Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Afqlir; Enzeevu

Active ingredient: Aflibercept

Sponsor: Sandoz Pty Ltd

October 2025

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACV	Advisory Committee on Vaccines
ADA	Anti-drug antibody
AMD	Age-related macular degeneration
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CHO	Chinese hamster ovary
CMI	Consumer Medicines Information
CNV	Choroidal neovascularisation
CRVO	Central retinal vein occlusion
CSFT	Central subfield thickness
DLP	Data lock point
DME	Diabetic macular oedema
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
EMA	European Medicines Agency
ETDRS	Early treatment diabetic retinopathy study
EU	European Union
FAS	Full analysis set
Fc	Fragment crystallisable
FDA	Food and Drug Administration (United States of America)
HRVO	Hemiretinal vein occlusion
IgG1	Immunoglobulin G, Subtype 1.
IOP	Intraocular pressure
IVT	Intravitreal
LISY	Liquid in (prefilled) syringe (Study 304).
LIVI	Liquid-in- a (single use) vial (Study 301)
LIVI Kit	One single-use vial, filter needle, injection needle, syringe (Study 303)
Myopic CNV	Myopic choroidal neovascularisation

Abbreviation	Meaning
nAb	Neutralising antibody
nAMD	Neovascular (wet) age-related macular degeneration
NPDR	Non-proliferative diabetic retinopathy
PD	Pharmacodynamics
PDR	Proliferative diabetic retinopathy
PFS	Pre-filled syringe
PI	Product Information
PIGF	Placental growth factor
PK	Pharmacokinetics
PM	Pathologic myopia
PSUR	Periodic safety update report
RMP	Risk management plan
RPE	Retinal pigment epithelium
RVO	Retinal vein occlusion
SAE	Serious adverse event
SD	Standard deviation
SOK583/ SOK583A1	Afqlir/ Enzeevu; Sponsor's proposed biosimilar to Eylea (aflibercept)
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
VEGF	Vascular endothelial-derived growth factor

Product submission

Submission details

Type of submission:	New biosimilar entity
Product names:	Afqlir; Enzeevu
Active ingredient:	Aflibercept
Decision:	Approved
Date of decision:	15 May 2025
Date of entry onto ARTG:	27 May 2025
ARTG numbers:	445957 – Enzeevu (aflibercept) 40 mg/mL solution for intravitreal injection (pre-filled syringe) 445958 – Enzeevu (aflibercept) 40 mg/mL solution for intravitreal injection vial with needle 445959 - Afqlir (aflibercept) 40 mg/mL solution for intravitreal injection (pre-filled syringe) 445960 – Afqlir (aflibercept) 40 mg/mL solution for intravitreal injection vial with needle
▼*Black Triangle Scheme*	No
for the current submission:	
Sponsor's name and address:	Sandoz Pty Ltd 100 Pacific Highway North Sydney, NSW 2060
Dose forms:	2 mg aflibercept, injection volume of 50 µL.
Strength:	40 mg/mL
Containers:	Single-use vial or pre-filled syringe (PFS).
Pack sizes:	Each carton includes a single type I glass vial or a sealed blister pack with a sterile pre-filled type I glass syringe.
Approved therapeutic use for the current submission:	*Afqlir/ Enzeevu (aflibercept) 2 mg is indicated in adults for the treatment of:* • *neovascular (wet) age-related macular degeneration (wet AMD)* • *visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)* • *visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)* • *diabetic macular oedema (DME)* • *visual impairment due to myopic choroidal neovascularisation (myopic CNV).*

Route of administration:	Intravitreal injection It must only be administered by a qualified ophthalmologist experienced in administering intravitreal injections.
Dosage:	***Treatment of neovascular (wet) age-related macular degeneration (wet AMD)*** Afqlir/ Enzeevu 2 mg treatment is initiated with one Afqlir/ Enzeevu 2 mg injection per month for three consecutive months, followed by one injection every two months. ***Treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*** Afqlir/ Enzeevu 2 mg treatment is initiated with one Afqlir/ Enzeevu 2 mg injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. ***Treatment of visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)*** Afqlir/ Enzeevu 2 mg treatment is initiated with one Afqlir/ Enzeevu 2 mg injection per month for three consecutive months. After the first three monthly injections, the treatment interval may be adjusted based on visual and/or anatomic outcomes. ***Treatment of diabetic macular oedema (DME)*** Afqlir/ Enzeevu 2 mg treatment is initiated with one Afqlir/ Enzeevu 2 mg injection per month for five consecutive months. ***Treatment of visual impairment due to myopic choroidal neovascularisation (myopic CNV)*** Afqlir/ Enzeevu 2 mg treatment is initiated with one Afqlir/ Enzeevu 2 mg injection (equivalent to 50 µL). For further information regarding dosage, such as dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	Category D There are limited data on the use of aflibercept in pregnant women. Women of childbearing potential have to use effective contraception during treatment and for at least 3 months after the last intravitreal injection of aflibercept 2 mg. Enzeevu should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. The treating ophthalmologist in consultation with the treating obstetrician need to consider the individual benefit-risk balance for each patient. This includes a consideration of timing of treatment, delaying treatment and other potential treatment options.

Studies in animals have shown reproductive toxicity, including a series of external, visceral, skeletal malformations, after systemic administration.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Sandoz Pty Ltd to register Afqlir and Enzeevu (aflibercept) 40 mg/mL, in a vial containing 50 µL (2 mg) aflibercept or a pre-filled syringe containing 50 µL (2 mg) aflibercept for the following proposed indications:[1]

Afqlir/ Enzeevu are indicated in adults for the treatment of:

- *neovascular (wet) age-related macular degeneration (wet AMD),*
- *visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO),*
- *visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO),*
- *diabetic macular oedema (DME)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV).*

This is a Category 1 Type A submission for a biosimilar product. The proposed drugs Afqlir/ Enzeevu (also referred to as SOK583) contain aflibercept 2mg as the active ingredient. The Australian (AU) reference product is Eylea 2mg (aflibercept).

Disease or condition

Neovascular age-related macular degeneration

Age-related macular degeneration (AMD) is a progressive degenerative disease of the photoreceptors of the macula and the supporting retinal pigment epithelium. The disease is characterised by loss of central vision and is the most common cause of severe central vision loss and legal blindness among adults in the Western world. An estimated 15% of people with AMD progress to legal blindness. Age related macular degeneration (AMD) is a leading cause of irreversible blindness among the elderly population in Australia, and internationally[2,3] and is likely to increase as the population ages. It poses a significant financial burden to the Australia economy.

[1] This is the original indication proposed by the sponsor when the TGA commenced the assessment of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Fleckenstein, M., Schmitz-Valckenberg, S., & Chakravarthy, U. (2024). Age-Related Macular Degeneration: A Review. *JAMA*, *331*(2), 147–157. https://doi.org/10.1001/jama.2023.26074

[3] Keel, S., Xie, J., Foreman, J., van Wijngaarden, P., Taylor, H. R., & Dirani, M. (2017). Prevalence of Age-Related Macular Degeneration in Australia: The Australian National Eye Health Survey. *JAMA ophthalmology*, *135*(11), 1242–1249. https://doi.org/10.1001/jamaophthalmol.2017.4182

Whilst pathogenesis is not well understood, it is thought to be multifactorial and polygenic, with age as the single most important risk factor. AMD occurs in two forms, non-neovascular (also known as dry, or non-exudative) and neovascular (also known as wet, or exudative). Non-neovascular AMD is the more common form, occurring in 75% of AMD patients, and can progress to neovascular AMD in a minority of patients. The non-neovascular form is characterized by yellow deposits under the retina (drusen), changes in the retinal pigment epithelium (RPE) and geographic atrophy.

Neovascular AMD occurs when neovascular vessels from the choroid grow through defects in Bruch's membrane and proliferate underneath the retinal pigment epithelium or the retina. The exudate from these vessels results in the elevation of the retina due to oedema resulting in visual distortion. Repeated haemorrhages can lead to fibrosis, macular scar formation, and permanent vision loss.

First line treatment involves intravitreal injections of anti-vascular endothelial-derived growth factor (anti-VEGF) agents, which causes regression of neovascular membranes and improves visual acuity. Photodynamic therapy is an alternative treatment option.[2,4,5]

Macular oedema secondary to retinal vein occlusion (branch or central)

Retinal vein occlusion (RVO) is an important cause of visual loss globally; the prevalence increases with age. Classification depends on the anatomic location of the occlusion, with branch vein occlusion (BRVO) occurring more commonly than central retinal vein occlusion (CRVO), and hemiretinal vein occlusion (HRVO) being the least frequent form. Pathophysiology differs between BRVO and CRVO. BRVO is thought to be due an atherosclerotic arteriole occluding a vein at an arteriovenous crossing, whereas CRVO is thought to be due to primary formation of a thrombus occurring because of impaired venous drainage. The effect of a RVO on visual acuity depends on the type and location of the occlusion, and the development of macular oedema. Other complications of a RVO can include neovascularisation and vitreous haemorrhage.[6] Vascular endothelial-derived growth factor (VEGF) is a cytokine released by hypoxic cells. It increases vascular permeability and leads to the development of macular oedema in vein occlusions.

Anti-VEGF agents are the first-line therapy for macular oedema secondary to BRVO or CRVO. Second-line treatments include intravitreal glucocorticoid injection or laser photocoagulation.[7]

Diabetic macular oedema

Diabetic retinopathy (DR) is the principal cause of impaired vision in people aged between 25 and 74 years, with visual loss occurring due to macular oedema, haemorrhage, retinal detachment, or neovascular glaucoma. DR occurs as either a non-proliferative type or a proliferative (neovascular) type. Diabetic macular oedema can occur at any stage or severity of DR across both types.[8]

[4] Anguita, R., Tasiopoulou, A., Shahid, S., Roth, J., Sim, S. Y., & Patel, P. J. (2021). A Review of Aflibercept Treatment for Macular Disease. *Ophthalmology and therapy*, *10*(3), 413–428. https://doi.org/10.1007/s40123-021-00354-1

[5] Vavvas, D.G (2023) Age-related macular degeneration. Up to Date; Updated August 28, 2025. https://www.uptodate.com/contents/age-related-macular-degeneration

[6] Han, D.P. & Ahmad, B. (2023). Retinal vein occlusion: Epidemiology, clinical manifestations, and diagnosis. Up to Date; Updated June 23, 2025. https://www.uptodate.com/contents/retinal-vein-occlusion-epidemiology-clinical-manifestations-and-diagnosis

[7] Han, D.P. & Ahmad, B. (2023). Retinal vein occlusion: Treatment. Up to Date; Updated October 29, 2024. https://www.uptodate.com/contents/retinal-vein-occlusion-treatment

[8] D'Amico D.J. & Shah A.R. (2023) Diabetic retinopathy: Classification and clinical features. Updated March 20, 2025. https://www.uptodate.com/contents/diabetic-retinopathy-classification-and-clinical-features.

The physiopathology of DR and diabetic macular oedema (DMO) is complex and poorly understood. High levels of VEGF-A have been identified in the retina and vitreous of patients with DMO and DR. This signal protein increases vascular permeability and progression from non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR).

Intravitreal anti-VEGF agents are considered the first-line treatment for DMO and can be combined with adjunct laser photocoagulation therapy. Intravitreal glucocorticoids are used first-line in some patient populations, or second line for DMO refractory to anti-VEGF and laser photocoagulation therapy. Vitrectomy is an option for those unresponsive to medical therapy.[9]

Myopic choroidal neovascularisation

Pathologic myopia (PM) is a possible consequence of myopia, particularly in eyes with high myopia (spherical equivalent of at least 6.0 dioptres). It is characterised with degenerative macular changes that present with different patterns of chorioretinal atrophy. It has been suggested that PM is characterized by progressive elongation of the globe and abnormal choroidal vasculature with additional degenerative changes. The presence of 'plus' lesions, which include lacquer cracks, myopic CNV, and Fuchs' spots, may lead to central vision loss.

Myopic CNV recurs frequently, is usually bilateral, and has a poor long-term prognosis even with treatment. Although the pathogenesis of myopic CNV is not entirely clear, VEGF has been shown to be elevated in the aqueous humour and its role implicated in the active stages of the disease characterised by neovessel formation.

Anti-VEGF therapy is the first-line treatment for myopic CNV; however, effectiveness can gradually decline after the initial several years of disease treatment. Photodynamic therapy is an alternative but inferior therapy option.

Current treatment options

Anti-VEGF agents currently approved in Australia for the same indications proposed for SOK583 are:

- aflibercept 2mg (Eylea), and aflibercept 2mg (Pavblu/ Eyzurci) approved for:
  - neovascular AMD
  - macular oedema secondary to BRVO or CRVO
  - DME
  - myopic choroidal neovascularisation
- ranibizumab (Lucentis), approved for:
  - neovascular AMD
  - DME
  - choroidal neovascularisation secondary to pathologic myopia
  - macular oedema secondary to RVO

[9] D'Amico D.J. & Shah A.R. (2023) Diabetic retinopathy: Prevention and treatment. Updated June 11, 2025. https://www.uptodate.com/contents/diabetic-retinopathy-prevention-and-treatment?search=Diabetic%20macular%20oedema%20&source=search_result&selectedTitle=1~14&usage_type=default&display_rank=1

- faricimab (Vabysmo)
  - neovascular AMD
  - DME
- brolucizumab (Beovu)
  - neovascular AMD
  - DME

Clinical rationale

Vascular endothelial-derived growth factor (VEGF) plays an important role in maintaining the physiological condition of the retina under normal conditions. Dysregulation of VEGF can result in pathological alterations including hyperpermeability of the retinal capillaries and migration and proliferation of retinal endothelial cells and is thought to be important in the pathogenesis of neovascular eye disease.[4,5] A variety of ocular diseases are associated with pathologic neovascularisation and vascular leakage, and/or can result in thickening and oedema of the retina, which is thought to contribute to vision loss.

Aflibercept is a soluble decoy receptor that binds vascular endothelial growth factor-A (VEGF-A), VEGF-B, and placental growth factor (PIGF) with a greater affinity than the body's native receptors. It is called a decoy receptor since VEGF does not bind to its original receptors and mistakenly binds with aflibercept, thereby reducing VEGF activity.[10]

Aflibercept is administered by intravitreal injection into the eye. Recommended dosing schedules depend on the indicated condition being treated and maintenance dosing regimens are physician determined and are guided by visual and/or anatomic outcomes. The minimum interval between doses into the same eye is one month.

Regulatory status

Australian regulatory status

This product is considered a new biosimilar medicine for Australian regulatory purposes.

The ARTG start date for the reference product, Eylea, was 7 March 2012.

International regulatory status

At the time the TGA considered this submission, a similar submission had been considered by other regulatory agencies. The following table summarises these submissions and provides the indications where approved.

[10] Karth, P.A. & Swinney, C. (2015) Aflibercept. EyeWiki: American Academy of Ophthalmology. Updated January 27, 2025. https://eyewiki.org/Aflibercept

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
United States (FDA)	10 August 2023	Approved on 9 August 2024	*Enzeevu (aflibercept-abzv) - The indication is the treatment of neovascular (wet) Age-Related Macular Degeneration (AMD).*
European Union (EMA)	22 August 2023	Approved on 19 September 2024.	*Afqlir - indicated in adults for the treatment of:* • *neovascular (wet) age-related macular degeneration (AMD),* • *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or CRVO)* • *visual impairment due to diabetic macular oedema (DME)* • *visual impairment due to myopic choroidal neovascularisation (myopic CNV).*

Registration timeline

The following table captures the key steps and dates for this submission.

This submission was evaluated under the standard prescription medicines registration process.

Table 2: Timeline for Submission PM-2024-01570-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	31 May 2024
Evaluation completed (End of round 2)	12 February 2025
Registration decision (Outcome)	15 May 2025
Registration in the ARTG completed	27 May 2025
Number of working days from submission dossier acceptance to registration decision*	200

*Statutory timeframe for standard submissions is 255 working days

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

Aflibercept (SOK583) is a fusion protein consisting of portions of human vascular endothelial growth factor receptors 1 (VEGFR-1) and 2 (VEGFR-2), and the Fc (fragment crystallisable) portion of IgG1; designed to bind (trap) vascular endothelial growth factor-A (VEGF-A), vascular endothelial growth factor-B (VEGF-B), and placental growth factor (PlGF).

The manufacturing process for Aflibercept drug substance uses a recombinant Chinese hamster ovary (CHO) cell line. For manufacture of Aflibercept, a fed-batch process with preceding expansion batches, followed by a primary separation and a series of purification steps, typical for monoclonal antibodies, including chromatography steps as well as virus removal and inactivation steps, has been developed.

Stability data have been generated under real time and stressed conditions to characterise the stability profile of the active ingredient and to establish a shelf life. The real time data submitted support a shelf life of 48 months when stored at ≤ -60°C, protected from light.

Afqlir/Enzeevu vial

- Store at 2°C to 8°C (Refrigerate. Do not freeze).
- Keep vial in the carton to protect from light.
- Prior to usage, the unopened vial may be stored at room temperature up to 30°C for up to 14 days.

Afqlir/Enzeevu PFS

- Store at 2°C to 8°C (Refrigerate. Do not freeze).
- Store in the original package in order to protect from light.
- Prior to usage, the pre-filled syringe in unopened blister may be stored at room temperature up to 30°C for up to 14 days.

There are no objections on quality grounds to the approval of new strength and formulation of Afqlir 40 mg/mL vial, Enzeevu 40 mg/mL vial, Afqlir 40mg/mL PFS, and Enzeevu 40 mg/mL PFS.

Nonclinical evaluation summary

The sponsor, Sandoz Pty Ltd, has applied to register Afqlir and Enzeevu containing the active ingredient aflibercept, intended as a biosimilar to Eylea 2 mg (40 mg/mL). The proposed indications, intravitreal (IVT) and dosing regimen and route match those of Eylea. However, the formulation of Afqlir/Enzeevu differs from that for Eylea: trehalose in place of sucrose and sodium chloride, L-histidine and L-histidine hydrochloride monohydrate in place of sodium phosphate monobasic monohydrate and sodium phosphate dibasic heptahydrate.

The nonclinical dossier contained a comparative study on pharmacokinetics (systemic exposure and ocular distribution) following single IVT dosing. The scope of the nonclinical program is adequate under the relevant EU guideline. This study was conducted using EU-sourced Eylea as

the reference product. No data were provided in Module 4 to verify the comparability of the EU-sourced and Australian-sourced Eylea.

In an ocular distribution study in rabbits, there were no significant differences in pharmacokinetic parameters for aflibercept in the vitreous humour following IVT dosing of Afqlir and EU Eylea. Systemic aflibercept exposures were also comparable.

The ability of the nonclinical studies to support comparability to Australian Eylea depends on the conclusion of the Module 3 Evaluator regarding the identity of Eylea products across jurisdictions. Provided that EU-sourced Eylea is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Afqlir and Enzeevu.

Clinical evaluation summary

Summary of clinical studies

The clinical program includes pivotal comparative clinical study and 2 supportive studies. Study summary details are outlined in table 3. During clinical development, SOK583 was supplied as 3 presentations:

- Liquid in a single-use vial (LIVI) used in Study 301
- LIVI kit (1 single-use vial, filter needle, injection needle, and syringe) used in Study 303
- Liquid in (prefilled) syringe (LISY) used in Study 304.

Table 3: Overview of clinical studies included in the SOK583 development program.

Study No.	Study design and objective Population	Number of subjects	Duration of treatment and follow-up	Dosage and batch numbers
Study 301 (Pivotal)	A multicenter, randomized, double-masked, 2-arm parallel study to demonstrate similar efficacy, safety, and immunogenicity of SOK583 and Eylea EU as per Eylea approved treatment regimen in subjects with nAMD Male and female subjects with nAMD 50 years or older and naïve to anti-VEGF treatment	N=485 [1] SOK583: N=245 Eylea EU: N=240	IVT administration of 2 mg of SOK583 or Eylea EU in the study eye, every 4 weeks at Baseline, Week 4, and Week 8, and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48. Total duration: Up to 54 weeks, including up to 2 weeks of screening, 48 weeks of treatment, and up to 4 weeks follow-up after dose	SOK583: 40 mg/mL, LIVI, up to 8 IVT injections of 2 mg/0.05 mL Eylea EU: 40 mg/ mL, vial, up to 8 IVT injections of 2 mg/0.05 mL Batch numbers: SOK583: 3-FIN-3644, 3-FIN-3645 Eylea EU: KT05TB5, KT0957P, KT095CJ, KT0BBC7
Study 303 (Supportive)	An open-label, single-arm, multicenter study to evaluate the safety of use of LIVI kit containing SOK583 Male and female subjects with nAMD 50 years or older who required and had previously received IVT treatment with Eylea	N=36 SOK583: N=36	Single IVT administration of 2 mg of SOK583 in the study eye followed by a 30-day safety follow-up	SOK583: 40 mg/mL, LIVI kit, single IVT injection of 2 mg/0.05 mL Batch number: SOK583: 3-FIN-3644
Study 304 (Supportive)	An open-label, single-arm, multicenter study to evaluate the safety of use of a LISY containing SOK583 Male and female subjects with nAMD 50 years or older who required and had previously received IVT treatment with Eylea	N=30 SOK583: N=30	Single IVT administration of 2 mg of SOK583 in the study eye followed by a 30-day safety follow-up	SOK583: 40 mg/mL, LISY, single IVT injection of 2 mg/0.05 mL Batch number: SOK583: 21D21GA

Pharmacology

SOK583 has been developed as a biosimilar to Eylea (aflibercept). Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human immunoglobulin G1. It acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors and thereby can inhibit

the binding and activation of these cognate VEGF receptors. They are both are manufactured by recombinant DNA technology and are expressed in a Chinese hamster ovary cell expression system.

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor (VEGFR)-1 and VEGFR-2 extracellular domains fused to the fragment crystallizable portion (Fc) of a human immunoglobulin isotype class G subclass 1 monoclonal antibody. The mechanism of action involves aflibercept acting as a soluble decoy receptor that binds VEGF type A (VEGF-A) and placental growth factor (PlGF) and thereby inhibiting binding and activation of VEGFR-1 and VEGFR-2.

Among the many angiogenic factors identified in vascular regulation, the VEGF superfamily and the VEGFRs play a decisive role in both physiological and pathological angiogenesis, and, in particular, vascular permeability. Of the VEGF family members, VEGF-A contributes to angiogenesis, activating quiescent endothelial cells and promoting vascular permeability through VEGFR-1 binding, and stimulating cell proliferation through VEGFR-2 binding. It also plays a role in mobilizing and recruiting endothelial progenitor cells to sites of neovascularization and tissue regeneration.[11,12] Endothelial cell response to VEGF-A leads to neovascularization and vascular permeability that contribute to disease pathology in neovascular eye disease. VEGF-A levels have been found to be elevated in the vitreous of patients with neovascular (wet) age-related macular degeneration (AMD), diabetic macular oedema, retinal vein occlusion, and myopic choroidal neovascularization.[10]

Placental growth factor (PlGF) is also implicated in pathological angiogenesis, especially in retinal disorders, and may work synergistically with VEGF. Animal models have shown that PlGF mediates permeability and neovascularization and inflammation. However, its contribution in pathological ocular neovascularization in humans has not been fully elucidated, and its role as a potential primary therapeutic target is not well understood.[11]

Pharmacokinetics (PK)

Study 301 was the only study in the SOK583 clinical development program that included a PK assessment of SOK583 and Eylea EU in subjects with nAMD. 43 patients from study 301 were included in the PK analysis set. PK results are descriptive in nature.

Aflibercept is administered intravitreally, directly at the site of action. After IVT administration, aflibercept is temporarily bioavailable in the circulation but the systemic concentrations are highly variable and too low to elicit PD effects, as known from systemic administration of VEGF-inhibitors in oncology. Therefore, no PK similarity study was conducted; rather a PK sub-study was included in Study 301. Total and free aflibercept concentrations were assessed at baseline (pre-dose) on Day 1 and 24 hours after the first injection (Day 2) and the third injection (Day 58).

Free (plasma) and total (serum) aflibercept concentrations were low and comparable between subjects in the SOK583 group and the Eylea EU group at each visit. Results from the PK sub-study showed median free drug serum concentrations at day 58 (week 8) for the SOK583 and aflibercept (EU) treatment groups were 30.5 ng/mL and 24.7 ng/mL, respectively.

[11] Nguyen, Q. D., De Falco, S., Behar-Cohen, F., Lam, W. C., Li, X., Reichhart, N., Ricci, F., Pluim, J., & Li, W. W. (2018). Placental growth factor and its potential role in diabetic retinopathy and other ocular neovascular diseases. *Acta ophthalmologica*, *96*(1), e1–e9. https://doi.org/10.1111/aos.13325

[12] Shibuya M. (2014). VEGF-VEGFR Signals in Health and Disease. *Biomolecules & therapeutics*, *22*(1), 1–9. https://doi.org/10.4062/biomolther.2013.113

Pharmacodynamics (PD)

Evaluation of systemic VEGF-A concentration was an exploratory objective in study 301. This was undertaken once study 301 was already ongoing and thus evaluated at week 48 (pre-dose) and 52 (post dose). Results on retinal thickness and choroidal neovascularization lesion size from study 301 are discussed under the clinical efficacy section. Systemic VEGF-A concentrations at Week 48 (pre-dose) and Week 52 and changes from Week 48 to Week 52 were comparable between the SOK583 group and the Eylea EU group.

Efficacy

CSOK583A12301 (Study 301) was the only study submitted containing evaluable efficacy data.

Study 301[13]

This study is a phase III, 52-week, multicentre, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea, administered intravitreally, in anti-VEGF naïve patients with neovascular age-related macular degeneration. See table 4 for study objectives and endpoints. The primary efficacy population was the per protocol set. (PPS)

Table 4: Objectives and related endpoints – study 301.

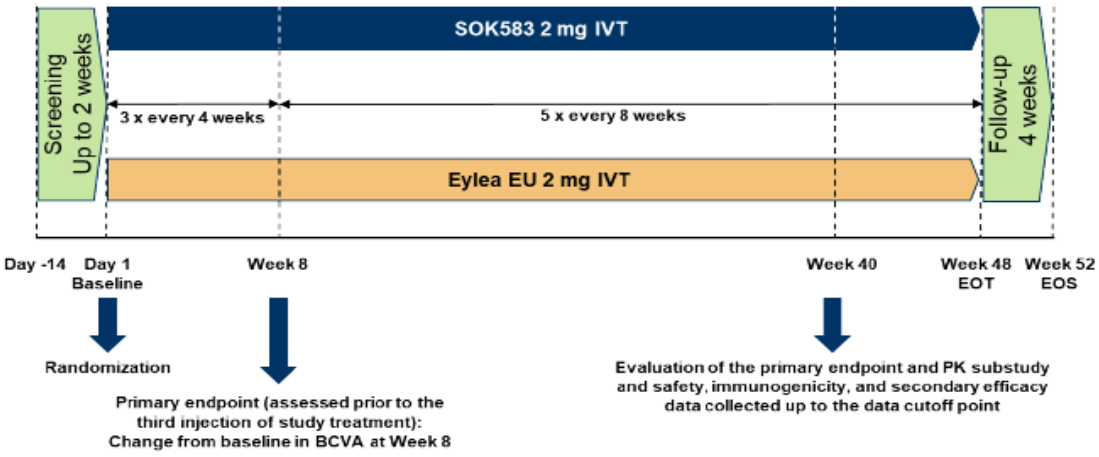
Objective(s)	Endpoint(s)
Primary Objective(s)	Endpoint(s) for primary objective(s)
• To demonstrate similar efficacy of SOK583 and Eylea EU in terms of BCVA	• Mean change from baseline in BCVA score using ETDRS testing charts at Week 8
Secondary Objective(s)	Endpoint(s) for secondary objective(s)
• To evaluate if the anatomical outcome of SOK583 is similar to Eylea EU	• Mean change in CSFT using SD-OCT from baseline to Week 1, 4, 8, 24 and 52 • Mean change of CNV lesion size using FA from screening to Week 8 and 52
• To evaluate if the efficacy of SOK583 is similar to Eylea EU in terms of BCVA	• Mean change from baseline in BCVA score using ETDRS testing charts at Week 24 and 52
• To evaluate if SOK583 is similar to Eylea EU in terms of safety	• Incidence of ocular and non-ocular AEs over 52 weeks
• To evaluate if SOK583 is similar to Eylea EU in terms of immunogenicity	• Development of binding and neutralizing ADAs up to Week 52
• To evaluate the systemic exposure of SOK583 and Eylea EU in participants of the PK assessment	• Aflibercept concentration assessments at baseline (pre-dose) and 24 hours after the first and third injections
Exploratory Objective	Endpoint(s) for exploratory objective
• To evaluate systemic VEGF concentration in participants treated with SOK583 or Eylea EU	• Systemic VEGF concentration assessments at Week 48 (pre-dose) and Week 52

Study design

Participants were randomised to receive SOK583 or the reference product. The study schema is shown in figure 1. The study did not include a treatment transition from Eylea EU to SOK583.

[13] Bordon, A. F., Kaiser, P. K., Wolf, A., Cen, L., Heyn, J., Urosevic, D., Dodeller, F., Allmannsberger, L., & Silva, R. (2024). Efficacy and safety of the proposed biosimilar aflibercept, SDZ-AFL, in patients with neovascular age related macular degeneration: 52-week results from the Phase 3 Mylight Study. *Retina (Philadelphia, Pa.)*, *44*(10), 1704–1713. https://doi.org/10.1097/IAE.0000000000004174

Figure 1: Study design of study 301: pivotal efficacy, safety, and immunogenicity study.



Eligible subjects were adults aged 50 years and older with neovascular (wet) AMD in the study eye. Subjects were naïve to anti-VEGF treatment.

Subjects received aflibercept 2mg: SOK583 (40 mg/mL) or Eylea EU (40 mg/mL) every 4 weeks at Baseline, Week 4, and Week 8, and thereafter every 8 weeks at Weeks 16, 24, 32, 40, and 48. Only 1 eye was selected as study eye in each patient. If the fellow eye developed nAMD or another condition during the study, treatment with standard of care approved in the respective country was at the discretion of the investigator.

Results

485 subjects were randomized in the study, and 484 (99.8%) subjects received at least 1 dose of SOK583 or Eylea EU. One subject had no post-baseline best-corrected visual acuity (BCVA) assessment, thus leaving 483 subjects in the full analysis set. 431 randomized subjects (88.9%) completed treatment, and 438 subjects (90.3%) completed the study. Most subjects (SOK583: 204 subjects, 83.6%; Eylea EU: 207 subjects, 86.3%) received the maximum number of 8 injections. The mean numbers (SD) of injections were 7.6 (1.17) in the SOK583 group and 7.6 (1.23) in the Eylea EU group

There were 483 subjects (n=243 for SOK583, n=240 for Eylea EU in the full analysis set (FAS) set. Of these 273 (56.5%) were female, 429 (88.8%) were white, and 450 (93.2%) were not Hispanic or Latino. The mean (SD) age was 75.8 (7.79) years, range 53 to 94 year. The overall mean (SD) BCVA early treatment diabetic retinopathy study (ETDRS) letter score at baseline was 59.4 (10.37). Demographics and baseline disease characteristics were generally balanced between treatment groups and were similar for the PPS.

Primary efficacy endpoint

At week 8, the observed mean (SD) change from baseline in BCVA was 6.5 (8.98) in the SOK583 group and 6.8 (7.46) in the aflibercept EU group. The point estimate of the least squares mean difference in change from baseline in BCVA at week 8 between the treatment groups was -0.3 with a 2-sided 95% CI (-1.8, 1.3) which was within the prespecified similarity margin of (-3.5, 3.5). Therefore, therapeutic equivalence in terms of change from baseline in BCVA score was concluded.

Sensitivity analyses were performed using the per-protocol set and FAS based on last observation carried forward imputation and results were consistent with results from the primary efficacy analysis.

Results for subgroup analyses were consistent with results from the primary efficacy analysis. Any differences were small and not considered clinically relevant.

Secondary efficacy endpoints

Mean changes from baseline in central subfield thickness (CSFT) using SD-OCT, in CNV lesion size, and in BCVA score were similar between the SOK583 and Eylea EU groups for subjects in the FAS and the PPS. (see figures 2,3) Mean changes from baseline in BCVA score were similar between the SOK583 group and the Eylea EU group for subjects in the FAS and in the PPS at Weeks 24 and 52 and all other time points. (Figure 4)

Figure 2: Mean change from baseline (SD) in CSFT using SD-OCT up to Week 52 (FAS).

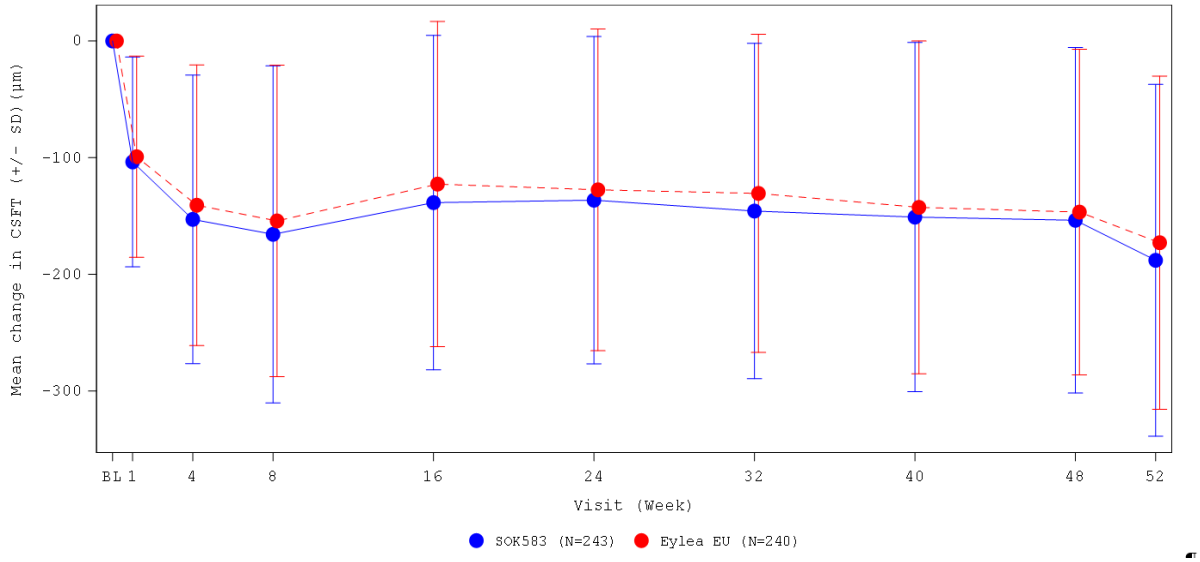


Figure 3: Mean change from baseline (SD) in CNV lesion size using FA at Weeks 8 and 52 (FAS).

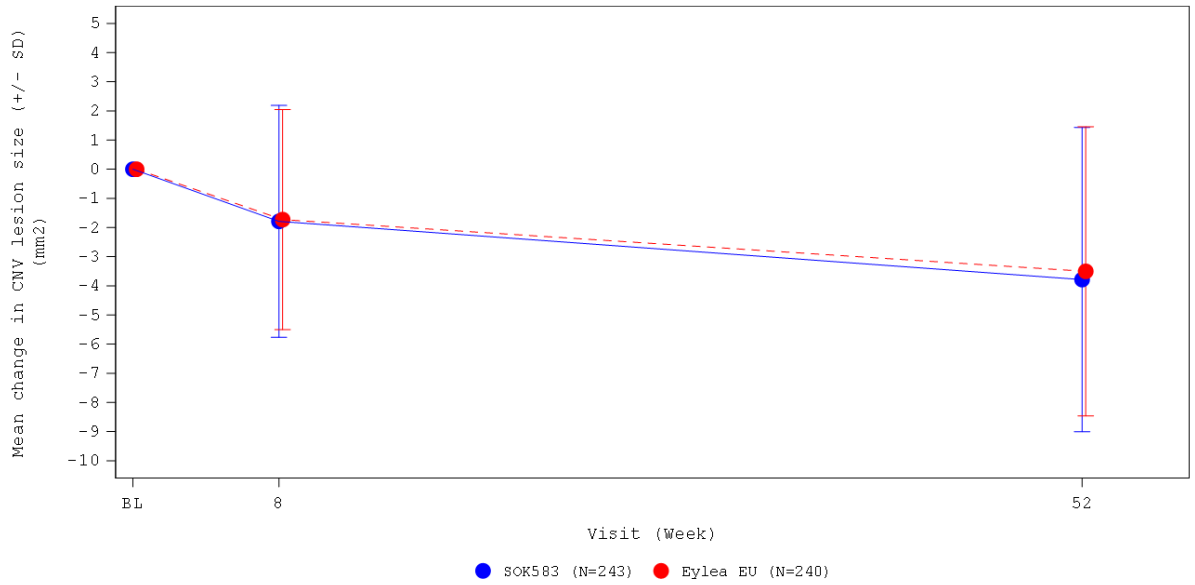
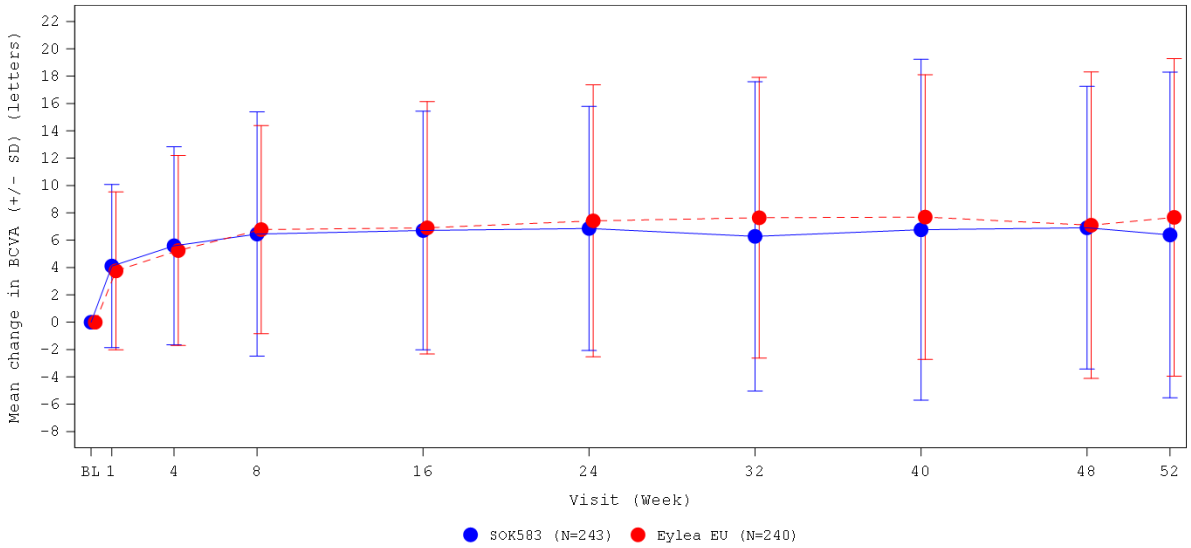


Figure 4: Mean change from baseline in BCVA score.



Efficacy conclusions

The results of the Study 301 primary efficacy endpoint analysis demonstrate equivalence between SOK583 and the reference product within the equivalence margin specified by the Sponsor for the treatment of neovascular AMD.

Persistence of efficacy (through week 52) was observed in Study 301.

Safety

The following studies contributed safety data in the evaluation of SOK583:

- Study 301: a confirmatory randomized, double-masked, 2-arm study to compare efficacy, safety, and immunogenicity of SOK583 to Eylea EU in subjects with nAMD. This study provided most of the safety data for SOK583. The SAF comprises all 484 subjects who were treated.

The following 2 studies provided supportive data:

- Study 303: a supportive, open-label, single-arm study in subjects with nAMD to evaluate the safety of SOK583 (40 mg/mL) provided in a vial kit.
- Study 304: a supportive, open-label, single-arm study in subjects with nAMD to evaluate the safety of SOK583 (40 mg/mL) provided in a PFS.

Study 301[13]

Of the 484 randomized subjects who had received study treatment (safety analysis set), 431 (88.9%) completed treatment, and 438 (90.3%) completed the study. A total of 53 (10.9%) discontinued treatment early, and 47 (9.7%) discontinued the study early. Primary reasons for discontinuation were withdrawal by subject (19, 3.9%), adverse events (7, 1.4%), physician decision (7, 1.4%), and death (6 s, 1.2%).

Of the safety set (484 patients) there were 244 patients treated with SOK583.

No relevant differences in the exposure to study treatment between treatment groups were observed. Subjects received means (SD) 7.6 (± 1.17) injections in the SOK583 group and 7.6 (± 1.23) injections in the Eylea EU group; 204 (83.6%) in the SOK583 group and 207 (86.3%) in the Eylea EU group received the maximum number of 8 injections.

Adverse events

- Overall, 353 subjects [179 (73.4%) in SOK583, 174 (72.5%) in Eylea EU] experienced at least 1 treatment-emergent adverse event (TEAE), with a small number (n=6, and n=9) thought to be treatment related. (Table 5) There were no clinically relevant differences between the SOK583 and Eylea EU groups in ocular TEAEs in the study eye or the fellow eye and in non-ocular TEAEs.

Table 5: Overview of TEAEs (SAF) – CSOK583A12301.

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

- The most frequently reported ocular TEAEs in the study eye were visual acuity reduced (SOK583: 10, 4.1%; Eylea EU: 12, 5.0%), retinal pigment epithelial tear (SOK583: 9, 3.7%; Eylea EU: 7, 2.9%), and conjunctival haemorrhage (SOK583: 9, 3.7%; Eylea EU: 4, 1.7%).
- The most frequently reported non-ocular TEAEs were COVID-19 (SOK583: 19, 7.8%; Eylea EU: 24, 10.0%), hypertension (SOK583: 12, 4.9%; Eylea EU: 17, 7.1%), back pain (SOK583: 8, 3.3%; Eylea EU: 7, 2.9%), osteoarthritis (SOK583: 2, 0.8%; Eylea EU: 9, 3.8%), atrial fibrillation (SOK583: 8, 3.3%; Eylea EU: 2, 0.8%), and nasopharyngitis (SOK583: 7, 2.9%; Eylea EU: 5, 2.1%)
- There were no clinically relevant differences between the 2 treatment groups regarding ocular TEAEs in the study eye related to study treatment or study procedure.
- Most subjects reported ocular and non-ocular TEAEs of mild or moderate severity (SOK583: 159, 65.2%; Eylea EU: 154, 64.2%).
- The overall proportions of subjects with ocular TEAEs in the fellow eye were comparable between the SOK583 and Eylea EU groups (55, 22.5%, vs. 51, 21.3%).
- There were no clinically relevant differences between the SOK583 and Eylea EU groups in ocular TEAEs in the study eye or non-ocular TEAEs leading to study discontinuation.

Severe adverse events

- Five subjects reported severe ocular (SOK585: 2, Eylea EU: 3) TEAEs; none thought treatment related.
- No subject in the SOK583 group reported severe ocular TEAEs in the fellow eye. 1 subject (0.4%) in the Eylea EU group reported a severe ocular TEAE of retinal haemorrhage in the fellow eye.
- There were no clinically relevant differences between the SOK583 and Eylea EU groups regarding ocular TEAEs in the study eye related to study treatment (SOK583: 6, 2.5%; Eylea EU: 7, 2.9%) or study procedure (SOK583: 28, 11.5%; Eylea EU: 26, 10.8%).

- Thirty-four subjects reported severe non-ocular TEAEs (SOK583: 18, 7.4%; Eylea EU: 16, 6.7%); most frequently as cardiac disorders (SOK583: 3, 1.2%; Eylea EU: 4, 1.7%), respiratory, thoracic and mediastinal disorders (SOK583: 3, 1.2%; Eylea EU: 2, 0.8%), infections and infestations (SOK583: 2, 0.8%; Eylea EU: 4, 1.7%) and neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOK583: 2 , 0.8%; Eylea EU: 3, 1.3%).
- One subject in the SOK583 group experienced a non-ocular TEAE (serious adverse event - SAE) of coronary artery stenosis related to study treatment, which led to treatment interruption.
- A review of arterial thromboembolic events found there were 5 counts of serious cerebral infarction/cerebrovascular accident/ischaemic stroke/transient ischaemic attack in the SOK583 arm, compared to 0 in the Eylea arm. It is noted in the original VIEW 1 and 2 studies for Eylea was 3.3% (Elyea PI).

Deaths

There were 5 subjects who died during the study, 4 subjects (1.6%) in the SOK583 group and 1 subject (0.4%) in the Eylea EU group. The deaths were considered not related to study treatment or study procedure by the investigator. One further subject in the SOK583 group experienced a fatal SAE not related to study treatment (had missing start date due to a lack of a hospital record).

Immunogenicity

Immunogenicity was assessed in Study 301 by measuring anti-drug antibodies (ADAs) and neutralising antibodies (Nabs) in serum and included 95.5% and 96.3% of the subjects randomised to receive SOK583 and Eylea EU, respectively.

- Most subjects were ADA negative at each timepoint throughout the study.
- The numbers and proportions of subjects with immune responses post-baseline were small and similar between the SOK583 and Eylea EU groups (2, 0.9%, vs 6, 2.6%).
- ADAs developed post-baseline were neutralizing.
- Most ADA positive samples were titre negative or had a low titre of 1:10.
- Four subjects (SOK583: 1, 0.4%, Eylea EU: 3, 1.2%) had persistent ADA responses.

Ocular TEAEs in the study eye, in the fellow eye, and non-ocular TEAEs were analysed for the following subgroups.

- Region (US, Europe, rest of world)
- Age category (< 75 years, ≥ 75 years)
- Sex (male, female)
- Race (White, other)

The most notable result was that SAEs were especially more common in the SOK583 arm in those aged under 75 years (15.5% vs. 8.2%).

No clinically relevant differences between the 2 groups were observed for any laboratory parameters.

There were no clinically relevant differences between the SOK583 and Eylea EU groups in the vital signs' parameters or in intraocular pressure (IOP) at any visit or in changes from baseline in vital signs parameters.

Studies SOK583A12303 (Study 303) and CSOK583A12304 (study 304)

Studies 303 and 304 are open-label, single-arm, multicentre studies in patients with neovascular age-related macular degeneration to evaluate the safety of SOK583 provided in a vial kit and pre-filled syringe, respectively.

Two reports were provided for each study, a clinical study report that provides data on adverse events, and an observational study report that provides information on the ability of ophthalmologists and assistants to prepare and administer IVT injections using the vial kit or PFS.

Subjects aged 50 years and over, diagnosed with nAMD and already under IVT Eylea treatment were enrolled. A single dose of SOK583 2mg was administered intravitreally on day 1, supplied as a vial kit in study 303 and PFS in study 304. Safety was evaluated on day 1, day 8±2 and day 31±4.

The FAS included 36 subjects in study 303 and 30 subjects in study 304. Mean age was 81 years in study 303 and 79 years in study 304.

Results

- The observed safety profile of SOK583 was in line with the established safety profile of Eylea.
- In Study 303, 18 subjects reported ocular or non-ocular TEAEs, most of which were mild and not related to study treatment or study procedure. Most frequently reported TEAE in the study eye was intraocular pressure that increased within 10 minutes after injection, all cases were resolved within 60 minutes after the IVT injection. 2 subjects discontinued the study due to SAEs (arthralgia, cystitis), which were not related to study treatment or study procedure.
- In Study 304, 3 subjects reported non-serious ocular or non-ocular TEAEs, all of which were mild and not related to study treatment or study procedure. For 1 subject, a TEAE of intraocular pressure increased was reported 5 minutes after injection', which resolved within 60 minutes after the IVT injection.
- Twenty-two subjects in Study 303 and 7 subjects in Study 304 experienced transient increases in IOP ≥ 10 mmHg at 5 minutes post injection, which returned to normal within 60 minutes postinjection.
- No deaths were reported in either study.
- Seven ophthalmologists and 5 assistants administered 36 IVT injections using the vial kit, and 4 ophthalmologists and 3 assistants administered 30 IVT injections using the PFS. One error was observed with the vial kit where the ophthalmologist failed to clean the vial septum before withdrawing the drug, and no errors were observed with the PFS.

Risk management plan

The sponsor, Sandoz Pty Ltd, submitted EU-RMP version 1.1 (dated 19 March 2024; DLP 14 July 2023) and ASA version 1.0 (dated 05 April 2024) in support of this application. At Round 2, the sponsor submitted an updated ASA version 1.1 (dated 05 December 2024) associated to the EU-RMP version 1.2 (dated 16 July 2024, DLP 14 July 2023). At round 3, the sponsor submitted updated ASA version 1.2 (dated 13 February 2025).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are in Table 6. The TGA may request an updated Risk Management Plan (RMP) at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 6: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Endophthalmitis (likely infectious origin)	✓†	–	✓	✓*
	Intraocular inflammation	✓†	–	✓	✓*
	Transient intraocular pressure increase	✓†	–	✓	✓*
	Retinal pigment epithelial tears	✓	–	✓	✓*
	Cataract (especially of traumatic origin)	✓	–	✓	✓*
Important potential risks	Medication errors	✓	–	✓	✓*
	Off-label use and misuse	✓	–	✓	✓*
	Embryo-fetotoxicity	✓	–	✓	✓*
Missing information	None	–	–	–	–

†Follow-up questionnaires

* Educational material (Patient Guide)

RMP evaluator recommendations regarding conditions of registration

- The summary of safety concerns of this biosimilar are consistent with the originator, Eylea 2mg and is acceptable.
- Routine pharmacovigilance activities only are proposed for all safety concerns, which include specific follow-up questionnaires for the important identified risks of 'Endophthalmitis (likely infectious origin)', 'Intraocular inflammation' and 'Transient intraocular pressure increase'. At round 2, the sponsor has also committed to collecting information on Aboriginal and Torres Strait Islander ethnicity with the follow up questionnaires.
- Although the pharmacovigilance plan generally aligns with the originator product, to address the concerns regarding arterial thromboembolic events, PSUR submission is requested, together with a commitment to report all-cause mortality in PSURs.
- Additionally, to align with the innovator Eylea, the sponsor is requested to commit to the use of specific follow up forms for arterial thromboembolic events in Australia, and to report on these events in the Afqlir PSUR. At round 3, the sponsor has agreed to these requests, and the pharmacovigilance plan is acceptable from an RMP perspective.
- The sponsor has proposed routine risk minimisation activities for all safety concerns. Additional risk minimisation activities in the form of educational materials that consist of a Prescriber Guide and a Patient Guide were initially proposed for all safety concerns. However, at Round 2, the sponsor confirmed that only the Patient Guide will be implemented in Australia as requested to align with the originator product. The sponsor committed to submitting the Patient Guide to the TGA at least 6 weeks prior to launch for review. The CMI has been revised as requested and the risk minimisation plan is acceptable.

Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

SOK583 (Afqlir/Enzeevu) has been developed as a biosimilar to Eylea 2mg (aflibercept), with a similar biochemical structure, biological function and route of administration (intravitreal [IVT] injection). The medical need for Eylea (aflibercept) in the approved indications is well documented, as it has meaningful benefit to the various patient populations. Comprehensive comparisons of physicochemical and biological quality attributes were undertaken to demonstrate biosimilarity of SOK583 to Eylea (EU).

One comparative clinical study was provided (Study 301) which compared the efficacy of SOK583 to the reference product, Eylea licensed in the EU (aflibercept (EU)), as the primary objective, with safety and immunogenicity as secondary objectives This study was a randomized, double-masked, active controlled study in adult subjects with neovascular (wet) AMD.

Similarity in clinical efficacy was established between SOK583 and aflibercept (EU) based on the 2-sided 95% CI of the mean difference in change from baseline in BCVA (measured by ETDRS letter score) at week 8 and was within the prespecified equivalence margin specified by the sponsor. Furthermore, sensitivity analyses and descriptive analyses of secondary endpoints showed no clinically meaningful differences between SOK583 and Eylea (aflibercept). Persistence of efficacy (through week 52) was observed in Study 301 and there was no evidence of tolerance.

Studies 303, and 304 showed that that SOK583 in LIVI (single use vial) and LISY (prefilled syringe) can be used effectively and safely by trained retina specialists to administer SOK583 for the proposed indications.

Safety results from Study 301 and Studies 303 and 304 showed no clinically important differences between SOK583 and Eylea 2mg (aflibercept). No new safety signals were identified. A low incidence of binding ADAs was observed for all treatment groups.

Results from Study 301 PK sub-study confirmed low systemic exposure of unbound (free) drug concentrations following IVT administration of SOK583 or aflibercept (EU) in neovascular (wet) AMD. This is important consideration for the scientific justification for extrapolation to other indications sought in this submission. There is also PD similarity of SOK583 to Eylea (aflibercept) based on the anatomic endpoints of change from baseline in CSFT and CNV area size over the study duration. Immunogenicity profiles are also similar. Together with the known common mechanism of action across all indications, these data further support similarity between SOK583 and Eylea 2mg (aflibercept) and support the justification to include non-neovascular (wet) AMD in the indications being sought in this submission.

Proposed action

Biosimilarity of SOK583 to Eylea 2mg (aflibercept) has been demonstrated. The TGA plans to approve SOK583 (Afqlir/Enzeevu) containing aflibercept 2mg for the following indications [same as for EYLEA (2mg)].

For the treatment of the following in adults:

- *neovascular (wet) age-related macular degeneration (wet AMD)*
- *visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*
- *visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)*
- *diabetic macular oedema (DMO/DME)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV)*

Approval will depend on satisfactory negotiation of the PI, CMI and the conditions of registration.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Afqlir and Enzeevu (aflibercept) 2 mg for injection (volume of 50 µL) via a single-use vial or pre-filled syringe, indicated for:

Afqlir/ Enzeevu (aflibercept) 2 mg is indicated in adults for the treatment of:

- *neovascular (wet) age-related macular degeneration (wet AMD)*
- *visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)*
- *visual impairment due to macular oedema secondary to branch retinal vein occlusion (BRVO)*
- *diabetic macular oedema (DME)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV).*

Specific conditions of registration

- The Afqlir/Enzeevu EU-Risk Management Plan (RMP) version 1.2 (dated 16 July 2024, data lock point 14 July 2023), with Australia-Specific Annex (ASA) version 1.2 (dated 13 February 2025), included with submission PM-2024-01570-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- **Laboratory testing & compliance with Certified Product Details (CPD)**

  - All batches of Enzeevu/Afqlir aflibercept supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - When requested by the TGA, the Sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the Product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results http://www.tga.gov.au/ws-labs-index and periodically in testing reports on the TGA website.

- **Certified product details**

  The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

  A template for preparation of CPD for biological prescription medicines can be obtained from the TGA website [for the form] https://www.tga.gov.au/form/certified-product-details-cpd-biologicalprescription-medicines [for the CPD guidance] https://www.tga.gov.au/guidance-7-certified-product-details

- It is a specific condition of registration for biosimilar medicines that the Product Information and Consumer Medicine Information documents be updated within ONE month of safety-related changes made by the reference product. It is your responsibility to routinely check the TGA website at www.ebs.tga.gov.au for any updates to the innovator Product Information.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6203 1605
https://www.tga.gov.au

Reference/Publication #