Clinical trial results:
A 52-week multicenter, randomized, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SOK583A1 to Eylea®, administered intravitreally, in patients with neovascular age-related macular degeneration.

Summary

EudraCT number	2019-004838-41
Trial protocol	DE LT LV FR SK BG HU PT AT CZ
Global end of trial date	10 May 2023

Results information

Result version number	v1 (current)
This version publication date	08 May 2024
First version publication date	08 May 2024

Trial information

Trial identification

Sponsor protocol code	CSOK583A12301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04864834
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hexal AG
Sponsor organisation address	Industriestr. 25, Holzkirchen, Germany, 83607
Public contact	Clinical Disclosure Office, Hexal AG, +49 8024/ 908 0 ,
Scientific contact	Clinical Disclosure Office, Hexal AG, +49 8024/ 908 0 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate similar efficacy of SOK583A1 and Eylea EU in terms of BCVA.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 May 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Israel: 27
Country: Number of subjects enrolled	Japan: 26
Country: Number of subjects enrolled	Spain: 38
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Slovakia: 35
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 78
Country: Number of subjects enrolled	Latvia: 32
Country: Number of subjects enrolled	Lithuania: 20
Worldwide total number of subjects	485
EEA total number of subjects	320

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	44
From 65 to 84 years	376
85 years and over	65

Subject disposition

Recruitment

Recruitment details:

In total 723 subjects were screened in 16 countries and 119 sites, 485 patients were randomized in 103 sites.

Pre-assignment

Screening details:

A total of 723 subjects were screened. 485 subjects were randomized. 431 of the 485 randomized subjects completed treatment, and 438 subjects completed the study.

Pre-assignment period milestones

Number of subjects started	723[1]
Number of subjects completed	485

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screening failures: 238

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The total numbers per country (485) are the number of randomized patients and not the number of screened patients (723).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SOK583A1 (40 mg/mL)

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	SOK583A1
Investigational medicinal product code	
Other name	proposed biosimilar aflibercept
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

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

Arm title	Eylea EU (40 mg/mL)

Arm description:

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

Arm type	Active comparator

Investigational medicinal product name	Eylea EU
Investigational medicinal product code	
Other name	aflibercept
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

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

Number of subjects in period 1	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)
Started	245	240
Completed	220	218
Not completed	25	22
Adverse event, serious fatal	5	1
Physician decision	4	3
Consent withdrawn by subject	8	11
Adverse event, non-fatal	4	3
Randomized by mistake without study treatment	1	-
Lost to follow-up	2	3
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	SOK583A1 (40 mg/mL)
Reporting group description:	
Intravitreal (IVT) administration of 2 mg of SOK583A1 in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48.	
Reporting group title	Eylea EU (40 mg/mL)
Reporting group description:	
IVT administration of 2 mg of Eylea EU in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48. EU: European	

Reporting group values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)	Total
Number of subjects	245	240	485
Age categorical Units: Subjects			
Adults: >=50	245	240	485
Age continuous Units: years			
arithmetic mean	75.8	75.7	
standard deviation	± 7.82	± 7.72	-
Gender categorical Units: Subjects			
Female	139	136	275
Male	106	104	210

End points

End points reporting groups

Reporting group title	SOK583A1 (40 mg/mL)
Reporting group description:	
Intravitreal (IVT) administration of 2 mg of SOK583A1 in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48.	
Reporting group title	Eylea EU (40 mg/mL)
Reporting group description:	
IVT administration of 2 mg of Eylea EU in the study eye, every 4 weeks (q4w) at Baseline, Week 4 and Week 8, and thereafter every 8 weeks (q8w) at week 16, 24, 32, 40 and 48. EU: European	

Primary: Mean change from baseline in BCVA score using ETDRS testing charts at Week 8

End point title	Mean change from baseline in BCVA score using ETDRS testing charts at Week 8
End point description:	
The primary aim of the study is to demonstrate equivalence of change in BCVA score from Baseline at Week 8 between participants with nAMD treated with SOK583A1 and participants treated with Eylea EU. The primary analysis will be performed on the Per-Protocol Set (PPS), which is the most appropriate analysis set to use when testing for equivalence. ETDRS: Early Treatment Diabetic Retinopathy Study EU: European	
End point type	Primary
End point timeframe:	
Change from baseline in mean BCVA score at Week 8	

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	226		
Units: letters				
arithmetic mean (standard deviation)	6.5 (± 8.98)	6.8 (± 7.46)		

Statistical analyses

Statistical analysis title	SOK583A1 vs Eylea EU
Comparison groups	SOK583A1 (40 mg/mL) v Eylea EU (40 mg/mL)
Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.77

Secondary: Mean change in CSFT using SD-OCT from Baseline to Week 1, 4, 8, 24 and 52

End point title	Mean change in CSFT using SD-OCT from Baseline to Week 1, 4, 8, 24 and 52
End point description:	
End point type	Secondary
End point timeframe:	
Week 1, 4, 8, 24 and 52	

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	238		
Units: µm				
arithmetic mean (standard deviation)				
Week 1	-103.6 (± 89.91)	-99.2 (± 86.18)		
Week 4	-152.9 (± 123.55)	-140.7 (± 120.25)		
Week 8	-165.7 (± 144.35)	-154.2 (± 133.43)		
Week 24	-136.4 (± 140.19)	-127.5 (± 137.87)		
Week 52	-187.9 (± 150.7)	-172.9 (± 142.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change of CNV lesion

End point title	Mean change of CNV lesion
End point description:	
End point type	Secondary
End point timeframe:	
Week 8 and 52	

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	237		
Units: mm^2				
arithmetic mean (standard deviation)				
Week 8	-1.7877 (± 3.97567)	-1.7274 (± 3.77398)		
Week 52	-3.7845 (± 5.21911)	-3.5026 (± 4.96036)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in BCVA score using EDTRS testing charts at Week 24 and 52

End point title	Mean change from Baseline in BCVA score using EDTRS testing charts at Week 24 and 52

End point description:

End point type	Secondary

End point timeframe:

Week 24 and 52

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	240		
Units: Letters				
arithmetic mean (standard deviation)				
Week 24	6.9 (± 8.93)	7.4 (± 9.95)		
Week 52	6.4 (± 11.91)	7.7 (± 11.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Similarity Between SOK583A1 and Eylea EU in Terms of Safety

End point title	Similarity Between SOK583A1 and Eylea EU in Terms of Safety

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	240		
Units: Participants				
Ocular AEs in the study eye	84	78		
Ocular AEs in the fellow eye	55	51		
Non-ocular AEs	141	141		

Statistical analyses

No statistical analyses for this end point

Secondary: Similarity Between SOK583A1 and Eylea EU in Terms of Immunogenicity

End point title	Similarity Between SOK583A1 and Eylea EU in Terms of Immunogenicity

End point description:

End point type	Secondary

End point timeframe:

Week 52

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	234	231		
Units: Participants				
ADA positive	2	6		
ADA negative	232	225		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Exposure to SOK583A1 and Eylea EU in Participants of the Pharmacokinetic (PK) Assessment

End point title	Systemic Exposure to SOK583A1 and Eylea EU in Participants of the Pharmacokinetic (PK) Assessment

End point description:

End point type	Secondary

End point timeframe:

Baseline (pre-dose) and 24 hours after the first injection (day 2) and third injection (day 58)

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	20		
Units: mg/mL				
arithmetic mean (standard deviation)				
Day 1 (Baseline)	0.0 (± 0.0)	0.0 (± 0.0)		
Day 2	32.0 (± 24.0)	33.3 (± 24.6)		
Day 58	31.7 (± 21.9)	33.6 (± 25.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Analysis Systemic VEGF Concentrations in Patients Treated With Aflibercept

End point title	Analysis Systemic VEGF Concentrations in Patients Treated With Aflibercept

End point description:

End point type	Secondary

End point timeframe:

Assessment at Week 48 (pre-dose) and Week 52

End point values	SOK583A1 (40 mg/mL)	Eylea EU (40 mg/mL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: mg/mL				
arithmetic mean (standard deviation)				
Week 48 (pre-dose)	86.44 (± 77.962)	80.09 (± 92.155)		
Week 52	75.14 (± 20.892)	73.38 (± 20.169)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From study treatment start date to the end of the study participation.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	Eylea EU
Reporting group description: Eylea EU	
Reporting group title	SOK583
Reporting group description: SOK583	

Serious adverse events	Eylea EU	SOK583	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 240 (12.50%)	39 / 244 (15.98%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cancer stage IV			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant fibrous histiocytoma			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung adenocarcinoma			

subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 240 (0.00%)	3 / 244 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 240 (0.83%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			

subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 240 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 240 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 240 (0.83%)	4 / 244 (1.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 240 (0.00%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			

subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	1 / 240 (0.42%)	2 / 244 (0.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal obstruction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal adhesions			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Biliary obstruction			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 240 (0.42%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 240 (0.83%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 240 (0.83%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 240 (0.42%)	0 / 244 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Hyponatraemia			
subjects affected / exposed	0 / 240 (0.00%)	1 / 244 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Eylea EU	SOK583	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 240 (26.25%)	58 / 244 (23.77%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	16 / 240 (6.67%)	11 / 244 (4.51%)	
occurrences (all)	17	12	
Eye disorders			
Neovascular age-related macular degeneration			
subjects affected / exposed	25 / 240 (10.42%)	25 / 244 (10.25%)	
occurrences (all)	25	25	
Visual acuity reduced			
subjects affected / exposed	12 / 240 (5.00%)	11 / 244 (4.51%)	
occurrences (all)	13	13	
Infections and infestations			
COVID-19			
subjects affected / exposed	23 / 240 (9.58%)	19 / 244 (7.79%)	
occurrences (all)	23	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2022	This amendment to version 3.0 of the protocol of Study CSOK583A12301 includes the evaluation of systemic VEGF concentrations at Week 48 (pre-dose) and Week 52. The aim of this assessment is to evaluate the concentrations of systemic VEGF in the 2 treatment groups at Week 52, i.e. 4 weeks after IVA treatment with aflibercept. VEGF concentration at Week 48 (pre-dose) will be used as baseline value to calculate the relative change in VEGF between Week 48 and Week 52. The VEGF evaluation was recommended by EMA in a scientific advice. This amendment applies to those participants who agree to additional blood collection for the evaluation of systemic VEGF concentrations. They will document their agreement by signing the corresponding ICF.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported