Clinical trial results:
A Phase III Randomized, Double-Masked, Parallel Group, Multicenter Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration

Summary

EudraCT number	2019-004132-37
Trial protocol	HU CZ BG PL SK
Global end of trial date	08 September 2022

Results information

Result version number	v1 (current)
This version publication date	16 July 2023
First version publication date	16 July 2023

Trial information

Trial identification

Sponsor protocol code	SCD411-CP101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04480463
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 144376

Notes:

Sponsors

Sponsor organisation name	SamChunDang Pharm. Co. Ltd.
Sponsor organisation address	351, Hyoryeong-ro, Seocho-gu, Seoul, Korea, Republic of, 06643
Public contact	Clinical Development, SamChunDang Pharm. Co. Ltd, +82 31-869-7327, scd411clinical@scd.co.kr
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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	05 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2022
Global end of trial reached?	Yes
Global end of trial date	08 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove the equivalence of SCD411 as compared with Eylea (aflibercept) in best corrected visual acuity (BCVA) after 8 weeks of treatment among subjects with wet AMD.

Protection of trial subjects:

The study was to be performed in accordance with the ethical principles that had their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations. A written informed consent in compliance with regulatory authority regulations (eg, US Title 21 Code of Federal Regulations Part 50) was to be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involved risk to the subject. If the ICF was revised during the course of the study, all active participating subjects had to sign the revised form.
Before recruitment and enrollment, each prospective subject was to be given a full explanation of the study and be allowed to read the approved ICF. The investigator was to address all questions raised by the subject. Once the investigator was assured that the subject understood the implications of participating in the study, the subject was to be asked to give consent to participate in the study by signing the ICF. The investigator or designee was to also sign the ICF.

Background therapy:

A total of 317 subjects (55.3%) received at least one prior medication in the study eye, most commonly (>20.0% subjects) anticholinergics (263 subjects [45.9%]) and local anesthetics (144 subjects [25.1%]). A total of 303 subjects (52.9%) received at least one prior medication in the fellow eye, most commonly (>20.0% subjects) anticholinergics (248 subjects [43.3%]) and local anaesthetics (124 subjects [21.6%]). A total of 476 subjects (83.1%) received at least one concomitant medication in the study eye, most commonly (>20.0% subjects) local anesthetics (416 subjects [72.6%]), anticholinergics (288 subjects [50.3%]), fluoroquinolones (263 subjects [45.9%]), and other anti-infectives (236 subjects [41.2%]). A total of 326 subjects (56.9%) received at least one concomitant medication in the fellow eye, most commonly (>20.0% subjects) anticholinergics (227 subjects [39.6%]) and local anesthetics (124 subjects [21.6%]).

A total of 538 subjects (93.9%) received at least one non-ocular prior medication, most commonly (>20.0% subjects) other diagnostic agents (256 subjects [44.7%]), 3-hydroxy-3-methylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors (189 subjects [33.0%]), other viral vaccines (138 subjects [24.1%]), dihydropyridine derivatives (117 subjects [20.4%]), selective beta blocking agents (115 subjects [20.1%]), and platelet aggregation inhibitors excluding heparin (115 subjects [20.1%]). A total of 552 subjects (96.3%) received at least one non-ocular concomitant medication, most commonly (>20.0% subjects) other viral vaccines (328 subjects [57.2%]), other diagnostic agents (252 subjects [44.0%]), HMG CoA reductase inhibitors (203 subjects [35.4%]), proton pump inhibitors (136 subjects [23.7%]), platelet aggregation inhibitors excluding heparin (132 subjects [23.0%]), selective beta blocking agents (128 subjects [22.3%]), and dihydropyridine derivatives (126 subjects [22.0%]).

Evidence for comparator:

Eylea (comparator)

Actual start date of recruitment	13 August 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	Slovakia: 29
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Latvia: 23
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Israel: 84
Country: Number of subjects enrolled	Japan: 60
Country: Number of subjects enrolled	Korea, Republic of: 118
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	573
EEA total number of subjects	232

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)	73
From 65 to 84 years	250
85 years and over	250

Subject disposition

Recruitment

Recruitment details:

A total of 576 subjects were randomly assigned to receive either SCD411 (288 subjects) or Eylea (288 subjects) treatment. Two subjects (Subject 1215002 and Subject 1717008) met the exclusion criteria but were randomized in error. Subject 5003008 also did not receive any study drug injection. These 3 subjects were excluded from all analyses sets.

Pre-assignment

Screening details:

A total of 914 subjects were assessed for eligibility across 132 sites in 14 countries. Upon entry into the study, subjects were assigned a screening number. Subjects who met all inclusion and none of the exclusion criteria were to return to the clinic on Day 1 for further evaluation.

Period 1

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

Blinding implementation details:

This was a double-masked study. To prevent bias in treatment assignment, eligible subjects were randomly assigned using the IRT.
Subjects and study site staff involved in subject management and study assessments were masked to study treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	SCD411 group

Arm description:

SCD411 was a proposed biosimilar of Eylea having aflibercept as the active substance. SCD411 was administered as IVT injection of 2 mg (0.05 mL) every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg (0.05 mL) injection once every 8 weeks (2 months).

Arm type	Experimental
Investigational medicinal product name	Aflibercept biosimilar
Investigational medicinal product code	
Other name	SCD411
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

SCD411 was administered as IVT injection of 2 mg (0.05 mL) every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg (0.05 mL) injection once every 8 weeks (2 months).

Arm title	Eylea group

Arm description:

Eylea was administered as IVT injection of 2 mg (0.05 ml) every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 ml) injection once every 8 weeks (2 months).

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Eylea has been approved for the treatment of wet AMD when administered as IVT injection of 2 mg (0.05 mL) every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg (0.05 mL) injection once every 8 weeks (2 months).

Number of subjects in period 1	SCD411 group	Eylea group
Started	287	286
Completed	260	259
Not completed	27	27
Consent withdrawn by subject	8	6
Subject missed first 2 doses of IP	-	1
Adverse event, non-fatal	5	4
Other	5	4
Death	-	1
Investigator decision	-	2
Lost to follow-up	4	3
Sponsor decision	2	5
BCVA decrease of ≥30 letters	1	-
Protocol deviation	2	1

Baseline characteristics

Reporting groups	
Reporting group title	SCD411 group
Reporting group description:	
SCD411 was a proposed biosimilar of Eylea having aflibercept as the active substance. SCD411 was administered as IVT injection of 2 mg (0.05 mL) every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg (0.05 mL) injection once every 8 weeks (2 months).	
Reporting group title	Eylea group
Reporting group description:	
Eylea was administered as IVT injection of 2 mg (0.05 ml) every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 ml) injection once every 8 weeks (2 months).	

Reporting group values	SCD411 group	Eylea group	Total
Number of subjects	287	286	573
Age categorical			
Units: Subjects			
Adults (18-64 years)	33	40	73
From 65-84 years	131	119	250
85 years and over	123	127	250
Age continuous			
Units: years			
median	73.0	73.0	
full range (min-max)	54 to 95	50 to 98	-
Gender categorical			
Units: Subjects			
Female	149	147	296
Male	138	139	277
BCVA score for Study Eye			
Best corrected visual acuity (BCVA) score for Study Eye			
Units: letters			
arithmetic mean	58.6	59.9	
standard deviation	± 10.75	± 10.60	-

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): The FAS included all randomized subjects who received at least 1 injection of the study drug. Numbers were based on planned treatment group.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Set (PPS): Included all subjects in the Full Analysis Set, excluding those with significant protocol deviations. Numbers were based on planned treatment group.	

Reporting group values	Full Analysis Set	Per Protocol Set	
Number of subjects	573	558	
Age categorical Units: Subjects			
Adults (18-64 years)	73	71	
From 65-84 years	250	239	
85 years and over	250	248	
Age continuous Units: years			
median	73.0	73.0	
full range (min-max)	50 to 98	50 to 98	
Gender categorical Units: Subjects			
Female	296	289	
Male	277	269	
BCVA score for Study Eye			
Best corrected visual acuity (BCVA) score for Study Eye			
Units: letters			
arithmetic mean	59.3	59.3	
standard deviation	± 10.69	± 10.69	

End points

End points reporting groups

Reporting group title	SCD411 group
Reporting group description:	
SCD411 was a proposed biosimilar of Eylea having aflibercept as the active substance. SCD411 was administered as IVT injection of 2 mg (0.05 mL) every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg (0.05 mL) injection once every 8 weeks (2 months).	
Reporting group title	Eylea group
Reporting group description:	
Eylea was administered as IVT injection of 2 mg (0.05 ml) every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 ml) injection once every 8 weeks (2 months).	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS): The FAS included all randomized subjects who received at least 1 injection of the study drug. Numbers were based on planned treatment group.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
Per Protocol Set (PPS): Included all subjects in the Full Analysis Set, excluding those with significant protocol deviations. Numbers were based on planned treatment group.	

Primary: Change from Baseline in BCVA Score for Study Eye in FAS at Week 8

End point title	Change from Baseline in BCVA Score for Study Eye in FAS at Week 8
End point description:	
The primary endpoint was the change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 8. The BCVA score was comparable at Baseline among the treatment groups in the FAS. At Week 8, both treatment groups showed similar improvement from Baseline in the BCVA scores: a mean of 5.5 and 5.8 letters and an LS mean of 5.5 and 5.9 letters in the SCD411 and Eylea groups, respectively.	
End point type	Primary
End point timeframe:	
From baseline through 8 weeks	

End point values	SCD411 group	Eylea group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	287	286		
Units: letters				
arithmetic mean (standard deviation)				
Baseline	58.6 (± 10.75)	59.9 (± 10.60)		
Unadjusted Week 8	64.2 (± 13.32)	65.7 (± 13.08)		

Statistical analyses

Statistical analysis title	Statistical analysis - FAS

Statistical analysis description:

The change from baseline in BCVA score for study eye at Week 8 for the primary estimand was summarized and analyzed using MMRM analysis (Mixed-effects model for repeated measures).

Comparison groups	SCD411 group v Eylea group
Number of subjects included in analysis	573
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.1
Variability estimate	Standard error of the mean
Dispersion value	0.74

Notes:

[1] - LS mean difference (SCD411 – Eylea), MMRM. The MMRM analysis included the change from baseline as dependent variable; visit, treatment group, and visit × treatment group as fixed effects, and baseline BCVA score as a covariate. An unstructured covariance matrix was used. Degrees of freedom were approximated using Kenward-Roger approach.

Primary: Change from Baseline in BCVA Score for Study Eye in PPS at Week 8

End point title	Change from Baseline in BCVA Score for Study Eye in PPS at Week 8

End point description:

The primary endpoint was the change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 8. The BCVA score was comparable at Baseline among the treatment groups in the PPS. At Week 8, the analysis based on the PPS yielded results similar to those of the FAS.

End point type	Primary

End point timeframe:

From baseline through 8 weeks

End point values	SCD411 group	Eylea group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	275	283		
Units: letters				
arithmetic mean (standard deviation)				
Baseline	58.4 (± 10.85)	59.9 (± 10.65)		
Unadjusted Week 8	63.9 (± 13.38)	65.7 (± 13.12)		

Statistical analyses

Statistical analysis title	Statistical analysis - PPS

Statistical analysis description:

The change from baseline in BCVA score for study eye at Week 8 for the primary estimand was summarized and analyzed using MMRM analysis (Mixed-effects model for repeated measures).

Comparison groups	Eylea group v SCD411 group

Number of subjects included in analysis	558
Analysis specification	Pre-specified
Analysis type	equivalence[2]
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.75

Notes:

[2] - LS mean difference (SCD411 – Eylea), MMRM. The MMRM analysis included the change from baseline as dependent variable; visit, treatment group, and visit × treatment group as fixed effects, and baseline BCVA score as a covariate. An unstructured covariance matrix was used. Degrees of freedom were approximated using Kenward-Roger approach.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed beginning at enrollment (date of signed informed consent) and up to 28 days after the last dose of the study drug.

Adverse event reporting additional description:

Overall, SCD411 was well-tolerated with a favorable safety profile that was comparable with Eylea in the total population. The incidence of ocular and non-ocular TEAEs was similar among the 2 treatment groups. No TEAEs leading to death were reported in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	SCD411 group

Reporting group description:

Subjects who were randomized at baseline /Day 1 to receive SCD411 every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 ml) injection once every 8 weeks (2 months).

Reporting group title	Eylea group

Reporting group description:

Subjects who were randomized at baseline /Day 1 to receive Eylea every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 ml) injection once every 8 weeks (2 months).

Serious adverse events	SCD411 group	Eylea group	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 287 (11.15%)	31 / 286 (10.84%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
High-grade B-cell lymphoma			

subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage 0			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (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 / 287 (0.35%)	0 / 286 (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			
Asthenia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (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 / 287 (0.00%)	1 / 286 (0.35%)	
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			
Sleep apnoea syndrome			
subjects affected / exposed	2 / 287 (0.70%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
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			
Femoral neck fracture			

subjects affected / exposed	1 / 287 (0.35%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
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	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venom poisoning			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 287 (0.00%)	2 / 286 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			

subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 287 (0.35%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intracranial mass			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	2 / 287 (0.70%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal pigment epithelial tear			
subjects affected / exposed	2 / 287 (0.70%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amaurosis fugax			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (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			
Haematuria			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			

subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endophthalmitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 287 (0.70%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergilloma			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone tuberculosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (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	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 286 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 286 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SCD411 group	Eylea group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 287 (20.56%)	55 / 286 (19.23%)	
Eye disorders			
Punctate keratitis			
subjects affected / exposed	2 / 287 (0.70%)	0 / 286 (0.00%)	
occurrences (all)	2	0	
Visual acuity reduced			
subjects affected / exposed	13 / 287 (4.53%)	13 / 286 (4.55%)	
occurrences (all)	13	13	
Conjunctivitis allergic			
subjects affected / exposed	2 / 287 (0.70%)	0 / 286 (0.00%)	
occurrences (all)	2	0	
Neovascular age-related macular degeneration			
subjects affected / exposed	19 / 287 (6.62%)	13 / 286 (4.55%)	
occurrences (all)	19	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 287 (0.00%)	2 / 286 (0.70%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 287 (0.00%)	2 / 286 (0.70%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 287 (0.70%)	2 / 286 (0.70%)	
occurrences (all)	2	2	
Osteoporosis			
subjects affected / exposed	0 / 287 (0.00%)	2 / 286 (0.70%)	
occurrences (all)	0	2	
Infections and infestations			
COVID-19			
subjects affected / exposed	18 / 287 (6.27%)	21 / 286 (7.34%)	
occurrences (all)	18	21	
Nasopharyngitis			

subjects affected / exposed occurrences (all)	3 / 287 (1.05%) 3	0 / 286 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2020	The following is a summary of the major changes implemented with Protocol Amendment 1, Version 2.0, dated 24 Nov 2020: • Section 2.5 Estimands: This section was revised as per the United States Food and Drug Administration (US FDA) requirement of changing the Full Analysis Set (FAS) and the recommendation of not discontinuing subjects from the study when they discontinue study treatment. • Section 3.1 Study Design • Section 4.1.1 Inclusion Criteria • Section 4.1.2 Exclusion Criteria • A new Section 4.2 Selection of Study Eye was added as per the US FDA requirement to clearly define the study eye in the protocol. • Section 4.3.1 Discontinuation From Study Treatment and Section 4.3.2 Withdrawal From the Study • Section 4.3.3 Handling of Withdrawals • Section 4.3.4 Screen Failures • Section 5.2 Treatments Administered • Section 5.2.1 Treatment of Fellow Eye • Section 5.3 Identity of IP: As per the US FDA request, the source of Eylea was updated. • Section 5.8.1 Rescue Treatment • Section 5.8.2 Prohibited Medications • Section 6.1.3 Early Termination/End-of-Study • Section 6.3.3.6 Suspected Unexpected Serious Adverse Reactions (SUSAR) and Nonserious Adverse Events of Special Interest (AESIs) • Section 6.4 Pharmacokinetic Assessments • Section 6.7 Pregnancy • Section 7.1 Estimands and Intercurrent Events • Section 7.2 Sample Size Determination • Section 7.3 Analysis Sets: The definition of the FAS was updated as per the request from US FDA. The definitions of the Safety Set and the PK Set were updated for clarity. • Section 7.5.1.1 Primary Efficacy Outcome Measures • Section 7.5.1.2 Secondary Efficacy Outcome Measures • Section 11.2.2 Protocol Deviations • Section 12 Reference List: The reference list was updated with the European Medicines Agency's (EMA) overview of Eylea.
24 January 2022	The following is a summary of the major changes implemented with Protocol Amendment 2, Version 3.0, dated 24 Jan 2022: • Exclusion criterion 29 (Synopsis; Section 4.1.2): For subjects with a history or evidence of cardiac conditions was reworded for clarity. • Statistical methods (Synopsis; Section 3.1 Study Design; Section 7 Statistical Analytical Plan; Section 7.5.6 Interim Analyses): Interim analysis was added to support regulatory filing to the Pharmaceutical and Medical Devices Agency (PMDA). • Section 6.3.3.1 Definitions of Adverse Events; Section 6.3.3.4 Reporting Adverse Events; Section 6.3.3.8 Assessment of Causality: An assessment of AEs was included for the IVT injection procedure. • Section 6.6 Independent Data Monitoring Committee; Section 11.1.1 External Data Monitoring Committee; Section 11.4 Final Report: Text was modified to reflect the addition of an interim analysis. • Throughout the protocol: Changes were made to achieve consistency between different sections of the protocol and statistical analysis plan (SAP) and to improve the readability and overall quality of the document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported