standard manufacturing steps, such as thawing of active substance, dissolving of excipients, compounding, sterile filtration, aseptic vial filling, labelling and packaging. It is considered that the process is adequately controlled and that process parameters and in-process controls are adequately set to control the process leading to consistent quality of the

product. The flow diagram with related IPCs has been provided, the acceptance criteria for the IPCs are appropriately justified. No intermediates are produced for SOK583 LIVI.

Hold times are proposed for the following steps: thawing time and transport time of DS, compounding of excipients, compounding of DP, sterile filtration, intermediate storage after microbial filtration, storage in filling vessel and final storage in warehouse.

Process validation/verification

The process validation of SOK583 LIVI was performed by testing consecutive batches produced at commercial scale manufactured by the proposed manufacturing sites, using the same processes and the same equipment as the batches intended for commercial supply. Results indicate that the routine manufacturing process, which utilises a qualified manufacturing plant, equipment, materials, operating conditions and controls, will consistently produce a product meeting the pre-defined specifications.

The following steps have been validated: process validation of primary packaged product; hold time (HT) validation; deviations during PV and post-PV process improvements, sterilising filter validation; sterilisation and depyrogenation of primary packaging components; media fill data; microbiological control and quality; process validation of finished dosage form; transport qualification / shipping verification. A description of ongoing process verification is provided.

All critical process and all in-process controls were within the defined ranges and all analytical data at release complied with the specifications.

Some clarifications were requested to the applicant regarding validation during the procedure. The clarifications provided were appropriate. The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate.

Product specification

The DP release specification testing panel includes tests for appearance & description (color, clarity, appearance of the container, pH, and osmolality), testing of identity, testing of purity and impurities, testing of potency, quantity, contaminants (endotoxin and sterility) and general tests. CCI is tested during stability. The proposed specifications for DP release are considered adequate.
The LIVI specification panel is proposed based on product/process characterisation, release and stability results of representative DP batches, CQA assessment, QTPP, historically observed range of QAs of the reference product, analytical method capabilities, control strategy, prior knowledge and currently recognized standards.

The applicant is recommended to revise the acceptance criteria for additional specification tests for the DS and both DP under a post-approval variation (REC1). 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. Batch analysis data on four batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the DP 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 considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC)

No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The descriptions and validation of analytical methods specific for SOK583 LIVI are adequate. Most methods are the same as for SOK583 DS. Compendial methods were performed according to the Ph Eur. The compendial methods used to detect bacterial endotoxins and to test sterility were verified for LIVI.

Batch analysis

Batch analysis data are included in the dossier. All of them fulfil the specifications set at time of their release and the commercial specification.

Reference materials

The reference standard used for release and stability testing of the DP presentations is the same as proposed for the SOK583 DS. No other product-specific reference standards are used in the testing of the DP.

Stability of the product

Real time/real condition stability data were provided for three registration, full scale batches and on three full scale process validation (PV) batches of the finished product stored at (5 ± 3°C) for up to 36 months. Stability data under accelerated storage (25 ± 2°C/60 ± 5% RH) for up to 6 months and, stress storage (40 ± 2°C/75 ± 5% RH), were provided.

Additional studies carried out to assess the stability of SOK583 DP include the study of label claim storage conditions (30 ± 2°C/75 ± 5% RH); a freeze/thaw study; an out of fridge (OOF) study (25 ± 2°C/60 ± 5% RH); and a photostability study.

All batches were manufactured on commercial scale according to the anticipated final process and filled in the anticipated final primary packaging and they are representative of commercial production. All samples are stored inverted and protected from light, except for photostability studies where samples are stored upright.

Specification tests related to appearance and description, purity and impurities, quantity, potency, microbiology and general tests, were included in the stability specification.

A shelf life of 36 months at the long-term storage condition of 5 ± 3°C and in the current container is proposed. This shelf life is justified by the 36 months real time stability data of three registration stability batches and supported by 18 months stability data for three process validation batches. The provided stability data comply with the currently proposed drug product DP specification. A statistical analysis supports a shelf life of > 60 months for all critical quality attributes tested.

Finished medicinal product (SOK583 in PFS; LISY)

Description of the product and pharmaceutical development

SOK583 DP 40 mg/mL LISY is a sterile single-use, preservative free, colorless to slightly brownish-yellow solution for intravitreal injection presented in prefilled syringe (PFS).

SOK583 LISY finished product (DP) and its composition are appropriately described. The nominal composition is the same as the LIVI with the only difference being of the overfill volume. This is accepted. No overages are proposed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no excipients of human or animal origin, or novel excipients used for formulation of SOK583 DP. The excipients are contained within DPs previously approved for intravitreal injection. CoAs are provided.

LISY is produced using standard manufacturing steps, including DS thawing, dissolving of excipients, compounding, sterile filtration and aseptic filling in syringe. An outer surface sterilisation is performed on the pre-filled syringe. The manufacturing process was developed based on a thorough evaluation of the process steps and parameters at lab and large scale regarding their impact on DP quality.

The primary packaging material is a pre-filled syringe (type I glass) marked with a dosing line, with a plunger stopper (elastomeric rubber) and a Luer lock adaptor with a tip cap (elastomeric rubber).

These components and their auxiliary materials, which are in contact with the DP solution, comply with Ph. Eur. requirements.

Additional components for the device are a plunger rod and a backstop, which are assembled to the PFS and ensure device functionality. These components do not contact the DP or sterile fluid path and comply with ISO 10993-1.

The secondary packaging consists of the assembled PFS placed in a blister tray and packed in a folding box.

The applicant has presented a Notified Body Opinion Report for compliance of the device incorporated into an integral drug-device combination product with Annex I of Regulation (EU) 2017/745 on Medical Devices. The information provided for the container closure system is considered acceptable.

Compatibility of the SOK583 DP formulation with the primary packaging material has been demonstrated.

The applicant has performed a compatibility study of DP with the injection materials in PFS.

Shipping verification was addressed by means of simulated shipping studies.

Manufacture of the product and process controls

LISY is produced using standard manufacturing steps including DS thawing, dissolving of excipients, compounding, sterile filtration, aseptic filling, assembly, outer surface sterilisation and packaging. Sterility of the DP in the final container is ensured by 1) a sterilizing filtration followed by aseptic filling and 2) an outer surface sterilisation step of the pre-filled syringe. The narrative description of the aseptic filling and the sterilisation of the outer surface of the pre-filled syringes, step includes sufficient detail. It is considered that the process is adequately controlled and that process parameters and in-process controls are adequately set to control the process leading to consistent quality of the product.

the acceptance criteria for the IPCs are appropriately justified.

Hold times are proposed for the following steps: thawing time and transport time of DS, compounding of excipients, compounding of DP, sterile filtration, intermediate storage after microbial filtration, storage in filling vessel and final storage in warehouse.

Process validation/verification
Validation of the DP manufacturing process has been accomplished with consecutive batches of LISY produced at commercial scale using the same processes and the same equipment as the batches intended for commercial supply.

Process parameters, IPCs and hold times were evaluated during production of commercial scale batches. The obtained values met the validation criteria for all samples tested.
The following steps have been validated: sterilizing filtration, finished dosage form in PFS assembled and packaged, microbiological control, hold times, and shipping. Aseptic process validation is performed using media fills under the conditions that are representative of the manufacturing process and include all routine maximum permitted holding times, the routine accepted interventions, the line speed, fill volume and the maximum permitted filling time.

Process performance and product quality are monitored as part of the Ongoing Process Verification.
In summary, the overall information presented in this section is now considered

Product specification

The DP release specification testing panel includes tests for appearance & description (color, clarity, appearance of the container and blister, pH, osmolality), testing of identity (identity and primary structure), testing of purity and impurities (purity; impurities), testing of potency, quantity, contaminants (endotoxin and sterility) and general tests. CCI is tested during stability. The proposed specifications for DP release are considered adequate.

The specification limits proposed for LISY have been calculated using combined data from LISY and LIVI for statistical analyses. The applicant has provided during the procedure additional data that supports comparability of the two products LIVI and LISY, which is acceptable. 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. Batch analysis data on four batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data, it can be concluded that it is not necessary to include any elemental impurity controls in the DP 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 considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

The descriptions and validation of analytical methods specific for SOK583 LIVI are adequate. Most methods are the same as for SOK583 DS. Compendial methods were performed according to the Ph. Eur. The compendial methods used to detect bacterial endotoxins and to test sterility were verified for LISY.

Batch analysis

Batch analysis data are included in the dossier. All of them fulfil the specifications set at time of their release and the commercial specification.

Reference materials

The reference standard used for release and stability testing of the DP presentations is the same as proposed for the SOK583 DS. No other product-specific reference standards are used in the testing of the DP.

Stability of the product

Real time/real condition stability data of three registration, full scale batches for SOK583_PFS (LISY); and on three full scale process validation (PV) batches of the finished product stored at (5 ± 3°C) for up to 12 months have been provided. Stability data under accelerated storage (25 ± 2°C/60 ± 5% RH) for up to 6 months and have been provided.

The shelf-life specification panel includes testing of color, clarity, visual seal integrity, pH, purity and product-derived impurities, potency, quantity, endotoxin, sterility, CCIT, particulate matter, break out and sliding force (BOSF) and blister seal integrity. The proposed specification panel for DP shelf-life is considered adequate. Stability studies have also been performed at accelerated and stress conditions with RS and PV batches.

A freeze/thaw study has been initiated.
A photostability study confirmed that SOK583 DP is sensitive to light.

The proposed shelf-life for LISY is 24 months at 5 ± 3°C protected from light. It is based on 12 months of real time stability data for LISY PV batches and on 24 months stability data from LIVI registration batches.
The post-approval stability protocols for registration and process validation batches are provided. The applicant commits to conduct and complete the stability studies for LISY (RS batches and PV batches) to the end of the testing program and commits to investigate OOS results or atypical trends and to report any affecting product batches released on the market to competent authorities.

Adventitious agents

No materials of human or animal origin were used during cell bank preparation of the MCB and WCB or during SOK583 DS production. The consumables are considered of no concern with regard to TSE risk as the suppliers have expressed a rigorous processing in compliance with the Guidance (EMA/410/01).

The cell banking system manufacturing and characterisation is described.

Non-viral adventitious agents are.

A description of the tests performed on cell banks and bulk harvest is provided. The testing performed is in line with the ICH Q5A (R1).

The design of the viral clearance study is clearly presented and considered to be in accordance with ICH Q5A (R1).

Biosimilarity

Analytical similarity of SOK583 was assessed in a comprehensive similarity exercise using US-licensed Eylea and EU-approved Eylea as reference medicinal product. The comparability assessment was, for the most part, conducted as per the relevant EU and ICH guidelines on the development of similar biological medicinal products. A comprehensive analytical similarity study between SOK583A1 to the reference product Eylea was conducted, whereby SOK583A1 active substance was compared to Eylea finished product. To overcome the formal requirement to demonstrate biosimilarity at finished product level a supporting comparability exercise between SOK583 DS and DP was conducted. Further, comparability was investigated between SOK583 LISY and SOK583 LIVI to demonstrate the analytical bridge of both presentations used in clinical study and comparability between Eylea LISY and LIVI product sourced from US and EU to justify pooling of the reference product presentations. Overall, the proposed strategy was discussed in the 2022 scientific advice and is considered appropriate.

The applicant defines a list of Quality Attributes which will be assessed in the biosimilarity exercise and organised them based on a risk assessment analysis. Predominately, the risk ranking of the QAs is kept the same as provided in the EMA/SA/0000109005 (2022) scientific advice and an appropriate justification is provided for lowering the risk of several QAs concerning the glycan variants.

QAs were either evaluated against a quality range (mean ± x SD of EU/US Eylea) or assessed qualitatively (this option was selected for most attributes). Basically, the min-max range of the test is compared to the quality range of the reference. In case differences are observed the raw data is looked at for decision making on similarity.

The number of batches analysed for each QA results from risk ranking, availability of material at the time of analysis, method variability, anticipated process variability, orthogonal approaches, shelf-life coverage, and number of batches amenable to the specific analytical method.

The applicant has presented in the biosimilarity assessment all representative commercial-scale batches of SOK583 DS and SOK583 DP (LIVI and LISY). As the reference medicinal Product, a sufficient number of EU-authorized Eylea batches were assessed. In addition, US-licensed Eylea batches were included in the biosimilarity exercise. Eylea batches were split into aliquots and stored at controlled condition. Assessment of Eylea stability when stored in frozen conditions was performed only in one EU lot. This approach was not fully supported and data from more EU- and US-Eylea lots was requested. The applicant commits to include a similar stability assessment as the one performed to EU-Eylea lot with 2 additional EU-Eylea batches under a post-approval commitment (REC2).

SOK583 DP (LIVI and LISY), EU-authorised Eylea and US-licensed Eylea include 40 mg/mL of active substance. SOK583 DP and Eylea differ in the excipient composition; 10 mM Histidine, 213 mM Trehalose, and 0.03% Polysorbate-20 versus 10 mM Na-phosphate, 40 mM NaCl, 5% sucrose, and 0.03% Polysorbate-20, respectively. In addition, pH differs from a value of 5.7 to 6.2.

The biosimilarity assessment focuses on the comparability between SOK583 DS with either EU-Eylea (LIVI/LISY) or US-Eylea (LIVI/LISY). Additional comparability assessments include EU- and US-Eylea (LIVI/LISY), SOK583 DS against SOK583 DP (LIVI/LISY), and SOK583 LIVI vs SOK583 LISY.

In general, the proposed biosimilarity strategy is considered acceptable and the information provided is adequate.

The information is summarised in Table 1 below.

Table 1: Summary of biosimilarity assessment between SOK583 DS with either EU-Eylea DP (LIVI/LISY) or US-Eylea DP (LIVI/LISY).

Quality attribute	Test method	Key findings
Biological Characterization		
Inhibition of VEGF-A-165 induced cell proliferation (HUVEC)	Cell-based assay (HUVEC)	Comparable
Target binding VEGF-A		
Inhibition of VEGF-A-165 induced VEGFR2 dimerization	Cell-based assay	Comparable
Binding to VEGF-A-165	ELISA	Comparable
	SPR	Comparable
Binding to VEGF-A isoforms: VEGF-A-110	ELISA	Comparable
	SPR	Higher for SOK583 (justified)[1]
Binding to VEGF-A isoforms: VEGF-A-121-	ELISA	Comparable
	SPR	Higher for SOK583 (justified)[1]
Binding to VEGF-A isoforms: VEGF-A-189	ELISA	Comparable
	SPR	Higher for SOK583 (justified)[1]
Target binding PlGF		
Inhibition of PlGF-2 induced VEGFR1 dimerization	Cell-based assay	Comparable
Binding to PlGF-2	ELISA	Comparable
	SPR	Comparable
Binding to isoform PlGF-1	ELISA	Comparable
	SPR	Comparable
Binding to isoform PlGF-4	SPR	Comparable
Target binding VEGF-B		
Binding to VEGF-B-167	ELISA	Comparable
Binding to VEGF-B-167	SPR	Higher for SOK583 (justified)[1]
Additional assays		
Absence of binding to VEGF-C	ELISA	Comparable
Absence of binding to VEGF-D	ELISA	Comparable
C1q binding	ELISA	Comparable
Antibody-dependent cellular cytotoxicity	Cell-based assay	Comparable absence of ADCC activity
Complement-dependent cytotoxicity	Cell-based assay	Comparable absence of CDC activity
Galectin-1 binding	BLI	Comparable
Receptor binding		
Neonatal Fc receptor binding	SPR	Comparable
Fcγ receptor binding: FcγRIa	SPR	Comparable
Fcγ receptor binding: FcγRIIa (R167)	SPR	Lower for SOK583 (justified)[1]
Fcγ receptor binding: FcγRIIa (H167)	SPR	Lower for SOK583 (justified)[1]
Fcγ receptor binding: FcγRIIb	SPR	Lower for SOK583 (justified)[1]

Quality attribute	Test method	Key findings
Fcγ receptor binding: FcγRIIIa (V158)	SPR	Lower for SOK583 (justified)[1]
Fcγ receptor binding: FcγRIIIa (F158)	SPR	Lower for SOK583 (justified)[1]
Fcγ receptor binding: FcγRIIIb	SPR	Lower for SOK583 (justified)[1]
Structure and product-related variants		
Primary structure, cysteine chemistry variants and higher order structure		
Primary structure	rPepMap-MS	Identical
	Intact MS	Identical
Sequence variants	rPepMap-MS	Comparable
Free cysteines	Ellman's assay [mol SH/mol protein]	Lower levels in SOK583 (justified)[1]
Disulfide variants/ isoforms	nrPepMap-MS	Identical
Higher order structure	CD	Comparable
	FTIR	Comparable
	DSF (Tm1) [°C]	Comparable
	DSF (Tm2) [°C]	Comparable
Size variants		
Dimers and aggregates	SEC	Lower levels in SOK583 (justified)[1]
	AUC - dimers	Lower levels in SOK583 (justified)[1]
	AUC – higher oligomers	Comparable
Protein fragments	rCE-SDS	Lower levels in SOK583 (justified)[1]
Purity	nrCE-SDS	Higher in SOK583 (justified)[1]

Quality attribute	Test method	Key findings
Charge variants and C-/N-terminal extensions/truncations		
Main, acidic and basic charge variants	iCE Main	Higher in SOK583 (justified)[1]
	iCE sum of acidic variants	Lower levels in SOK583 (justified)[1]
	iCE sum of basic variants	Comparable
Asn deamidation in receptor part: N84	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Asn deamidation in receptor part: N99	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Asn deamidation in receptor part: N152	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Asparagine deamidation in Fc part	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Asp isomerisation in receptor part	rPepMap-MS	Comparable
Asp isomerisation in Fc part	rPepMap-MS	Comparable
C-terminal lysine	rPepMap-MS	Lower levels in SOK583 (justified)[1]
C-terminal prolinamide	rPepMap-MS	Higher levels in SOK583 (justified)[1]
N-terminal extension (+SG)	rPepMap-MS	Lower levels in SOK583 (justified)[1]
N-terminal truncation (-SD)	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Glycation (receptor part)	Intact-MS	Comparable
Glycation (Fc part)	Intact-MS	Comparable
Glycation (K311)	rPepMap-MS	Comparable
Oxidized variants		
Methionine 10 oxidation	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Methionine 20 oxidation	rPepMap-MS	Comparable
Methionine 192 oxidation	rPepMap-MS	Higher levels in SOK583 (justified)[1]
Methionine 237 oxidation	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Methionine 413 oxidation	rPepMap-MS	Lower levels in SOK583 (justified)[1]
Glycan variant		
N-glycan terminal GlcNAc	Glycanmap	Higher levels in SOK583 (justified)[1]
Non-fucosylated N-glycans	Glycanmap	Comparable
High mannose N-glycans	Glycanmap	Lower levels in SOK583 (justified)[1]
N-glycan β-galactosylation	Glycanmap	Higher levels in SOK583 (justified)[1]
N-glycan Gal-α(1,3)-Gal	Glycanmap	Lower levels in SOK583 (justified)[1]
N-glycan sialylation (NANA)	Glycanmap (overall)	Comparable
	rPepMap-MS (site-specific N68)	Comparable
	rPepMap-MS (site-specific N123)	Comparable
N-glycan sialylation (NGNA)	Glycanmap (overall)	Lower levels in SOK583 (justified)[1]

Quality attribute	Test method	Key findings
	rPepMap-MS (site-specific N68)	Not detected
	rPepMap-MS (site-specific N123)	Comparable
N-glycosylation site occupancy	rCE-SDS	Lower levels of species devoid of 1 N-glycan in SOK583 (justified)[1]
	rPepMap-MS (site-specific N36)	Higher levels of non-occupied N36 in SOK583 (justified)[1]
	rPepMap-MS (site-specific N68)	Comparable
	rPepMap-MS (site-specific N123)	Comparable
	rPepMap-MS (site-specific N196)	Comparable
	rPepMap-MS (site-specific N282)	Higher levels of non-occupied N282 in SOK583 (justified)[1]
	RP-HPLC hydrophobic variants (Peak 1)	Lower levels in SOK583 (justified)[1]
	RP-HPLC hydrophobic variants (Peak 2)	Higher levels in SOK583 (justified)[1]
	RP-HPLC hydrophobic variants (Peak 3)	Comparable
O-glycans	rPepMap-MS	Comparable
Drug product-related attributes		
API concentration in DP	UV-Vis	Comparable

[1] Observed differences are not considered to have clinical relevance

Regarding the Critical Quality Attributes (CQAs) assessment, the applicant has performed a determination of the CQAs and a determination of the criticality score following the guideline ICH Q9. Each CQA received a score based on its impact and the degree of uncertainty. The criticality ranking is based on two factors: impact and uncertainty/certainty of that impact.

The applicant has performed a comprehensive analysis to show similarity between SOK583 DS, SOK583 DP and US- and EU-authorised Eylea. This assessment includes a deep biological characterisation, primary structure and related variants and a DP related quality attributes sections.

Biological characterisation

A comprehensive biological characterisation assessment is set including the following tests:

- Primary biological activity determined by inhibition of HUVEC cell proliferation,
- Inhibition of VEGF-A induced VEGFR-2 dimerisation,
- VEGF-A (165, 110, 121 and 189) binding by ELISA and SPR,
- Inhibition of PlGF-2 induced VEGFR1 dimerisation,
- PlGF binding by ELISA and SPR,
- VEGF-B (167) binding by ELISA and SPR,
- Absence of binding to VEGF-C and VEGF-D by ELISA,
- Binding to Fc receptors and C1q,
- Absence of Fc-mediated effector functions (ADCC, CDC), and
- Galectin-1 binding.

HUVEC assay is the main test to reflect Aflibercept´s Mechanism of Action (MoA) and shows consistent results when comparing SOK583 with Eylea. In this experiment, VEGF-A (165) ligand was tested to determine the similarity in the biological activity of SOK583. The applicant shows in the results minor differences between SOK583 and Eylea.

Inhibition of VEGF-A induced VEGFR-2 dimerisation is a complementary cell-based assay to determine similarity of SOK583-Eylea MoA. Results confirm similarity between SOK583 and Eylea, even though a higher relative potency was found on SOK583. The applicant confirms that soluble VEGF-A (165) was included in this experiment.

VEGF-A (165, 110, 121 and 189) binding by ELISA and SPR. In general, ELISA showed a higher affinity of SOK583 compared to Eylea. This result was more evident by SPR. Again, a higher purity in SOK583 lots may explain this result, which has been discussed above.

Inhibition of PlGF-2 induced VEGFR1 dimerisation and PlGF binding by ELISA and SPR. PIGF-2 only binds to VEGFR1 and not to VEGFR2. The role of PlGF in neoangiogenesis and the contribution of PlGF inhibition to the therapeutic activity of aflibercept are not yet defined. Results support the similarity between SOK583 and Eylea with an apparent higher affinity by ELISA of SOK583.

VEGF-B (167) binding by ELISA and SPR. Like PlGF, VEGF-B only binds VEGFR1 and induces poor signalling. The analysis shows a higher affinity of SOK583 for VEGF-B in both ELISA and SPR studies.

Absence of binding to VEGF-C and VEGF-D by ELISA. Results are very consistent between batches and show no binding of SOK583 and Eylea to VEGF-C and VEGF-D.

Binding to Fc receptors and C1q. Analysis of Fc receptors binging includes relative binding affinities determined by SPR for FcRn, FcγRIa, FcγRIIa (Arg/His), FcγRIIb, FcγRIIIa (Phe/Val), and FcγRIIIb. Results for FcRn are similar for SOK583 and Eylea. In the rest of Fc receptors, Eylea shows a higher affinity compared to SOK583 with the exception of FcγRIa. The applicant justifies these results stating that the differences may be caused by lower levels of non-fucosylated N-glycans in the Fc part of SOK583 (FcγRIII) and by differences in SOK583 Fc-galactosylation and impurities (FcγRII). Finally, C1q binding is similar in SOK583 and Eylea.

Absence of Fc-mediated effector functions (ADCC, CDC). Even though differences in Fc receptors binding are found in previous section, all SOK583 and Eylea lots show no ADCC and CDC activity.

Galectin-1 binding. SOK583 and Eylea show a similar binding to Galectin-1.

Primary structure and product-related variants

A comprehensive physicochemical characterisation has been performed to support the similarity of SOK583 and Eylea. The following quality attributes were tested:

- Primary structure, cysteine chemistry variants and higher order structure,
- Molecular size variants,
- Charge variants,
- Oxidation, and
- Glycan variants.

Primary structure

Cysteine chemistry variants and higher order structure. Amino acid sequence of SOK583 and Eylea has been confirmed at peptide level and at amino acid level. Some amino acid mistranslations were detected at a very low level and in similar frequencies in SOK583 and Eylea with no apparent effect on potency. The analysis of intact glycosylated SOK583 and Eylea and the subunits showed a similar pattern of elongations (+SG) and truncations (-SD), which were also detected in SOK583 characterisation. The disulphide bridges are similar in both SOK583 and Eylea. Finally, SOK583 and Eylea higher order structures and melting temperatures were similar.

Molecular size variants

SOK583 showed lower levels of fragments and as expected, higher purity when compared with Eylea. A similar situation occurs with the analysis of dimers and aggregates by both SEC and AUC. Higher frequency of aggregates is found in Eylea.

Charge variants

SOK583 and Eylea show a similar charge variant profile, however, when quantifying the charge species, there was a lower level of acidic species in SOK583 and conversely a higher level of the main peak. No difference was found in the frequency of basic variants. The applicant justifies these results due to the lower levels of asparagine deamidation in SOK583 DS compared to Eylea. As stated above, SOK583 showed lower frequencies of deamidation in Asn residues (N84, N99, N152 and PENNYK peptide) while isomerisation of Asp was similar in the receptor region and in the Fc domain. SOK583 batches show consistently lower frequencies of elongated and truncated variants in the N-terminal region. In the C-terminal, Lys variant (+K) also shows lower frequency in SOK583 while C-terminal prolinamide variant is more frequent. Finally, glycation is more common in the Receptor domain compared to the Fc region and no apparent differences in their distribution are found between SOK583 and Eylea.

Oxidation

Methionine oxidation is also assessed. No difference is found between SOK583 and Eylea in the residue M20. SOK583 shows a less frequent oxidation in residues M10, M237 and M413, while the frequency is slightly higher in M192.

A distributional bias was observed regarding oxidation, size and charge variants. The levels observed for QAs such as methionine oxidation, HMW (dimers/aggregates) and LMW (fragments) variants and Asn deamidation products (N99, N152) are lower in SOK583 compared to US/EU Eylea. The applicant explains this difference by a higher purity of SOK583, which is desirable in terms of lower immunogenicity, but adversely impacting the potency of SOK 583A1 resulting in higher bioactivity in the HUVEC assay for SOK583. In a structure-function evaluation, the observed shift in potency was proven on a molecular level.

Glycan variants

The overall N-glycan profiles of SOK583 and Eylea are very similar with some minor differences. The analysis of the distribution of the different glycan species showed some variations. NGNA syaliation, high mannose N-glycan levels, and alpha-galactose levels are less frequent in SOK583, while terminal GlcNAc and galactosylation levels are slightly higher. No difference is found in NANA syaliation and in non-fucosylated N-glycan levels between SOK583 and Eylea. After the analysis of Site-specific glycan analysis by rPepMap-MS, a slightly higher frequency of NANA syaliation was found in residue N68 and N123, more evident in N123. As stated in Fc receptors binding, non-fucosylation may be involved in the reduced affinity of FcγRIII and, as expected, levels of non-fucosylation in residue N282 are clearly lower in SOK583, while no differences are found in the frequency on phosphoglycated ligands in residue N36. As stated in the SOK583 Characterisation section, the fully glycosylated protein chain contains five N-glycans (HP2) and it can be found chains with only four N-glycans (HP1). In nearly all HP1 variants, position N68 is non-glycosylated. This observation is consistently reproduced in the similarity assessment, showing nearly identical levels of HP1 variant and that the main non-glycosylated site is N68.

Finished product related quality attributes

Protein concentration was determined in SOK583 DP, US-Eylea and EU-Eylea , finding no differences between the three formulations.

A Forced Degradation study has been performed to support the similarity assessment between SOK583 and reference product Eylea.
A comparability assessment between the four data sets of Eylea US LIVI , Eylea EU LIVI , Eylea US LISY and Eylea EU LISY was conducted to establish quality ranges based on the pooled Eylea LIVI and LISY data sets and to use EU-sourced Eylea LIVI to supply the clinical study CSOK583A12301.

A comprehensive comparability analysis between SOK583 DS and DP has been performed. SOK583 LIVI and LISY batches and their corresponding DS batches were used.

The comparability conclusion is supported and data has been presented showing LIVI and LISY lots in different colors for a better understanding of the figures, as requested.

Overall, SOK583 DS material can be regarded as representative of the DP material. The potential impact of the manufacturing process has been evaluated and found differences are justified by analytical method variability, the significance of the difference, the impact with respect to the reference product data and its variability.

A comprehensive comparability analysis between SOK583 LIVI and LISY has been performed.

The similarity condition has been defined and operating characteristics has been discussed.

A comprehensive description of analytical methods that have been used for the characterisation of SOK583 (aflibercept) drug substance (DS), drug product (DP) and in-house reference material has been provided. The methods were also used for comparability and final similarity exercise between SOK583 solution for injection in vial (LIVI) and in pre-filled syringe (LISY) and the reference product Eylea.

Description of each method to determine a QA and its qualification/validation has been performed properly and previous inconsistencies have been corrected.

Overall, SOK583 solution for injection in vial (LIVI) and in pre-filled syringe (LISY) and the reference product Eylea can be regarded as representative of the DP material and considered to be biosimilar.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

No major objections were raised and the list of other concerns has now been addressed. Two post-approval recommendations have been raised.

Conclusions on the chemical, pharmaceutical and biological aspects

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

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:

Table 2: Recommendations for future quality development

Area	Number	Description	Classification*
Quality	1	The applicant is recommended to revise several specification limits, when additional batch analyses data and stability data are available, under a post-approval variation	REC
Quality	2	The applicant is recommended to present the data of the stability assessment of two additional EU-Eylea batches. A stability plan of 36 months has been established and data will be presented in the context of a post-approval commitment.	REC

2.3.1. Non-clinical aspects

2.3.2. Introduction

The pharmacological activity of SOK583 and EU-Eylea was compared in a series of in vitro functional and binding assays.

2.3.2.1. Primary pharmacodynamic studies

The similarity assessment is primarily based on a cell-based assay regarding the inhibition of VEGF-A dependent cell proliferation, as well as on dimerization assays conducted for both VEGF-A and PlGF-2. It was complemented by a comprehensive battery of binding assays which covered the main isoforms of VEGF-A (VEGF-A (165), VEGF-A (110), VEGF-A (121) and VEGF-A (189)), PlGF (PlGF-1, PlGF-2, PlGF-4) and VEGF-B (VEGF-B (167)). As it was discussed in the EMA Scientific Advice EMA/CHMP/SAWP/233863/2018, VEGF-A isoforms 121, 165 and 189, and the biologically active plasmin-cleaved VEGF-A110 are the major forms of VEGF in vivo and comprise forms with high or low affinity to the extracellular matrix. In addition, the similarity exercise considered the absence of binding to VEGF-C and VEGF-D and the similar binding to Galectin-1. Finally, the binding to FcRn, FcγRs and C1q was assessed, and the absence of effector functions was further confirmed by evaluating ADCC and CDC.

Overall, from a nonclinical point of view the similarity exercise is deemed adequate for a biosimilar application and is in line with relevant guidelines, respectively EMA Guideline on similar biological medicinal products (CHMP/437/04 Rev 1) and 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). For additional assessment of the comparability please, refer to the quality AR.

2.3.2.2. Secondary pharmacodynamic studies

N/A

2.3.3. Pharmacokinetics

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), states that if no concern arises from in vitro assays nor from product-inherent factors, an in vivo pharmacokinetic/biodistribution study is usually not considered necessary.

However, the applicant presented the results from a 15 days non-GLP pharmacokinetics study conducted in NZW rabbits in response to a non-European regulatory agency requirement. Local and systemic distribution of aflibercept was assessed after a single IVT dose with either SOK583 or EU-Eylea (18 animals/treatment group) in both eyes at a dose level of 1.20 mg/eye. Results showed a similar pharmacokinetic profile in vitreous humour for SOK583 (Cmax= 979 µg/mL, AUC0-inf= 131000 h*µg/mL) and EU-Eylea (Cmax= 888 µg/mL, AUC0-inf= 120000 h*µg/mL). Aflibercepts distribution in serum was also comparable for SOK583 (Cmax= 2280 ng/mL) and EU-Eylea (C max= 2000 ng/mL).

Bioanalytical study reports of the validation of the analytical methods are included for the three direct measurements performed in the in vivo study, that is, serum and vitreous humour aflibercept concentrations and ADA presence. It is deemed adequate.

The study was conducted with commercial EU-Eylea and a commercial SOK583 batch, therefore it is considered that the comparator and the test item are representative of the clinical setting. The formulation of SOK583 is different from EU-Eylea but all excipients are commonly used in IVT formulations and the change in formulation does not affect ocular PK.

2.3.4. Toxicology

2.3.4.1. Single dose toxicity

In the *in vivo* PK study conducted in rabbits no signs of toxicological effects nor differences between animals treated with SOK583 and reference product were observed. According to the results of the in vitro comparability studies, no differences in toxicity are expected between SOK583 and EU-Eylea.

No dedicated single dose toxicity studies were conducted, and it is deemed adequate.

2.3.4.2. Tolerance

Findings detected in the in vivo PK study in rabbits showed mild procedure-related symptoms similar to those observed with EU-Eylea. The treatment was well tolerated and no test item-related observations were observed. No dedicated local tolerance studies are required.

2.3.5. Ecotoxicity/environmental risk assessment

No ERA studies were conducted. The active substance is a protein, therefore aflibercept is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The nonclinical dossier submitted in support of this MAA for the Eylea biosimilar Afqlir (SOK583) includes a series of in vitro functional and binding assays designed to demonstrate similarity between SOK583 and EU-Eylea. In vivo pharmacology studies were not conducted, and this is considered adequate.

From a non-clinical point of view, the similarity assessment conducted *in vitro* (based on e.g., cell proliferation assays, dimerization assays and binding assays) is deemed adequate for a biosimilar application and is in line with relevant guidelines. For additional assessment of the comparability please, refer to the quality section of this report.

Regarding PK, although according to European guidelines no in vivo studies are necessary, the applicant presented the results from a 15 days non-GLP pharmacokinetics study conducted in NZW rabbits in response to a non-European regulatory agency requirement. Local and systemic distribution of aflibercept after a single IVT dose with either SOK583 or EU-Eylea showed a similar pharmacokinetic profile of SOK583 and EU-Eylea in both vitreous humour and serum.

The bioanalytical study reports of the validation of the analytical methods for measurements of serum and vitreous humour aflibercept concentrations and ADA presence are deemed adequate.

The study was conducted with commercial EU-Eylea and a commercial SOK583 batch, therefore it is considered that the comparator and the test item are representative of the clinical setting. The differences in formulations of SOK583 and EU-Eylea did not affect ocular PK and it is not expected that the formulation change has an impact on the toxicity profile of SOK583.

This was confirmed in the assessment of local tolerance included in this in vivo PK study, where only mild procedure-related symptoms similar to those observed with EU-Eylea were detected. No test item-related observations were observed.

According to the results of the in vitro comparability studies, no differences in toxicity are expected between SOK583 and EU-Eylea and no dedicated toxicity studies are necessary.

The applicant is aware of the 3R principles and has explained the reasons for the conduct of the *in vivo* study. In that sense, it is acknowledged that the study included both an evaluation of PK and local tolerance.

2.3.7. Conclusion on non-clinical aspects

Overall, the available non-clinical data support the biosimilarity of Afqlir versus the EU reference product Eylea.

2.4. Clinical aspects

2.4.1. 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 3: Tabular overview of clinical studies

Study No.	Study design and objective Population	Number of subjects	Duration of treatment and follow-up	Dosage and batch numbers
Study 301 (Pivotal)	A multicenter, randomized, double-masked, 2-arm parallel study to demonstrate similar efficacy, safety, and immunogenicity of SOK583 and Eylea EU as per Eylea approved treatment regimen in subjects with nAMD Male and female subjects with nAMD 50 years or older and naïve to anti-VEGF treatment	N=485 [1] SOK583: N=245 Eylea EU: N=240	IVT administration of 2 mg of SOK583 or Eylea EU in the study eye, every 4 weeks at Baseline, Week◦4, and Week 8, and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48. Total duration: Up to 54 weeks, including up to 2 weeks of screening, 48 weeks of treatment, and up to 4◦weeks follow-up after dose	SOK583: 40 mg/mL, LIVI, up to 8 IVT injections of 2 mg/0.05 mL Eylea EU: 40 mg/ mL, vial, up to 8 IVT injections of 2 mg/0.05 mL Batch numbers: SOK583: 3-FIN-3644, 3-FIN-3645 Eylea EU: KT05TB5, KT0957P, KT095CJ, KT0BBC7
Study 303 (Supportive)	An open-label, single-arm, multicenter study to evaluate the safety of use of LIVI kit containing SOK583 Male and female subjects with nAMD 50 years or older who required and had previously received IVT treatment with Eylea	N=36 SOK583: N=36	Single IVT administration of 2 mg of SOK583 in the study eye followed by a 30-day safety follow-up	SOK583: 40 mg/mL, LIVI kit, single IVT injection of 2 mg/0.05 mL Batch number: SOK583: 3-FIN-3644
Study 304 (Supportive)	An open-label, single-arm, multicenter study to evaluate the safety of use of a LISY containing SOK583 Male and female subjects with nAMD 50 years or older who required and had previously received IVT treatment with Eylea	N=30 SOK583: N=30	Single IVT administration of 2 mg of SOK583 in the study eye followed by a 30-day safety follow-up	SOK583: 40 mg/mL, LISY, single IVT injection of 2 mg/0.05 mL Batch number: SOK583: 21D21GA
[1] One subject in the SOK583 group was randomized by mistake and did not receive study treatment.				

2.4.2. Clinical pharmacology

2.4.2.1. 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, as known from systemic administration of VEGF-inhibitors in oncology. Therefore, no PK similarity study was conducted; rather a PK substudy was included in study 301 to confirm that the low systemic concentrations of IVT administered SOK583 and Eylea EU were within the same range.

Analytical methods

The validated bioanalytical methods used to analyse clinical samples of Study 301 were ELISA (total aflibercept and free aflibercept), ECL bridging immunogenicity assay (anti-aflibercept antibodies) and CLB assay (neutralizing anti-aflibercept antibodies).

The analytical methods used to analyse clinical samples of Study 301 are shown in Table 4 below:

Table 4. Summary of bioanalytical methods used in Study 301

Clinical Study	Analyte(s)	Bioanalytical method	Bioanalytical testing site
301	Total aflibercept	ELISA	Hexal AG/Sandoz Biopharmaceuticals (Germany)
	Free aflibercept	ELISA	Hexal AG/Sandoz Biopharmaceuticals (Germany)
	Anti-aflibercept antibodies	ECL bridging immunogenicity assay	Hexal AG/Sandoz Biopharmaceuticals (Germany)
	Neutralizing anti-aflibercept antibodies	CLB assay	Hexal AG/Sandoz Biopharmaceuticals (Germany)

Bioequivalence

PK samples for determination of total aflibercept were collected from the subjects participating in the PK substudy on Day 1 (pre-dose and 24 (±1) hours after the first dose) and on Day 58 (week 8, approximately 24 (±1) after the third dose).

Serum samples for ADA analysis were collected pre-dose at baseline period, during the treatment period on days 8, 29, 57, 113, 169 and 281, and during the follow-up period at day 365.

Additionally, blood samples for determination of total aflibercept concentration were collected from all subjects at the same time points as ADA sample collection was performed to support result interpretation of immunogenicity analysis.

Pharmacokinetic and statistical analysis

Free (plasma) aflibercept concentration data on Day 58 (Week 8) were analysed to assess if there was any difference indicative of nonsimilarity between the 2 treatment groups. According to the applicant, significant non-similarity was to be claimed if the lower limit of the 90% CI of the GMR between SOK583 and Eylea EU was above 1.43. The value of 1.43 was taken from the upper bound of the CI [0.70, 1.43], which is recommended for highly variable drug products in the EMA guideline on the investigation of bioequivalence (European Medicines Agency 2010). According to the applicant, use of this widened acceptance range was justified considering the low and highly variable systemic aflibercept concentrations observed after IVT administration.

The GMR was evaluated by the SOK583/Eylea EU (Test/Reference) ratio of the geometric mean. The 90% CI for GMR was derived for Day 58 (Week 8) from LS mean values of the log_transformed data (free aflibercept).

Protocol deviations

The PKS consisted of 43 subjects (SOK583: 23 subjects; Eylea EU: 20 subjects) following the exclusion of 1 subject in the Eylea EU group who received both SOK583 and Eylea EU in the study eye.

PK samples were missing or results were not included in the analysis for 2 subjects on Day 2 and for 4 subjects on Day 58. Reasons were samples were not taken on Day 2 for 2 subjects, 2 subjects received aflibercept in the fellow eye between Day 2 and Day 58, and subjects missed visits for reasons not related to COVID-19.

Of the 43 subjects in the PKS, 33 subjects (76.7%) had an important protocol deviation (Table 5).

Table 5: Protocol deviations reported for subjects in the PKS up to Day 58

Protocol Deviation	SOK583 N=23 n (%)	Eylea EU N=20 n (%)	Total N=43 n (%)
Number of subjects with any important protocol deviation	13 (56.5)	8 (40.0)	21 (48.8)
VISIT DATE OUT OF WINDOW FROM PROTOCOL SCHEDULE	7 (30.4)	3 (15.0)	10 (23.3)
PRESENCE OF INFECTION WITHIN 2 WEEKS BEFORE SCREEN.; AND/ OR UNDERLYING OR ADVANCED, SEVERE AND UNCONTROLLED CO-CONDITION, PE OR CLINICAL LAB FINDING WHICH ADD RISK FOR PARTICIPANT (PI OPINION)	5 (21.7)	2 (10.0)	7 (16.3)
MEASUREMENT OF THE IOP WAS PERFORMED LESS THAN 30 MINUTES AFTER TREATMENT	2 (8.7)	3 (15.0)	5 (11.6)
RANDOMIZED TO INCORRECT STRATA	2 (8.7)	0 (0.0)	2 (4.7)
HISTORY OF HYPERSENSITIVITY TO ANY OF THE STUDY TREATMENT OR EXCIPIENTS, OR CLINICALLY RELEVANT SENSITIVITY TO FLUORESCEIN DYE	1 (4.3)	0 (0.0)	1 (2.3)
MISSED VISIT NOT RELATED TO COVID-19	1 (4.3)	1 (5.0)	2 (4.7)
ADA AND/OR PK (AT VISIT) SAMPLES NOT DRAWN PRIOR TO IVT INJECTION	0 (0.0)	1 (5.0)	1 (2.3)
UNCONTROLLED BP (SYSTOLIC >=160 MMHG OR DIASTOLIC >= 100MMHG AT SCREENING)	0 (0.0)	1 (5.0)	1 (2.3)

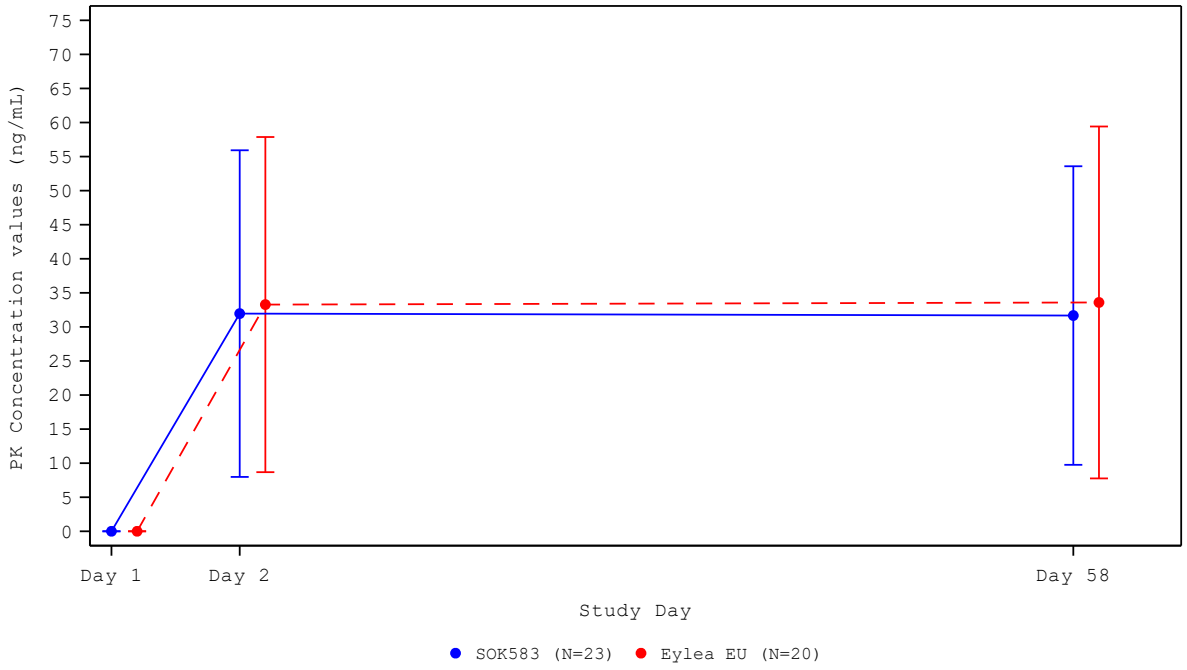
IOP=intraocular pressure
Protocol deviations up to Day 58 were included in this analysis.
A subject with multiple occurrences of a protocol deviation is counted only once for that specific protocol deviation criterion.
Subjects may have multiple protocol deviations.
Protocol deviations are sorted in descending frequency, as reported in the SOK583 column.
Source: [5.3.5.1-301-Listing 16.2.2-1]

Table 6: Free (plasma) aflibercept concentrations (ng/mL) by visit (PKS)

Visit	Statistics	SOK583 N=23	Eylea EU N=20
Day 1 (Baseline)	n	21	20
	n of BLQ	21	20
	Mean (SD)	0.0 (0.0)	0.0 (0.0)
	CV%		
	Median	0.0	0.0
	Min, Max	0.0, 0.0	0.0, 0.0
Visit 2, Day 2	n	21	20
	n of BLQ	2	0
	Mean (SD)	32.0 (24.0)	33.3 (24.6)
	CV%	75.0	73.9
	Median	25.8	27.4
	Min, Max	0.0, 91.2	7.7, 93.4
Visit 5, Day 58	n	22	17
	n of BLQ	1	1
	Mean (SD)	31.7 (21.9)	33.6 (25.8)
	CV%	69.2	76.9
	Median	30.5	24.7
	Min, Max	0.0, 80.9	0.0, 97.2

PK samples were missing or results were not included in the analysis for 2 subjects on Day 2 and for 4 subjects on Day 58. Reasons were samples were not taken on Day 2 for 1 subject (5.3.5.1-301-Listing 16.2.9-4), 2 subjects received aflibercept in the fellow eye between Day 2 and Day 58 (5.3.5.1-301-Listing 16.2.5-4), 1 subject missed visits for reasons not related to COVID-19 on Days 2 and 58, and 1 subject missed visits for reasons not related to COVID-19 on Day 58 (5.3.5.1-301-Listing 16.2.2-1).
Source: 5.3.5.1-301-Table 14.3-1.5.1

Figure 2: Free plasma concentration data with mean +/- SD (PKS)



Source: 5.3.5.1-301-Figure 11-4

Table 7: Summary of free (plasma) aflibercept concentration (ng/mL) at Week 8 (PKS)

Visit	Statistics	SOK583 N=23	Eylea EU N=20
Day 58 (Week 8)	n	22	17
	n of BLQ	1	1
	Mean (SD)	31.7 (21.9)	33.6 (25.8)
	CV%	69.2	76.9
	Median	30.5	24.7
	Min, Max	0.0, 80.9	0.0, 97.2
	Geometric mean	26.4	27.9
	Geometric CV	0.9	0.9
	GMR (SOK583/Eylea EU)	0.95	
	90% CI of GMR	(0.62, 1.44)	

PK samples were missing or results were not included in the analysis for 4 subjects on Day 58. Reasons were 2 subjects received aflibercept in the fellow eye between Day 2 and Day 58 (5.3.5.1-301-Listing 16.2.5-4) and 2 subjects missed visits for reasons not related to COVID-19 (5.3.5.1-301-Listing 16.2.2-1).
Source: 5.3.5.1-301-Table 11-5

2.4.2.2. Pharmacodynamics

No dedicated (comparative) pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. However, immunogenicity testing and an exploratory analysis of free vascular endothelial growth factor (VEGF) in plasma were performed.

Mechanism of action

Aflibercept acts as a soluble decoy receptor that binds VEGF-A, VEGF-B and placental growth factor (PlGF) and thereby inhibits the binding and activation of their cognate VEGF receptors.

VEGF-A, VEGF-B and PlGF are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells. VEGF-A acts via two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF and VEGF-B binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. PlGF can synergize with VEGF-A in these processes and is also known to promote leucocyte infiltration and vascular inflammation; however, the clinical importance of the inhibition of PlGF and VEGF-B in nAMD is not fully elucidated.

Primary and secondary pharmacology

Free VEGF in plasma

The exploratory analysis of free VEGF in plasma was implemented in a subgroup of patients upon request by EMA (on 22-Apr-2022). For this exploratory objective, the endpoints were systemic VEGF concentration assessments at Week 48 (pre-dose) and Week 52 as well as the percentage change in VEGF concentrations from Week 48 to Week 52 as displayed in the below table.

Table 8: Summary of VEGF concentration (pg/mL) data and change from Week 48 at Week 52 (VEGF Analysis Set)

Visit	Statistics	SOK583 N=60	Eylea EU N=67
Week 48	n	57	62
	n of BLQ	0	0
	Mean (SD)	86.44 (77.962)	80.09 (92.155)
	CV%	90.197	115.059
	Geometric mean	71.97	65.19
	Geometric CV	56.407	55.484
	Median	61.20	57.55
	Min, Max	36.2, 540.0	25.4, 700.0
Week 52	n	60	67
	n of BLQ	0	0
	Mean (SD)	75.14 (20.892)	73.38 (20.169)
	CV%	27.802	27.487
	Geometric mean	72.43	71.00
	Geometric CV	27.996	25.858
	Median	72.45	71.00
	Min, Max	31.2, 138.0	36.9, 150.0
Change (Week 48 to Week 52)	n	57	62
	Mean (SD)	-10.10 (72.325)	-6.83 (82.270)
	CV%	-716.090	-1205.275
	Geometric mean	14.31	11.46
	Geometric CV	151.951	133.955
	Median	6.40	11.80
	Min, Max	-417.0, 84.5	-550.0, 72.8
Percentage change (Week 48 to Week 52)	n	57	62
	Mean (SD)	12.56 (45.670)	15.69 (34.432)
	CV%	363.716	219.433
	Geometric mean	26.20	21.34
	Geometric CV	155.608	148.218
	Median	13.65	19.36

Visit	Statistics	SOK583 N=60	Eylea EU N=67
	Min, Max	-77.2, 167.3	-78.6, 96.6

Week 48 value was pre-dose value.
Change and percentage change were calculated for non-missing values at both Week 48 and Week 52.
n=number of subjects with evaluable concentrations. Geometric CV=sqrt(exp(SD^2)-1); where SD values were based on log-transformed data.
Geometric mean values were calculated on log transformed values. Mean values were back-transformed to get geometric mean values.
Source: [5.3.5.1-301-Table 14.3-1.6]

Immunogenicity

Immunogenicity of SOK583 and Eylea EU was investigated in study 301 only.

Table 9: ADA incidence at baseline (pre-existing ADAs) (SAF)

Visit	Category	SOK583 N=244[1)] n (%)	Eylea EU N=240[1)] n (%)
Baseline	ADA positive	3 (1.2)	4 (1.7)
	NAb positive	0 (0.0)	0 (0.0)
	NAb negative	3 (1.2)	4 (1.7)
	ADA negative	235 (96.3)	233 (97.1)

All subjects for the safety analysis set were included in pre-existing ADA analysis
[1)] Total number of subjects (N) differs from ADA positive/negative count, as no baseline samples were available from 9 subjects
Source: [5.3.5.1-301-Listing 16.02-09-02]

Table 10: ADA incidence, persistence and neutralizing antibodies (Immunogenicity Analysis Set)

Visit	Category	SOK583 N=234 n (%)	Eylea EU N=231 n (%)
Baseline	ADA positive	0 (0.0)	0 (0.0)
	NAb positive	0 (0.0)	0 (0.0)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	234 (100.0)	231 (100.0)

Week 1	ADA positive	1 (0.4)	1 (0.4)
	NAb positive	1 (0.4)	1 (0.4)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	218 (93.2)	215 (93.1)
Week 4	ADA positive	1 (0.4)	1 (0.4)
	NAb positive	1 (0.4)	1 (0.4)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	226 (96.6)	219 (94.8)
Week 8	ADA positive	1 (0.4)	2 (0.9)
	NAb positive	1 (0.4)	2 (0.9)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	223 (95.3)	217 (93.9)
Week 16	ADA positive	2 (0.9)	2 (0.9)
	NAb positive	2 (0.9)	2 (0.9)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	221 (94.4)	220 (95.2)
Week 24	ADA positive	2 (0.9)	3 (1.3)
	NAb positive	2 (0.9)	3 (1.3)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	222 (94.9)	215 (93.1)
Week 40	ADA positive	1 (0.4)	3 (1.3)
	NAb positive	1 (0.4)	3 (1.3)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	213 (91.0)	208 (90.0)
Week 52	ADA positive	1 (0.4)	5 (2.2)
	NAb positive	1 (0.4)	5 (2.2)
	NAb negative	0 (0.0)	0 (0.0)
	ADA negative	213 (91.0)	212 (91.8)
Overall (Up to Week 52) [a)]	ADA positive	2 (0.9)	6 (2.6)
	NAb positive	2 (0.9)	6 (2.6)
	NAb negative	0 (0.0)	0 (0.0)
	Transient [b)]	1 (0.4)	3 (1.3)
	Persistent [c)]	1 (0.4)	3 (1.3)
	ADA negative	232 (99.1)	225 (97.4)

Only subjects with negative baseline ADA responses were included in ADA analysis.

[a)] 'Overall' indicates subjects with at least one ADA positive result (recorded as positive) up to Week 52.

[b)] Subjects with an overall ADA positive result, who do not show a persistent ADA response; these subjects were counted as both positive and transient.

[c)] Subjects experiencing two ADA positive results post baseline, followed by a positive ADA result at Week 52; these subjects were counted as both positive and persistent.

Source: [5.3.5.1-301-Table 14.3-1.4.1]

Impact of ADA on PK

Of the 44 subjects included in the PK substudy, no subjects were ADA/NAb-positive.

Impact of ADA on efficacy

Due to the overall low number of ADA positive subjects (2 subjects (0.9%) in the SOK583 treatment group and 6 subjects (2.6%) in the Eylea EU treatment group) a formal analysis of the impact of the ADA/Nab status on clinical efficacy was not conducted, as the result of such analysis will be inconclusive.

Impact of ADA on safety

Based on the clinical assessment conducted in Study 301, an evaluation of non-ocular and ocular AE in the study eye as well as in the fellow eye, based on the ADA status was performed in the subjects of the SAF. Overall, ADA positive subjects in the SAF (4/244 in the SOK583 group and 10/240 in the Eylea EU group) are comprised of treatment-emergent ADA positive subjects (from the IAS) as well as treatment-enhanced ADA positive subjects (ADA positive at baseline as well as after treatment). A very limited number of ADA positive subjects in the SOK583 (1 subject, 25%) or Eylea EU (5 subjects, 50.0%) treatment groups showed ocular AE in the study eye. For 1 of those subjects from the Eylea EU treatment group an eye inflammation in the study eye was reported. Ocular AEs of similar proportions were reported for ADA negative subjects in both treatment groups (30.5% for SOK583 and 30.0% for Eylea EU).

Table 11: Ocular adverse events in the study eye in ADA positive subjects (SAF)

Table 6-8 Ocular adverse events in the study eye in ADA positive subjects (SAF)

Primary system organ class Preferred term	SOK583 N=4 n (%)	Eylea EU N=10 n (%)
Number of subjects with at least one event	1 (25.0)	5 (50.0)
Eye disorders	1 (25.0)	3 (30.0)
Keratic precipitates	1 (25.0)	0 (0.0)
Eye inflammation	0 (0.0)	1 (10.0)
Posterior capsule opacification	0 (0.0)	1 (10.0)
Retinal fibrosis	0 (0.0)	1 (10.0)
Visual acuity reduced	0 (0.0)	2 (20.0)
Vitreous haemorrhage	0 (0.0)	1 (10.0)
Investigations	0 (0.0)	2 (20.0)
Intraocular pressure increased	0 (0.0)	2 (20.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (10.0)
Actinic keratosis[1)]	0 (0.0)	1 (10.0)

[1)] AE was counted as ocular as the anatomical location affected was the eye lid
Source: [5.3.5.1-301-Table 14.3.1-2.1.2]

Furthermore, evaluation of ocular TEAEs in the non-study eye of ADA positive and ADA negative subjects did not reveal any specific events which might be linked to an immunogenic response. In addition, no non-ocular adverse events being reasonably indicative of an immunogenic potential of aflibercept were observed in the ADA positive subjects of both treatment groups. Furthermore, no hypersensitivity reactions were reported in ADA positive subjects.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

Following EMA scientific advice EMA/CHMP/SAWP/233863/2018, a PK study to support demonstration of biosimilarity was not conducted because it was agreed that the administration of aflibercept to healthy volunteers is not ethically defendable. Furthermore, it was agreed that due to low and variable systemic concentrations of aflibercept after IVT administration (Eylea SmPC) and the efficacy of aflibercept in neovascular retinopathy is not associated with its systemic exposure, it is not meaningful to base biosimilarity conclusions on a PK comparison of systemic exposure. However, systemic concentration data is helpful to compare SOK583 levels versus Eylea EU levels (confirm they are as low and in a similar range as for the originator). This is considered acceptable.

No dedicated human PK studies were conducted. Supportive PK analyses were conducted in a subset of patients enrolled in study 301, as was supported by CHMP in the Scientific Advice (EMA/CHMP/SAWP/233863/2018).

Overall, method validation for the quantification of total and free aflibercept and PK sample analysis for Study 301 was carried out according to ICH M10 Guideline. Additionally, method validation for the detection of ADA and NAb was carried out following the Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the state of the art. Some issues were raised initially as other concerns, mainly regarding inspection history, stability validation and specificity evaluation for NAb analysis, however these were addressed and solved during the procedure.

At least 20 subjects in each study arm were planned to be included in the PK subset. This target has been met, since while 44 patients participated in the PK substudy, 43 subjects (SOK583: 23 subjects; Eylea EU: 20 subjects) were included; however, one subject received both treatments and this was an exclusion criterion. The extent of PK sampling is therefore considered sufficient and the strategy is endorsed. Demographics and baseline characteristics were well balanced between the two treatment groups in the PK analysis set. According to the applicant, the proportion of subjects with important protocol deviations and by category were similar between the two treatment groups in the PKS. As a response to the Day 120 LoQ, an overview of the protocol deviations for the patients included in the PKS has been provided. The majority of protocol deviations in the PKS were due to "visit date out of window", at Day 29 or Day 5. This did however not affect the PK assessment done 24 hours post-dose at Day 2 or Day 58 for which all sampling for PK was done within 24 hours (±1 hour) post-dose as defined in the study protocol. Other protocol deviations, e.g. presence of infection, are not likely to have any impact on the PK assessment.

Sampling was performed pre-dose at day 1 and 24 hours post-dose at day 1 and at day 58 (which is around the expected Tmax). Overall, PK data were compared as recommended by EMA in a Scientific Advice where CHMP recommended collecting PK data around Tmax to confirm that the systemic exposure of SOK583A1 is low and in a similar range as for the originator. All samples at baseline were below the lower limit of quantification in both treatment arms. According to which is stated in the protocol: "The concentrations will be summarized by treatment and time point for which the concentrations below LLOQ will be treated as zero", baseline results were set to zero and excluded from analysis of geometric mean. This approach is endorsed. The mean values for plasma concentrations of free aflibercept were similar in both treatment arms both at Day 2 (32.0 ng/mL and 33.3 ng/mL) and at Day 58 (31.7 ng/mL and 33.6 ng/mL). The maximum concentrations observed at any time point in each treatment group were slightly higher in the Eylea EU group (91.2 ng/mL in the SOK583 group vs. 97.2 ng/mL in the Eylea EU group). Of note, for total aflibercept, no 90% CI were provided for SOK583 and Eylea EU at Day 1, 2 and 58. However, this is not further pursued, as the point estimates were similar between both products.

The success criteria defined by the applicant are not agreed, because in a parallel study the (inter-subject) variability will be high and the width of the 90% CI will be wide to make extremely unlikely that the whole 90% CI is above 143%. The lack of precision plays in favour of showing that the products are not sufficiently different. The product should be extremely different (e.g. 2-fold higher systemic exposure) in order to fail.

It would have been more reasonable to use as success criteria the demonstration of equivalence within a widened acceptance range, for example 70-143%. Based on the observed point estimate of 95% and the upper limit of the 90% CI of the GMR of test/reference of 144, it can be considered that the systemic exposure is similar with the applied product compared to the reference product.

Pharmacodynamics

No dedicated (comparative) pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. This is acceptable for this biosimilar application since it relies on the information already known of the reference product. PD aspects were sufficiently addressed by assessing CSFT determined by SD-OCT and CNV lesion size in the pivotal clinical study 301. In addition, immunogenicity testing and an exploratory analysis of free VEGF in plasma were performed.

With regard to the analysis of VEGF, the week 48 pre-dose samples were used as baseline samples since the study was already ongoing when the applicant received the recommendation in a CHMP scientific advice. Since it has been reported that VEGF levels return to baseline values 2 months after IVT administration of aflibercept (Wang et al, 2014), this is considered to represent a reasonable approach to estimate a baseline value. The outcome of the exploratory objective of systemic VEGF concentrations has been provided with the response to the Day 120 LoQ. The differences between the treatment arms, both pre-dose at week 48 and 4 weeks after the last dose were small. At week 52, circulating mean levels of VEGF were reduced with 10 (SOK583) and 7 (Eylea) pg/mL compared to the week 48 measurement. Although the percentage of suppression was larger in the SOK583 treatment arm (approx. 14% vs. 9%), the differences between the treatment arms does not seem important and in a similar range. Overall, the analysis provides further support that there are no important differences between the two treatments.

Immunogenicity of SOK583 and Eylea EU was investigated in study 301 only. Samples were taken pre-dose at baseline period, during the treatment period on days 8, 29, 57, 113, 169 and 281, and during the follow-up period at day 365. This approach followed Scientific Advice and is endorsed. Of the 484 subjects in the Safety Set, 19 were excluded from the IAS: 9 subjects with no baseline samples available, 7 subjects with positive ADA responses at baseline, and 3 subjects who received both study treatments in the study eye. This is considered acceptable. At baseline, comparable proportions of patients were positive for pre-existing ADAs: 3/244 (1.2%) of subjects in the SOK583 group and 4/240 (1.7%) in the Eylea EU group. The pre-treatment incidence of immunoreactivity to aflibercept was similar to what was observed in the phase III studies of Eylea (1% to 3%) (Eylea EPAR). Of these 7 subjects, 2 subjects each in the SOK583 and the Eylea EU groups remained ADA positive until the last measurement.

Throughout the study duration the proportion of treatment-emergent ADA positive subjects was low in both groups. The overall (up to Week 52) incidence of treatment-emergent ADAs reported in this study was lower in the patients in the SOK583 arm compared to the Eylea EU arm (0.9% vs 2.6%), but both incidences are comparable to what was reported in the phase III studies of Eylea after 52 weeks of treatment with aflibercept (1% to 3%) (Heier et al 2012). Only one subject (0.4%) in the SOK583 treatment group and three subjects (1.3%) in the Eylea EU treatment group showed a persistent ADA response. All ADA positive responses were also determined to be NAb positive. The

incidence of NAbs (0.9% for SOK583 and 2.6% for Eylea EU) was higher in both treatment groups in comparison to the NAb incidence reported from historical studies (one NAb positive patient reported within Eylea phase III VIEW1 and VIEW2 studies (Heier et al 2012). This higher incidence is explained by the applicant referring to the sensitivity of the NAb assay used in study 301 (43 ng/mL), in comparison to the originator NAb assay sensitivity of 940 ng/mL, which is acknowledged.

None of the 44 patients included in the PK substudy were ADA/Nab-positive. Thus, no conclusion can be made on the impact of ADA/NAb status on PK. The impact of immunogenicity on clinical efficacy was not analysed either, due to the overall low number of ADA positive subjects (2 subjects (0.9%) in the SOK583 treatment group and 6 subjects (2.6%) in the Eylea EU treatment group). This is understood and accepted.

With regard to the impact of immunogenicity on safety, the overall incidence of ocular TEAEs in the study eye and non-ocular TEAEs in ADA positive patients (treatment-emergent ADA positive subjects and treatment-enhanced ADA positive subjects) was higher in the Eylea EU group [5/10 (50.0%) and 9/10 (90.0%), respectively] compared to the SOK583 group [1/4 (25%) and 2/4 (50%)]. These imbalances are difficult to interpret due to the overall low number of ADA positive patients and should be viewed in conjunction with the overall safety profile and the totality of evidence. The proportion of ADA negative patients who had ocular TEAEs in the study eye and non-ocular TEAEs was comparable between both treatment groups (34.3% vs 31.7% and 57.6% vs 57.4%, respectively, for SOK583 and Eylea EU). Furthermore, evaluation of ocular TEAE in the non-study eye of ADA positive and ADA negative subjects did not reveal any specific events which might be linked to an immunogenic response. In addition, no non-ocular adverse events being reasonably indicative of an immunogenic potential of aflibercept were observed in the ADA positive subjects of both treatment groups. In particular, ADA or NAb positive results were not associated with specific TEAEs such as hypersensitivity reactions in any subject.

2.4.4. Conclusions on clinical pharmacology

Assessment of systemic aflibercept levels conducted in a subset of patients in the pivotal clinical study 301 supports biosimilarity, as mean values for plasma concentrations of free aflibercept at Tmax were similar between the reference product Eylea and proposed biosimilar SOK583.

Overall, the exploratory analysis of free VEGF in plasma provided further support that there are no important differences between the two treatments.

The overall immunogenicity profile appears to be lower for SOK583 compared to Eylea, but it was comparable to what was reported in the phase III studies of Eylea after 52 weeks of treatment with aflibercept. The impact of immunogenicity on PK and efficacy was not studied. With regard to the impact of immunogenicity on safety, the overall incidence of ocular TEAEs in the study eye and non-ocular TEAEs in ADA positive patients (treatment-emergent ADA positive subjects and treatment-enhanced ADA positive subjects) was higher in the Eylea EU group compared to the SOK583 group, but due to the low number of ADA positive patients these imbalances are not possible to interpret and should be viewed in conjunction with the overall safety profile and the totality of evidence.

2.4.5. Clinical efficacy

2.4.5.1. Main study

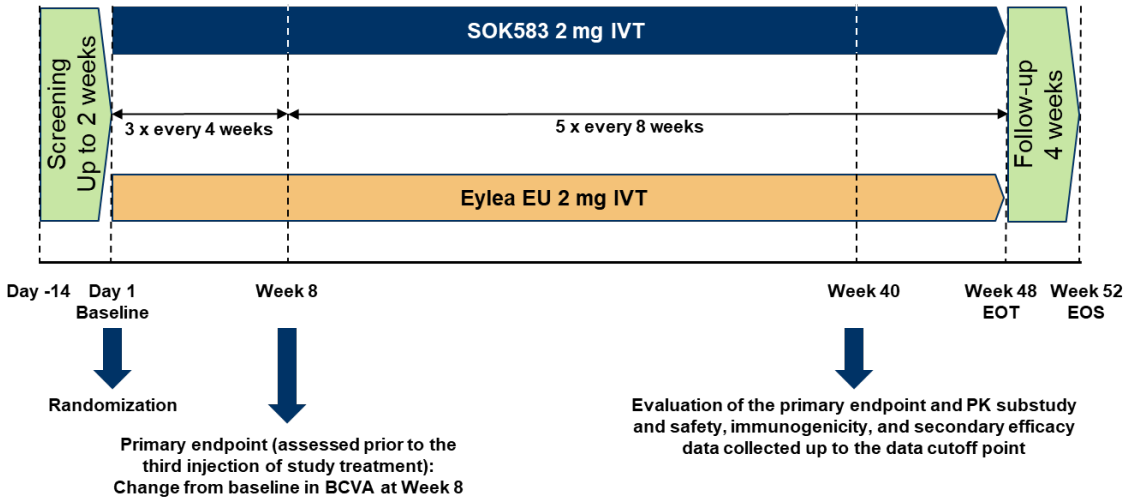
Study CSOK583A12301 (study 301)

A 52-week multicentre, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea, administered intravitreally, in patients with neovascular age-related macular degeneration.

Methods

This was a phase III, multicentre, randomised, double-masked, 2-arm parallel study in subjects with nAMD. The study compared the efficacy, safety, and immunogenicity of SOK583 and Eylea EU in subjects with nAMD 50 years or older and naïve to anti-VEGF treatment. Only 1 eye was selected as study eye. Unless justified by the Investigator, in cases where both eyes were eligible, the eye with the worse BCVA at baseline was selected as the study eye. If both eyes had the same BCVA, the right eye was selected as the study eye. The study duration for each individual subject was up to 54 weeks, including a screening period of up to 2 weeks, a treatment period of approximately 48 weeks of active treatment and a safety follow-up period of up to 4 weeks starting with the last administration of study treatment at Week 48.

Figure 3: Study flowchart



Study participants

Key inclusion criteria

Subjects eligible for inclusion in this study had to fulfil all of the key inclusion criteria:

- Participants must be 50 years of age or older at Screening
- Anti-VEGF treatment-naïve patients for either eye and systemically

- Study eye diagnosed with active CNV lesions (type 1 and/ or type 2) secondary to AMD and/or Retinal Angiomatous Proliferation lesions (type 3), affecting the central subfield. Active CNV lesion is defined by the presence of leakage as evidenced by fluorescein angiography, and intra- or subretinal fluid as evidenced by optical coherence tomography, both confirmed by the CRC at Screening
- Total area of CNV (including both classic and occult components) must comprise > 50% of the total lesion area in the study eye, confirmed by the CRC at Screening
- BCVA between 73 and 38 letters, both inclusive, in the study eye at Screening and Baseline using ETDRS testing charts
- Clear ocular media and adequate pupil dilatation in both eyes to permit good quality photographic imaging
- In cases where both eyes were eligible, the eye with the worse BCVA at Baseline was selected as the study eye. If both eyes had the same BCVA, it was recommended to select the right eye as the study eye. However, the investigator could select the eye with better visual acuity based on medical reasons or local ethical requirements; the selection needed to be justified.

Key exclusion criteria

Subjects fulfilling any of the exclusion criteria were not eligible for inclusion in this study:

- Concomitant conditions or ocular disorders in the study eye, including cataract and diabetic macular oedema, at Screening or Baseline which could, in the opinion of the Investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the course of the study
- Any active or suspected intraocular or periocular infection or active or suspected intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in either eye at Screening or Baseline
- Uncontrolled glaucoma in the study eye defined as IOP > 25 mmHg on medication or according to investigator's judgment at Screening or Baseline
- Presence of amblyopia, amaurosis or ocular disorders with BCVA <38 letters (ETDRS testing charts) in the fellow eye at Screening (except when due to conditions whose surgery may improve VA, e.g. cataract)
- Previous ocular treatments with any anti-VEGF or investigational drugs in either eye

Rescreening

Rescreening was allowed once.

Participants could be invited for a new Screening visit (rescreening) only under the following circumstances:

• Participants who did not meet the eligibility criteria could be invited once for a new Screening visit (rescreening).

• Participants who were retested for confirming the clinical significance of 1 or more safety labs or vital signs parameter during the initial screening (see above) and failed the related eligibility criterion or criteria could be rescreened once at an appropriate time-point based on the medical judgement.

• Participants who presented with a temporary medical condition precluding participation could be rescreened once. In this case, retesting was not permitted during rescreening for any reason.

• A participant could also be rescreened once in case of sample loss or damage.

Rescreening was NOT permitted if, based on medical judgment, any signs or symptoms assessed on Day -1 were suggestive of any significant illness and/or acute infection.

Participants who were randomized and failed to start study treatment, e.g. participants randomized in error, had to be considered early terminators. In this case, rescreening of the participant was not permitted.

Treatments

Subjects received study treatment (SOK583 40 mg/mL vial or Eylea EU 40 mg/mL vial) in the selected study eye only. Subjects received 8 IVT injections of fixed 2 mg of SOK583 or Eylea EU in the study eye, every 4 weeks at 3 consecutive visits (Baseline, Week 4, and Week 8) and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48.

Dose adjustments were not allowed for SOK583 or Eylea EU. Study treatment could be interrupted if warranted due to an AE.

Rescue medication for the study eye

Rescue treatment was not permitted in the study eye.

Per the investigator's discretion, at any time, if the nAMD in the study eye worsened, resulting in loss by ≥10 letters in BCVA at 2 consecutive visits or by ≥15 letters in BCVA at 1 visit compared with the best previous measurement, and the BCVA value of the study eye was not better than the baseline value, the subject may have required rescue treatment. In this case, study treatment was to be discontinued.

Objectives

The primary aim of the study was to demonstrate equivalence of change from Baseline in BCVA score at Week 8 between patients with nAMD treated with SOK583 or with Eylea EU, without important protocol deviations which affects the primary endpoint and adherent to the treatment and completed the treatment to Week 8.

The following statistical hypotheses were tested to assess equivalence between SOK583 and Eylea EU:

H0: $|\mu SOK583 - \mu Eylea| \geq \Delta$ versus H1: $|\mu SOK583 - \mu Eylea| < \Delta$, where μSOK583 and μEylea are the change from baseline in BCVA score at Week 8 for SOK583 and Eylea EU, respectively.

As per EMA requirement, therapeutic equivalence in terms of change from baseline in BCVA was concluded if the 95% CI for the difference in LS mean changes was contained within the interval [−3.5, +3.5]. This is statistically equivalent to calculating 2 independent one-sided tests at 2.5%-alpha level (one in each direction), of which both had to be successful.

The secondary efficacy objectives were:

- To evaluate if the anatomical outcome of SOK583 is similar to Eylea EU.
- To evaluate if the efficacy of SOK583 is similar to Eylea EU in terms of BCVA.

No hypotheses were tested for the secondary efficacy endpoints.

Outcomes/endpoints

Primary endpoint

Change from baseline in BCVA score at Week 8. BCVA was assessed using the ETDRS testing charts at an initial distance of 4 meters. The change from baseline in BCVA in letters was defined as difference between BCVA score between Week 8 and Baseline. Primary efficacy population was the PPS.

Secondary endpoints

- Mean change in CSFT using SD-OCT from Baseline to Weeks 1, 4, 8, 24 and 52.
- Mean change of CNV lesion size using FA from Screening to Weeks 8 and 52.
- Mean change from Baseline in BCVA score using EDTRS testing charts at Weeks 24 and 52.

Sample size

BCVA was assessed using the ETDRS testing charts at an initial distance of 4 meters. The change from baseline in BCVA in letters was defined as difference between the BCVA scores at Week 8 and Baseline.

An equivalence margin of ± 3.5 letters for the mean difference in BCVA change from baseline at 8 weeks was proposed to EMA, FDA, and PMDA. This margin was based on a meta-analysis of 8 randomized controlled studies in a total of almost 3000 patients receiving anti-VEGFs (aflibercept 2 mg, ranibizumab 0.5 mg), or sham injection in nAMD (ANCHOR, Brown et al 2009; MARINA, Rosenfeld et al 2006; HARBOR, Ho et al 2014; PIER 1, Regillo et al 2008; VIEW 1 and VIEW 2, Heier et al 2012; HAWK, NCT02307682, and HARRIER, NCT02434328; see also Dugel et al 2020).

The 8 studies were selected based on the dosing regimen, i.e. patients initially received 3 doses 1 month apart. BCVA in letters was assessed at 2 months (8 weeks) in all 8 studies. The mean change in BCVA at 2 months (8 weeks) and the standard error were extrapolated from the publications.

A fixed effect model with study (1 = studies comparing ranibizumab vs. non-VEGF-based treatments, or different dosing regimen of ranibizumab; and 2 = studies comparing anti-VEGF treatments) and treatment (aflibercept, ranibizumab, sham injection) as 2 fixed factors were fitted to the data. The inverse value of the variance was used as the exponential family dispersion parameter weight for each observation.

The meta-analysis provided a point estimate of the mean difference for change from baseline in BCVA at 8 weeks between aflibercept and sham injection of +8.8 letters with a 95% CI of (+7.00, +10.54). The proposed margin of 3.5 letters retained 50% of the treatment effect estimated from this meta-analysis. While EMA and PMDA accepted the proposed equivalence margin of ±3.5 letters, FDA recommended an equivalence margin of ± 3 letters based on a two-sided 90% CI. To fulfil EMA, FDA, and PMDA requirements with an expected dropout rate of 5%, a total of 460 randomized subjects were needed to achieve a study power of 90%.

Randomisation and blinding (masking)

Randomisation

Subjects were to be assigned to one of the following treatment groups in a ratio of 1:1: SOK583 or Eylea EU. This randomised study employed a centralized allocation method and used an IRT system to assign subjects to treatment groups.

Randomisation was stratified by region (US, Rest of the World, Japan), age (< 75 years and ≥ 75 years) and baseline BCVA categories (< 64 letters and ≥64 letters) to ensure a balanced and homogeneous allocation of subjects in each treatment group.

Treatment masking

This was a subject, investigator, and sponsor-masked study: subjects, investigators, and the sponsor remained masked to study treatment throughout the study, except as indicated below.

The identity of the study treatments could not be concealed because the SOK583 and Eylea EU vials differed in appearance. To maintain the double-masked design of the study it was necessary to involve unmasked staff at the study site for handling the study medication. Except the unmasked site staff identified below, all site staff (including study investigator and study nurse) was masked to study treatment throughout the study.

To ensure that study treatment remained masked to the subject and the investigator, receipt, handling, and administration of the IVT injection was performed by unmasked study site personnel not involved in any study assessments. All unmasked study documentation was to be kept strictly confidential and not accessible by the masked site staff. Unmasked site staff did not perform any clinical assessments (BCVA, disease activity assessments, complete ophthalmic examination, assessment of any ocular or non-ocular safety parameters, or assessment of causality of AEs for participants during the course of the study except an event reported immediately following IVT injection.). The unmasked investigator/site personnel, however, had to assess subject safety immediately after the injection.

Once the designated roles were determined, the roles were not to be switched at any time after randomisation. Every effort had to be made to limit the number of unmasked study personnel to ensure integrity of the masked study. Unmasking was permitted in case of subject emergencies and at the conclusion of the study.

Designated study team members were unmasked to the study treatment assignment after all subjects completed the Week 40 assessments and after the database was partially locked for the interim analysis. Subjects, investigators, and the rest of the study team remained masked until after the final database lock.

The primary analysis at Week 40 was performed with unmasking of specified sponsor and CRO personnel who were not directly involved in the conduct of the study. The unmasked personnel were not involved in the conduct of the remaining study. Subjects, investigators, and the rest of the study team remained masked to study treatment assignments until after the final database lock.

Statistical methods

Analysis sets

All Enrolled Analysis Set

The All Enrolled Set consisted of all subjects who signed the ICF.

Randomized Analysis Set (RAS)

The RAS consisted of all randomized subjects. The RAS also included all randomized subjects who were not treated. Subjects were analysed according to the treatment they have been assigned to during the randomization procedure.

Full Analysis Set (FAS)

The FAS included all randomized subjects to whom study treatment had been assigned by randomization, to whom at least 1 dose of study treatment had been administered, and for whom at least 1 post-baseline BCVA value was available. According to the intent to treat principle, subjects were analysed according to the study treatment they had been assigned to during the randomization procedure.

Safety Set (SAF)

The SAF included all randomized subjects who received at least 1 dose of study treatment. Subjects were analysed according to the study treatment received. Subjects who received multiple treatments (i.e. both SOK583 and Eylea EU) into the study eye were analysed according to the treatment arm from which they received the majority of treatments up to the last treatment received. In case of received equal number of treatments a subject was analysed according to the first treatment received.

Per-protocol Set (PPS)

The PPS was the primary analysis set for efficacy analyses.

The PPS was a subset of the FAS and was characterized by the following criteria:

• The primary BCVA assessments at baseline and Week 8 were available

• The subjects received treatment according to the protocol on Day 1 and Week 4

• The subjects did not experience any important protocol deviations affecting the primary endpoint up to Week 8

The primary endpoint mean change from baseline in BCVA at Week 8 was analysed using the PPS, which was a subset of the FAS and was characterized by the following criteria:

· The primary BCVA assessments at Baseline and Week 8 were available

· The subjects received treatment according to the protocol on Day 1 and Day 57 (Week 8)

· The subjects did not experience any important protocol deviations affecting the primary endpoint up to Week 8

The primary analysis was to demonstrate similarity between SOK583 and Eylea EU with respect to the primary endpoint. This primary analysis was performed when all randomized subjects had completed Week 40 or discontinued before Week 40. At this point, a partial database lock of the available data was performed.

The primary analysis included all available efficacy data that had been collected up to the respective data cutoff.

ANCOVA was performed, and the model included study treatment as a factor and baseline BCVA and age as continuous covariates. The LS means for the treatments were calculated and the CIs for the difference between SOK583 and Eylea EU was obtained from the ANCOVA model.

As per EMA requirement, therapeutic equivalence in terms of change from baseline in BCVA was concluded if the 95% CI for the difference in LS mean changes was contained within the interval [−3.5, +3.5]. This is statistically equivalent to calculating 2 independent one sided tests at 2.5%-alpha level (one in each direction), of which both had to be successful.

Region was also included as an administrative stratification factor to ensure a balanced allocation of subjects in each region for relevant region-specific subgroup analyses. Therefore, these 2 stratification factors were not included in the statistical model.

The secondary efficacy endpoints were analysed descriptively.

Handling of intercurrent events

The primary analysis included only those subjects who adhered to and completed treatment up to Week 8 and who did not have important protocol deviations that would affect the primary endpoint during this time; therefore, there were no intercurrent events for the observed PP estimand.

Handling of missing values not related to intercurrent events

The primary analysis was performed on the PPS with primary BCVA assessments available at baseline and Week 8; therefore, there were no or minimum missing data for the primary endpoint, and missing data were not imputed for the primary analysis.

Sensitivity and supplementary analyses of the primary endpoint

The 95% and 90% CIs of the differences in LS means from the ANCOVA for BCVA change from baseline from the MMRM model on the PPS were within [-3.5, +3.5] and [-3.0, +3.0], respectively. In addition, the results from the supplementary analyses of ANCOVA for BCVA change from baseline using LOCF and from the MMRM on the FAS, respectively, were in line with those from the primary analysis and the sensitivity analysis.

The results from the sensitivity and supplementary analyses corroborate the therapeutic equivalence of SOK583 and Eylea EU demonstrated by the results of the primary endpoint.

Planned subgroup analyses

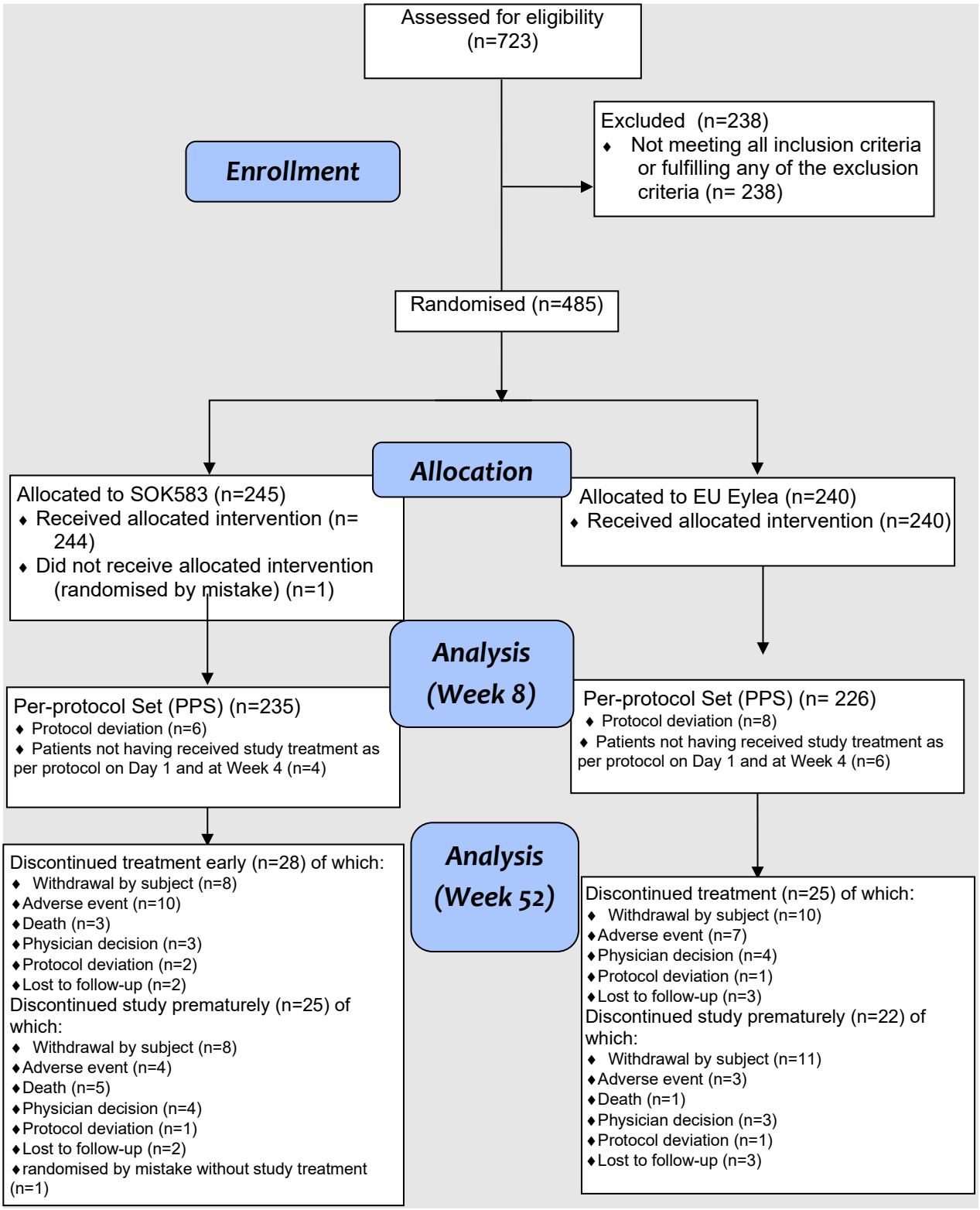
Subgroup analyses were planned to be performed for the primary endpoint change from Baseline in BCVA at Week 8. The analyses of the Subgroup of interest were planned to be descriptively performed only. CNV lesion size value collected before treatment administration was planned be analysed as Baseline CNV lesion size values.

Interim analysis

An interim analysis was performed after all participants had completed Week 40 or discontinued prior to Week 40. Formal testing of the primary endpoint with full level alpha was planned to be performed at the primary analysis time point. A final analysis was performed after all participants completed Week 52 (or discontinued prior to Week 52).

Results

Figure 4: Participant flow



Recruitment

Study initiation date: 30-Mar-2021 (date of first informed consent form signing)

Study completion date: 10-May-2023 (last subject last visit)

Database lock date: 14-Jul-2023

Earlier reports from the same study: A report (Week 40 analysis) describing the results of the planned interim analysis after all randomized subjects completed Week 40 or discontinued prior to Week 40 was completed on 13-Jul-2023. This report evaluated the primary endpoint results at Week 8 and included all safety, immunogenicity, and efficacy data collected up to the date of the data cutoff (15-Feb-2023).

Conduct of the study

Protocol amendments

The study protocol was amended 3 times.

Protocol version 2.0 incorporating amendment 1 (29-Jan-2021) was issued before screening of subjects started.

The amended protocol included recommendations provided by IRBs/IECs and ANSM and introduced the following key changes:

- The blood sample volume was corrected (25 mL was changed to 31 mL)
- Minor changes and clarification on the inclusion criterion #4 and exclusion criteria #3, 4, 9, 13, 14, 18, 19, 26, and 28 without changing their meaning.
    - Inclusion criterion #4: Types of CNV (types 1 and 2) and Retinal Angiomatous Proliferation lesions (type 3) were added.
    - Exclusion criterion #3: Diabetic retinopathy was removed, allowing subjects with CNV caused by diabetic retinopathy to be included in the study.
    - Exclusion criterion #4: Wording was aligned with the Eylea SmPC by including suspected intraocular or periocular infection and intraocular inflammation as reasons for excluding subjects.
    - Exclusion criteria #9 and 14: Timing of events (allowed yttrium aluminium garnet (YAG) posterior capsulotomy and prohibited use of topical ocular corticosteroids) was changed from prior to screening to prior to baseline.
    - Exclusion criterion #13: Timing of prohibited use of intra or periocular was changed from 180 days to within a 6-month period prior to baseline.
    - Exclusion criterion #28: For female subjects with reported natural (spontaneous) amenorrhea, FSH testing was required in absence of medical documentation.
- Use of bevacizumab for the fellow eye was only allowed if approved in the respective country.
- Coagulation tests and FSH testing at screening were included.
- A newborn follow-up period in case of pregnancy was included.

Protocol version 3.0 incorporating amendment 2 (07-Dec-2021) was issued after 161 of the 460 planned subjects had received study treatment.

The amended protocol included recommendations on SAE reporting provided by BfArM (SAEs needed to be reported immediately, without undue delay, but under no circumstances later than within 24 hours of learning of its occurrence).

Additionally, definition criteria for pathologic myopia (exclusion criterion #3) were modified by removing the specification of axial length, and corresponding diagnostic methods were adapted. The combination of determining the spherical equivalent and analysing the images assessed at screening were considered sufficient to exclude subjects adequately from the study.

The analyses of the primary estimand were updated and clarified. The study protocol language was additionally updated in line with the updated Sandoz protocol template, e.g. by clarifying discontinuation of study treatment and from study and related ICF handling.

Protocol version 4.0 incorporating amendment 3 (28-Jun-2022) was issued when recruitment was 100% complete and 3 subjects had completed the study.

The amended protocol included the evaluation of systemic VEGF concentrations at Week 48 (pre-dose) and Week 52. The aim of this assessment was to evaluate the concentrations of systemic VEGF in the 2 treatment groups at Week 52, i.e. 4 weeks after IVT treatment with aflibercept. VEGF concentration at Week 48 (pre-dose) was used as baseline value to calculate the relative change in VEGF between Week 48 and Week 52. The VEGF evaluation was recommended by EMA in a scientific advice (22-Apr-2022).

This amendment applied to those subjects who agreed to additional blood collection for the evaluation of systemic VEGF concentrations. They documented their agreement by signing the corresponding ICF.

In response to an EMA recommendation, PK success criteria (assessment of non-similarity between the SOK583 and Eylea) were specified in the SAP.

The amended protocol introduced the following key changes:

- The evaluation of systemic VEGF concentrations was added as an exploratory objective.
- The blood volume required for the evaluations of systemic VEGF concentration was added.
- Details of the updated ICF on evaluation of systemic VEGF concentrations were added.
- The analysis set for the evaluation of systemic VEGF concentrations was added.

Other minor changes included a correction of the wording of the secondary endpoint CNV lesion size. Mean changes of CNV lesion size using FA from screening to Week 8 and 52 were to be evaluated.

Protocol deviations

Important protocol deviations were defined as those that significantly impacted the completeness, accuracy, and/or reliability of the study data, or significantly affected the subject's rights, safety, or well-being.

Overall, 327 subjects (67.7%) of the FAS had at least 1 important protocol deviation. The overall high number of subjects with important protocol deviations is due to the conservative approach taken when defining protocol deviations, e.g. by including deviations from the tight visit time windows or timing of the IOP measurements.

None of the protocol deviations raised any safety concern at the time of study inclusion and during routine medical monitoring of the study, as assessed by the investigators.

Table 12: Protocol deviations (FAS)

Protocol deviation	SOK583 N=243 [1] n (%)	Eylea EU N=240 n (%)
Number of subjects with any important protocol deviation	168 (69.1)	159 (66.3)
Number of subjects with important protocol deviation leading to exclusion from PPS	6 (2.5)	9 (3.8)
Missed visit not related to COVID-19	3 (1.2)	2 (0.8)
Incorrect treatment kit administered in the study eye in error	1 (0.4)	2 (0.8)
Study eye: Absence of CRC confirmed active nAMD in appropriate location	1 (0.4)	0 (0.0)
Subject received investigational product with temperature excursion	1 (0.4)	2 (0.8)
Prohibited ocular fellow eye or systemic medication	0 (0.0)	2 (0.8)
Study treatment injection not administered as per protocol treatment schedule	0 (0.0)	1 (1.4)
Number of subjects with important protocol deviation not leading to exclusion from PPS	166 (68.3)	158 (65.8)
Visit date out of window from protocol schedule	84 (34.6)	87 (36.3)
Presence of infection within 2 weeks before screening; and/or underlying or advanced, severe, and uncontrolled co-condition, physical examination or clinical laboratory finding which add risk for subject (principal investigator opinion)[2]	58 (23.9)	53 (22.1)
Measurement of the IOP was performed less than 30 minutes after treatment	52 (21.4)	56 (23.3)
Missed visit not related to COVID-19	34 (14.0)	22 (9.2)
Other[3,4]	60 (24.7)	53 (22.1)

A subject with multiple occurrences of a protocol deviation is counted only once for that specific protocol deviation criterion.
Subjects may have multiple protocol deviations.
Protocol deviations are sorted in descending frequency, as reported in the SOK583 column.

1 One subject in the SOK583 group was excluded from the FAS because no postbaseline BCVA was available for the subject.

2 Main reason was that subjects did not have all safety laboratory results available at the time of randomisation

3 'Other' contains protocol deviations not leading to exclusion from PPS reported for less than 10% of subjects in any treatment group. Subjects with multiple protocol deviations are counted multiple times.

4 Use of concomitant medication was erroneously reported as important protocol deviation of prohibited concomitant medication-4/prohibited fellow eye or systemic medication for 5 subjects in [Listing 16.2-2.1]:

Day	Event
314	Treatment of a TEAE (pleurisy) ([Listing 16.2.5-2.2], [Listing 16.2.7-1])
240	Treatment of a TEAE (colitis microscopic) (Listing 16.2.5-2.2, Listing 16.2.7-1)
222	Treatment of a TEAE (asthma) (Listing 16.2.5-2.2, Listing 16.2.7-1)

163, 198	Last dose of study treatment had been given before the event (Day 162) [Listing 16.2.5-1]
134	Last dose of study treatment had been given before the event (Day 106) (Listing 16.2.5-1)

This error was detected only after final database lock. The affected Listing 16.2-2.1 and Table 14.1-6 were therefore not corrected. As these were important protocol deviations not leading to exclusion from the PPS, Listing 16.2.3-1 and the definition of the PPS were not affected.

Source: [5.3.5.1-301-Table 10-2]

Baseline data

Table 13: Demographic characteristics (PPS and FAS)

	PPS		FAS	
Characteristics/ Categories/Statistics	**SOK583 N=235**	**Eylea EU N=226**	**SOK583 N=243**	**Eylea EU N=240**
Age (years)				
n	235	226	243	240
Mean (SD)	75.7 (7.80)	75.7 (7.70)	75.8 (7.82)	75.7 (7.72)
Median	76.0	76.0	76.0	76.0
Min, Max	53, 94	54, 94	53, 94	54, 94
Age - n (%)				
< 75 years	99 (42.1)	91 (40.3)	103 (42.4)	98 (40.8)
≥ 75 years	136 (57.9)	135 (59.7)	140 (57.6)	142 (59.2)
Sex - (%)				
Male	104 (44.3)	99 (43.8)	106 (43.6)	104 (43.3)
Female	131 (55.7)	127 (56.2)	137 (56.4)	136 (56.7)
Race - n (%)				
White	208 (88.5)	204 (90.3)	215 (88.5)	214 (89.2)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Asian	15 (6.4)	9 (4.0)	16 (6.6)	12 (5.0)
Indian	2 (0.9)	0 (0.0)	2 (0.8)	0 (0.0)
Japanese	12 (5.1)	9 (4.0)	13 (5.3)	12 (5.0)
Korean	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Missing	12 (5.1)	13 (5.8)	12 (4.9)	13 (5.4)
Ethnicity - n (%)				
Hispanic or Latino	12 (5.1)	8 (3.5)	12 (4.9)	9 (3.8)
Not Hispanic or Latino	217 (92.3)	212 (93.8)	225 (92.6)	225 (93.8)
Not reported	5 (2.1)	6 (2.7)	5 (2.1)	6 (2.5)
Unknown	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)
Ancestry - n (%)				
Japanese				
First generation	4 (1.7)	3 (1.3)	4 (1.6)	5 (2.1)
Second generation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Third generation	8 (3.4)	6 (2.7)	9 (3.7)	7 (2.9)
Region - n (%)				

Characteristics/ Categories/Statistics	PPS		FAS	
	SOK583 N=235	Eylea EU N=226	SOK583 N=243	Eylea EU N=240
United States	45 (19.1)	39 (17.3)	46 (18.9)	42 (17.5)
Europe	152 (64.7)	155 (68.6)	158 (65.0)	161 (67.1)
Rest of World	38 (16.2)	32 (14.2)	39 (16.0)	37 (15.4)

Source: 5.3.5.1-301-Table 10-4

Table 14: Baseline ocular characteristics for the study eye (PPS and FAS)

Baseline characteristic	PPS		FAS	
	SOK583 N=235	Eylea EU N=226	SOK583 N=243	Eylea EU N=240
Primary diagnosis of nAMD - n (%)	235 (100.0)	226 (100.0)	243 (100.0)	240 (100.0)
Time since diagnosis of nAMD (in days)				
n	235	226	243	240
Mean (SD)	63.4 (219.18)	45.8 (145.38)	62.1 (215.69)	44.4 (141.23)
Median	12.0	12.0	12.0	12.5
Min, Max	1, 2075	1, 1347	1, 2075	1, 1347
Time since diagnosis of nAMD - n (%)				
< 30 days	172 (73.2)	169 (74.8)	177 (72.8)	179 (74.6)
30 - 90 days	40 (17.0)	40 (17.7)	43 (17.7)	44 (18.3)
> 90 days	23 (9.8)	17 (7.5)	23 (9.5)	17 (7.1)
Unilateral vs. bilateral nAMD - n (%)				
Unilateral	210 (89.4)	209 (92.5)	218 (89.7)	221 (92.1)
Bilateral	25 (10.6)	17 (7.5)	25 (10.3)	19 (7.9)
Iris color - n (%)				
Black	4 (1.7)	2 (0.9)	5 (2.1)	3 (1.3)
Blue	78 (33.2)	70 (31.0)	79 (32.5)	74 (30.8)
Brown	94 (40.0)	79 (35.0)	97 (39.9)	85 (35.4)
Gray	10 (4.3)	21 (9.3)	10 (4.1)	21 (8.8)
Green	22 (9.4)	24 (10.6)	22 (9.1)	25 (10.4)
Hazel	17 (7.2)	20 (8.8)	18 (7.4)	21 (8.8)
Other	10 (4.3)	9 (4.0)	10 (4.1)	10 (4.2)
Missing	0 (0.0)	1 (0.4)	2 (0.8)	1 (0.4)
Definition of the study eye - n (%)				
Left	103 (43.8)	98 (43.4)	107 (44.0)	105 (43.8)
Right	132 (56.2)	128 (56.6)	136 (56.0)	135 (56.3)
Intraocular pressure (mmHg)				
n	235	226	243	240
Mean (SD)	14.9 (3.05)	15.2 (2.94)	14.9 (3.04)	15.2 (2.92)
Median	15.0	15.0	15.0	15.0
Min, Max	8, 23	8, 24	8, 23	8, 24
BCVA (letters read)				
n	235	226	243	240
Mean (SD)	59.7 (10.15)	59.7 (10.37)	59.7 (10.05)	59.4 (10.37)
Median	61.0	62.0	61.0	61.5

	PPS		FAS	
Baseline characteristic	**SOK583 N=235**	**Eylea EU N=226**	**SOK583 N=243**	**Eylea EU N=240**
Min, Max	38, 73	38, 73	38, 73	38, 73
BCVA (letters read) - n (%)				
< 64 letters	134 (57.0)	133 (58.8)	139 (57.2)	144 (60.0)
≥ 64 letters	101 (43.0)	93 (41.2)	104 (42.8)	96 (40.0)
Lesion type - n (%)				
Predominantly classic	8 (3.4)	13 (5.8)	8 (3.3)	13 (5.4)
Minimally classic	12 (5.1)	17 (7.5)	12 (4.9)	17 (7.1)
Occult	190 (80.9)	170 (75.2)	198 (81.5)	182 (75.8)
Classic	19 (8.1)	20 (8.8)	19 (7.8)	21 (8.8)
CNV absent	6 (2.6)	5 (2.2)	6 (2.5)	6 (2.5)
Missing	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Foveal involvement - n (%)				
Subfoveal	184 (78.3)	170 (75.2)	192 (79.0)	178 (74.2)
Extrafoveal	15 (6.4)	20 (8.8)	15 (6.2)	22 (9.2)
Juxtafoveal	30 (12.8)	30 (13.3)	30 (12.3)	33 (13.8)
Missing	6 (2.6)	6 (2.7)	6 (2.5)	7 (2.9)
CNV lesion size (mm^2) [1]				
n	234	223	242	237
Mean (SD)	5.7384 (5.04850)	5.5481 (4.68381)	5.7590 (5.03035)	5.4383 (4.62344)
Median	4.3660	4.1600	4.3660	3.9000
Min, Max	0.000, 33.382	0.000, 28.630	0.000, 33.382	0.000, 28.630
Presence of subretinal fluid - n (%)				
Present	214 (91.1)	212 (93.8)	222 (91.4)	224 (93.3)
Absent	21 (8.9)	14 (6.2)	21 (8.6)	16 (6.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Presence of intraretinal fluid/cyst - n (%)				
Present	131 (55.7)	127 (56.2)	134 (55.1)	134 (55.8)
Absent	104 (44.3)	97 (42.9)	109 (44.9)	104 (43.3)
Missing	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.8)
CSFT-total (µm)				
n	235	225	243	238
Mean (SD)	493.6 (170.37)	476.7 (166.46)	493.8 (169.25)	471.8 (163.85)
Median	454.0	434.0	455.0	426.0
Min, Max	186, 1104	163, 1082	186, 1104	163, 1082
CSFT-total (µm) - n (%)				
< 400 µm	81 (34.5)	83 (36.7)	83 (34.2)	90 (37.5)
≥ 400 µm	154 (65.5)	142 (62.8)	160 (65.8)	148 (61.7)
Missing	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.8)

Baseline characteristic	PPS		FAS	
	SOK583 N=235	Eylea EU N=226	SOK583 N=243	Eylea EU N=240

Occult is considered present if at least 1 of the 3 sub-types (Fibrovascular PED, SEROUS PED, and Late Leakage) is present.
"Predominantly classic" category includes both "Predominantly classic" and "Pure classic" sub-categories.
1 For CNV lesion size, the value measured at screening was used as baseline value.
Source: 5.3.5.1-301-Table 10-5

Medical history and concurrent illnesses

Comparable numbers of subjects in the SOK583 group and the Eylea EU group reported ocular medical history events in the study eye (SOK583: 192 subjects, 79.0%; Eylea EU: 184 subjects, 76.7%) or the fellow eye (SOK583: 196 subjects, 80.7%; Eylea EU: 193 subjects, 80.4%)). On a PT level, medical history events in the study eye and in the fellow eye were well balanced between the 2 treatment groups. The most frequently reported ocular medical history events in the study eye (≥10% of subjects in any treatment group) are listed by preferred term in the following table:

Table 15: Most frequently reported ocular medical history events in the study eye (equal or greater than 10% of subjects in any treatment group) (FAS)

Preferred term	SOK583 N=243 n (%)	Eylea EU N=240 n (%)
Cataract	161 (67.1%)	145 (60.4%)
Pseudophakia	72 (29.6)	70 (29.2)
Dry age-related macular degeneration	25 (10.3%)	40 (16.7%)

Preferred terms are sorted in descending frequency, as reported in the SOK583 column.
A subject with multiple occurrences within the same preferred term or system organ class is counted only once in each specific category.
MedDRA version 26.0.
Source: Table 14.1-5.1.1

Non-ocular medical history events were well balanced between the 2 treatment groups and were reported by comparable numbers of subjects in the SOK583 group and the Eylea EU group (238 subjects, 97.9%, vs. 232 subjects, 96.7%). The most frequently reported non-ocular medical history events (≥10% of subjects in any treatment group) are listed by preferred term in the following table:

Table 16: Most frequently reported non-ocular medical history events (equal or greater than 10% of subjects in any treatment group) (FAS)

Preferred term	SOK583 N=243 n (%)	Eylea EU N=240 n (%)
Hypertension	171 (70.4)	157 (65.4)
Menopause	65 (26.7)	56 (23.3)
Hypercholesterolaemia	61 (25.1)	53 (22.1)
Postmenopause	55 (22.6)	59 (24.6)
Type 2 diabetes mellitus	53 (21.8)	44 (18.3)
Osteoarthritis	45 (18.5)	49 (20.4)

Preferred term	SOK583 N=243 n (%)	Eylea EU N=240 n (%)
Gastrooesophageal reflux disease	38 (15.6)	34 (14.2)
Osteoporosis	34 (14.0)	26 (10.8)
Benign prostatic hyperplasia	33 (13.6)	23 (9.6)
Hypothyroidism	32 (13.2)	28 (11.7)
Hyperlipidaemia	28 (11.5)	36 (15.0)
Depression	18 (7.4)	27 (11.3)

Preferred terms are sorted in descending frequency, as reported in the SOK583 column.
A subject with multiple occurrences within the same preferred term or system organ class is counted only once in each specific category.
MedDRA version 26.0.
Source: Table 14.1-5.2

Prior medication and non-drug therapies/procedures

There were no clinically relevant differences between the 2 treatment groups in their use of prior ocular medication for the study eye or the fellow eye as well as in their use of prior non-ocular medication.

No clinically relevant differences between the 2 treatment groups were reported for prior ocular non-drug therapies/procedures for the study eye or the fellow eye and for prior non-ocular nondrug therapies/procedures.

Concomitant medication and non-drug therapies/procedures

All subjects in the SOK583 group and in the Eylea EU group reported concomitant ocular medication for the study eye (SOK583: 244 subjects, 100.0%; Eylea EU: 240 subjects, 100.0%) and most subjects in each treatment group for the fellow eye (SOK583: 210 subjects, 86.1%; Eylea EU: 200 subjects, 83.3%).

Most frequently reported ocular medications for the study eye were local anaesthetics (SOK583: 234 subjects, 95.9%; Eylea EU: 230 subjects, 95.8%), other anti-infectives (SOK583: 197 subjects, 80.7%; Eylea EU: 192 subjects, 80.0%), anticholinergics (SOK583: 209 subjects, 85.7%; Eylea EU: 206 subjects, 85.8%), fluoroquinolones (SOK583: 101 subjects, 41.4%; Eylea EU: 90 subjects, 37.5%), sympathomimetics excl. antiglaucoma preparations (SOK583: 105 subjects, 43.0%; Eylea EU: 110 subjects, 45.8%), and colouring agents (SOK583: 75 subjects, 30.7%; Eylea EU: 80 subjects, 33.3).

All subjects in the SOK583 group and in the Eylea EU group reported concomitant non-ocular medication (SOK583: 244 subjects, 100.0%; Eylea EU: 240 subjects, 100.0%). No clinically relevant differences in the use of concomitant non-ocular medications were observed between the 2 treatment groups.

No clinically relevant differences between the 2 treatment groups were reported for concomitant ocular non-drug therapies/procedures for the study eye or the fellow eye and for concomitant non-ocular non-drug therapies/procedures.

No clinically relevant differences between the 2 treatment groups were reported for prohibited concomitant ocular medications. Prohibited non-ocular medications and prohibited non-drug therapies/procedures were not reported.

Anti-VEGF medications for the fellow eye are summarized in Table 17.

Table 17

Table 14.1-8.6
Anti-VEGF medications by ATC class and preferred term for the fellow eye
(Safety Set)

ATC class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Any ATC class	30 (12.3)	27 (11.3)
ANTINEOVASCULARISATION AGENTS	30 (12.3)	27 (11.3)
AFLIBERCEPT	23 (9.4)	19 (7.9)
RANIBIZUMAB	3 (1.2)	6 (2.5)
BEVACIZUMAB	2 (0.8)	4 (1.7)
BROLUCIZUMAB	2 (0.8)	0 (0.0)

Numbers analysed

Table 2-3 summarizes the analysis sets by treatment group.

485 subjects were randomized in the study, 484 of whom received at least 1 dose of study treatment and were included in the SAF. 1 subject was randomized by mistake into the SOK583 group and discontinued the study before receiving study treatment; consequently, the subject was not included in the SAF and the FAS.

The FAS comprised 483 subjects as 1 subject in the SOK583 group was excluded from the FAS because no post-baseline BCVA was available for the subject.

A total of 461 subjects of the 483 subjects in the FAS were included in the PPS (primary analysis set for efficacy analyses). 15 subjects with protocol deviations affecting the primary endpoint up to Week 8 (mostly missed visits not related to COVID-19, incorrect treatment kit administered in the study eye in error, or receiving investigational product with temperature excursion) and 7 subjects not having received study treatment as per protocol on Day 1 and at Week 4 with no BCVA assessments available at baseline and Week 8 were excluded from the PPS.

Table 18: **Analysis sets (RAS**)

Analysis set	**SOK583 N=245 n (%)**	**Eylea EU N=240 n (%)**
Randomized Analysis Set (RAS) [1]	245	240
Full Analysis Set (FAS) [2]	243 (99.2)	240 (100.0)
Safety Set (SAF)	244 (99.6)	240 (100.0)
Per-protocol Set (PPS)	235 (95.9)	226 (94.2)
PK Analysis Set (PKS)	23 (9.4)	20 (8.3)
Immunogenicity Analysis set	234 (95.5)	231 (96.3)
VEGF Analysis Set	60 (24.5)	67 (27.9)

Percentages are based on the number of subjects in the RAS.
[1] One subject in the SOK583 group was randomized by mistake and discontinued the study before receiving study treatment.
[2] One subject in the SOK583 group was excluded from the FAS because no post-baseline BCVA was available for the subject.

Source: 5.3.5.1-5.3.5.1-Table 10-3

Outcomes and estimation

Primary efficacy results

Primary efficacy analysis (PPS)- ANCOVA

The primary endpoint of the study was the change from baseline in BCVA score at Week 8. BCVA was assessed using the ETDRS testing charts at an initial distance of 4 meters. The change from baseline in BCVA in letters was defined as difference between BCVA score between Week 8 and Baseline. Primary efficacy population was the PPS.

The difference in LS mean changes was -0.3 letters for the PPS; the 95% CI: (-1.8, 1.3) letters and 90% CI: (-1.5, 1.0) letters were contained within the prespecified intervals [−3.5, +3.5] (EMA and PMDA requirement) and [−3.0, +3.0] (FDA requirement), respectively (Table 19).

Table 19: Primary efficacy analysis (PPS) - Summary statistics and ANCOVA for change from baseline in BCVA score at Week 8

	SOK583 N=235	**Eylea EU N=226**
Descriptive statistics		
n	235	226
Mean (SD)	6.5 (8.98)	6.8 (7.46)
Median	7.0	8.0
Min, Max	-36, 40	-25, 28
1st, 3rd quartile	3.0, 11.0	3.0, 11.0
ANCOVA		
LS mean		
LS mean (95% CI)	6.5 (5.5, 7.6)	6.8 (5.7, 7.9)
LS mean difference (SOK583 - Eylea)		
Difference (SE)		-0.3 (0.77)
95% CI for treatment difference		-1.8, 1.3
90% CI for treatment difference		-1.5, 1.0

Baseline was the pre-dose BCVA score prior to the first aflibercept (SOK583 or Eylea EU) injection. ANCOVA included treatment as a factor and baseline BCVA and age as continuous covariates. Coefficients/p-values of the covariates baseline BCVA and age were -0.076/0.046 and -0.062/0.218, respectively.

Source: 5.3.5.1-301-Table 11-1

Sensitivity analysis (PPS) - MMRM model

The 95% and 90% CIs of the differences in LS means from the ANCOVA for BCVA change from baseline at Week 8 from the MMRM model on the PPS (Table 20) were within [-3.5, +3.5] and [-3.0, +3.0], respectively.

Table 20: Sensitivity analysis (PPS) – MMRM model for change from baseline in BCVA score at Week

Table 11-2 Sensitivity analysis (PPS) - MMRM model for change from baseline in BCVA score at Week 8

	SOK583 N=235	Eylea EU N=226
n	235	226
LS mean (95% CI)	6.5 (5.5, 7.6)	6.8 (5.7, 7.9)
LS mean difference (SOK583 - Eylea)		
Difference (SE)		-0.3 (0.77)
95% CI for treatment difference		-1.8, 1.3
90% CI for treatment difference		-1.5, 1.0

Baseline was the pre-dose BCVA score prior to the first aflibercept (SOK583 or Eylea EU) injection. Subjects with both baseline BCVA value and at least 1 available value at Week 4 or Week 8 were included in the analysis.
The MMRM model included treatment, visit, and interaction between time and treatment as categorical variables, and age and baseline BCVA as continuous variables.

Supplementary analyses (FAS)

The results from the supplementary analyses of ANCOVA for BCVA change from baseline using LOCF imputation and from the MMRM model on the FAS (Table 21 and Table 22, respectively) were in line with those from the primary analysis and the sensitivity analysis.

Table 21

Table 11-3 Supplementary analysis (FAS) - ANCOVA for change from baseline in BCVA score at Week 8 using LOCF imputation

	SOK583 N=243	Eylea EU N=240
Descriptive statistics		
n	243	239 [1]
Mean (SD)	6.4 (8.91)	6.7 (7.58)
Median	7.0	7.0
Min, Max	-36, 40	-25, 29
1st, 3rd quartile	2.0, 11.0	3.0, 11.0
ANCOVA		
LS mean		
LS mean (95% CI)	6.4 (5.3, 7.4)	6.7 (5.6, 7.7)
LS mean difference (SOK583 - Eylea)		
Difference (SE)		-0.3 (0.75)
95% CI for treatment difference		-1.8, 1.2
90% CI for treatment difference		-1.5, 0.9

Baseline was the pre-dose BCVA score prior to the first aflibercept (SOK583 or Eylea EU) injection.
ANCOVA included treatment as a factor and baseline BCVA and age as continuous covariates.
LOCF method was used for missing data at Week 8. Observed values from both scheduled and unscheduled visits were used for the LOCF imputation. For subjects with no post-baseline value, no imputation was performed.

[1] Subject 5015009 did not have any post-baseline BCVA measurement to be carried forwarded as Week 8 LOCF.

Source: Table 14.2-3.1

Table 22

Table 11-4 Supplementary analysis (FAS) - MMRM model for change from baseline in BCVA score at Week 8

	SOK583 N=243	Eylea EU N=240
n	242	235
LS mean (95% CI)	6.4 (5.4, 7.5)	6.8 (5.7, 7.8)
LS mean difference (SOK583 - Eylea)		
Difference (SE)		-0.3 (0.76)
95% CI for treatment difference		-1.8, 1.1
90% CI for treatment difference		-1.6, 0.9

Baseline was the pre-dose BCVA score prior to the first aflibercept (SOK583 or Eylea EU) injection. Subjects with both baseline BCVA value and at least 1 available value at Week 4 or Week 8 were included in the analysis.
The MMRM model included treatment, visit, and interaction between time and treatment as categorical variables and age and baseline BCVA as continuous variables.

Secondary endpoints

Mean change from baseline in CSFT using SD-OCT

Mean changes from baseline in CSFT using SD-OCT were similar between the SOK583 group and the Eylea EU group for subjects in the FAS (Figure 5) and for subjects in the PPS (Figure 6) at Weeks 1, 4, 8, 24, and all other time points up to Week 52.

Figure 5: Mean change from baseline (SD) in CSFT using SD-OCT up to Week 52 (FAS)

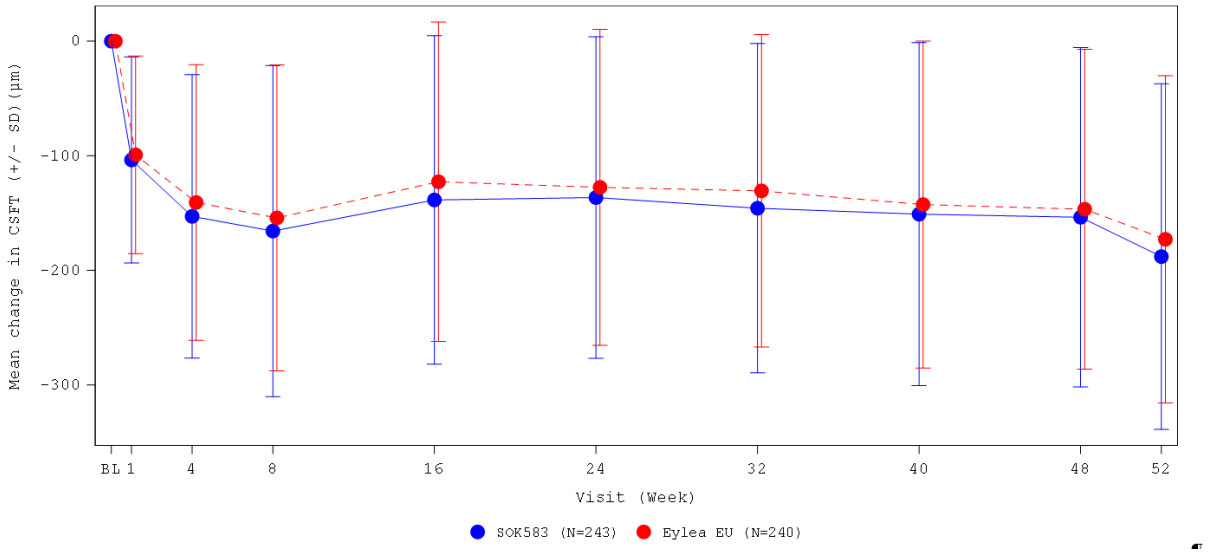
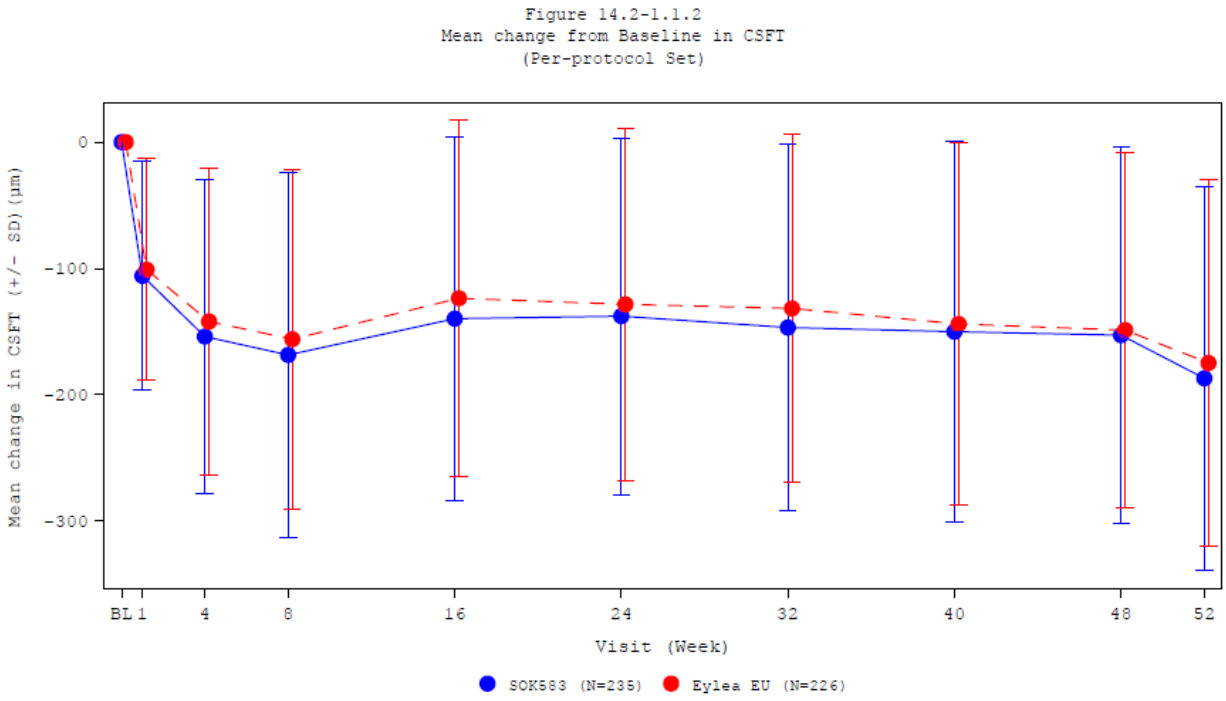


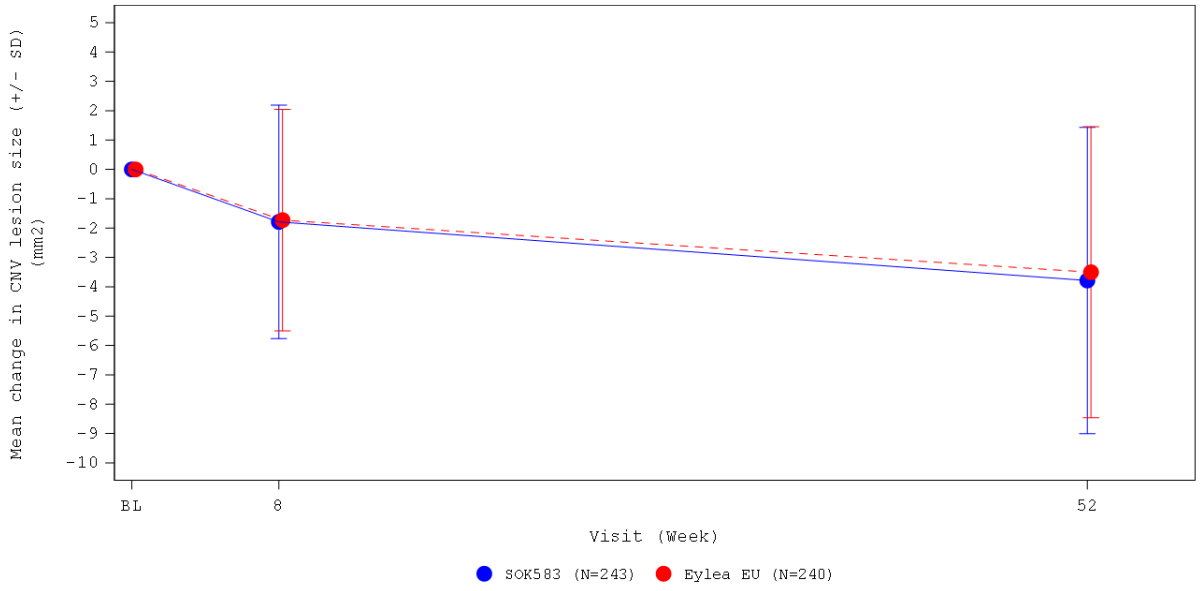
Figure 6: Mean change from Baseline in CSFT (Per -protocol Set)



Mean change from baseline (SD) in CNV lesion size using FA

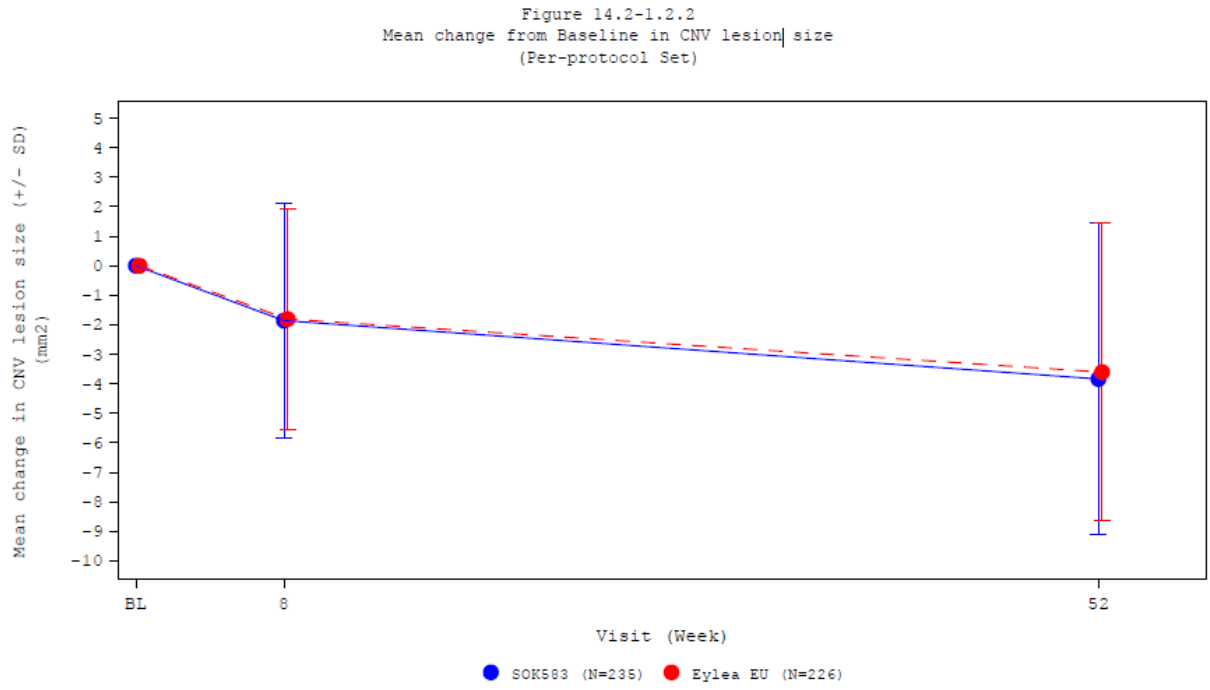
Mean changes from baseline in CNV lesion size at Weeks 8 and 52 were similar between the SOK583 group and the Eylea EU group for subjects in the FAS (Figure 7) and for subjects in the PPS (Figure 8). (Note: The value of CNV lesion size measured at screening was used as baseline value.)

Figure 7: Mean change from baseline (SD) in CNV lesion size using FA at Weeks 8 and 52 (FAS)



The value of CNV lesion size measured at screening was used as baseline value.
Source: Figure 14.2-1.2.1

Figure 8: Mean change from baseline in CNV lesion size (Per-Protocol Set)



Mean change from baseline in BCVA score

Mean changes from baseline in BCVA score were similar between the SOK583 group and the Eylea EU group for subjects in the FAS (Figure 9) and for subjects in the PPS (Figure 10) at Weeks 24 and all other time points up to Week 52.

Figure 9:Mean change from baseline (SD) in BCVA score up to Week 52 (FAS)

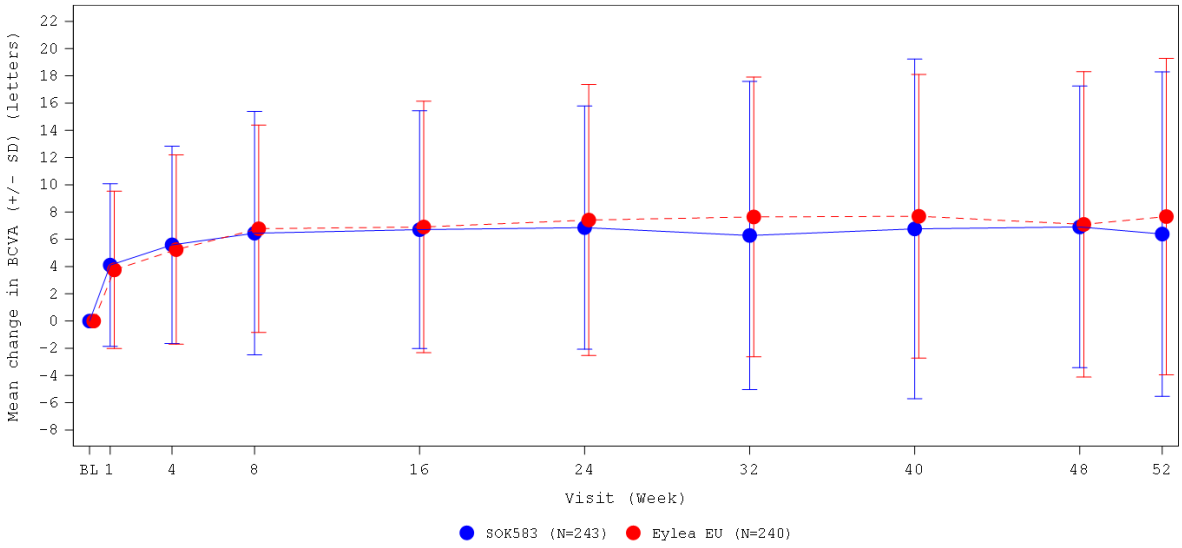
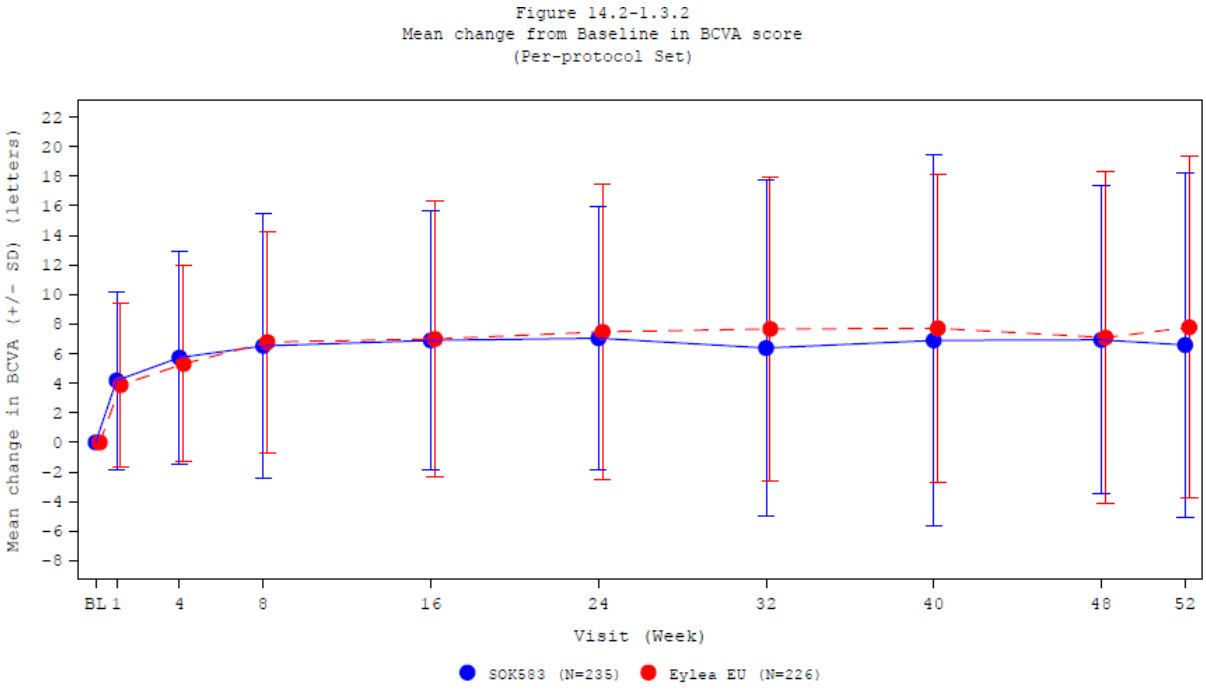


Figure 10: Mean change from Baseline in BCVA score (Per-protocol Set)



Ancillary analyses

Descriptive analyses on the proportion of subjects in the PPS gaining and losing BCVA at weeks 8 and 52 are provided in Table 23 and Table 24 below.

Table 23: Analyses of the proportions of subjects with vision loss (PPS)

Endpoint	SOK583 N=235	Eylea EU N=226	Difference (SOK – Eylea EU) (95% CI)
>=5 letters loss from baseline			
Week 8 %(n/m)	7.7 (18/235)	7.1 (16/226)	0.6
95% CI	(4.6, 11.8)	(4.1, 11.2)	(-4.2, 5.3)
Week 52 %(n/m)	11.8 (26/220)	11.6 (25/216)	0.2
95% CI	(7.9, 16.8)	(7.6, 16.6)	(-5.8, 6.3)
>=10 letters loss from baseline			
Week 8 %(n/m)	4.7 (11/235)	2.2 (5/226)	2.5
95% CI	(2.4, 8.2)	(0.7, 5.1)	(-0.8, 5.8)

Endpoint	SOK583 N=235	Eylea EU N=226	Difference (SOK – Eylea EU) (95% CI)
Week 52 %(n/m)	9.1 (20/220)	7.4 (16/216)	1.7
95% CI	(5.6, 13.7)	(4.3, 11.8)	(-3.5, 6.8)
>=15 letters loss from baseline			
Week 8 %(n/m)	3.0 (7/235)	1.3 (3/226)	1.7
95% CI	(1.2, 6.0)	(0.3, 3.8)	(-1.0, 4.3)
Week 52 %(n/m)	4.5 (10/220)	5.1 (11/216)	-0.5
95% CI	(2.2, 8.2)	(2.6, 8.9)	(-4.6, 3.5)

m: number of participants with evaluable data at a visit

Table 24: Analyses of the proportions of subjects with vision gain (PPS)

Endpoint	SOK583 N=235	Eylea EU N=226	Difference (SOK - Eylea EU) (95% CI)
>=5 letters gain from baseline			
Week 8 %(n/m)	62.1 (146/235)	65.0 (147/226)	-2.9
95% CI	(55.6, 68.4)	(58.4, 71.2)	(-11.7, 5.9)
Week 52 %(n/m)	64.1 (141/220)	69.9 (151/216)	-5.8
95% CI	(57.4, 70.4)	(63.3, 75.9)	(-14.6, 3.0)
>=10 letters gain from baseline			
Week 8 %(n/m)	32.8 (77/235)	38.1 (86/226)	-5.3
95% CI	(26.8, 39.2)	(31.7, 44.7)	(-14.0, 3.4)
Week 52 %(n/m)	42.3 (93/220)	48.1 (104/216)	-5.9

Endpoint	SOK583 N=235	Eylea EU N=226	Difference (SOK - Eylea EU) (95% CI)
95% CI	(35.7, 49.1)	(41.3, 55.0)	(-15.2, 3.5)
>=15 letters gain from baseline			
Week 8 %(n/m)	15.3 (36/235)	11.5 (26/226)	3.8
95% CI	(11.0, 20.6)	(7.7, 16.4)	(-2.4, 10.0)
Week 52 %(n/m)	20.0 (44/220)	23.6 (51/216)	-3.6
95% CI	(14.9, 25.9)	(18.1, 29.8)	(-11.4, 4.1)

m: number of participants with evaluable data at a visit

2.4.5.2. Summary of main efficacy results

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

Table 25: Summary of efficacy for trial CSOK583A12301

Title: A 52-week multicenter, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea®, administered intravitreally, in patients with neovascular age-related macular degeneration		
Study identifier	Protocol number: CSOK583A12301 EUDRACT number: 2019-004838-41	
Design	This was an international, multicentre, randomized, double-masked, 2-arm parallel study in subjects with neovascular age-related macular degeneration (nAMD), with a total duration of 52 weeks. A descriptive pharmacokinetics substudy was included to evaluate systemic concentrations of intravitreally (IVT) administered SOK583 and EU-authorized Eylea® (Eylea EU).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks not applicable not applicable
Hypothesis	Equivalence	
Treatments groups	SOK583	IVT injection of fixed 2 mg of SOK583 in the study eye every 4 weeks at 3 consecutive visits (baseline, Week 4, and Week 8), and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48 number of randomized subjects: 245 number of treated subjects: 244

	Eylea EU		IVT injection of fixed 2 mg of Eylea EU in the study eye every 4 weeks at 3 consecutive visits (baseline, Week 4, and Week 8), and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48 number of randomized subjects: 240 number of treated subjects: 240
Endpoints and definitions	Primary endpoint	change from baseline in BCVA score at Week 8	Change from baseline in best corrected visual acuity (BCVA) score using early treatment diabetic retinopathy study (ETDRS) testing charts at Week 8 Analysis population: per-protocol set (PPS) Therapeutic equivalence in terms of change from baseline in BCVA was concluded if the 95% confidence interval (CI) for the difference in least square (LS) mean changes was contained within the interval [−3.5, +3.5]. This is statistically equivalent to calculating 2 independent one-sided tests at 2.5%-alpha level (one in each direction), of which both had to be successful. Analysis of covariance (ANCOVA) was performed, and the model included study treatment as a factor and baseline BCVA and age as continuous covariates. The LS means for the treatments were calculated and the CIs for the difference between SOK583 and Eylea EU was obtained from the ANCOVA model. Consistent with the 2 one-sided tests for bioequivalence at the 2.5% significance level, 95% CIs for change from baseline in BCVA were derived.
	Other, specify: Sensitivity analysis of the primary endpoint	change from baseline in BCVA score at Week 8 using MMRM (PPS)	To compare the results from the ANCOVA model for the primary analysis with a mixed-model repeated measures (MMRM) model was performed. The MMRM model included study treatment, visit, and interaction between time and treatment as categorical variables, and age and baseline BCVA as continuous variables. Analysis population: PPS
	Other, specify: Supplemental analysis of the primary endpoint	change from baseline in BCVA score at Week 8 using LOCF (FAS)	A supplementary analysis using the same statistical model of ANCOVA as for the primary analysis was performed. Missing data were imputed using last observation carried over (LOCF) imputation. Observed values from both scheduled and unscheduled visits were used for the LOCF imputation. No imputation was performed for subjects with no post-baseline value. Analysis population: full analysis set (FAS)
	Other, specify: Supplemental analysis of the primary endpoint	change from baseline in BCVA score at Week 8 using MMRM (FAS)	See sensitivity analysis above. Analysis population: FAS
Database lock	14-Jul-2023		

Results and analysis			
Analysis description	**Primary analysis**		
Analysis population and time point description	Per protocol The PPS was a subset of the FAS and was characterized by the following criteria: • The primary BCVA assessments at baseline and Week 8 were available • The subjects received treatment according to the protocol on Day 1 and Day 57 (Week 8) • The subjects did not experience any important protocol deviations affecting the primary endpoint up to Week 8		
Descriptive statistics and estimate variability	Treatment group	SOK583	Eylea EU
	Number of subjects	235	226
	change from baseline in BCVA score at Week 8 (mean)	6.5	6.8
	standard deviation	8.98	7.46
	change from baseline in BCVA score at Week 8 (median)	7.0	8.0
	minimum, maximum	-36, 40	-25, 28
	ANCOVA: change from baseline in BCVA score at Week 8 (LS mean) 95% CI	6.5 5.5, 7.6	6.8 5.7, 7.9
Effect estimate per comparison	Primary endpoint	Comparison groups	SOK583 - Eylea EU
		difference between groups	-0.3
		standard error	0.77
		95% CI	-1.8, 1.3
Notes	485 subjects were randomized in the study. The FAS comprised 483 subjects: 1 subject was randomized by mistake and did not receive study treatment, and 1 subject was excluded from the FAS because no post-baseline BCVA score was available for the subject. 461 subjects of the 483 subjects in the FAS subjects were included in the PPS. 14 subjects with protocol deviations affecting the primary endpoint up to Week 8 (mostly missed visits not related to COVID-19, incorrect treatment kit administered in the study eye in error, or receiving investigational product with temperature excursion), 8 subjects not having received study treatment as per protocol on Day 1 and at Week 4 were excluded from the PPS. The number of subjects with protocol deviations and other reasons for exclusion from the PPS were well balanced between the 2 treatment groups. The number of the remaining evaluable subjects was sufficient for the efficacy analysis.		
Analysis description	**Other, specify: sensitivity analysis: change from baseline in BCVA score at Week 8 using MMRM (PPS)** This analysis was pre-specified in the statistical analysis plan prior to database lock.		

Analysis population and time point description	PPS (description see above) Week 8		
Descriptive statistics and estimate variability	Treatment group	SOK583	Eylea EU
	Number of subjects	235	226
	change from baseline in BCVA score at Week 8 using MMRM (LS mean) 95% CI	6.5 5.5, 7.6	6.8 5.7, 7.9
Effect estimate per comparison	Sensitivity analysis of the primary endpoint	Comparison groups	SOK583 - Eylea EU
		difference between groups	-0.3
		standard error	0.77
		95% CI	-1.8, 1.3
Analysis description	**Other, specify: supplementary analysis: change from baseline in BCVA score at Week 8 using LOCF (FAS)** This analysis was pre-specified in the statistical analysis plan prior to database lock.		
Analysis population and time point description	FAS The FAS included all randomized subjects to whom study treatment had been assigned by randomization, to whom at least 1 dose of study treatment had been administered, and for whom at least 1 post-baseline BCVA value was available. According to the intent to treat principle, subjects were analysed according to the study treatment they had been assigned to during the randomization procedure. Week 8		
Descriptive statistics and estimate variability	Treatment group	SOK583	Eylea EU
	Number of subjects	243	240
	change from baseline in BCVA score at Week 8 using LOCF (mean)	6.4	6.7
	standard deviation	8.91	7.58
	ANCOVA: change from baseline in BCVA score at Week 8 (LS mean) 95% CI	6.4 5.3, 7.4	6.7 5.6, 7.7
Effect estimate per comparison	Supplementary analysis of the primary endpoint	Comparison groups	SOK583 - Eylea EU
		difference between groups	-0.3
		standard error	0.75
		95% CI	-1.8, 1.2
Analysis description	**Other, specify: supplementary analysis: change from baseline in BCVA score at Week 8 using MMRM (FAS)** This analysis was pre-specified in the statistical analysis plan prior to database lock.		

Analysis population and time point description	FAS (description see above) Week 8		
Descriptive statistics and estimate variability	Treatment group	SOK583	Eylea EU
	Number of subjects	243	240
	change from baseline in BCVA score at Week 8 using MMRM (LS mean) 95% CI	6.4 5.4, 7.5	6.8 5.7, 7.8
Effect estimate per comparison	Supplementary analysis of the primary endpoint	Comparison groups	SOK583 - Eylea EU
		difference between groups	-0.3
		standard error	0.76
		95% CI	-1.8, 1.1

2.4.6. Discussion on clinical efficacy

Design and conduct of clinical studies

One single pivotal phase III study (301) has been performed to demonstrate biosimilarity of SOK583 and EU-authorised Eylea with regard to efficacy. Study 301 was a multicentre, randomised, double-masked, active controlled, comparative clinical study in subjects with neovascular age-related macular degeneration (nAMD). It is acceptable that no further clinical studies have been conducted to demonstrate similarity in efficacy between SOK583 and Eylea in other indications approved for EU Eylea. Study 301 was ongoing at the time of the initial dossier submission. The applicant provided the results of the planned interim analysis (Week 40 analysis) including all the data collected up to the date of the data cutoff (15-Feb-2023) with the initial marketing authorisation application. The final CSR of study 301 (Week 52 analysis) was provided with the responses to Day 120 LoQ.

Two additional studies were conducted:

- Study 303: An open-label, single-arm, multicentre study in patients with neovascular age-related macular degeneration to evaluate the safety of SOK583 (40 mg/mL), a proposed aflibercept biosimilar product, provided in a vial kit.
- Study 304: An open-label, single-arm, multicentre study in patients with neovascular age-related macular degeneration to evaluate the safety of SOK583A1 (40 mg/mL), a proposed aflibercept biosimilar product, provided in a prefilled syringe.

These two studies were aimed to assess the safety profile of two different formulations of SOK583 (a vial and a prefilled syringe). As patients included in these studies received a single dose and no efficacy parameters were measured no further reference will be made in the efficacy section. These studies will be taken into account only for the safety evaluation.

Overall, the design of the pivotal Phase III study is considered adequate and generally in line with previous EMA-scientific advices. In particular, the CHMP recommended 12-month study duration to assess long-term efficacy and safety/immunogenicity (EMA/CHMP/SAWP/233863/2018), and study design was extended to 52 weeks study duration, which is acknowledged. This study consists of a screening period, treatment period and follow up period.

The selected patient population (nAMD patients) is considered a relevant and sensitive study population for the detection of potential differences between SOK583 and the reference product and less prone to be impacted by the underlying disease (as compared to RVO or DME). This was endorsed by the EMA (EMA/CHMP/SAWP/233863/2018).

The inclusion and exclusion criteria are acceptable and in line with the scientific advice provided for the proposed study population. An upper BCVA boundary of 73 letters (20/40) and a lowest baseline BCVA of 38 (20/200) was recommended for study inclusion by the CHMP during prior SA (EMA/CHMP/SAWP/347653/2019) in order to ensure that the study population was sensitive enough to BCVA changes. This was followed by the applicant.

This was a subject, investigator, and sponsor-masked study. However, since the identity of the study treatments could not be concealed because the SOK583 and Eylea EU vials differed in appearance, to maintain the double-masked design of the study it was necessary to involve unmasked staff at the study site for the receipt, handling, and administration of the IVT injection. The unmasked study site personnel were not involved in any study assessments (BCVA, disease activity assessments, complete ophthalmic examination, assessment of any ocular or non-ocular safety parameters, or assessment of causality of AEs for participants during the course of the study except an event reported immediately following IVT injection), but they had to assess subject safety immediately after the injection. This is acceptable. In addition, it should be noted that designated study team members were unmasked to the study treatment assignment after all subjects completed the Week 40 assessments and after the database was partially locked for the interim analysis. Subjects, investigators, and the rest of the study team were to remain masked until after the final database lock, however the study integrity could be put partially at risk. No questions are however asked in this context.

The biosimilar aflibercept product and the originator product EU Eylea were administered intravitreally at a dose of 2 mg to the study eye every 4 weeks at Baseline, Week 4 and Week 8, and thereafter every 8 weeks at week 16, 24, 32, 40 and 48. This dosing regimen is one of the options for nAMD treatment as per the SmPC of Eylea, which also states that "based on the physician's judgement of visual and/or anatomic outcomes, the treatment interval may be maintained at two months or further extended using a treat-and-extend dosing regimen, where injection intervals are increased in 2- or 4-weekly increments to maintain stable visual and/or anatomic outcomes". However, flexible dosing is not considered reasonable in a trial aimed at evaluating biosimilarity and therefore, the chosen dosing regimen is considered acceptable to demonstrate clinical equivalence. Criteria for administration of rescue medication and IP discontinuation were sufficiently defined. The rescue criteria regarding BCVA could have been more stringent e.g. loss of ≥5 letters in BCVA over 2 consecutive compared to the previous best value instead of the ≥10 letter loss. Furthermore, according to the current practice, re-treatment is also initiated in case of an increased retinal thickness, or in case of a new vision-threatening haemorrhage due to macular degeneration. These criteria would also have been appropriate to include; however, for obvious reasons, no changes can be made at this stage.

BCVA, CSFT and CNV lesion size were assessed to demonstrate similar efficacy of SOK583 and Eylea EU, which is line with recommendations provided in the Scientific Advice (EMA/CHMP/SAWP/347653/2019).

The primary objective of the study was to demonstrate similar efficacy of SOK583 and Eylea EU in terms of BCVA. The primary endpoint was mean change from baseline in BCVA score using ETDRS testing charts at Week 8. Given that the maximum improvement of BCVA appeared to be reached starting at 12 weeks in VIEW 1 and VIEW 2 pivotal aflibercept studies, 8 weeks is considered a sensitive time-point to detect any differences between SOK583 and Eylea in terms of BCVA change from baseline. Therefore, the primary endpoint 'change in BVCA letters at week 8 compared to baseline' is considered an appropriate primary endpoint for the assessment of biosimilarity.

The proposed equivalence range for the mean difference in the primary endpoint for the wet AMD population of ± 3.5 letters was agreed to in the CHMP Scientific Advice (EMA/CHMP/SAWP/347653/2019). Since a 5 letter loss in BCVA has been used as a retreatment criterion in several protocols and the 3.5 letter margin is well away from the 5 letters, it was therefore agreed that 3.5 letters in BCVA has little clinical relevance and the proposed margin was thus considered acceptable.

The applicant applied the primary analysis for assessing equivalence between a biosimilar and an innovator product based on the PP population, who adhered to and completed treatment and did not have important protocol deviations. This strategy is acceptable. For the equivalence analysis also the FAS population will be of importance and both are expected to lead to the same positive conclusion.

Secondary endpoints evaluated the change in CSFT and BCVA from baseline at different time points over the study course (at weeks 1, 4, 8, 24 and 52 for CSFT and at weeks 24 and 52 for BCVA), as recommended by the CHMP Scientific Advice to cover the time-response curve over a longer period (including earlier and later time-points) compared to the primary endpoint, to further strengthen the evidence for biosimilarity (EMA/CHMP/SAWP/347653/2019). Although the evaluation of BCVA score earlier than Week 8 recommended by the Scientific Advice was not formally included among the secondary endpoints (only BCVA change at Week 24 and Week 52 were planned) BCVA was assessed at weeks 1 and 4 during the study, as CSFT was, covering earlier time-points in the time-response curve. The change in CNV area was also included as secondary endpoint, as recommended (EMA/CHMP/SAWP/347653/2019); the evaluation at weeks 8 and 52 is acceptable.

Planned analyses

The primary analysis was performed utilizing ANCOVA model considering baseline BCVA and age as continuous covariates in the PPS and region was only included to ensure a balanced allocation of subjects.

For the secondary efficacy endpoints summary statistics for mean change from baseline in BCVA score, mean change in CSFT using SD-OCT from Baseline at Week 1, 4, 8, 24 and 52 and mean change of CNV lesion size using FA from Baseline at Week 8 and 52 were provided. Secondary endpoints analyses did not allow control of type I error and may therefore be considered as exploratory analyses.

For the primary endpoint, sensitivity and supplementary analyses were conducted. A MMRM model was submitted as sensitivity analysis on the PPS within [-3.5, +3.5] and [-3.0, +3.0] for BCVA change from baseline. However, the MMRM model with missing data assumed to be missing at random requires justification. With the responses to D120 LoQ, the applicant provided a tipping point sensitivity analysis to evaluate the robustness of the current PP estimator in testing equivalence, which is in accordance with ICH E9 (R1) addendum recommendation to address intercurrent events, since it allows to explore the impact of bias of the PP estimand from the proposed principal stratum casual estimand. The applicant showed that equivalence could be established in most scenarios in the figure 3, which is acceptable.

In addition, an ANCOVA for BCVA change from baseline using LOCF on the FAS was conducted as supplementary analysis. However, the LOCF approach has several disadvantages. First, since the bias depends on many factors (including true evolutions after dropout and proportion of missingness in the treatment arms), it does not necessarily yield a conservative estimation of the treatment effect. Second, the imputation may also distort the variance structure, which may lead to over- as well as underestimation of the precision. For these reasons in order to assess the robustness of analysis results, the applicant was asked to conduct a supplementary analysis for the FAS population on MMRM that is sufficiently sensitive to detect differences between the treatment arms on the primary endpoint with an adequate imputation technique. The applicant revised the missing data imputation methods to

use FCS regression as multiple imputation and this method assumed that the missing data were MAR. On this point, the applicant stated the reason to include age, baseline BCVA and CNV lesion size based on historical studies and added auxiliary variables (BCVA variables (Week 1, Week 4, and Week 8)), which were correlated with variables that could be used in the data analysis stage. Overall, it is acceptable, since the variables included could contribute to reduce bias and make the MAR assumptions more plausible. In addition, the results from MMRM supplementary analysis were in line with those from the primary analysis, which is acceptable.

Subgroup analysis

The applicant planned subgroups of interest analyses for the primary endpoint change from Baseline in BCVA at Week 8, which were planned to be performed descriptively only. However, the third version (24-Nov-2022) of the SAP removed the batchwise subgroup analysis.

Sample size determination

The applicant performed a meta-analysis of 8 randomised controlled studies in a total of almost 3000 patients receiving anti-VEGFs (aflibercept 2 mg, ranibizumab 0.5 mg), or sham injection in nAMD and as a conservative approach, the mean difference for change from a baseline in BCVA at 8 weeks between aflibercept and sham injection of +8.8 letters with a 95% CI of (+7.00, +10.54). Based on this estimate, the applicant proposes an equivalence margin of [-3.5, 3.5] preserving the effect of about 50% in the case of EMA. As FDA recommended an equivalence margin of [-3.0, 3.0], and the applicant estimated a dropout rate of 5%, a total of 460 subjects were planned to be randomized in order to meet both requirements with a final statistical power of 90%. The proposed equivalence margin and sample size assumptions are considered acceptable and the calculations are reproducible.

There were 5 SAP versions.

The fourth version (24-Mar-2023) removed the sensitivity analysis of primary endpoint based on LOCF approach with a MMRM. The applicant showed the results from the supplementary analyses of ANCOVA for BCVA change from baseline using LOCF imputation on the FAS. Since the concomitant use of LOCF approach with MMRM is discouraged, this modification is endorsed.

Three protocol amendments were made. Amendment 1 was issued before screening of subjects started, amendment 2 was issued after 161 of the 460 planned subjects had received study treatment and amendment 3 was issued when recruitment was 100% complete and 3 subjects had completed the study. None of the amendments are considered to affect the interpretability of the study.

The proportion of subjects having important protocol deviations though very high, was similar in both treatment arms (SOK583: 69.1%; Eylea EU: 66.3%). The applicant explains the high number of patients with important protocol deviations by the conservative approach taken when defining protocol deviations, e.g. by including deviations from the tight visit time windows or timing of the IOP measurements, which is acknowledged.

A total of 15 subjects (2.9%; SOK583 2.5%; Eylea EU: 3.8%) in the FAS had important protocol deviations affecting the primary endpoint up to Week 8 (mostly missed visits not related to COVID-19, incorrect treatment kit administered in the study eye in error, or receiving investigational product with temperature excursion), which led to exclusion of these subjects from the PPS, with no significant imbalances between treatment groups. Overall, the retention of subjects in the PPS was high (approximately 95%) which is reassuring.

As outlined in the updated clinical study report, due to inadequate masking of study treatment and procedures at 3 study sites, data were unmasked. The applicant states that data integrity was not compromised by these events after the site monitors were replaced but further clarification was requested. The applicant has provided further information on the events. There is some remaining

uncertainty on the timing of a potential unmasking in relation to the primary efficacy evaluation for 3 of the 4 concerned subjects and for 2 of these events, it was unclear whether unmasking took place or not. Nevertheless, the appropriate measures such as replacing staff and re-training to avoid further unmasking have been taken and the integrity of the study is not considered at risk. The events as such are further considered unlikely to have an impact on the outcome of the study and the issue not further pursued.

After the interim analysis cut-off, it was identified that 15 subjects had 17 missing protocol deviations. All subjects were correctly allocated in the respective analysis sets and there was minimal impact on the analysis. No change was made to the interim analysis data set; the updates will be reflected only in the final analysis.

Protocol deviations not leading to exclusion from the PPS containing missed visits not related to COVID-19 were 32 (13.2%) for SOK583 vs 22(9.2%) for Eylea EU according to information from the CSR. The applicant was asked to clarify the effect of the exclusion of Missed visits not related to COVID-19 on the sensitivity analysis of the primary endpoint from PPS. The applicant provided the detail of the subjects with missed visits not related to COVID-19 at other time points than baseline or Week 8 and all of them are placed in a number visit different to visit 5 (day 57, week 8). Therefore, they had no effect on the primary efficacy analysis in these cases. Only 5 subjects had no BCVA assessment at visit 5 (week 8) and were excluded from the PPS and not included in the primary endpoint and sensitivity analyses, which is acceptable.

Efficacy data and additional analyses

Of a total of 723 screened subjects, 485 subjects (67%) were randomised. The reasons for screen failures were due to failing to meet the patient selection criteria. Specifically, the majority of ineligible subjects failed on the criteria of having an active CNV lesion or failing to have a baseline BCVA between 73 and 38 letters. Other reasons for screen failure included underlying and/or previous conditions, both systemic and ocular, or previous treatments. The applicant has further presented published data supporting that the rate of screen failures was similar to those reported for trials with aflibercept. One subject was randomised by mistake into the SOK583 group and did not receive study treatment, leading to 484 randomised patients who received study treatment (SOK583: 244 subjects, 99.6%; Eylea EU: 240 subjects, 100%). Study discontinuation rate was slightly higher in the SOK583 group by Week 52 (10.2% vs. 9.2%), with the greatest imbalance in the reasons for study discontinuation being death [SOK583: 5 (2.0%), Eylea EU: 1 (0.4%)].

In the context of rescue treatment in the study eyes, it was unclear how many subjects in each treatment arm discontinued the study drugs (SOK583 or EU-Eylea) secondary to worsening of nAMD in the study eye, i.e., due to loss of BCVA (according to the defined rescue criteria), due to increases in the macular oedema (CST) or due to retinal haemorrhage. It was further unclear how many subjects in each treatment arm received alternative therapy for the treatment of nAMD in the study eye. As a response to the Day 120 LoQ, the applicant has presented the requested data from the final, week 52 analysis. In summary, one subject discontinued the study due to macular oedema (alternative therapy unknown), and two subjects due to retinal haemorrhage (one treated with ranibizumab, one unknown). In addition, in the SOK583 treatment arm, two subjects discontinued study treatment due to retinal haemorrhage and were given 1) ranibizumab and aflibercept and, 2) ranibizumab and bevacizumab. In the Eylea treatment arm, the single subject that discontinued the study experienced retinal haemorrhage and continued treatment with aflibercept. Two additional subjects discontinued study treatment due to macular oedema and retinal haemorrhage and were given 1) bevacizumab and aflibercept and, 2) ranibizumab and bevacizumab. Overall, the numbers of insufficiently controlled

subjects are in line with what would be expected during treatment with aflibercept. There were no important differences between the two treatment arms.

Overall, demographic and baseline ocular characteristics for the study eye were well balanced between the two treatment groups for subjects in the PPS and FAS. However, the time since diagnosis of nAMD was somewhat longer for subjects in the SOK583 treatment group (PPS: 63 vs. 46 days for the Eylea treatment group). This appears to be reflected in a slightly larger CNV lesion size and a slightly larger CSFT. No concerns are however, raised as the differences were modest, a longer duration since diagnosis would rather lead to a reduced treatment effect than the opposite, and the baseline BCVA didn't differ between the two treatment arms.

Mean age was 75.7 years in both PPS and FAS population. More subjects were enrolled from EU than from other regions (around 68% vs 18% from USA and 15% the rest of the world respectively). The majority of subjects were white (89%) and female (56%).

Overall, the study population reflects the intended condition in EU. Reported demographics appear balanced across treatment groups and do not give rise to concern.

In both studies, baseline ocular characteristics in the study were generally balanced across treatment groups. Most of the patients had been recently diagnosed (74% < 1 month) and the mean BCVA score was 59.7 letters. The majority presented with subretinal fluid (93%) and around 56% presented with intraretinal fluid.

Both treatment arms were similar regarding medical history, prior medications and treatments, as well as concomitant medications.

With regard to the primary efficacy endpoint, for the subjects included in the analysis of the PPS, the mean change in BCVA score from Baseline to Week 8 was 6.5 and 6.8 in the SOK583 and Eylea EU group, respectively. In both treatment groups, the effect size was what would be expected after treatment with aflibercept. The difference in LS mean changes in BCVA score at Week 8 was -0.3 letters, and the 95% CI for the treatment difference was [-1.8, 1.3], which is within the predefined and accepted equivalence range of -3.5 to +3.5 letters.

A sensitivity analysis to compare the results from the ANCOVA model for the primary estimand with an MMRM model on the PPS was performed, showing also a difference in LS mean changes in BCVA score at Week 8 of -0.3 letters, with a 95% CI for the treatment difference of [-1.8, 1.3].

The FAS included 243 patients in the SOK583 group and 240 in the Eylea EU group (Table 2-3 of module 2.7.3). The results from the supplementary analyses of ANCOVA for BCVA change from baseline using LOCF imputation (-0.3 [-1.8, 1.2]) and from the MMRM model (-0.3 [-1.8, 1.1]) on the FAS were in line with those from the primary analysis and the sensitivity analysis.

According to the presented results equivalent efficacy was shown for the primary endpoint in the PPS and the FAS.

Subjects at some sites in Asia underwent BCVA testing using numerical charts instead of the standard letter charts. Albeit recognising that the majority of study participants were recruited from Europe (66%) followed by the US (18%), it was not clear in how many subjects BCVA was evaluated using the numerical charts. The extent of concordance between the numerical and the letter chart or whether this has a potential impact on the primary outcome was also unclear. In the response to the Day 120 LoQ, the applicant referred to a reasonably conducted cross-sectional study by Chaikitmongkol et al (JAMA Ophthalmol. 2018) where test-retest comparison (Pearson correlation coefficient ≥0.81) as well as the concordance (F test ≥ 0.92) between the numerical and the alphabetical charts was strong in the visually impaired subsets (BCVA 20/20-20/40 n=40, BCVA 20/50-20/100 n=40, and BCVA 20/125-20/200 n=14). Considering the reassuring comparison, within a clinical trial, small systematic

differences between letter and numerical charts would likely not have a large effect on group comparisons, as BCVA will be measured as change from baseline. Further, considering the relatively limited number of subjects that were evaluated with the numerical chart (25/485), it is considered unlikely that the use of the two charts would have impacted the BCVA outcomes to such extent that biosimilarity would be questioned. The issue is therefore considered resolved.

With regard to secondary endpoints, mean changes from baseline in CSFT using SD-OCT at Weeks 1, 4, 8, 24 and 52, in CNV lesion size at Week 8 and 52, and in BCVA score at Weeks 24 and 52 were similar between the SOK583 and Eylea EU groups for subjects in the FAS and the PPS. Of note, the reduction in CSFT was numerically greater with SOK583 than with Eylea EU for all time-points that were evaluated in both the PPS and the FAS. The improvement in BCVA from baseline was slightly but numerically larger with Eylea EU than with SOK583 from week 8 onwards. This does not pose any question about biosimilarity.

Although the outcomes based on the data provided on mean visual acuity support biosimilarity, the conduct of responder analyses, i.e., gains and losses of ≥5, ≥10 and ≥15 letters in BCVA are expected to provide additional information to support similarity. In the descriptive responder analyses of the gain/loss of BCVA at weeks 8 and 52 provided as a response to the LoQ, there was a trend of a numerical favour for Eylea in the majority of the analyses. However, the differences between treatment arms were small and regarded of no clinical significance thus not contradicting biosimilarity.

Globally, the results from the subgroup analyses were consistent with those of the primary endpoint analyses. Differences in the mean change from baseline in BCVA score at Week 8 between treatment groups in a subgroup and between subgroups in a subgroup category were small and not considered clinically relevant.

2.4.7. Conclusions on clinical efficacy

From an efficacy perspective, the clinical data indicate similarity between the proposed biosimilar Afqlir (SOK583) and the reference product Eylea EU.

2.4.8. Clinical safety

The safety of SOK583 was evaluated in study CSOK583A12301 (301), a confirmatory, multicentre, randomized, active-controlled, double-masked, 2-arm parallel study and two supportive, open-label single-arm, multicentre safety studies.

Study 301 was an efficacy, safety, and immunogenicity study in male and female subjects ≥ 50 years old, anti-VEGF treatment-naïve for both eyes, and diagnosed with active CNV secondary to AMD in the study eye. The comparator drug in Study 301 was Eylea EU.

Studies CSOK583A12303 (303) and CSOK583A12304 (304) were two supportive safety studies to demonstrate the safe use of the LIVI (study 303) or LISY (study 304) in subjects with nAMD who required and had previously received IVT treatment with Eylea. Both studies were conducted in male and female subjects ≥ 50 years old.

No pooling of safety data was performed due to differences in the study populations included in the 3 studies (i.e. subjects naive to anti-VEGF treatment in Study 301 vs. subjects pretreated with Eylea US in Studies 303 and 304) and study duration (1 year treatment in Study 301 vs. one single administration in Studies 303 and 304). Moreover, some safety parameters were differently measured between pivotal Study 301 and the 2 supportive safety studies.

In Study 301, 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, coagulation, and urinalysis. Safety assessments additionally included immunogenicity testing, and regular assessments of vital signs, physical condition, and body weight. Furthermore, a complete ophthalmic examination consisting of slit-lamp examination, IOP measurement, and fundus exam/ophthalmoscopy was performed. Development of binding and neutralising antidrug antibodies (ADAs) up to Week 52 was assessed too.

Table 26: Evaluation and visit schedule

Table 9-5 Evaluation and visit schedule

Period		**Treatment**										**Follow-up**
Visit Name	**Screening**	**Baseline**		**Treatment Period**								**Safety (EOS)**
Week				**1**	**4**	**8**		**16**	**24**	**32**	**40**	**48**	**52**
Visit number	**V1**	**V2**		**V3**	**V4**	**V5**		**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Day	**-14 to -1**	**1**	**2[5]**	**8**	**29**	**57**	**58[5]**	**113**	**169**	**225**	**281**	**337**	**365**
Visit window	**+ 7**			**± 3**	**± 3**	**± 3**		**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Obtain informed consent	X												
PK informed consent (only for 20 subjects per group)[1]	X												
Randomization		X											
Demography	X												
Inclusion/exclusion criteria	X	X											
Medical history/current medical conditions	X												
Prior/Concomitant medications	X	X	X[5]	X	X	X	X[5]	X	X	X	X	X	X
Physical examination	S												S
Vital Signs	X	X	X[5]	X	X	X	X[5]	X	X	X	X	X	X
Pregnancy serum test[2]	X[2]												X[2]
Pregnancy urine test[2]		S[2]		S[2]	S[2]	S[2]		S[2]	S[2]	S[2]	S[2]	S[2]	
FSH[3]	X[3]												
Laboratory assessments (hematology, biochemistry, urinalysis, coagulation)[4]	X[4]					X[4]			X[4]				X[4]
Blood (serum) sampling ADA (all subjects, pre-dose)		X		X	X	X		X	X		X		X

[3] Only in the absence of medical documentation to confirm the women was not of child-bearing potential in cases of surgical bilateral oophorectomy without a hysterectomy, and reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile

[4] All blood draws were to be performed prior to fluorescein administration and prior to receiving the IVT injection; urinalysis was to be done locally at site, using dipstick

[5] PK substudy subjects only; PK assessment were done in 20 subjects per group only, at selected sites. Samples were to be collected pre-dose at V2; 24 (±1) h post-dose at V2 and 24 (±1) hour post-dose at V5. The collection of blood for total drug concentration on Day 2 and Day 58 had to be done only for subjects participating in the PK study.

[6] Assessments had to be done prior to the IVT injections; BCVA had to be performed in the study eye in all visits and in both eyes at screening; at baseline, only study eye BCVA needed to be tested and documented at eCRF; in cases where both eyes were eligible per screening data, BCVA had to be performed for both eyes at baseline to select the study eye.

SD-OCT was performed in the study eye during all visits and in the fellow eye at screening only. FA and CF photography were done in the study eye at screening, Week 8 and Week 52, and in the fellow eye at screening only. Except for screening, if the fellow eye was examined in accordance with clinical practice and the investigator's discretion, the data were to be documented in the eCRF only in case of an AE. Details on study eye selection were provided in Section 9.3.1.

[7] Includes slit-lamp exam, IOP measurement, and fundus exam. Dilation for the fundus exam was at the discretion of the investigator. Ophthalmic exam was performed in both eyes at screening. All other evaluations were study eye only or also in the fellow eye at discretion of investigator.

[8] The study eye was evaluated 0-5 minutes and 30-60 minutes post-injection to ensure that the injection procedure and/or the investigational product did not endanger the health of the eye. It included an evaluation of central retinal artery perfusion via gross assessment of vision and measurement of IOP. Direct visualization to assess the central retinal artery, presence of retinal detachment, and presence of new intraocular hemorrhage(s) might have been appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement. Subjects were to be instructed to contact the investigator immediately to report symptoms as e.g. eye pain, redness of the eye, photophobia, blurring of vision.

[9] Only in subjects who agreed to the evaluation of systemic VEGF concentrations (Week 48 and 52). Plasma samples were taken from subjects receiving anti-VEGF treatment for the study eye only. Subjects receiving anti-VEGF treatment for both eyes were excluded from participation in the evaluation of systemic VEGF concentrations at Week 48 and Week 52.

[10] Plasma sample needed to be taken pre-dose.

In Studies 303 and 304, safety assessments consisted of collecting all AEs, SAEs, including their severity and relationship to study treatment or ocular injection procedure. Safety assessments also included vital signs, physical condition, and body weight. Furthermore, slit-lamp examination, IOP

measurement, and ophthalmoscopy were performed. Safety laboratory evaluations were only to be performed if required to assure subject safety.

AEs were coded using MedDRA version 24.1 (Studies 303 and 304) and version 25.1 (Study 301).

2.4.8.1. Patient exposure

Table 27: Patient exposure

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	N/A	N/A	N/A	N/A
Blinded studies (active -controlled)	485 SOK583: N=245 Eylea: N=240	484 SOK583: N=244 Eylea: N=240	484 SOK583: N=244 Eylea: N=240	52 weeks SOK583: N=215 Eylea: N=215
Open studies	66	66	66	0
Post marketing	N/A	N/A	N/A	N/A
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.

Patient disposition

Patient disposition by treatment is summarized in Section 3.3.1.4.2 *Participant flow*.

Other characteristics

For the following data refer to Section *3.3.1.4.2 Baseline data*:

- Demographics
- Baseline General and Disease Characteristics
- Medical and Surgical History
- Prior Medications and Treatments
- Concomitant Medications

Overall extent of exposure

Overall, 484 subjects randomised 1:1 (244 in the SOK583 arm and 240 in Eylea arm) received study treatment in the main study 301. 1 subject was randomised by mistake into the SOK583 group and did not receive study treatment.

Subjects diagnosed with active CNV secondary to AMD received up to 8 IVT injections of SOK583 or Eylea EU into the study eye at fixed doses of 2 mg/0.05 mL every 4 weeks at baseline, Week 4, and Week 8, and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48. Dose adjustments were not allowed.

All 484 randomised subjects who had received study treatment were included in the analysis. A total of 438 subjects of the 485 randomized subjects (90.3%) completed the study. A total of 53 randomised subjects (10.9%) discontinued treatment early for a variety of reasons. These included 18 subjects (3.7%) who decided to discontinue, 17 subjects (3.5%) who discontinued due to AEs, and 4 subjects (0.8%) who died. Patient disposition by treatment is summarised in Section 3.3.1.422 Participant flow.

The mean (SD) number of injections was 7.6 (± 1.17) injections in the SOK583 group and 7.6 (± 1.23) in the Eylea EU group; 204 subjects (83.6%) in the SOK583 group and 207subjects (86.3%) in the Eylea EU group received the maximum number of 8 injections.

In the supportive studies 303 and 304, subjects diagnosed with nAMD who required IVT treatment with Eylea received a single IVT injection of 2 mg (fixed dosing volume of 0.05 mL) SOK583. Dose adjustments were not allowed. The total study duration was 31 days, including a safety follow-up of 30 days after injection.

Each of the subjects in the FAS received a single injection of SOK583 (40 mg/mL) on Day 1. In total, 72 mg SOK583 (2 mg in 0.05 mL) were administered to 36 subjects in Study 303, and 60 mg SOK583 (2 mg in 0.05 mL) were administered to 30 subjects in Study 304.

Safety analysis sets

Study 301

The SAF included all randomised subjects who received at least 1 dose of study treatment (SOK583 or Eylea EU). Subjects were analysed according to the study treatment received.

Studies 303 and 304

The analysis set used for analyses of disposition, baseline variables, and safety data in Studies 303 and 304 was the FAS. The FAS included all enrolled subjects who received a single injection of SOK583.

2.4.8.2. Adverse events

Overview of TEAEs

Study 301

Table 12-1 summarises the frequency of subjects reporting at least 1 TEAE, SAE, or TEAE leading to discontinuation.

Table 28 Overview of TEAEs (SAF)

Category	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Number of subjects with at least 1 TEAE	179 (73.4)	174 (72.5)
TEAE suspected to be treatment-related	6 (2.5)	7 (2.9)
Ocular TEAE in the study eye suspected to be related to study procedure	28 (11.5)	26 (10.8)
Ocular TEAE in the study eye suspected to be related to study procedure and study drug	1 (0.4)	1 (0.4)
Severe TEAE suspected to be treatment-related	1 (0.4)	0 (0.0)
SAE	39 (16.0)	30 (12.5)
SAE suspected to be treatment-related	2 (0.8)	1 (0.4)
TEAE leading to study drug discontinuation	11 (4.5)	8 (3.3)
AE leading to death	4 (1.6)	1 (0.4)

Only subjects with TEAEs as per SAP are included.
Subjects with more than 1 TEAE in each category were counted only once in that category.
One subject in the SOK583 group experienced a fatal SAE. This SAE had a missing start date due to a lack of a hospital record and was not considered TEAE as per imputation rule; this SAE is therefore not included in this table and Table 14.3.1-1.
Source: Table 14.3.1-1

Table 2-1 presents **ocular TEAEs in the study eye** by primary SOCs and PTs reported by ≥ 2% of subjects in any treatment group.

Table 2-1 **Ocular TEAEs in the study eye, regardless of study treatment relationship, by primary system organ class and preferred term (at least 2% of subjects in any treatment group) (Safety set)**

Primary system organ class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Number of subjects with at least 1 event	84 (34.4)	78 (32.5)
Eye disorders	74 (30.3)	72 (30.0)
Visual acuity reduced	10 (4.1)	12 (5.0)
Retinal pigment epithelial tear	9 (3.7)	7 (2.9)
Conjunctival haemorrhage	9 (3.7)	4 (1.7)
Neovascular age-related macular degeneration	7 (2.9)	2 (0.8)
Cataract	5 (2.0)	2 (0.8)
Eye pain	5 (2.0)	3 (1.3)
Vitreous floaters	5 (2.1)	5 (2.2)
Visual impairment	2 (0.8)	6 (2.5)
Punctate keratitis	1 (0.4)	5 (2.1)
Injury, poisoning and procedural complications	6 (2.5)	1 (0.43)
Infections and infestations	4 (1.6)	5 (2.1)
Investigations	2 (0.8)	6 (2.5)

Only subjects with TEAEs as per SAP are included.

A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.
Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.
MedDRA version 26.0.
Source: 5.3.5.1-301-Table 12-2

The overall proportions of subjects with **ocular TEAEs in the fellow eye** were 22.5% in the SOK583 group compared to 21.3% in the Eylea EU group. The proportions of subjects with TEAEs at SOC and PT levels were comparable between the 2 treatment groups. At SOC level, Eye disorders (SOK583: 46 subjects, 18.9%; Eylea EU: 45 subjects, 18.8%) were most frequently reported by subjects. Most PTs were reported only once and no trends of TEAEs were observed in a treatment group or SOC. Neovascular age-related degeneration (SOK583: 18 subjects, 7.4%; Eylea EU: 23 subjects, 9.6%) was the most frequently reported PT.

The overall proportions of subjects with **non-ocular TEAEs** were 57.8% in the SOK583 group compared to 58.8% in the Eylea EU group. At SOC level, Infections and infestations (SOK583: 59 subjects, 24.2%; Eylea EU: 56 subjects, 23.3%), Investigations (SOK583: 33 subjects, 13.5%; Eylea EU: 27 subjects, 11.3%), Gastrointestinal disorders (SOK583: 25 subjects, 10.2%; Eylea EU: 14 subjects, 5.8%) and Musculoskeletal and connective tissue disorders (SOK583: 24 subjects, 9.8%; Eylea EU: 28 subjects, 11.7%) were most frequently reported by subjects. Most TEAEs under the SOC Infections and infestations comprised PTs related to respiratory tract infections (i.e. COVID-19, nasopharyngitis, sinusitis, bronchitis). None of them was related to study treatment or study procedure. Other PTs were only reported by 1 or 2 subjects in a treatment group. Most PTs were reported only once, and no trends of TEAEs were observed in a treatment group or SOC. The most frequently reported PTs were COVID-19 (SOK583: 19 subjects, 7.8%; Eylea EU: 24 subjects, 10.0%), hypertension (SOK583: 12 subjects, 4.9%; Eylea EU: 17 subjects, 7.1%), back pain (SOK583: 8 subjects, 3.3%; Eylea EU: 7 subjects, 2.9%), osteoarthritis (SOK583: 2 subjects, 0.8%; Eylea EU: 9 subjects, 3.8%), atrial fibrillation (SOK583: 8 subjects, 3.3%; Eylea EU: 2 subjects, 0.8%), and nasopharyngitis (SOK583: 7 subjects, 2.9%; Eylea EU: 5 subjects, 2.1%).

Supportive Studies 303 and 304

In Study 303, 16 subjects (44.4%) experienced at least 1 **ocular TEAE in the study eye**, namely intraocular pressure increased (15 subjects, 41.7%), conjunctival haemorrhage (1 subject, 2.8%), and vitreous floaters (1 subject, 2.8%, in addition to a TEAE of IOP increased), most of which were mild and not related to study treatment or study procedure. 1 subject (2.8%) with an ocular TEAE of IOP increased in the study eye additionally experienced a conjunctival haemorrhage in the fellow eye. No further subjects experienced ocular TEAEs in the fellow eye. One subject (2.8%) experienced a moderate TEAE of IOP increased in the study eye that was not considered related to study treatment or study procedure. All events of IOP resolved within 1 day.

In Study 304, 2 subjects (6.7%) experienced at least 1 ocular TEAE in the study eye. 1 subject experienced a TEAE of IOP increased in the study eye on Day 1, which resolved on the same day. As per the investigator, the TEAE was mild and not suspected to be related to study treatment or study procedure. Another subject experienced TEAEs of foreign body sensation in eyes and ocular discomfort on Day 2. The TEAE of foreign body sensation resolved on the same day, and the TEAE of ocular discomfort on Day 8. As per the investigator, both TEAEs were mild and not suspected to be related to study treatment or study procedure.

In Study 303, 3 subjects (8.3%) experienced **non-ocular TEAEs**, 2 (5.6%) of which occurred under the SOC Infections and infestations (1 case of COVID-19 and 1 case of cystitis). 1 subject (2.8%) experienced a TEAE of arthralgia. The TEAEs of cystitis and arthralgia were reported as SAEs and led to study discontinuation of the subjects. Another subject experienced a moderate TEAE of COVID-19 27 days after receiving study treatment. The TEAE resolved after 11 days and the subject completed the study. All non-ocular TEAEs were assessed as not related to the study treatment by the investigator.

In Study 304, 1 subject (3.3%) reported a non-ocular TEAE of hypertension on Day 8, which was not resolved at the end of study. As per the investigator, the TEAE was mild and not suspected to be related to study treatment or study procedure. The high blood pressure (138/90 mmHg at Baseline and 142/100 mmHg on Day 8) did not fulfil the criteria of clinically notable.

Adverse events related to study treatment or study procedure

Study 301

Table 2-2 presents **ocular TEAEs in the study eye by primary SOCs and PTs related to study treatment** as assessed by the investigator.

Table 2-2 Ocular TEAEs in the study eye related to study treatment, by primary system organ class and preferred term (SAF)

Primary system organ class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Number of subjects with at least 1 event	5 (2.0)	7 (2.9)
Eye disorders	5 (2.0)	7 (2.9)
Retinal pigment epithelial tear	3 (1.2)	2 (0.8)
Macular thickening	1 (0.4)	0 (0.0)
Visual impairment	1 (0.4)	2 (0.8)
Vitreoretinal traction syndrome	1 (0.4)	0 (0.0)
Age-related macular degeneration	0 (0.0)	1 (0.4)
Eye inflammation	0 (0.0)	1 (0.4)
Iritis	0 (0.0)	1 (0.4)
Macular hole	0 (0.0)	1 (0.4)
Macular oedema	0 (0.0)	1 (0.4)
Ocular hypertension	0 (0.0)	1 (0.4)
Retinal vasculitis	0 (0.0)	1 (0.4)
Vitreous floaters	0 (0.0)	1 (0.4)

Only subjects with TEAEs as per SAP are included.
A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.
Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.
MedDRA version 26.0.
Source: 5.3.5.1-301-Table 12-6

Table 2-3 presents **ocular TEAEs in the study eye by primary SOCs and PTs related to study procedure.**

Table 2-3 Ocular TEAEs in the study eye related to study procedure, by primary system organ class and preferred term (SAF)

Primary system organ class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Number of subjects with at least 1 event	28 (11.5)	26 (10.8)
Eye disorders	24 (9.8)	19 (7.9)

Primary system organ class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Conjunctival haemorrhage	7 (2.9)	3 (1.3)
Eye pain	5 (2.0)	3 (1.3)
Corneal erosion	2 (0.8)	2 (0.8)
Keratitis	2 (0.8)	0 (0.0)
Vitreous detachment	2 (0.8)	0 (0.0)
Vitreous floaters	2 (0.8)	2 (0.8)
Vitreous opacities	2 (0.8)	0 (0.0)
Conjunctival suffusion	1 (0.4)	1 (0.4)
Corneal disorder	1 (0.4)	0 (0.0)
Eye irritation	1 (0.4)	1 (0.4)
Lacrimation increased	1 (0.4)	0 (0.0)
Periorbital oedema	1 (0.4)	0 (0.0)
Photophobia	1 (0.4)	0 (0.0)
Retinal pigment epithelial tear	1 (0.4)	0 (0.0)
Conjunctival irritation	0 (0.0)	1 (0.4)
Corneal irritation	0 (0.0)	1 (0.4)
Ocular hyperaemia	0 (0.0)	1 (0.4)
Periorbital pain	0 (0.0)	1 (0.4)
Photopsia	0 (0.0)	1 (0.4)
Punctate keratitis	0 (0.0)	2 (0.8)
Retinal detachment	0 (0.0)	1 (0.4)
General disorders and administration site conditions	3 (1.2)	3 (1.3)
Sensation of foreign body	2 (0.8)	0 (0.0)
Injection site pain	1 (0.4)	3 (1.3)
Injury, poisoning and procedural complications	3 (1.2)	0 (0.0)
Intra-ocular injection complication	2 (0.8)	0 (0.0)
Injection related reaction	1 (0.4)	0 (0.0)
Post procedural complication	1 (0.4)	0 (0.0)
Investigations	1 (0.4)	5 (2.1)
Intraocular pressure increased	1 (0.4)	5 (2.1)

Infections and infestations	0 (0.0)	1 (0.4)
Conjunctivitis	0 (0.0)	1 (0.4)
Psychiatric disorders	0 (0.0)	1 (0.4)
Tension1	0 (0.0)	1 (0.4)

Only subjects with TEAEs as per SAP are included.

A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.

Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

1 The reported term was 'feeling of tension in the left eye'. MedDRA version 26.0.

Source: 5.3.5.1-301-Table 12-6

TEAEs related to study treatment and study procedure were reported for 1 subject (0.4%) in the SOK583 group (retinal pigment epithelial tear of moderate severity) and for 1 subject (0.4%) in the Eylea EU group (vitreous floaters of mild severity).

There were no **ocular TEAEs in the fellow eye related to study treatment**.

1 subject in the SOK583 group experienced a severe **non-ocular TEAE of coronary artery stenosis related to study treatment,** which was reported as an SAE and led to study treatment interruption. No study treatment-related non-ocular TEAEs were reported for subjects in the Eylea EU group.

Supportive studies 303 and 304

In Study 303, 1 subject (2.8%) experienced a **TEAE** of IOP increased 5 minutes after study treatment administration that was assessed as **related to the study treatment** by the investigator. The TEAE was mild and non-serious. The event resolved within 60 minutes and did not lead to study discontinuation.

In Study 304, no subject experienced TEAEs suspected to be treatment-related.

In Study 303, 7 subjects (19.4%) experienced mild, non-serious **TEAEs** that were suspected to be **related to the study procedure by the investigator** (6 cases of intraocular pressure increased and 1 case of conjunctival haemorrhage). The 6 TEAEs of intraocular pressure increased resolved within 1 day and the TEAE of conjunctival haemorrhage resolved after 25 days. None of the TEAEs suspected to be related to the study procedure led to study discontinuation.

In Study 304, no subject experienced TEAEs suspected to be related to the study procedure.

In Study 303, 1 subject (2.8%) experienced a **TEAE** of IOP increased 5 minutes after study treatment administration that was assessed as **related both to the study treatment and study procedure** by the investigator. The TEAE was mild and non-serious. The event resolved within 60 minutes and did not lead to study discontinuation. In Study 304, no subject experienced TEAEs suspected to be related to study treatment and study procedure.

No subject experienced **non-ocular TEAEs assessed as related to the study treatment** in studies 303 and 304.

Adverse events by severity

Study 301

Table 2-4 presents **severe ocular TEAEs in the study eye** by primary SOCs and PTs. Overall, 5 subjects reported severe ocular TEAEs in the study eye (SOK583: 2 subjects, 0.8%; Eylea EU: 3 subjects, 1.3%).

None of the severe ocular TEAEs in the study eye were related to study treatment or study procedure.

Overall, 3 subjects reported severe TEAEs in the study eye that were ongoing at study completion. One subject in the SOK583 group experienced retinal haemorrhage on Day 223, which was reported as an SAE and led to treatment discontinuation and later to study discontinuation. The subject received vitrectomy and alteplase, perflutren, acetazolamide, brimonidine, dorzolamide/timolol, lidocaine, bupivacaine, atropine, sulfur hexafluoride, dexamethasone/neomycin/polymyxin B, cefazolin, and methylprednisolone. Other TEAEs reported for the subject in the study eye were hyphaema, retinal detachment, and vitreous haemorrhage (Day 335). The subject received another vitrectomy for treatment. The other 2 ongoing severe TEAEs in the study eye (one in the SOK583 group: visual impairment; one in the Eylea EU group: nAMD) were non-serious, no action was taken with study treatment, and no medication was given.

Of the remaining severe TEAEs in the study eye, one subject in the Eylea EU group reported visual acuity reduced together with moderate TEAEs of peripapillary subretinal haemorrhage and subretinal fluid, which led to treatment and study discontinuation. The subject was treated with aflibercept (Eylea) afterwards.

The other 2 severe TEAEs in the study eye were non-serious, resolved, no action was taken with study treatment, and no medication was given.

Table 2-4.- Severe ocular TEAEs in the study eye regardless of relationship to study treatment or study procedure, by primary system organ class and preferred term (SAF)

Primary system organ class **Preferred term** **Severity**	**SOK583** **N=244** **n (%)**	**Eylea EU** **N=240** **n (%)**
Number of subjects with at least 1 event	84 (34.4)	78 (32.5)
Mild	59 (24.2)	49 (20.4)
Moderate	23 (9.4)	26 (10.8)
Severe	2 (0.8)	3 (1.3)
Severe TEAEs		
Eye disorders	2 (0.8)	3 (1.3)
Retinal detachment	1 (0.4)	0 (0.0)
Retinal haemorrhage	1 (0.4)	0 (0.0)
Visual impairment	1 (0.4)	0 (0.0)
Vitreous haemorrhage	1 (0.4)	0 (0.0)
Age-related macular degeneration	0 (0.0)	1 (0.4)

Neovascular age-related macular degeneration	0 (0.0)	1 (0.4)
Visual acuity reduced	0 (0.0)	2 (0.8)
Injury, poisoning and procedural complications	1 (0.4)	0 (0.0)
Hyphaema	1 (0.4)	0 (0.0)

Only subjects with TEAEs as per SAP are included

A subject with multiple severity grades for an TEAE is only counted under the maximum grade. Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

MedDRA version 26.0.

No subject in the SOK583 group reported **severe ocular TEAEs in the fellow eye**. 1 subject (0.4%) in the Eylea EU group reported a severe ocular TEAE of retinal haemorrhage in the fellow eye.

Table 2-5 presents **severe non-ocular TEAEs** by primary SOCs and PTs. Overall, 34 subjects reported severe non-ocular TEAEs (SOK583: 18 subjects, 7.4%; Eylea EU: 16 subjects, 6.7%).

Six subjects had severe TEAEs with fatal outcome (SOK583: 5 subjects; Eylea EU: 1 subject), and 11 subjects had severe TEAEs that were ongoing at study completion (SOK583: 5 subjects; Eylea EU: 6 subjects). 28 subjects (SOK583: 14 subjects; Eylea EU: 14 subjects) received treatment for their severe non-ocular TEAEs. None of the severe non-ocular TEAEs but 1 SAE of coronary artery stenosis (see below "Serious Adverse Events") were related to study treatment or study procedure.

For 1 subject in the SOK583 group, 6 severe non-ocular TEAEs were reported (spondylolisthesis, myocardial infarction, atrial fibrillation, coronary artery disease, coronary artery occlusion, dyspnoea), 5 of which were reported as SAEs (myocardial infarction, atrial fibrillation, coronary artery disease, coronary artery occlusion, dyspnoea). These events were not related to study drug or study procedure and did not lead to study discontinuation. All events resolved except for the spondylolisthesis and coronary artery disease.

9 severe non-ocular TEAEs led to study discontinuation.

Overall, 3 subjects experienced severe non-ocular TEAEs that led to interruption of study treatment (SOK583: one subject had a SAE of cerebral infarction; another subject had a SAE of coronary artery stenosis, related to study treatment; Eylea EU: one subject had a SAE of pneumonia). The 3 subjects received medication, and the events resolved.

Table 2-5 Severe non-ocular TEAEs, regardless of relationship to study treatment, by primary system organ class and preferred term (SAF)

Primary system organ class Preferred term Severity	**SOK583 N=244 n (%)**	**Eylea EU N=240 n (%)**
Number of subjects with at least 1 event	141 (57.8)	141 (58.8)
Mild	61 (25.0)	70 (29.2)
Moderate	62 (25.4)	55 (22.9)

Severe	18 (7.4)	16 (6.7)

Severe TEAEs		
Cardiac disorders	3 (1.2)	4 (1.7)
Atrial fibrillation	1 (0.4)	2 (0.8)
Cardiac failure congestive	1 (0.4)	0 (0.0)
Coronary artery disease	1 (0.4)	0 (0.0)
Coronary artery stenosis	1 (0.4)	0 (0.0)
Coronary artery occlusion	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.4)	0 (0.0)
Arrhythmia	0 (0.0)	1 (0.4)
Atrial tachycardia	0 (0.0)	1 (0.4)
Cardiac arrest	0 (0.0)	1 (0.4)
Sinus node dysfunction	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	3 (1.2)	2 (0.8)
Atelectasis	1 (0.4)	0 (0.0)
Dyspnoea	1 (0.4)	0 (0.0)
Pleurisy	1 (0.4)	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)	1 (0.4)
Pulmonary embolism	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	3 (1.2)	1 (0.4)
Osteoarthritis	2 (0.8)	1 (0.4)
Spondylolisthesis	1 (0.4)	0 (0.0)
General disorders and administration site conditions	3 (1.2)	0 (0.0)
Death	3 (1.2)	0 (0.0)
Nervous system disorders	3 (1.2)	0 (0.0)
Cerebral infarction	2 (0.8)	0 (0.0)
Syncope	1 (0.4)	0 (0.0)
Gastrointestinal disorders	3 (1.2)	0 (0.0)
Large intestinal obstruction	1 (0.4)	0 (0.0)
Oesophageal varices haemorrhage	1 (0.4)	0 (0.0)
Umbilical hernia	1 (0.4)	0 (0.0)
Infections and infestations	2 (0.8)	4 (1.7)

Parotitis	1 (0.4)	0 (0.0)
Urinary tract infection	1 (0.4)	0 (0.0)
COVID-19	0 (0.0)	1 (0.4)
Pneumonia	0 (0.0)	3 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.8)	3 (1.3)
Adenocarcinoma of colon	1 (0.4)	0 (0.0)
Lung neoplasm	1 (0.4)	0 (0.0)
Breast cancer	0 (0.0)	1 (0.4)
Hepatic cancer	0 (0.0)	1 (0.4)
Renal cancer stage IV	0 (0.0)	1 (0.4)
Injury, poisoning and procedural complications	2 (0.8)	1 (0.4)
Femur fracture	1 (0.4)	0 (0.0)
Patella fracture	1 (0.4)	0 (0.0)
Tendon injury	0 (0.0)	1 (0.4)

Metabolism and nutrition disorders	1 (0.4)	1 (0.4)
Dehydration	1 (0.4)	0 (0.0)
Malnutrition	0 (0.0)	1 (0.4)
Hepatobiliary disorders	1 (0.4)	1 (0.4)
Cholecystitis	1 (0.4)	0 (0.0)
Bile duct stone	0 (0.0)	1 (0.4)
Biliary obstruction	0 (0.0)	1 (0.4)
Blood and lymphatic system disorders	1 (0.4)	0 (0.0)
Anaemia	1 (0.4)	0 (0.0)
Immune system disorders	0 (0.0)	1 (0.4)
Sarcoidosis	0 (0.0)	1 (0.4)
Vascular disorders	0 (0.0)	1 (0.4)
Aortic aneurysm	0 (0.0)	1 (0.4)

Only subjects with TEAEs as per SAP are included.

A subject with multiple severity grades for an TEAE is only counted under the maximum grade. Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

Note: One subject in the SOK583 group experienced a severe and fatal AE of cerebrovascular accident (verbatim: stroke) not related to study treatment or study procedure that had a missing start date due to a lack of a hospital record and was not considered a TEAE as per imputation rule; this AE is therefore not included in Table 14.3.1-3.3

Supportive studies 303 and 304

In Study 303, 1 subject (2.8%) experienced a **moderate ocular TEAE** of IOP increased while no subject experienced **severe ocular TEAEs**.

In Study 304, there were no **moderate or severe non-ocular TEAEs** reported during the study.

2.4.8.3. Serious adverse events, deaths, and other significant events

Six subjects died during study 301, 5 subjects (2.0%) in the SOK583 group and 1 subject (0.4%) in the Eylea EU group. None of the deaths was considered related to study treatment or study procedure by the investigator. No deaths occurred during the supportive studies 303 and 304.

Serious adverse events

Study 301

Table 7 presents ocular and non-ocular SAEs by primary SOCs and PTs.

4 subjects reported SAEs related to study treatment or study procedure as per the investigator's judgement:

- 1 subject in the SOK583 group experienced a SAE of mild vitreoretinal traction syndrome on Day 78, which was considered related to study treatment as per investigator judgement. The event resolved after 7 days. The event led to emergency unmasking and study discontinuation of the subject. The event vitreoretinal traction syndrome was reported as a SUSAR.

  1 subject in the SOK583 group with a medical history of hypertension and myocardial infarction experienced a not related SAE of moderate atrial fibrillation on Day 200 and a study treatment-related SAE of severe coronary artery stenosis as per investigator judgement on Day 203. The event coronary artery stenosis was reported as a SUSAR. Study treatment was interrupted due to the coronary artery stenosis. Both events resolved after 160 and 157 days, respectively. Study treatment was resumed on Day 344 (Week 48).
  The event coronary artery stenosis was confounded by the presence of potential risk factors such as the current conditions of hypertension, post-myocardial infarct, hyperlipidaemia, and historical condition of myocardial infarction in this elderly subject. The Sponsor assessed the event as likely related (suspected) since the causal role of study treatment could not be completely denied. Therefore, an investigator notification was issued.

- 1 subject in the Eylea EU group experienced a study procedure-related SAE of moderate retinal detachment on Day 248, which resolved after 3 days.

- 1 subject in the Eylea EU group experienced a study treatment-related SAE of moderate visual impairment on Day 340, which had not resolved at the end of the study.

Table 7

Ocular and non-ocular SAEs, regardless of relationship to study treatment or study procedure, by primary system organ class and preferred term (SAF)

Primary system organ class Preferred term	SOK583 N=244 n (%)	Eylea EU N=240 n (%)
Ocular SAEs in the study eye		
Number of subjects with at least 1 event	4 (1.6)	2 (0.8)
Eye disorders	3 (1.2)	2 (0.8)
Retinal haemorrhage	2 (0.8)	0 (0.0)
Vitreoretinal traction syndrome	1 (0.4)	0 (0.0)
Retinal detachment	0 (0.0)	1 (0.4)
Visual impairment	0 (0.0)	1 (0.4)
Infections and infestations	1 (0.4)	0 (0.0)
Ophthalmic herpes zoster	1 (0.4)	0 (0.0)
Ocular SAEs in the fellow eye		
Number of subjects with at least 1 event	0 (0.0)	2 (0.8)
Eye disorders	0 (0.0)	2 (0.8)
Retinal haemorrhage	0 (0.0)	1 (0.4)
Visual acuity reduced	0 (0.0)	1 (0.4)
Non-ocular SAEs (at least 0.8% of subjects in any treatment group) [1]		
Number of subjects with at least 1 event	35 (14.2)	27 (11.3)
Cardiac disorders	8 (3.3)	7 (2.9)
Atrial fibrillation	4 (1.6)	2 (0.8)
Coronary artery stenosis	2 (0.8)	0 (0.0)
Nervous system disorders	6 (2.5)	1 (0.4)
Cerebral infarction	2 (0.8)	0 (0.0)
Injury, poisoning and procedural complications	5 (2.0)	1 (0.4)
Femur fracture	2 (0.8)	0 (0.0)
Gastrointestinal disorders	5 (2.0)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	4 (1.6)	4 (1.7)
Dyspnoea	1 (0.4)	2 (0.8)
General disorders and administration site conditions	3 (1.2)	1 (0.4)
Death	3 (1.2)	0 (0.0)
Infections and infestations	3 (1.2)	4 (1.7)
Bronchitis	0 (0.0)	2 (0.8)
Pneumonia	0 (0.0)	2 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.2)	5 (2.1)
Musculoskeletal and connective tissue disorders	2 (0.8)	2 (0.8)
Vascular disorders	2 (0.8)	2 (0.8)

Only subjects with TEAEs as per SAP are included.
A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.
Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

[1] One subject in the SOK583 group experienced a non-ocular SAE (cerebrovascular accident; verbatim: stroke). This SAE had a missing start date due to a lack of a hospital record and was not considered a TEAE as per imputation rule; it is therefore not included in this table. MedDRA version 26.0.

Supportive studies 303 and 304

No ocular SAEs were reported in these studies. Two (5.6%) subjects experienced non-ocular SAEs in Study 303. 1 subject experienced a severe SAE of arthralgia that was resolving when the subject discontinued the study. The SAE was assessed as not related to the study treatment or study procedure by the investigator.

1 subject experienced a mild event of cystitis that led to hospitalisation. The SAE resolved and the subject discontinued the study due to this SAE. The SAE was assessed as not related to the study treatment by the investigator.

Non-ocular SAEs were not reported in Study 304

Adverse events according to the risks listed in the Eylea EU RMP

Study 301

At the time of the final CSR, the following important risks were listed for Eylea in the EU RMP: the important identified risks of endophthalmitis (likely infectious origin), intraocular inflammation, transient intraocular pressure increase, retinal pigment epithelial tears, and cataract (especially of traumatic origin); the important potential risks of medication errors, off-label use and misuse, and embryo-fetotoxicity (Bayer EMA 2023). All the above has been reflected accordingly in Afqlir RMP.Ocular TEAEs in the study eye were reported by 11 subjects (4.5%) in the SOK583 group and 14 subjects (5.8%) in the Eylea EU group. Retinal pigment epithelial tears and IOP increased were the most frequently reported events. Other TEAEs were reported only once, all in the Eylea EU group. None of the events of IOP increased was related to study treatment. For 1 subject (0.4%) in the SOK583 group and 5 subjects (2.1%) in the Eylea EU group, TEAEs of IOP increased were reported to be related to study procedure (Table 9).

Ocular TEAEs for the fellow eye (retinal pigment epithelial tear and IOP increased) were reported for 2 subjects (0.8%) in the SOK583 and for 3 subjects (1.3%) in the Eylea EU group. These events were not related to study treatment.

For one subject in the SOK583 group (0.4%), a serious, not related, non-ocular TEAE of device malfunction was reported in the SOC Product issues. This, however, was an event of breast prosthesis impairment (verbatim) and is therefore not considered an event of medication error as listed in the Eylea EU RMP.

Table 9	Ocular TEAEs in the study eyer according to the risks listed in Eylea EU RMP, by primary system organ class and preferred term (SAF)			
		Regardless of relationship to study drug or study procedure		Related to study treatment	
Primary system organ class **Preferred term**		**SOK583 N=244 n (%)**	**Eylea EU N=240 n (%)**	**SOK583 N=244 n (%)**	**Eylea EU N=240 n (%)**
Number of subjects with at least 1 event		11 (4.5)	14 (5.8)	3 (1.2)	4 (1.7)
Eye disorders		9 (3.7)	9 (3.8)	3 (1.2)	4 (1.7)
Retinal pigment epithelial tear		9 (3.7)	7 (2.9)	3 (1.2)	2 (0.8)
Eye inflammation		0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Iritis		0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Ocular hypertension		0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Retinal vasculitis		0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Investigations		2 (0.8)	6 (2.5)	0 (0.0)	0 (0.0)
Intraocular pressure increased		2 (0.8)	6 (2.5)	0 (0.0)	0 (0.0)

Only subjects with TEAEs as per SAP are included.
A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.
Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

MedDRA version 26.0.

Supportive studies 303 and 304

TEAEs of IOP increased were collected as defined in the study protocol (i.e. IOP $\geqslant$ 26 mmHg should be reported as AE and any clinically significant changes by the discretion of the Investigator should be also reported as AEs.). In study 303, 15 subjects (41.7%) experienced TEAEs of IOP increased (Table 12-3). All of them occurred within 10 minutes after study treatment administration and resolved within 65 minutes. None of them were serious or severe. 2 subjects (5.6%) experienced TEAEs that were assessed as related to study treatment by the investigator.

In study 304, one subject (3.3%) experienced a TEAE according to a risk listed in the Eylea RMP (IOP increased), which was not suspected to be treatment-related or study procedure-related.

Table 12-3 Subjects with TEAEs of intraocular pressure (increase of ≥10 mmHg from pre-injection and/or measurement of ≥26 mmHg)

Subject identifier	Intraocular pressure (mmHg)		
	Pre-injection	5 minutes post-injection	60 minutes post-injection
[redacted]	21	35	17
[redacted]	14	28	14
[redacted]	14	26	15
[redacted]	13	28	16
[redacted]	18	34	16
[redacted]	20	37	18
[redacted]	14	30	15
[redacted]	10	32	16
[redacted]	16	32	20
[redacted]	13	34	18
[redacted]	14	27	18
[redacted]	15	26	14
[redacted]	14	31	19
[redacted]	21	35	17
[redacted]	20	27	19

Source: Listing 16.2.7-1.2 and [Listing 16.2.9-2]

ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

The following description of selected adverse reactions is proposed for the SmPC:

In the wet AMD phase III studies, there was an increased incidence of conjunctival haemorrhage in patients receiving anti-thrombotic agents. This increased incidence was comparable between patients treated with ranibizumab and aflibercept.

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.

A low incidence rate of arterial thromboembolic events was observed in the aflibercept clinical trials in patients with AMD, DME, RVO and myopic CNV and ROP. Across indications no notable difference between the groups treated with aflibercept and the respective comparator groups were observed.

As with all therapeutic proteins, there is a potential for immunogenicity with Afqlir.

2.4.8.4. Laboratory findings

Clinical laboratory evaluations

Study 301

Laboratory assessments (haematology, biochemistry, urinalysis, coagulation) were scheduled at Screening, Week 8, Week 24 and Week 52. Shift tables related to clinically notable laboratory ranges that compared the baseline result (number and percentage of subjects with low, normal, and high values based on prespecified normal laboratory reference ranges) with the change in category at any

post-baseline assessment were constructed for haematology, clinical chemistry, and coagulation parameters (CSR Table 14.3-1.1, not shown in this report).

No clinically relevant differences between the 2 treatment groups were observed for any of the laboratory parameters in study 301.

Clinical laboratory parameters were consistent with the subject population under study.

The proportions of subjects reporting any individual TEAE related to abnormal laboratory parameters in the 2 treatment groups were comparable and did not exceed 2.5%.

No SAE related to abnormal laboratory parameters was reported for the study 301.

Supportive studies 303 and 304

Clinical laboratory evaluations were not performed in studies 303 and 304. No TEAEs related to abnormal laboratory findings were observed in these studies.

Vital signs

Systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature were measured in all studies.

Study 301

Vital sign measurements were scheduled for Screening, Baseline, Week 1, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, Week 48 and Week 52. A summary table presenting vital signs results by visit and changes from baseline has been provided (CSR Table 14.3-1.2, not shown in this report). Individual vital signs results are provided in Listing 16.2.9-1 (CSR, not shown in this report).

There were no clinically relevant differences between the SOK583 and Eylea EU groups in the vital sign parameters at any visit or in changes from baseline in vital sign parameters.

The proportions of subjects reporting any individual TEAE related to vital signs in the 2 treatment groups were comparable and did not exceed 2.1%.

One SAE related to vital signs was reported. 1 subjectin the SOK583 group experienced blood pressure increased that was reported as an SAE on Day 91. A medical history of hypertension was reported for the subject. The event was not considered related to study treatment or study procedure. The event resolved after 7 days.

Supportive studies 303 and 304

In both studies, vital sign measurements were performed at baseline and in the two follow up visits (day 8 and Day 31).

In Study 303, 2 subjects (5.6%) had vital sign measurements that fulfilled at least 1 of the clinically notable criteria. 1 subject (2.8%) with no medical history of hypertension or use of anti-hypertensive medication had high systolic blood pressure meeting the criteria of clinically notable on Day 29. Another subject with a medical history of hypertension and use of anti-hypertensive medication at study start had low diastolic blood pressure meeting the criteria of clinically notable on Day 29.

In Study 304, 2 subjects (6.7%) with a medical history of hypertension and use of anti-hypertensive medication at study start had 1 measurement of high diastolic blood pressure meeting the criteria of clinically notable (1 subject on Day 8 and another on Day 31). For 1 subject, a TEAE of hypertension was reported. The high blood pressure reported as a TEAE did however not fulfil the criteria of clinically notable.

Intraocular pressure

Post-injection changes in IOP compared to pre-injection were assessed in all studies.

Study 301

IOP was measured before each IVT injection and between 30 to 60 minutes after each injection. IOP measurements 0 to 5 minutes after the IVT injections were left to the discretion of the investigator.

A summary table with IOP results obtained at post-injection by visit and changes from baseline is presented in the CSR (Table 14.3-1.3, not shown in this report). Individual IOP results of subjects are provided in Listing 16.2.9-3 (not shown in this report).

Mean post-injection IOP remained below 17.5 mmHg in both groups at all visits. 11 subjects (4.9%) in the SOK583 group and 5 subjects (2.1%) in the Eylea EU group experienced post injection IOP ≥ 25 mmHg, of which 1 in the SOK583 group and 4 in the Eylea EU group were considered clinically relevant by the investigator and reported as TEAEs. 3 subjects (1.2%) in the SOK583 group and 2 subjects in the Eylea EU group (0.8%) experienced changes ≥10 mmHg from baseline and had post-injection IOP values >25 mmHg. In the SOK583 group, these values were observed within 4 minutes post-injection and were thus to be expected (Sharei et al 2010). In the Eylea EU group, these values were observed after 30 minutes post-injection. None of these measurements were considered clinically relevant by the investigator.

29 subjects (11.9%) in the SOK583 group and 12 subjects (5.0%) in the Eylea EU group experienced IOP increases ≥ 10 mmHg compared to baseline values, most of which (SOK583: 23 subjects; Eylea EU: 11 subjects) comprised post-injection IOP values < 25 mmHg and were therefore not considered clinically relevant.

2 patients (0.8%) in the SOK583 arm and 6 patients in the Eylea EU arm (2.5%) reported at least one TEAE of IOP increased.

Supportive studies 3034 and 304

In studies 303 and 304, IOP was measured before the IVT injection, between 0 to 5 minutes, and within 60 minutes after the injection. IOP was also measured on Day 8 and Day 31.

In Study 303, increases in IOP were reported in 22 subjects (61.1%). An increase of ≥ 10 mmHg in IOP was reported in 21 subjects (58.3%). 15 subjects (41.6%) had an IOP ≥ 26 mmHg. TEAEs of intraocular pressure increased were reported for 15 subjects. IOP returned to normal values within 60 minutes after injection for all subjects.

In Study 304, increases in IOP were reported in 7 subjects (23.3%). In 6 (20.0%) out of these 7 subjects, an increase of ≥ 10 mmHg in IOP as compared to pre-injection was reported. In another subject, IOP was 30 mmHg (measurement of ≥26 mmHg) and was reported as a TEAE of IOP increased. In all 7 subjects, the high IOP measured 5 minutes post-injection decreased to normal at 60 minutes post-injection.

2.4.8.5. Immunological events

See *Immunogenicity* in section 3.3.1.2.

2.4.8.6. Discontinuation due to adverse events

Study 301

Ocular TEAEs in the study eye leading to study discontinuation were reported for 4 subjects (1.6%) in the SOK583 group and 2 subjects (0.8%) in the Eylea EU group, and non-ocular TEAEs leading to study discontinuation for 4 subjects (1.6%) and 3 subjects (1.3%), respectively. Ocular TEAEs in the fellow eye leading to study discontinuation were not reported (Table 8)

Table 8	**Ocular and non-ocular TEAEs, regardless of relationship to study treatment or study procedure, leading to study discontinuation, by primary system organ class and preferred term (SAF)**	
Primary system organ class **Preferred term**	**SOK583** **N=244** **n (%)**	**Eylea EU** **N=240** **n (%)**
Ocular TEAEs in the study eye		
Number of subjects with at least 1 event	4 (1.6)	2 (0.8)
Eye disorders	4 (1.6)	2 (0.8)
Macular oedema	1 (0.4)	0 (0.0)
Neovascular age-related macular degeneration	1 (0.4)	0 (0.0)
Retinal haemorrhage	1 (0.4)	1 (0.4)
Vitreoretinal traction syndrome	1 (0.4)	0 (0.0)
Retinal vasculitis	0 (0.0)	1 (0.4)
Subretinal fluid	0 (0.0)	1 (0.4)
Ocular TEAEs in the fellow eye		
Number of subjects with at least 1 event	0 (0.0)	0 (0.0)
Non-ocular TEAEs		
Number of subjects with at least 1 event	4 (1.6)	3 (1.3)
General disorders and administration site conditions	3 (1.2)	0 (0.0)
Death	3 (1.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	2 (0.8)
Lung neoplasm	1 (0.4)	0 (0.0)
Breast cancer	0 (0.0)	1 (0.4)

Renal cancer stage IV	0 (0.0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	1 (0.4)	0 (0.0)
Pleurisy	1 (0.4)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (0.4)
Cardiac arrest	0 (0.0)	1 (0.4)

Only subjects with TEAEs as per SAP are included.
A subject with multiple occurrences of an event within the same primary system organ class or preferred term is counted only once.
Primary system organ classes and preferred terms are sorted in descending frequency, as reported in the 'SOK583' column.

MedDRA version 26.0.

2 subjects experienced TEAEs that led to emergency unmasking and study discontinuation:

• 1 subject in the SOK583 group experienced vitreoretinal traction syndrome in the study eye on Day 78. The event was reported as a SAE and was mild in severity and related to study treatment as per the investigator. It resolved after 7 days without medication given. The event vitreoretinal traction syndrome was reported as a SUSAR.

• 1 subject in the Eylea EU group experienced mild retinal vasculitis in the study eye on Day 7 that led to withdrawal of study treatment and study discontinuation. The subject additionally experienced mild ocular hypertension on the same day that led to discontinuation of study treatment. Both events were related to study treatment and resolved after 56 days.

11 subjects (4.5%) in the SOK583 group and 8 subjects (3.3%) in the Eylea EU group reported TEAEs leading to discontinuation of study treatment. These numbers include 7 subjects in the SOK583 group and 4 subjects in the Eylea EU group who reported TEAEs leading to both study discontinuation and discontinuation of study treatment, who are listed in Table 8. 4 subjects in the SOK583 group and 4 subjects in the Eylea EU group experienced TEAEs that led to discontinuation of study treatment but not to study discontinuation.

Supportive Studies 303 and 304

In Study 303, 2 subjects (5.6%) discontinued from the study due to TEAEs (1 case of arthralgia and 1 case of cystitis). Both TEAEs were categorised as SAEs and were considered as not related to the study treatment by the investigator.

There were no TEAEs leading to study discontinuation in Study 304.

2.4.8.7. Post marketing experience

Not applicable.

2.4.9. Discussion on clinical safety

The clinical safety assessment of SOK583 is based on one Phase III study (CSOK583A12301, study -301) in adult treatment-naïve patients with active CNV secondary to AMD and two supportive Phase IIIb studies (CSOK583A12303 and CSOK583A12304) in patients with nAMD who required and had previously received IVT treatment with Eylea. Safety data was not pooled due to differences in the

study populations included in the three studies (study 301 was a randomised, double-masked, parallel 2-arm study while studies 303 and 304 were open-label single arm studies) and study duration (1 year treatment in Study 301 vs. one single administration in Studies 303 and 304), which is acceptable for a biosimilar application. Moreover, some safety parameters were differently measured between pivotal Study 301 and the 2 supportive safety studies.

In the following assessment, safety data from study 301 will be used as the main clinical safety database, as it stems from a double-masked, controlled, randomised trial. The two Phase IIIb studies will be used as supportive safety database and will be included where considered appropriate.

Study 301 was planned as a 52-week study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea EU, administered IVT, in patients with nAMD. Vital signs, ophthalmologic examinations and AEs were assessed at every visit of the study, and laboratory tests, physical examination and immunogenicity were assessed less frequently, but throughout the study duration of 52 weeks, which is considered appropriate.

The initial CSR provided by the applicant (week 40 analysis) described the results of the planned interim analysis after all randomised subjects completed Week 40 or discontinued prior to Week 40. As agreed in a scientific advice with EMA (EMA/CHMP/SAWP/233863/2018), the applicant provided Week 52 final analysis with responses to Day 120 LoQ. Overall, the updated safety information presented in the final CSR of study 301 is consistent with the information presented in the Week 40 CSR.

A total of 310 nAMD patients (244 in study 301, 36 in study 303 and 30 in study 304) have received at least one dose of SOK583. In study 301, the mean number of injections were 7.6 in both the SOK583 group and 7.6 the Eylea EU group. Therefore, no relevant differences in the exposure to study treatment between the two treatment groups were observed.

In study 301, in total, 215 patients (88.1%) in the SOK583 group [compared to 215 (89.6%) in the Eylea group] completed the Week 48 visit, which is reasonable for a biosimilar candidate.

The total safety database is considered sufficient to assess the comparability of common (≥1/100 to <1/10) and very common (≥1/10) adverse events. However, as expected, it is too small to inform on less frequently occurring adverse events. This approach is considered adequate for biosimilar development.

A total of 47 subjects (9.7%) discontinued the study prematurely, including 25 patients (10.2%) in the SOK583 group and 22 (9.2%) in the Eylea EU group. These included 19 subjects (3.9%) [8 (3.3%) in the SOK583 group and 11 (4.6%) in the Eylea EU group] who decided to discontinue, 7 subjects (1.4%) [4 (1.6%) in the SOK583 group and 3 (1.3%) in the Eylea EU group] who discontinued due to AEs, and 6 subjects (1.2%) [5 (2.0%) in the SOK583 group and 1 (0.4%) in the Eylea EU group] who died.

In study 303, 36 subjects were screened and enrolled into the study. 2 subjects (5.6%) discontinued the study due to SAEs, and 34 subjects (94.4%) completed the study. In study 304, 30 subjects were screened and enrolled into the study. All 30 subjects completed the study. No subject discontinued the study.

The excipients in the formulation of SOK583A1 are different from that of the Eylea formulation. To ensure the safety of subjects and a reliable PK, efficacy, and immunogenicity assessment, subjects were excluded in case of history of hypersensitivity to any of the study treatments or its excipients, or clinically relevant sensitivity to fluorescein dye, as assessed by the Investigator, which is considered appropriate.

In the pivotal study, the overall incidence of TEAE was comparable between the study arms (SOK583: 73.4%; Eylea EU: 72.5%).

Overall, a slightly higher proportion of patients reported ocular TEAEs in the study eye in the SOK583 arm compared to the Eylea EU arm (84 subjects, 34.4%, vs. 78 subjects, 32.5%). The most frequently reported ocular TEAEs in the study eye were visual acuity reduced (SOK583: 4.1%; Eylea EU: 5.0%), retinal pigment epithelial tear (SOK583: 3.7%; Eylea EU: 2.9%) and conjunctival haemorrhage (SOK583: 3.7%; Eylea EU: 1.7%). The eye disorder conjunctival haemorrhage and eye pain were reported more frequently in the SOK583 arm, while others were more frequently observed in the Eylea arm. Most of those TEAEs are known undesirable effects of Eylea (SmPC), except periorbital oedema, sensation of foreign body and injection related reaction, which occurred in the SOK583 treatment arm. With the Day 120 LoQ, the applicant has provided more details on the occurrence of periorbital oedema after SOK583 treatment. The event was of moderate severity and appeared on the day of the 6th treatment administration of SOK583. The event resolved the following day without any additional treatment and did not lead to discontinuation of treatment or study. The event was suspected to be associated with the injection procedure and although this has apparently not been reported previously, it seems a plausible and at least not unlikely explanation. No further action is deemed necessary.

The overall proportions of subjects with ocular TEAEs in the fellow eye were comparable between the SOK583 and Eylea EU groups (22.5% vs. 21.3%, respectively). The frequency of TEAEs in the SOC Eye disorders was similar in both arms (18.9% in the SOK583 group vs. 18.8% in the Eylea EU arm). Neovascular age-related degeneration (SOK583: 7.4%; Eylea EU: 9.6%) was the most frequently reported TEAE in the fellow eye in both treatment groups.

The overall proportions of subjects with non-ocular TEAEs were similar between the SOK583 and Eylea EU groups (141 subjects, 57.8%, vs. 141 subjects, 58.8%). The most frequently reported non-ocular TEAEs were COVID-19 (SOK583: 7.8%; Eylea EU: 10.0%), hypertension (SOK583: 4.9%; Eylea EU: 7.1%), back pain (SOK583: 3.3%; Eylea EU: 2.9%), osteoarthritis (SOK583: 0.8%; Eylea EU: 3.8%), atrial fibrillation (SOK583: 3.3%; Eylea EU: 0.8%), and nasopharyngitis (SOK583: 2.9%; Eylea EU: 2.1%). Some imbalances between treatment groups were noted in the frequency of atrial fibrillation and arterial thromboembolic events (including the PTs cerebral infarction, cerebrovascular accident, ischaemic stroke, transient ischaemic attack, acute myocardial infarction, myocardial infarction and myocardial ischaemia). However, these differences are not considered clinically meaningful, since most of the subjects in both treatment groups had prior or active vascular or cardiovascular comorbidities, which is consistent with the age of the study population (mean: 75.7 years) and the frequency of these events is in line with what was reported in other intravitreal aflibercept studies or the reported prevalence in patients in that age range.

The severity of ocular TEAEs in the study eye and non-ocular TEAEs was comparable between treatment arms. The majority of them were mild or moderate (SOK583: 33.6% and 50.4%; Eylea EU: 31.2% and 52.1%, respectively). Severe ocular TEAEs in the study eye were reported slightly more frequently in the Eylea group (3 patients, 1.3%) compared to the SOK583 group (2 patients, 0.8%), whereas severe non-ocular TEAEs were reported slightly more frequently in the SOK583 group (SOK583: 18 subjects, 7.4%; Eylea EU: 16 subjects, 6.7%). Most PTs were reported only once, and no trends of TEAEs were observed in a treatment group. No life-threatening ocular TEAEs were reported. Nevertheless, the applicant was asked to provide information on the duration of severe TEAEs, whether these required treatment and whether these resolved and no concerns arose with regard to severe TEAEs.

Ocular TEAEs in the study eye considered related to study treatment were slightly less frequently reported in the SOK583 group than in the Eylea EU group (2.0% and 2.9%, respectively). All of them were reported in the SOC Eye disorders with most PTs reported only once, and no trends of TEAEs in a treatment group were observed. On the other hand, ocular TEAEs in the study eye considered related to the study procedure were slightly more frequently reported in the SOK583 group than in the Eylea EU group (11.5% and 10.8%, respectively), with no notable differences between the treatment arms in

the frequencies at SOC and PT levels. Ocular TEAEs in the study eye related to study treatment and study procedure were reported for one subject (0.4%) in the SOK583 group (retinal pigment epithelial tear of moderate severity) and for one subject (0.4%) in the Eylea EU group (vitreous floaters of mild severity). Overall, there were no clinically relevant differences between the 2 treatment groups regarding ocular TEAEs in the study eye related to study treatment and/or study procedure. With regard to non-ocular TEAEs, one subject in the SOK583 group experienced a severe non-ocular TEAE of coronary artery stenosis related to study treatment, which was reported as a SAE and led to study treatment interruption; no study treatment-related TEAEs were reported for subjects in the Eylea EU group.

In the supportive studies the most frequent ocular TEAE in the study eye was IOP increased. In study 303, the proportion of patients who experienced TEAEs of IOP increased (41.7%) was significantly higher than in study 301 (0.8% in the SOK583 group and 2.5% in the Eylea EU group) and study 304 (3.3%). It should be noted that study 301 protocol (8.4.5 Post-injection assessment) stated that any clinically relevant abnormalities in post-injection IOP should be recorded as an AE (see also further below), whereas in studies 303 and 304, the protocol stated that IOP $\geq$ 26 mmHg should be reported as AE and any clinically significant changes by discretion of the Investigator should be also reported as AEs. However, the incidence of IOP increases is only higher in study 303, where aflibercept was administered using vials, while the incidence in study 304, which used pre-filled syringes, is in line with what was observed in study 301. The applicant could not provide a justification for these findings but this issue was not further pursued since study 303 was a supportive study**.**

Of note, a DHPC was released in April 2021 in relation to the reported cluster of IOP increase when using the Eylea pre-filled syringe, compared with administration with Luer-lock syringe of Eylea in vials. Incorrect handling in the preparation and injection was suspected as the most probable root cause of the observed cases. In order to mitigate this risk, correct handling of the pre-filled syringe and training were recommended, as well as patient's vision evaluation and IOP monitoring immediately after the intravitreal injection. The potential risk of over-injection has been considered during the development of the SOK583 PFS and appropriate risk control measures (a smaller syringe and instructions on the product labeling and SmPC) have been implemented.

No signs indicative of increased hypersensitivity due to differences in the formulation of excipients between SOK583 and Eylea were observed.

Serious ocular TEAEs in the study eye were reported in less than 2% of the patients in both treatment groups, with more patients in the SOK583 group reporting them [4/244 (1.6%)] compared to the Eylea EU group [2/240 (0.8%)]. All the PTs were reported only in one patient, except retinal haemorrhage, which was reported in two patients in the SOK583 group (vs none in the Eylea EU group). While the low rate of serious ocular TEAEs in the study eye in both groups is reassuring, it makes it difficult to draw conclusions, although no obvious trend of a difference in terms of incidence between treatment arms was observed.

Serious non-ocular TEAEs were slightly more frequent in the SOK583 arm (14.2% vs 11.3%). Even though most PTs were reported only once, some imbalances between treatment groups were noted in the frequency of atrial fibrillation [SOK583: 4 patients (1.6%); Eylea EU: 2 patients (0.8%)] and arterial thromboembolic events (including the PTs cerebral infarction, ischaemic stroke, transient ischaemic attack, acute myocardial infarction and myocardial infarction) [SOK583: 5 patients (2.0%); Eylea EU: 0 patients]. However, these differences are not considered clinically meaningful, since most of the subjects in both treatment groups had prior or active vascular or cardiovascular comorbidities, which is consistent with the age of the study population (mean: 75.7 years) and the frequency of these events is in line with what was reported in other intravitreal aflibercept studies or the reported prevalence in patients in that age range. In addition, one subject in the SOK583 group experienced a

non-ocular SAE (stroke). This SAE had a missing start date due to a lack of a hospital record and was not considered a TEAE as per imputation rule; it was therefore not included in the SAE tables.

The applicant states that 4 subjects had SAEs related to study treatment or study procedure. 2 of these were reported in the SOK583 group (1 case of mild vitreoretinal traction syndrome and 1 case of severe coronary artery stenosis) and 2 in the Eylea EU group (1 case of moderate retinal detachment and 1 case of moderate visual impairment).

In total six subjects died during the clinical development programme (all of them in study 301), 5 subjects (2.0%) in the SOK583 group and 1 subject (0.4%) in the Eylea EU group. One subject in the SOK583 group experienced a fatal SAE that had a missing start date due to a lack of a hospital record and was not considered TEAE as per imputation rule. All the causes of death were of non-ocular nature. The narratives for all patients have been provided by the applicant. Although all the events leading to death were considered not related to the study drug or study, all patients had prior/concomitant co-morbidities and the causes of most of the deaths are consistent with the age of the study population, the applicant was asked to discuss the imbalance in the number of deaths between treatment groups. All the patients who died had prior/concomitant vascular and cardiovascular comorbidities. Furthermore, three of the deaths can be attributed to the patients' comorbidities, one was caused by a lung neoplasm and two occurred as a consequence of accidents and none of the death cases was related to the study treatment or study procedure. In addition, the number of death cases and the observed difference between the 2 treatment groups were comparable with reports from other studies using IVT aflibercept. Therefore, no concerns arise with regard to the cases of death reported in this study.

For the events listed as important identified risks in the Eylea EU RMP (endophthalmitis, intraocular inflammation, transient intraocular pressure increased, retinal pigment epithelial tears and cataract), in study 301, there were no notable differences between treatment groups.

According to the initial CSR of study 301, there were overall few discontinuations due to a TEAE. More patients in the SOK583 group discontinued treatment due to an ocular TEAE in the study eye compared to the Eylea EU group (4 vs. 2 subjects or 1.6% vs 0.8%). Discontinuations due to non-ocular TEAE were similar in both groups (1.6% vs 1.3%). Overall, excluding deaths, 15 subjects discontinued the study or study treatment due to TEAEs (SOK583: 7 subjects; Eylea EU: 8 subjects). Of these, 5 subjects experienced SAEs (SOK583:3; Eylea EU: 2), one of which was related to study treatment, led to emergency unmasking, and was reported as a suspected unexpected serious adverse reaction in the SOK583 group (vitreoretinal traction syndrome). 5 other subjects (SOK583:1; Eylea EU:4) reported TEAEs related to study treatment, all of which were non-serious. None of the TEAEs leading to study or study treatment discontinuation was related to study procedure. After the clinical cut-off date of the Week 40 analysis, one subject reported a non-serious TEAE leading to study treatment discontinuation (SOK583, moderate colitis microscopic). The TEAE of colitis microscopic was not related to study treatment or study procedure and was ongoing (outcome: not recovered/not resolved) at the time of study completion.

Supportive studies 303 and 304 were single dose studies. Formally, discontinuation of study treatment was therefore not applicable. In study 303, two subjects discontinued from the study due to serious adverse events (1 case of arthralgia and 1 case of cystitis), none of them related to study treatment. There were no TEAEs leading to study discontinuation in study 304.

No clinically relevant differences between the 2 treatment groups were observed for any of the laboratory parameters (haematology, clinical chemistry, coagulation, and urinalysis) or vital signs in Study 301 up to the clinical cut-off date. A slightly higher proportion of patients reported TEAEs in the SOC Investigations in the SOK583 group compared to the Eylea EU group (12.3% vs 10.8%). The proportions of subjects reporting any individual TEAE related to abnormal laboratory parameters or

vital signs under the SOC Investigations in the two treatment groups were comparable and did not exceed 2.5%. No SAE related to abnormal laboratory parameters was reported. One SAE related to vital signs was reported (blood pressure increased). A medical history of hypertension was reported for a subject with a medical history of hypertension in the SOK583 group. The event was not related to study treatment or study procedure and resolved after 7 days.

As defined for Study 301, "clinically relevant changes that are observed during the post-injection assessment should be reported as adverse events". According to the Study report, 2 (0.8%) vs. 6 (2.5%) subjects in the SOK583 and the Eylea treatment arms, respectively, experienced a TEAE of IOP increased regardless of relationship to treatment/procedure (Table 14.3.1-2.1). Of these, IOP increased was reported to be related to study procedure in more patients in the Eylea EU group (2.1% vs 0.4% in the SOK583 group). For all subjects, the increase in IOP was transient. Mean post-injection IOP remained below 17.5 mmHg in both groups until the data cut-off date. However, according to the initial Summary of Clinical Safety (Listing 16.2.9-3), post-injection IOP ≥ 25 mmHg was observed more frequently in the SOK583 group than in the Eylea EU group (4.9% vs 2.9%). Similarly, IOP increases ≥ 10 mmHg compared to baseline values were experienced by more patients in the SOK583 group compared to the Eylea EU group (11.4% vs 5.0%). While acknowledging that transient increases in IOP are to be expected after an IVT injection and that also these events resolved, the applicant was asked to discuss these imbalances, to explain how clinically relevant changes in IOP were defined and why most of the post-injection increases in IOP, notably in the SOK583 treatment arm, were not classified as adverse events. The discrepancies in the reporting have been explained and it has been clarified that "clinically relevant changes" were not specifically defined but based on the investigator's judgement. Consequently, they were not reported as TEAEs. In retrospect, a more detailed definition of a clinically relevant change in IOP would have been helpful. However, for the vast majority events of post-injection increases in IOP, it is reasonable not to report them as TEAEs as the increases resolved within one hour.

2.4.10. Conclusions on clinical safety

The overall safety profile of SOK583 is in line with known adverse events of Eylea EU (SmPC). Some events were reported more frequently in the SOK583, while others were more frequent in the Eylea arm. Biosimilarity is considered supported from a safety perspective.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 29 - Summary of the safety concerns

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

2.5.2. Pharmacovigilance plan

Routine pharmacovigilance activities beyond ADRs reporting and signal detection include specific adverse reaction follow-up checklists to collect data to further characterise and/or closely monitor the safety concerns of:

- Endophthalmitis (likely infectious origin);
- Transient intraocular pressure increase

No additional pharmacovigilance activities are deemed necessary

2.5.3. 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 30 Summary of pharmacovigilance activities and risk minimization activities by safety concerns

Safety concern	Risk minimization measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	Routine risk minimization measures: SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimization measures: SmPC sections 4.2, 4.3, and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist Additional pharmacovigilance activities: None
Transient intraocular pressure increase	Routine risk minimization measures: SmPC section 4.2 where the availability of sterile equipment for paracentesis is recommended SmPC sections 4.4, 4.8, and 4.9 PL sections 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Adverse reaction follow-up checklist Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	
Retinal pigment epithelial tears	Routine risk minimization measures: SmPC section 4.4 where cautions in case of patients with risk factors retinal pigment epithelial tears are recommended SmPC section 4.8 PL sections 2 and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Cataract (especially of traumatic origin)	Routine risk minimization measures: SmPC sections 4.2 and 4.8 SmPC section 4.4 where the use of proper aseptic injection techniques is mandated PL sections 2, 3, and 4 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	
Medication errors	Routine risk minimization measures: SmPC sections 4.2, 4.9, and 6.6 PL sections 1 and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Off-label use and misuse	Routine risk minimization measures: SmPC sections 4.1, 4.3, 4.4, and 4.6 PL sections 1, 2, and 3 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures: Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Embryo-fetotoxicity	Routine risk minimization measures: SmPC sections 4.4, 4.6, and 5.3 PL section 2 Other routine risk minimization measures beyond the Product Information: Medicinal product subject to restricted medical prescription. Aflibercept must only be administered by a qualified physician experienced in administering intravitreal injections. Additional risk minimization measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Educational material: To make patients (for adults) and physicians aware of identified and potential risks (prescriber guide; in addition, patient guide "Your guide to Afqlir", and its audio version).	

Of note, the key elements of the educational materials (as also summarised in Annex IID of the PI) are aligned with those of the reference product aflibercept (Eylea) and the other approved biosimilars in the EU.

The educational program should target both patients and physicians, to inform them about the important (identified and potential) risks of Afqlir, ultimately to minimize their occurrence and consequences in routine clinical practice.

All ophthalmological clinics where Afqlir will be administered should be provided with an educational package including information for both physicians and patients.

The educational materials should be distributed as paper version and/or through a digital communication method (digital platform) to the target audience. Their detailed contents and format, the overall feasibility of the programme, its implementation / planned distribution modalities, and any other aspect, should be agreed accordingly with the concerned national competent authority (NCA) in each EU member state where Afqlir will be marketed.

2.5.4. Conclusion

The CHMP considers that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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.

2.7. Product information

2.7.1. 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.*

2.7.2. Additional monitoring

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

Afqlir (also referred to as SOK583) has been developed as a biosimilar to the reference product Eylea.

The administration route (intravitreal), posology, and the claimed indications are identical to the reference product as described in the SmPC of Eylea, except for the treatment of retinopathy of prematurity (ROP) with zone I (stage1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease of ROP in preterm infants, which has not been claimed for the pre-filled syringe.

The reference product Eylea® (INN: aflibercept) is represented by US-licensed Eylea® and EU-approved Eylea®. SOK583 and Eylea® contain aflibercept as active pharmaceutical ingredient. SOK583 DP 40 mg/mL (2 mg/0.05 mL) is presented as either liquid in vial (LIVI) or liquid in prefilled syringe (LISY). US-licensed Eylea® includes 25 batches in total (16 LIVI and 9 LISY batches. EU-authorized Eylea® includes 31 batches in total (23 LIVI and 8 LISY batches. 9 SOK583 DS batches and 14 SOK583 DP lots were also included in the Comparability analyses.

Critical Quality Attributes are properly defined for Biological Activity, Physicochemical Properties and Quantity and a Forced Degradation study is provided. In addition, the individual comparability exercises are included. In general, the biosimilarity exercise is considered adequate with minor issues to be solved.

The **clinical development** consisted of one pivotal phase III clinical study (CSOK583A12301), a multicentre, randomised, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea, administered intravitreally, in patients with neovascular age-related macular degeneration. The design of the clinical study has been discussed in three CHMP scientific advices, which were mostly followed by the applicant.

In addition, two supportive safety clinical studies were conducted (CSOK583A12303 and CSOK583A12304) to demonstrate the safe use of the LIVI kit (Study 303) or LISY (Study 304) in subjects with nAMD who had previously received IVT treatment with Eylea. Both studies were requested by FDA to support the human factors evaluation of SOK583.

3.2. Results supporting biosimilarity

Quality

The biosimilarity assessment between SOK583 and Eylea was performed by two major exercises, a comprehensive Biological characterization including biological activity and physicochemical properties and a forced degradation study.

Biological activity was determined by means of two different cell-based assays, a HUVEC proliferation assay and the inhibition of ligand-induced dimerization. HUVEC proliferation assay describes the proposed mechanism of action of SOK583 and the inhibition of ligand-induced dimerization is considered a complementary assay. Results of these test support similarity between SOK583 and Eylea although minor differences were detected. The applicants justifies a better outcome of SOK583 due to higher levels of impurities detected in Eylea lots. Ligand binding analyses by ELISA and SPR also support biosimilarity. Four VEGF-A isoforms, VEGF-B, PIGF-2 and Glectin-1 showed in general similar binding affinities to SOK583 and Eylea. Absence of binding to VEGF-C and VEGF-D was also consistent. Regarding Fc region, the different binding affinities to Fc receptors (FcγRI, FcγRII, FcγRIII, and FcRn) was assessed as well as C1q binding. Similar results were obtained in these Fc binding analyses.

Physicochemical Properties were assessed defining SOK583 and Eylea´s primary structure and product-related variants. Primary and Higher order structure supports biosimilarity between SOK583 and Eylea. A better purity profile regarding dimers and fragments was observed in SOK583 lots, which may be caused by the suboptimal storage conditions of Eylea lots. The absence of major differences in charge variants, oxidation and glycan variants also contribute in supporting the Biosimilarity assessment

The Forced Degradation study includes different stress conditions to determine the degradation profile of SOK583 and Eylea. This stress conditions included Mechanical stress, Freeze/thaw cycles, elevated temperature, oxidation stress, high and low pH, and light exposure. In general, the degradation profile was similar in SOK583 and Eylea with the exception of Biological activity of Eylea in response to light exposure. Relative potency of Eylea lots was more strongly affected than SOK583 lots

Clinical

Pharmacokinetics

Assessment of systemic aflibercept levels conducted in a subset of 44 patients in the pivotal clinical study 301 support biosimilarity, as mean values for plasma concentrations of free aflibercept at Tmax were similar between the reference product Eylea and proposed biosimilar SOK583.

Pharmacodynamics

In the exploratory analysis of free VEGF, the levels were similar in the two treatment arms 4 weeks after treatment.

Immunogenicity

At baseline, comparable proportions of patients were positive for pre-existing ADAs (SOK583: 1.2%; Eylea EU: 1.7%). Throughout the study duration the proportion of treatment-emergent ADA positive subjects was low in both groups. The overall (up to Week 52) incidence of treatment-emergent ADAs reported in this study was lower in the patients in the SOK583 arm compared to the Eylea EU arm (0.9% vs 2.6%), but both incidences are comparable to what was reported in the phase III studies of Eylea after 52 weeks of treatment with aflibercept (1% to 3%).

Efficacy

Primary endpoint: In the PPS, the difference in LS mean changes from baseline in BCVA score at Week 8 was -0.3 letters and the 95% CI (-1.8, 1.3) letters was contained within the predefined equivalence range [−3.5, +3.5]. This was supported by the sensitivity analysis: the difference in LS means of BCVA change from baseline using MMRM model using the PPS was -0.3 letters and the 95% CI (-1.8, 1.3) letters was contained within the predefined equivalence range [−3.5, +3.5]. The results from the supplementary analyses of ANCOVA for BCVA change from baseline using LOCF imputation and from

the MMRM model on the FAS were in line with those from the primary analysis and the sensitivity analysis: -0.3 letters (95%CI: -1.8; 1.2) and -0.3 letters (95%CI: -1.8; 1.1), respectively.

Secondary endpoints: mean changes from baseline in CSFT using SD-OCT at Weeks 1, 4, 8, 24, in CNV lesion size at Week 8, and in BCVA score at Week 24 were similar between the SOK583 and Eylea EU groups for subjects in the FAS and the PPS.

Exploratory analyses: Albeit a numerical trend of a favour for Eylea, in the responder analyses, i.e. gains and losses of ≥5, ≥10 and ≥15 letters in BCVA, the differences were small and without clinical relevance.

Safety

Overall, 310 nAMD subjects (244 in study 301, 36 in study 303 and 30 in study 304), received study treatment with SOK583. In study 301, in total, 215 patients (88.1%) in the SOK583 group [compared to 215 (89.6%) in the Eylea group] completed Week 48 visit. The safety database is considered appropriate for a biosimilar candidate.

The overall incidence of TEAE was comparable between the study arms (SOK583: 73.4%; Eylea EU: 72.5%) and the majority of all TEAE was mild to moderate in severity.

The overall proportions of subjects with **non-ocular** TEAEs were similar between the SOK583 and Eylea EU groups.

The overall incidences of **ocular** TEAEs in the study eye were similar, although slightly higher in the SOK583 arm compared to the Eylea EU arm (84 subjects, 34.4%, vs. 78 subjects, 32.5%, respectively).

The occurrence of study treatment and/or study procedure related TEAEs was highly comparable between treatment arms.

The safety profile in both study arms was in line with the known safety profile of Eylea (SmPC).

3.3. Uncertainties and limitations about biosimilarity

Quality

Even though some concerns raised in the evaluation, the information provided preliminarily supports Biosimilarity between SOK583 and Eylea. These minor concerns should be addressed before a final conclusion is made.

Clinical

Pharmacokinetics

The impact of ADA on PK has not been studied because no subjects in the PK subset were ADA positive. The impact of ADA on efficacy has not been studied due to the overall low number of ADA positive subjects (0.9% in the SOK583 group and 2.2%in the Eylea EU group). Thus, no conclusion can be made on the impact of ADA status on PK and efficacy.

3.4. Discussion on biosimilarity

A comprehensive similarity exercise using US-licensed Eylea® and EU-approved Eylea® as reference medicinal product has been performed to assess Analytical similarity of SOK583. The comparability assessment was conducted as per the relevant EU and ICH guidelines on the development of similar biological medicinal products. The biosimilarity assessment focuses on the comparability between

SOK583 DS with either EU-Eylea (LIVI/LISY) or US-Eylea (LIVI/LISY). Additional individual comparability assessments include EU- and US-Eylea (LIVI/LISY), SOK583 DS against SOK583 DP (LIVI/LISY), and SOK583 DP LIVI vs SOK583 DP LISY. The applicant defines a list of quality attributes which will be assessed in the biosimilarity exercise and organised them based on a risk assessment analysis.

In general, the proposed biosimilarity strategy is considered acceptable and the information provided is adequate.

The biosimilarity assessment includes a comprehensive comparability exercise with Biological characterization, Primary Structure and Related Variants and DP related quality attributes sections. In addition, a Forced Degradation study has been included to support the Biosimilarity conclusion.

The Biological characterization showed that biological activity, ligand binding profiles and affinities for Fc receptors and C1q of SOK583 and Eylea are comparable. In addition, no ADCC and CDC activities were detected. SOK583 and Eylea showed similar physicochemical properties with a trend to higher purity in SOK583. This observation might be explained due to the suboptimal storage in freezing conditions of Eylea aliquots, which were formulated to be stores in a refrigerator. This suboptimal storage conditions may also explain some minor differences in charge and oxidation variants differences. No differences on Protein Concentration were found.

In the Forced Degradation study, four SOK583 DP lots (two LIVI and two LISY, PPQ) were compared to four Eylea batches (one LIVI and one LISY batch sourced from EU and US). The results of this assessment further supported Biosimilarity with the exception of light stress. The relative potency (HUVEC and VEGF-A ELISA) of Eylea lots was prominently affected by light exposure compared with SOK583 lots, which showed a better stability profile.

Assessment of systemic aflibercept levels conducted in a subset of patients in the pivotal clinical study 301 support biosimilarity, as mean values for plasma concentrations of free aflibercept at Tmax were similar between the reference product Eylea and proposed biosimilar SOK583.

At baseline, comparable proportions of patients were positive for pre-existing ADAs: 3/244 (1.2%) of subjects in the SOK583 group and 4/240 (1.7%) in the Eylea EU group. Throughout the study duration the proportion of treatment-emergent ADA positive subjects was low in both groups. The overall incidence of treatment-emergent ADAs reported in this study was lower in the patients in the SOK583 arm compared to the Eylea EU arm (0.9% vs 2.6%), but both incidences are comparable to what was reported in the phase III studies of Eylea after 52 weeks of treatment with aflibercept (1% to 3%). In an exploratory analysis, circulating levels of VEGF were also similar between treatment arms.

The pivotal clinical study CSOK583A12301 was adequately designed to demonstrate clinical equivalence between Afqlir (SOK583) and Eylea EU on an efficacy, as well as safety level. The selected study population of patients with nAMD, as well as primary and secondary efficacy endpoints are deemed appropriate for this biosimilarity exercise. The primary efficacy endpoint, change in BCVA from baseline to Week 8, was well within the pre-defined equivalence range of +/- 3.5 letters and demonstrated equivalent efficacy in the primary endpoint. Biosimilarity was further confirmed by secondary endpoints, which included change in CSFT from Baseline to Week 1, 4, 8, 24 and 52, change in CNV lesion size from Screening to Week 8 and 52 and change in BCVA at Weeks 24 and 52.

The overall safety profile of SOK583 is in line with known adverse events of Eylea (SmPC).

Overall, the clinical data suggest similarity between Afqlir (SOK583) and Eylea EU 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 (vial and pre-filled syringe) and in in preterm infants for the treatment of retinopathy of prematurity (ROP) (only pre-filled syringe). The clinical development program for the proposed biosimilar SOK583 comprised a single pivotal Phase III study (study 301) to investigate Eylea and SOK583 regarding efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with nAMD.

The applicant plans to obtain approval for nAMD and all other adult indications of Eylea, 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 Advices (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."

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

Additional considerations

In case of approval of Afqlir for adult use as proposed by the applicant, a potential for off-label use of Afqlir for the treatment of retinopathy of prematurity (ROP) in preterm infants would exist, since that indication, which has not been claimed for Afqlir, is approved for Eylea in the EU.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Afqlir 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 Afqlir is favourable in the following indication(s):

neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),

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

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

conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Afqlir.

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 Afqlir is marketed, ophthalmological clinics where Afqlir 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 30 G needle, and angle of injection
- The pre-filled syringe and the vial are for single use only
- The need to expel excess volume of the syringe before injecting Afqlir 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 Afqlir

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

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