SANDOZ A Novartis Division

Sandoz Biopharmaceuticals Clinical Development

SOK583A1 (INN: aflibercept)

CSOK583A12303 / NCT05282004

An open-label, single-arm, multicenter study in patients with neovascular age-related macular degeneration to evaluate the safety of SOK583A1 (40 mg/mL), a proposed aflibercept biosimilar product, provided in a vial kit

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
14-Dec-2021	Prior to DB lock	Creation of final version	N/A - First version	NA

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
CRF	Case Report Form
CSR	Clinical Study report
DBL	Database Lock
eCRS	Electronic Case Retrieval Sheet
FAS	Full Analysis Set
IOP	Intraocular pressure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
nAMD	Neovascular age-related macular degeneration
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System organ class
SOK583A1	Product code of Sandoz' proposed aflibercept containing biosimilar product
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, Listings
WHO	World Health Organization

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 1.0 dated 14-Sep-2021.

A detailed description of the planned TFLs to be presented in the CSRs will be provided in accompanying TFL Shells document.

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

1.1 Study design

This is an open-label, single arm, multicenter, Phase IIIb study in subjects with (wet) neovascular age-related macular degeneration, eligible for IVT aflibercept treatment. Screening and Baseline may be performed on the same day. A follow-up visit will be performed on-site on Day 8 (±2 days) and on Day 31 (+4 days - end of study visit).

Subjects who consent will undergo all screening activities to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all inclusion criteria and none of the exclusion criteria will receive 1 injection of SOK583A1 (2 mg/0.05 mL) provided in a vial kit.

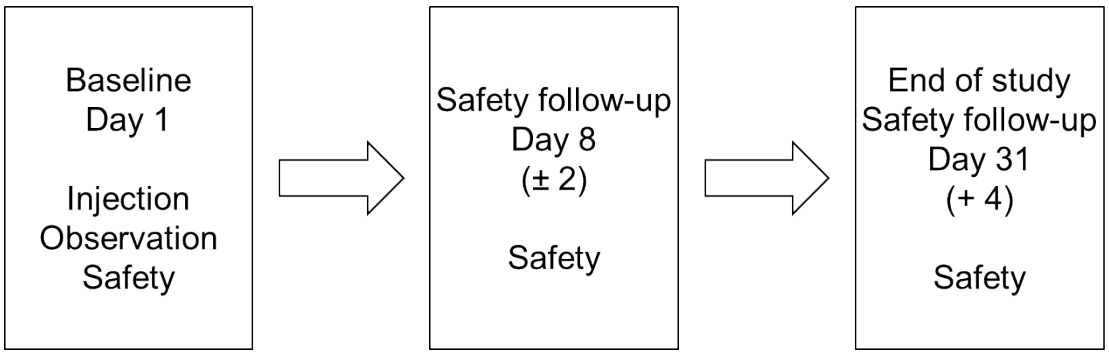
The study population will be male and female subjects ≥ 50 years old who are treated with Eylea (intravitreally) due to nAMD and have received at least 2 injections during the induction phase already. Thirty-eight subjects are expected to be injected at approximately 3 sites in the United States of America.

Randomization is not applicable for this open-label study.

The primary analysis will be conducted after DBL.

No interim analyses are planned.

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimands

The primary objective and endpoint is given in Table 1-1 below.

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• Evaluate the safety of use of a vial kit containing SOK583A1 (40 mg/mL) in subjects requiring IVT aflibercept treatment	• Occurrence of ocular or non-ocular AEs during the study-reporting period

Secondary objectives and endpoints are not defined for this study.

2 Statistical methods

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).

Medical coding will be conducted for AEs and Medical History using MedDRA version 24.1 or higher. Coding for medication and procedures will be performed using WHODrug Global B3 September 2021 or later.

2.1.1 General definitions

Study treatment refers to SOK583A1 (2 mg/0.05 mL) provided in a vial kit.

Baseline is defined as the last available assessment collected prior to study treatment.

The date of study treatment administration is defined as Study Day 1. All other study days will be labeled relative to Day 1.

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

The study day for a scheduled or unscheduled visit after Day 1 is defined as:

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

The study day for a scheduled or unscheduled visit before Day 1 is defined as:

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

2.2 Analysis sets

The only analysis set defined is the Full Analysis Set (FAS) which will include all enrolled subjects who receive an injection of study treatment.

The FAS will be used for the analysis of all variables.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The number of subjects screened and treated will be summarized.

The number and percentage of subjects who complete or discontinue from the study will be summarized including the reasons for discontinuation.

The number and percentage of subjects with important protocol deviations will be summarized by deviation category. A listing of important protocol deviations will be provided.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data at screening (age at study entry, gender, race, ethnicity, body height, body weight and BMI) will be summarized descriptively.

Baseline ocular characteristics including primary diagnosis and date of diagnosis will be listed for the study eye.

Medical histories and current medical conditions will be coded with the MedDRA Version 24.1 or higher. All medical histories and current medical conditions will be listed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The total number of subjects who received an injection of study treatment will be presented.

2.4.2 Prior, concomitant and post therapies

Medications will be coded according to the ATC classification system.

Non-drug therapies and procedures will be coded using MedDRA version 24.1 or higher.

Prior and concomitant medications and non-drug therapies and procedures will be listed.

2.5 Analysis supporting primary objective(s)

Data analysis will be performed when all subjects have completed the study.

2.5.1 Primary endpoint(s)

The incidence of ocular and non-ocular AEs are the primary endpoints. The primary endpoints will be analyzed for the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

No formal hypothesis testing will be performed in this study.

See Section 2.7.1 for details of the analyses to be performed for AEs.

2.5.3 Handling of missing values

This is a single dose, open-label study with 3 scheduled visits over the period of 1 month. Therefore, missing data will not be imputed.

2.5.4 Sensitivity analyses

Not applicable.

2.5.5 Supplementary analyses

Not applicable.

2.6 Analysis supporting secondary objectives

No secondary objectives are defined for this study.

2.7 Safety analyses

All safety analyses will be performed for the FAS.

2.7.1 Adverse events (AEs)

AEs will be coded using MedDRA version 24.1 or higher.

All AEs will be listed. SAEs will be listed separately.

Summaries will include all TEAEs which are defined as AEs that develop after start of study treatment or any events already present that worsens following exposure to study treatment until the subject discontinues or completes the study.

An overview table will summarize the number and percentage of subjects with at least 1 of the following TEAEs: any TEAE, TEAE suspected to be treatment-related, SAE, SAE suspected to be treatment-related, AESI, TEAE leading to discontinuation and TEAE leading to death. Subjects with more than 1 TEAE in a particular category will be counted only once in that category.

The number and percentage of subjects who reported TEAEs will be summarized by primary SOC and PT for:

- all TEAEs
- all TEAEs by maximum severity

Separate summaries will be provided for study treatment related TEAEs, SAEs, and TEAEs leading to discontinuation of the study. Analyses will be performed for ocular AEs for the study eye only and non-ocular AEs. Ocular AEs for the fellow eye will be listed only.

Listing of all AEs will be provided. SAEs will be listed separately.

If a subject reports more than one AE with the same PT, the AE will be counted only once for that PT. If a subject reports more than one AE within the same primary SOC, the subject will be counted only once for that SOC.

2.7.1.1 Adverse events of special interest / grouping of AEs

AESI is defined in the latest version of eCRS core safety topics, using the safety profiling plan flag at the time of analysis implementation (i.e. study database lock). Listing will be provided for AESI.

2.7.1.2 Adverse event reporting for clinicaltrials.gov

For the legal requirements of clinicaltrials.gov, two required tables on TEAEs which are not SAEs with an incidence greater than or equal to x% (default is 5% but a lower cut off may be applied and this will be determined based on the final data) and on treatment emergent SAEs will be provided by SOC and PT for the FAS.

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/non SAE has to be checked in a block e.g. among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.7.2 Deaths

All deaths recorded during the study will be listed.

2.7.3 Laboratory data

Laboratory data is not collected in this study.

2.7.4 Other safety data

2.7.4.1 Intraocular pressure (IOP)

All IOP measurements will be listed for subjects who fulfil at least one of the following criteria:

- IOP ≥ 26 mmHg
- Increase ≥ 10 mmHg from pre-injection IOP to post-injection IOP within a visit

2.7.4.2 Vital signs

All vital signs measurements will be listed for subjects who fulfil at least one of the following clinically notable criteria:

Table 2-1 Clinically notable criteria for vital signs

Variable	Category	Critical Values
Systolic blood	High	Either >180 with an increase from baseline >30 or >200 absolute

Variable	Category	Critical Values
pressure (mmHg)	Low	Either <90 with a decrease from baseline >30 or <75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline >20 or >115 absolute
	Low	Either <50 with a decrease from baseline > 20 or <40 absolute
Pulse rate (bpm)	High	Either >120 with an increase from baseline of >25 or >130 absolute
	Low	Either <50 with a decrease from baseline >30 or <40 absolute

2.8 Interim analysis

No interim analysis is planned for this study.

3 Sample size calculation

No formal statistical power calculations to determine sample size were performed for this study.

4 Change to protocol specified analyses

Protocol section 12.2 states that relevant medical histories and current medical conditions at baseline will be summarized. Given the small sample size, these data will be listed only.

Protocol section 12.3 states that concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarized. Given the small sample size, these data will be listed only.

Protocol section 12.4.2 states that AE presentations will be presented for the fellow eye. AEs reported for the fellow eye will be listed only.

Protocol section 12.4.2 states that pre-injection and post-injection IOP measurements will be listed. Instead, IOP measurements will only be listed for subjects who have at least IOP measurement meeting the criteria defined in Section 2.7.4.1.

Protocol section 12.4.2 states that all vital signs data will be listed. Instead, vital signs measurements will only be listed for subjects who have at least 1 vital signs measurement meeting the criteria defined in Section 2.7.4.2.

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.

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 (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 (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.

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.

5.1.3 Concomitant medication date imputation

No imputation for concomitant medication as data will be listed only.

5.1.3.1 Prior therapies date imputation

No imputation for prior therapies as data will be listed only.

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 WHODRUG Global B3 terminology.

The MedDRA version 24.1 or higher and WHODRUG Global B3 September 2021 or later will be used and will be described in the footnote of relevant outputs.

5.3 Statistical models

No hypothesis testing will be performed for this study.

5.4 Rule of exclusion criteria of analysis sets

Only one analysis set is defined, the FAS. No protocol deviations are defined which lead to exclusion from the FAS.

6 Reference

Not applicable.