SANDOZ A Novartis Division

Sandoz Biopharmaceuticals Clinical Development

SOK583A1 (INN: aflibercept)

Clinical Trial Protocol CSOK583A12304 / NCT05161806

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 prefilled syringe

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List of abbreviations

AE	Adverse event
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set
FDA	Food and Drug Administration
IFU	Instructions for Use
IMP	Investigational medicinal product
IOP	Intraocular pressure
IVT	Intravitreal(ly)
PFS	Prefilled syringe
SAE	Serious adverse event
SOK583A1	Product code of Sandoz' proposed aflibercept containing biosimilar product
US PI	US Prescribing information
VEGF	Vascular endothelial growth factor

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical study activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment 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 from study treatment	Point/time when the participant permanently stops receiving the study treatment 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 participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	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 data/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. The action of enrolling 1 or more participants
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical study information to sponsors and other oversight authorities, as appropriate
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Off-site	Describes study activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)

Participant	A study participant (can be a healthy volunteer or a patient). “Participant” terminology is used in the protocol whereas term “Subject” is used in data collection. In this study, a participant is a patient with (wet) neovascular age-related macular degeneration, requiring IVT administration of 2 mg aflibercept due to nAMD, 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 informed consent. 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 collected by the investigator that is coded and transferred to the Sponsor for the purpose of the clinical study. This data includes participant identifier information and study information.
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	Testing of vital signs can be repeated once to confirm clinical significance or to exclude technical errors. If the repeat test evaluation or result remains outside of the specified range for vital signs, the participant must be considered as a Screen Failure
Remote	Describes any study activities performed at a location that is not the investigative site where the investigator will conduct the study, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one 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 treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the study.
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.

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.
Withdrawal of study consent (WoC) / Opposition to use of data	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data (opposition to use data) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol summary

Protocol number	CSOK583A12304
Full Title	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 prefilled syringe
Brief title	Study of the safety of use of intravitreal SOK583A1 provided in a prefilled syringe
Sponsor and Clinical Phase	Sandoz Inc., 100 College Road West, Princeton, NJ 08540, USA Phase IIIb
Investigation type	Drug (Biosimilar)
Study type	Interventional
Purpose and rationale	This is a multicenter, open label Phase IIIb study to evaluate the safety of use of a PFS containing SOK583A1 (40 mg/mL) and to support the collection of observations of the PFS use for intravitreal injection, when utilized by qualified ophthalmologists, who follow the IFU appropriately to prepare and administer IVT injections to patients, suffering from nAMD.
Primary Objective(s)	The primary objective of the study is to evaluate the safety of use of a PFS containing SOK583A1 (40 mg/mL) in patients requiring IVT aflibercept treatment (capturing the AEs), when utilized by qualified ophthalmologists, supported by trained assistants, who follow the IFU appropriately, to prepare and administer IVT injections to patients, suffering from nAMD.
Study design	This is an open-label, single arm, multicenter, Phase IIIb study in patients with (wet) neovascular age-related macular degeneration, eligible for IVT aflibercept treatment. Screening and Baseline (Day 1) may be performed on the same day. A follow-up visit on-site will be performed on Day 8 (±2 days) and on Day 31 (+4 days - end of study visit). Demonstration of the safety use of the PFS containing SOK583A1 will be based on the performance of at least 3 different ophthalmologist teams. Participants will receive study medication once. Only patients already under IVT Eylea treatment and hence are familiar with the IVT procedure are eligible for the study. Administration of the study medication will be embedded into the routine treatment scheme. In compliance with the US label the recommended dose for aflibercept is 2 mg (0.05 mL) administered by IVT injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via IVT injection once every 8 weeks (2 months). A narrow window of flexibility for the drug administration (in accordance with the biosimilar safety and efficacy study CSOK583A12301) is possible: ± 3 days during the initial phase (first 3 months) and ± 7 days during the maintenance phase (thereafter). The participants of this study will be also part of an observational study, in which the ability of Health Care Professionals (HCPs), including

	qualified ophthalmologists and assistants who may perform the preparation steps, will be assessed to prepare and administer to patients intravitreal (IVT) injection using SOK583A1 2 mg Device and to follow the Instructions for Use (IFU).
Study population	Male and female patients ≥ 50 years of age treated with Eylea (intravitreally) due to nAMD and have received at least two injections during the induction phase already; 38 participants will be included into this clinical study.
Key Inclusion criteria	• Patients ≥ 50 years of age at baseline • Patients diagnosed with nAMD (uni- or bilateral) • Patients already under IVT Eylea treatment (last injection of the induction period or maintenance phase) • Willing and able to comply with all study procedures, and be likely to complete the study • Signed informed consent must be obtained before any assessment is performed
Key Exclusion criteria	• Active, suspected or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye at baseline, which is of clinical significance according to the investigator's judgment, such as active infections of the anterior segment; this includes conjunctivitis (except mild blepharitis), keratitis, scleritis, idiopathic or autoimmune associated uveitis or endophthalmitis • Any uncontrolled ocular hypertension or glaucoma in the study eye (defined as IOP ≥ 26 mmHg, despite treatment with anti-glaucomatous medication) • History of a medical, ocular or non-ocular condition, that in the judgment of the investigator, would preclude a safe administration of investigational product • Visual Acuity Score (VAS) worse than 20/200 on a Snellen chart, the generally accepted level of legal blindness • Topical ocular corticosteroids administered for at least 30 consecutive days within 3 months prior to screening • Systemic treatment with long-acting corticosteroids (more than 10 mg prednisolone equivalent) within 3 months prior to screening Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol • Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye any time during the past 3 months • Receipt of any systemic anti-VEGF within the last 6 months prior to enrollment • Uncontrolled hypertension (defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening) • Participants who do not comply with the local COVID-19 regulations of the study site
Study treatment	SOK583A1 provided in a PFS, which includes 2 mg aflibercept in 0.05 mL for IVT administration.

Key safety assessments	AEs that occur during the study period will be monitored and reported.
Other assessments	Observation of the preparation and the injection using the PFS. This is described in a separate study protocol.
Data analysis	All safety analyses will be performed descriptively.
Key words	Open label study, intravitreal injection, biosimilar, aflibercept, PFS

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®; hereafter referred to as 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 licensed for ophthalmological indications in the EU to Bayer Pharma AG and in the US to Regeneron Pharmaceuticals Inc. (Eylea US PI). The development of SOK583A1 aims for the treatment of all indications currently approved for Eylea. Biosimilarity will be supported by the totality of evidence from analytical, efficacy, safety, and immunogenicity data of an ongoing Phase III study.

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 US PI).

Study CSOK583A12301 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 CSOK583A12301 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.

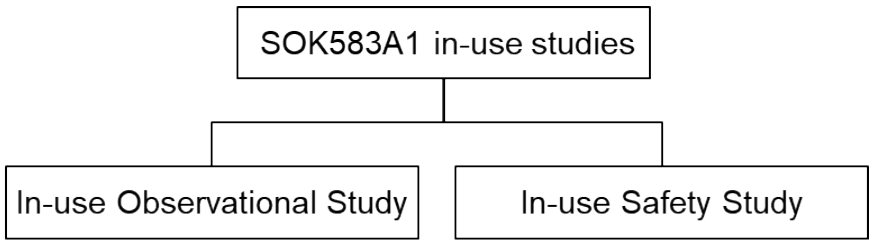
In the pivotal study, SOK583A1 will be available in a vial only and not in a PFS (intended for commercial use). During the FDA BPD Type 2 meeting held in 06/2019, it was confirmed that a clinical in-use study for the PFS is required. This study will evaluate the ability of ophthalmologists and their assistants to perform the preparation and administration of SOK583A1 following the IFU for the PFS (described in the observational protocol).

Therefore, the current study will be performed for safety purposes (capturing AEs to follow Good Clinical Practice guidelines - described in this clinical protocol) and will support the observational study for collection of observations on PFS use for IVT injection. There will be 2 separate protocols as follows:

- **The clinical study protocol** is designed to collect safety data obtained from the IVT injections conducted with the use of the PFS (described within this document).
- **The observational study protocol** (provided separately, with protocol number "PRT-SOK583_02_HFSP_Observational Study Protocol_PFS_vs1.0 ([redacted], 8566 0012a)-0003951390" is designed to evaluate the ability of observational study participants, including qualified ophthalmologists and assistants who may perform the preparation steps, to prepare and administer IVT injections to patients using SOK583A1 2 mg PFS and to follow the IFU. The study will be considered successful if all Healthcare Professionals demonstrate success on all safety critical tasks and essential tasks. In case of unsuccessful task completion, the root cause analysis will evaluate whether the IFU was the cause of unsuccessful task completion. Furthermore, it also includes to evaluate if a potential (technical) issues of the presentation lead to this result.

Figure 1-1 illustrates the proposed studies for the SOK583A1 in-use program. This protocol will cover the clinical (safety) study of this program only.

Figure 1-1 Studies conducted in the SOK583A1 in-use program



1.2 Purpose

The clinical protocol describes a multicenter, open label Phase IIIb study, intended to evaluate the safety of use of a PFS containing SOK583A1 (40 mg/mL), when utilized by qualified ophthalmologists, who follow the IFU appropriately to prepare and administer IVT injections to patients, suffering from nAMD. Safety aspects will be assessed for the application as well as for the IMP.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

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

3 Study design

This is an open-label, single arm, multicenter, Phase IIIb study in patients 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).

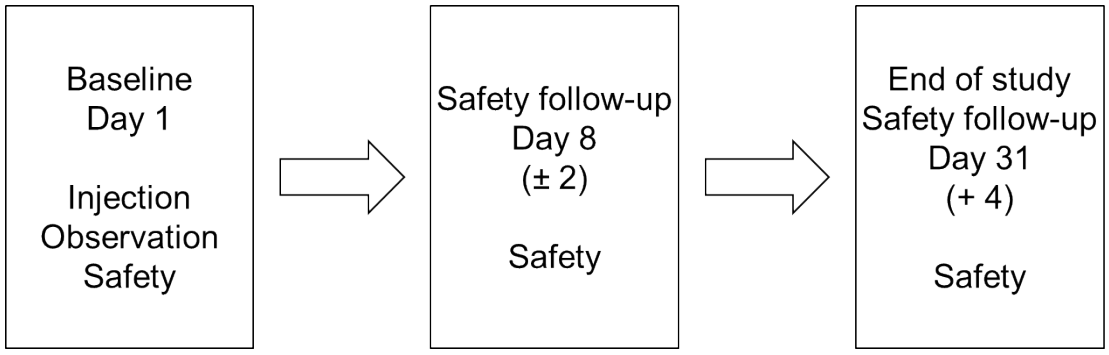
Demonstration the safety of using of the PFS containing SOK583A1 will be based on the performance of at least 3 different ophthalmologist teams.

The use of the PFS will be analyzed and rated by external observers. The details of the observational study will be described in detail in a separate study protocol.

Participating nAMD patients will receive study medication once. Only patients already under IVT Eylea treatment and hence are familiar with the IVT procedure are eligible for the study. Administration of the study medication will be embedded into the routine treatment scheme. In compliance with the US label the recommended dose for aflibercept is 2 mg (0.05 mL) administered by IVT injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via IVT injection once every 8 weeks (2 months). A narrow window of flexibility for the drug administration (in accordance with the biosimilar

safety and efficacy study CSOK583A12301) is possible: ± 3 days during the initial phase (first 3 months) and ± 7 days during the maintenance phase (after 3 months).

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

The study will evaluate the safety of use of SOK583A1 (40 mg/mL) provided in a PFS (also including safety of the IMP) where in addition under a separate study protocol, the ability to follow the IFU and giving the IVT SOK583A1 injection to patients requiring IVT aflibercept treatment due to nAMD is observed. To support registration of the PFS containing SOK583A1 in the US, the FDA has requested a human factor/clinical in-use study, which will evaluate the ability of the Health Care Professional professionals to follow the IFU to prepare the injection and administer the product to the vitreous (Meeting Type: Biosimilar, Meeting Category: FDA BPD Type 2 meeting, FDA Meeting Minutes of 12-Jun-2019). The results of the human factor evaluations and the results from the safety observations will be described in a separate report.

4.2 Rationale for dose/regimen and duration of treatment

Each participant who enters the study will be given a single injection of SOK583A1 (40 mg/mL) provided in a PFS embedded into their routine treatment scheme. SOK583A1 is being developed as a biosimilar product to Eylea. Therefore, the dose of the study medication was chosen according to the current Eylea US PI for IVT aflibercept injection.

One injection will be given to support the observation of use of the PFS based on the IFU. Participants will be considered to have completed the study after the evaluations on Day 31 (+4 days). Afterwards, the participant will receive Eylea again (after the appropriate time interval).

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Control drugs (comparator/placebo) or combination drugs are not planned in this study.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis is not planned for this study.

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.

Eylea has been licensed and commercialized world-wide since 2011. Clinical studies provided evidence of efficacy and safety in all approved indications. 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 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 increase in intraocular pressure (Eylea US PI). SAEs are also reported in a low incidence: hypersensitivity, endophthalmitis and retinal detachments, and a potential risk of thromboembolic events.

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, to participate in the study, they must adhere to the contraception requirements outlines in the exclusion criteria. If there are any questions that the participant will not reliably comply, they should not be entered or continue in the 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. Since no data are available so far, we cannot exclude that a switch from Eylea to SOK583A1 may result in the development of anti-drug antibodies.

Further details of the known and potential risks and benefits associated with aflibercept are presented in the Investigator Brochure 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 aflibercept 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 (Royal College of Ophthalmology).

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.

Based on the available data and the current literature, no specific dispositions need to be done due to COVID-19 vaccination.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and study integrity are listed in relevant sections. Notification of the public health emergency should be discussed with Sandoz prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Study population

The study population will be male and female patients ≥ 50 years old who are diagnosed with nAMD and requiring IVT treatment with Eylea and have received at least 2 injections during the induction phase already. Thirty-eight participants are expected to be injected at approximately 3 sites in the US.

5.1 Inclusion criteria

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

1. Patients ≥ 50 years of age at baseline
2. Patients diagnosed with nAMD (uni- or bilateral)
3. Patients already under IVT Eylea treatment (last injection of the induction period or maintenance phase)
4. Willing and able to comply with all study procedures, and be likely to complete the study
5. Signed informed consent must be obtained before any assessment is performed

5.2 Exclusion criteria

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

1. Active or recent (within 4 weeks) intraocular inflammation (grade trace or above) in the study eye at baseline, which is of clinical significance according to the investigator's judgment, such as active infections of the anterior segment; this includes conjunctivitis (except mild blepharitis), keratitis, scleritis, idiopathic or autoimmune associated uveitis or endophthalmitis

2. Any uncontrolled ocular hypertension or glaucoma in the study eye (defined as IOP ≥ 26 mmHg, despite treatment with anti-glaucomatous medication)
3. History of a medical, ocular or non-ocular condition, that in the judgment of the investigator, would preclude a safe administration of investigational product
4. Visual Acuity Score (VAS) worse than 20/200 on a Snellen chart, the generally accepted level of legal blindness
5. Topical ocular corticosteroids administered for at least 30 consecutive days within 3 months prior to screening
6. Systemic treatment with long-acting corticosteroids (more than 10 mg prednisolone equivalent) within 3 months prior to screening
7. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol
8. Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye any time during the past 3 months
9. Receipt of any systemic anti-VEGF within the last 6 months prior to enrollment
10. Pregnant or nursing (lactating) women or women of child-bearing potential (WOCBP) is defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Baseline, unless they are using highly effective methods of contraception during dosing of study treatment.

    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. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. 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 study treatment. 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 patients on the study, the vasectomized male partner should be the sole partner for that patients.
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment No additional exclusions may be

applied by the investigator, to ensure that the study population will be representative of all eligible patients.

Women are considered post-menopausal and not of childbearing 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 childbearing potential.

11. Uncontrolled hypertension (defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening)
12. Participants who do not comply with the local COVID-19 regulations of the study site

6 Treatment

6.1 Study treatment

SOK583A1 is formulated as a sterile solution aseptically filled in a PFS for single use. The study medication SOK583A1 will be provided in a PFS, with 40 mg/mL of aflibercept solution for IVT injection (2 mg/0.05 mL).

The Sponsor will ensure sufficient supplies of SOK583A1 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 Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
SOK583A1 (40 mg/mL)	Solution for injection	IVT	PFS (2 mg/0.05 mL)	Sponsor (local)

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

This is a single-arm, open-label study where all patients will receive a single injection of SOK583A1 (40 mg/mL) provided in a PFS at Baseline.

6.1.4 Treatment duration

The total study duration for the individual participant is approximately 31 days. Screening and IVT injection of SOK583A1 may be done on the same day. A follow-up visit will be performed on Day 8 (±2 days) and on Day 31 (+4 days - end of study visit).

6.2 Other treatment(s)

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 Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Sponsor medical monitor or qualified delegate before enrolling a participant or allowing a new medication to be started. If the participant is already enrolled, contact the Sponsor or qualified delegate to determine if the participant should continue participation in the study.

6.2.2 Prohibited medication

Prohibited medications after the start of 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 the study. Any medication which may be required to treat ocular or systemic AEs and permitted oral or injectable contraceptives for female participants are allowed and must be recorded in the appropriate eCRF page.

The standard of care or other approved treatment according to the investigator choice 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 (except if for treatment of AE)
Study eye: Laser treatment for AMD	Discontinue study
Systemic: Systemic corticosteroids for 15 or more consecutive days[1]	Discontinue study
Systemic: anti-VEGF therapy	Discontinue study
Study eye, fellow eye and systemic: Patients under any investigational drug, biologic or device (not authorized for use)	Discontinue study

[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

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

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

The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant''s source document.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

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

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 local legal requirements. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator 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 field monitors during site or remote monitoring visits, and at the completion of the study.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation and guidelines. Otherwise, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Sponsor monitor or to the Sponsor address provided in the investigator folder at each site.

The study treatment and all required clinical study supplies will be distributed direct to the participant utilizing an extension of the IND for compliance purposes.

6.3.1.2 Handling of other treatment

6.3.2 Instruction for prescribing and taking study treatment

The IVT injection will be carried out under controlled, aseptic conditions per local clinical practice. The study eye will be assessed before and after IVT injection to ensure that the procedure and/or the study treatment had not endangered the health of the eye. An IVT injection is contraindicated in patients with active or suspected ocular or periocular infections and in patients with active or suspected intraocular inflammation; therefore, the investigator should verify that these conditions are not present in either eye (study and fellow eyes) prior to every injection.

Used study treatment will be recorded/databased. Date and time of the injection to the patient will be recorded in the eCRF.

The conduct of IVT injections will be observed by an external study team member to ensure compliance with the proposed commercial instruction for use.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled, i.e. signed the ICF, for screening and is retained for the participant throughout his/her participation in the study. The Participant No. consists of the Center Number (Center No.) (as assigned by the Sponsor to the investigative site) with a sequential Participant No. suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments or modifications are not possible.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

This is not in scope, since each patient receives only a single injection of aflibercept 2 mg provided in a PFS.

6.6.2 Recommended treatment of adverse events

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.

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) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. 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). Since videotaping is necessary for the observational study and the patient might be seen on this video as well, patients must also specifically agree to this procedure. 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 for aflibercept can be found in the Eylea US PI. 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 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.

Women of childbearing 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 to participate in the study, they must adhere to the contraception requirements.

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

8 Visit schedule and assessments

Table 8.1 Assessment schedule lists all assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Screening and Baseline may be performed on the same day. A follow-up visit will be performed on Day 8 (±2 days) and on Day 31 (+4 days - end of study visit). The safety assessment will include ocular and non-ocular assessments according to clinical practice (e.g. blood pressure, IOP, slitlamp, ophthalmoscopy). Any occurred events on this period should be collected in the source, and SAEs must be reported to the Sponsor safety according instructions in Section 10.1.3.

The conduct of the IVT injection and preparation will be observed and videotaped by an external member and will follow observational study protocol (PRT-SOK583_02_HFSP_Observational Study Protocol_PFS_vs1.0 ([redacted], 8566 0012a)-0003951390), to ensure compliance with IFU.

Table 8-1 Assessment schedule

	Open Label Treatment	Safety Follow-Up	Safety Follow-Up (EOS)
	Baseline	Follow-Up	Follow-Up
	Day 1	Day 8±2	Day 31+4
Informed consent	X		
Inclusion / Exclusion criteria	X		
Demography	X		
Medical history	X		
Prior/Concomitant medication	X	X	X
Study drug administration	X		
Observation of IFU and the use of the PFS[1]	X		
Adverse Events	X	X	X
Pregnancy Test	S		
Vital signs	X	X	X
Intraocular Pressure (IOP)	X	X	X
Ocular Assessments (slit lamp, ophthalmoscopy)	S	S	S

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] The conduct of IVT injections will be observed by an external study team member to ensure compliance with the IFU; this will be described in a separate observational study protocol

8.1 Screening

Screening

Participants 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).

Rescreening is not allowed in this study.

Retesting

Measurement of vital signs can be repeated once to confirm clinical significance or to exclude technical errors. If the repeat test evaluation or result remains outside of the specified range for vital signs, the participant must be considered as a Screen Failure.

8.1.1 Information to be collected on screening failures

There is no separate screening period planned for this study. Patient's Eligibility will be assessed at Screening Visit. 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). Afterwards, patient's eligibility will be assessed.

Patients who sign an informed consent but do not receive the IVT injection will be considered a screen failure and the reason for the screen failure will be also documented. The demographic information, informed consent, and Inclusion/Exclusion data must be completed in the eCRF and also be kept in the source documents for screen failure subjects. No data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE (see SAE section for reporting details).

8.2 Participant demographics/other baseline characteristics

The following data will be collected: age, sex, race, ethnicity, vital signs, study eye, IOP, prior concomitant medications, medical history, and current medical conditions.

8.3 Safety

The investigator will perform safety assessments according to clinical practice (e.g. slitlamp, IOP measurement, ophthalmoscopy). IOP $\geq$ 26 mmHg should be reported as AE and any clinically significant changes by the discretion of the Investigator should be also reported as AEs. The safety assessments selected are standard for this indication and patient population.

The assessment schedule is provided in Table 8-1.

For details on AE collection and reporting, refer to Section 10.1.

8.3.1 Pregnancy and assessments of fertility

A urine pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion in the study.

Additional pregnancy testing might be performed if requested by local requirements.

8.4 Additional assessments

Additional assessments include the following and will be specified in the observational study protocol (PRT-SOK583_02_HFSP_Observational Study Protocol_PFS_vs1.0 ([redacted], 8566 0012a)-0003951390).

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

This is a single dose study, therefore discontinuation of study treatment is not applicable.

Patients who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdrawal of informed consent in Section 9.1.2). **Where possible, they should return for the safety assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, and letter) should be made to contact the patients/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the patients cannot or is unwilling to attend a follow up visit during the study period, the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

9.1.2 Discontinuation from study

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient:

- Does not want to participate in the study anymore and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

All efforts should be made to complete the assessments prior to study withdrawal. If the participant agrees, a final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table.

The Sponsor will continue to keep and use collected study information (including any data resulting from analysis of a patient's samples until the time of withdrawal) according to the applicable law.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore, and
- Does not allow further visits or assessments, and
- Does not want any further study related contacts

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 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.

In this situation, it is not allowed to conduct further assessments and the data that would have been collected at subsequent visits will be considered missing. Further attempts to contact the participant are also not permitted 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 should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 Study completion and post-study treatment

Study completion is defined as when the last patient finishes the End of Study Visit, 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.

9.4 Early study termination by the Sponsor

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, the Sponsor will always consider the patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for

contacting the patients, when the patient should come for a final visit) and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or Sponsor depending on the local regulation will be responsible for informing IRBs / IECs of the early termination of the trial.

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 patient 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 patient and identifying AEs.

The qualified medical personnel of the sponsor will be readily available to advise on trial related medical questions or problems.

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

AEs must be recorded in the Adverse Events eCRF 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):

1. The severity grade includes the following:
   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. 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 trial drug, they happen 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 patient.
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 one or more of the following:

- no action taken (further observation only)
- Concomitant medication or non-drug therapy given.

6. Its outcome
    a. not recovered/not resolved
    b. recovered/resolved
    c. recovering/resolving
    d. recovered/resolved with sequelae
    e. fatal
    f. unknown

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

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 30 days, following the injection.

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) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

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

10.1.2 Serious adverse events

A 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 patient 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 (please 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 patient's general condition

  - treatment on an emergency outpatient 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 patient 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 patient 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 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.

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to the Sponsor safety within 24 hours of learning of its occurrence. SAEs will be reported in paper form. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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 within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered 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 Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a chief medical officer & 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 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Safety events occurring during the study will be reported as AEs in the eCRF. Device malfunction observations are to be reported to the respective Sponsor Country Organization Quality Assurance.

10.1.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to the 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 Sponsors 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 and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

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 only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (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, please see the respective sections.

10.2 Additional safety monitoring

No additional safety monitoring is planned in this study.

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 database lock, the investigator will receive copies of the patient 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

The Sponsor's personnel or designated Contract Research Organization (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 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked 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 Sponsor representative will review the protocol and data capture requirements (i.e. eSource DDE or 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 and 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, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form 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 eCRFs 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

12.1 Analysis sets

The FAS includes all enrolled patients who receive a dose of study treatment.

12.2 Participant demographics and other baseline characteristics

Demographic data will be listed and summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for all patients.

12.3 Treatments

Descriptive summary statistics for exposure to study treatment will be provided for the FAS.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all patients.

12.4 Analysis supporting primary objectives

12.4.1 Definition of primary endpoint(s)

Occurrence of ocular or non-ocular AEs during the study-reporting period.

12.4.2 Statistical model, hypothesis, and method of analysis

No formal hypothesis tests will be performed in this study. All safety analyses will be performed descriptively using the FAS.

Adverse events

The number (and percentage) of patients with treatment-emergent AEs (events started after the single dose of study treatment or events present prior to start of study treatment but which 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 summaries will be provided for study treatment related AEs, SAEs, other significant AEs leading to discontinuation of the study. Separate presentations will be provided related to ocular events in the study eye and fellow eye and systemic events. Patient listings of all AEs will be provided. Other serious or clinically significant non-fatal AEs will be listed separately.

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

Ophthalmic examinations

Pre-injection and post-injection IOP measurements will be listed. In addition, the IOP during follow-up visit will also be listed.

Vital signs

Vital signs data will be collected and listed.

12.5 Sample size

The sample size has been discussed during a FDA BPD Type 2 meeting in June 2019. A sample size of at least 30 patients has been agreed by FDA. To avoid unexpected issues in terms of withdraws, missing or incomplete data, 38 patients will be included per study (30 minimum required plus a buffer).

Primary endpoint(s)

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

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 informed consent form, 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 a 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 the 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 the 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 trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT, etc.).

For details on the Sponsor publication policy including authorship criteria, please refer to the Sponsor publication policy training materials that were provided to you at the initiation visit.

13.4 Quality Control and Quality Assurance

The 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 the Sponsor's 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 the

Sponsor and not use it for any purpose other than the study, except for the appropriate monitoring on 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.

15 References

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