Sandoz Biopharmaceuticals Clinical Development

SOK583A1 (INN: aflibercept)

Clinical Trial Protocol CSOK583A12301 / NCT04864834

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

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CF	Color fundus photography
CI	Confidence interval
CMO&PS	Chief Medical Office and Patient Safety
CNV	Choroidal neovascularization
COVID-19	Coronavirus disease of 2019
CRC	Central Reading Center
CRO	Contract Research Organization
CSR	Clinical study report
CSFT	Central Subfield Thickness
DBL	Database lock
eCRF	Electronic Case Report/Record Form
EOS	End of Study visit
ETDRS	Early Treatment Diabetic Retinopathy Study
EqM	Equivalence margin
Eylea EU	Europe-authorized Eylea®; the registered trademark sign "®" will be omitted for Eylea in this document
FA	Fluorescein Angiography
FAS	Full Analysis Set
FCS	Fully conditional specification
FSH	Follicle-stimulating hormone
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Global Clinical Supply
IAS	Immunogenicity Analysis Set
ICF	Informed Consent Form
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVT	Intravitreal
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification

MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-model repeated measures
nAMD	Neovascular age-related macular degeneration
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PP	Per-Protocol
PPS	Per Protocol Set
q4w	Every 4 weeks
q8w	Every 8 weeks
RAS	Randomized Analysis Set
RPE	Retinal Pigment Epithelium
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome - Corona Virus - 2
SD	Standard deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SmPC	Summary of Product Characteristics
SOK583A1	Product code of Sandoz' proposed aflibercept containing biosimilar product
US PI	United States Prescribing Information
VEGF	Vascular Endothelium Growth Factor

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Central subfield thickness	Average thickness of circular area within 1 mm diameter around the foveal center from retinal pigment epithelium (RPE) to internal limiting membrane, inclusively
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve masking of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment (SOK583A1 or Eylea EU) and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation of study treatment	Point/time when the participant permanently stops receiving the study treatment (SOK583A1 or Eylea EU) for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the study participant in a time unit
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source documents used at the point of care
End of the clinical study	The end of the clinical study is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the study objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Fellow eye	The participant's contralateral eye not treated with study treatment
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/treatment	The drug whose properties are being tested in the study
Masked/evaluating Investigator	For the entire study duration and all study participants, the masked/evaluating Investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the injections)
Medication number	A unique identifier on the label of medication kits in studies that dispense study drug using an IRT system.

Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization, but have been inadvertently randomized into the study
Other treatments	Treatment that may be needed or allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A patient with the condition of interest for the study, i.e. neovascular age-related macular degeneration, and who is willing to participate in the study and signed the ICF
Participant Number	A unique number assigned to each participant upon signing the ICF. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the study design (e.g. Screening, Treatment, Follow up) which are described in the Protocol. Periods define the study phases and will be used in clinical study database setup and eventually in analysis
Personal data	Participant information (participant identifier information, study information and biological samples) collected by the Investigator that is transferred to Sponsor for the purpose of the clinical study
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Retesting	Safety laboratory tests and vital signs can be repeated once to confirm clinical significance or to exclude technical errors, as specified by the protocol. If the repeat test evaluation or result remains outside of the specified range for laboratory or vital signs, the participant must be considered as a Screen Failure
Screen Failure	A participant who did not meet 1 or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical study	The start of the clinical study is defined as the signature of the informed consent by the first participant
Study eye	The participant's eye which complies with all eligibility criteria and is selected to be treated with study treatment
Study treatment	Any drug or combination of drugs or intervention administered to the study participant as part of the required study procedures
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing

	the related clinical question of interest, which might or might not be the same as the study treatment.
Unmasked treating Investigator	For the entire study duration and all study participants, the unmasked treating Investigator only performs the injection and assesses participant safety following the injection
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Visual acuity assessor	The visual acuity assessor (which could be a masked/evaluating Investigator) performs the BCVA assessments and is masked to the assigned treatment
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 3

Amendment rationale

This amendment to version 3.0 of the protocol of Study CSOK583A12301 includes the evaluation of systemic VEGF concentrations at Week 48 (pre-dose) and Week 52. The aim of this assessment is to evaluate the concentrations of systemic VEGF in the 2 treatment groups at Week 52, i.e. 4 weeks after IVA treatment with aflibercept. VEGF concentration at Week 48 (pre-dose) will be 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.

This amendment applies to those participants who agree to additional blood collection for the evaluation of systemic VEGF concentrations. They will document their agreement by signing the corresponding ICF.

Study status

The study is ongoing. First participant first visit was on 11-May-2021, and recruitment was completed on 22-May-2022. The Sponsor will make all efforts to recruit as many participants as possible for the VEGF assessment.

Changes to the protocol

Section 2

- The evaluation of systemic VEGF concentrations was added as an exploratory objective

Section 4.5.1

- The evaluations of systemic VEGF concentration were added (including the required blood volume)

Section 7

- Details of the updated ICF on evaluation of systemic VEGF concentrations were added

Section 8

- The collection of additional blood samples was included in Table 8-1

Section 8.5.3 (new section)

- The evaluation of systemic VEGF concentration was added

Section 12.1

- The analysis set for the evaluation of systemic VEGF concentrations was added

Section 12.5.3

- Additional assessment for the PK substudy was added

Section 12.6.1 (new section)

- The analysis of systemic VEGF concentrations was added

Other minor changes to wording were made. This includes 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 will be evaluated.

Changes to specific sections of the protocol are shown in the track changes version ~~using strike through red font~~ for deletions and red underlined font for insertions.

This amended protocol will be sent to the IEC/IRBs and HAs for approval or notification as required according to local regulations.

The inclusion of additional time points for blood collection is a substantial change to the protocol.

An additional ICF will be composed and the eCRF will be updated in accordance with this amendment.

Amendment 2

Amendment rationale

The amendment to the version 2.0 of the protocol of Study CSOK583A12301 includes recommendations on SAE reporting provided by BfArM (SAEs need 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 and corresponding diagnostic methods were adapted. The combination of determining the spherical equivalent and analyzing the images assessed at screening are considered to be sufficient to exclude patients 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.

Study status

The study is ongoing. First participant first visit was on 11-May-2021, and, as of 30-Nov-2021, 161 participants have received study treatment.

Changes to the protocol

Section 2.1

- The justification and attributes for primary estimands were revised

Section 4.5

- Results from the safety review of the first 20 participants treated in the study was included in the benefit-risk assessment

Section 5.2

- Definition criteria of pathologic myopia was modified in exclusion criterion #3

Section 6.6.3

- Breaking the masking code of a participant for further treatment after disease progression was removed (related to the updated Sandoz protocol template)

Section 9.1

- Wording on withdrawal of study treatment was revised (new Section 9.1.1) (related to the updated Sandoz protocol template)
- Wording on discontinuation from study was added (new Section 9.1.2) (related to the updated Sandoz protocol template)

Section 9.2

- A participant's opposition to use data/biological samples was added (related to the updated Sandoz protocol template)

Section 9.4

- Reasons for early study termination by the Sponsor were updated (related to the updated Sandoz protocol template)

Section 10.1.3

- Instructions for SAE reporting were updated based on recommendations by the BfArM and the updated Sandoz protocol template

Section 10.1.4

- Pregnancy reporting was updated (related to the updated Sandoz protocol template)

Section 12.1

- Wording for analysis sets was revised

Section 12.4.3

- Wording for handling of remaining intercurrent events was revised

Section 12.4.4

- Handling of missing values not related to intercurrent events for primary estimands was revised

Section 12.4.5

- Sensitive analyses for primary estimands was updated

Section 12.5.1

- Subgroup analysis for secondary efficacy endpoint by ADA status was removed

Other minor changes to wording were made. Changes to specific sections of the protocol are shown in the track changes version using ~~strike through red font for deletions~~ and red underlined for insertions.

This amended protocol will be sent to the IEC/IRBs and HA for approval or notification as required according to local regulations.

The change of exclusion criterion #3 described in this amended protocol is a substantial change to the protocol.

The ICF and eCRF were updated in accordance with this amendment.

Amendment 1

Amendment rationale

Amendment to the version 1.0 of the protocol of Study CSOK583A12301 includes recommendations provided by IRBs/IECs and ANSM. Additionally, the study protocol language were modified to improve clarity, accuracy and ensure better adherence to the protocol.

Study status

Screening enrolment has not yet started. The first participant first visit is planned for Apr-2021. Protocol version 1.0 has been submitted to Health Authorities, IECs and IRBs.

Changes to the protocol

Protocol summary

- The study title was corrected (‘administered intravitreally’ had been missing)
- The exclusion criterion related to infection or inflammation in either eye was aligned with Exclusion Criterion #4 without changing the meaning

Section 4.5.1

- The blood sample volume was corrected

Section 5.2

- Minor changes and clarification on the inclusion criterion #4 without changing the meaning
- Minor changes and clarification on the exclusion criteria #3, 4 (in line with the Eylea SmPC), 9, 13, 14 18, 19, 28 without changing the meaning

Section 6.1

- Investigational and control drugs will be supplied by the local Sponsor. This was corrected in Table 6-1

Section 6.2

- Clarification added on Table 6-2 Prohibited medication about the use of bevacizumab

Section 6.4

- Correction on the drug supply open label kit description
- Correction on Sponsor staff or delegate information

Section 6.7.2

- Clarification on the intravitreal procedure which should follow the Site Investigational Product (IP) Administration and Handling Manual, local practice and local guidelines
- Clarification and alignment with exclusion criterion #4

Section 8

- The assessments performed on Day 2 and Day 58 (PK sub-study participants only) were clarified in Table 8-1
- Coagulation tests were included in Table 8-1
- FSH testing at screening were included in the Table 8-1

- BCVA assessment and study eye and fellow eye documentation during Screening and Baseline visits were clarified in Table 8-1

Section 8.2

- The need of documentation of Year of Birth data on the medical source was added

Section 8.3.1

- Clarification on the selection of the study eye in case of both eyes are eligible during screening

Section 8.3.2

- Clarification about OCT technology validation and certification provided by CRC

Section 8.4

- The requirement for equipment calibration and maintenance was added
- The information that CF and FA images will be stored at CRC was added

Section 8.4.3

- Tonometer specifications were removed in order to allow sites to use their standard of care equipment
- The reference to a manual of procedures was removed because sufficient information and further instructions are provided at this section

Section 8.4.5

- Post-injection procedures were clarified

Section 10.1.4

- A newborn follow-up period in case of pregnancy was included

Section 15

- The list of references was updated by removing references not cited in the protocol

Other minor clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version using ~~strike through red font for deletions~~ and red underlined for insertions.

This amended protocol will be sent to the IEC/IRBs and HA for approval or notification as required according to local regulations.

The changes described in this amended protocol are not substantial.

The ICF was updated in accordance with this amendment. No changes on the eCRF are needed.

Protocol summary

Protocol number	CSOK583A12301
Full 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
Brief Title	Phase III study assessing the efficacy, safety and immunogenicity of SOK583A1 versus Eylea® in patients with neovascular age-related macular degeneration
Sponsor and Clinical Phase	Phase III Hexal AG, Industriestr. 25, 83607 Holzkirchen, Germany and Sandoz Inc., 100 College Road West, Princeton, NJ 08540, USA
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To demonstrate similar efficacy, safety and immunogenicity of SOK583A1 and Eylea EU as per Eylea approved treatment regimen in patients with nAMD
Primary Objective(s)	To demonstrate similar efficacy of SOK583A1 and Eylea EU in terms of BCVA. The endpoint for primary objective is the mean change from Baseline in BCVA score using ETDRS testing charts at Week 8. The primary clinical question of interest is: Does SOK583A1 have similar efficacy as Eylea EU in terms of mean change in BCVA score in participants with nAMD who are anti-VEGF naive, without important protocol deviations and adherent to the treatment and completed the treatment to Week 8?
Secondary Objectives	To evaluate if the anatomical outcome of SOK583A1 is similar to Eylea EU • Mean change in CSFT using SD-OCT from Baseline to Week 1, 4, 8, 24 and 52 • Mean change of CNV lesion size using FA from Screening to Week 8 and 52 To evaluate if the efficacy of SOK583A1 is similar to Eylea EU in terms of BCVA • Mean change from Baseline in BCVA score using ETDRS testing charts at Week 24 and 52 To evaluate if SOK583A1 is similar to Eylea EU in terms of safety • Incidence of ocular and non-ocular AEs over 52 weeks To evaluate if SOK583A1 is similar to Eylea EU in terms of immunogenicity • Development of binding and neutralizing ADAs up to Week 52 To evaluate the systemic exposure of SOK583A1 and Eylea EU in participants of the PK assessment • Aflibercept concentration assessments at Baseline and 24 hours after the first and third injections

Exploratory objective	To evaluate systemic VEGF concentrations in participants treated with SOK583A1 or Eylea EU • VEGF concentration assessment at Week 48 (pre-dose) and Week 52
Study design	This is an international, multicenter, randomized, double-masked, 2-arm parallel study, in patients with nAMD, with a total duration of 52 weeks. The study participants will be randomized at Baseline in a 1:1 ratio into 2 treatment groups: SOK583A1: IVT administration of 2 mg of SOK583A1 in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at Weeks 16, 24, 32, 40 and 48. Eylea EU: IVT administration of 2 mg of Eylea EU in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at Weeks 16, 24, 32, 40 and 48.
Population	The study will randomize 460 male and female patients that are 50 years of age or older, anti-VEGF treatment naive for both eyes, with active CNV secondary to AMD in the study eye
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study. • Participants must be 50 years of age or older at Screening • Anti-VEGF treatment-naive for both eyes with active CNV lesions secondary to AMD that affect the central subfield in the study eye • Total area of CNV (including both classic and occult components) must comprise > 50% of the total lesion area in the study eye • Intra- and/or subretinal fluid affecting the central subfield of the study eye • BCVA between 73 and 38 letters, inclusive, in the study eye at Screening and Baseline using ETDRS testing charts
Key Exclusion criteria	• Concomitant conditions or ocular disorders in the study eye, including cataract and diabetic macular edema, 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 inflammation in either eye • Uncontrolled glaucoma defined as IOP > 25 mmHg on medication, or according to Investigator's judgement, at Screening or Baseline, in the study eye • Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 38 letters using ETDRS testing charts at Screening • Previous ocular treatments with any anti-VEGF or investigational drugs in either eye
Study treatment	SOK583A1 2 mg/0.05 mL Eylea EU 2 mg/0.05 mL

Treatment of interest	The randomized treatment (the investigational treatment SOK583A1 or the control treatment Eylea EU)
Efficacy assessments	• BCVA using ETDRS testing charts • Spectral Domain Optical Coherence Tomography (SD-OCT) • Color fundus photography and fluorescein angiography
Pharmacokinetic assessments	Aflibercept concentration assessments before the first injection (Baseline, pre-dose) and 24 hours after the first and third injections
Pharmacodynamic assessment	Systemic VEGF concentration assessment at Week 48 (pre-dose) and Week 52
Key safety assessments	• AE monitoring • Ophthalmic examination • Vital signs • Laboratory assessments • Anti-drug antibodies • Pregnancy testing
Data analysis	To evaluate the primary objective, ANCOVA will be performed for change in BCVA score from baseline to Week 8; the model will include treatment as a factor, and Baseline BCVA and age as continuous covariates. The primary objective, for which analysis will be conducted in the Per Protocol Set (PPS), is considered met if: 1. For EMA requirement: the 95% CI for the difference in change in BCVA score from baseline to Week 8 is completely contained within the equivalence interval of [-3.5, 3.5]. 2. For FDA requirement: the 90% CI for the difference in change in BCVA score from baseline to Week 8 is completely contained within the equivalence interval of [-3.0, 3.0]. Summary statistics for continuous variables will include the number of nonmissing observations, mean, SD, minimum, median, and maximum. Summary statistics for discrete variables will be presented in contingency tables and will include absolute (n) and relative frequencies (%).
Key words	Age-related macular degeneration, anti-VEGF, biosimilar

1 Introduction

1.1 Background

AMD is the leading cause of severe vision loss affecting 10%-13% of individuals over the age of 65 years in North America, Europe, and Australia (Kawasaki et al 2010; Rein et al 2009; Smith et al 2001). Genetic, environmental and health factors play an important role in the pathogenesis of the disease.

AMD is classified into 2 clinical subtypes: the non-neovascular or dry form and the neovascular (exudative) or wet form (Ferris et al 1984; Lim et al 2012; Miller et al 2013). Neovascular AMD is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris et al 1984). These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss (Shah et al 2007; Shah et al 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder et al 2003). Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of antivascular endothelial growth factor (anti-VEGF) treatments (Ferris et al 1983; Sommer et al 1991; Wong et al 2008).

VEGF has been shown to be elevated in patients with nAMD, and is thought to play a key role in the neovascularization process (Spilsbury et al 2000). The use of IVT pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with nAMD (Bloch et al 2012; Campbell et al 2012). Anti-VEGF treatments, such as ranibizumab (Lucentis®), aflibercept (Eylea®) and brolicuzumab (Beovu®), inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema.

SOK583A1 (INN: aflibercept) is being developed by Sandoz as a proposed biosimilar to the aflibercept product Eylea® (hereafter referred to as Eylea) licensed for ophthalmological indications in the EU to Bayer Pharma AG and in the US to Regeneron Pharmaceuticals Inc. (Eylea EU SmPC; Eylea US PI). The development of SOK583A1 aims for the treatment of all indications currently approved for Eylea (since the receptor and mechanism of action of aflibercept are the same in the different ophthalmological indications). Biosimilarity will be supported by the totality of evidence from analytical, clinical PK, efficacy, safety and immunogenicity data.

Development of biosimilars

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized biological medicinal product with demonstrated similarity in physico-chemical characteristics, biological activity, efficacy and safety, based on a comprehensive comparability exercise (Weise et al 2011; Schneider et al 2012). It is intended to be used at the same dose(s) and dosing regimen(s) to treat the same disease(s) as the reference product. The development and commercialization of biosimilars can help address unmet medical needs by

improving access to well-established therapeutic interventions while improving healthcare affordability (McCamish and Woollett 2012).

Biological medicinal products are derived from living cells or organisms and consist of relatively large and complex molecular entities. Due to the inherent variability of the biological system as well as potential manufacturing process changes introduced over time, any resulting biological will display a certain range of variability, even between different batches of the same originator product (Weise et al 2011). Manufacturers and Health Authorities are managing this variability based on the principle that changes in quality attributes can be accepted as long as they do not alter the safety and efficacy of the biologic product (Schiestl et al 2011).

Development of SOK583A1

SOK583A1 contains the same active ingredient, aflibercept, as Eylea. Aflibercept is a fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 by recombinant DNA technology. Aflibercept functions as a decoy receptor ("VEGF trap"), binding to VEGF A and B and placental growth factor (PIGF), thus blocking the binding and activation of cognate VEGF receptors (Eylea EU SmPC; Eylea US PI).

Study CSOK583A12301 (hereinafter referred to as 'Study A12301') is the first clinical study in which SOK583A1 is being administered in humans. Aflibercept is administered via IVT, directly at the site of action, and the systemic exposure is low and variable following IVT injection. The efficacy of aflibercept for neovascular retinopathy is not associated with the systemic PK. Hence, study A12301 includes only a descriptive PK substudy to confirm that the low systemic exposure of SOK583A1 is within the same range observed following Eylea EU after IVT administration (Eylea EU SmPC; Eylea US PI).

The study aims, by using a sensitive indication and endpoints, to detect any clinically meaningful differences in comparison to Eylea. Accordingly, nAMD has been selected as the indication for this study for the following reasons:

- the pivotal studies of Eylea have been conducted in this indication
- nAMD is considered as a sensitive indication based on the magnitude of aflibercept's efficacy demonstrated in previous phase III anti-VEGF trials and the absence of concomitant medication for underlying disease, and therefore, representative indication for a biosimilar study.

1.2 Purpose

The purpose of the study is to demonstrate similar efficacy, safety and immunogenicity of SOK583A1 and Eylea EU as per Eylea approved treatment regimen in patients with nAMD. This study is part of the clinical development program of SOK583A1, and has been set up to support worldwide registration of SOK583A1 as a proposed biosimilar product to Eylea.

2 Objectives and endpoints

The study design, objectives and endpoints have been discussed and agreed with FDA, EMA and PMDA. For the detailed description of the primary endpoint and its statistical analysis, see Section 12.4 Analysis of the primary estimand.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate similar efficacy of SOK583A1 and Eylea EU in terms of BCVA	• Mean change from baseline in BCVA score using ETDRS testing charts at Week 8
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate if the anatomical outcome of SOK583A1 is similar to Eylea EU	• Mean change in CSFT using SD-OCT from Baseline to Week 1, 4, 8, 24 and 52 • Mean change of CNV lesion size using FA from Screening to Week 8 and 52
• To evaluate if the efficacy of SOK583A1 is similar to Eylea EU in terms of BCVA	• Mean change from Baseline in BCVA score using EDTRS testing charts at Week 24 and 52
• To evaluate if SOK583A1 is similar to Eylea EU in terms of safety	• Incidence of ocular and non-ocular AEs over 52 weeks
• To evaluate if SOK583A1 is similar to Eylea EU in terms of immunogenicity	• Development of binding and neutralizing ADAs up to Week 52
• To evaluate the systemic exposure of SOK583A1 and Eylea EU in participants of the PK assessment	• Aflibercept concentration assessments at Baseline (pre-dose) and 24 hours after the first and third injections
Exploratory Objective	**Endpoint(s) for exploratory objective**
• To evaluate systemic VEGF concentration in participants treated with SOK583A1 or Eylea EU	• Systemic VEGF concentration assessments at Week 48 (pre-dose) and Week 52

2.1 Primary estimands

The primary clinical question of interest is: Does SOK583A1 have similar efficacy as Eylea-EU in terms of mean change in BCVA score in participants with nAMD who are anti-VEGF naive, without important protocol deviations and adherent to the treatment and completed the treatment to Week 8?

The justification for using observed per-protocol (PP) estimand (Lou et al 2019) as the primary estimand is that given the sequential approach of biosimilar development, similarity between test and reference product on an analytical and nonclinical level will have already demonstrated before the initiation of the clinical studies. This provides a rationale to assume that the ideal-exact equality condition is satisfied. The observed PP estimand will also prioritize sensitivity to detect differences between treatments if any exists by assessing the treatment effect for participants who follow the intention of the protocol as closely as possible.

The primary estimand is described by the following attributes:

1. Population: anti-VEGF treatment-naïve patients with nAMD without important protocol deviations and adherent to the treatment and completed the treatment (2 IVT injections) to Week 8). Further details on the population are provided in Section 5 Population
2. Endpoint: change from baseline in mean BCVA score at Week 8
3. Treatment of interest: the randomized treatment (SOK583A1 or Eylea EU). Further details on the treatment are provided in Section 6 Treatment
4. Since the primary analysis is only on those participants who adhere to and complete treatment and do not have important protocol deviations, there will be no intercurrent events for the observed PP estimand.
5. The summary measure: difference in mean change from baseline to Week 8 in BCVA scores between SOK583A1 and Eylea EU.

2.2 Secondary estimands

Not applicable

3 Study design

This is an international, multicenter, randomized, double-masked, 2-arm parallel study, in patients with nAMD, with a total duration of 52 weeks. A total of 460 study participants will be randomized at Baseline in a 1:1 ratio into 2 treatment groups. The randomization will be stratified by region (US, Rest of the World, Japan), age (< 75 years and ≥ 75 years) and Baseline BCVA categories (< 64 letters and ≥ 64letters).

The study consists of 3 periods: a Screening Period of up to 2 weeks (+ 1 week in case of technical errors, e.g, laboratory results could not be obtained, samples were lost, destroyed, hemolized, or images were of insufficient quality) to assess participant's eligibility, the Treatment Period (Baseline to Week 48) and a Follow-up Period (Week 48 to Week 52). An outline of the study periods is presented in Figure 3-1 Study design, and a detailed visit and assessment schedule is provided in Table 8-1 Assessment schedule.

Screening Period (screening to randomization, Day -14 to Baseline)

The Screening Period begins with the first screening procedure once the participant has provided written informed consent to participate in the study and ends at randomization visit (Baseline) of the study. The Screening Period of up to 2 (+ 1) weeks will be used to assess eligibility of the participants. As participants with nAMD require rapid therapeutic intervention, the screening period must be kept as short as possible.

Retesting BCVA or imaging assessments with the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the participant is not allowed. Imaging can be retested only in case of technical errors.

Rescreening is allowed once. For rescreening and retesting details, see Section 8.1 Screening.

Participants must have the diagnosis of nAMD in the study eye confirmed at Screening by the CRC.

Treatment Period (Baseline to Week 48)

Only 1 eye will be selected as study eye and treated with study treatment (SOK583A1 or Eylea EU). The Treatment Period begins with randomization (Baseline) and ends with the completion of Week 48 treatment and assessments. After confirmation of eligibility, participants will be randomized in a 1:1 ratio into either the SOK583A1 or the Eylea EU treatment group. During the Treatment Period, participants will receive a single IVT injection of fixed 2 mg of SOK583A1 or Eylea EU in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at Weeks 16, 24, 32, 40 and 48.

A study visit schedule will be established at the time of randomization for all participants. All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule or as close to the designated day/time as possible, according to the allowed visit window (Table 8-1 Assessment schedule). All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for the study treatment, i.e. 2 consecutive injections should be spaced by at least 21 days. For more details, please refer to Section 8 Visit schedule and assessments.

Week 48 corresponds to the last treatment visit.

For ADA assessment, serum samples will be collected before drug administration at Baseline and at Weeks 1, 4, 8, 16, 24 and 40, and at EOS. Samples to determine aflibercept serum concentrations will be obtained at the same time as immunogenicity samples.

For PK assessment, serum and plasma samples will be collected from 20 participants per treatment group (total of 40 participants) before the first study drug injection and 24 (±1) hours after the first (Visit 2) and third study drug injections (Visit 5). For the 40 participants in the PK substudy, extra visits will be necessary 24 hours after the first (Visit 2) and third study drug injections (Visit 5). See Section 8 Visit schedules and assessment and Table 8-1 Assessment schedule.

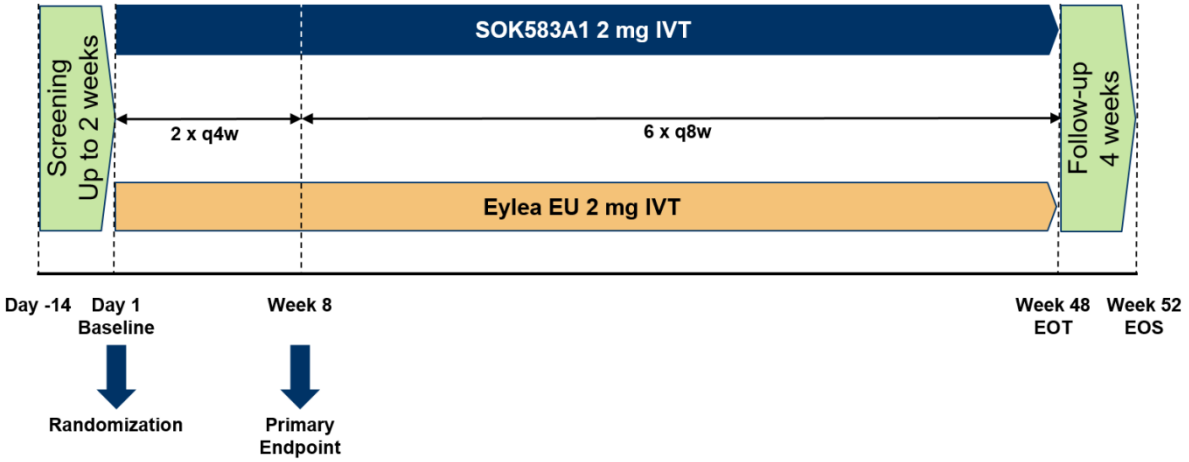
For the evaluation of systemic VEGF concentrations, plasma will be collected at Week 48 (pre-dose) and Week 52 in participants who agree to the additional blood collection.

Follow-up Period (Week 48 to Week 52)

The Follow-up Period consists of 4 weeks for the safety follow-up after the last injection administered at Week 48. The last study assessments will be performed at the EOS visit, at Week 52, 4 weeks (± 7 days), after the last study drug administration (Table 8-1).

Participants who withdraw from the study prior to study completion or participants who discontinue the study treatment for any reason, will be asked to return for an early discontinuation (EOS) visit, 4 weeks (± 7 days) after their last study drug administration.

Figure 3-1 Study design



The Screening Period should be completed up to 2 weeks. It can be extended to up to 3 weeks in total in case of technical errors when retesting is needed (laboratory results could not be obtained, samples were lost, destroyed or hemolyzed or images with insufficient quality).

4 Rationale

4.1 Rationale for study design

This study is part of the clinical development program for SOK583A1 and aims to support worldwide registration of SOK583A1 as a proposed biosimilar product to Eylea. The concept study design has been discussed and agreed with FDA, EMA, and PMDA.

The main indication of Eylea is the treatment of nAMD which was supported by the results of 2 parallel Phase III studies of aflibercept VIEW 1 and VIEW 2 (0.5 and 2.0 mg IVT doses; 2 regimens, every 4 weeks and every 8 weeks) compared with the control arm (ranibizumab 0.5 mg IVT, every 4 weeks). At 52 weeks, all aflibercept groups were non-inferior to the ranibizumab group with equal stabilization of vision in 95% of eyes (Heier et al 2012). Aflibercept 2 mg q8w IVT, after the loading phase of 3 injections q4w, is an established standard of care option for patients with nAMD with consistency of the approved dose and posology across the countries.

The study has a parallel-group design with a total duration of 52 weeks. The overall study design closely resembles the Eylea or similar studies investigating non-inferiority of other anti-VEGF drugs with the aflibercept. The proposed treatment scheme and dosing is in line with the authorized label and standard of care. The primary endpoint analysis is based on BCVA data collected up to 8 weeks. Further evaluation of efficacy, PK, safety and immunogenicity is based on data up to Week 52.

The primary efficacy endpoint based on BCVA (ETDRS testing charts letters, measured at starting distance of 4 meters) will be assessed by masked personnel. Historically, the change from Baseline in BCVA at a selected time point is considered appropriate as the primary efficacy endpoint in confirmatory nAMD studies. In Eylea's pivotal studies, VIEW 1 and VIEW 2 (Heier et al 2012), the mean BCVA change from Baseline reached a plateau starting at Week

12 (upon maintenance treatment q8w), and therefore at an earlier time point (Week 8), the BCVA is still ascending before the maximal treatment effect is reached. BCVA change from baseline at Week 8 is considered a sensitive endpoint to detect a potential clinically meaningful efficacy difference between SOK583A1 and Eylea.

The study will recruit anti-VEGF naive nAMD participants with BCVA at Screening and Baseline between 73 to 38 letters, both inclusive, in the study eye. By limiting the upper BCVA to 73 letters, the study will include participants that have a potential for at least 10 letters gain in visual acuity, thereby avoiding a ceiling effect. In the same way, since it would be difficult to evaluate decreases in visual acuity at a level worse than legal blindness, BCVA of 38 letters was established as the lower limit for eligibility.

The participants must have CNV lesions secondary to AMD, defined by the presence of leakage evidenced by fluorescein angiography and intra- or subretinal fluid, as evidenced by optical coherence tomography.

Equivalence testing related to the primary efficacy parameter BCVA will be based on a margin of 3.5 letters for EMA analysis and 3.0 letters for FDA analysis. A change in BCVA > 5 letters is considered relevant in the clinical practice regardless of the underlying disease. Therefore, this equivalence margin provides assurance that any proof of equivalence only occurs if the observed treatment differences are of no clinical relevance.

Randomization will be stratified by region (US, Rest of the World, Japan), age (<75 years and ≥ 75 years) and Baseline BCVA categories (< 64 letters and ≥ 64 letters) in order to ensure a balanced and homogeneous allocation of participants in each arm.

Masked treatment for 48 weeks followed by a safety follow-up of 4 weeks allows for a 1 year safety evaluation of SOK583A1 compared with Eylea EU. 4 weeks for safety follow up are considered acceptable period based on the site of study drug administration and the fact that the majority of AEs being local.

4.2 Rationale for dose/regimen and duration of treatment

SOK583A1 is being developed as a similar biological medicinal product to Eylea. Therefore, the dose, frequency and route of administration of the study medication are chosen according to Eylea pivotal trials and the current Eylea US PI and in line with Eylea EU SmPC for the treatment of nAMD.

4.3 Rationale for choice of control drugs (comparator)

SOK583A1 is being developed as a similar biological medicinal product to Eylea. EU-authorized Eylea has been chosen as the comparator in this study to confirm similarity in terms of efficacy, safety and immunogenicity.

4.4 Purpose and timing of interim analyses

An interim analysis will be performed after randomized patients completed Week 40 or discontinued prior to Week 40. The purpose of interim analysis is to allow for initial dossier submission of the primary endpoint results evaluated at Week 8, including all safety and

efficacy data collected up to the data cutoff point, which is considered sufficient by FDA, EMA, and PMDA for initial dossier submission.

Participants will remain in the study and will continue to receive masked treatment through the planned treatment duration of 48 weeks, to allow further evaluation of efficacy and safety. Treatment masking of individual participants and data will remain intact for all participants, masked Investigators and staff and selected staff from the Sponsor until the final DBL has occurred; see Table 6-3 Masking and unmasking plan. Additional information is presented in Section 12.7 Interim analyses.

4.5 Risks and benefits

The risk to participants in this study may be minimized by compliance with the eligibility criteria and the study procedures, as well as close clinical monitoring for any safety signals.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlines in the exclusion criteria. If there is any questions that the participant will not reliably comply, they should not be entered or continue in the study.

Eylea has been licensed and commercialized world-wide since 2011. Clinical studies provided evidence of efficacy and safety in all approved indications, including nAMD. Since approval of Eylea, an extensive post-marketing experience has been gathered which confirms Eylea's established safety and efficacy profile and demonstrates its favorable risk-benefit ratio (Eylea EU SmPC; Eylea US PI).

In terms of safety profile, IVT aflibercept is well tolerated across all indications. The most common AEs for Eylea (≥ 5%) are conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased (Eylea US PI). SAEs are also reported in a low incidence: hypersensitivity, endophthalmitis and retinal detachments, and a potential risk of thromboembolic events.

One of the potential risks associated with any biopharmaceutical product is the induction of an immunogenic response, and therefore assessment of ADA development is planned throughout study.

From the currently available analytical data, it is concluded that SOK583A1 and Eylea are similar at the physicochemical and functional level. SOK583A1 is therefore expected to have similar efficacy, safety and immunogenicity profile. All participants of the study will therefore be receiving active therapy with a similar expectation of benefit. The contraindications, precautions and warnings of Eylea will also apply to SOK583A1.

A safety review of the first 20 participants in Study A12301 showed that IVT injections of SOK583A1 or Eylea EU were safe and well tolerated in patients with nAMD. No treatment-emergent AEs were recorded. No new safety signal was detected.

Further details of the known and potential risks and benefits associated with aflibercept are presented in the Investigator's Brochure and Eylea EU SmPC and Eylea US PI.

COVID-19 (SARS-Cov-2 virus) Pandemic considerations

During the global pandemic, the safety of clinical study participants remains paramount at all times. The responsibility of the investigator is to continually and carefully assess the benefit-risk ratio for each patient as the pandemic develops and needs to take all necessary measures to maintain patient safety at all times.

Study treatment IVT injection of Eylea/SOK583A1 does not put patients at increased risk of COVID-19 infection, as aflibercept has no immunomodulatory or immunosuppressant effects. However, given their age, patients with nAMD are at higher risk for developing a more severe COVID-19 course of disease. As patients with nAMD are at risk for complete and permanent loss of vision, according to the American Academy of Ophthalmology, IVT injections for nAMD fall under the category of essential care and the treatment should not be stopped due to the risk of permanent vision loss (American Academy of Ophthalmology). The Royal College of Ophthalmologists Medical Retinal Management Plan during COVID-19 recommends for new patients with nAMD to be treated with a loading phase of 3 injections of anti-VEGF and then continued on q8w, which is in line with the study's treatment schedule (Royal College of Ophthalmology). Maintaining a regular schedule of eye injections is important in retaining the vision and missing even one appointment can have a negative effect since nAMD progresses rapidly and can produce sudden and severe central vision loss if not treated (Blinder et al 2003).

The Investigator is responsible to assure that patients with infections at screening are excluded from study participation, and study participants are not exposed to increased risk through participation in the study. If required to assure patient safety, the Investigator may conduct unscheduled laboratory assessments at any time during the study. This includes but is not limited to e.g. SARS-Cov-2 testing taking into consideration local government policy and site's own procedures. Testing result and any AEs associated with disease should be managed and documented as described in Section 10 Safety monitoring and reporting.

4.5.1 Blood sample volume

A volume of approximately 140 mL is planned to be collected over a period of 52 weeks, from each participant as part of the study. Additional samples may be required for safety monitoring.

In case of participation in the PK substudy, approximately 31 mL of blood will be additionally collected.

For those participants who agree to blood collection for the evaluation of systemic VEGF concentrations, approximately 12 mL of blood will be additionally collected.

Timing of blood sample collection is outlined in Table 8-1 Assessment schedule. A summary blood log is provided in the Laboratory Manual. Instructions for all sample collection, blood sample volume, processing, storage, and shipment information is also available in the Laboratory Manual.

5 Study population

The study will enroll male and female patients who are 50 years of age or older, anti-VEGF treatment naive for both eyes, and diagnosed with active CNV secondary to AMD in the study

eye. A total of 460 participants will be randomized. Participants who drop out after they have been randomized will not be replaced.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Participants must be 50 years of age or older at Screening
3. Anti-VEGF treatment-naive patients for either eye and systemically
4. 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
5. 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
6. BCVA between 73 and 38 letters, both inclusive, in the study eye at Screening and Baseline using ETDRS testing charts
7. Willing and able to comply with all study procedures, and be likely to complete the study
8. Clear ocular media and adequate pupil dilatation in both eyes to permit good quality photographic imaging

In cases where both eyes are eligible, the eye with the worse BCVA at Baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye. However, the Investigator may select the eye with better visual acuity based on medical reasons or local ethical requirements, which must be justified.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

Ocular conditions and treatments:

1. Previous treatment with any anti-VEGF therapy in either eye or investigational drugs in study eye or fellow eye, at any time prior to Baseline
2. Participant has received any approved treatment for nAMD (other than vitamin and dietary supplements) in the study eye and at any time prior the Baseline
3. Presence of other causes of CNV, including pathologic myopia (spherical equivalent of –8 diopters or more negative), ocular histoplasmosis syndrome, angioid streaks,choroidal rupture, or multifocal choroiditis in the study eye, assessed by imaging at screening by CRC and appropriately stated in the multi-modal eligibility confirmation report
4. 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

5. Subfoveal fibrosis, atrophy, or scarring extending > 50% of total lesion area in the study eye as assessed by the Investigator at Screening and confirmed by the CRC prior to randomization
6. Subretinal hemorrhage that is ≥ 50% of the total lesion area in the study eye, or if the subretinal hemorrhage involving the fovea is 1 or more disc areas (≥ 2.54 mm^2) in size in the study eye, as assessed by FA and confirmed by the CRC
7. Retinal pigment epithelium (RPE) rip/tear in the study eye at Screening or Baseline
8. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Baseline
9. History or evidence of the following, in the study eye:
    - Intraocular (including cataract surgery) or refractive surgery within the 90 day period prior to Baseline. The yttrium aluminum garnet (YAG) posterior capsulotomy is allowed no later than 4 weeks prior to Baseline
    - Previous penetrating keratoplasty or vitrectomy
    - Previous panretinal photocoagulation
    - Previous photodynamic therapy
    - Previous submacular surgery or other surgical intervention for AMD
    - Retinal detachment or treatment or surgery for retinal detachment
    - Any history of macular hole of stage 2 and above
    - Prior trabeculectomy or other filtration surgery
    - Ocular trauma within 6 months prior to Baseline
10. History of hypersensitivity to any of the study treatments or its excipients, or clinically relevant sensitivity to fluorescein dye, as assessed by the Investigator
11. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment at Screening or Baseline
12. Aphakia and/or absence of the posterior capsule in the study eye at Screening or Baseline, unless it occurred as a result of a YAG posterior capsulotomy in association with prior posterior chamber intraocular lens implantation
13. Intra or periocular use of corticosteroids in the study eye within a 6 month period prior to Baseline
14. Use of topical ocular corticosteroids in the study eye for 30 or more consecutive days within the 90 days period prior to Baseline
15. Previous therapeutic radiation near the region of the study eye
16. Concomitant conditions or ocular disorders in the study eye, including media opacities, cataract and diabetic macular edema, at Screening or Baseline which could, in the opinion of the Investigator, prevent response to study treatment or may confound interpretation of study results (efficacy and safety), compromise visual acuity or require medical or surgical intervention during the course of the study
17. 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)
18. Presence of Scleromalacia in either eye

19. Participants requiring anti-VEGF treatment of the fellow eye at Baseline will not be eligible for the PK substudy

Systemic conditions and treatments:

20. Previous systemic treatment with any anti-VEGF therapy
21. Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to Baseline, with the exception of low stable doses of corticosteroids (defined as ≤ 10 mg prednisolone or equivalent dose used for 90 days or more prior to Baseline).
22. Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening
23. Stroke or myocardial infarction during the 6-month period prior to Baseline
24. Participation in an investigational systemic drug, biologic, or device study within 30 days or duration of 5 half-lives of the investigational product (whichever is longer) prior to Baseline. Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary
25. Presence of infection at Screening or active infection within 2 weeks before Screening
26. Underlying advanced, severe and uncontrolled concomitant condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, inflammatory, infectious or gastrointestinal), physical examination finding, or clinical laboratory finding which in the opinion of the Investigator place the participant at unacceptable risk from participation in the study
27. History of a medical condition (including, but not limited to chronic disease, immunosuppression, metabolic dysfunction, prior exposure to other drugs that may pose risk of infection or allergic reactions) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product, or that might affect participant safety or interpretation of the study results.
28. Pregnant or nursing (lactating) women and women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping the medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone

contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment she is considered not of child-bearing potential. If natural (spontaneous) amenorrhea with an appropriate clinical profile has been reported for a female participant for 12 months, in the absence of the above medical documentation, FSH testing is required for this female participant regardless of reported reproductive/menopausal status at Screening (Section 8.4.4 Pregnancy and assessments of fertility).

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment

SOK583A1 is formulated as a sterile solution aseptically filled in a sterile glass vial for single use and the content of the vial must not be split.

The study medications SOK583A1 and Eylea EU will be supplied in study kits, each kit containing one sterile glass vial for single use, with 40 mg/ml of aflibercept solution for IVT injection (2 mg/50 µL).

The Sponsor will ensure sufficient supplies of SOK583A1 and Eylea EU for treatment use to allow for the completion of the study.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
SOK583A1 (40 mg/mL)	Solution for injection	Intravitreal (IVT)	Glass Vial (2 mg/0.05 mL)	Sponsor (local and global)
Eylea EU (40 mg/mL)	Solution for injection	Intravitreal (IVT)	Glass Vial (2 mg/0.05 mL)	Sponsor (local and global)

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Participants, including the 40 participants in the PK substudy, will be assigned at Baseline visit to 1 of the following 2 treatment arms/groups with approximately 230 participants in each arm in a ratio of 1:1.

- SOK583A1: IVT administration of 2 mg of SOK583A1 in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48.
- Eylea: IVT administration of 2 mg of Eylea in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48.

6.1.4 Treatment duration

The planned duration of treatment is 48 weeks as discussed in Section 3 Study design.

Discontinuation of study treatment for a participant occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the participant or the Investigator.

Participants who prematurely discontinue study treatment for any reason except withdrawal of consent should have the EOS visit scheduled 4 weeks after the last study treatment administration.

For discontinuation details, see Section 9 Study discontinuation and completion.

6.2 Other treatment(s)

In the study eye, no other treatments for nAMD other than the study treatment, are permitted throughout the course of the study.

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRF. Additionally, the eCRF will also capture data on medications (used within the past 90 days) and procedures administered prior to study start.

During the study, if the fellow eye develops nAMD or other condition, it may also be treated with standard of care approved in the respective country at the discretion of the Investigator. Fellow eye treatment will be captured in the eCRF. The fellow eye should be treated and monitored according to the routine practice and AEs captured in the eCRF. It is recommended that the fellow eye and study eye are not treated on the same day if the site routine permits.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact the Sponsor/delegated CRO medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Sponsor/delegated CRO to determine if the participant should continue to take study treatment or should discontinue the study treatment.

6.2.2 Prohibited medication

Prohibited medications after the start if the study (i.e. ICF signature) are displayed in Table 6-2 Prohibited medication. Any participant who receives one of these treatments will be discontinued from study treatment. Any medication which may be required to treat ocular or systemic AEs and permitted oral or injectable contraceptives for female participants are permitted and must be recorded in the appropriate eCRF page.

The standard of care or other approved treatment according to the Investigator practice for nAMD and other diseases in the fellow eye are permitted and must be recorded in the appropriate eCRF page.

Table 6-2 Prohibited medication

Medication	Action taken
Study eye: Intra-or periocular corticosteroids	Discontinue study treatment (except if for treatment of AE)
Study eye: Laser treatment for AMD	Discontinue study treatment
Study eye: Anti-VEGF therapy other than study treatment	Discontinue study treatment
Systemic: Systemic corticosteroids for 15 or more consecutive days[1]	Discontinue study treatment
Systemic: anti-VEGF therapy	Discontinue study treatment
Study eye, fellow eye and systemic: Any investigational drug, biologic or device (with the exception of over-the-counter vitamins, supplements or diets). Bevacizumab for the fellow eye is not allowed if not approved for nAMD in the respective country	Discontinue study treatment

[1] Permitted: low stable doses of corticosteroids (≤10 mg prednisolone or equivalent dose used for 90 days or more prior to Baseline), inhaled, nasal, intra-articular and short term (< 14 consecutive days) oral corticosteroids or dermal steroids

6.2.3 Rescue medication for the study eye

Rescue treatment is not permitted in the study eye.

Per the Investigator's discretion, at any time, if the study eye nAMD gets worse resulting in a ≥ 10 letters loss in BCVA at 2 consecutive visits or a ≥15 letters loss in BCVA at 1 visit compared with the best previous measurement, and the study eye BCVA value is not better than the baseline value, the participant may require rescue treatment. In this case, the study treatment should be discontinued.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number, which is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the study. A new Participant Number consists of the Center Number (Center Number) (as assigned by Sponsor to the investigative site) with a sequential Participant Number suffixed to it, so that each participant's participation is numbered uniquely across the entire

database. Upon signing the ICF, the participant is assigned to the next sequential Participant Number available.

In case of participant is rescreened, the participant will need to sign a new ICF and a new Participant Number will be assigned by the EDC system. The date of the new Informed Consent signature must be entered on the appropriate eCRF under the new Participant Number. Informed Consent for a rescreened participant must be obtained prior to performing any study-related assessments.

6.3.2 Treatment assignment, randomization

At Baseline visit all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms in a 1:1 ratio. Approximately 460 participants will be randomized. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria (confirmed by CRC). The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by PK data collection, region (US, Rest of the World, Japan), age (< 75 years and ≥ 75 years) and Baseline BCVA categories (< 64 letters and ≥ 64 letters) in order to ensure a balanced and homogeneous allocation of participants in each arm. For participants of the PK substudy (those who sign both the main ICF and the PK ICF), randomization will be stratified by age and Baseline BCVA categories, and a list of randomization numbers will be generated by IRT with a 1:1 randomization ratio to SOK583A1 or Eylea EU. For all other participants (those who sign only the main ICF), randomization will be stratified by region, age and Baseline BCVA categories and a list of randomization numbers will be generated by IRT with a 1:1 randomization ratio to SOK583A1 or Eylea EU.

The randomization scheme for participants will be reviewed and approved by a member of the Sponsor Randomization Office.

6.4 Treatment masking

This is a participant, Investigator, and Sponsor-masked study. Participants, Investigators, and the Sponsor will remain masked to study treatment throughout the study, except where indicated below.

The identity of the study treatments cannot be concealed since the appearance of the vials differs. To maintain the double-masked design of the study it is necessary to involve unmasked staff at the study site for handling the study medication.

Treatment masking of individual participants will remain intact until the final DBL has occurred by ensuring: randomization data are kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study except the unmasked injecting physician. The masked personnel and participants will remain masked to the treatment assignment until the final DBL. Following final DBL all roles may be considered unmasked.

An independent masked review of fundus photography, fluorescein angiography and optical coherence tomography (SD-OCT) images will be performed at a CRC.

Site staff

With the exception of any unmasked site staff identified below, all site staff (including study Investigator and study nurse) will be masked to study treatment throughout the study.

Unmasking a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Drug product will be supplied in open label kits, so an unmasked pharmacist/unmasked study personnel who is independent of the study team will be required in order to maintain the mask. This unmasked pharmacist/unmasked study personnel will receive treatment allocation/kit numbers from the IRT with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unmasked pharmacist/unmasked study personnel to ensure that the treatment assignments are concealed from the rest of the site staff.

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

Once the designated roles are determined, the roles should not be switched at any time after randomization. Every effort must be made to limit the number of unmasked study personnel to ensure integrity of the masked study.

Sponsor staff or delegate

The following unmasked Sponsor or delegate roles are required for this study:

- Unmasked CRO field monitor(s), unmasked CRO Clinical Operations Lead and unmasked CRO Project Manager
- Unmasked clinical staff managing drug re-supply to site or interacting with unmasked field monitors/unmasked clinical lead, e.g. unmasked Sponsor clinical manager
- Unmasked designated study team members for primary endpoint analysis during the interim analysis
- Unmasked quality assurance staff and unmasked compliance manager

The unmasked field monitors are required to review drug accountability and allocation at site. The unmasked monitors are not provided with a randomization list directly but will be unmasked through review of source documentation compiled by the unmasked pharmacist/unmasked site personnel, which details treatment allocation to individual participants. The unmasked monitors will also be able to review the treatment allocation cards/randomization list provided to the unmasked pharmacist/unmasked site personnel

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug products. These individuals are not provided with randomization lists directly, but may be unmasked through communication of drug re-supply needs via the unmasked site pharmacists/unmasked site personnel.

An independent masked review of color fundus photography, fluorescein angiography and optical coherence tomography images for participants in the study will be performed at a CRC.

After all participants have completed Week 40 assessment and after the database has been partially locked for the interim analysis designated study team members will be unmasked to the study medication assignment. Participant, investigators and the rest of the study team will remain masked until after the final DBL. Details will be provided in a blinding charter.

All unmasked personnel will keep randomization lists and data or information that could unmask other study team members confidential and secure until final clinical DBL. Following final DBL all roles may be considered unmasked. See Table 6-3 for an overview of the masking and unmasking plan.

Table 6-3 Masking and unmasking plan

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation and dosing**	**Safety event (single participant unmasked)**	**Interim analysis**
Participants	M	M	UI	M
Site staff	M	M	UI	M
Central Laboratory, CRC	M	M	M	M
Unmasked site staff e.g. pharmacy staff, medication administrating Investigator and staff	NA	U	U	NA
Global Clinical Supply and Randomization Office	U	U	U	NA
Unmasked Sponsor/delegate staff e.g. for study treatment re-supply GCS), unmasked monitor(s), unmasked CRO Clinical Operations Lead and unmasked CRO Project Manager	NA	U	U	NA

	Time or Event			
Role	**Randomization list generated**	**Treatment allocation and dosing**	**Safety event (single participant unmasked)**	**Interim analysis**
Pharmacovigilance Sponsor staff	NA	NA	UI	NA
Sponsor/delegate staff involved in primary endpoint analysis	M	M	M	U
All other Sponsor staff not identified above (study team, project team, management and decision boards, support functions)	M	M	M	M

M=remains masked; NA=not applicable in this study; U=unmasked; UI=allowed to be unmasked on individual participant level

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted. Study treatment can be interrupted if warranted due to an AE.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

IRT needs to be accessed by unmasked study personnel at every visit, even if the study treatment is not needed at that visit as per the assessment of the Investigator. Registration of all visits in the IRT system is necessary and when treatment is warranted, IRT will provide a medication (kit) number to administer the assigned investigational product to the participant. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the unmasked study personnel or by unmasked field monitor on the appropriate study treatment dispensing form.

Exposure to the study treatment will be based on the number of injections administered. Compliance with the study treatment will be assessed by the unmasked field monitor at each visit using vial counts and information provided by the pharmacist or by the unmasked study personnel.

6.6.2 Recommended treatment of adverse events

The Investigators will follow local guidelines and their best medical practice and judgement to treat AEs accordingly. Medication used to treat AEs must be recorded in the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Sponsor monitor for the site and the study team that the code has been broken.

It is the masked or unmasked Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unmasking can be performed at any time.

6.7 Preparation and dispensation

Each study site must have masked and unmasked study personnel. Sites will be supplied with study drug in packaging as described under investigational and control drugs (Section 6.1.1 Investigational and control drugs). No vials, kits or study treatment will be handed out to the participants.

A unique medication number is printed on the study medication label.

Unmasked study personnel will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the participant, unmasked study personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated unmasked person at the study site, handled and stored safely and properly and kept in a secured location to which only the unmasked Investigator and designated unmasked site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Sponsor Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The unmasked study personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unmasked monitors during site visits or remotely and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the site pharmacist or designee, after approval from the unmasked study personnel will return all unused study treatment, and a copy of the completed drug accountability log to the unmasked Sponsor address or unmasked CRO monitor provided in the Investigator folder at each site.

6.7.1.2 Handling of additional treatment

See Section 6.2.1 Concomitant therapy for fellow eye treatment documentation.

6.7.2 Instruction for prescribing and taking study treatment

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

The treatment period will be divided into 2 periods for the IVT injections of SOK583A1 and Eylea EU, with different intervals, as per approved regimen:

- In the loading period, treatment with SOK583A1 or Eylea EU will occur every 4 weeks for 3 injections, 1 injection per visit (Baseline, Week 4, Week 8)
- Maintenance period: Participants will receive one injection of SOK583A1 or Eylea EU 2 mg every 8 weeks for 5 injections, 1 injection per visit (Week 16, Week 24, Week 32, Week 40 and Week 48)

Study treatment should be administered in the study eye on the day of the study visit, or if not possible, within +3 days after the study visit, except for the Baseline, in which study treatment administration should occur within the next 24 hours, as described in Section 8 Visit schedule and assessments. If the assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 Efficacy and pre-injection safety measures (tonometry, slit lamp and fundus examinations) described in Section 8.4.3 Complete ophthalmic examination. If study visit assessments and the corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in opinion of the Investigator, may be impacted by the study treatment or injection procedure, treatment needs to be cancelled. Any adverse events must be recorded in the eCRF.

The IVT injection procedures, including aseptic and antimicrobial requirements, should follow the Site Investigational Product (IP) administration and Handling Manual, and local clinical practice guidelines. The IVT injection will be performed by the unmasked Investigator. The unmasked study personnel and injecting physician must not perform assessment of any ocular or non-ocular safety parameters, or assess causality of AEs for participants during the course of the study.

IVT injection is contra-indicated in participants with active or suspected ocular or periocular infections and in participants with active or suspected intraocular inflammation. Therefore, Investigators should verify that these conditions are not present in either eye prior to every injection.

Treatment dose adjustments and/or interruptions are not permitted unless interruptions are warranted by an AE.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) or participant's legal representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the legal representative gives consent, an impartial witness should also sign the ICF reassuring that participant was explained with the ICF content. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Participant must be able to read, understand and willing to sign the informed consent. If unable to read due to visual impairment, informed consent must be read to verbatim by an impartial witness or a family member.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The participant or representative/ legal representative will receive a copy of the fully signed and dated ICF. The signed ICF should remain in the Investigator site file or, if locally required, in the subject's note/file of the medical institution. The process of obtaining informed consent must be documented in the participant source documents.

The Sponsor or delegate will provide to Investigators in a separate document a proposed ICF that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed ICF suggested by the Investigator must be agreed by Sponsor before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between Investigator's Brochure updates will be communicated as appropriate, for example, via an Investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following ICFs are included in this study:

- Main study consent
- An optional PK descriptive analysis for 40 participants in total, which requires a separate consent form signature. The consent form will describe the additional blood samples and

study visits required. It is required as part of this protocol that the Investigator from selected sites presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main ICF.

- An optional evaluation of systemic VEGF concentration at Week 48 (pre-dose) and Week 52. The ICF describes the additional blood samples required at the specific time points. The Investigator at selected sites presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as for the main ICF.
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements.

Declining to participate in these optional assessments (PK descriptive analysis or VEGF evaluation) will in no way affect the participant's ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Sponsor after IRB/IEC approval.

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

A planned study visit schedule will be established at Baseline for all participants. All post-Baseline and/ or subsequent scheduled visits will be calculated based on the Baseline visit date. All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule or as close to the designated day/time as possible, according to the visit window (Table 8-1). All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for the study treatment, i.e. 2 consecutive injections should be spaced by at least 21 days. Treatment is intended to be administered on the day of study visit, or if not possible, within 3 days after the study visit when the per-protocol assessments took place, except Baseline, in which study treatment administration should occur within the next 24 hours. For a given protocol visit (except for Baseline), assessments can be performed on two consecutive days in which both days must occur within the visit window

For all visits, efficacy and safety assessments should be performed prior to any administration of study treatment.

Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the EOS visit will be performed, except the color fundus photography and fluorescein angiography if there was color fundus photography and fluorescein angiography within the previous 12 weeks. At this final visit, all

dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the eCRF.

Table 8-1 Assessment 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 participants per arm)[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 participants, pre-dose)		X		X	X	X		X	X		X		X

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**
Blood (serum) sampling for total drug concentration, pre-dose		X	X[5]	X	X	X	X[5]	X	X		X		X
Blood (plasma) sampling for systemic VEGF concentrations												X[9,10]	X[9]
Blood (plasma) sampling for PK (only for 20 participants per arm)[5]		X[5]	X[5]				X[5]						
BCVA[6]	X	X		X	X	X		X	X	X	X	X	X
Complete Ophthalmic Exam[7]	X	X		X	X	X		X	X	X	X	X	X
SD-OCT [6]	X	X		X	X	X		X	X	X	X	X	X
Color Fundus Photography[6]	X					X							X
Fluorescein Angiography[6]	X					X							X
SOK583A1/ Eylea EU IVT administration		X			X	X		X	X	X	X	X	
Post-injection assessment[8]		X			X	X		X	X	X	X	X	
Adverse Events	X	X	X[5]	X	X	X	X[5]	X	X	X	X	X	X

X=assessment to be recorded in the clinical database or received electronically from a vendor

S=assessment to be recorded in the source documentation only

[1] PK analysis Informed Consent must be obtained from 20 participants per arm, from selected sites.

[2] Only in women with childbearing potential; during the study, urine pregnancy testing should be done at monthly intervals. When a visit is not planned for a month (during the maintenance period), site team should schedule clinic visits monthly for urine pregnancy tests. The positive urine test needs to be confirmed with serum test.

[3] Only in the absence of medical documentation to confirm the women is 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 should be performed prior to fluorescein administration and prior to receiving the IVT injection; urinalysis should be done locally at site, using dipstick

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

[6] Assessments must be done prior to the IVT injections; BCVA must be performed in the study eye in all visits and in both eyes at Screening; at Baseline, only study eye BCVA needs to be tested and documented at eCRF; in cases where both eyes are eligible per Screening data, BCVA has to be performed for both eyes at Baseline in order to select the Study eye.

SD-OCT will be performed in the study eye in all visits and in the fellow eye at Screening only. FA and Color fundus photography will be done in the study eye at Screening, Week 8 and Week 52, and in the fellow eye at Screening only. With the exception of Screening, if the fellow eye is examined in accordance with clinical practice and the Investigator's discretion, the data should be documented in the eCRF only in case of an AE. Details on study eye selection are provided in Section 5.1.

[7] Includes slit-lamp exam, IOP measurement, and fundus exam. Dilation for the fundus exam is at the discretion of the Investigator. Ophthalmic exam will be performed in both eyes at Screening. All other evaluations are study eye only or also in the fellow eye at discretion of investigator.

[8] The study eye will be evaluated 0-5 minutes and 30-60 minutes post-injection to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye. It includes 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, presence of new intraocular hemorrhage(s) might be appropriate at the discretion of the Investigator and/or based on the results of gross assessment of vision and IOP measurement). Participants should 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 participants who agree to the evaluation of systemic VEGF concentrations (Week 48 and 52). Plasma samples will be taken from subjects receiving anti-VEGF treatment for the study eye only. Subjects receiving anti-VEGF treatment for both eyes are excluded from participation in the evaluation of systemic VEGF concentrations at Week 48 and Week 52.

[10] Blood sample needs to be taken pre-dose.

8.1 Screening

Screening

The participant must have signed and dated the ICF before any study procedures, including screening procedures, are performed. The Screening Period starts with the first screening procedure (other than signing the ICF). Screening procedures may be performed on multiple days but must be completed within 14 days, up to 2 (+1) weeks, prior to randomization. The screening procedures are:

- Informed consent (in addition to the main study Informed consent, the 40 participants of the PK substudy must sign also the PK Informed consent)
- Demographic and medical history information, including prior/concomitant medications used within 90 days
- Physical examination
- Vital signs (blood pressure, pulse, respiratory rate and body temperature)
- Serum pregnancy test if the participant is female and of childbearing potential
- Serum FSH fertility test in case of absence of medical documentation to confirm the female participant is not of child-bearing potential (surgical bilateral oophorectomy without a hysterectomy, and/or reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile)
- Blood samples for blood chemistry/hematology (blood draws should be performed prior to injection of fluorescein dye)
- Local dipstick urinalysis
- BCVA on both eyes
- Complete ophthalmic examination of both eyes, including slit-lamp exam, IOP measurement and fundus exam
- SD-OCT on both eyes (the images should be submitted within 24 hours to the CRC for eligibility determination)
- FA on both eyes (the images should be submitted within 24 hours to the CRC for eligibility determination). FA images from a previous routine evaluation may be used as long as FA was performed within 3 days of the screening visit.
- 3-field color fundus photography on both eyes (the images should be submitted within 24 hours to the CRC for eligibility determination)
- Participant registration, including screen failures, in the EDC system for obtaining the participant ID number
- Contact IRT to enter participant ID number
- Monitor/reporting AEs
- Schedule Baseline Visit

Retesting

Only retesting of safety laboratory tests and vital signs is permitted and only under the following circumstances:

- Safety laboratory tests and vital signs can be repeated ONCE in order to confirm the clinical significance, if the participant has completed Screening events but failed 1 or more eligibility criterion related to safety laboratory and vital signs
  and
- the repeat test can be completed within 14 days (if repeated within 14 days, the other screening assessments do not need to be repeated).
- The Investigator may perform retesting also to rule out any technical or measurement error(s) or in case of loss or sample damage prior to analysis.

If a repeat test evaluation or result remains outside of the specified range for laboratory or vital signs, the participant must be considered as a screening failure. The participant may however be rescreened (see below).

Retesting will NOT be permitted for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the participant.

Medical judgment should be exercised to ensure that treatment is not withheld in order for a participant to participate in the study.

Rescreening

Participants may be invited for a new Screening visit (rescreening) only under the following circumstances. Prior to rescreening, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

- Participants who do not meet the eligibility criteria may 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 can be rescreened once at an appropriate time-point based on the medical judgement.
- Participants who present with a temporary medical condition precluding participation may be rescreened once. In this case, retesting is not permitted during rescreening for any reason.
- A participant can also be rescreened once in case of sample loss or damage.

For rescreening, the following conditions will be required:

- Participant must sign a new ICF before any study-specific assessment.
- Participant must be logged as a screen failure into the IRT and entered as a rescreen. A participant not entered into IRT as a rescreen will not be eligible for randomization.
- A new screening window of up to 2 weeks must commence from the time of re-consent.
- All screening procedures must be repeated if rescreening is to occur beyond 14 days from the original Screening visit date

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

Participants who are randomized and fail to start study treatment, e.g. participants randomized in error, must be considered early terminators. The reason for early termination must be recorded on the disposition eCRF. In this case, rescreening of the participant is not permitted.

8.1.1 Information to be collected on screening failures

Participants who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screening failure participants. No other data will be entered into the clinical database for participants who are screening failures, unless the participant experienced a SAE during the screening phase (see Section 10.1.3 for SAE reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screening failure that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered early terminators. The reason for early termination should be recorded on the appropriate eCRF as well as on the screening and enrollment log.

8.2 Participant demographics/other baseline characteristics

Participants demographic and Baseline characteristics data to be collected include: age at screening, gender, race/ethnicity, relevant medical history/current medical condition present before signing ICF, prior/current medications, primary diagnosis of nAMD, time since diagnosis of nAMD (in days), whether nAMD is unilateral or bilateral, iris color, definition of the study eye, intraocular pressure, BCVA (both as a continuous variable and using categories (< 64 letters and ≥ 64 letters), ophthalmic examinations, retinal imaging, lesion type (predominately classic, minimally classic, occult), foveal involvement (subfoveal, extrafoveal, undeterminable), CNV lesion size, presence of subretinal fluid, presence of intraretinal fluid/cyst, presence of sub RPE fluid, (CSFT), vital signs, laboratory lab results, pregnancy test, and adverse events.

Year of birth should be collected and documented at source document only on-site.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF page whenever, in their judgment, the test abnormality occurred prior to the informed consent signature.

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

8.3 Efficacy

The following parameters will be assessed to demonstrate similar efficacy of SOK583A1 and Eylea EU:

- BCVA score using ETDRS testing charts starting at 4 meters
- CSFT using SD-OCT
- Choroidal neovascularization lesion size by FA and Color Fundus Photography

All efficacy assessments should be performed prior to any administration of study treatment.

8.3.1 Visual acuity

ETDRS visual acuity testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Visual acuity of the study eye will be assessed at each study visit and the fellow eye will be assessed at Screening only, using BCVA (best correction determined from protocol refraction). In cases where both eyes are eligible for the study during the Screening Period, the definition of study eye will be based upon the Baseline Visit evaluations. BCVA results from the eye selected by the investigator as the study eye must be documented in the eCRF. The fellow eye BCVA and the rationale for selection of study eye should be documented at source document only. BCVA measurements will be taken in a sitting position using ETDRS-like visual acuity testing charts. The details of the procedure and training materials will be provided in the applicable manual. Certifications of the assessment procedures and assessors will occur prior to any evaluation of study participants.

Participants at sites in some Asian countries will undergo BCVA testing using numerical charts instead of letters charts.

8.3.2 Spectral-domain optical coherence tomography (SD-OCT)

SD-OCT will be assessed in the study eye at every visit and in fellow eye at Screening only. Although SD-OCT is the preferred method and is referred to throughout the protocol, other types of OCT can be used, if agreed to and validated by the Central Reading Centre as specified in the applicable manual. These assessments will be performed by a trained technician or Investigator at the sites and should be performed after BCVA assessment and prior to any study drug administration. The SD-OCT machine used for an individual participants should not change for the duration of the study. CSFT and central foveal thickness will be measured by SD-OCT. The CSFT represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center.

A CRC will be used in this study. The CRC will provide sites with a Study Manual and trainings materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC, as specified at the Manual. All SD-OCT images will be obtained by trained and study-certified site personnel at the study site and forwarded to the CRC for independent standardized analysis and storage. At the Screening Visit, SD-OCT images will be submitted to the CRC for eligibility determination. Feedback from the CRC will be provided to the sites via email or fax. For further procedural details, refer to applicable manual provided by the CRC.

8.3.3 Color fundus (CF) photography and fluorescein angiography (FA)

Three-field CF photography and fluorescein angiography will be performed in the study eye at Screening, Week 8 and EOS visits and in the fellow eye at the Screening only. In case of

premature termination there is no need to repeat the color fundus photography and fluorescein angiography if there was CF photography and FA within the previous 12 weeks.

A standardized procedure for the collection of FA and 3-field CF images is provided by the CRC in a separate manual. Certification of the equipment and examiners at each site will occur prior to evaluation of study participants. All CF and FA images will be obtained by trained and study-certified site personnel at the study sites and forwarded to the CRC for independent standardized analysis and storage. At the Screening Visit, retinal images will be sent to CRC for eligibility determination. Feedback from the CRC will be provided to the sites via email or fax.

FA images from previous routine evaluations may be used as long as they were performed within 3 days of the Screening visit using CRC-certified equipment and examiners.

8.3.4 Appropriateness of efficacy assessments

All study procedures related to the assessment of efficacy are standard for this indication and patient population and are well established in the field of ophthalmologic clinical practice and clinical research. In particular, the imaging assessments, SD-OCT and FA, are standard diagnostic tools used in registration studies of Eylea and other anti-VEGF therapies. The assessment of BCVA, as a measure of retinal function, will be performed using standard procedures extensively used in clinical studies.

8.4 Safety

Safety assessments will include physical examination, vital signs, ophthalmic examinations, laboratory evaluation as well as monitoring and recording type, frequency, and severity for all AEs. Safety assessments are specified below with Table 8-1 Assessment schedule detailing when each assessment is to be performed.

All equipment including applications/software must be calibrated, validated and/or maintained according to the applicable regulations/guidelines, manufacturer's recommendations and local practices prior to performing any study specific activities.

For details on AE collection and reporting, see Section 10.1.1 Adverse events.

Table 8-2 Assessments and specifications

Assessment	Specification
Physical examination	Physical examination will be performed at Screening and at the EOS visit, as a general health check according to local clinical practice. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF page that captures medical history. Clinical significant findings identified after signing informed consent which meet the definition of an AE must be recorded as an adverse event on the Adverse Event section of the eCRF.
Vital signs	Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg), body temperature, respiratory rate (in breaths per minute) and pulse rates (in beats per minute) and will be collected in all visits before treatment and blood collection. Body temperature should be collected according to the standard local practice.

Assessment	Specification
	After the participant has been sitting for 5 minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff. If the blood pressure measurement is elevated as specified in the exclusion criteria, at the Screening visit, the blood pressure measurement must be repeated after 20 minutes. If the repeated measurement is elevated, then the participant is not eligible to be enrolled into the study. The results will be recorded in the eCRF.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at applicable visits (Screening, Week 8, Week 24 and EOS visit), except the urine, which will be analyzed at each site. Samples for Bioanalytical testing (aflibercept concentrations, immunogenicity testing) will be performed at the Sponsor laboratory or a qualified contract laboratory. CCI

CCI

Details on the collection, shipment of the samples and reporting of the results by the central laboratory are provided in the applicable manual.

All blood samples will be obtained by venipuncture, at the time points outlined in Table 8-1 Assessment schedule. The date and time of blood collection will be recorded in the participant's medical record.

Unscheduled laboratory assessments may be obtained at any time during the study to assess any perceived safety concerns.

No specific action is pre-defined within the protocol to respond to specific abnormal laboratory values, as it will be decided by the Investigator, taking into account the overall status of the participant.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse events as appropriate. Clinically notable laboratory findings are defined in the Laboratory Manual.

Table 8-3 Laboratory assessments

Test category	Test name
Hematology	Hematocrit, hemoglobin, red blood cells count (RBC), white blood cells count (WBC) with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and quantitative platelet count
Chemistry	Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium, magnesium), uric acid, urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT)/alanine

Test category	Test name
	aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH)
Urinalysis	Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessment. Dipstick measurements for specific gravity, pH, protein, glucose, ketones, bilirubin, nitrite, leucocyte and urine occult blood
Coagulation	International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum/urine pregnancy test (see Section 8.4.4 Pregnancy and assessments of fertility)
Additional Test	FSH (see Section 8.4.4 Pregnancy and assessments of fertility)

8.4.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity and the emergence of antibodies to human recombinant proteins is well documented. Antibodies directed against a therapeutic agent may have neutralizing activity and interfere with the efficacy of the treatment. For safety reasons, evaluation for ADA has been included in this study.

8.4.2.1 Immunogenicity blood sample collection and handling

Immunogenicity will be assessed by measuring ADA levels in serum of all participants. Blood samples for ADA assessment will be collected from all participants randomized and treated at the time points defined in the assessment schedule in Table 8-1. Additional sampling and evaluation for ADAs will be collected (unscheduled samples) in case of signals of an unexpected ocular inflammation.

Sample collection, labeling, processing of serum, shipment and storage should be performed as per instructions provided in the laboratory manual.

The actual exact sample collection date and time must be recorded on the appropriate CRF. Communication of immunogenicity results to Investigators occurs after DBL and finalization of the Clinical Study Report.

8.4.2.2 Analytical methods for ADA

Immunogenicity of SOK583A1 as determined by the formation of antibodies against the drug will be evaluated by using validated immunoassays. The validation procedure and serum sample analysis will follow international guidelines.

All samples will first be analyzed in a screening assay. Study samples with a result below the validated screening cut-point are negative for binding ADA and will be reported accordingly. In the event of a positive result (result above the screening cut-point) the sample will be additionally analyzed in a secondary confirmatory assay (specificity assay). In case the assay signal can be reduced after addition of excess of SOK583A1 beyond the validated confirmatory cut-point, a sample will be reported as confirmed positive. In contrast, samples with a result above the screening cut-point in the screening assay but which are negative in the confirmatory assay will be reported as negative.

The titer of confirmed positive results will be reported. In addition, confirmed positive ADA samples will be analyzed for their neutralization potential in a neutralizing antibody assay.

Serum samples to determine total drug concentrations will be obtained at the same time as immunogenicity samples to support result interpretation. For details on the drug concentration determinations, see also Section 8.5.1 Pharmacokinetics.

All immunogenicity assays will be performed at the Sponsor's bioanalytical laboratory or a qualified contract laboratory.

8.4.3 Complete ophthalmic examination

Pupil dilatation for slit lamp examination and ophthalmoscopy can be performed as optional according to local practice. The ophthalmic exam will consist of the following:

- **Slit-lamp examination** – included evaluation of the lids/lashes, conjunctiva, cornea, iris, lens, and aqueous reaction (cells and flare). This test should be completed at every scheduled visit to examine the study eye. The fellow eye will be examined at Screening and on the discretion of the masked Investigator. The test results will be recorded in the source documents only. Any clinically significant abnormalities (as judged by the masked Investigator) should be recorded on the AE page of the eCRF.
- **IOP measurement** – The tonometry method must remain consistent throughout the study for each participant. The IOP should be assessed by the masked Investigator/masked staff in the study eye, pre-dose and post-dose at every scheduled visit with the exception of the assessment 0-5 minutes after the IVT injection, which may be conducted, if needed, by the unmasked Investigator at his/her discretion. The study eye IOP values (mmHg) must be entered into the eCRF.

  In the fellow eye, IOP will be assessed at Screening and the value (mmHg) must be entered into the eCRF. In the other visits, fellow eye IOP assessment is done on the discretion of the Investigator and the values will be documented at medical source only.

  Treatment and close monitoring of IOP should be performed by the Investigator according to local clinical practice for any non-transient elevation in the IOP (≥ 25 mmHg). Intravitreal procedure is not recommended unless normalization of IOP has been achieved. Post-dose IOP should be assessed after every IVT injection, between 30-60 minutes after injection and if IOP ≥ 25 mmHg, assessment should be repeated until back to normal.

  Any clinically relevant abnormalities in either eye should be recorded on the AE page of the eCRF.
- **Fundus exam/Ophthalmoscopy** – includes evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilatation for the fundus exam is at the discretion of the masked Investigator. This test should be conducted by the Investigator at the Screening visit and at all other visits, in the study eye. The fellow eye will be examined at Screening and on the discretion of the Investigator. An examination of the peripheral retina must also be conducted to ensure that the IVT injection can safely be performed. The test results will be recorded in the source documents only. Any clinically significant abnormalities (as judged by the masked Investigator) should be recorded on the AE page of the eCRF.

8.4.4 Pregnancy and assessments of fertility

For women 50 years or older in the study, pregnancy is not expected. However, to avoid exceptional rare occurrences, all pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Highly effective contraception is required for women of child-bearing potential during the study drug administration and for 3 months after stopping the study drug.

A serum pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at Screening visit and then, at EOS. During the study, urine pregnancy testing should be done at monthly intervals. When a visit is not planned for a month (during the maintenance period), the clinical site team should schedule clinic visits monthly for urine pregnancy tests. The positive urine test needs to be confirmed with serum test. If positive, the participant must be discontinued from study treatment. Refer to Table 8-1 Assessment schedule. Results of all pregnancy testing must be available as source documentation.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening

8.4.5 Post-injection assessment

The study eye will be assessed before, immediately after 0-5 minutes and after 30-60 minutes after each IVT injection. The unmasked Investigator is responsible to conduct the assessment occurring immediately after the injection (0-5 minutes post-injection assessment). All other post-injection assessments must be performed by the masked Investigator. These assessments include gross assessments of:

- vision (e.g. count fingers, hand motion, light perception, no light perception),
- the status of the central retina artery, by direct visualization, at the discretion of the investigator,
- presence of retinal detachment, by direct observation of the retina, at the discretion of the Investigator,
- presence of new intraocular hemorrhage, at the discretion of the Investigator,
- measurement of IOP immediately after 0-5 minutes of IVT injection, at the discretion of the Investigator.

IOP measurement is mandatory after 30-60 minutes after each IVT injection. In case of abnormal findings, assessments will continue on intervals at the discretion of the Investigator, until the central retinal artery is adequately perfused and the IOP is back to normal.

Any participant who develops significantly raised IOP (≥ 25mmHg) or a non-adequately perfused central retinal artery at any time during the study should be monitored according to the Investigator's clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol. If, at the conclusion of the required evaluation period following an injection there are no safety concerns, the participant will leave the site. If any concern or immediate toxicity is noted, the participant will remain at the site and will be treated according to the designated evaluating physician's clinical judgment. If any issues regarding IOP are noted during the post-injection assessment, then the participant should be scheduled for a follow up visit (Unscheduled Visit) the day following injection, if required in the opinion of the Investigator.

Clinically relevant changes that are observed during the post-injection assessment should be reported as AEs. Participants should be instructed to contact the Investigator immediately to report symptoms as e.g. eye pain, redness of the eye, photophobia, blurring of vision.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population and also aligned with the safety assessments as per Eylea's safety profile (Eylea EU SmPC; Eylea US PI).

8.5 Additional assessments

8.5.1 Pharmacokinetics

Free aflibercept and total aflibercept will be quantified in plasma and serum, respectively, using validated assays detecting both Eylea and SOK583A1. Concentrations will be expressed in mass per volume units.

Concentrations below the LLOQ and missing data will be labeled as such in the Bioanalytical Report and respective data transfers. The concentrations will be summarized by treatment and time point for which the concentrations below LLOQ will be treated as zero.

8.5.1.1 Pharmacokinetics blood sample collection and handling

PK samples for determination of free and total aflibercept will be collected from 20 participants per arm at Visit 2 (pre-dose and 24 (±1) hours after the first dose) and Visit 5 (approximately 24 (±1) hours post-dose), as defined in the assessment schedule.

Additionally, blood samples for determination of total drug concentration will be collected from all participants at the same time points as ADA sample collection is performed (see assessment schedule indicated in Table 8-1 Assessment schedule), to support result interpretation of immunogenicity analysis. Total drug blood samples will also be taken at unscheduled time points, in case of additional sampling and ADA evaluation (unscheduled samples) as indicated in Section 8.4.2.2 Analytical methods for ADA.

Sample collection, labeling, processing to serum or plasma, shipment and storage should be performed as per instructions provided in the laboratory manual.

8.5.1.2 Analytical methods for pharmacokinetics

Two bioanalytical methods will be used to determine free and total aflibercept concentrations in plasma or serum samples, respectively, obtained for nAMD participants in this study. Briefly, the concentration of free or total aflibercept will be determined in validated immunoassays. The concentration of aflibercept in the study samples will be determined by interpolation using a standard curve with known concentrations of aflibercept. Concentrations will be expressed in mass per volume unites (ng/mL). All assessments will be performed at the Sponsor's bioanalytical laboratory or a qualified contract laboratory.

8.5.2 Imaging

The methods for assessment and recording of SD-OCT, color fundus photography and FA are specified in the Central Reading Center Imaging Manual.

8.5.3 Systemic VEGF concentrations

Only patients receiving anti-VEGF treatment for the study eye are eligible for evaluation of systemic VEGF concentrations. Subjects receiving anti-VEGF treatment for both eyes are excluded from participation in the evaluation of systemic VEGF concentrations.

Blood (plasma) samples will be collected from those participants who agree to additional blood collection for evaluation of systemic VEGF concentrations at Visit 10 (Week 48, pre-dose) and Visit 11 (Week 52).

Sample collection, labeling, processing to plasma, shipment and storage should be performed as per instructions provided in the laboratory manual.

Free VEGF will be quantified in plasma using a validated assay. The concentration of free VEGF in the study samples will be determined by interpolation using a standard curve with known concentrations of VEGF. Concentrations will be expressed in mass per volume units (pg/mL).

All assessments will be performed at the Sponsor's bioanalytical laboratory or a qualified contract laboratory.

9 Discontinuation and completion

9.1 Discontinuation of study treatment and from study

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any), and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

The Investigator and/or referring physician will recommend the appropriate follow-up medical care, if needed, for all participants who are prematurely withdrawn from the study.

Participants who started study treatment but prematurely discontinued treatment and/or study will not be replaced.

Discontinuation of study treatment is required under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of rescue treatment in the study eye or prohibited treatment as per recommendations in Section 6.2.2 Prohibited medication
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unmasking as per Section 6.6.3 Emergency breaking of assigned treatment code

If discontinuation of study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue from study treatment agree to return for the EOS assessments indicated in the assessment schedule (refer to Section 8 Visit schedule and assessments).

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new/concomitant treatments
- Adverse events/Serious Adverse Events

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment and inform the date and primary reason for stopping the study treatment

If discontinuation occurs because the treatment code has been broken, see Section 6.6.3 Emergency breaking of assigned treatment code.

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8 Visit schedule and assessments).

9.1.3 Lost to follow up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw

consent/oppose to the use of their data/biological samples, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want further visits or assessments (including further study-related contacts)

This request should be documented in written (depending on local regulations) and recorded in the source documentation.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8 Visit schedule and assessments).

Sponsor will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their EOS and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All randomized and/or treated participants should have a safety follow-up visit (EOS) conducted 4 weeks after last administration of study treatment. The information collected must

be included at eCRF and is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 SAE reporting. Documentation of attempts to contact the participant should be recorded in the source documentation.

The Investigator is advised to provide appropriate follow-up nAMD treatment for all participants completing the study or prematurely withdrawn from the study.

9.4 Early study termination by the Sponsor

The study can be terminated by Sponsor at any time. The Sponsor may terminate this study prematurely, either in its entirety or at any study site.

Reasons for early termination, but not limited to:

- Failure by the participant and/or the study site to comply with the protocol (e.g. noncompliance), the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator/failure of the Investigator to enter study participants at an acceptable rate
- Recommendations from applicable board(s) after review of safety data based on the number and/or severity of suspected unexpected serious adverse reactions (SUSARs)/SAEs/AEs in the study, or new data becoming available, which raise concern about the safety profile of the study treatment.
- **High frequency** of adverse events
- Recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of further study drug development

In taking the decision to terminate, Sponsor will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible for a final visit and treated as a participant who discontinued from study treatment. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Sponsor/delegated depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the study.

10 Safety monitoring, reporting, and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participant and identifying AEs.

Sponsor qualified medical personnel will be readily available to advise on study related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information as far as possible. If the event is serious, see Section 10.1.2 Serious adverse events:

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment or the ocular injection procedure. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the study drug, but they occur in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All AEs must be treated appropriately. Treatment may include 1 or more of the following:

- no action taken (e.g. further observation only)
- study drug interrupted/withdrawn
- concomitant medication or non-drug therapy given
- participant hospitalized/participant's hospitalization prolonged (Section 10.1.2)

6. Its outcome:
   - not recovered/not resolved
   - recovered/resolved
   - recovering/resolving
   - recovered/resolved with sequelae
   - fatal
   - unknown

Conditions that were already present at the time of informed consent should be recorded in the medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued for at least 4 weeks following the last dose of study treatment. For participants that have withdrawn consent or discontinued treatment; see Section 9.1 Discontinuation.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) regarding any changes in severity, suspected relationship to the study drug, interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory are included in the Laboratory Manual.

10.1.2 Serious adverse events

An SAE is defined as any AE (appearance of (or worsening of any pre-existing)) undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency out-patient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 4 weeks after the last administration of study treatment must be reported to Sponsor safety immediately, without undue delay, but under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, under no circumstances later than within 24 hours of the Investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered as completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the Investigator for Health Authority reporting. The sponsor may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance

2011/C 172/01 or as per national regulatory requirements in participating countries. The incidence of key AEs, such as intraocular inflammation or endophthalmitis, will be followed closely by the sponsor during the study duration.

Any SAEs experienced after the last visit (EOS) should only be reported to Sponsor Safety if the Investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female study participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the study participant. The participant must be given adequate time to read, review and sign pregnancy consent form. This consent form is necessary to allow Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Sponsor CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. The newborn should be followed up for 12 months after the date of delivery.

Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety CMO&PS only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, see the corresponding sections above.

10.2 Additional Safety Monitoring

Not applicable

10.3 Committees

A Data Monitoring Committee is considered not required for the study A12301 based on following reasons:

- the study is performed in patients with nAMD, which is a non-critical (i.e. not life-threatening) indication in a non-special (e.g. pediatrics or mentally disabled) population
- analytical data demonstrate a high degree of structural and functional similarity between SOK583A1 and Eylea
- the safety of excipients used for SOK583A1 formulation has been shown with other medications available in the market for treatment of nAMD
- the safety profile of aflibercept is established and well known
- the Sponsor will closely review all adverse events, specially, post-injection endophthalmitis, intraocular infections/inflammations, and will conduct clinical and product safety assessments; selective unmasking may be considered in case of a significant concern is identified during the study conduct

No interim analyses for early stopping or design modification are planned.

11 Data Collection and Database management

11.1 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final DBL, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Sponsor personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated masked Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical

classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to the Sponsor. Color fundus photography, fluorescein angiograms, and OCT images will be processed centrally by the CRC and the results will be sent electronically to Sponsor. The data manager staff will perform a reconciliation of the data entered on the eCRF versus what is received from the CRC and central labs.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all study treatment changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Sponsor (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the designated clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Sponsor.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Sponsor development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a delegated Sponsor/CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the Investigators and their staff. During the study, Sponsor employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized CRA organization. Additionally, a central analytics organization may analyze data, identify risks and trends for site operational parameters, and provide reports to Sponsor clinical teams to assist with study oversight.

The Investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, retinal images and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The Investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Sponsor monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional

checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Data analysis will be performed at 2 time points: an interim analysis after all subjects completed Week 40 or discontinued before Week 40 and a final analysis after all subjects completed the study. Analysis of the primary endpoint (mean change from Baseline in BCVA at Week 8) will be conducted on all participants in the Per-Protocol Set (PPS) at the interim analysis. Any efficacy and safety data of participants collected during the study will also be analyzed for the final analysis

Any data analysis carried out independently by the Investigator should be submitted to the Sponsor before publication or presentation.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized participants. The RAS will include all participants who were randomized including those that were not treated.

The Full Analysis Set (FAS) comprises all randomized participants to whom study treatment has been assigned by randomization, to whom at least one treatment was administered and for which at least one post-baseline BCVA value is available. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed according to the study treatment received.

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

- The primary BCVA assessments at baseline and Week 8 are available
- The participants received treatment according to the protocol at Day 1 and Week 4
- The participants have not experienced any important protocol deviations up to Week 8

The criteria to qualify a protocol deviation as important regarding the evaluation of the study's primary objective will be provided in the SAP.

The PK Analysis Set (PKS) will be the analysis set used for analyzing free and total drug concentration in a subset of participants. The PKS comprises participants with at least one evaluable post-baseline drug concentration assessment. Participants requiring both eyes treatment at baseline are not eligible for the PK substudy. Participants who start with uni-lateral nAMD at baseline but convert to bi-lateral nAMD during PK assessment period and get aflibercept treatment will be excluded from PK analysis.

The VEGF Analysis Set will be the analysis set used for evaluating systemic VEGF concentrations in a subset of participants. The VEGF Analysis Set comprises those participants who received study treatment at Week 48 and have a VEGF concentration assessment at Week 52. Participants requiring treatment of both eyes are not eligible for the evaluation of systemic VEGF concentrations.

The Immunogenicity Analysis Set (IAS) consists of all randomized patients who received at least one dose of the investigational treatment (SOK583A1 or Eylea EU) and have immunogenicity blood samples collected and analyzed at Baseline and at least 1 time point post-baseline. Patients with positive immunogenicity at Baseline will be excluded from IAS.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS, PPS and Safety Set. Descriptive statistics will be produced for age as a continuous variable, but age will also be included as age categories (< 75 years and ≥ 75 years), and BCVA as a continuous variable and BCVA categories (< 64 letters and ≥ 64 letters).

Categorical data will be presented as frequencies and percentages. For continuous data, mean, SD, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, for all participants in the FAS by treatment group.

12.3 Treatments

Study medication administration will be summarized for all participants in the Safety Set by treatment. All treatment-related information will also be listed by treatment. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The extent of treatment exposure will be presented based on the overall number of injections and the number of participants injected per visit using the Safety set.

Prior medications (any medication taken up to 90 days prior to Screening) and concomitant medications (ocular and non-ocular) will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group. Additionally, the number and percentage of participants who had procedures performed during the study will be summarized by SOC and PT according to MedDRA terminology.

12.4 Analysis of the primary estimand

12.4.1 Definition of primary endpoint(s)

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

12.4.2 Statistical model, hypothesis, and method of analysis

The primary aim of the study is to demonstrate equivalence of change in BCVA score from Baseline at Week 8 between participants with nAMD treated with SOK583A1 and participants treated with Eylea EU. The primary analysis will be performed on the PPS, which is the most

appropriate analysis set to use when testing for equivalence. The justification of the corresponding primary estimand is detailed in Section 2.1 Primary estimands.

FDA and EMA have different requirements on the equivalence testing for the primary endpoint :

- EMA equivalence testing requirements: To demonstrate the equivalence of the difference in change from baseline at Week 8 in BCVA, the resulting 95% CI of the difference must lie within the equivalence interval of [-3.5, 3.5].
- FDA equivalence testing requirements: To demonstrate the equivalence of the difference in change from baseline at Week 8 in BCVA, the resulting 90% CI of the difference must lie within the equivalence interval of [-3.0, 3.0].

The following statistical hypotheses will be tested to assess equivalence between SOK583A1 and Eylea EU in terms of change from baseline in BCVA score at Week 8.

H0: $|SOK583A1 - Eylea| \geq \Delta$ versus H1: $|SOK583A1 - Eylea| < \Delta$

Therapeutic equivalence in terms of change from Baseline in BCVA for EMA requirement will be concluded if the 95% CI for the difference in mean changes is 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 have to be successful.

Therapeutic equivalence in terms of change from baseline in BCVA for FDA requirement will be concluded if the 90% CI for the difference in mean changes is contained within the interval [−3.0; 3.0]. This is statistically equivalent to calculating 2 independent one-sided tests at a 5%-alpha level, of which both have to be successful.

Analysis of covariance (ANCOVA) will be performed and the model will include treatment as a factor, and Baseline BCVA and age as continuous covariates. The least-squares means for the treatments will be calculated and the CIs for the difference in the 2 products will be obtained from the ANCOVA model. Consistent with the two one-sided tests for bioequivalence at the 2.5% significance level (Schuirmann 1987), 95% CIs for change from Baseline in BCVA will be derived. Similarly, 90% CIs for change from Baseline in BCVA will be obtained.

12.4.3 Handling of remaining intercurrent events of primary estimand

Since the primary analysis is only on those participants who adhere to and complete treatment and do not have important protocol deviations, there will be no intercurrent events for the observed PP estimand.

12.4.4 Handling of missing values not related with intercurrent events

As primary analysis will be performed on PPS as defined in section 12.1, there will be no or minimum missing data for primary endpoint, the change from baseline at Week 8 in BCVA scores. Therefore, no imputation for missing data will be performed for primary analysis.

12.4.5 Sensitivity analyses for primary estimand

A sensitivity analysis will be conducted to impute missing data using last observation carried forward (LOCF) method if missing data of primary endpoint is observed in PPS. Observed

values from both scheduled and unscheduled visits will be used for the LOCF imputation. For participants with no post-baseline value, no imputation will be performed.

In addition, sensitivity analysis to compare the results from the ANCOVA model for the primary estimand with a MMRM model will be performed. The MMRM model will include treatment, visit and interaction between time and treatment as categorical variables, and age and baseline BCVA as continuous variables. As the model can handle partial data from a participant when estimating the variance-covariance matrix, participants with both baseline BCVA value and at least one available value at Week 4 or Week 8 will be included in the analysis. This sensitivity MMRM analysis will be conducted using the PPS.

12.4.6 Supplementary analysis

To explore the robustness of inferences from the primary observed PP estimand, a supplementary analysis on FAS using the same statistical model of ANCOVA as for the primary analysis will be performed. Missing data will be imputed using LOCF imputation. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For participants with no post-baseline value, no imputation will be performed.

Sensitivity analysis to compare the results from the ANCOVA model for supplementary analysis with a MMRM model will be performed. The MMRM model will include treatment, visit and interaction between time and treatment as categorical variables, and age and baseline BCVA as continuous variables. As the model can handle partial data from a participant when estimating the variance-covariance matrix, participants with both baseline BCVA value and at least one available value at Week 4 or Week 8 will be included in the analysis. This sensitivity MMRM analysis will be conducted using the FAS.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoint(s)

- Mean change in BCVA score from Baseline to Week 24 and Week 52 will be summarized descriptively by treatment.
- Mean change in CSFT (as determined by SD-OCT from CRC) from baseline to Weeks 1, 4, 8, 24 and 52 will be summarized descriptively by treatment
- Mean change of CNV lesion size using FA from Screening to Weeks 8 and 52 will be summarized descriptively by treatment

12.5.2 Safety endpoints

For all safety analyses, the Safety Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from Baseline summaries). Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to 4 weeks after the date of the last actual administration of any study treatment.

There are no formal safety hypotheses in this study. All safety analyses will be performed using the Safety Set. The safety endpoints are based on the variables from the safety assessments which include:

- Ocular and non-ocular and systemic treatment-emergent AEs and SAEs
- Ophthalmic examinations
- Vital signs
- Laboratory results
- Post-injection assessments
- ADA (development of binding and neutralizing ADA up to Week 52)

Adverse events

A treatment-emergent AE is defined as any AE that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment. All information obtained on adverse events will be displayed by treatment group and participant

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-masked treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity

Separate presentations will be provided related to ocular events in the study eye and fellow eye and systemic events. Sensitivity safety analyses excluding participants requiring treatment of a fellow eye during study will be performed. Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

Additional subgroup analyses by ADA status (positive, negative) will be performed.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

There is no planned statistical testing in the safety analyses. Listings of death, SAEs, AEs leading to study treatment discontinuation, AE leading to study withdrawal and study treatment related AEs will be provided.

Vital signs

All vital signs data (blood pressure, pulse, respiratory rate and body temperature) will be listed by treatment group, participant, and visit/time. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by

treatment and visit/time. Shift tables using the low/normal/high/(low and high) classification will be used to compare baseline value to post baseline value by treatment and visit.

Values outside the extended normal range will be listed by participant and treatment arm and flagged in data listings.

Ophthalmic examinations

Pre-injection IOP measurements will be presented descriptively (absolute values and change from baseline). Post-injection IOP measurements will be listed.

Immunogenicity

For all immunogenicity analyses, the IAS will be used. All immunogenicity results will be listed by treatment group, participant, and visit. The incidence of participants who develop binding ADAs and neutralizing antibodies (NAbs) by visit and overall will be compared between treatment, descriptively. In addition, summary of the immunogenicity results of the participants that received aflibercept treatment in the fellow eye will be presented.

12.5.3 Pharmacokinetics

Free (plasma) and total (serum) aflibercept concentration data of participants included in the PKS will be listed by treatment, participant, and sampling time point. Descriptive summary statistics for free and total drug concentrations will be provided by treatment and sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include arithmetic mean, SD, coefficient of variation, median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics.

Additionally, success criteria (assessment of non-similarity between the SOK583A1 and Eylea) will be specified in the SAP before DBL as per EMA recommendation.

12.6 Analysis of exploratory endpoints

12.6.1 Evaluation of systemic VEGF concentrations

Free plasma VEGF concentration data of participants included in the VEGF Analysis Set will be listed by treatment, participant, and sampling time point. Descriptive summary statistics for free VEGF concentrations will be provided by treatment and sampling time point, including the frequency (n, %) of concentrations below the LLOQ. Percentage change in VEGF concentrations from Week 48 to Week 52 will also be summarized.

Summary statistics will include arithmetic mean, SD, coefficient of variation, median, minimum, and maximum.

12.7 Interim analyses

An Interim analysis will be performed after all participants have completed Week 40 or discontinued prior to Week 40. Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point. A final analysis will be performed after all

participants have completed Week 52 (or discontinued prior to Week 52). The Clinical Study Report post final analysis at Week 52 will be cumulative and will also include the analyses from Week 40 cut-off primary Clinical Study Report.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Margin justification

The equivalence margin for the mean difference in the primary endpoint was discussed and have been agreed with FDA, EMA and PMDA.

The meta-analysis for justification of the equivalence margin is based on data from eight studies of anti-VEGF therapies in nAMD patients: 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); and HAWK and HARRIER (Dugel et al 2020). All studies included in the analysis are randomized controlled trials (RCTs) with a total of 3562 patients treated with aflibercept 2 mg, ranibizumab 0.5 mg, or having received a sham injection. BCVA in letters at two months (8 weeks) was assessed in all of the studies. A meta-analysis was performed with the available data from these studies to support the proposed EQ margin. The mean change in BCVA at two months (8 weeks) and the standard error were extrapolated from the respective publication. 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 for the data. The inverse value of the variance was used as the exponential family dispersion parameter weight for each observation. The results from the meta-analysis are presented in Table 12-1 and Table 12-2.

Table 12-1 Treatment Least Square Means at Week 8

			95% CI	
Treatment	**Estimate**	**Standard Error**	**Lower**	**Upper**
Aflibercept 2 mg	6.1626	0.4210	5.3374	6.9878
Ranibizumab 0.5 mg	6.7229	0.2931	6.1485	7.2973
Sham Injection	-2.6135	0.6813	-3.9488	-1.2782

Table 12-2 Differences of Treatment Least Square Means at Week 8

			95% CI	
Treatment Comparisons	**Estimate**	**Standard Error**	**Lower**	**Upper**
Aflibercept 2 mg vs Sham Injection	8.7761	0.9018	7.0087	10.5436
Ranibizumab 0.5 mg vs Sham Injection	9.3364	0.7269	7.9118	10.7610
Aflibercept 2 mg vs Ranibizumab 0.5 mg	-0.5602	0.5337	-1.6063	0.4858

The point estimate of the mean difference for change from baseline in BCVA at 8 weeks between aflibercept and sham injection is +8.8 letters with a 95% CI of (+7.00, +10.54).

The lower bound of the 95% CI is used to justify an appropriate margin.

EMA and PMDA considered the proposed margin of ± 3.5 letters as acceptable as it retains at least 50% of the treatment effect and is well away from the 5 letters (a 5 letters loss in BCVA has been used as a retreatment criterion in several studies).

FDA considered a margin of ± 3.0 letters as acceptable.

Based on EMA and PMDA requirements:

The sample size is based on considering EqM (equivalence margin) of ± 3.5 letters, using a 95% CI and SD of 10 letters for the change from Baseline in BCVA at Week 8. Assuming no difference between SOK583A1 and Eylea, at least 214 participants per treatment group (428 evaluable participants in total) will be required for the study with 90% power to show equivalence of SOK583A1 to Eylea. The limits of a two-sided 95% CI will exclude a difference in means of more than 3.5 letters in the change from Baseline in BCVA.

Based on FDA requirements:

The sample size is based on considering EqM (equivalence margin) of ± 3.0 letters, using a 90% CI and SD of 9.5 letters for the change from Baseline in BCVA at Week 8. Assuming no difference between SOK583A1 and Eylea, at least 218 participants per treatment group (436 evaluable participants in total) will be required for the study with 90% power to show equivalence of SOK583A1 to Eylea. The limits of a two-sided 90% CI will exclude a difference in means of more than 3.0 letters in the change from Baseline in BCVA.

Combined sample size:

The sample size of 460 participants planned to be randomized in the study will cover both FDA and EMA requirements, including the expected drop-out rate of 5%. As COVID-19 pandemic situation may evolve during the study conduct, leading to higher overall proportion of missing data, an assessment to change the assumption for the drop-out rate will be performed and the sample size increased accordingly.

Table 12-3 Assumptions for sample size calculations based on FDA and EMA requirements

	EMA	FDA
Confidence level	95%	90%
Power	90%	90%
EqM	3.5 letters	3.0 letters
Treatment difference	0	0
SD	10 letters	9.5 letters
N per treatment arm	214	218
Drop-out rate	5%	5%
Sample size	452	460

12.8.2 Secondary endpoint(s)

None of the secondary endpoints are considered as key secondary endpoints and therefore no sample size calculation was performed for these.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a study, the Investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the study protocol, written ICF, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign the protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Sponsor monitors, auditors, Sponsor Quality Assurance representatives, designated agents of Sponsor, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this study will be submitted for publication and posted in a publicly accessible database of clinical study results, such as the Novartis clinical study results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

Details of the Sponsor publication policy including authorship criteria based on the Sponsor publication policy will be provided as training materials at the study Investigator Meetings and included into the Site File.

Any data analysis conducted independently by the Investigators should be submitted to the Sponsor before publication or presentation.

13.4 Quality Control and Quality Assurance

Sponsor maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of Investigator sites, vendors, and Sponsor systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical study. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Sponsor processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Sponsor and not use it for any purpose other than the study, except for the appropriate monitoring of study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

Not applicable