Sandoz Biopharmaceuticals Clinical Development

SOK583 (INN: aflibercept) / NCT04864834

CSOK583A12301

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

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
13-Apr-2021	Prior to DB lock	Creation of final version	N/A - First version	NA
28-Feb-2022	Prior to DB lock	Updates made to be consistent with amended study protocol	Second version	General update: new SAP template was applied. Wordings were updated to increase clarity. Section 1: study design figure was updated as per the amended study protocol (V3.0). New Table 1-1 Primary assessment schedule was added. Original Table 1-1 was updated to Table 1-2 Objectives and related endpoints Estimands was moved to section 1.2 per new SAP template and the wordings were updated as per the amended study protocol (V3.0). Table 2-1: additional criteria were updated. Section 2.5: co-primary estimand was removed. Missing data handling methods were updated as per the amended study protocol (V3.0).
08-Nov-2022	Prior to DB lock	Updates made to be consistent with amended study protocol and mail communication to update study treatment name.	Version 3.0	Section 1.2 : CCI [redacted] and update to timepoint for secondary endpoint based on CNV lesion size. Section 2.2 : All Enrolled Analysis Set and VEGF Analysis Set added. Section 2.2.1: Batchwise subgroup analysis removed. Section 2.8 : Updated on PK Endpoint to add analysis on PK Similarity Section 2.9 added for analysis of Pharmacodynamic Endpoint. Section 5.3.3 added to address statistical analysis on endpoint based on PK Similarity. Study Treatment name SOK583A1 updated to SOK583 based on mail communication. Section 2.2 , 2.3.2, 2.7.1 : All Enrolled Analysis Set added and Listings to provided based on All Enrolled Set for Demographic , AE & Medical History. Section 2.3.1 : Analysis on Reason for Screen failure removed. Section 2.3.2: Medical History Added and analysis set changed for Demographic listing.Section 2.6.3 added on analysis of Japanese Population. Section 2.7.1: Batchwise analysis removed for AE tables.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				Section 2.8, 2.9: Section Updated for analysis part. Section 2.10.3 updated Section 5.3.3 & 5.4 added. Table 2-1, Criteria added
24-Mar-2023	Prior to DB Lock	- PD criteria updates, analysis added for study procedure, CM & TEAE definition updates, - Sensitivity Analysis removed due to no missing values, Immunogenicity analysis updated to reflect overall evaluation for both W40 and W52. - Information on prohibited medication / procedure added.	Version 4.0	1. MedDRA Version updated 2. Table 2-1 updated by updating information in COMD01, COMD02 and removal of PD OTH22. Section 2.3.1 updated for change in population set of Importatnt PD listings and population set of analysis set table. - Section 2.2 updated to clarify the term “requiring” in the definition of PKS and VEGF analysis set. 2. Section 2.2.1 subgroup analysis added on TEAE by sugroup of interest. - Section 2.5.7 merged with section 2.2.1 - Section 2.2.1 updated on Japan population consideration. 3. Section 2.4 updated for more brief definion of Concomitant Medication. - Section 2.4.1 & 2.4.2 updated for precise information on analysis. 3. Section 2.6.2 updated based on analysis on BCVA to display for all post-baseline visits. - CNV values with CNV ABSENT will be considered as Zero for analysis purpose. 4. Section 2.7.1 updated to add analysis on Ocular TEAE related on study procedure. - Updates to perform sensitivity analysis based on fellow-eye. -TEAE definition updated in more brief. - Relationship of Study procedure and Injection procedure. 5. Section 2.7.4.2 updated for additional information on value consideration for post-injection IOP based on communication with Medical Lead. 6. Section 2.7.1.1 updated to substitute AESI as “AE according to the risks listed in Eylea EU RMP” as decided in November’s Clinical Strategy Team 2.0. 7. Subgroup analysis based on Japanese population is removed except for analysis output same as primary objective as per Clinical Strategy Team decisions.

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
				8. Section 5.1.4 added for partial nAMD start date imputation. Section 5.1 updated for AE & CM imputation rule as per data cut-off. 9. Section 5.4 ATC code list updated & List of Prohibited procedures 10. Section 2.10.2 updated to add analysis on duration of exposure. 11. Sensitivity Analysis of Primary endpoint based on LOCF approach is removed from analysis. 12. Section 2.7.4.3 updated to perform overall evaluation At Week 40 & Week 52 both. definition added on persistent.
03-Apr-2023	Before DBL	To align with condition of protocol on prohibited medication	Version 5.0	1. Updates in Table 2-1 to clearly specify prohibited medication criteria and to align as per protocol defined. 2. Section 2.2 , Handling analysis scenario if subject receives both treatments into the study eye.
22-Jun-2023	Before Week 52 (Final) DBL	Update for final analysis; VEGF analysis set definition update, updates in Persistent definition for Overall (Week 52)	Version 6.0	Section 2.2 , 2.3.1, 2.7.1, 2.7.4.3, 5.3.4

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ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CI	Confidence interval
CM	Concomitant medication
CNV	Choroidal neovascularization
COVID-19	Coronavirus disease of 2019
CRC	Central Reading Center
CSR	Clinical study report
CSFT	Central Subfield Thickness
CTD	Common Technical Document
CV	Coefficient of variation
eCRF	Electronic Case Report/Record Form
eCRS	Electronic Case Retrieval Sheet
ETDRS	Early Treatment Diabetic Retinopathy Study
EqM	Equivalence margin
Eylea EU	EU-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
FDA	Food and Drug Administration
GCV	Geometric coefficient of variation
GM	Geometric mean
GMR	Geometric mean ratio
IAS	Immunogenicity analysis set
ICF	Informed Consent Form
IOP	Intraocular pressure
IRT	Interactive Response Technology
IVT	Intravitreal
LS	Least Squares
LLOQ	Lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-model repeated measures
nAMD	Neovascular age-related macular degeneration
PD	Protocol deviation
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)

PP	Per-protocol
PPS	Per-protocol analysis set
PT	Preferred Term
RAS	Randomized analysis set
RMP	Risk Management Plan
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SD-OCT	Spectral-Domain Optical Coherence Tomography
SE	Standard error
SOC	System Organ Class
SOK583	Product code of Sandoz' proposed aflibercept containing biosimilar product
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures and Listing
VEGF	Vascular Endothelium Growth Factor
WHODD	World Health Organization Drug Dictionary

1 Introduction

The purpose of the SAP is to describe the implementation of the statistical analyses planned in the protocol. The analyses described are based on the Clinical Study Protocol (CSP) Version 4.0 (incorporating amendment 3), dated 28-Jun-2022, and on the Annotated Case Report Forms (aCRF), dated 15-Feb-2023. The operational part of the study, including the statistical programming, will be conducted by a CRO.

The planned analyses and the results for this study will be presented in the CSR for primary and final analyses. The primary CSR will include the analyses from the interim analysis performed at Week 40, and the final CSR, the cumulative analyses at Week 52.

A detailed description of the planned TFLs to be presented in the CSRs will be provided in accompanying TFL Shells document. TFLs with new data after primary analysis will be generated for the final analysis at Week 52. TFLs for primary endpoint analysis and baseline data are not planned to be reproduced.

Any deviations from this SAP with rationale will be described in the CSR.

1.1 Study design

Study CSOK583A12301 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 either the SOK583 or the Eylea EU treatment group.

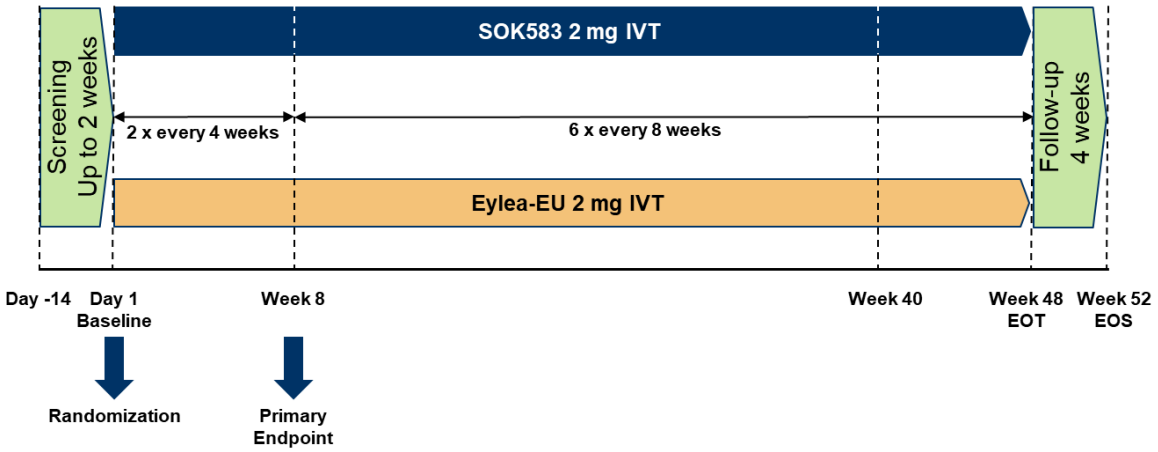
Randomization will be stratified by the following factors:

For participants of the PK substudy (those who sign both the main ICF and the PK ICF), randomization will be stratified by age category (< 75 years and ≥ 75 years) and Baseline BCVA category. A list of randomization numbers will be generated by IRT with a 1:1 randomization ratio to SOK583 or Eylea EU.

For all other participants (those who sign the main ICF only), randomization will be stratified by region, age category and Baseline BCVA category and a list of randomization numbers will be generated by IRT with a 1:1 randomization ratio to SOK583 or Eylea EU.

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).

Figure 1-1 Study Design



Only 1 eye will be selected as study eye and treated with study treatment (SOK583 or Eylea EU). During the Treatment Period, participants will receive a single IVT injection of fixed 2 mg of SOK583 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.

Table 1-1 Primary 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**
BCVA[1]	X	X	X	X	X	X	X	X	X	X	X
SOK583/ Eylea EU IVT administration		X		X	X	X	X	X	X	X	

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

[1] 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.

1.2 Study objectives and endpoints and estimands

Table 1-2 Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate similar efficacy of SOK583 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 SOK583 is similar to Eylea EU	• Mean change in CSFT using SD-OCT from Baseline to Week 1, 4, 8, 24 and 52

Objective(s)	Endpoint(s)
	• Mean change of CNV lesion size using FA from Screening to Week 8 and 52
• To evaluate if the efficacy of SOK583 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 SOK583 is similar to Eylea EU in terms of safety	• Incidence of ocular and non-ocular AEs over 52 weeks
• To evaluate if SOK583 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 SOK583 and Eylea EU in patients of the PK assessment	• Aflibercept concentration assessments at Baseline (pre-dose) and 24 hours after the first and third injections
Exploratory Objective	**Endpoint for exploratory objective**
To evaluate systemic VEGF concentrations in participants treated with SOK583 or Eylea EU	• VEGF concentration assessment at Week 48 (pre-dose) and Week 52

1.2.1 Primary estimand(s)

The primary clinical question of interest is: Does SOK583 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). Important protocol deviations which affect the primary endpoint are provided in Table 2-1.
2. Endpoint: change from baseline in BCVA score at Week 8
3. Treatment of interest: the randomized treatment (SOK583 or Eylea EU).
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 SOK583 and Eylea EU.

2 Statistical methods

Analysis of the primary endpoint (mean change from Baseline in BCVA at Week 8) will be conducted on all patients with nAMD who are anti-VEGF naive, without important protocol deviations and adherent to the treatment and completed the treatment (2 IVT injections) to Week 8 for the interim analysis. Any efficacy and safety data of study participants collected during the study will also be analyzed for the final analysis.

FDA, EMA and PMDA have different requirements for equivalence testing of the primary endpoint:

1. EMA and PMDA 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].
2. 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].

2.1 Data analysis general information

Data will be analyzed by the CRO Biostatistics and Statistical Programming group according to the data analysis Section 12 of the study protocol and analyses planned in this document unless otherwise specified.

All statistical analyses will be performed using SAS® (SAS Institute, Cary NC, USA, version 9.4 or higher version).

Medical coding will be conducted for AEs and Medical History using MedDRA version 26.0 or higher. Coding for medication and procedures will be performed using WHODrugGlobalB3 Mar 2023 or later.

There will be 2 analysis time points in this study. The first and interim analysis will be performed when all randomized participants have completed Week 40 or discontinued before Week 40. This analysis is considered as the primary analysis. The second and final analysis will be performed when all participants have completed the study.

The primary analysis at Week 40 will be performed with an unmasking of specified individuals from the Sponsor who are not involved in the direct conduct of the study. The biostatistician who is directly involved in the conduct of the study will remain masked to treatment assignments while the study is in progress.

A blinded/unblinded charter document will summarize the procedures and actions to maintain masking to the actual treatment assignment. This document will be finalized prior to unmasking of the study at the time of the primary analysis at Week 40.

The statistical analyses described in this document cover the analyses for both the primary analysis at Week 40 and the second and final analysis.

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), mean, SD, minimum, median, and maximum. Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of patients included in the analysis set under

consideration unless otherwise specified. Where appropriate, two-sided CIs for point estimates of the mean or proportion will be provided. Point estimates and two-sided CIs of treatment group differences will be provided as appropriate.

Summary statistics will be presented by treatment group (and day and time point, as applicable) unless otherwise stated.

The following treatment groups will be presented:

- SOK583
- Eylea EU
- Total (wherever required)

2.1.1 General definitions

Investigational treatment or study treatment refers to SOK583 2mg and Eylea EU 2mg IVT injections.

Baseline (Day 1) is the date of the first study treatment in the study. Baseline assessment is defined as the last available assessment collected prior to the first study treatment. Baseline assessments may occur at Baseline or Screening visits.

All data collected after the first study treatment are defined as *post-baseline*.

The *study day* for a post-baseline scheduled or unscheduled visit is defined as:

Study day = (date of visit) – (date of first study treatment) + 1

The *study day* for a scheduled or unscheduled visit before Baseline is defined as:

Study day = (date of visit) – (date of first study treatment)

On-treatment assessment/event is defined as any assessment/event in the period after the first dose of study treatment and on or before last administration of study treatment plus 4 weeks (28 days).

End of Study (EOS) refers to the EOS visit if used in the context of individual participant.

All data collected at unscheduled visits will not be used in 'by-visit' tabulation or graphs, but will be included for analyses based on all post-baseline assessments, such as safety narratives, summary of maximum decrease or increase from Baseline for laboratory and vital signs data. All data collected at unscheduled visits will be included in listings.

2.2 Analysis sets

All Enrolled Analysis Set

All Enrolled Set consists of all participants who signed the Informed Consent Form.

Randomized Analysis Set

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

Participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

Full Analysis Set

The Full Analysis Set (FAS) comprises all randomized participants to whom study treatment has been assigned by randomization, to whom at least 1 dose of study treatment has been administered and for whom at least 1 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.

Safety Set

The Safety Set (SAF) includes all randomized participants who received at least 1 dose of study treatment. Participants will be analyzed according to the study treatment received. Participants received multiple treatments (i.e. both SOK583 and Eylea EU) into the study eye will be analyzed according to the treatment arm from which they received majority of treatments up to the last treatment received. In case of received equal number of treatments it will be analyzed according to the first treatment received.

Per-protocol Set

The Per-protocol Set (PPS) is a subset 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 affecting the primary endpoint up to Week 8

The criteria to qualify a protocol deviation as important regarding the evaluation of the study's primary objective is provided in Table 2-1.

Table 2-1 Important protocol deviations leading to exclusion from PPS

PD identifier	Protocol deviation term for reporting	Additional criteria
INCL03	Participant is not anti-VEGF naive for both eyes and systemically	
INCL04	Study eye: absence of CRC confirmed active nAMD in appropriate location	
INCL06	Study eye: BCVA not between 73 and 38 letters, inclusive, at Baseline	
EXCL01	Both eyes: participant received previous treatment with anti-VEGF or investigational drugs at any time prior the Baseline	
EXCL02	Study eye: participant received any approved treatment for nAMD (other than vitamins and dietary supplements) at any time prior the Baseline	
EXCL03	Study eye: presence of other causes of CNV than nAMD	

PD identifier	Protocol deviation term for reporting	Additional criteria
EXCL05	Study eye: CRC confirmed central subfield affected by fibrosis, atrophy or scarring > 50% of total lesion area	
EXCL06	Study eye: CRC confirmed sub-retinal hemorrhage ≥50% of total lesion area; or involving the fovea 1 or more disc area in size	
EXCL07	Study eye: retinal pigment epithelium rip/ tear at Screening or Baseline	
EXCL08	Study eye: current vitreous hemorrhage or history of vitreous hemorrhage within 4 weeks prior to Baseline	
EXCL09	Study eye: history or evidence of a concurrent intraocular condition, trauma or medical and/ or surgery intervention prior the Baseline, within the period specified at the EXC 9 of the protocol	Additional medical assessment will be performed
EXCL20	Previous systemic treatment with any anti-VEGF therapy	
EXCL24	Participation in investigational systemic drug, biologic, or device study within 30 days or duration of 5 half-lives of the investigational product prior to Baseline	Additional medical assessment will be performed
WITH03	IVT injection administered after the participant withdrew consent	At visits: V2, or V3, or V4
WITH04	Assessments performed after the participant withdrew consent	At visits: V2, or V3, or V4, or V5
TRT02	Randomized by error and study drug was not administered	
TRT03	Incorrect treatment kit administered in the study eye in error	At visits: V2, or V3, or V4 Incorrect treatment
TRT05	Study treatment injection not administered as per protocol treatment schedule	At visits: V2, or V4 With additional medical assessment
TRT06	Participant received expired investigational product	At visits: V2, or V4
TRT07	Participant received lower or over-dose of study treatment at a single visit	At visits: V2, or V4 With additional medical assessment
TRT08	Participant received investigational product with temperature excursion	At visits: V2, or V4
COMD01	Prohibited ocular medication and/ or procedure in the study eye	At visits: Before V5
COMD02	Prohibited ocular medication in fellow eye OR systemic medication	Before V5, cases with ocular (ophthalmic route) administration of Bevacizumab anti-VEGF treatment in the fellow eye OR

PD identifier	Protocol deviation term for reporting	Additional criteria
		Before V5, cases with non-ocular administration and anti-VEGF ATC Code.
OTH01	BCVA assessment not performed at a scheduled visit	At visits: V2, or V5
OTH04	Subject potentially unmasked to study treatment	At visits: V2, or V3, or V4, or V5 Before primary endpoint assessment
OTH05	Unmasked personnel (or masked personnel accidentally unmasked) performed BCVA assessments for the study eye	At visits: V2, or V3, or V4 or V5
OTH06	BCVA assessment for the study eye not performed correctly with relevant potential to confound the BCVA assessments	At visits: V2 or V5 With additional medical assessment
OTH20	Missed Visit not related to COVID-19	At visits : V5

Participants of Per Protocol Analysis set (PPS) will be analyzed according to the study treatment received.

PK Analysis Set

The PK Analysis Set (PKS) will be the analysis set used for analyzing free and total drug concentration in the subset of participants participating in the PK substudy. The PKS comprises Subjects who sign PK sub study ICF and having at least 1 evaluable post-baseline drug concentration assessment are considered for PK substudy. However, Subjects requiring (i.e. receiving) both eyes treatment at baseline (i.e. Day 1 as per assessment schedule) are not eligible for PK substudy. Participants receiving both the treatments (i.e. SOK583 and Eylea EU) into the study eye will be excluded from PKS. Participants will be analyzed according to the study treatment received.

Immunogenicity Analysis Set

The Immunogenicity Analysis Set (IAS) consists of all randomized patients who received at least 1 dose of the investigational treatment (SOK583 or Eylea EU) and have immunogenicity blood samples collected and analyzed at Baseline and at least 1 time point post-baseline. Participants with positive immunogenicity at Baseline will be excluded from the IAS. Participants receiving both the treatments (i.e. SOK583 and Eylea EU) into the study eye will be excluded from IAS. Participants will be analyzed according to the study treatment received.

VEGF Analysis Set

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 (i.e. receiving) both eyes treatment during the study will be excluded. Participants receiving (by mistake) both the treatments (i.e. SOK583 and Eylea EU)

into the study eye will be excluded from VEGF analysis set. Participants will be analyzed according to the study treatment received.

2.2.1 Subgroup of interest

The subgroups of interest are:

- Region (US, Europe, Rest of the World)
- Age category (< 75 years and ≥ 75 years)
- Sex (male and female)
- Race (White, Other)
- Baseline BCVA category (< 64 and ≥ 64 letters)
- Baseline lesion type (predominantly classic, minimally classic, occult)
- Baseline CNV lesion size (< 0.5 mm^2, 0.5-1.8 mm^2, > 1.8 mm^2) (Latest value Collected at Screening Visit)
- Baseline intraretinal fluid status (Absent, Present)
- Baseline subretinal fluid status (Absent, Present)

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

The subpopulation of Japanese subjects will be additionally analyzed in a specific subgroup analysis. Japanese subjects who are included in the subgroup analyses will be identified as Japanese according to the corresponding ethnicity data, irrespective of residency. The table produced for the Japanese subpopulation will be specified in the TFL Shells document. The subgroup analysis will follow the same statistical methods as described for the entire population.

Subgroup analyses will be also performed for TEAE overview and for ocular TEAEs in the study eye and for non-ocular TEAEs for the following subgroups:

- Age category (<75 years and ≥ 75 years)
- Sex (male and female)
- Region (US, Europe, Rest of the World).

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number of participants screened, and the number of participants screen failed will be presented. In addition, the number of participants re-screened will be given.

Participants disposition will be summarized (n and percentages) by the treatment group. Percentages will be based on the number of patients in RAS.

The summary will include the following information:

- Number of participants who completed the treatment

- Number of participants who discontinued the treatment early
- Number of participants who terminated the study prematurely, overall and by visit
- Reason for discontinuation of the treatment
- Reason for discontinuation of the study

If there were dosing errors where participants received treatment other than the one they were randomized to, separate summaries will be presented based on 'as treated', while the 'as treated' status will be derived from the majority of treatments received. If there is a tie, the latest treatment will be used.

A listing of participants who discontinued treatment earlier or prematurely discontinued study and the primary reason for discontinuation will be presented. The listing will identify the visits completed and when the study or treatment was discontinued. Additional listing for participants with differences in the disposition status for the treatment and the study, including participants with missing disposition status on the Disposition eCRF, will be presented. In addition, a listing of patients along with the PPS, IAS, VEGF and PKS analysis set that they were excluded from and the corresponding reasons will be presented.

The number of participants included in the analysis sets by treatment group will be presented. All Enrolled set will be presented without treatment group only for Total counts. Percentages will be based on the number of participants in RAS.

All important protocol deviations will be reviewed on an ongoing basis, at a minimum once a month from First Participant First Visit (FPFV), as defined in Data Quality Plan (DQP).

The protocol deviations leading to exclusion from PPS are shown in Table 2-1. This classification concerns the impact that the important protocol deviations are expected to have on the statistical analysis of the primary endpoint. The protocol deviations leading to exclusion of participants from PPS will be summarized.

The number and percentage of participants in the FAS with important protocol deviations will be summarized by treatment group. A listing of important protocol deviations will be generated based on All Enrolled Set.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed for All Enrolled Set and summarized descriptively by treatment group for the FAS, PPS, SAF, and PKS. Demographic summaries will include age at screening (both as a continuous variable and using categories < 75 years and ≥ 75 years), sex, race, ethnicity, and ancestry. Baseline characteristics summary will consist of 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), lesion type (predominately classic, minimally classic, occult), foveal involvement (subfoveal, extrafoveal, undeterminable), CNV lesion size (tertiles), presence of subretinal fluid, presence of intraretinal fluid/cyst, and CSFT).

Relevant ocular medical histories and ocular current medical conditions at baseline for the study eye and for the fellow eye will be summarized by SOC and PT, for all participants in the FAS

by treatment group. In addition, a similar summary will be included for the non-ocular medical histories and current medical conditions. Medical History of Disease will be listed for All Enrolled Set

2.4 Treatments (study treatment, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Study medication administration information will be listed by treatment.

The extent of exposure / compliance by treatment will be presented based on the overall number of injections and the number of participants injected per visit using the SAF.

The number and percent of participants who received study treatment, missed a treatment and missed visits or discontinued treatment will be summarized cumulatively by visit. Frequency of all observed dosing patterns up to and including Week 48, missed treatments and wrong treatments will be presented using SAF and PPS.

2.4.2 Prior, concomitant and post therapies

Ocular and non-ocular prior medications (any medication taken up to 90 days prior to Screening) and concomitant medications (ocular and non-ocular) will be listed separately and summarized according to the ATC classification system, by treatment group using SAF. Prior medications are defined as treatments taken and stopped prior first IVT injection. Concomitant medications are defined as treatment taken at least once on or after first IVT injections (including those which were started prior first IVT injection and continued into the treatment period). Ocular medications will be presented separately for the study eye and the fellow eye. Additionally, the number and percentage of patients who had prior and concomitant non-drug therapies/ procedures performed during the study will be summarized by SOC and PT according to MedDRA terminology using SAF. Prior and concomitant non-drug therapies/procedures are defined in the same way as done for prior and concomitant medications. These summaries will be presented separately for the study eye and the fellow eye.

Prohibited concomitant medications and anti-VEGF treatments for the fellow eye will be summarized by ATC and PT according to WHODD terminology using SAF. Appendix 5.4 lists ATC for some prohibited medications. Subjects with prohibited concomitant medications will be listed using SAF.

Prohibited Concomitant Procedures / non-drug therapies (if any) for study eye will be summarized by SOC & PT for subjects with indication of AMD. Appendix 5.4 lists for some preferred terms of prohibited procedures.

2.5 Analysis supporting primary objective(s)

Data analysis will be performed at 2 time points. The primary analysis is to demonstrate comparability of SOK583 to Eylea EU treatment with respect to the primary endpoint. This primary analysis will be performed when all randomized participants have completed Week 40 or discontinued before Week 40. At this point, a partial database lock of the available data will be completed. The primary analysis will also include all available efficacy and safety data that

have been collected up until the partial database lock. The final analysis will occur when all randomized participants have completed the study. A full CSR will be generated at both analysis time points.

2.5.1 Primary endpoint(s)

Primary endpoint is the change from baseline in BCVA score at Week 8. 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.

2.5.2 Statistical hypothesis, model, and method of analysis

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

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

H_0: $|\mu_{SOK583} - \mu_{Eylea}| \geq \Delta$ versus H_1: $|\mu_{SOK583} - \mu_{Eylea}| < \Delta$,

where μ_{SOK583} and μ_{Eylea} are the change from baseline in BCVA score at Week 8 for SOK583 and Eylea EU, respectively.

Therapeutic equivalence in terms of change from Baseline in BCVA for EMA and PMDA 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.

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 derived.

Participation in the PK substudy is included as an administrative stratification factor in order to ensure the required number of participants and to limit the operational burden. Region is also included as an administrative stratification factor in order to ensure a balanced allocation of participants in each region for relevant region-specific subgroup analyses. Therefore, these 2 stratification factors will not be included in the statistical model.

The primary analysis will be performed on the PPS, which is defined in Section 2.2.

2.5.3 Handling of intercurrent events

Since the primary analysis is only on those participants who adhere to and complete treatment up to Week 8 and do not have important protocol deviations that would affect the primary endpoint during this time, there will be no intercurrent events for the observed PP estimand.

2.5.4 Handling of missing values not related with intercurrent events

As primary analysis will be performed on PPS as defined in Section 2.2, there will be no 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.

2.5.5 Sensitivity analyses

A 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. The sensitivity MMRM analyses will be conducted using the PPS observed data.

2.5.6 Supplementary analyses

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.

A 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 observed data.

2.6 Analysis supporting secondary efficacy objective(s)

The secondary efficacy objectives are:

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

2.6.1 Secondary endpoints

The secondary efficacy endpoints are:

- Mean change in CSFT using SD-OCT from Baseline to Weeks 1, 4, 8, 24 and 52
- Mean change of CNV lesion size using FA from Screening to Weeks 8 and 52

- Mean change from Baseline in BCVA score using EDTRS testing charts at Weeks 24 and 52

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested for the secondary efficacy endpoints.

CSFT values and associated changes from Baseline will be summarized descriptively by treatment group for Baseline, Week 1, Week 4, Week 8, Week 24 and Week 52. Mean change from Baseline in CSFT to Week 52 will be graphically presented.

CNV lesion size values and associated changes from Baseline assessment will be summarized descriptively by treatment group for Baseline, Week 8 and Week 52. Mean change from Baseline in CNV lesion size to Week 52 will be graphically presented. Note that the Baseline assessment for CNV lesion size was performed at Screening. The latest CNV lesion size value collected before administration at screening visit will therefore be considered as Baseline values to derive change values for post-baseline visit.

For CNV lesion size it was assumed that if Type of CNV is “CNV ABSENT” then this would indicate that lesion shrinks to zero mm^2. Hence, for subjectsfor whom Type of CNV is “CNV ABSENT” and parameters “Area of Lesion within CNV status” and “Area of CNV within Lesion” are missing or Not Applicable at a visit, lesion size values (i.e. Area of CNV within Lesion Measurement) will be imputed to Zero values for this visit for analysis purpose only.

BCVA values and associated changes from Baseline will be summarized descriptively by treatment group for all scheduled post-baseline visits, including Week 24 and Week 52. Mean change from Baseline in BCVA to Week 52 will be graphically presented. The analyses will be done using the FAS and the PPS.

2.7 Safety analyses

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 AEs will summarize only on-treatment events, with a start date during the on-treatment period (TEAEs).

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 SAF. The safety endpoints are based on the variables from the safety assessments, which include:

- Ocular and non-ocular TEAEs and SAEs
- Ophthalmic examinations
- Vital signs
- Laboratory results
- Post-injection assessments

- ADA (development of binding and neutralizing ADA up to Week 52)

The reporting of core safety topics will be defined with eCRS using the safety profiling plan flag. The eCRS safety topics will be finalized before the time of analysis implementation (i.e. before study database lock) and documented appropriately.

2.7.1 Adverse events

A TEAE 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 until the end of study. All information obtained on AEs will be displayed by treatment group and participant.

Treated subject with completely missing start date and end date information will be considered as TEAE. Subjects with completely missing end date information on Adverse events will be considered as Ongoing.

TEAEs will be summarized by primary SOC and PT according to the MedDRA terminology. Non-treatment-emergent AEs will be listed by All Enrolled Set.

An overview table will summarize the number and percentage of participants with at least 1 of the following TEAEs: any TEAE, TEAE suspected to be treatment-related, severe TEAE suspected to be treatment-related, SAE, SAE suspected to be treatment-related, TEAE leading to study treatment discontinuation, ocular TEAE related to study procedure for study eye, ocular TEAE related to either of treatment or study procedure or both and TEAE leading to death (it should be noted that the relationship to the ocular injection procedure was captured as relationship to study procedure in the eCRF). Participants with more than 1 TEAE in a particular category will be counted only once in that category.

The number (and percentage) of participants with TEAE will be summarized in the following ways:

- by treatment, primary SOC and PT
- by treatment, primary SOC, PT and maximum severity

Separate presentations will be provided related to ocular events in the study eye and fellow eye and to systemic events. Sensitivity safety analyses will be performed by excluding participants those who are receiving ocular anti-VEGF treatment in fellow eye during study. Separate summaries will be provided for TEAEs suspected to be related to study treatment, deaths, SAEs, other significant TEAEs leading to study discontinuation. Summaries will be provided for ocular TEAEs in the study eye related to study procedure by treatment, primary SOC and PT; and by treatment, primary SOC, PT and maximum severity.

CCI [redacted]

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

Listings of deaths, SAEs, TEAEs leading to study treatment discontinuation, TEAE leading to study discontinuation and study treatment related TEAEs will be provided.

2.7.1.1 Adverse events according to the risks listed in the Eylea EU Risk Management Plan

Separate presentations of AE according to the risks listed in the Eylea EU RMP will be provided related to ocular events in the study eye and fellow eye and to systemic events. In addition, a summary of AE suspected to be treatment-related will be added. The definition of AE according to the risks listed in the Eylea EU RMP will be based on the risks described in the Eyleas RMP public summary effective during data analysis.

2.7.2 Deaths

All deaths that occurred during the study will be identified on the AE eCRF page and will be summarized using counts and percentages by SOC and PT according to the MedDRA dictionary. A participant listing will be presented for all deaths including date and cause of death.

2.7.3 Laboratory data

The following laboratory safety tests will be measured:

Table 2-2 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 aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH)
Coagulation	International normalized ratio (INR), activated partial thromboplastin time (APTT)
Pregnancy Test	Serum/urine pregnancy test

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 for hematology, coagulation, and clinical chemistry tests by treatment and visit will be presented graphically using boxplots.

Shift tables using the low/normal/high/(low and high) classification will be used to compare baseline to the post baseline value by visit for hematology, coagulation, and clinical chemistry tests. Subjects with status of "Not Done" or missing values at visit will be considered as missing for descriptive statistics.

Any laboratory values given as <X.X in the database will be imputed with the value of the number without the sign for the descriptive statistics and the calculation of changes from baseline, e.g. a value of <2.2 will be imputed as 2.2 for the calculations. There will be no imputation in the data listings; all values will be displayed as recorded in the database.

Only scheduled lab tests will be used in tables and if there are repeated labs, only the first value will be used, unless there are problems with the quality of the first specimen.

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

2.7.4 Other safety data

2.7.4.1 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.

2.7.4.2 Ophthalmic examinations

Descriptive summaries of pre-injection observed values and change from baseline IOP values will be presented at each study visit by treatment. For post-injection values, scheduled IOP measured at 30-60 min after injection should be considered for analysis as post-injection IOP values.

A listing of all participants with observed IOP mmHg at any scheduled or unscheduled visit will be presented based on Safety set.

2.8 Pharmacokinetic endpoints

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 (LLOQ for free drug in plasma is 5 ng/mL and for total drug in serum is 20 ng/mL). Subjects of PKS who start with uni-lateral nAMD at baseline but convert to bi-lateral nAMD and receive anti-VEGF treatment in the fellow eye during PK assessment period (Day 1 to Day 58) , their Day 58 data will be excluded from the analysis.

Summary statistics will include arithmetic mean, SD, CV, median, minimum, maximum, GM and GCV.

PK data will be compared as per recommendation by EMA to support that there are no significant differences between SOK583 and Eylea EU. Free (plasma) aflibercept concentration data on V5 will be used to assess if there is any difference indicative of non-similarity between two treatment groups. Significant non-similarity will be claimed when the lower limit of 90% CI of the GMR between SOK583 and Elyea EU is above 1.43. The value 1.43 is from confidence interval [0.70, 1.43] recommended for highly variable drug products in the EMA guideline on the investigation of bioequivalence (EMA 2010). This widened acceptance range is justified considering the low and highly variable systemic concentrations of aflibercept observed after IVT administration. These systemic concentrations are too low to induce any PD effects and are thus not clinically relevant (Kaiser et al 2019). No lower margin is defined for this assessment as a lower systemic exposure of SOK583 vs Eylea EU is not clinically relevant.

GM and GCV values will be derived on log-transformed values for each of the treatment group. Frequency of count of subjects with BLQ values will be presented. LLOQ values will be excluded from calculation of GM and GCV.

Geometric mean ratio will be evaluated by (T/R) ratio of GM.

90% CI for GMR will be derived for Visit 5 (free plasma aflibercept) from Least Square Mean values of log transformed data.

2.9 Pharmacodynamic endpoints

The pharmacodynamic endpoint is VEGF concentration assessment at Week 48 (pre-dose) and Week 52.

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. Change in VEGF concentration and percentage change in VEGF concentrations from Week 48 to Week 52 will also be summarized. Change will be calculated only if both time point values are available. For summary statistics of free VEGF concentrations and for calculation of the change in VEGF concentration, values below LLOQ will be imputed with LLOQ/2. (LLOQ for free VEGF is 3.52 pg/mL).

Summary statistics will include arithmetic mean, GM, GCV, SD, CV, median, minimum, and maximum.

Free plasma VEGF concentration data of participants included in the VEGF Analysis Set will be listed by treatment, participant, and sampling time point.

2.10 Other additional analyses

The additional analyses will not be included in the CSR.

2.10.1 Additional analyses for publication purposes

The following analyses will be performed for publication purposes:

- Number and percentage of participants maintaining vision (losing <15-letter in BCVA from Baseline to Week 8, Week 24 and Week 52)
- Number and percentage of participants with a gain of ≥15-letter OR BCVA score ≥ 84 letters in BCVA from Baseline to each post-baseline visit

Note: Participants with BCVA value of 84 letters or more at a postbaseline visit will be considered as responders for the corresponding endpoint. This is to account for a ceiling effect, for those participants with BCVA values at baseline ≥70 letters.

- Number and percent of participants with presence of intraretinal fluid (central subfield) at Baseline, Week 8 and Week 52 will be presented.

2.10.2 Analyses for the Risk Management Plan

As core safety topics might change throughout the study, reporting of safety topics for the Risk Management Plan will be defined with eCRS and will be included in the TFL Shells document, but not in the SAP.

The safety topics and eCRS are based on the important identified and important potential risks defined for Eylea and will be retrieved from the Eylea RMP public summary at the time of CSR preparation. These would constitute also the risks to be described in the SOK583 RMP.

The PTs for the safety topics will be extracted from eCRS to the SAS dataset. The eCRS safety topics will be finalized at the time of the final CSR.

Summary Statistics will be performed for risks identified in the study.

Duration of exposure and subject exposure will be evaluated for the study and separately for age group, gender, and race to report in RMP. Summary statistics will be provided for overall and group wise parameters.

Duration of exposure (Days) = (Date of last treatment dose date – first dose date +1)

Duration of exposure (Years) = (Sum of Duration of exposure for all subjects who were administered study drug (days)) / 365.25

2.10.3 Analyses for results posting to EudraCT and ClinicalTrials.gov

The following summaries will be included using SAF:

- Deaths and serious adverse events by SOC and PT
- Non-serious adverse events by SOC and PT

2.11 Interim analysis

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 CSR post final analysis at Week 52 will be cumulative and will also include analyses of Week 40 cut-off primary CSR (e.g. primary endpoint analysis).

3 Sample size calculation

3.1 Primary endpoint(s)

Margin justification

The EqM 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 EqM. 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 3-1 and Table 3-2.

Table 3-1 Treatment Least Square Means at Week 8

Treatment	Estimate	Standard Error	95% CI 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 3-2 Differences of Treatment Least Square Means at Week 8

Treatment Comparisons	Estimate	Standard Error	95% CI 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 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 SOK583 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 SOK583 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 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 SOK583 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 SOK583 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 the 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 3-3 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

3.2 Secondary endpoint(s)

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

- Sensitivity analysis based on LOCF approach is removed , as PP analysis set already removes subjects with missing values at Week 8.

The protocol specified urinalysis lab parameter test was removed from analysis.

5 Appendix

5.1 Imputation rules

5.1.1 Study treatment

Missing or partial dates are not allowed in completing the study treatment administration eCRF page. The end date of study treatment will be the last date of dose administration.

5.1.2 AE date imputation

5.1.2.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (end of study date/data cut-off date, 31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (end of study date/data cut-off date, last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

In all cases when dates are imputed, the non-missing date part should be considered as collected and only the missing part should be imputed.

5.1.2.2 Adverse event start date imputation

Completely missing AE start dates will not be imputed.

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Imputations rules using the AE start reference date:

1. If the AE start date ‘year’ value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date ‘year’ value is less than the treatment start date year value, the AE started before treatment. Therefore:
   a. If AE ‘month’ is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
   b. Else if AE ‘month’ is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

In all cases when dates are imputed, the non-missing date part should be considered as only the missing part should be inputted.

5.1.3 Concomitant medication and non-drug therapy/procedure date imputation

5.1.3.1 Concomitant medication date imputation

5.1.3.1.1 Concomitant medication/therapy end date imputation

1. If CM end day is missing and CM month/year are non-missing then impute CM day as the minimum of study end date/data cut-off date and the last day of the month.
2. If CM end day/month are missing and CM year is non-missing then impute CM day as the minimum of study end date/data cut-off date and the end of the year (31DECYYYY).
3. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.3.1.2 Concomitant medication start date imputation

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:

a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the treatment start date year value:
   a. And the CM month is missing or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
   b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

In all cases when dates are imputed, the non-missing date part should be considered as collected and only the missing part should be imputed.

5.1.3.2 Non-drug therapies/procedures date imputation

Same imputation rules as for CM will apply.

5.1.4 Partial start date for nAMD

1. If the first diagnosis day/ month are missing and the year is non-missing:
   a. If the year part of the first diagnosis date is equal to the year part of the inform consent date, then the imputed first diagnosis date is set to the year start point (01JanYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-year point (01JulYYYY).
2. If the first diagnosis day is missing and the month/year are non-missing:
   a. If the month and year part of the first diagnosis date is equal to the month and year part of the inform consent date, then the imputed first diagnosis date is set to the month start point (01MONYYYY).
   b. Otherwise the imputed first diagnosis date is set to the mid-month point (15MONYYYY).

5.2 AEs coding/grading

AEs will be coded using the MedDRA terminology. No grading system for AEs will be used.

Medical history and prior/concomitant non drug therapies/ procedures will be coded using the MedDRA terminology.

Prior/concomitant medications will be coded using the WHODRUGGlobalB3 terminology.

The MedDRA version 26.0 or higher and WHODRUG GlobalB3 03-2023 or later will be used and will be described in the footnote of relevant outputs.

5.3 Statistical models

5.3.1 Primary analysis

5.3.1.1 ANCOVA

The ANCOVA model for the primary efficacy endpoint will be fitted using PROC MIXED procedure. Change from Baseline in BCVA at Week 8 will be the dependent variable in the model and categorical effect of randomized treatment assignment, Baseline BCVA value and age at Screening as continuous variables will be the independent variables. Summarization of the inferential statistics will include the LS means, SE of the estimates and both 90% and 95% 2-sided CI (using alpha = 0.05 to calculate 95% CI for EMA and PMDA and alpha = 0.1 to calculate 90% CI for FDA).

5.3.2 Sensitivity analysis

5.3.2.1 MMRM

The MMRM model will be used for the sensitivity and supplementary analysis for the primary efficacy endpoint. The analysis model will include treatment, visit and interaction between time and randomized treatment as categorical variables, and age at Screening and baseline BCVA value as continuous variables. An unstructured (co)variance structure will be used to model the within-participants errors. The Kenward-Roger approximation will be used to approximate the denominator degrees of freedom. Estimation and testing of SOK583 minus Eylea EU effect will be based on model generated LS means. The adjusted mean change in BCVA from Baseline at Week 8 for each treatment group will be estimated in the framework of this model, as well as the between-group differences (comparing SOK583 to Eylea EU) and the CIs for the adjusted mean. The analysis will be performed using alpha = 0.05 to calculate 95% CI for EMA and PMDA and alpha = 0.1 to calculate 90% CI for FDA.

5.3.3 PK Analysis

PK concentration data for V5 will be evaluated for (free plasma aflibercept). PROC MEANS or any related SAS procedure will be used to analyze the descriptive stats (n, mean, stddev, CV, median, minimum and maximum) from free plasma concentration data. Geometric means will be evaluated applying exponential function on mean values of log-transformed data. Geometric CV will be evaluated applying exponential function on CV values of log-transformed data. Formula used for Geometric CV is applying square root on values of (exp (std^2-1)). Geometric mean ratio will be evaluated by (Test/Reference) ratio of Geometric Means.

Geometric mean ratio CI will be evaluated using LS MEAN values from PROC GLM on log transformed data. 90% CI of LSMEAN difference will be evaluated at alpha=0.10. 90% CI values will be back transformed (applying exponential) to get the 90% CI of geometric mean ratio values. Analysis values should be assumed with unequal variances.

5.3.4 Rule of exclusion criteria of analysis sets

Table 5-1 Participant classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
RAS	NA	Not randomized
FAS	NA	Not in RAS; Did not receive at least 1 study IVT injection; Did not have at least 1 post-baseline BCVA value available.
PPS	See Table 2-1 for the list of the PD IDs	Not in FAS; BCVA assessments at baseline and Week 8 are not available; Did not receive treatment according to the protocol at Day 1 and Week 4.
SAF	NA	Did not receive at least one study IVT injection.
PKS	NA	Did not have at least 1 evaluable post-baseline drug concentration assessment; Subjects requiring (i.e. receiving) both eyes anti-vegf treatment at baseline (i.e. Day 1 as per assessment schedule) are not eligible for PK substudy. Subjects receiving multiple treatments (both SOK583 and Eylea EU) in the study eye will be excluded
IAS	NA	Did not receive at least 1 study IVT injection; Did not have immunogenicity blood samples collected and analyzed at Baseline and at least 1 time point post-baseline; Had positive immunogenicity at Baseline . Subjects receiving multiple treatments (both SOK583 and Eylea EU) in the study eye will be excluded
VEGF Analysis Set	NA	Did not receive treatment at Week 48 in the study eye ; Did not have VEGF concentration assessment at Week 52; Subjects requiring (i.e. receiving) anti-vegf treatment in both eyes during the study . Subjects receiving by mistake multiple treatments (both SOK583 and Eylea EU) in the study eye will be excluded

5.4 Prohibited Medications and Procedures

5.4.1 ATC codes for anti-VEGF treatment

L01FG, L01XX, L01XY, S01LA, L01XC,

5.4.2 ATC codes for corticosteroid treatment

C05AA, D07AA, D07AB, D07AC, H02AB, N02CB, R01AD, R03BA, S02BA, S03BA, S01BA, S01BB, H02BX

5.4.3 Preferred Terms for Prohibited Procedures

Laser Therapy, Retinal Laser Coagulation, Eye laser surgery & Laser floater treatment.

6 References

References will be made available upon request.

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