19 June 2025
EMA/CHMP/193207/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vgenfli

International non-proprietary name: aflibercept

Procedure No. EMEA/H/C/006192/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADA	anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
AUC	area under the concentration-time curve
AUC*0-672*	Area under the concentration-time curve from hour 0 to hour 672, estimated by the linear trapezoidal rule
AUC*0-inf*	area under the concentration-time curve from zero to an infinite time
AUC*0-t*	area under the concentration-time curve from zero to the last quantifiable time point
AUC*0-tau*	area under the concentration-time curve from zero to the end of the dosing period
BCVA	best corrected visual acuity
BLQ	below limit of quantification;
BMI	body mass index
BOCF	baseline observation carried forward
BRVO	branch retinal vein occlusion
C1q	Complement component 1q
CDC	Complement-dependent cytotoxicity
CI	confidence interval
C*max*	maximum plasma concentration
CMC	Chemistry, manufacturing and controls
CNV	choroidal neovascularization
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRT	central retinal thickness
CRVO	central retinal vein occlusion
DME	diabetic macular edema
DP	drug product
DS	drug substance
ECL	Electrochemiluminescence
eCRF	electronic case report form

ELISA	Enzyme-linked Immunosorbent Assay
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	full analysis set
Fc	crystallizable fragment
FcR	Fc receptor
FP	fundus photography
GCP	Good Clinical Practice
GMT	geometric mean titer
HUVEC	Human umbilical vein endothelial cell
IDMC	Independent Data Monitoring Committee
Ig	immunoglobulin
IND	investigational new drug
IOP	intraocular pressure
IVT	intravitreal
K*D*	Equilibrium dissociation constant
kDa	Kilo-Dalton
KDR	Kinase insert domain receptor
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LS	least square
mFAS	modified Full Analysis Set
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
NAb	neutralizing antibodies
OCT	optical coherence tomography
PD	pharmacodynamic
PFS	pre-filled syringe
PK	pharmacokinetic(s)
PlGF	Placental growth factor
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PPS	Per Protocol Set
PT	preferred term

ROP	retinopathy of prematurity
SAE	serious adverse event
SAP	statistical analysis plan
SCD411	Biosimilar aflibercept
SD	standard deviation
SOC	system organ class
SPR	Surface plasmon resonance
t*1/2*	elimination half-life
TEAE	treatment-emergent adverse events
t*max*	time to reach maximum plasma concentration
US FDA	Unites States Food and Drug Administration
ULOQ	Upper limit of quantification
USA	United States of America
VEGF	vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
VHR	Vitreous humor from the right eye
wAMD	wet age-related macular degeneration

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zaklady Farmaceutyczne Polpharma S.A. submitted on 9 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Vgenfli, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2022.

The applicant applied for the following indication:

Vgenfli is indicated for adults for the treatment of

- *neovascular (wet) age-related macular degeneration (AMD) (see section 5.1)*
- *visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1)*
- *visual impairment due to diabetic macular oedema (DME) (see section 5.1)*
- *visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).*

The following paediatric indication initially claimed in the submission

- *retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease*

has been excluded by the applicant from the indications for VGENFLI during the procedure (after D120).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal product.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union

- Marketing authorisation number: EU/1/12/797/001-002

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which comparability tests and studies have been conducted:

- Product name, strength, pharmaceutical form: Eylea 40 mg/mL solution for injection
- Marketing authorisation holder: Bayer AG
- Date of authorisation: 22-11-2012
- Marketing authorisation granted by: Union
- Marketing authorisation number(s): EU/1/12/797/001-002

1.3. Information on paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
20 July 2017	EMEA/H/SA/3594/1/2017/III	*Kerstin Wickström, Andrea Laslop*
27 June 2019	EMEA/H/SA/3594/1/FU/1/2019/II	*Christian Gartner, Rune Kjeken*
16 December 2021	EMA/SA/0000070158	*Finbarr Leacy, Andreas Kirisits*

The applicant received scientific advice on the development of a proposed biosimilar aflibercept for the treatment of the same indications as for Eylea (i.e. visual impairment due to diabetic macular oedema (DME), age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), myopic choroidal neovascularisation (CNV), diabetic retinopathy (DR) and neovascular glaucoma (NVG)) from the CHMP on 20 July 2017 (EMEA/H/SA/3594/1/2017/III). The scientific advice pertained to the following aspects:

Quality: Cell banking, active substance and finished product release testing and stability testing, the quality comparability exercise, in vitro test program.

Toxico-pharmacological development: nonclinical studies.

Clinical: First-in-human trial in patients with wet age-related macular degeneration (wet AMD) trial 1, Design of the Phase III comparative trial to Eylea® in patients with wet AMD (Trial 2) to investigate similarity of SCD411 and the reference product Eylea® in terms of clinical efficacy and safety (including Primary endpoint, comparators, statistical approach, non-inferiority margin, immunogenicity), extrapolation to other approved indications of the reference product, the Submission strategy and source of reference product in the clinical trials.

The applicant received scientific advice on the development of a proposed biosimilar Aflibercept for the treatment of the same indications as for Eylea (i.e. visual impairment due to diabetic macular oedema (DME), age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), myopic choroidal neovascularisation (CNV), diabetic retinopathy (DR) and neovascular glaucoma (NVG)) from the CHMP on 27 June 2019 EMEA/H/SA/3594/1/FU/1/2019/II. The scientific advice pertained to the following aspects:

Clinical: assessment of pharmacokinetics, study design of the Phase III comparative trial for clinical efficacy and safety including equivalence margin, timepoints for blood sampling, sample size, patient inclusion-, exclusion, discontinuation criteria, handling of affected patient's second eye, and immunogenicity testing.

The applicant received scientific advice on the development of a proposed biosimilar Aflibercept for the treatment of the same indications as for Eylea (i.e. visual impairment due to diabetic macular oedema (DME), age-related macular degeneration (AMD), macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), myopic choroidal neovascularisation (CNV), diabetic retinopathy (DR) and neovascular glaucoma (NVG)) from the CHMP on 16 December 2021 (EMA/SA/0000070158). The scientific advice pertained to the following clinical aspects:

•planned interim analysis and unmasking of certain study data.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: John Joseph Borg Co-Rapporteur: Frantisek Drafi

The application was received by the EMA on	9 February 2024
The procedure started on	28 March 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 June 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 March 2025
A GMP inspection was placed at the AS manufacturing site between 13/01/2025 and 21/01/2025 and the outcome of the inspection carried out was issued on	28 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 March 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vgenfli on	19 June 2025

2. Scientific discussion

2.1. About the product

Vgenfli has been developed as a biosimilar to the reference product Eylea (INN: aflibercept).

Aflibercept is in the pharmaceutical group 'ophthalmologicals / antineovascularisation agents' (ATC code: S01LA05).

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.

The claimed therapeutic indications for Vgenfli are in adults for treatment of

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

The indication of treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease in preterm infants – granted to Eylea 40 mg/mL solution for injection in pre-filled syringe - is not claimed.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is a biosimilar to the reference medicinal product Eylea and is presented as a solution for injection containing 40 mg/mL of aflibercept (SCD411) as active substance (AS).

Other ingredients are sodium acetate trihydrate, acetic acid, sucrose, sodium chloride, polysorbate 20 and water for injections (WFI).

The product is available in two presentations:

- a single-dose 1 mL long luer-lock pre-filled syringe (PFS), containing a solution for intravitreal injection, made of cyclo-olefin polymer (COP) resin, with a tip cap made of chlorinated butyl rubber. The syringe is closed with a piston made of chlorinated butyl rubber coated with cross-linked silicone.
- a type I glass vial containing a solution for intravitreal injection with an elastomeric rubber stopper and aluminium cap, and an 18 G filter needle.

2.2.2. Active substance

2.2.2.1. General information

The active substance aflibercept (INN) is a recombinant fusion protein consisting of human vascular endothelial growth factor receptor-1 (VEGFR-1) and VEGF receptor-2 (VEGFR-2) extracellular domains fused to the Fc portion of human IgG1. It is produced in Chinese hamster ovary (CHO) cells. The fusion

protein is composed of two identical polypeptide chains (432 amino acid residues each) linked by disulfide bonds at hinge region of Fc region with a total molecular weight of approximately 97 kDa (deglycosylated). Each aflibercept contains five N-glycosylation sites.

Aflibercept interferes with the biological actions of VEGF-A by tightly binding to it and preventing VEGF-A from interacting with its receptors. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration. Aflibercept can also bind to other VEGFR-1 ligands, notably PlGF.

2.2.2.2. Manufacture, characterisation and process controls

The manufacturing site of AS is Mycenax Biotech Inc., Taiwan. For this site, the compliance with EU-GMP was not demonstrated and a MO was raised. During the assessment, the GMP compliance was confirmed and the corresponding EU-GMP certificated is provided.

Essential information on the active substance manufacturing process including flow chart and detailed description has been provided. The active substance is manufactured using CHO cells and it encompasses upstream and downstream purification processing steps as outlined below.

Upstream processing starts with the thaw of one vial of the working cell bank (WCB) and cell expansion through shake flasks and bioreactors of increasing size. Cultivation is terminated with the harvest of the bioreactor when culture viability and SCD411 concentration comply with the pre-defined acceptance criteria. For the harvest, the bioreactor is connected to a filtration line for clarification and cell removal. The filtrate is collected and stored until being further processed.

Downstream processing continues with affinity chromatography to capture and concentrate SCD411 protein solution and to remove process-related impurities. Formulated active substance is stored in 1L polycarbonate bottles at -80°C.

Control of materials

Raw materials used for cell culture and purification are listed in the dossier. Where applicable, reference is made to compendial monographs. Sufficient specifications for non-compendial material qualification are provided. No raw materials derived from human and/or animal sources are used in the process. The compositions of the cell culture media and feed solutions at each cell culture step are described. Agreements are in place with the suppliers to notify the MAH in case of changes to the medium. Quantitative compositions of buffers used during downstream purification are provided. Information on resins and filters used during downstream processing is considered sufficient.

The generation of the cell substrate is well described. Sufficient information on the host cell line and its adaption to growth in suspension under serum- and protein-free conditions has been provided and the cloning strategy has been adequately described. The nucleotide sequence of aflibercept has been provided and confirmed to be in-line with the published protein sequence.

A two-tiered banking system consisting of a master cell bank (MCB) and a working cell bank has been established in accordance with ICH Q5D. Future WCBs will be established following the same approach as used for the implementation of the current WCB. Information on the establishment and control of future WCBs is presented including adequate control of population doubling levels / days in cultivation.

The characterisation testing program of MCB and WCB is considered adequate to identify relevant phenotypic and genotypic characteristics. Limited testing panel as proposed for WCBs is considered justified based on complex and similar testing panels for MCB. Limited testing panel as proposed for WCBs is considered justified based on complex and similar testing panels for MCB. Cell bank storage stability will be tested annually. This is considered adequate.

Post production cells (PPCs) with extended population doubling (PDLs) at the limit of in-vitro cell age (LIVCA) have been established from End of Production cells (EoPs, commercial-scale GMP run) at small-scale comparable to the commercial manufacturing process. Cell growth, productivity and product quality of active substance resulting from small-scale PPCs were comparable to commercial scale active substance. Overall, genetic stability of PPC at LIVCA is considered confirmed.

Control of critical steps and intermediates

Definition of parameters and tests as well as classification was initially done based on risk assessment and process characterisation studies as outlined in the dossier. Acceptance criteria and action limits were established at that time. Following the process validation activities, the risk assessment was repeated to fine-tune the classification of process parameter and associated normal operating ranges (NORs) and proven acceptable ranges (PARs) as well as the classification of process tests and respective acceptance criteria. This is considered acceptable.

Specifically, critical process parameters (CPPs), key process parameters (KPPs) and non-key process parameters (non-KPPs) were defined for the commercial manufacturing. For the ranked process parameters, NORs and PARs were established. The process is controlled by in-process controls (IPCs), in-process monitoring (IPM) and for-information-only (FIO) tests. Respective acceptance criteria and action limits were established.

Overall, the NORs, PARs and set points of the proposed process parameters and the acceptance criteria of the process controls are adequately aligned. Also, acceptable definitions are provided for the proposed classes of process parameters and tests.

There are no intermediates defined for the SCD411 active substance manufacturing process.

For the active substance manufacturing process, process control acceptance criteria should be re-evaluated after completion of 30 commercial scale batches by end of Q2 of 2028 (REC).

Process validation

Process validation of the commercial active substance manufacturing process was performed by manufacture of upstream batches and downstream batches. Overall, results of the process parameters and process controls of the process validation batches met the pre-defined acceptance criteria. Subsequently to the process validation activities, re-evaluation of criticality ranking of process parameters as well as of acceptance ranges of process tests has been done. This is described in the "Continuous process verification (CPV) plan". The content of this CPV plan is considered to be sufficiently aligned with the content included in the dossier sections describing the company's commitment for future commercial manufacture. Summarising the provided process validation data, the active substance manufacturing process can be considered in a validated state.

During process validation activities, depletion of process-related impurities, such as bacterial endotoxins, residual protein A, host cell protein (HCP) and residual DNA has been monitored. Based on the provided data, implementation of adequate process controls is considered sufficiently justified.

The AS manufacturing process has been validated adequately, demonstrating that the purification process consistently produces aflibercept AS (SCD411) of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Development of SCD411 active substance manufacturing process was performed at different manufacturing sites. Essentially, the manufacturing process evolved over three process phases. In the beginning there was a developmental lab-scale process and afterwards a pilot scale process. The pilot

scale process had been up-scaled to the commercial scale process. The commercial scale process was also used for production of the clinical material of SCD411.

The differences between the process scales as well as within the commercial scale process have been outlined and are considered minor. Also, the AS formulations used in pilot scale and commercial scale manufacture are differing. Comparative batch data are provided including batches of the lab-scale, pilot scale and commercial scale. Overall, the presented data are found comparable and complying with the AS specification being in place at the time of analysis.

Hold time studies for process intermediates are described and respective data including both physico-chemical and biological test parameters are presented. The concluded hold times and hold conditions are considered adequate.

Process characterisation studies are described in detail. Development of the control strategy proposed for SCD411 active substance manufacturing process, including the criticality assessments and deduced ranking of process parameters and tests is considered adequately described. Likewise, and based on the provided data, the representativeness of the proposed scale-down models is considered reasonably demonstrated.

Resin life-time of the four chromatography columns and life-time of the membrane used for UF/DF during SCD411 active substance manufacturing process has been defined based on small scale studies. Generally, the provided small scale studies are considered appropriate to estimate and set the maximum number of life cycles, however, commercial scale verification of the proposed resin/membrane life-times should be performed on an ongoing basis and in accordance with a protocol. Such protocol including product related parameters like AS quality attributes as well as resin performance parameters along with respective acceptance criteria is provided and considered acceptable.

Characterisation

Characterisation was based on a number of representative AS batches of commercial scale. The panel of methods applied is sufficiently broad and complementary and covers structural quality attributes (AA sequence and variations), higher order structure, molecular weight, purity, as well as biological and biofunctional quality attributes covering different cell-based assays as well as a large number of binding assays to the various targets. It is acknowledged that the company replaced the gel-based methods used by column-based methods to allow quantification of impurities and increase precision and accuracy of analysis.

The amino acid sequence was adequately verified with 100% coverage including modification of Asn and Met by deamidation or oxidation as well as N- and C-terminal variability (clipping of terminal Lys only). It was demonstrated that the cysteines were correctly linked in the predicted intra- and interchain disulphide bridges. As complementary test on potentially free cysteines (formed either by stress or by insufficient linkage of all molecules), a commercially available sensitive thiol assay kit was used. Characterisation of secondary and tertiary structure revealed some methodological limitations reflected by differing results obtained by different methods. Since the correct three-dimensional structure is not questioned per se – on condition that the manufacturing process conditions are adequate - such method-related differences are noted but do not constitute a concern.

Molecular weight determinations are precise and accurate for the deglycosylated and reduced molecule. Results on the native molecule are average-based due to the variability of the N-glycan chains. Likewise, the methods on apparent molecular weight do not deliver accurate results of the MW but are taken as orthogonal information on size and shape of the molecule.

The glycan structure as inherently variable structural feature was addressed by several complementary analytical approaches.

No O-linked oligosaccharide structures could be detected. The company adequately explained how the low levels of GalNAc were detected in the absence of O-glycans.

Charge heterogeneity is analysed by using both a gel-based and a column-based method.

Determination of the extinction coefficient is considered acceptably accurate.

Biological and functional potency is addressed by a large number of orthogonal assays. Assays also considered the various binding partners / targets as well as their isoforms. Cell-based assays confirmed biological activity with respect to proliferation-/, cell migration-/, or phosphorylation-inhibition. Various binding assays with varying targets and their different isoforms were performed (i.e. VEGF-A165 and VEGF family, PlGFs and galectin). Binding affinity to relevant Fc receptors was addressed as expected. The panel of biological assays is very comprehensive and includes testing for the absence of effector functions such as ADCC and CDC.

Overall, characterisation is presented in a satisfactory way. The company´s justification that characterisation is not as detailed as the exercise for similarity evaluation is noted and acceptable since characterisation is still considered sufficiently detailed.

Impurities

Characterisation of impurities includes the product-related variants that were already covered in the structural elucidation section, i.e. oxidation and deamidation of amino acid residues, truncation of the amino acid chain and aggregation (higher molecular weight species).

Process-related impurities are adequately addressed and cover the main candidates, i.e. residual DNA, residual HCP and residual protein A. Clearance factors for suitable, selected process steps are calculated. Moreover, these tests are included in the AS specification for routine testing.

2.2.2.3. Specification

The AS specification contains tests for general attributes, content, biological activity (cell-based assay and binding assay), several complementary tests for identity, tests for heterogeneity and purity/impurities, sialic acid content and N-glycan profile, residual process-related impurities, and the safety-related tests on microbial purity.

Unique method identifiers for in-house test procedures used are included in the specifications. For compendial methods, reference to the respective Ph. Eur. monograph and (if applicable) the specific test employed (e.g. visible particle test, bioburden test) is included.

Analytical procedures

Sufficiently detailed method descriptions including materials, dilutions, reference materials, system suitability testing criteria and reporting of results are provided. A number of in-house methods as well as few compendial ones is used. Both for the compendial and the in-house analytical methods sufficient and adequate information is provided to substantiate that the analytical methods can be considered being in a validated state.

Regarding the HCP assay, the coverage of the detecting antibody used in the HCP assay was very high. Thus, the detecting antibody of the HCP assay can be considered properly qualified.

It is noted that AS and FP are tested for endotoxin using the LAL test. Since the Ph. Eur. recently adopted the general text 2.6.32 on recombinant Factor C for Endotoxin control, the applicant indicated

that evaluations will be initiated to identify steps to be taken to allow transfer of the test for bacterial endotoxins from currently Ph. Eur. 2.6.14 to Ph. Eur. 2.6.32. This is endorsed.

Batch analysis

For batch analyses a large data set is provided including commercial scale and pilot scale batches. Generally, the batch data are found complying with the specification being in place at the time of analysis.

Justification of specification

The provided justification of specification acceptance criteria is approvable. The applicant has committed to re-evaluate the acceptance criteria for certain assays after manufacture of 30 commercial batches (REC).

Reference Standards or Materials

Evolvement and establishment of reference standards is described with sufficient transparency. After a phase of using interim reference standards, the company established a two-tier system with a primary reference standard (PRS) and a working reference standard (WRS).

Descriptions of qualification and requalification procedures for the primary and secondary standards were amended with the necessary detail. In particular, potency assignment for the primary reference standard was clearly defined. Trending analysis of potency assays of primary reference standards is performed in order to avoid potential drift.

Container closure

Sufficient information is provided on the container closure system (CCS) used for AS storage. The CCS consists of polycarbonate bottles with silicone-lined polypropylene copolymer (PPCO) screw caps. The container complies with Ph. Eur. 3.1.9. and extended information was provided on Extractable and leachables, BSE/TSE compliance and biocompatibility, leading to the conclusion that the AS container closure system is adequate.

2.2.2.4. Stability

SCD411 AS is claimed to be stable for at least 36 months at -80°C ± 10°C storage. Stability data provided cover both long-term conditions at -80°C ± 10 °C and accelerated conditions at 5°C.

Overall, the stability protocol is acceptable, and the chosen analytical procedures are considered stability-indicating. The container closure system used for the stability studies is confirmed to represent the CCS used at commercial scale.

The stability study encompassing the PPQ batches is now terminated. Long-term and accelerated conditions stability data are available.

In general, the provided stability data generated at long-term conditions and accelerated conditions could demonstrate compliance with the pre-defined acceptance criteria. Based on the provided data, the claimed active substance shelf-life is considered sufficiently supported.

From the freeze/thaw studies performed with both pilot and commercial scale batches the maximum number of freeze/thaw cycles was determined.

2.2.3. Finished Medicinal Product

2 . 2 . 3 . 1 . Description of the product and pharmaceutical development

Composition of the finished product

The FP has been developed as a biosimilar to Eylea and is presented as a solution for injection containing aflibercept (SCD411) as active substance. Other ingredients are sodium acetate trihydrate, acetic acid, sucrose, sodium chloride, polysorbate 20 and water for injections (WFI). The strength (40 mg/ml) of the FP is identical to that of the reference product (RP). The SCD411 FP is presented as a sterile, ready-to-use solution for intravitreal injection in type I glass vials (identical to RP) and additionally in pre-filled syringes. All components, their amount per vial, PFS, per dose and per mL, function, and reference to their quality standards are indicated. There are no differences of the formulation between the vial and PFS presentations. All excipients are well known pharmaceutical ingredients and their quality is compliant with pharmacopeia standards. There are no novel excipients used in the finished product formulation. No overages are applied during the manufacture of SCD411 FP.

Formulation development

The various steps of formulation development and the respective studies (one pre-study, two main optimization studies) performed to identify the most stable commercial formulation have been described in detail. Parameters taken into account were the buffer system and concentration, tonicity modifiers, surfactant employed as well as pH range, osmolality, protein aggregates and degradation, and (subvisible) particle formation. The data provided are considered adequate and support the use of the final commercial formulation. The commercial formulation was already used during phase 3 clinical studies. The discussion on the composition is considered sufficient.

Physicochemical and biological properties of the AS and FP have been properly addressed.

Control of excipients

Excipients present in the FP are of compendial nature and comply with Ph. Eur./USP/NF specifications. Excipients are tested with compendial methods; hence validation is not required. No excipients of human or animal origin, and no novel excipients are used in the manufacture of the FP. The provided information is acceptable, and no concerns are raised.

Manufacturing process development

The FP has been developed in two presentations: first, a vial presentation was developed and subsequently a pre-filled syringe. The manufacturing process for both presentations is nearly identical (up to filling and packaging) and is a common process for aqueous sterile finished products, which cannot be subjected to terminal sterilisation. The process comprises the following steps: thawing and dilution of AS, pre-filtration, sterile filtration, aseptic filling, capping of vial or assembly of syringe, labelling, for PFS also blister packaging and surface sterilization, and packaging in cartons. For PFS in blister package, additionally low temperature vaporized hydrogen peroxide sterilization is performed to ensure sterility of the outside of the PFS. The choice of sterilisation procedure is considered adequate based on the nature and respective sensitivity of the active substance being a protein.

Following a risk-based approach manufacturing process development studies were performed to evaluate unit operations of the FP manufacturing process and their impact on FP quality, employing Quality by Design (QbD) principles without claiming design spaces. The overall control strategy was defined based on the results from these studies. The quality target product profile (QTPP) has been provided. Manufacturing process development took into account the Critical Quality Attributes (CQAs) for a sterile solution in a vial and PFS. For identification of CPPs, a risk assessment employing a FMEA was used. CPPs identified were investigated for establishment of acceptable ranges, including normal operating ranges or proven acceptable ranges in process characterization (PC) design space studies. Following the completion of these studies, a re-assessment of the CPPs was performed based on knowledge obtained from cGMP manufacture and PC studies. The process controls as well FP batch data confirmed the suitability of the manufacturing process design and support the adequacy and

consistency of the vial and PFS FP manufacturing process to ensure an adequate quality of the FP. In general, this approach is considered adequate.

Compatibility studies

Product contact materials comprising the sterile filter have been evaluated for their impact on FP quality and were found to have no negative impact. The sample matrix was found to affect the filter integrity test (bubble point), therefore, flushing the filter prior filter integrity testing is required.

Container closure system

The primary container system for the FP vial presentation consists of 3 mL colourless borosilicate type I glass vial with a grey butyl rubber stopper with transparent fluoropolymer film coating crimped with an aluminium cap. A stainless-steel needle with integrated filter is co-packed for extraction of the FP from the vial. The syringe and needle types and sizes to be employed for administration for the FP in vials are recommended while the needle for withdrawal of FP from the vial is provided and specified.

The primary container system for the PFS presentation consists of a 1 mL long luer-lock syringe made of COP with a chlorinated butyl rubber tip cap. The barrel is siliconized with polydimethylsiloxane. The syringe is closed with a piston made of chlorinated butyl rubber coated with cross-linked silicone which is operated by a plastic plunger rod. The syringes are packed in blisters. The sterilisation procedures and conditions of the container closure components for FP vial and PFS presentation have been included, indicating the method of sterilisation (compendial conditions), and the identification of the sterilisation site.

Specifications, exemplary certificates and drawings have been provided for the vial and stopper as well as for the syringe with tip cap and the piston.

For the FP vial and PFS presentations, information with respect to protection, safety and compatibility has been provided. This includes testing of container closure integrity, extractables/leachables, compatibility with the recommended syringe/needle combination as well as transportation studies. In general, the studies performed are considered adequate. The extractable compounds found and their toxicological impact in the amount determined have been further discussed; no risk to patient safety was identified. The studies for leachables on FP PFS presentation are still ongoing. The applicant has confirmed that the outstanding results will be submitted in case of leachables exceeding AET.

Initially, the proposed indication included paediatric population. This was raised as a multidisciplinary Major objection (MO) during the procedure due to missing specific paediatric medical device. In response to this, the applicant agreed to remove reference to paediatric population.

A use-related risk assessment was performed comparing SCD411 PFS FP and Eylea PFS to identify the differences between the two devices and evaluate any risks during use. The differences found were considered minor and do not represent a risk for increase in use errors for the patients.

The PFS of SCD411 FP is an administration device for which Art 117 of the Regulation (EU) 2017/745 (MDR) applies. During the assessment a MO was raised due to missing information on the medical device. Conformance to the GSPR outlined in Annex I of MDR 2017/745 has been confirmed by provision of a Notified Body Opinion. Furthermore, documentation in accordance with the Guideline on quality documentation for medicinal products when used with a medical device (EMA/CHMP/QWP/BWP/259165/2019) has been provided for the PFS. The MO was considered solved.

Microbiological attributes

Sterility of the FP in both presentations is ensured by bioburden reduction filtration, sterile filtration, aseptic filling and integrity of the container closure systems. Generally, the applicant provided

sufficient information to ensure, that the FP in vial and PFS is suitably designed to maintain sterility during assembly, storage, shipping and distribution prior to use.

2.2.3.2. Manufacture of the product and process controls

As stated in AS section, for FP manufacturing site, the compliance with EU-GMP was not demonstrated and a MO was raised. During the assessment, the GMP compliance was confirmed and the corresponding EU-GMP certificate is provided. All sites involved in manufacture and quality control (QC) testing of the finished product operate in accordance with EU GMP.

The manufacturing process has been described in adequate detail, including provision of flow diagrams with respective process parameter and in-process controls.

In summary, frozen AS solution is thawed, pooled, resuspended, and diluted to the target concentration using formulation buffer. The bulk FP solution is filtered and stored at 2-8°C before sterile filtration. Sterile filtration is performed, and the filtered solution is aseptically filled into either sterile vials for the vial presentation or COP syringes for the PFS presentation. The sterile filter setup has been unequivocally specified.

The vials or syringes are closed and after visual inspection, labelling is performed. Manufacturing of the syringe includes an additional assembly step for insertion of the plunger rod and a finger grip. The labelled and assembled syringes are packed into blister packs and the sealed blisters are subjected to vapor hydrogen peroxide (VHP) treatment.

No intermediates are defined for the FP manufacturing process. Holding times are included in the process and are supported by validation data. The maximum FP manufacturing time has been indicated.

Control of critical steps and intermediates

An adequate description of the FP control strategy for both presentation forms has been provided. Determination and establishment of the process controls is based on risk evaluation approaches and has been indicated during process development studies. Criticality assessment of process parameters and in-process tests has been detailed and is considered acceptable. Critical, key and non-critical process parameters, in-process control tests and monitoring as well as validated hold times are indicated with ranges or limits in accordance with the knowledge gained during development. For each unit operation, batch data / process data are provided for the process parameter and process controls. Critical material attributes potentially impacting FP quality have been identified and are controlled.

Process validation / verification

The manufacturing process validation has been performed following a classical approach based on multiple consecutive commercial FP batches of vial and PFS presentation. The results obtained of all process parameter and process controls have been provided and are in compliance with the pre-defined limits/ranges and acceptance criteria. Also, the results of release testing of the validation batches are in compliance with the specification. The aseptic filling of the vial and PFS presentation has been validated by media fill studies, summarising study data have been provided. The FP hold time after sterile filtration and before filling has been based on these studies. The FP packaging processes have been validated for both vial and PFS presentation. Based on the results of these studies, the maximum allowable packaging time for each presentation has been established. Further, it is ensured that the packaging process performs consistently and ensures product quality. Bulk filled and closed vials or PFS are shipped for labelling and secondary packaging. After completion, the FP is shipped for storage and supply in European markets. Data from simulated shipping studies in summer and winter season have been provided. Additionally, a performance qualification study for the shipment procedure

is planned, considering the time required from the transportation of test products to the test site to the completion of QC testing and report issuance. Respective data will be provided.

Data is expected to be provided in Q3 of 2026 (REC).

During process characterisation studies, sterile filter compatibility testing and challenge test has been performed. Compatibility of the filters was analysed. In addition, the impact of process solution and formulation buffer on filter integrity testing was investigated. A study on extractable substances from the (sterile-) filter employed in the FP manufacturing process has been provided. Based on the results of the extractable study, determination of leachables has not been performed which is acceptable.

The hold time for the sterile bulk is defined in the dossier. Maximum operation times for the visual inspection of vials and PFS, for the labeling of the vials and for the labeling and assembly of the PFS have been defined. Homogeneity during filling has been properly validated, including vials/PFS filled at the beginning, middle and end of a fill run.

Hold times and hold conditions during FP manufacture as well as reprocessing in case of sterile filter failure have been established and adequately validated.

2.2.3.3. Product specification

Specifications have been provided for both FP presentations, each comprising the same set of parameters and identical acceptance criteria regarding release and shelf life. The specifications for both presentations contain the following parameter with nearly identical criteria: the parameters for general test, Content, Biological activity, Identity, Heterogeneity/Purity/Impurities and safety. In general, the parameters tested are considered adequate for the product and route of administration. The analytical methods employed for testing have been indicated.

Additional tests for purity and impurities have been developed and implemented in the FP specification. The methods have been described in detail. Validation of both methods and successful transfer is completed.

Analytical procedures

References have been made to the compendial methods employed as well as the in-house procedures performed. The in-house methods, with only some exceptions, are also used for the AS and discussed above. Generally, the analytical procedures specific to the FP have been adequately detailed.

Validation of analytical procedures

Validation of analytical procedures specific to FP has been adequately performed and/or suitability of methods verified. Suitability testing for analysis of sub-visible particles and for device performance has not been performed but justified based on their status as pharmacopoeial methods, which is considered acceptable. Studies evaluating Low Endotoxin Recovery (LER) have been performed and included in the dossier.

Batch analyses

Batch data have been provided for multiple batches of FP vial presentation and PFS FP presentation. All data are in compliance with the specifications in place at the time of testing. No trends are obvious for any parameter tested.

Characterisation of impurities

No FP specific impurities have been identified.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). It was concluded that the risk for presence of nitrosamine impurities in the FP is considered low requiring no additional control or mitigation actions, which is considered acceptable.

In accordance with ICH guideline Q3D(R2) on elemental impurities, a risk assessment was conducted to determine the materials that contribute to the potential for inclusion of elemental impurities in the FP. Ten elements were considered for the risk assessment. Their introduction in the finished product was theoretically evaluated and it was concluded by the applicant, that the risk for presence of elemental impurities in the FP is considered low requiring no additional control or mitigation actions. This conclusion is endorsed.

Justification of specification

Generally, the justification of specification is considered acceptable for most parameters.

Reference materials

Reference standard used for finished product testing is the same as for the active substance.

2.2.3.4. Stability of the product

A shelf life of 24 months stored at 5 ± 3 °C for the FP vial and the FP PFS presentations is proposed.

Stability studies in compliance with ICH Q1A (R2) and Q5C have been performed and are partly still ongoing. They include multiple commercial scale FP batches each of the PFS and vial presentation with storage at long-term conditions of 5±3°C and at accelerated conditions of 25±2°C, 60±5% RH. The studies are completed for the first FP batches (vial presentation) while the stability studies on the rest are still ongoing at long-term conditions (24 months data available). As regards FP in PFS presentation, the stability data are available up to 24 months for the first batches while the stability studies on the rest are still ongoing for long-term conditions. For all PFS stability batches, studies are completed for the accelerated conditions.

The ICH stability studies are supported by initial stability studies (pre-ICH) studies comprising two batches of FP, one batch manufactured from pilot scale AS and one from commercial scale. The batches have been stored under the same long-term and accelerated conditions as indicated for the ICH studies.

Procedures used for stability testing are those performed during routine release test of the finished product. The sampling and testing strategy is presented.

All vial FP batches stored at long-term conditions for up to 24 months and at the accelerated conditions for 3 months complied with the specification.

The results of the photostability studies demonstrate for both FP presentation forms an increase in aggregates and oxidation level and a substantial decrease of bioactivity and VEGF-target binding. Based on these considerations, it was concluded that FP vial and PFS should be kept protected from light.

Potential degradation pathways were analysed by forced degradation studies employing thermal-, acidic-/basic- and oxidative stress. Overall, thermal, acidic and oxidative stress conditions showed substantial impact on product quality attributes. Degradation was observed with regard to aggregate

formation as well as decreased target binding and biological activity, particularly under oxidative stress conditions.

Further, the effect of exposure of aged FP (vial and PFS) with low PS20 content to physical stress conditions (heat, agitation and freeze-thaw) was analysed and demonstrated not to impact the stability of the CQAs of the FP.

In general, the stability studies performed and respective data provided are considered adequate and relevant stability-indicating parameter and degradation pathways of the product have been identified.

Based on available stability data, the shelf-life for vial and PFS presentation and storage conditions as stated in the SmPC (2 years at 2 °C to 8 °C) are acceptable.

Section P.8.1 of the dossier is harmonised with the information in the SmPC as regards the FP storage outside of refrigeration. It is stated that although the available stability data support a 3-month storage period of the FP at 25°C, the product (both vial and PFS) can only be stored for a maximum of 24 hours outside the refrigerator but below 25°C.

2.2.3.5. Biosimilarity

Similarity evaluation

A tabulated comparison of formulation differences of test and reference product is presented. Critical quality attributes of aflibercept were identified and rated for the level of criticality. In relation to the known impact of CQAs/Quality Attributes on activity, PK/PD, safety, and immunogenicity the quality attributes were grouped into three tiers with differently stringent acceptance criteria for evaluation. This approach is supported.

For the test product SCD411, multiple batches of vial and PFS FP were used in similarity evaluation.

The panel of analytical methods used to evaluate similarity is comprehensive. It covers the necessary structural quality attributes of aflibercept as well as its biological activity from various angles.
From a structural point of view, some differences were detected with respect to the level of oxidated and deamidated Met and Asn residues of the polypeptide backbone. For the reference product, the level of Asn deamidation were higher than the test product; conversely the test product showed higher levels of oxidation at particular Met sites. These differences are discussed in relation to the biological and functional assays further below.

No relevant differences were observed with respect to disulphide bridging and higher order structure / three-dimensional conformation.

The molecular weight of the deglycosylated and reduced molecule is the same for both test and reference product as expected. It is not too meaningful to compare the native molecular weight (as measured by mass spectrometry) since glycosylation introduces inherent variability to the molecular weight. Several methods are applied to compare the apparent molecular weight of test and reference product. Even though those methods are indirect measurements, similarity could be concluded.

Glycosylation was compared with respect to site occupancy, oligosaccharide profile and site-specific glycosylation, based on a broad and comprehensive panel of analytical methods. Taking into account the inherent variability of glycosylation, differences beyond this inherent variability were observed with respect to the level of fucosylation, galactosylation and sialylation.

The absence of O-glycans was confirmed for both test and reference product.

No differences in charge heterogeneity could be detected.

To justify the observed differences in glycosylation, the company performed a large number of biological and biofunctional assays in order to evaluate any potential impact of differences in glycosylation on biological responses. Analysis comprised cell-based assays to compare VEGF-induced cell proliferation, migration, and phosphorylation. No meaningful differences were observed between test and reference product. Binding assays comprised target binding of VEGF-A165 by ELISA. Considering the tight acceptance criteria the conclusion on similarity is acceptable. By SPR, binding to the VEGF family, to PlGFs and Gal-1, and to Fcγ-receptors was compared. For all assays except for binding to FcγRIIIA, binding can be considered comparable taking into account analytical variability. The differences in fucosylation are thought to influence binding affinity. However, as effector functions can be excluded for aflibercept (as demonstrated by comparative ADCC and CDC assays with positive control), this identified difference in binding to FcγRIIIA (both isoforms) is not considered relevant in evaluation of similarity.

Taken together, despite differences in binding behaviour to FcγRIIIA (that are not considered to impact efficacy and safety), similarity to the reference product can be concluded for the candidate biosimilar product based on the vast majority of comparative tests performed.

Comparative stability studies

In accordance with the biosimilar Guideline (EMA/CHMP/BWP/247713/2012), the company presented comparative stability studies under accelerated conditions as well as under forced degradation conditions (thermal -, light/photo -, acidic, basic and oxidative stress). The studies were intended to reveal any potential differences in degradation behaviour between test and reference product.

The studies under accelerated conditions were concluded with the overall message that there is no difference in degradation behaviour under accelerated storage conditions. The initial levels of degradation products sometimes differed between test and reference product, but the rate of degradation was considered the same for all parameters /quality attributes investigated except PS20 content.

During forced degradation studies, the reference product showed a higher deamidation rate while the test product showed a higher oxidation rate. It is acknowledged that the forced degradation conditions are harsh and aren´t relevant for the stability of the FP under long-term storage conditions. However, compared to the reference product, a higher susceptibility of the test product to oxidative degradation was observed. In order to elucidate the route cause for this behaviour, comprehensively designed studies were presented. Besides, the company included a method into the FP specification to ensure adequate control of Met oxidation during shelf life of the finished product.

The conclusion on similarity of the test product to the reference product can therefore be supported since the company could exclude that structural differences of aflibercept are responsible for the different susceptibility to oxidative stress. The company elucidated that inactive components are responsible for this different behaviour, hence biosimilarity can be concluded based on the results of the comparability exercise performed.

Table 1:Summary of similarity testing results – Vial & PFS FP vs. EU-Eylea vial & PFS FP similarity ranges

Attribute	**Parameter**	**Key finding**
Primary structure	Primary sequence	Identical
	N-terminal amino acids	Identical
	Amino acid variations	

Attribute	Parameter	Key finding
	• C-terminal lysine loss [%] • Deamidation [%] • Oxidation [%]	Similar Minor difference with no impact on target binding and potency. Minor difference with no impact on target binding and potency
	Analysis of disulfide bonds	Identical
Higher order structure	UV/Vis absorbance spectra	Similar
	Secondary and tertiary structure	
	Helix content and β sheet content	
	Conformational stability	Within similarity range
Molecular weight	Intact molecular weight [Da]	Similar
	Apparent molecular weight (SDS-PAGE)	Similar
	Apparent molecular weight (SEC-MALS) [kDa]	Similar
	Apparent molecular weight (SV-AUC) [kDa]	Similar
Glycan structure	Occupancy of N-linked glycan chains [%]	Within similarity range
	N-linked oligosaccharide profile [%]	Minor differences correlating to reduced FcRIIIa binding. No impact on target binding and potency.
	O-linked oligosaccharide profile	Similar
	Monosaccharide composition [%] • GlcN content • GalN content • Gal content • Man content • Fuc content	Similar
	Quantitative sialic acid content	Similar
Purity and product- related impurities	Charge variant profile	Similar
	Monomer purity – SE-HPLC [%]	Similar
Protein content	Protein content [mg/mL]	Similar
Extinction coefficient	Mass extinction coefficient [$Lg^{-1}cm^{-1}$]	Similar
Potency – Neutralisation of the VEGF signaling pathways	Inhibition of VEGF induced cell proliferation	Similar
	Inhibition of VEGF induced cell migration	Similar
	Inhibition of VEGFR2 phosphorylation	Similar
Target binding	Binding to VEGF-A165 (relative potency) [%]	Similar with only 2 vial DP batches marginally outside the range attributed to inherent

Attribute	Parameter	Key finding
		assay variation. No impact on potency.
	Binding affinity (K_D) to the VEGF family	Similar with only a few batches marginally outside the stringent range
	Selectivity to the VEGF family	Similar
	Binding affinity (K_D) to PlGF and galectin-1	Similar with only a few batches outside of the stringent range for Galectin-1
Fc related activity	Binding affinity (KD) to Fc receptors • binding affinity to FcRI • binding affinity to FcRIIa • binding affinity to FcRIIIa_158V • binding affinity to FcRIIIa_158F • binding affinity to FcRn	Similar with only a few batches having slightly lower binding affinity for FcRIIa and all batches having lower binding affinity for FcRIIIa. No impact on safety and efficacy as effector functions are not relevant biological functions of SCD411.
	Binding affinity to C1q	Similar
	Absence of ADCC	Similar
	Absence of CDC	Similar

2.2.3.6. Adventitious agents

Apart from the CHO expression cell line, no materials of animal origin were used in the AS and FP manufacturing processes. Cell line origin and adaption to suspension growth in chemically defined media is described. Information on measures and controls concerning non-viral adventitious agents including TSE is considered adequate.

Extensive testing for viruses has been performed on the MCB and PPCs and limited testing on the WCB. The testing program is acceptable. There was no evidence for contamination with adventitious viruses apart from intracytoplasmic A-type retrovirus-like particles.

Virus validation studies have been performed on two chromatography steps, low pH treatment and virus filtration. Four model viruses were chosen. Down-scaling for the column steps, low pH and virus filtration is considered appropriate. Virus validation studies were considered adequate.

In summary, virus clearance data presented by the applicant show that the purification process contains several steps with orthogonal mechanism, which are considered effective for eliminating potential viral contamination. As regards the safety calculation for retrovirus-like particles a high safety margin was demonstrated. Adequate information has been provided in relation to virus safety.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

This product is presented as a solution for injection 40 mg/mL aflibercept and is available in two presentations: vial and PFS.

From a quality point of view, the application is considered approvable. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

For the manufacturing site of AS and FP, the compliance with EU-GMP was not demonstrated and a MO was raised. During the assessment, the GMP compliance was confirmed and the corresponding EU-GMP certificate is provided.

Essential information on the active substance manufacturing process including flow chart and detailed description has been provided. AS is manufactured using CHO cells. Active substance manufacture encompasses upstream expansion of cells until harvest and downstream purification processing comprising chromatographic steps. The AS manufacturing process and process validation is in general adequately described. The AS was characterised with sufficient detail. With respect to characterisation of impurities, the method panel for product-related impurities was amended with orthogonal methods. An acceptable AS specification with test parameter, analytical methods and acceptance criteria has been provided.

The FP manufacturing process has been described in adequate detail, including development and control strategy.

A second MO was raised due to missing information on the medical device. This was considered solved during the assessment by provision of a Notified Body Opinion and detailed documentation for the PFS.

Biosimilarity evaluation was performed based on an acceptable number of reference product batches for setting acceptance criteria for similarity evaluation. The panel of methods performed is satisfactory covering structural as well as biologicals quality attributes with the necessary level of depth. Similarity criteria were overall achieved for all tests performed with minor excursions for single batches most likely attributable to analytical variability. The only exception is an expected difference in binding behaviour for one of the Fcγ-receptors – not considered relevant for efficacy and safety. During comparative forced degradation studies, a higher susceptibility of the test product towards oxidation was observed as compared to the reference product. Substantial clarification on the root causes for this different kinetics of degradation under oxidative stress was provided and hence allowed a scientifically sound conclusion on biosimilarity.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to AS process control and specifications acceptance criteria and FP shipping qualification study. These points are put forward and agreed as recommendations for future quality development.

2.2.5. Conclusions on chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

Biosimilarity can be concluded based on the results of the comparability exercise performed.

For future quality development, 3 points were agreed as recommendations which pertain to re-evaluation of the AS process control and specifications acceptance criteria, and the FP shipping qualification study.

In conclusion, the dossier presented by the applicant for the marketing authorisation application contains adequate and complete information, to support the approval of this application.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. For the active substance manufacturing process, process control acceptance criteria should be re-evaluated after completion of 30 commercial scale batches by end of Q2 of 2028.

2. For the active substance specification, acceptance criteria should be re-evaluated for certain quality attributes after completion of 30 commercial scale batches by end of Q2 of 2028.

3. For the finished product, results of the shipping process qualification study should be provided by Q3 of 2026.

2.3. Non-clinical aspects

2.3.1. Introduction

In vitro studies were conducted as part of the quality comparability exercise program. Further non-clinical *in vivo* studies are not required.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

In the submitted non-clinical overview and summary, the applicant concluded that the results of the *in vitro* pharmacology exercises are considered to confirm a high degree of similarity between Vgenfli and Eylea® reference product in terms of their primary pharmacodynamic properties. These *in vitro* primary pharmacodynamic studies were conducted as part of the quality comparability exercise program.

The "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA/CHMP/BMWP/403543/2010] states that *in vivo* animal studies may not be considered necessary if the comparability exercise between the test product and the reference product is considered satisfactory in the *in vitro* studies, and no other factors of concerns are identified. In line with the quoted CHMP Scientific Advice (EMEA/H/SA/3594/1/2017/III), it is agreed that further non-clinical *in vivo* studies would not contribute to the bio-similarity exercise.

2.3.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.2.3. Safety pharmacology programme

No safety pharmacology studies have been submitted in line with the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.2.4. Pharmacodynamic drug interactions

No comparative studies assessing pharmacodynamic drug interactions have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

2.3.3. Pharmacokinetics

In line with the CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), requested by the applicant in preparation of the proposed biosimilar product application, standard comparative non-clinical *in vivo* studies in animals are not deemed to add significant information to the similarity approach. Due to their high variability, animal models are valued to be too insensitive to highlight differences in comparative studies on pharmacokinetic as well as safety levels.

2.3.4. Toxicology

In line with the CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), requested by the applicant in preparation of the proposed biosimilar product application, standard comparative non-clinical *in vivo* studies in animals are not deemed to add significant information to the similarity approach. Due to their high variability, animal models are valued to be too insensitive to highlight differences in comparative studies on pharmacokinetic as well as safety levels.

The Vgenfli formulation is a solution in water for injections containing the excipients sodium acetate trihydrate, acetic acid, sucrose, sodium chloride, and polysorbate 20. Compared to the list of excipients of the reference medicinal product Eylea®, and as mentioned in the CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), no new excipient or any excipient of concern is identified. The excipients are therefore considered well established for the intended intravitreal administration with no anticipated safety concerns.

2.3.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not submitting any environmental risk assessment studies since the proposed biosimilar product, Vgenfli, is intended to substitute the reference medicinal product on the market. Therefore, the approval of Vgenfli will not result in an increase of the total quantity of the recombinant aflibercept active substance released into the environment and will hence not result in an increase of risk to the environment.

The submitted justification to not submit ERA studies is endorsed as it is agreed that the proposed biosimilar medicinal product is intended for substitution of the reference medicinal product and will therefore not lead to an increased exposure to the environment. Moreover, in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use, since the proposed product, Vgenfli, is a protein, no ERA studies are required to be submitted since due to its nature, it is unlikely to result in a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In the submitted non-clinical overview and summary, the applicant concluded that the results of the *in vitro* pharmacology exercises are considered to confirm a high degree of similarity between Vgenfli and Eylea® reference product in terms of their primary pharmacodynamic properties. These *in vitro* primary pharmacodynamic studies were conducted as part of the quality comparability exercise program.

The "Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues" [EMA/CHMP/BMWP/403543/2010] states that *in vivo* animal studies may not be considered necessary if the comparability exercise between the test product and the reference product is considered satisfactory in the *in vitro* studies, and no other factors of concerns are identified. In line with the quoted CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), it is agreed that further non-clinical *in vivo* studies would not contribute to the bio-similarity exercise.

No secondary pharmacodynamic studies, no safety pharmacology studies, and no comparative studies assessing pharmacodynamic drug interactions have been submitted in line with relevant guidelines including the CHMP guidance on similar biological medicinal products containing monoclonal antibodies (EMA/CHMP/BMWP/403543/2010).

Pharmacokinetics

In line with the CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), requested by the applicant in preparation of the proposed biosimilar product application, standard comparative non-clinical *in vivo* studies in animals are not deemed to add significant information to the similarity approach. Due to their high variability, animal models are valued to be too insensitive to highlight differences in comparative studies on pharmacokinetic as well as safety levels. The CHMP agrees that further non-clinical *in vivo* studies would not contribute to the bio-similarity exercise.

Toxicology & Environmental risk assessment

In line with the CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), requested by the applicant in preparation of the proposed biosimilar product application, standard comparative non-clinical *in vivo* studies in animals are not deemed to add significant information to the similarity approach. Due to their high variability, animal models are valued to be too insensitive to highlight differences in comparative studies on pharmacokinetic as well as safety levels. The CHMP agrees that further non-clinical *in vivo* studies would not contribute to the bio-similarity exercise.

The non-clinical data in the proposed biosimilar product SmPC is aligned to the latest approved SmPC published for the centrally authorised reference medicinal product Eylea®. The non-clinical data in the proposed SmPC is therefore acceptable.

The product Vgenfli is a biosimilar medicinal product. The active substance, aflibercept, is a protein, the use of which is not expected to pose a risk to the environment. Moreover, aflibercept is already used in existing marketed products including the reference medicinal product and no significant increase in environmental exposure is anticipated. An environmental risk assessment is therefore not required.

2.3.7. Conclusion on the non-clinical aspects

In vitro primary pharmacodynamic studies were conducted as part of the quality comparability exercise program. In line with the quoted CHMP scientific advice (EMEA/H/SA/3594/1/2017/III), and the relevant EMA scientific guidelines on similar biological medicinal products, it is agreed that further non-clinical *in vivo* studies are not required. In line with the relevant EMA scientific guidelines on similar biological medicinal products, no secondary pharmacodynamic studies, no safety pharmacology studies, and no comparative studies assessing pharmacodynamic drug interactions are required.

No non-clinical *in vivo* pharmacokinetic studies are required to be submitted.

No non-clinical *in vivo* toxicity studies are required to be submitted. The non-clinical data in the proposed SmPC is acceptable.

The SCD411 formulation of aflibercept contains only well-established excipients of pharmacopoeial quality but not novel excipients as defined in the Guideline on Excipients in the Dossier for MAA of a Medicinal Product (EMEA/CHMP/QWP/396951/2006). The differences between SCD411 and the RMP are the buffer system, the concentration of two excipients, and the pH. None of these differences is expected to pose a safety concern for the SCD411 similarity exercise.

The quality comparability exercise program in the Quality part of the dossier includes in vitro primary pharmacology studies. A high degree of similarity between the proposed drug product, SCD411, and the EU Eylea reference product for target binding affinity and functional biological activity was demonstrated.

No in vivo pharmacology, pharmacokinetic, or toxicology studies were submitted; however, the applicant performed a single-dose PK study in rabbits and a repeat-dose toxicity study in cynomolgus monkeys to meet global (PMDA) requirements. It is not believed that standard comparative non-clinical in vivo animal research significantly advances the similarity strategy. Animal models are thought to be too insensitive to highlight differences in comparative research on safety and pharmacokinetic levels because of their high variability. It is neither warranted nor recommended to perform additional non-clinical in vivo research given the substantial similarity between SCD411 and the RMP.

In the case of biosimilars, an environmental risk assessment is not needed; the applicant's justification is acceptable.

Overall, the nonclinical in vitro package that was provided is deemed acceptable, and no unexpected results were noticed. No further concerns were raised due to the lack of unexpected findings or results. There were no major differences between SCD411 and the comparator sourced from the EU from a nonclinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

Table 2: Tabular overview of clinical studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
Study SCD411-CP101	Phase 3 BE study to demonstrate biosimilarity between VGENFLI and Eylea Randomized, double masked,	576 subjects with wet AMD were enrolled in this study across approximately 155 sites in 14 countries. Males – 277 (48,3%)	Subjects were treated with study treatment every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48	The exploratory objective of this study was the comparison of PK parameters of VGENFLI (SCD411) and Eylea and the quantification of free and bound Eylea and VGENFLI (SCD411). A subset of approximately 40

	parallel group and multicentre; Subjects were randomly assigned in 1:1 ratio to receive VGENFLI (SCD411) or Eylea IVT injections Phase 3 efficacy, safety, tolerability, PK, and immunoge-nicety	Females – 296 (51,7%) White – 382 (66,7%) Asian – 187 (32,6%) Not Hispanic nor Latino – 554 (96,7%) **Subset** A subset of 44 patients (N=23 VGENFLI (SCD411) N=21 Eylea) was to be selected for collection of PK samples.	VGENFLI (SCD411): 40 mg/mL, liquid in (single-use) vial, 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 m	subjects (20 per group) was selected for collection of PK samples. • Free (plasma) and total (serum) aflibercept concentrations at Baseline (pre-dose) and 24 hours after the first and third injections • Systemic VEGF concentration assessments[2] at Week 48 (pre-dose) and Week 52 • Serum antibodies against aflibercept • Neutralizing anti-aflibercept antibodies (Nabs)

2.4.2. Clinical pharmacology

Aflibercept is administered IVT, directly at the site of action, and its efficacy is not associated with its systemic exposure. 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 substudy was included in study SCD411-CP101 to confirm that the low systemic concentrations of IVT administered SCD411 (Vgenfli) and Eylea EU were within the same range.

Analytical methods

The validated analytical method ECL-0358 (CB-2277) was used for the determination of free SCD411 in human plasma using electrochemiluminescence (ECL) assay. A biotinylated recombinant human VEGF isoform 165 was used as capture reagent and [redacted] antibody was used as detection reagent. The lower limit of quantification (LLOQ) was [redacted] ng/mL, and the upper limit of quantification (ULOQ) was [redacted] ng/mL. The quality concentrations were [redacted] ng/mL (higher), [redacted] ng/mL (middle), and [redacted] ng/mL (lower).

The validated analytical method ECL-0435 (CB-2517) was used for the determination of free Eylea in human plasma using ECL assay. A biotinylated recombinant human VEGF isoform 165 was used as capture reagent and [redacted] antibody was used as

detection reagent. The LLOQ was [redacted] ng/mL, and the ULOQ was [redacted] ng/mL. The quality concentrations were [redacted] ng/mL (higher), [redacted] ng/mL (middle), and [redacted] ng/mL (lower). The validated analytical method 22PK016 was used for the determination of VEGF-SCD411 complex and VEGF-Eylea complex in human plasma using ECL assay. This immunoassay is a sandwich ECL assay based on Meso Scale Discovery technology. A biotinylated antihuman VEGF165 was used as capture reagent and [redacted] antibody was used as detection reagent. The LLOQ was [redacted] ng/mL, and the ULOQ was [redacted] ng/mL (Bioanalytical Sample Analysis Report).

The validated analytical method ECL-0365 (CB-2293, CB-2294, CB-2295) was used for the detection of antibodies to VGENFLI (SCD411) in human serum using ECL assay. A [redacted] (SCD411) was used as capture reagent and [redacted] was used as detection reagent (Bioanalytical Sample Analysis Report).

The validated analytical method ECL-0409 (CB-2445) was used for the detection of neutralizing antibodies to VGENFLI (SCD411) in human serum using ECL assay. A biotinylated VEGF was used as capture reagent and [redacted] was used as detection reagent (Bioanalytical Sample Analysis Report).

2.4.2.1. Validation of an Electrochemiluminescence (ECL) Assay for the Quantification of Complex VEGF: SCD411 DP and Complex VEGF: EYLEA in Human Plasma

Summary description of the method

Briefly, the streptavidin pre-coated surface of MSD GOLD 96-well QuickPlex plate is saturated with biotinylated VEGF165 in order to constrain the capture reagent on a solid phase. After the minimal required dilution (MRD 1[redacted]), unknown samples, calibration standards and quality controls are incubated in pre-coated and washed MSD microplates. During this assay step, the analyte, is specifically captured while the unbound material can be removed. Following a wash cycle, SCD411 and EYLEA proteins specifically bound to the $VEGF_{165}$ protein are detected adding [redacted] antibody. After a final wash step, MSD Read Buffer is added and signals acquired using the MESO QuickPlex SQ 120 reader and the calculations are performed in Watson software version 7.5.1 or higher.

MSD's electrochemiluminescence detection technology exploits [redacted] labels that emit light upon electrochemical stimulation initiated at the electrode surface of MSD microplates. The measured ECL signals are directly proportional to the quantity of SCD411 and EYLEA in calibration standards, quality controls or samples.

METHOD SUMMARY

Validation Study Number:	8445-456
Analyte name(s):	VEGF165-SCD411 Complex
Species Matrix:	Human Sodium Heparin Plasma
Lower Limit of Quantitation (LLOQ):	[redacted] ng/mL
Upper Limit of Quantitation [redacted]OQ):	[redacted] ng/mL
Suggested Sample Aliquot Size:	1.0 mL requested (0.5 mL minimum)
Minimum Required Dilution (MRD):	1/[redacted]
Plate Type: [redacted]	MSD GOLD™ 96-Well Streptavidin QuickPlex Plate, Cat. N[redacted]
Capture Reagent:	VEGF165, rHuman, Biotin
Detection Reagent:	[redacted]
Curve Fit; Weighting Factor:	4-PL; $1/y^2$
Sample Storage Temperature:	-60°C to -80°C
Freeze/Thaw Stability:	Up to [redacted] freeze-thaw cycles at nominal -20°C Up to [redacted] freeze-thaw cycles at nominal -70°C
Room Temperature Stability:	Up to [redacted] hour[redacted] minutes
Refrigerated Stability:	Up to [redacted] hours [redacted] minutes
Long Term Stability:	[redacted] days at nominal -20°C and -70°C, on-going
Method Selectivity:	Passing: normal, hemolyzed, lipemic, disease state
Dilution Linearity:	1/[redacted]
Assay-specific Training Required:	No
Original Author:	Labcorp Early Development Laboratories Inc.

	Concentrations		
	Nominal Concentration	Three decimal places	
	Standard Deviation	One decimal place	
	Percentage Values	One decimal place	

17.1 Appendix 1: Validated Parameters Summary

Validation				
	Validation Title	Validation of an Electrochemiluminescence (ECL) Assay for the Quantification of Complex VEGF: SCD411 DP and Complex VEGF: EYLEA in Human Plasma		
	Validation ID(s)	8445-456		
Range Qualification				
	Population	**Calibration Standard Concentration (ng/mL)**	**Anchor Points (ng/mL)**	**Source Reference**
	Normal Human Plasma	[redacted]	[redacted] (lower), [redacted] (upper)	Table 1
Inter- and Intra-Assay Accuracy and Precision				
	Population	**QC Concentration (ng/mL)**	**Intra-Assay %Bias %CV**	**Inter-Assay %Bias %CV**	**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	LLOQ: [redacted]	%Bias = [redacted]% %CV = [redacted]%	%Bias = [redacted]% %CV = [redacted]%	Table 4
		LQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		MQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		HQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		ULOQ: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
	Normal Human Plasma (VEGF: EYLEA)	LLOQ: [redacted]	%Bias = [redacted]% %CV = [redacted]%	%Bias = [redacted]% %CV = [redacted]%	Table 19
		LQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		MQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		HQC: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
		ULOQ: [redacted]	%Bias = [redacted]% %CV = [redacted]%		
Selectivity (Matrix interference)					
	Individual Population	**QC Concentration (ng/mL)**	**Met Criteria**		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Blank	[redacted]/10		Table 5
		LLOQ ([redacted])	[redacted]/10		
		HQC ([redacted])	[redacted]/10		
		Overall Pass rate	[redacted]/10 ([redacted]%)		
	Disease State (Age-Related Macular Degeneration) Human Plasma (VEGF: SCD411)	Blank	[redacted]/10		Table 6
		LLOQ ([redacted])	[redacted]/10		
		HQC ([redacted])	[redacted]/10		
		Overall Pass rate	[redacted]/10 ([redacted]%)		
	Normal Human Plasma (VEGF: EYLEA)	Blank	[redacted]/10		Table 21
		LLOQ ([redacted])	[redacted]/10		
		HQC ([redacted])	[redacted]/10		
		Overall Pass rate	[redacted]/10 ([redacted]%)		
	Disease State (Age-Related Macular Degeneration)	Blank	[redacted]/10		Table 22

	Human Plasma (VEGF: EYLEA)				
		LLOQ [redacted]	/10		
		HQC [redacted]	/10		
		Overall Pass rate	/10 ([redacted]%)		

Lipemic Selectivity

	Individual Population	QC Concentration (ng/mL)	Met Criteria		Source Reference
	Normal Human Plasma (VEGF: SCD411)	Blank	/5		Table 7
		LLOQ [redacted]	/5		
		HQC [redacted]	/5		
		Overall Pass rate	/5 ([redacted]%)		
	Normal Human Plasma (VEGF: EYLEA)	Blank	/5		Table 24
		LLOQ [redacted]	/5		
		HQC [redacted]	/5		
		Overall Pass rate	/5 ([redacted]%)		

Hemolyzed Selectivity

	Individual Population	QC Concentration (ng/mL)	Met Criteria		Source Reference
	Normal Human Plasma (VEGF: SCD411)	Blank	/5		Table 8
		LLOQ [redacted]	/5		
		HQC [redacted]	/5		
		Overall Pass rate	/5 [redacted]%)		
	Normal Human Plasma (VEGF: EYLEA)	Blank	/5		Table 23
		LLOQ [redacted]	/5		
		HQC [redacted]	/5		
		Overall Pass rate	/5 [redacted]%)		

Dilution Linearity

	Population	UHQC Concentration (ng/mL)	Highest Dilution Achieved	Diluent for Additional Dilution	Source Reference
	Normal Human Plasma (VEGF: SCD411)	[redacted]	1 in [redacted]	Sample Dilution Buffer	Table 9
	Normal Human Plasma (VEGF: EYLEA)	[redacted]	1 in [redacted]	Sample Dilution Buffer	Table 20

Hook Effect

	Population		Source Reference
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: No apparent hook effect observed at concentrations up to [redacted] ng/mL	Table 9
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: No apparent hook effect observed at concentrations up to [redacted] ng/mL	Table 20

Specificity

	Population	Source Reference

	Normal Human Plasma	Met Criteria: No apparent specificity observed at LLOQ and ULOQ in the presence of up to [redacted] ng/mL of Human IgG	Table 10
Freeze-Thaw Stability (-15 to -30C)			
	Population		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: [redacted] cycles thawed for [redacted] hr ± [redacted] min cumulatively at Room Temperature	Table 11
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: [redacted] cycles thawed for [redacted] hr ± [redacted] min cumulatively at Room Temperature	Table 25
Freeze-Thaw Stability (-60 to -80C)			
	Population		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: [redacted] cycles thawed for [redacted] hr ± [redacted] min cumulatively at Room Temperature	Table 12
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: [redacted] cycles thawed for [redacted] hr ± [redacted] min cumulatively at Room Temperature	Table 26
Bench Top Stability			
	Population		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: [redacted] hours at Room Temperature	Table 13
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: [redacted] hours at Room Temperature	Table 28
Refrigerated Stability			
	Population		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: [redacted] hours at 2-8 °C	Table 14
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: [redacted] hours at 2-8 °C	Table 27
Long Term Stability			
	Population		**Source Reference**
	Normal Human Plasma (VEGF: SCD411)	Met Criteria: [redacted] days stored at -15 to -30°C	Table 17
		Met Criteria: [redacted] days stored at -60 to -80°C	Table 18
	Normal Human Plasma (VEGF: EYLEA)	Met Criteria: [redacted] days stored at -15 to -30°C	Table 31
		Met Criteria: [redacted] days stored at -60 to -80°C	Table 32
Run Information			
	Run size (Exclusive of Calibrators and Assay Run Controls)		
	1 plate holds 41 samples		

2.4.2.2. Validation of a Method for the Determination of Free SCD411 DP in Human Plasma using Electrochemiluminescence (ECL) and Validation of a Method for the Determination of Free EYLEA in Human Plasma using Electrochemiluminescence (ECL)

The two methods are essentially the same; therefore, they are described only once. The results are signalled to distinguish the difference between the two methods.

Summary description of the method

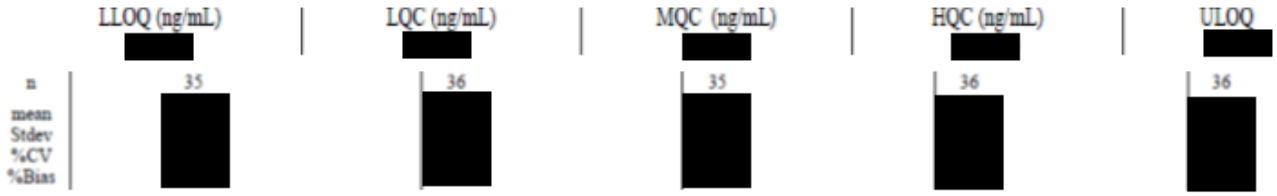
The principle of the method is to quantify free SCD411 in human plasma. The assay begins with MSD streptavidin coated microtiter plates coated with biotinylated VEGF165. Following the capture incubation, the plates are washed and blocking buffer is added and incubated. Another wash step follows and then calibrators, controls and samples which have pre-diluted to the MRD are added to the plates and incubated. Another wash step follows, and then the detection antibody, [redacted] is added and incubated. Following a final wash step, a 2X MSD read buffer is added to all the wells. The plate is then read using the MSD SQ120 QuickPlex. Results are expressed in Relative Light Unit (RLU), producing a signal in proportion to the binding activity of SCD411 in human plasma. The signal data is recorded by the MSD instrument and analysed in Watson 7.5.1 or higher version.

MSD's electroluminescence detection technology exploits [redacted] that emit light upon electrochemical simulation initiated at the electrode surface of MSD microplates. The measured ECL signals are directly proportional to the quantity of SCD411 and Eylea in calibration standards, quality controls or samples.

Validation Study Number:	8445-454
Mnemonic:	CB-2277
Method Type:	Electrochemiluminescence (ECL)
Curve Fit; Weighting Factor:	4-Parameter Logistic (4-PL); $1/Y^2$
Analyte Name(s):	SCD411 DP
Species Matrix:	Human Plasma
Sample Volume:	1.0 mL requested (0.5 mL minimum)
Calibrator/Quality Control:	SCD411 DP
Plate type:	MSD streptavidin coated plates L55SA-1
Capture Reagent:	Biotinylated Recombinant Human VEGF, Isoform 165 (Biotin-rHuVEGF$_{165}$)
Detection Reagents:	[redacted]
Minimum Required Dilution (MRD):	1[redacted]
Lower Limit of Quantitation (LLOQ):	[redacted] ng/mL
Upper Limit of Quantitation (ULOQ):	[redacted] ng/mL
Sample Storage Temperature:	-60 to -80°C
Freeze/Thaw Stability:	Up to [redacted] cycles at nominal -70°C Up to [redacted] cycles at nominal -20°C
Room Temperature Stability:	Up to [redacted] hours, [redacted] minutes
Refrigerated Temperature (2 to 8°C) Stability:	Up to [redacted] hours, [redacted] minutes
Long Term Stability:	Up to [redacted] days at nominal -70°C, on-going Up to [redacted] days at nominal -20°C, on-going
Dilutional Linearity:	Linearity shown for up to a 1/[redacted] dilution
Method Developed By:	Labcorp Early Development Laboratories Inc.

No summary is provided for the parameter results achieved during validation of his method. Therefore, a few examples were drawn from the full report with extensive detailed results tables.

As an example, extracts of the tables for Intra (within) and Inter (between) assay Bias and Precision of Quality Control Sample Data for SCD411 DP in Human Plasma as well as for the overall quality control sample data are presented.



The same is presented for the Eylea method

Overall Quality Control Sample Data for EYLEA in Human Plasma

Analytical Run # CB-2517-8445-455-	Watson run ID	Replicate	LQC (ng/mL)				MQC (ng/mL)				HQC (ng/mL)			
			Result	%Bias	Mean Result	%CV	Result	%Bias	Mean Result	%CV	Result	%Bias	Mean Result	%CV
stats of passing runs only	n		68				68				68			
	mean													
	Stdev													
	%CV													
	%Bias													
	%TE													
stats of all runs	n		73				73				73			
	mean													
	Stdev													
	%CV													
	%Bias													

2.4.2.3. Validation for the Detection, Confirmation, and Titration of Anti-EYLEA and Anti-SCD411 Antibodies in Human Serum

A quasi-quantitative assay for the determination of anti-SCD411 antibodies in human serum was successfully validated for a run size of up to 41 samples (analysed in duplicate and inclusive of a Negative Control (NC), Positive Controls (PC) and validation samples).

PRINCIPLES OF THE METHOD

Screening Assay

The screening assay involves diluting the PCs, NCs and samples to an MRD in assay buffer, followed by acid dissociation. Then the acid dissociated and neutralized controls and serum samples are mixed with [redacted] and [redacted]) to allow anti-SCD411 antibodies in the samples to form a complex with the labelled SCD411 moieties, followed by addition of the mixtures to a Streptavidin coated plate that is blocked prior to use. The [redacted] in the complex will bind to the Streptavidin in the wells, allowing unbound material to be washed away. The plate is then washed and a tripropylamine (TPA) containing MSD read buffer is added to the plate. In the presence of TPA and electric current, ruthenium produces a chemiluminescent signal. Only the controls and samples that contain antibody bound to both [redacted] and [redacted] will generate chemiluminescent response. The signal produced is proportional to the amount of anti-SCD411 present in serum.

Confirmation Assay

Samples that test positive in the screening assay are further evaluated in a confirmation assay. Samples are diluted to MRD with assay buffer or assay buffer containing excess drug. The mixtures are incubated and then tested as described previously for the screening assay procedure.

Titration Assay

Samples that tested positive in the confirmation assay are analyzed in a titration assay to determine the titer. The titration assay follows the same format as the screening assay except that samples are diluted incrementally with blank negative control matrix (or NC) prior to MRD. The titer of a sample is determined as the reciprocal of the value, which is calculated by multiplying the MRD of the assay, by the highest serial dilution yielding a response greater than or equal to the screening assay cut point and the following dilution yielding a response below the assay cut point.

Validated Method:	ECL-0365 (Screen: CB-2293, Confirm: CB-2294, Titer: CB-2295)
Species:	Human
Matrix:	Serum
Analyte:	Antibodies to SCD411
Positive Control Levels:	[redacted] ng/mL (LPC2) [redacted] ng/mL (MPC) [redacted] ng/mL (HPC)
Minimum Required Dilution (MRD)	1 in[redacted]
Normalization Factor:	[redacted]
Screening Cutpoint:	Mean NC response x[redacted]
Confirmation Cutpoint:	[redacted]%
Intra and Inter-assay Precision (Screening):	Requirements fulfilled
Intra and Inter-assay Precision (Confirmation):	Requirements fulfilled
Relative Sensitivity:	[redacted] ng/mL
Drug Tolerance:	PC at [redacted] ng/mL can be detected in the presence of [redacted] µg/mL of SCD411. PC at [redacted] ng/mL can be detected in the presence of [redacted] µg/mL of EYLEA.
Selectivity (Individual Recovery):	Requirements fulfilled
Hook Effect (Prozone):	Absence of a hook effect observed up to [redacted] ng/mL
Specificity:	Requirements fulfilled
Freeze/Thaw Stability:	Up to [redacted] freeze/thaw cycles
Bench Top Stability:	Up to [redacted] hours [redacted] minutes
Refrigerator Stability (2 to 8°C):	Up to [redacted] hours [redacted] minutes

The data in the provided report indicates that the method described is suitable for the detection of anti- SCD411 antibodies in human serum and has been successfully validated for a run size of up to 41 samples, as per the summary of validated parameters.

Intra/Inter-assay Precision

Screening

Screening intra-assay and inter-assay precision for SCD411 was assessed in analytical runs Val-067 to Val-069 and Val-074 to Val-076. Three sets of controls were analyzed on each plate, by at least two analysts over two days. Within each analytical run the intra-assay precision was calculated (%CVmean), all runs achieved target criteria at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) and within a precision range of %-%.

The Inter-assay precision at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) was determined from the %CV of the mean responses over the six analytical runs. All PC levels were acceptable and within the target criteria of ≤20%. Screening intra-assay and inter-assay precision for EYLEA was assessed in analytical runs Val-055 to Val-060. Three sets of controls were analyzed on each plate, by at least two analysts over two days. Within each analytical run the intra-assay precision was calculated (%CV mean), all runs achieved target criteria at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) and within a precision range of %-%, except for the MPC (%) and HPC (%) level in Val-060, which failed this parameter due to unverifiable QC concentrations. The Inter-assay precision at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) was determined from the %CV of the mean responses over the six analytical runs. All PC levels were acceptable and within the target criteria of ≤20%.

Confirmation

Confirmation intra-assay and inter-assay precision for SCD411 was assessed. Three sets of controls (with and without drug) were analysed on each plate, by at least two analysts over two days. The intra-and inter-assay precision was calculated using the method of analysis of variance (ANOVA). The intra-assay precision of the %inhibition was assessed using a pooled coefficient of variation (%CV mean) which was assessed at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels, all PCs were acceptable and within the target criteria of ⩽20%. Within each analytical run the intra-assay precision of the %inhibition was calculated (%CV mean), all runs achieved target criteria at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels and within a precision range of %-%, except the LPC2 level in Val-068, which had a %CV mean of %.

The inter-assay precision of the %inhibition at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels was determined from the %CV over the six analytical runs. All PC levels were acceptable and within the target criteria of ⩽20%, excluding the data from Val-068.

Confirmation intra-assay and inter-assay precision for EYLEA was assessed in analytical runs Val-055 to Val-060. Three sets of controls (with and without drug) were analyzed on each plate, by at least two analysts over two days. The intra-and inter-assay precision was calculated using the method of analysis of variance (ANOVA). The intra-assay precision of the %inhibition was assessed using a pooled coefficient of variation (%CV mean) which was assessed at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels, all PCs were acceptable and within the target criteria of ⩽20%. Within each analytical run the intra-assay precision of the %inhibition was calculated (%CV mean), all runs achieved target criteria at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels and within a precision range of %-%, except the HPC level in Val-060, which had a %CVmean of %. The inter-assay precision of the %inhibition at the LPC2 (ng/mL), MPC (ng/mL), and HPC (ng/mL) levels was determined from the %CV over the six analytical runs. All PC levels were acceptable and within the target criteria of ⩽20%, excluding the data from Val-060.

Tables for Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-EYLEA and Anti SCD in Human Serum for LPC, MPC and HPC controls were extracted and are presented below.

Table 3: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-EYLEA in Human Serum LPC ([redacted] ng/mL)

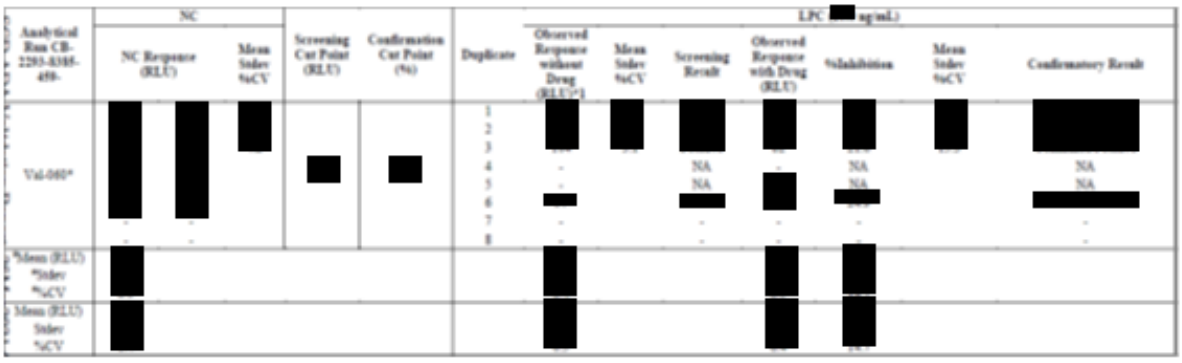


Table 4: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-EYLEA in Human Serum MPC ([redacted] ng/mL)

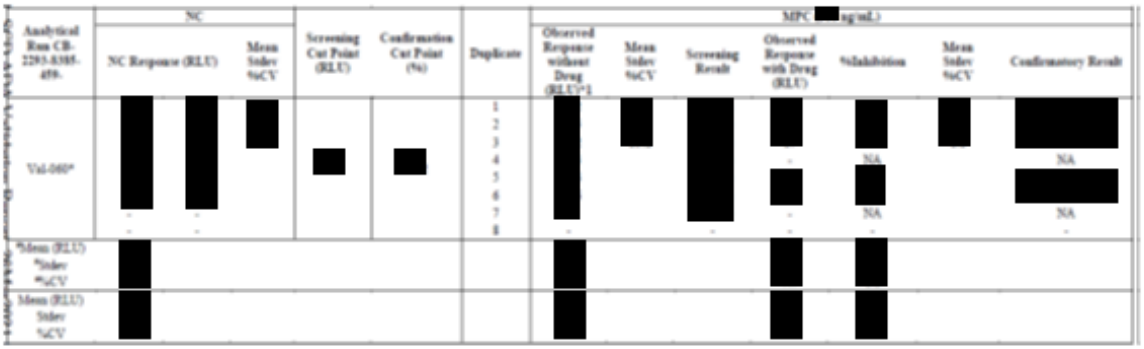


Table 5: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-EYLEA in Human Serum HPC ([redacted] ng/mL)

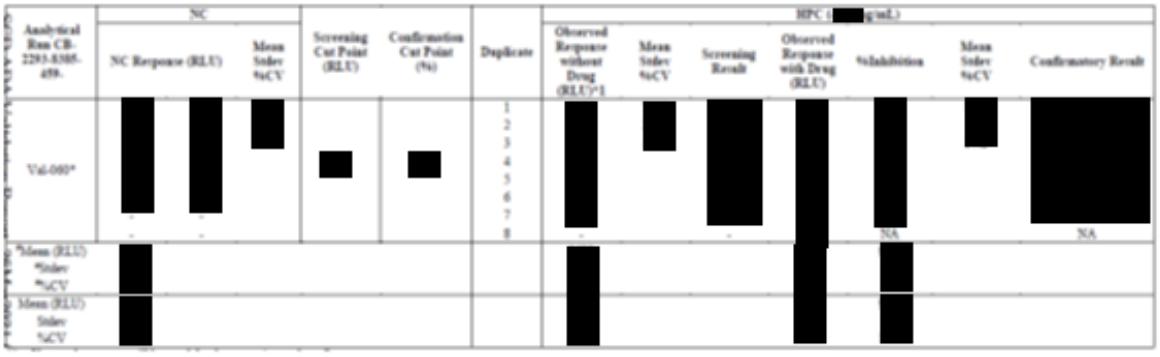


Table 6: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-SCD in Human Serum LPC ([redacted] ng/mL)

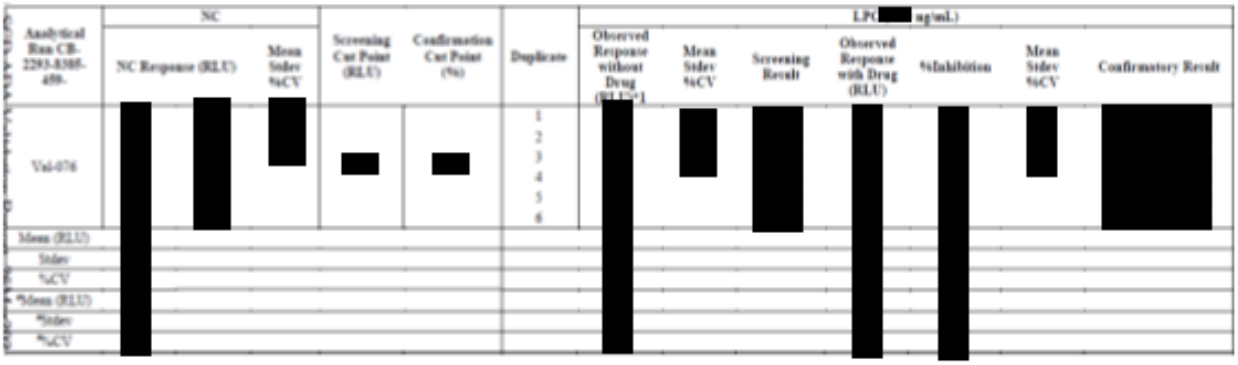


Table 7: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-SCD in Human Serum MPC ([redacted] ng/mL)

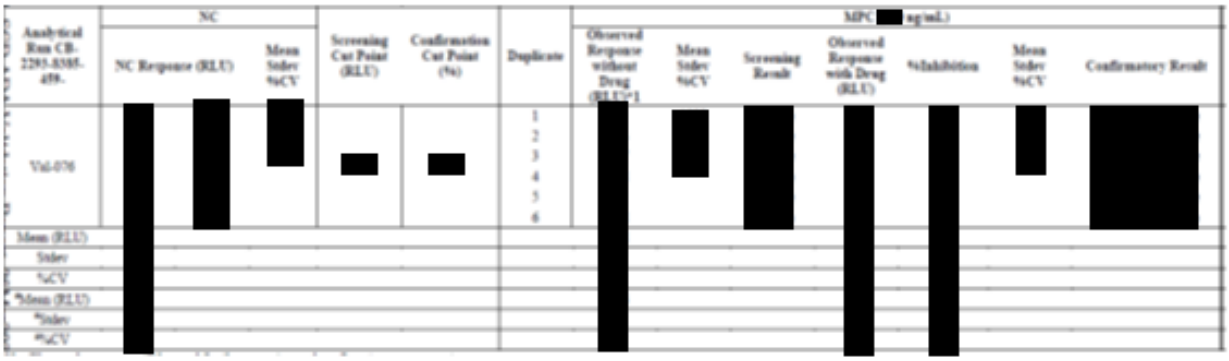


Table 8: Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-SCD in Human Serum HPC ([redacted] ng/mL)

freeze/thaw cycles (inclusive of the freeze/thaw analysis performed on the day of analysis). Precision was acceptable at LPC and HPC for all cycles and RLU responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] freeze/thaw cycles when stored at nominal -80ºC.

Bench Top Stability

Bench top stability was assessed in Val-098 after stability samples were subjected to [redacted] hours ± [redacted] hours at room temperature. Precision was acceptable at LPC and HPC for all cycles and RLU responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] hours and [redacted] minutes when stored on the bench at room temperature.

Refrigerator Stability

Refrigerator stability was assessed in Val-098 after stability samples were subjected to [redacted] hours ± [redacted] hours at 2 to 8°C. Precision was acceptable at LPC and HPC for all cycles and signal responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] hours and [redacted] minutes when stored refrigerated.

2.4.2.4. Validation of an Immunoassay for Detection of Neutralizing Antibodies to SCD411 in Human Serum

A qualitative assay for the detection of Neutralizing Antibodies (Nab) to SCD411 in human serum was successfully validated for a run size of up to 41 samples (analyzed in duplicate and inclusive of a Negative Control (NC), Positive Controls (PC) and validation samples).

The following table provides a summary of the validated parameters:

Table 9:Summary of the validated parameters

Validated Method:	ECL-0409 (Screen: CB-2445)
Species:	Human
Matrix:	Serum
Analyte:	Neutralizing Antibodies to SCD411
Positive Control Levels:	[redacted] ng/mL (LPC) [redacted] ng/mL (MPC) [redacted] ng/mL (HPC)
Minimum Required Dilution (MRD)	1 in [redacted] in assay buffer
Normalization Factor:	[redacted]
Screening Cutpoint:	Mean NC response x Normalization factor
Intra and Inter-assay Precision:	Requirements fulfilled
Drug Tolerance:	PC at [redacted] ng/mL can be detected in the presence of [redacted] to [redacted] ng/mL of SCD411
Selectivity (Normal, Lipemic, and Hemolyzed Individual Recovery):	Requirements fulfilled
Hook Effect (Prozone):	Absence of a hook effect observed up to [redacted] ng/mL
Freeze/Thaw Stability:	Up to [redacted] freeze/thaw cycles at nominal -20°C and -70°C
Bench Top Stability:	Up to [redacted] hours [redacted] minutes
Refrigerator Stability (2 to 8°C):	Up to [redacted] hours [redacted] minutes
Long Term Stability (LTS):	[redacted] days at nominal -70°C* [redacted] days at nominal -20°C*

Partial description of methods

LPC Determination Assessment

The LPC determination was assessed in analytical runs Val-013 to Val-016 by preparing by preparing [redacted]-fold serial dilutions of the positive control at a HPC level spanning the screening cutpoint in NC and tested in four assay runs by two analysts in two days. A back calculated concentration which was equivalent to the screen floating cutpoint (PSCP) was calculated for each dilution series. The LPC was calculated as per the Protocol, where the LPC was calculated at a 99% confidence level, which theoretically the LPC should generate a response which will be at or above the screening floating cutpoint (PSCP) for 99% of the data generated. From the assessment, the concentration for the LPC was determined as [redacted] ng/mL (Table 13).

Assay Sensitivity

Assay Sensitivity is defined as the lowest concentration at which a PC preparation consistently generated a signal above the CP in the assay. The sensitivity of the assay was assessed in analytical runs Val-013 to Val-016. The sensitivity of the assay was calculated to be [redacted] ng/mL (Table 14).

Intra/Inter-assay Precision

Screening

Screening intra-assay and inter-assay precision was assessed in analytical runs Val-021 to Val-026. Six sets of controls were analysed on each plate, by at least two analysts over two days. Within each

analytical run the intra-assay precision was calculated (%CV mean), all runs achieved target criteria at the LPC, MPC, and HPC and within a precision range of [redacted]%-[redacted]%, except for the HPC level in Val-023 and Val-024, which had a %CV mean of [redacted]% and [redacted]%, respectively.

The Inter-assay precision at the LPC, MPC, and HPC was determined from the %CV of the mean responses over the six analytical runs. The LPC and MPC levels were acceptable and within the target criteria of ⩽20% with a reported %CV of [redacted]% and [redacted]%, respectively; however, the HPC level reported a [redacted]% (Table 15). Since the intra-assay precision was acceptable and the variation between assay plates will be controlled by the established system suitability range, the slightly higher variation noted in the inter-assay precision is considered to have limited impact on clinical sample analysis. Additionally, target criteria of <20% will be utilized for sample analysis.

Titre Assessment

The titration assay precision was evaluated using the data generated from the determination of the LPC concentration analytical runs, Val-013 to Val-016. Titers were determined as a reciprocal of the value, which was calculated by multiplying the 1 in [redacted] (MRD) by the highest serial dilution at which the corresponding response was greater or equal to the floating cutpoint (PSCP). The median titer which was calculated across all runs was 1 in [redacted]. Titer sample intra and inter-assay precision were deemed acceptable when the individual titer determinants were ± 1 dilutions of the median target titer, allowing a dilution range of 1 in [redacted] to 1 in [redacted]. All titer determinants were within the range of the median target titer, which supported the intra-and inter-assay precision criteria was achievable within the assay (Table 15).

Table 10: Determination of the LPC concentration and intra/inter-assay precision for titration assay

Analytical Run CB-2280-8385-950	Screening Cut Point (RLU)	Duplicate	Concentration (ng/mL) 1 in X	Back Calculated Conc at PSCP (ng/mL)	Dilution ≥ PSCP
Val-013	[redacted]	1 2 3	[redacted]	[redacted]	[redacted]
Mean Response without Drug (RLU) Stdev %CV			[redacted]	- - -	- - -
Val-014	[redacted]	1 2 3	[redacted]	[redacted]	[redacted]
Mean Response without Drug (RLU) Stdev %CV			[redacted]	- - -	- - -
Val-015	[redacted]	1 2 3	[redacted]	[redacted]	[redacted]
Mean Response without Drug (RLU) Stdev %CV			[redacted]	- - -	- - -
Val-016	[redacted]	1 2 3	[redacted]	[redacted]	[redacted]
Mean Response without Drug (RLU) Stdev %CV			[redacted]	- - -	- - -

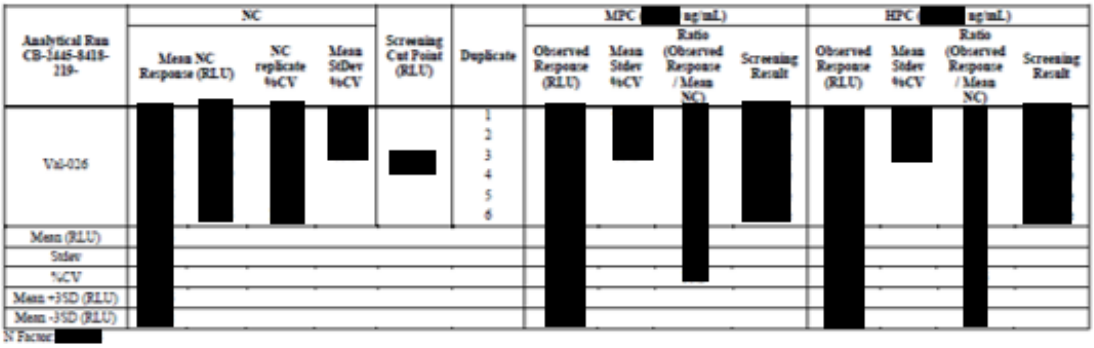
Bold - Value below and above cut point
NF Factor: [redacted]
Concentration at cut point =Forecast(Cutpoint,Concentration A:concentration B,Signal A: Signal B)

Inter-assay stats for Determination of the LPC Concentration		
	Back Calculated Conc at PSCP (ng/mL)	Dilution ≥ PSCP
Mean (ng/mL)	[redacted]	-
Stdev	[redacted]	-
%CV	[redacted]	-
LPC Conc (ng/mL) (Mean + [redacted] *SD)	[redacted]	-
Assay sensitivity (ng/mL (Mean+ [redacted] * SD)	[redacted]	-
Median target titer	-	[redacted]

Table 11: Intra & Inter-Assay Precision for Screening Assay

Analytical Run CB-2445-8418-219-	NC: Mean NC Response (RLU)	NC: NC replicate %CV	NC: Mean StDev %CV	Screening Cut Point (RLU)	Duplicate	LPC ([redacted] ng/mL): Observed Response (RLU)	LPC: Mean Stdev %CV	LPC: Ratio (Observed Response / Mean NC)	LPC: Screening Result
Val-026	[redacted]	[redacted]	[redacted]	[redacted]	1 2 3 4 5 6	[redacted]	[redacted]	[redacted]	[redacted]
Mean (RLU)									
Stdev									
%CV									
Mean +3SD (RLU)									
Mean -3SD (RLU)									

N Factor: [redacted]



Freeze/Thaw Stability

Freeze/thaw stability was assessed in Val-036 and Val-037 after stability samples were subjected to [redacted], [redacted], [redacted] and [redacted] freeze/thaw cycles (inclusive of the freeze/thaw analysis performed on the day of analysis). Precision was acceptable at LPC and HPC for all cycles and RLU responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] freeze/thaw cycles when stored at nominal -20ºC.

Bench Top Stability

Bench top stability was assessed in Val -036 after stability samples were subjected to [redacted] hours ± [redacted] hours at room temperature. Precision was acceptable at LPC and HPC for all cycles and RLU responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] hours and [redacted] minutes when stored on the bench at room temperature.

Refrigerator Stability

Refrigerator stability was assessed in Val-036 after stability samples were subjected to [redacted] hours ± [redacted] hours at 2 to 8°C. Precision was acceptable at LPC and HPC for all cycles and signal responses were within system suitability ranges. The data indicated that stability was retained for up to [redacted] hours and [redacted] minutes when stored refrigerated.

2.4.2.5. Final Bioanalytical Sample Analysis Report

2.4.2.5.1. Determination of SCD411 and Eylea® in Human Serum and Plasma Samples by ECL for Protocol Number SCD411-CP101 Clinical Study

Plasma samples received, analysed and reported

Table 12: Plasma samples

PK Plasma Samples Received		
	Primary Samples Received	984
	Back-up Samples Received	2
ECL-0358 (CB-2277)	Samples Analyzed	248
	Sample Results Reported	248
ECL-0435 (CB-2517)	Samples Analyzed	244
	Sample Results Reported	244
22PK016	Samples Analyzed	492
	Sample Results Reported	492

ADA Serum Samples Received		
ECL-0365 (CB-2293; CB-2294; CB-2295)	Primary Samples Received	3248
	Back-up Samples Received	63
	Samples Analyzed	3272 (including Back-up Samples)
	Sample Results Reported	3272 (including Back-up Samples)

NAb Serum Samples Received		
ECL-0409 (CB-2445)	Primary Samples Received	3246
	Back-up Samples Received	13
	Samples Analyzed	896
	Sample Results Reported	896

Reassay and incurred samples reanalysis

Incurred sample reproducibility (ISR) was performed on 33 total samples. One sample had an ISR result that was below the limit of quantitation, and one sample had one duplicate result outside of limit, neither are included in the overall ISR statistics. Therefore, of the 31 samples, [redacted]% met the required criteria indicating that the method generated reproducible results and was fit for purpose.

A total of four samples underwent sample reassay due to one duplicate result outside of limits.

Protocol deviations occurred during this study and were documented in the data. These deviations were considered not to affect the integrity of the data generated during the conduct of this study.

Sample Stability and Study Duration ECL-0358 (CB-2277)

The longest possible storage duration of free SCD411 DP in human plasma samples (from first sample collection on [redacted] to the last sample analysis on [redacted]) is [redacted] days. All samples were analysed within established storage stability duration, as well as established benchtop and freeze/thaw stability. Thus far, stability of Human QC samples after storage in a freezer set to maintain -60 to -80℃ for up to [redacted] days was established and reported in the method validation, Labcorp Method ECL-0358.

The following tables for the Determination of Free SCD411 DP and free Eylea DP in Human Plasma (CB-2277) as well as for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma (22PK016) covering different results of the bioanalysis were provided: (1) Analytical Run Summary; (2) Precision and Accuracy of Calibration Standard Data; (3) Parameter Curve Fit; (4) Quality Control Samples; (5) Sample Results; (6) Analytical Reassay Summary; (7) Incurred Sample Reanalysis Data.

Due to the extent of these tables and in the absence of a summary table, in this report, only a few of them were extracted from the full report.

Table 13: Precision and Accuracy of Calibration Standard Data for Free SCD411 DP in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)							
		[redacted]							
Overall Mean		[redacted]							
S.D.		[redacted]							
%CV		[redacted]							
%Bias		[redacted]							
n		9	9	9	9	9	9	9	9

Table 14: Parameter Curve Fit for Free SCD411 in Human Plasma

Analytical Run Date	Analytical Run Number	Min	Slope	Ed50	Max	LLOQ (ng/mL)	ULOQ (ng/mL)	R-Squared
Overall Mean		[redacted]						
S.D.		[redacted]						
%CV		[redacted]						
n		9	9	9	9			9

Table 15: Quality Control Samples for Free SCD411 in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)		
		[redacted]		
Mean		[redacted]		
S.D.				
%CV				
%Bias				
Accuracy				
Total Error %				
n		18	18	18

Table 16: Precision and Accuracy of Calibration Standard Data for Free Eylea DP in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)							
Overall Mean		[redacted]							
S.D.									
%CV									
%Bias									
n		10	10	10	10	10	10	10	10

Table 17: Parameter Curve Fit for Free Eylea DP in Human Plasma

Analytical Run Date	Analytical Run Number	Min	Max	Slope	Ed50	LLOQ (ng/mL)	ULOQ (ng/mL)	R-Squared
Overall Mean		[redacted]						
S.D.								
%CV								
n		10	10	10	10			10

Table 18: Quality Control Samples for free EYLEA in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)		
Mean		[redacted]		
S.D.				
%CV				
%Bias				
Accuracy				
Total Error %				
n		20	20	20

Table 19: Precision and Accuracy of Calibration Standard Data for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)							
Overall Mean		[redacted]							
S.D.									
%CV									
%Bias									
n		18	18	18	18	18	18	18	18

Table 20: Parameter Curve Fit for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma

Analytical Run Date	Analytical Run Number	Min	Slope	Ed50	Max	LLOQ (ng/mL)	ULOQ (ng/mL)	R-Squared
Overall Mean		[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
S.D.								
%CV								
n		18	18	18	18			18

Table 21: Quality Control Samples for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma

Analytical Run Date	Analytical Run Number	Calculated Concentration (ng/mL)		
20-Apr-2022	424	[redacted]	[redacted]	[redacted]
Mean		[redacted]	[redacted]	[redacted]
S.D.				
%CV				
%Bias				
Accuracy				
Total Error %				
n		36	36	36

<u>Detection of Antibodies and neutralising antibodies to SCD411 have also been provided</u>

2.4.2.5.2. Detection of Antibodies to SCD411 in Human Serum

Selected and abbreviated tables

Table 22: Negative Controls for Anti-SCD411 in Human Serum

Inter-assay Mean (RLU)		[redacted]	[redacted]		[redacted]	
Inter-assay Stdev						
Inter-assay %CV						
N		2441	427		427	
Analytical Run ID	Date	(RLU)	(RLU)	%CV	(RLU)	N

Table 23: Screen and Titer Control Sample Data for Anti-SCD411 in Human Serum (LPC)

Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	LPC [redacted] ng/mL Observed Response (RLU)	%CV	Ratio (LPC / NC)	Screening Result
550	25-Oct-2022	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inter-assay Mean (RLU)				[redacted]		[redacted]		[redacted]	
Inter-assay Stdev									
Inter-assay %CV									
N				334		668		664	

Table 24: Screen and Titer Control Sample Data for Anti-SCD411 in Human Serum (HPC)

Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	HPC [redacted] ng/mL Observed Response (RLU)	%CV	Ratio (HPC / NC)	Screening Result
Inter-assay Mean (RL				[redacted]		[redacted]		[redacted]	
Inter-assay Stdev									
Inter-assay %CV									
N				334		668		665	

[1] Above upper limit of HPC ratio ([redacted])

[2] Above upper limit of LPC ratio ([redacted])

Table 25: Immunodepletion Control Sample Data for Anti-SCD411 in Human Serum (LPC)

Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	LPC ([redacted] ng/mL) Observed Response without Drug (RLU)	%CV	Ratio (Observed without Drug / NC)	Observed Response with Drug (RLU)	%CV	%Inhibition	Confirmatory Result
Inter-assay Mean (RLU)						[redacted]		[redacted]	[redacted]		[redacted]	
Inter-assay Stdev												
Inter-assay %CV												
N						184		184	184		184	

Confirmatory Cut Point: [redacted]%

Table 26: Immunodepletion Control Sample Data for Anti-SCD411 in Human Serum (HPC)

Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	HPC ([redacted] ng/mL) Observed Response without Drug (RLU)	%CV	Ratio (Observed without Drug / NC)	Observed Response with Drug (RLU)	%CV	%Inhibition	Confirmatory Result
Inter-assay Mean (RLU)						[redacted]		[redacted]	[redacted]		[redacted]	
Inter-assay Stdev												
Inter-assay %CV												
N						184		177	184		184	

Confirmatory Cut Point: [redacted]%

[1] Below lower limit of HPC ratio ([redacted])

Table 27: Negative Controls for NAb SCD411 in Human Serum

Analytical Run ID	Run Assay Date	Individual NC Response (RLU)	Mean NC Response (RLU)	%CV	Plate-Specific Cut Point (RLU)	N
Inter-assay Mean (RLU)		[redacted]			[redacted]	
Inter-assay Stdev						
Inter-assay %CV						
N		131			25	

Reason deactivated:
[1] Failed Acceptance Criteria
[2] Exceeds acceptance criteria

Table 28: Screen Control Sample Data for NAb SCD411 in Human Serum (LPC)

						LPC ([redacted] ng/mL)			
Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	Observed Response (RLU)	%CV	Ratio (LPC / NC)	Screening Result
Inter-assay Mean (RLU)				[redacted]		[redacted]		[redacted]	
Inter-assay Stdev									
Inter-assay %CV									
N				26		52		52	

Table 29: Screen Control Sample Data for NAb SCD411 in Human Serum (HPC)

						HPC ([redacted] ng/mL)			
Analytical Run	Analytical Run Date	Mean NC Response (RLU)	Mean NC %CV	Plate-Specific Cut Point (RLU)	Duplicate	Observed Response (RLU)	%CV	Ratio (HPC / NC)	Screening Result
Inter-assay Mean (RLU)				[redacted]		[redacted]		[redacted]	
Inter-assay Stdev									
Inter-assay %CV									
N				26		52		52	

2.4.2.6. Pharmacokinetics

SCD411 contains the active substance aflibercept, which is administered by IVT injection to exert local effects in the eye. Aflibercept is slowly absorbed from the eye into the systemic circulation after intravitreal administration and is predominately observed in the systemic circulation as an inactive, stable complex with VEGF; however, only "free aflibercept" is able to bind endogenous VEGF. The available data regarding the PK of the reference product suggests that a proper PK characterization will not be possible after single IVT administration. In a PK substudy of Eylea, in 6 neovascular wet AMD patients with frequent sampling, maximum plasma concentrations (Cmax) of free aflibercept (systemic) were low.

It was evident that in some subjects, measurable blood levels of free aflibercept that would be pharmacologically active systemically were not registered after IVT administration. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks. Free and bound aflibercept are expected to be cleared by proteolytic catabolism.

Dose proportionality and time dependencies

For time dependency see section regarding the PK substudy.

Special populations

Pharmacokinetics has only been documented in the target population.

2.4.2.7. Pharmacodynamics

No dedicated (comparative) pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. However, immunogenicity testing and an exploratory analysis of free VEGF in plasma were performed.

Mechanism of action

Aflibercept acts as a soluble decoy receptor that binds primarily to VEGF-A and PlGF, reducing the circulating concentration of VEGF-A and PlGF available to bind their natural receptors, VEGFR-1 and VEGFR-2, which are expressed on the surface of endothelial cells.

Aflibercept inhibits the receptor binding of VEGF-A and PlGF and subsequently the angiogenic downstream signal cascade and functional activities.

Primary and secondary pharmacology

Not applicable

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

PK data analysis

No dedicated human Phase I PK studies were conducted. A demonstration of equivalence in PK between a biosimilar candidate and the reference product is an essential part of the comparability exercise. it is not scientifically meaningful to predict biosimilarity on a PK comparison of systemic exposure given the negligible and variable systemic concentrations of aflibercept following IVT administration.

To support the overall assessment of the systemic exposure of VGENFLI (SCD411) and Eylea, the PK profiles of SCD411 and Eylea were evaluated in the subgroup population in the pivotal study SCD411-CP101 This was performed to explore whether the low systemic concentrations of IVT administered SCD411 and Eylea were within the same range. Free and aflibercept was measured in the PK subset, which is deemed sufficient.

The reference product (used in the performed clinical trial) is EU Eylea® (Germany).

A total of 44 subjects (23 subjects in the SCD411 group and 21 subjects in Eylea group) were included in the PK Analysis Set.

Mean (±SD) free and bound plasma concentrations of SCD411 and aflibercept versus time are presented for the PK Analysis Set by treatment on linear and semi-logarithmic scales in Figure 1 and Figure 2, respectively.

Figure 1: Mean (±SD) Free Plasma Concentration versus Time Profiles for SCD411 and Eylea (Pharmacokinetic Analysis Set)

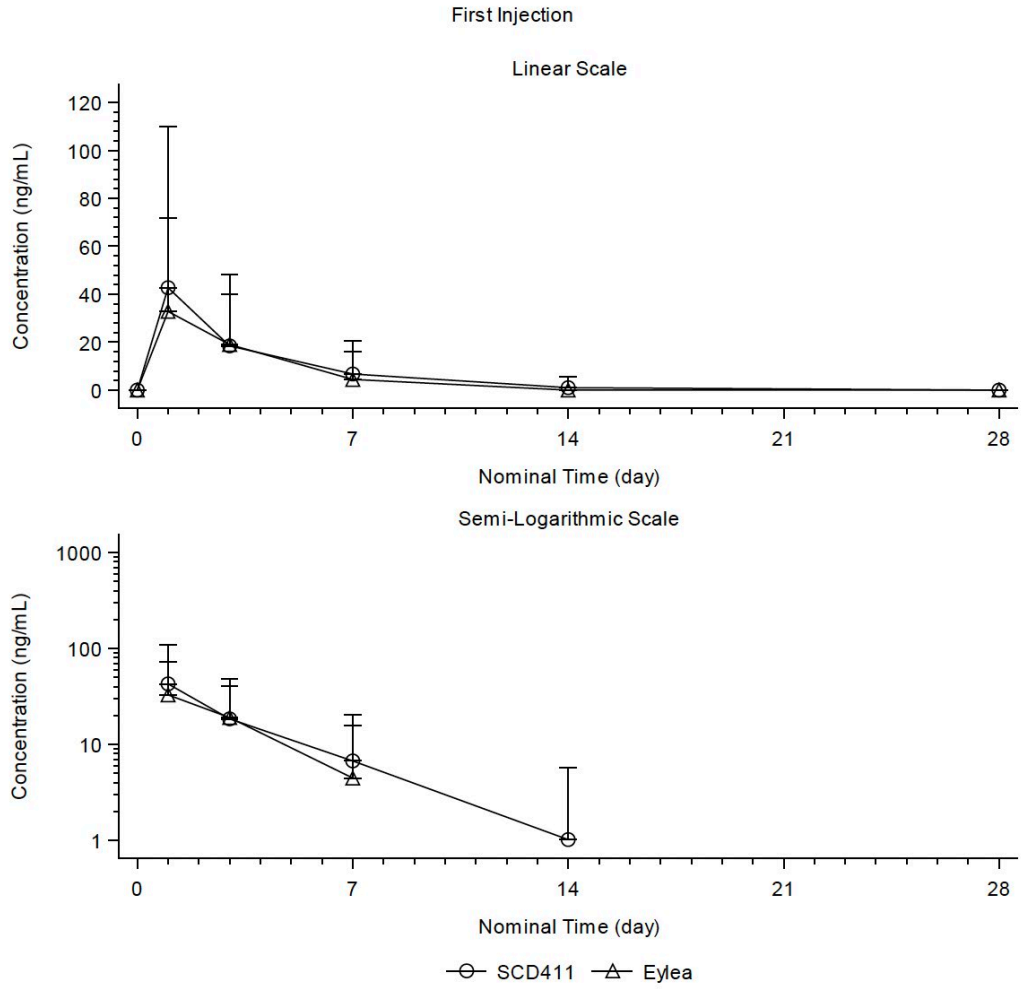
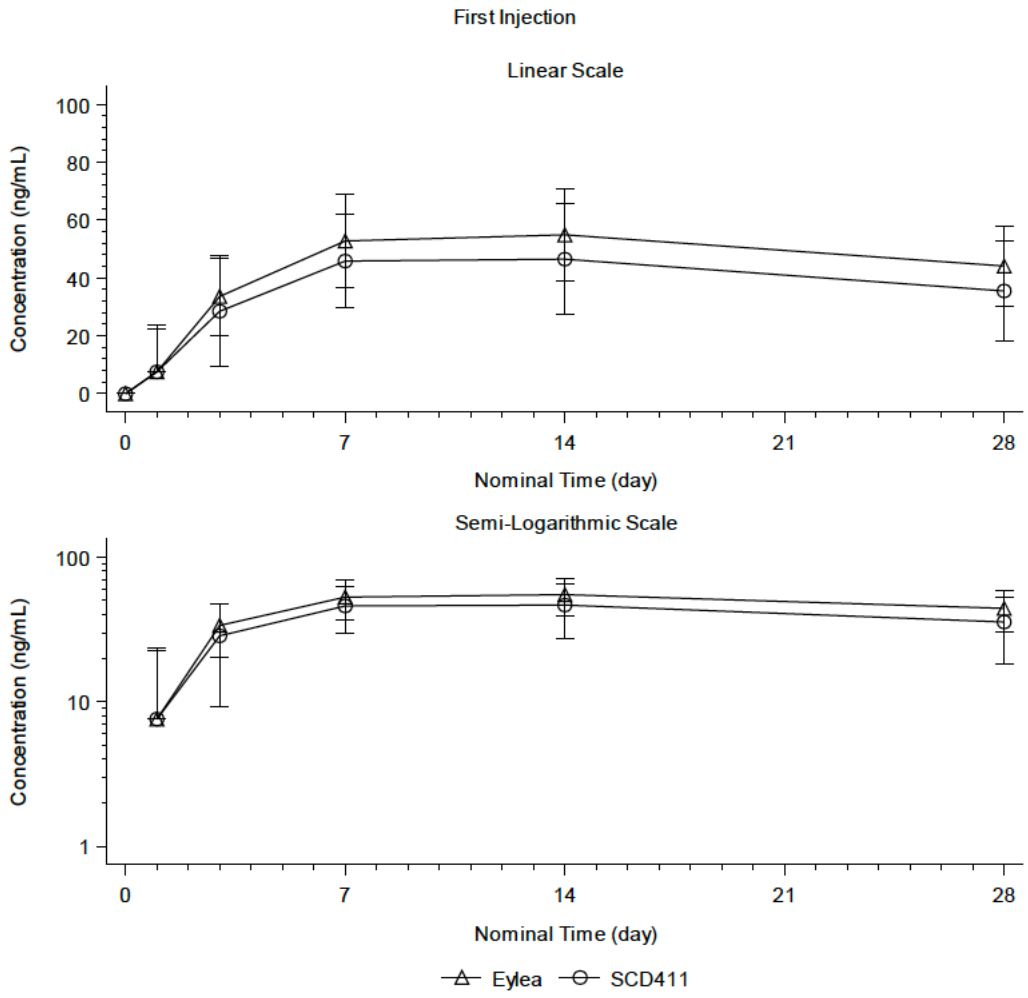


Figure 2: Mean (± SD) bound plasma concentration versus time profiles for SCD411 and Eylea (Pharmacokinetic Analysis Set)



Source: Figure 14.2.1.7.2.

Mean free plasma concentration versus time profiles of SCD411 following a single SCD411 IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection) were characterized by an absorption phase where peak concentrations were observed at the first postdose sampling timepoint, approximately 1day postdose (median t_{max} estimates; 0.98 day for both injection time points). Thereafter, SCD411 concentrations declined with a monophasic disposition, with measurable concentrations observed up to 14 days postdose for Day 1 (first injection) and Week 8 (third injection).

Comparatively, mean free plasma concentration versus time profiles of aflibercept following single Eylea IVT injection at 2 mg on Day 1 and Week 8 were characterized by a similar absorption phase as free SCD411 (median t_{max} estimate: 1.00 and 1.02 day, respectively). Following t_{max}, aflibercept concentrations declined with a monophasic disposition, with measurable concentrations observed up to 7 days postdose on Day 1 and Week 8.

Mean bound plasma concentration versus time profiles of SCD411 following a single SCD411 IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection) were characterized by a

slower absorption phase compared to free SCD411, with peak concentrations observed at 13.82 and 6.99 days (median t_{max} estimates), respectively. Thereafter, SCD411 concentrations declined gradually up to the end of the sampling period (28 days postdose) on Day 1 (first injection) and Week 8 (third injection).

Mean bound plasma concentration versus time profiles of aflibercept following a single Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection) were characterized by a similar absorption phase as bound SCD411. Following t_{max}, aflibercept concentrations declined gradually up to the end of the sampling period (28 days postdose) on Day 1 (first injection) and Week 8 (third injection).

Free and bound plasma PK of SCD411 and Eylea are summarized for the PK Analysis Set by treatment in Table 30 and Table 31, respectively.

Table 30: Summary of Free Plasma Pharmacokinetics of SCD411 and Eylea (Pharmacokinetic Analysis set)

		Free Plasma PK Parameters			
		SCD411 (N = 23)		Eylea (N = 21)	
Parameter (unit)	**Summary Statistic**	**First Injection**	**Third Injection**	**First Injection**	**Third Injection**
AUC_{0-t} (day*ng/mL)	n	5	5	2	5
	GM (%GCV)	250 (57.9)	401 (70.7)	413 (75.0)	200 (6.8)
	Median (Min, Max)	262 (155, 581)	350 (169, 946)	459 (257, 662)	203 (186, 217)
AUC_{0-tau} (day*ng/mL)	n	-	2	1	-
	GM (%GCV)	-	892 (35.6)	N/A (N/A)	-
	Median (Min, Max)	-	919 (699, 1140)	N/A (356, 356)	-
C_{max} (ng/mL)	n	10	11	9	10
	GM (%GCV)	58.9 (93.1)	50.7 (49.4)	49.3 (65.7)	43.0 (30.3)
	Median (Min, Max)	50.4 (26.3, 286)	51.5 (22.6, 105)	45.6 (23.5, 164)	38.0 (33.3, 83.3)
t_{max} (day)[a]	n	10	11	9	10
	Median (Min, Max)	0.98 (0.94, 2.98)	0.98 (0.91, 7.00)	1.00 (0.98, 2.94)	1.02 (0.99, 3.05)
$t_{1/2}$ (day)	n	-	2	-	-
	GM (%GCV)	-	6.58 (20.8)	-	-
	Median (Min, Max)	-	6.65 (5.69, 7.62)	-	-

Abbreviations: N, number of subjects in the analysis set in the treatment group, n, number of subjects in analysis; N/A, not applicable; PK, pharmacokinetic;

Note: AUC_{0-tau} and $t_{1/2}$ values were not calculated and were not included in the calculation of summary statistics where Rsq < 0.80. Subjects were excluded from the calculation of summary statistics where the full profile was BLQ. No PK parameters were estimated when the full profile was BLQ or less than 2 measurable concentrations were observed in the subjects profile. Where a subject profile had 2 quantifiable concentrations, AUC values have been excluded from the calculation of summary statistics.; AUC_{0-tau}, and $t_{1/2}$ values not reported where no data was available.

[a] For tmax, the median (minimum, maximum) values were presented.

Source: Table 14.3.7.3.

Table 31: Summary of Bound Plasma Pharmacokinetics of SCD411 and Eylea (Pharmacokinetic Analysis Set)

		Bound Plasma PK Parameters			
		SCD411 (N = 22)		Eylea (N = 21)	
Parameter (unit)	**Summary Statistic**	**First Injection**	**Third Injection**	**First Injection**	**Third Injection**
AUC_{0-t} (day*ng/mL)	n	21	19	21	20
	GM (%GCV)	1030 (34.7)	1930 (43.8)	1260 (23.7)	2080 (43.9)
	Median (Min, Max)	1010 (580, 2040)	1970 (938, 4900)	1220 (836, 2560)	2180 (492, 3190)
AUC_{0-tau} (day*ng/mL)	n	3	5	7	6
	GM (%GCV)	996 (29.7)	1680 (29.4)	1160 (15.0)	1960 (59.8)
	Median (Min, Max)	1100 (718, 1250)	1530 (1280, 2570)	1120 (919, 1410)	2290 (656, 2980)
C_{max} (ng/mL)	n	22	19	21	20
	GM (%GCV)	48.7 (33.8)	87.8 (36.7)	55.2 (25.3)	94.7 (27.5)
	Median (Min, Max)	49.6 (28.2, 86.1)	83.8 (43.6, 210)	55.4 (36.2, 108)	95.1 (56.3, 149)
t_{max} (day)[a]	n	22	19	21	20
	Median (Min, Max)	13.82 (1.00, 28.01)	6.99 (2.92, 14.00)	13.92 (6.79, 14.04)	7.03 (0.00, 27.94)
$t_{1/2}$ (day)	n	1	1	-	3
	GM (%GCV)	N/A (N/A)	N/A (N/A)	-	17.0 (29.0)
	Median (Min, Max)	N/A (20.7, 20.7)	N/A (16.8, 16.8)	-	18.9 (12.3, 21.0)

Abbreviations: N, number of subjects in the analysis set in the treatment group, n, number of subjects in the analysis; n/a, not applicable; $t_{1/2}$, elimination half-life; t_{max}, time to reach the maximum plasma concentration.

Note: AUC_{0-tau} and $t_{1/2}$ values were not calculated and were not included in the calculation of summary statistics where Rsq < 0.80. Subjects were excluded from the calculation of summary statistics where the full profile was BLQ. No PK parameters were estimated when the full profile was BLQ or less than 2 measurable concentrations were observed in the subjects profile. Where a subject profile had 2 quantifiable concentrations, AUC values have been excluded from the calculation of summary statistics.; AUC_{0-tau}, and $t_{1/2}$ values not reported where no data was available.

[a] For t_{max}, the median (minimum, maximum) values were presented.

Source: Table 14.3.7.4.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), peak free SCD411 and aflibercept concentrations were attained at a median tmax of 1 day, ranging from 0.91 to 7 days across both treatment groups. Lambda_z and all associated parameters were only reported where r2 ≥ 0.80 and where a minimum of 3 data points were used (Cmax was not to be included). Based on these criteria, characterization of the terminal elimination phase was limited for both free SCD411 and aflibercept, with geometric mean t1/2 of 6.58 days (based on data available from 2 subjects) for free SCD411 following the third IVT injection on Week 8, while $t_{1/2}$ values not determined for free aflibercept.

For free SCD411, the geometric mean peak (Cmax) and total (AUC0-t) plasma exposure values were 58.9 ng/mL and 250 day*ng/mL and 50.7 ng/mL and 401 day*ng/mL, for Day 1 (first injection) and Week 8 (third injection), respectively. For free aflibercept, the geometric mean peak (Cmax) and total (AUC0-t) plasma exposure values were 49.3 ng/mL and 413 day*ng/mL and 43.0 ng/mL and 200 day*ng/mL, for Day 1 (first injection) and Week 8 (third injection), respectively. Due to the limited terminal phase characterization, AUC0-inf could not be determined for free SCD411 or aflibercept on Day 1 (first injection) and Week 8 (third injection), while geometric mean AUC0-tau could only be determined for free SCD411 on Week 8 (third injection) (geometric mean: 892 day*ng/mL) and free aflibercept on Day 1 (first injection) (AUC0-tau value of 356 day*ng/mL, based on one subject only). The geometric CV values for Cmax, AUC0-t, and AUC0-tau for free SCD411 were moderate to high on Day 1 and Week 8, ranging from 35.6% to 93.1%. The geometric CV values for Cmax and AUC0-t were also high for free aflibercept on Day 1 (65.7% and 75.0%, respectively) although low to moderate variability was observed for AUC0-t and Cmax on Week 8 (6.8% and 30.3%, respectively).

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), peak bound SCD411 and aflibercept concentrations were attained earlier on Week 8 (third injection) compared to Day 1 (first injection); median t_{max} values were 14 days for bound SCD411 and aflibercept on Day 1 (first injection) and were 7 days on Week 8 (third injection). The t1/2 values for

bound SCD411 could only be determined for one subject, and these values were 20.7 and 16.8 days on Day 1 and Week 8, respectively. The geometric mean t1/2 was 17.0 days (3 subjects) for bound aflibercept on Week 8, with no value determined for bound aflibercept on Day 1.

For bound SCD411, the geometric mean peak (Cmax) and total (AUC0-t and AUC0-tau) plasma exposure values were 48.7 ng/mL, 1030 day*ng/mL, and 996 day*ng/mL and 87.8 ng/mL, 1930 day*ng/mL, and 1680 day*ng/mL, for Day 1 and Week 8, respectively. For bound aflibercept, the geometric mean peak (Cmax) and total (AUC0-t and AUC0-tau) plasma exposure values were 55.2 ng/mL, 1260 day*ng/mL, and 1160 day*ng/mL and 94.7 ng/mL, 2080 day*ng/mL, and 1960 day*ng/mL, for Day 1 and Week 8, respectively. Due to the limited terminal phase characterization, AUC0-inf could not be determined for bound SCD411 or aflibercept on Day 1 and Week 8. The geometric CV values for Cmax, AUC0-t, and AUC0-tau for bound SCD411 were moderate on Day 1 and Week 8, ranging from 29.4% to 43.8%. The geometric mean CV values for Cmax, AUC0-t, and AUC0-tau were low to moderate for bound aflibercept on Day 1 (15.0% to 25.3%) and moderate to high on Week 8 (27.5% to 59.8%) (see section 2.2.1.2).

Adequacy of methods and trial design for pharmacokinetic (PK) analysis

The PK analysis methods in the study comparing SCD411 (aflibercept biosimilar) to Eylea are detailed and systematic. The PK analysis was performed using non-compartmental analysis (NCA) with Phoenix® WinNonlin® software, which is an industry-standard for such analyses. Plasma concentrations were measured, and key PK parameters were calculated, including Cmax, Tmax, the AUC, and elimination half-life (t1/2).

The study design was a Phase III randomized, double-masked, parallel-group, multicenter study, which is appropriate for comparing the biosimilar to the reference product. The PK analysis set included 40 subjects (20 per group) with sufficient evaluable blood samples, ensuring robust data for analysis. The study also included interim analyses at predefined points to further assess safety, efficacy.

The dose selection of 2 mg for both SCD411 and Eylea administered via intravitreal injection (IVT) aligns with the standard therapeutic dose for treating neovascular age-related macular degeneration (AMD). This ensures the relevance and comparability of the PK data. No specific protein correction was found in the report, suggesting that the focus was on the direct measurement of free and bound plasma concentrations without additional correction factors.

The endpoints and the non-compartmental analysis model used were selected appropriately. The detailed measurement of free and bound plasma concentrations at multiple time points provided a comprehensive PK profile.

The study did not explicitly state the predefined margins for PK parameter comparisons. However, the close comparability of the geometric means and other summary statistics between SCD411 and Eylea suggests that the margins are within standard acceptable range for biosimilarity.

PK and PD comparability study results - comparability against Eylea:

The PK parameters such as AUC, Cmax, and Tmax for SCD411 and Eylea were found to be comparable. Similarly, the geometric mean Cmax for bound plasma after the third injection was 50.7 ng/mL for SCD411 and 43.0 ng/mL for Eylea, showing close values. However, after the third injection, the geometric mean AUC0-t for free plasma was 401 day*ng/mL for SCD411 and 200 day*ng/mL for Eylea, indicating a relatively higher exposure for the biosimilar product SCD411 over Eylea.

Impact of Anti-Drug Antibodies (ADA) on PK data

The report includes data on the impact of ADA on PK parameters. The presence of ADAs was monitored, and subjects who tested positive for ADAs were analyzed separately. E.g. subjects No.: 1611001, 1201007, 1202012, (etc.) who tested positive for ADAs after the first injection showed a

different PK profile compared to ADA-negative subjects. The studies evaluated the effect of ADAs on the PK profile of SCD411 and Eylea. ADA-positive subjects exhibited altered drug clearance and distribution. The results are summarised below:

1. Free SCD411 pharmacokinetics:

- For free SCD411 at Week 8 (third injection), the peak concentration (Cmax) was slightly greater for ADA-positive subjects (geometric mean for Cmax = 63.7 ng/mL) compared to ADA-negative subjects (geometric mean for Cmax = 38.6 ng/mL).

- For free Eylea at Week 8 (third injection), there were no differences in peak concentration between ADA-positive and ADA-negative subjects.

2. Bound SCD411 pharmacokinetics:

- For bound SCD411 at Week 8 (third injection), the peak concentration was slightly greater for ADA-positive subjects (geometric mean for Cmax = 107 ng/mL) compared to ADA-negative subjects (geometric mean for Cmax = 76.2 ng/mL).

- For bound Eylea at Week 8 (third injection), there were no differences in peak concentration between ADA-positive and ADA-negative subjects.

These findings indicate that ADA-positive subjects exhibited altered drug clearance and distribution, potentially leading to higher peak concentrations of SCD411. However, for Eylea, the differences between ADA-positive and ADA-negative subjects were not significant. The observed variations in pharmacokinetics for SCD411 among ADA-positive subjects suggest that immunogenicity could have a significant impact on the drug's pharmacokinetic profile rather than the differences being random observations. This implies that the presence of ADA can alter the pharmacokinetics of SCD411. For bound SCD411, the ADA-positive group showed higher peak concentrations and overall exposure compared to ADA-negative subjects, indicating a significant impact on the pharmacokinetic parameters.

2.4.4. Conclusions on clinical pharmacology

Pharmacokinetics

Pharmacokinetic assessments were performed in the current study following the first and the third doses of SCD411.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 and Week 8, the mean free SCD411 and aflibercept concentration versus time profiles were similarly characterized by an absorption phase where peak concentrations were observed at the first postdose sampling timepoint, with measurable concentrations observed up to 7 to 14 days postdose on Day 1 and Week 8.

The mean bound SCD411 and aflibercept concentration versus time profiles were similarly characterized by a slower absorption phase compared to free SCD411, with concentrations gradually declining up to the end of the sampling period (28 days). Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 and Week 8, peak (C_{max}) and total (AUC_{0-t}) exposure to free and bound SCD411 and aflibercept were comparable, when accounting for inter-subject variability.

The concentration versus time profiles of free SCD411 and aflibercept on Day 1 (first injection) and Week 8 (third injection) were similarly characterized by an absorption phase where peak concentrations were observed at the first post-dose sampling timepoint, approximately 1 day post-dose.

The concentration versus time profiles of bound SCD411 and aflibercept on Day 1 (first injection) and Week 8 (third injection) were characterized by a slower absorption phase compared to free SCD411 and aflibercept, with peak concentrations observed at 14 and 7 days, respectively.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), peak and total exposure to free and bound SCD411 was comparable to those observed for free and bound aflibercept.

The results were presented in figures containing Mean (±SD) Free and Bound Plasma Concentration versus Time Profiles for SCD411 and Eylea as well as in tables containing a Summary of Free and bound Plasma Pharmacokinetics of SCD411 and Eylea.

The data presented is clearly insufficient to draw any definite conclusions on the bioequivalence between SCD411 and Eylea. As it has already been stated, basing comparability on such scenario is regarded futile and thus not meaningful. However, the applicant provided conclusions based on these results. Those conclusions point to a difference in the absorption rate but fail to observe the differences in AUC_{0-t} for free aflibercept in SCD411 and Eylea as per table below.

Table 32: Absorption rate for free aflibercept in SCD411 and Eylea.

	Day 1		Week 8	
	SCD411	Eylea	SCD411	Eylea
GM (%GCV)	250 (57.9)	413 (75.0)	401 (70.7)	200 (6.8)
Median (Min, Max)	262 (155, 581)	459 (257,662)	350 (169,946)	203 (186, 217)

There seems to be a large difference when comparing AUC of both products administered on day 1 and week 8, even taking into account the large reported variability.

Immunogenicity

Approximately 7% of subjects who provided blood samples for immunogenicity assessment at baseline were ADA positive at baseline in the SCD411 group and the Eylea group.

Approximately 20% to 40% subjects in the SCD411 group and 19% to 52% subjects in the Eylea group who provided blood samples for immunogenicity assessment at postbaseline timepoints were ADA positive through Week 52 of the study.

The GMTs at Baseline were 2.1 and 2.3 for the SCD411 and Eylea groups, respectively. The GMTs from Week 4 to Week 52 were fluctuated between 1.87 and 2.31 in the SCD411 group and 1.66 and 2.14 in the Eylea group.

The incidence of NAb positive subjects was low. Of the subjects who provided blood samples for immunogenicity assessment at Baseline, 1.1% subjects in the SCD411 group and 2.2% subjects in the Eylea group were NAb positive at Baseline. Postbaseline, the incidence of NAb positive subjects remained <3% in the SCD411 group and mostly remained <4% in the Eylea group.

Based on the PK data available from a subgroup of patients in the phase 3 study SCD411-CP101, it is concluded that there are no major differences in systemic exposure between SCD411 and the reference product Eylea.

The applicant provided the requested data and a full discussion on the reasons for the failed runs, which were identified upon thorough investigation. Correction of the identified initial errors and

Incurred Sample Reanalysis provide further reassurance that these occurrences do not impact the study results. The occurrences of the failed runs do not impact the study results.

The applicant provided tables presenting the requested numbers, percentages and reasons for the exclusion of some validation runs in the ADA method as requested. The reasons for failure were identified and can be considered as common in the running of an assay such as this one. Moreover, only 0.8% of the total number of runs have failed. No impact on the final results can be imputed.

It should also be noted that failures were slight, falling close to the targeted ±20% Coefficient of Variation (hereafter, CV) criteria, and only occurred at the HPC level which is minimally impactful.

The applicant provided a statement that can be considered as an adequate response to the question: It is agreed that the failures were slight and do not affect most of the samples, whose levels fall within the LPC and MPC level. At the HPC level the %CVs fall close to the targeted ±20%. These failures can be considered as minimally impactful.

The discussion provides an acceptable explanation of these results. Moreover, in this case, the aim of the PK study was solely to generate descriptive data of test versus reference, not to show bioequivalence.

Having provided the full data allowed to summarized that the methods presented were reliable. Correction of the identified errors or system failures and Incurred Sample Reanalysis provide further reassurance that these occurrences do not impact the study results.

The applicant provided data summarising the protocol deviations for the patients included in the PKS, along with the Table containing the full data, supporting the summary. The conclusion that these deviations were minor and balanced between the treatments and have no significant or minimal impact on the PK analysis can be accepted.

It is acknowledged that (i) the systemic concentration of the free moieties involved do not impact efficacy due to the topical site of administration; (ii) this study was not intended to perform bioequivalence assessment; (iii) very low systemic exposure makes it difficult to reliably calculate AUC0-t; and (iv) the small number of evaluable subjects implies a very large difference between minimum and maximum values for this parameter in the different cases reflecting a very large variability. The argumentation of the applicant can be followed. It can be accepted that these values are not really relevant from clinical perspective.

The applicant provided a detailed explanation of the selection criteria and process to validate the data's credibility. It was clarified that it was countries selected because of organisational aspects of study conduct and not selection of individuals. The recruitment for PK substudy was set and maintained at 1:1 ratio. the subject size of PK was according to recommendations from FDA and EMA. The applicant also demonstrated that the PK subset was representative of the FAS population.

Conclusions on clinical pharmacology

The methods and trial design for the PK analysis were suitable for comparing SCD411 to Eylea. The results indicated comparable PK parameters between SCD411 and Eylea. The data demonstrated that SCD411 has a similar PK profile to Eylea, supporting its biosimilarity. The focus on ensuring systemic PK levels were sufficiently low to avoid systemic pharmacological concerns was achieved, aligning with regulatory expectations for intravitreal biosimilars. A formal PK comparison for biosimilarity was deemed unnecessary due to the large variability and low plasma concentration in the PK subset.

2.4.5. Clinical efficacy

2.4.5.1. Dose response studies

Not applicable

2.4.5.2. Main study(ies)

Table 33: Pivotal study SCD411-CP101

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
Study SCD411-CP101	Approximately 560 subjects with wet AMD were planned to be enrolled in the study across approximately 155 sites in 14 countries. First study visit – 13-AUG-2020 Last study visit – 08-SEP-2022 A total of 914 subjects were assessed for eligibility across 144 sites in 14 countries. A total of 576 subjects were randomly assigned to receive either VGENFLI (SCD411) (288 subjects) or Eylea (288 subjects) treatment.	This was a Phase 3, randomized, double-masked, parallel-group, and multicentre study to demonstrate the biosimilarity of VGENFLI (SCD411) compared with Eylea (aflibercept) among adult subjects with neovascular (wet) AMD.	Study drug SCD411 (proposed biosimilar to Eylea®) Dose, route of administration: SCD411 (proposed biosimilar of Eylea®) intravitreal (IVT) injection 2 mg every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg IVT injection once every 8 weeks (2 months) until Week 48. Subjects who continued to meet all inclusion and none of the exclusion criteria were randomly assigned in a 1:1 ratio to receive VGENFLI (SCD411) or Eylea injections on Day 1.	Patients with neovascular AMD **Inclusion criteria**: 1. Subject was capable of understanding the written informed consent, provided signed and witnessed written informed consent, and agreed to comply with protocol requirements 2. Age ⩾ 50 years 3. active choroidal subfoveal, juxtafoveal, or extrafoveal neovascularization lesions secondary to AMD evidenced by fluorescein angiography (FA) in the study eye at screening and confirmed by the central reading centre 4. Subject had the best corrected visual

			Randomization was stratified by subject participation in the PK substudy. Subjects from Australia, Bulgaria, the Czech Republic, Hungary, Israel, Japan, Latvia, Russia, Spain, and Slovakia did not participate in the PK substudy. Randomization was also stratified by subjects enrolled in Japan. All subjects were assessed once every 4 weeks. The End-of-Treatment (EOT) Visit was scheduled for Week 48.	acuity (BCVA) letter score of 73 to 35 using original series Early Treatment Diabetic Retinopathy Study (ETDRS) charts or 2702 series number charts in the study eye at screening and Week 0 (Day 1) prior to randomization. In addition, the fellow eye was not to have less than 35 letter score using the ETDRS chart or 2702 series number chart. 5. If the subject was a woman of childbearing potential, she should have had a negative serum pregnancy test at screening and agreed to use protocol-defined methods of contraception throughout the study until 3 months after the last injection of Eylea/Vgenfli (SCD411) 6. Male subjects with female partners of childbearing potential had to agree to use protocol-defined methods of contraception and agree to refrain from donating sperm throughout the study until 3 months after the last injection of Eylea/Vgenfli

				(SCD411) 7. Subject had the CNV area making up either 50% or more of the total lesion area and confirmed by the central reading centre **Exclusion criteria:** 1. Subject had any prior ocular (in the study eye and fellow eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins 2. Subject had any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins. 3. Subject's fellow eye showed signs of AMD that, in investigator's medical opinion, needed any treatment during the study period 4. Subject had received any prior treatment with anti-VEGF agents in both eyes (i.e., completely treatment naïve subjects only were to be included). 5. The total lesion size was >30.5 mm2, including blood,

				scars, atrophy, fibrosis, and neovascularization as assessed by FA in the study eye and confirmed by the central reading centre. 6. Subject had central retinal thickness (CRT) of <300 µm in the study eye and was confirmed by the central reading centre. 7. Subject had a subretinal haemorrhage that was either 50% or more of the total lesion area or if the blood was under the fovea and was 1 or more disc areas in size in the study eye and was confirmed by the central reading centre (if the blood was under the fovea, then the fovea had to be surrounded 270 degrees by visible CNV). 8. Subject had scar or fibrosis, making up >50% of the total lesion in the study eye and confirmed by the central reading centre 9. Subject had scar, fibrosis, or atrophy involving the centre of the fovea in the study eye and confirmed by the central reading

				centre. 10. Subject had retinal pigment epithelial tears or rips involving the macula in the study eye and confirmed by the central reading centre. 11. Subject had Lens Opacity Classification System II Grade IV cataract in the study eye, or other significant cataract in the study eye that in the investigator's opinion interfered with visualization of the retina or interfered with retinal imaging. 12. Subject had active intraocular/periocular infection and inflammation in either eye 13. Subject had a history of any vitreous haemorrhage in the study eye within 4 weeks prior to the Screening Visit. 14. Subject had other causes of CNV in the study eye as confirmed by the central reading centre. 15. Subject had a history or clinical evidence of diabetic retinopathy, DME, or any other vascular disease affecting the retina, other than

				AMD, in either eye 16. Prior vitrectomy to the study eye 17. History of retinal detachment treatment or surgery for retinal detachment in study eye 18. history of macular hole of Stage 2 and above in the study eye 19. history of uncomplicated intraocular or periocular surgery within 3 months of Day 1 on the study eye, except lid surgery, which may not have taken place within 1 month of Day 1. 20. aphakia in the study eye 21. history of glaucoma-filtering surgery within 3 months of Day 1 in the study eye. 22. history of corneal transplant in the study eye 23. history or evidence of any other clinically significant (CS) disorder, condition, or disease (e.g., co-existence of RVO, radiation retinopathy, diabetic retinopathy, glaucoma under treatment) in the study eye that, in

				the opinion of the investigator, would pose a risk to subject safety or interfere with the study evaluation, procedure, or complication 24. uncontrolled hypertension defined as systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg under appropriate antihypertensive treatment 25. hypersensitivity to aflibercept or medications used in this study (fluorescein, mydriatic eye drops, etc.). 26. Subject was a woman of childbearing potential who was pregnant or lactating at the Screening Visit and/or at the Baseline 27. contraindication to IVT injection according to the investigator's clinical judgment. 28. history of thrombotic events (eg, stroke, transient ischemic attacks, pulmonary embolism, deep vein thrombosis, or myocardial infarction) 29. history or evidence

				of cardiac conditions with congestive cardiac failure resulting in marked limitation of physical activity or inability to perform any physical activity without discomfort; subjects with ventricular arrhythmia requiring ongoing treatment; or subjects with atrial fibrillation 30. history of laser therapy in the macular region in the study eye 31. prior or concomitant treatment with IVT corticosteroids injection, IVT corticosteroid implant, subtenon corticosteroids, or peribulbar corticosteroids in the study eye 6 months before the Screening Visit. 32. prior or concomitant treatment involving the macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation) in the study eye 33. prior or concomitant treatment with pan-retinal photocoagulation in

				the study eye 90 days before the Screening Visit 34. concomitant or prior treatment with ethambutol (2 weeks prior to randomization); deferoxamine and topiramate (4 weeks prior to randomization); tamoxifen, hydroxychloroquine, chloroquine, or vigabatrin (8 weeks prior to randomization), and amiodarone (12 weeks prior to randomization). 35. investigational product for the treatment of ocular conditions (in either eye) and systemic conditions 30 days or 5 half-lives (whichever is longer) prior to randomization and throughout the study, except dietary supplements or vitamins 36. intraocular pressure (IOP) ⩾25 mmHg in spite of anti-glaucoma treatment 37. prior or ongoing systemic medical condition (including but not limited to infectious, inflammatory, psychiatric, neurological, renal, hepatic, respiratory

				conditions, or malignancies) or CS screening laboratory value that in the opinion of the investigator presented a safety risk, interfered with study compliance and follow-up, or confounded data interpretation throughout the study period

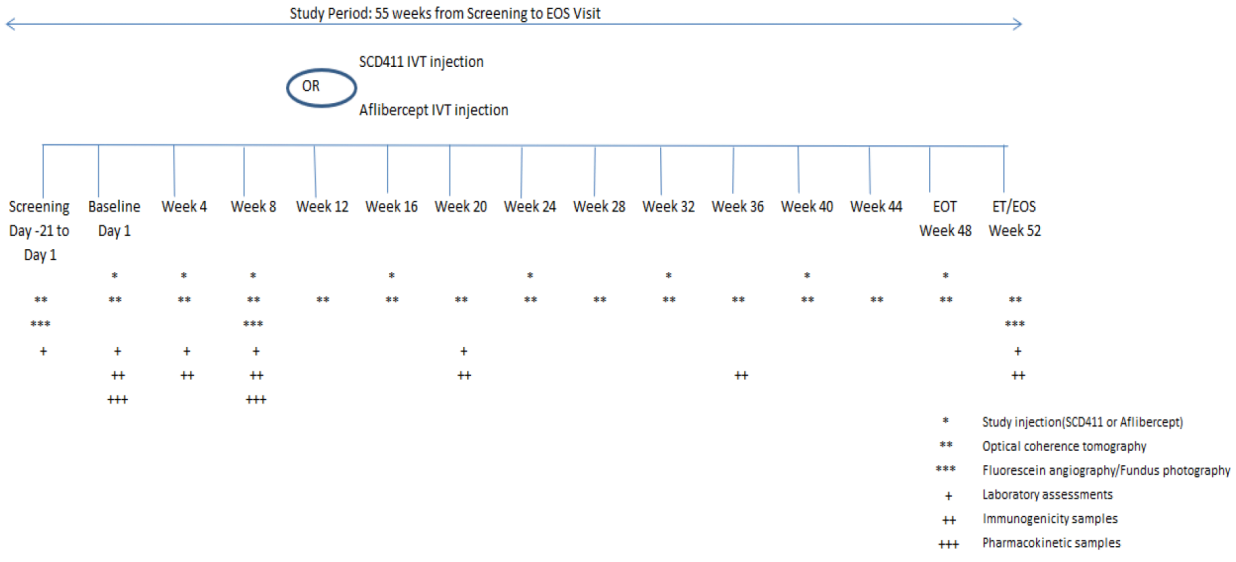
Study SCD411-CP101

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

Methods

Methods

Figure 3: Study schematic design for Study SCD411-CP101



Abbreviations: EOS, end-of-study; EOT, end-of-treatment; ET, early termination; IVT, intravitreal.

Study participants

See table above.

Treatments

See table above.

Objectives

The objective of the Vgenfli (SCD411) clinical program is to demonstrate biosimilarity to the European reference product Eylea (aflibercept). Based on the extensive analytical comparability testing using the same licensed reference product, the current study was designed to evaluate comparability between SCD411 and Eylea. Based on the data from Eylea clinical studies VIEW 1, VIEW 2, COPERNICUS, GALILEO, VIBRANT, VIVID, VISTA, and MYRROR, neovascular (wet) AMD was considered as the most suitable condition to prove similarity between SCD411 and Eylea as the reference product (Campochiaro et al 2015; Ikuno et al 2015; Yuzawa et al 2015; Pielen et al 2017; Mitchell et al 2018; Chen et al 2020).

The primary objective of this study was to demonstrate the equivalence in efficacy of SCD411 compared to Eylea in subjects with neovascular age-related macular degeneration (nAMD).

Equivalence between the main treatment groups was to be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3,8 letters, 3,8 letters].

The secondary objective was to:

compare the safety and tolerability of SCD411 and Eylea.

after 8 weeks and 52 weeks of treatment demonstrated by BCVA, CRT, and CNV;

the immunogenicity of SCD411 and Eylea by presenting information of the development of anti-SCD411 antibodies

The study was performed in subjects with neovascular age-related macular degeneration (nAMD).

A total of 914 subjects were assessed for eligibility across 144 sites in 14 countries. A total of 576 subjects were randomly assigned to receive either SCD411 (288 subjects) or Eylea (288 subjects) treatment.

The study consisted of a screening period of up to 3 weeks, a treatment period of up to 48 weeks, and a post-treatment follow-up period of up to 4 weeks. The total duration of study participation was up to 55 weeks.

A subset of 40 subjects (20 per group) was to be selected for collection of PK samples.

The primary objective was to prove the equivalence of SCD411 as compared with EU - Eylea® (aflibercept) in BCVA after 8 weeks of treatment among subjects with wet AMD. The primary endpoint was the change in BCVA measured by ETDRS letters score or 2702 charts at Week 8.

The secondary objective was to:

compare the safety and tolerability of SCD411 and EU - Eylea.

after 8 weeks and 52 weeks of treatment demonstrated by BCVA, CRT, and CNV;

the immunogenicity of SCD411 and EU - Eylea by presenting information of the development of anti-SCD411 antibodies

Outcomes/endpoints

<u>Primary endpoint</u>

The primary endpoint was the change in BCVA measured by ETDRS letters score or 2702 charts at Week 8.

Secondary endpoint

The secondary endpoint was to demonstrate:

- The change from baseline in BCVA score for the study eye at Week 52.
- The change from Baseline in BCVA Score, CRT, and CNV Area for Study Eye by Visit
- The gain of ≥ 15 letters in the BCVA score from baseline

Sample size

The equivalence margin agreed upon with EMA and PMDA was determined using the data presented from MARINA (and ANCHOR) and VIEW studies. These data were used to estimate the efficacy of aflibercept compared with the placebo treatment in subjects with wet AMD. It was shown that in MARINA, on average subjects lost 2.5 letters of BCVA over 2 months in the Sham-treated control arm and gained 5 letters in the treatment arm of 2 mg, and that in the VIEW studies 6.8 to 7.5 letters were gained among subjects with wet AMD at Week 8 into treatment on a 2 mg dose. Combining both study data, the treatment effect compared with the placebo was estimated at approximately 9.3 to 10 letters. A margin of 3.8 letters translated to a preservation of 59% to 62% of the difference between Eylea and Sham and was less than a 1 line change in VA. Equivalence discussions for EMA and PMDA were based upon a 95% CI approach or 2 one-sided tests (TOST) at the α=0.025 level.

A sample size of 266 subjects per treatment arm was selected as it provided at least 80% power for the US FDA, EMA, and PMDA analyses for the range of SD considered when using TOST on data from a parallel-group design.

Randomisation and blinding (masking)

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. Subjects who continued to meet all inclusion and none of the exclusion criteria were randomly assigned in a 1:1 ratio to receive IVT SCD411 or Eylea injections on Day 1.

Randomization was stratified by subject participation in the PK sub study. Subjects from Australia, Bulgaria, the Czech Republic, Hungary, Israel, Japan, Latvia, Russia, Spain, and Slovakia did not participate in the PK study.

Randomization was also stratified by subjects enrolled in Japan. Subjects were treated with the study drug every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48.

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. The sponsor, the delegated CRO, and imaging teams were also masked to the study treatment. Only the unmasked investigator involved in performing the IVT injections was unmasked to study treatment. These individuals were not allowed to discuss treatment and/or subject outcome with masked study staff, including the evaluating investigator.

The subject's treatment assignment was not to be broken until the end of the study unless medical treatment of the subject depended on knowing the study treatment that the subject had received. In the event that the treatment assignment needed to be unmasked because of a medical emergency, the investigator could unmask an individual subject's treatment allocation.

Statistical methods

The following general comments apply to all statistical analyses and data presentations:

Tabulations of summary statistics, graphical presentations, and statistical analyses were performed with SAS® software, Version 9.4.

Descriptive statistics for continuous variables in summary tables included the number of subjects in the analysis (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), and range (minimum, maximum). Descriptive statistics for categorical variables in summary tables included frequency counts and percentages. Graphical summaries of the data were presented.

For summary precision, mean, median, Q1 and Q3 were to have one more decimal place than the reported value, SD was to have 2 more decimal places than the reported value, minimum and maximum were to have the same decimal place as the reported value. Percentages and 95% confidence intervals (CIs) were to have one decimal place. When count data were to be presented, the percentage were to be suppressed when the count was zero in order to draw attention to the non-zero counts. A row denoted "Missing" was to be included in count tabulations where specified on the shells to account for dropouts and missing values.

The most recent non-missing measurement collected prior to the first administration of study drug was used as the baseline value.

Subgroup analyses were performed by region/country (Japan, non-Japan). Demographics and baseline characteristics, safety, efficacy, and immunogenicity endpoints were analysed by subgroups. Subgroup summaries were descriptive only with no statistical hypothesis testing performed.

All data obtained on the eCRF was provided in separate data listings showing individual subject values by treatment group and visit, if applicable.

For non-efficacy analysis, no analysis window mapping was applied. For efficacy analysis, analysis window was mapped only for the ET Visit.

As there was no direct comparison in the literature of Eylea to placebo/Sham, an indirect comparison was made by first comparing Eylea to Lucentis and then Lucentis to Placebo. The primary efficacy endpoint for the biosimilar comparison was made at 8 weeks. As the primary efficacy endpoints for the Phase 3 studies for Lucentis (MARINA, ANCHOR) and Eylea (VIEW 1, VIEW 2) were at 52 weeks, there was limited published data for the BCVA mean change from baseline at Week 8.

The Statistical Review from the US FDA Summary Basis of Approval for the original Eylea AMD submission contained appendices which provided summary statistics on the intention-to-treat (ITT) observed data for the BCVA mean and BCVA mean change from baseline by study visit, including Week 8 (DHHS 2011). This data, along with data from the Lucentis label (Lucentis® 2018) was used to estimate a difference between Eylea and Sham at Week 8 from the estimated 95% CI lower limit for the difference between (Lucentis – Sham).

The analysis sets were defined as follows:

Full analysis set - The FAS included all randomized subjects who received at least 1 injection of the study drug. Subjects were analysed according to the treatment group to which they were randomized. The primary set for efficacy analysis was the FAS.

Modified full analysis set - The modified FAS (mFAS) included all randomized subjects who received at least 1 injection of the study drug and had at least 1 postbaseline BCVA assessment in the study eye. Subjects were analysed according to the treatment group to which they were randomized. The PMDA required that the efficacy analysis be conducted based on the mFAS without multiple imputation (MI) as supportive analysis.

Per protocol set - The Per Protocol Set (PPS) included all subjects in the FAS, excluding those with significant protocol deviations. Subjects were analysed according to the treatment group to which they were randomized. For the EMA submission, the primary efficacy endpoint had to meet the equivalence for the PPS also.

Safety set – The Safety Set included all subjects who received at least 1 injection of the study drug. Subjects were analysed according to the treatment they actually received. The Safety Set was the primary analysis set for safety, tolerability, and immunogenicity analyses.

Pharmacokinetic analysis set - The Pharmacokinetic Analysis Set (PK Set) was the subset of subjects in the FAS who had sufficient evaluable blood samples. A subset of 40 subjects (20 per group) was selected for the collection of PK samples. Subjects were analysed according to the treatment they actually received. The PK Set was used for the estimation of PK endpoints.

The primary analysis of efficacy and all other efficacy and safety analyses were conducted at the Week 8 database lock, ie, after all subjects completed the Week 8 Visit or had been discontinued from the study prior to this visit. Distribution of the Week 8 analysis was restricted only to the IDMC members in order to minimize bias through the end of the study.

Interim analyses of safety, secondary efficacy endpoints, and PK parameters were to be performed once approximately 200 subjects completed Week 52 and all subjects completed Week 24 or had early discontinued from the study.

The Week 8 analysis and interim analyses were performed by an independent biostatistics group and results were distributed to a limited group of recipients including unmasked medical writing staff and limited sponsor representatives. The timing of the Week 8 database lock and the interim analysis database lock could have been coincided depending on subject enrolment and data cleaning/programming activities.

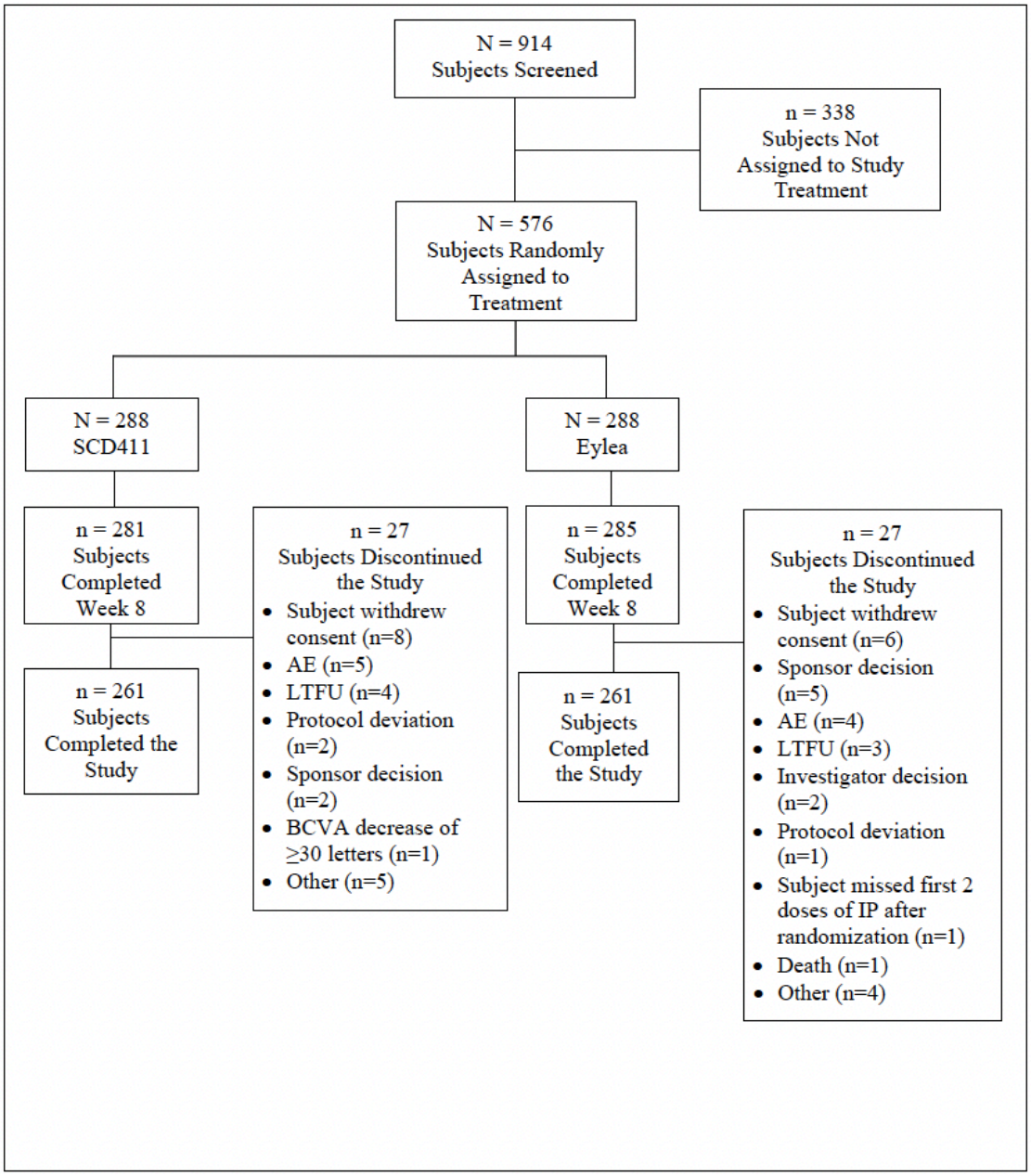
As the primary study endpoint was the bioequivalence comparison at Week 8, no type 1 error adjustments were required as the analyses performed at the Week 8 database lock were to be considered final for the primary efficacy endpoint. No type 1 error adjustments were planned for the secondary efficacy endpoints; therefore, no error adjustments were performed due to the interim analysis as all analyses after the primary analysis at the Week 8 database lock were considered secondary analyses.

Subgroup analyses were performed by region/country (Japan, non-Japan). Demographics and baseline characteristics, safety, efficacy, and immunogenicity endpoints were analysed in subgroups. Subgroup summaries were descriptive only with no statistical hypothesis testing performed.

Results

Participant flow

Figure 4: Participant flow



Recruitment

First study visit – 13-AUG-2020

Last study visit – 08-SEP-2022

Conduct of the study

Two major amendments and 2 country-specific (Slovakia- and Korea-specific) amendments were made to the original protocol dated 27 Mar 2020 and implemented. A country-specific amendment for Italy was released on 24 Jul 2020 but no subjects were recruited under this amendment.

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:

As per the request from the Israel regulatory agency, it was clarified that subjects in Israel will not participate in the PK substudy.

Stratification by subjects in Japan was added to the protocol as per the sponsor's decision.

The paragraph on study treatment discontinuation was updated as per the US FDA recommendation to minimize missing data by keeping subjects who discontinue study treatment in the study to continue with regularly scheduled visits, so that their efficacy and safety data after treatment discontinuation could be collected to support sensitivity analyses.

Figure 3-1 Study Schema was updated to remove the laboratory assessments at the Week 48 EOT Visit.

Section 4.1.1 Inclusion Criteria:

Inclusion criterion 3 was updated by adding the range of CNV lesions as per the request from the Korean Ministry of Food and Drug Safety (MFDS), which had been incorporated into the Korea-specific protocol amendment.

Inclusion criterion 7 was added as per the request from the Korean MFDS to clarify that CNV should be either 50% or more of the total lesion area in the inclusion criterion. This change had been applied to the Korea-specific protocol amendment.

Section 4.1.2 Exclusion Criteria:

Exclusion criterion 12 was updated to clarify that subjects with the conditions of intraocular/periocular infection and inflammation in either eye was to be excluded at Screening. This change had been applied to the Korea-specific protocol amendment.

The limit of systolic blood pressure was decreased from 180 to 160 mmHg in exclusion criterion 24, as per the request from the Slovakia regulatory agency. This change had been applied to the Slovakia-specific protocol amendment.

As per the requests from the Slovakia regulatory agency and the Korean MFDS, exclusion criterion 36 regarding the intraocular pressure (IOP) condition in spite of anti-glaucoma treatment was added according to the Summary of Product Characteristics. This change had been applied to both Slovakia- and Korea-specific protocol amendments.

As per the request from the Slovakia regulatory agency, subjects with a systemic medical condition were to be excluded from the study; therefore, exclusion criterion 37 was added.

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:

As per the US FDA recommendation to keep subjects who discontinued study treatment in the study to continue with their regularly scheduled visits, the reasons for withdrawal/discontinuation were listed separately.

For clarity, certain specific criteria for treatment discontinuation were moved to the section of discontinuation of study treatment.

Section 4.3.3 Handling of Withdrawals: The section was updated as per the US FDA recommendation to keep subjects who discontinue study treatment in the study and continue with their regularly scheduled visits.

Section 4.3.4 Screen Failures: Text was revised to clarify that if an image retransmission was requested from the central image centre vendor due to any possible technical issues, this was not to be considered rescreening.

Section 5.2 Treatments Administered: To further ensure the safety of subjects, the condition of pre-injection IOP was added and clarified in the protocol as per the request from the Russian regulatory agency. To avoid duplicated post-injection assessments of IOP and dilated fundoscopy by the masked and unmasked staff, both assessments were removed for the unmasked staff and were only to be conducted by the masked staff. The sponsor confirmed that the hand movement/finger counting checks by the unmasked team were sufficient for safety assessment.

Section 5.2.1 Treatment of Fellow Eye: This section was revised as per the sponsor's decision to allow treatment of fellow eye only with Eylea for the whole duration of the study.

Table 5-1: The VEGF treatment was updated as a prohibited medication, only applicable to the study eye. Additionally, the note on treatment of fellow eye was updated to reflect that it should be treated only with Eylea.

Section 5.3 Identity of IP: As per the US FDA request, the source of Eylea was updated.
Section 5.8.1 Rescue Treatment:

This section was updated as per the US FDA recommendation to let subjects who discontinued study treatment due to receipt of rescue treatment in the study to continue with their regularly scheduled visits.

Due to the sponsor's concern on the potential error caused by the IOP device, the condition for rescue treatment of an 'increase in the central subfield thickness of 100 µm compared with the latest assessment (optical coherence tomography [OCT]) by the investigator' was removed.

Section 5.8.2 Prohibited Medications: Prohibited medications applied to the fellow eye were removed as per the sponsor's decision to allow fellow eye treatment only with Eylea for the whole duration of the study.

Section 6.1.3 Early Termination/End-of-Study: This section was updated as per the US FDA request to keep subjects who discontinued study treatment in the study to continue with their regularly scheduled visits.

Section 6.3.3.6 Suspected Unexpected Serious Adverse Reactions (SUSAR) and Nonserious Adverse Events of Special Interest (AESIs): The title of the section and the body text on nonserious AESIs were removed because there is no definition of AESI in the protocol.

Section 6.4 Pharmacokinetic Assessments: A sentence was added to clarify that additional visits were to be arranged for collecting PK blood samples.

Section 6.7 Pregnancy: This section was updated to clarify that the serum pregnancy test was to be administered only to women of childbearing potential and to implement the change to keep subjects in the study to continue regularly scheduled visits and assessments after study treatment discontinuation. Additionally, follow-up for safety until the outcome of the pregnancy was known was emphasized.

Table 6-1 Schedule of Events: The footnotes to the Schedule of Events were updated to reflect changes in the text of the protocol.

Table 6-2 Clinical Laboratory Evaluations: The table of clinical laboratory evaluations was updated to include all the laboratory tests provided by the central laboratory.

Section 7.1 Estimands and Intercurrent Events: The section on estimands and intercurrent events was updated as per the US FDA request to change the FAS population and to not discontinue subjects from the study when they discontinued study treatment due to AE/lack of efficacy/rescue treatment.

Section 7.2 Sample Size Determination: Justification for the 3.8 letter equivalence margin was mentioned.

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: The section of primary efficacy outcome measures was updated as per the US FDA request to change the FAS population and to not discontinue subjects from the study when they discontinued study treatment due to AE/lack of efficacy/rescue treatment. The covariance structure was specified as per the request from US FDA.

Section 7.5.1.2 Secondary Efficacy Outcome Measures: The section on secondary efficacy outcome measures was updated as per the US FDA request to change the FAS population and to not discontinue subjects from the study when they discontinued study treatment due to AE/lack of efficacy/rescue treatment.

Section 11.2.2 Protocol Deviations: This section was updated as per the request from the Korean MFDS to list serious protocol violations in the protocol. The update had been applied to the Korea-specific protocol amendments.

Section 12 Reference List: The reference list was updated with the European Medicines Agency's (EMA) overview of Eylea.

Protocol Amendment 2, Version 3.0, dated 24 Jan 2022. The following is a summary of the major changes implemented with this amendment:

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.

Table 34: Baseline data

Parameter	SCD411 (N=287)	Eylea (N=286)	Total (N=573)
Age (years)			
n	287	286	573
Mean (SD)	73.5 (8.00)	73.6 (8.55)	73.5 (8.27)
Median	73.0	73.0	73.0
Q1, Q3	68.0, 79.0	68.0, 80.0	68.0, 80.0
Min, Max	54, 95	50, 98	50, 98
Age categories (years) - n (%)			
50 to <65	33 (11.5)	40 (14.0)	73 (12.7)
65 to <75	131 (45.6)	119 (41.6)	250 (43.6)
≥75	123 (42.9)	127 (44.4)	250 (43.6)
Sex - n (%)			
Male	138 (48.1)	139 (48.6)	277 (48.3)
Female	149 (51.9)	147 (51.4)	296 (51.7)
Childbearing potential	0	0	0
Non-childbearing potential	149 (51.9)	147 (51.4)	296 (51.7)
Race - n (%)			
White	188 (65.5)	194 (67.8)	382 (66.7)
Black or African American	1 (0.3)	1 (0.3)	2 (0.3)
Asian	97 (33.8)	90 (31.5)	187 (32.6)
American Indian or Alaska Native	1 (0.3)	1 (0.3)	2 (0.3)

Parameter	SCD411 (N=287)	Eylea (N=286)	Total (N=573)
Ethnicity - n (%)			
Hispanic or Latino	9 (3.1)	10 (3.5)	19 (3.3)
Not Hispanic or Latino	278 (96.9)	276 (96.5)	554 (96.7)
Country – n (%)			
Australia	7 (2.4)	6 (2.1)	13 (2.3)
Bulgaria	2 (0.7)	2 (0.7)	4 (0.7)
Czech Republic	3 (1.0)	3 (1.0)	6 (1.0)
Hungary	22 (7.7)	17 (5.9)	39 (6.8)
India	8 (2.8)	1 (0.3)	9 (1.6)
Israel	42 (14.6)	42 (14.7)	84 (14.7)
Japan	30 (10.5)	30 (10.5)	60 (10.5)
Latvia	10 (3.5)	13 (4.5)	23 (4.0)
Poland	37 (12.9)	50 (17.5)	87 (15.2)
Republic of Korea	59 (20.6)	59 (20.6)	118 (20.6)
Russian Federation	12 (4.2)	10 (3.5)	22 (3.8)
Slovakia	16 (5.6)	13 (4.5)	29 (5.1)
Spain	20 (7.0)	24 (8.4)	44 (7.7)
United States	19 (6.6)	16 (5.6)	35 (6.1)
Weight (kg)			
n	286	286	572
Mean (SD)	72.39 (15.244)	72.26 (14.280)	72.32 (14.757)
Median	70.00	71.40	70.00
Q1, Q3	61.20, 82.20	62.00, 84.00	61.65, 82.45
Min, Max	39.1, 130.0	39.6, 115.2	39.1, 130.0
Height (cm)			
n	286	286	572
Mean (SD)	164.02 (9.117)	164.64 (8.976)	164.33 (9.045)
Median	164.00	164.00	164.00
Q1, Q3	157.50, 170.00	159.30, 170.20	158.00, 170.00
Min, Max	145.0, 192.0	141.5, 187.0	141.5, 192.0

Parameter	SCD411 (N=287)	Eylea (N=286)	Total (N=573)
BMI (kg/m^2)			
n	286	286	572
Mean (SD)	26.81 (4.682)	26.53 (4.154)	26.67 (4.424)
Median	26.00	26.30	26.30
Q1, Q3	23.60, 29.60	23.70, 28.90	23.60, 29.20
Min, Max	16.1, 41.0	16.4, 44.0	16.1, 44.0

Abbreviations: BMI, body mass index; Max, maximum; Min, minimum; N, number of subjects in the analysis set for each treatment group; n, number of subjects in the analysis; Q1, first quartile; Q3, third quartile; SD, standard deviation.

Body Mass Index (BMI) = weight in kilograms/(height in meters)^2.

Note: Percentages were based on the number of subjects in Full Analysis Set for each treatment group.

Source data: Table 14.1.3.

Numbers analysed

See above

Outcomes and estimation

Results 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 5.8 letters in the SCD411 and Eylea groups, respectively. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.3 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. **The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.**

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. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.5 letters with 90% CI = -1.7 to 0.8 and 95% CI = -1.9 to 1.0. **The 95% CI was within the limit required for EMA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.**

For the Japanese subgroup, the BCVA score was comparable at Baseline among the treatment groups in the FAS. At Week 8, Eylea group showed an improvement of 6.7 letters (LS mean of 6.8 letters) in the BCVA score from baseline as compared with SCD411 group which showed an improvement of 4.3 letters (LS mean of 4.2 letters). The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -2.5 letters with 90% CI = -5.6 to 0.6 and 95% CI = -6.2 to 1.2.

For the non-Japanese subgroup, 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 5.7 and 5.7 letters and an LS mean of 5.6 and 5.7 letters in the SCD411 and Eylea groups, respectively. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.1 letters with 90% CI = -1.4 to 1.2 and 95% CI = -1.7 to 1.5.

The analysis based on the PPS yielded results similar to those of the FAS for both the Japanese and non-Japanese subgroups.

Overall, based on the results of the primary endpoint analysis (primary estimand: change from baseline in BCVA score for study eye at Week 8, without rescue therapy) for the FAS, SCD411 was found to be equivalent to Eylea. At Week 8, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.4 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups.

The tipping point analysis in FAS showed that the missing data of the primary endpoint (change from baseline in BCVA score at Week 8) needed to decrease by more than 9-fold of the treatment effect in the SCD411 group (LS mean change from baseline of 5.5 letters using MMRM analysis after MI) to tip the positive decision for 95% CI. As well, the missing data of the primary endpoint (change from baseline in BCVA score at Week 8) needed to decrease by more than 7-fold of the treatment effect in the SCD411 group (LS mean change from baseline of 5.5 letters using MMRM analysis after MI) to tip the positive decision for 90% CI. Such assumptions were considered very unlikely to be plausible, so the tipping point sensitivity analysis results confirmed the robustness of the results.

In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -2.5 letters with 90% CI = -5.6 to 0.6 and 95% CI = -6.2 to 1.2. In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.1 letters with 90% CI = -1.4 to 1.2 and 95% CI = -1.7 to 1.5.

The analysis of the primary endpoint based on the PPS yielded results similar to those of the FAS in the total population as well as the Japanese and non-Japanese subgroups.

The sensitivity and supportive analyses supported the primary analyses of the primary endpoint for the total population as well as the Japanese and non-Japanese subgroups.

The analysis of the secondary estimand based on the FAS yielded results same as that of the primary analysis of the Week 8 primary estimand based on the FAS.

Table 35: Protocol deviations

Protocol Deviations
All Randomized Subjects

Category [a]	SCD411 (N=288) n (%)	Eylea (N=288) n (%)	Total (N=576) n (%)
Total number of Non-Significant Protocol Deviation	813	780	1593
Total number of Significant Protocol Deviation	112	110	222
Subjects with at Least One Protocol Deviation	237 (82.3)	225 (78.1)	462 (80.2)
Subjects with at Least One Significant Protocol Deviation	86 (29.9)	72 (25.0)	158 (27.4)
VISIT SCHEDULING	37 (12.8)	32 (11.1)	69 (12.0)
STUDY PROCEDURES/ASSESSMENTS	27 (9.4)	23 (8.0)	50 (8.7)
MISSING ENDPOINT ASSESSMENTS	9 (3.1)	7 (2.4)	16 (2.8)
EXCLUSION CRITERIA	8 (2.8)	7 (2.4)	15 (2.6)
INV SAFETY RPTG (REG/SPONSOR)	4 (1.4)	8 (2.8)	12 (2.1)
INCLUSION CRITERIA	3 (1.0)	4 (1.4)	7 (1.2)
ICF PROCESS/TIMING	2 (0.7)	4 (1.4)	6 (1.0)
ACCIDENTAL UNBLINDING	1 (0.3)	4 (1.4)	5 (0.9)
STUDY TREATMENT COMPLIANCE	3 (1.0)	0	3 (0.5)
STUDY TREATMENT ADMIN/DISPENSE	1 (0.3)	1 (0.3)	2 (0.3)
STUDY TREATMENT RANDOMIZATION	1 (0.3)	1 (0.3)	2 (0.3)

Ancillary analyses

Subgroup analyses were performed by region/country (Japan, non-Japan). Demographics and baseline characteristics, safety, efficacy, and immunogenicity endpoints were analysed in subgroups. Subgroup summaries were descriptive only with no statistical hypothesis testing performed.

A total of 53 Japanese subjects (88.3%) completed the study treatment. All 60 Japanese subjects (100%) completed Week 8 of the study while 56 Japanese subjects (93.3%) had completed the study.

A total of 462 non-Japanese subjects (89.5%) completed the study treatment; 506 non-Japanese subjects (98.1%) completed Week 8 of the study while 466 non-Japanese subjects (90.3%) had completed the study.

In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -2.5 letters with 90% CI = -5.6 to 0.6 and 95% CI = -6.2 to 1.2. In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.1 letters with 90% CI = -1.4 to 1.2 and 95% CI = -1.7 to 1.5. The analysis of the primary endpoint based on the PPS yielded results similar to those of the FAS in the total population as well as the Japanese and non-Japanese subgroups.

The sensitivity and supportive analyses supported the primary analyses of the primary endpoint for the total population as well as the Japanese and non-Japanese subgroups.

2.4.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment, biosimilarity assessment (see later sections).

Table 36: Summary of efficacy for trial SCD411-CP101 A Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration

Title: SCD411-CP101 A Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration			
Study identifier	Study SCD411-CP101 EUDRA CT - 2019-004132-37 NCT number - NCT04480463 ISRCT not provided by the applicant IND 144376 location in eCTD - 5.3.5.1		
Design	This was a Phase 3, randomized, double-masked, parallel-group, and multicentre study to demonstrate the biosimilarity of SCD411 compared with Eylea® (aflibercept) among adult subjects with neovascular (wet) AMD. This was a 52 week study carried out to demonstrate equivalency between the study drug SCD411 and EU licenced Eylea®.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable not applicable
Hypothesis	Equivalence		
Treatments groups	SCD411		288 subject receiving SCD411 (Vgenfli) – 52 weeks
	EU-Eylea®		288 receiving reference product EU-Eylea® receiving it for 52 weeks
Endpoints and definitions	Primary endpoint		change in BCVA measured by ETDRS letters score or 2702 charts at Week 8.
	Secondary endpoint		The change from baseline in BCVA score for the study eye at Week 52
	Secondary endpoint		The change from Baseline in BCVA Score, CRT, and CNV Area for Study Eye by Visit
	Secondary endpoint		The gain of ≥ 15 letters in the BCVA score from baseline
Database lock	week 8		
Results and Analysis			

Title: SCD411-CP101 A Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration				
Study identifier	Study SCD411-CP101 EUDRA CT - 2019-004132-37 NCT number - NCT04480463 ISRCT not provided by the applicant IND 144376 location in eCTD - 5.3.5.1			
Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS Week 8			
Descriptive statistics and estimate variability Change From Baseline in BCVA Score for Study Eye at Week 8 (Primary Estimand, Multiple Imputation, Full Analysis Set)	Treatment group		SCD411	EU-Eylea
	Number of subjects		287	286
	Baseline	Mean	58.6 (10.75)	59.9 (10.60)
		Median	60.0	61.0
		Min, Max	35, 76	33,73
	Unadjusted Week 8	Imputed n/ Observed n	8/279	1/285
		Mean	64.2 (13.32)	65.7 (13.08)
		Median	67.0	68.6
		Min, Max	9, 90	15, 90
	Unadjusted change from baseline	Imputed n/ Observed n	8/279	1/285
		Mean	5.5 (9.58)	5.8 (8.06)
		Median	5.0	5.2
		Min, Max	-51, 37	-28, 31
	estimated mean change baseline (MMRM)	LS mean (SE) 95% CI	5.5 (0.53) 4.5, 6.5	5.9 (0.52) 4.8, 6.9

Title: SCD411-CP101 A Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration				
Study identifier	Study SCD411-CP101 EUDRA CT - 2019-004132-37 NCT number - NCT04480463 ISRCT not provided by the applicant IND 144376 location in eCTD - 5.3.5.1			
	estimated mean difference (SCD411-Eylea) MMRM	LS mean (SE) 90% CI 95% CI	-0.4 (0.74) -1.6, 0.9 1.8, 1.1	
	estimated mean change from baseline, ANCOVA	LS mean (SE) 95% CI	5.5 (0.53)	5.9 (0.52)
	estimated mean difference (SCD411-Eylea) ANCOVA	LS mean (SE) 90% CI 95% CI	-0.4 (0.74) -1.6, 0.8 -1.8, 1.1	
Change From Baseline in BCVA Score for Study Eye at Week 8 (Primary Estimand, Multiple Imputation, Per protocol set)	Number of subjects		275	283
	Baseline	Observed	275	283
		Mean	58.4 (10.85)	59.9 (10.65)
		Median	60	61.0
		min, max	35,76	15,90
	Unadjusted week 8	Imputed n/ Observed n	1/274	0/283
		Mean	63.9 (13.38)	65.7 (13.12)
		Median	67.0	69.0
		Min, Max	9, 88	15, 90
	Unadjusted change from baseline	Imputed n/ Observed n	1/274	0/283

Title: SCD411-CP101 A Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration				
Study identifier	Study SCD411-CP101 EUDRA CT - 2019-004132-37 NCT number - NCT04480463 ISRCT not provided by the applicant IND 144376 location in eCTD - 5.3.5.1			
		Mean	5.5 (9.66)	5.8 (8.05)
		Median	5.0	5.0
		Min, Max	-51, 37	-28,31
	estimated mean change baseline (MMRM)	LS mean (SE) 95% CI	5.4 (0.53) 4.4, 6.5	5.9 (0.53) 4.8, 6.9
	estimated mean difference (SCD411-Eylea) MMRM	LS mean (SE) 90% CI 95% CI	-0.5 (0.75) -1.7, 0.8 -1.9, 1.0	
	estimated mean change from baseline, ANCOVA	LS mean (SE) 95% CI	a. (0.53) 4.4, 6.5	5.9 (0.53) 4.8, 6.9
	estimated mean difference (SCD411-Eylea) ANCOVA	LS mean (SE) 90% CI 95% CI	-0.5 (0.75) -1.7, 0.7 -2.0, 1.0	

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, an LS mean of 5.5 and 5.9 letters for MMRM analysis, and an LS mean of 5.5 and 5.9 letters for ANCOVA in SCD411 and Eylea groups, respectively. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score by MMRM analysis was -0.4 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score by ANCOVA was -0.4 letters with 90% CI = -1.6 to 0.8 and 95% CI = -1.8 to 1.1. For both MMRM analysis and ANCOVA, the 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.

The BCVA score was comparable at baseline among the treatment groups in the PPS. At Week 8, the analysis based on PPS yielded results similar to those of FAS. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score by MMRM

analysis was -0.5 letters with 90% CI = -1.7 to 0.8 and 95% CI = -1.9 to 1.0. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score by ANCOVA was -0.5 letters with 90% CI = -1.7 to 0.7 and 95% CI = -2.0 to 1.0. For both MMRM analysis and ANCOVA, the 95% CI was within the limit required for EMA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.

2.4.5.4. Clinical studies in special populations

Not applicable.

2.4.5.5. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.4.5.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.4.5.7. Supportive study(ies)

Not applicable.

2.4.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The sponsor has conducted 1 clinical study, the first-in-human study with SCD411. Trial SCD411-CP101 was a phase III Randomized, Double-Masked, Parallel-Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age Related Macular Degeneration. This was a 52 week study carried out to demonstrate equivalency between the study drug SCD411 and EU licenced Eylea®.

The study is complete and final analysis results are presented by the applicant. It was a multicentre, randomised, double-masked, active controlled, comparative clinical study in subjects with neovascular age-related macular degeneration (nAMD). It is acceptable that no further clinical studies have been conducted to demonstrate similarity in efficacy between SCD411 (Vgenfli) and Eylea in indications approved for EU Eylea.

The study was conducted in subjects with neovascular age-related macular degeneration (nAMD). Neovascular AMD is one of the approved indications of Eylea in the EU. Other approved indications include visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to diabetic macular oedema (DME), and visual impairment due to myopic choroidal neovascularisation (myopic CNV). Neovascular AMD (nAMD) and DME are likely the most sensitive indication as compared to RVO, and CNV to detect possibly existing differences between the treatments. Patients with CNV secondary to myopia might need very few injections and are also not considered appropriate. Furthermore, studies with the originator showed that the treatment effect of aflibercept was largest in patients with nAMD (comparison against placebo).

The receptor and mechanism of action of aflibercept are the same across different ophthalmological indications approved for the reference product and aflibercept is directly delivered at its site of action. Since nAMD patients are generally considered a sensitive population for assessing similarity in clinical efficacy of aflibercept, to it is agreed that, if similarity is demonstrated in nAMD patients, the findings can be extrapolated to other indications approved for Eylea (CRVO/BRVO, DME and myopic CNV).

Only treatment-naïve patients were included in the study.

Biopharmaceutic studies have not been conducted with SCD411 because both SCD411 and Eylea are in solution form that are administered intravitreally to the site of action directly, having local effects without significant systemic absorption and distribution. The available data regarding the PK of the reference product suggests that a proper PK characterization will not be possible after single IVT administration.

In a PK substudy of Eylea, in 6 neovascular wet AMD patients with frequent sampling, maximum plasma concentrations (C_{max}) of free aflibercept (systemic) were low, with a mean of approximately 0.02 µg/mL (range 0 to 0.054) within 1 to 3 days after a 2 mg IVT injection and were undetectable 2 weeks following dosage in almost all patients. It was evident that in some subjects, measurable blood levels of free aflibercept that would be pharmacologically active systemically were not registered after IVT administration. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks. Free and bound aflibercept are expected to be cleared by proteolytic catabolism.

The stepwise development of SCD411 gave evidence for similarity of structural characteristics, physiochemical characteristics, and biological activities to Eylea. This similarity directly implies that SCD411 has the same pharmacokinetic property and mechanism of action as Eylea.

In the completed Phase 3 clinical study (Study SCD411-CP101) with SCD411, the following PK parameters were to be evaluated: area under the concentration-time curve (AUC) from time zero to the last quantifiable time point (AUC_{0-t}), AUC from time zero to the end of the dosing period (AUC_{0-tau}), AUC from time zero to infinite time (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), and elimination half-life ($t_{1/2}$) of SCD411 and Eylea.

Quantification of free and bound Eylea and SCD411 in plasma was performed using blood samples at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first (Day 1) and the third (Week 8) dose.

For free SCD411, the geometric mean peak (C_{max}) and total (AUC_{0-t}) plasma exposure values were 58.9 ng/mL and 250 day*ng/mL and 50.7 ng/mL and 401 day*ng/mL, for Day 1 (first injection) and at Week 8 (third injection), respectively. For free Eylea, the geometric mean peak (C_{max}) and total (AUC_{0-t}) plasma exposure values were 49.3 ng/mL and 413 day*ng/mL and 43.0 ng/mL and 200 day*ng/mL, for Day 1 (first injection) and at Week 8 (third injection), respectively.

For bound SCD411, the geometric mean peak (C_{max}) and total (AUC0-t and AUC0-tau) plasma exposure values were 48.7 ng/mL, 1030 day*ng/mL, and 996 day*ng/mL and 87.8 ng/mL, 1930 day*ng/mL, and 1680 day*ng/mL, for Day 1 (first injection) and Week 8 (third injection), respectively. For bound Eylea, the geometric mean peak (C_{max}) and total (AUC_{0-t} and AUC_{0-tau}) plasma exposure values were 55.2 ng/mL, 1260 day*ng/mL, and 1160 day*ng/mL and 94.7 ng/mL, 2080 day*ng/mL, and 1960 day*ng/mL, for Day 1 (first injection) and Week 8 (third injection), respectively

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and at Week 8 (third injection), peak (C_{max}) and total exposure (AUC0-t) to free and bound SCD411 was similarly comparable to those observed for free and bound Eylea.

The mean C_{max} of free aflibercept in the SCD411 arm was 0.082 and 0.055 and 0.059 and 0.045 µg/mL in the Eylea arm after Day 1 (first injection) and at Week 8 (third injection). These results are also similar to the results observed in clinical trials with Eylea (Eylea SmPC 2023). Only free aflibercept is able to bind endogenous VEGF; however, aflibercept is predominately observed in the systemic circulation as an inactive, stable complex with VEGF.

The inclusion criteria included patients ≥ 50 years of age with active choroidal subfoveal, juxtafoveal, or extrafoveal neovascularization lesions secondary to AMD evidenced by fluorescein angiography,

BCVA letter score was between 73 and 35, the CNV area making up either 50% or more of the total lesion area and confirmed by the central reading centre.

A total of 914 subjects were assessed for eligibility across 132 sites in 14 countries. A total of 576 subjects were randomly assigned to 1 of 2 treatment groups: 288 subjects each to the SCD411 group and Eylea group. A total of 515 subjects (89.4%) had completed the study treatment: 259 subjects (89.9%) in the SCD411 group and 256 subjects (88.9%) in the Eylea group, and 61 subjects (10.6%) had discontinued the study treatment: 29 subjects (10.1%) in the SCD411 group and 32 subjects (11.1%) in the Eylea group.

The study consisted of a screening period of up to 3 weeks, a treatment period up to 48 weeks, and a post-treatment follow-up period up to 4 weeks. The total duration of study participation was up to 55 weeks.

Subjects who continued to meet all inclusion and none of the exclusion criteria were randomly assigned in a 1:1 ratio to receive IVT SCD411 or Eylea injections on Day 1. Randomization was stratified by subject participation in the PK substudy and by the subjects enrolment in Japan. Subjects from 10 countries did not participate in the PK study (Australia, Bulgaria, the Czech Republic, Hungary, Israel, Japan, Latvia, Russia, Spain, and Slovakia).

The dosing schedule of SCD411 was to mimic that of Eylea in this study. 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). This dosage has been found to be efficacious in subjects with wet AMD and has an acceptable safety profile.

The reference product was EU - Eylea (Eylea 40 mg/mL, Bayer, marketing authorization number EU/1/12/797/002, date 2012-11-21).

VGENFLI (SCD411 - proposed biosimilar of Eylea®) intravitreal (IVT) injection 2 mg every 4 weeks (approximately every 28 days, monthly) for 3 consecutive doses, followed by a 2 mg IVT injection once every 8 weeks (2 months) until Week 48. This is the approved posology of EU – Eylea®.

The methods used for the primary (visual acuity) and secondary efficacy assessments represent standard used for respective assessments and are considered adequate.

The study completion rate was overall high and comparable between treatment arms.

A total of 576 subjects were randomly assigned to 1 of 2 treatment groups: 288 subjects each to the SCD411 group and Eylea group. A total of 515 subjects (89.4%) had completed the study treatment: 259 subjects (89.9%) in the SCD411 group and 256 subjects (88.9%) in the Eylea group, and 61 subjects (10.6%) had discontinued the study treatment: 29 subjects (10.1%) in the SCD411 group and 32 subjects (11.1%) in the Eylea group.

The most common reasons for discontinuing study treatment across treatment groups were AE (14 subjects [23.0%]), withdrawal of consent by the subject (13 subjects [21.3%]), and other (10 subjects [16.4%]).

A total of 566 subjects (98.3%) had completed Week 8 of the study: 281 subjects (97.6%) in the SCD411 group and 285 subjects (99.0%) in the Eylea group. A total of 522 subjects (90.6%) had completed the study: 261 subjects (90.6%) each in the SCD411 group and Eylea.

A total of 54 subjects (9.4%) had prematurely discontinued the study: 27 subjects (9.4%) each in the SCD411 and Eylea groups. The most common reasons for discontinuing the study across treatment groups were withdrawal of consent by the subject (14 subjects [25.9%]), AE (9 subjects [16.7%]), and other (9 subjects [16.7%]).

Based on the results of the primary endpoint analysis (primary estimand: change from baseline in BCVA score for study eye at Week 8, without rescue therapy) for the FAS, SCD411 was found to be equivalent to Eylea. At Week 8, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.4 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. **The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups**.

In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -2.5 letters with 90% CI = -5.6 to 0.6 and 95% CI = -6.2 to 1.2. In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.1 letters with 90% CI = -1.4 to 1.2 and 95% CI = -1.7 to 1.5.

The analysis of the primary endpoint based on the PPS yielded results similar to those of the FAS in the total population as well as the Japanese and non-Japanese subgroups.

The sensitivity and supportive analyses supported the primary analyses of the primary endpoint for the total population as well as the Japanese and non-Japanese subgroups.

Secondary endpoints

Change from baseline in BCVA score for study eye at week 52.

At Week 52, for the FAS, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was 1.3 letters with 90% CI = -0.4 to 2.9 and 95% CI = -0.7 to 3.2. In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was 1.0 letter with 90% CI = -3.6 to 5.6 and 95% CI = -4.5 to 6.5. In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was 1.3 letters with 90% CI = -0.5 to 3.1 and 95% CI = -0.8 to 3.4.

The analysis of the secondary endpoint of change from baseline in BCVA score at Week 52 based on the PPS yielded results similar to those of the FAS in the total population as well as the Japanese and non-Japanese subgroups.

Change from baseline in BCVA score , CRT, and CNV area for study eye by the visit

The analysis of change from baseline in BCVA score, CRT, and CNV area by visit for the total population as well as Japanese and non-Japanese subgroups showed that changes from baseline were similar between the treatment groups at Week 8.

The maximum increase in BCVA score being seen at Weeks 44 and 52 in the SCD411 group and at Week 52 in the Eylea group (mean change from baseline of 9.7 letters in the SCD411 group and 8.0 letters in the Eylea group). For the Japanese subgroup, in the study eye, the maximum increase in BCVA score was seen at Week 44 in the SCD411 group (mean change from baseline of 9.4 letters) and Week 20 in the Eylea group (mean change from baseline of 7.0 letters). For the non-Japanese subgroup, in the study eye, the maximum increase in BCVA score was seen at Week 52 in the SCD411 group (mean change from baseline of 9.9 letters) and Eylea group (mean change from baseline of 8.3 letters).

The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CRT at Week 8 was 0.5 µm (90% CI = -11.8 to 12.9 and 95% CI = -14.2 to 15.2) and at Week 52 was -10.7 µm (90% CI = -22.8 to 1.5 and 95% CI = -25.1 to 3.8). In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CRT at Week 8 was -7.8 µm (90% CI = -46.0 to 30.4 and 95% CI = -53.6 to

38.0) and at Week 52 was -26.4 µm (90% CI = -56.4 to 3.7 and 95% CI = -62.3 to 9.6). In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CRT at Week 8 was 1.8 µm (90% CI = -11.3 to 14.8 and 95% CI = -13.8 to 17.3) and at Week 52 was -8.9 µm with 90% CI = -22.0 to 4.3 and 95% CI = -24.6 to 6.8.

The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CNV area at Week 8 was 0.2146 mm^2 (90% CI = -0.1152 to 0.5444 and 95% CI = -0.1785 to 0.6078) and at Week 52 was -0.2837 mm^2 (90% CI = -0.6593 to 0.0919 and 95% CI = -0.7313 to 0.1639). In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CNV area at Week 8 was 1.0615 mm^2 (90% CI = 0.1540 to 1.9690 and 95% CI = -0.0254 to 2.1483) and at Week 52 was 0.4426 mm^2 (90% CI = -0.4698 to 1.3549 and 95% CI = -0.6504 to 1.5356). In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in CNV area at Week 8 was 0.1145 mm^2 (90% CI = -0.2346 to 0.4636 and 95% CI = -0.3017 to 0.5307) and at Week 52 was -0.3657 mm^2 (90% CI = -0.7675 to 0.0362 and 95% CI = -0.8447 to 0.1134).

Gain of ≥ 15 letters in BCVA score from baseline

The proportion of subjects who gained ≥15 letters in BCVA score was similar between the treatment groups at Week 8 in the FAS.

The difference in response rate (SCD411- Eylea) with respect to proportion of subjects who gained ≥15 letters in BCVA score at Week 8 was -0.4 (95% CI = -5.8 to 5.0) and at Week 52 was 6.9 (95% CI = -0.4 to 14.1). For the Japanese subgroup, the difference in response rate (SCD411-Eylea) with respect to proportion of subjects who gained ≥15 letters in BCVA score at Week 8 was -6.7 (95% CI = -24.7 to 10.4) and at Week 52 was 10.0 (95% CI = -10.7 to 30.7). For the non-Japanese subgroup, the difference in response rate (SCD411-Eylea) with respect to proportion of subjects who gained ≥15 letters in BCVA score at Week 8 was 0.3 (95% CI = -5.5 to 6.2) and at Week 52 was 6.5 (95% CI = -1.2 to 14.3).

Subgroup analyses (PK)

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), peak free SCD411 and Eylea concentrations were attained at a median tmax of 1 day, ranging from 0.91 to 7 days across both treatment groups. Lambda_z and all associated parameters were only reported where a minimum of 3 data points were used (C_{max} was not to be included) and where r2 ≥0.80. Based on these criteria, characterization of the terminal elimination phase was limited for both free SCD411 and Eylea, with geometric mean t1/2 of 6.58 days (based on data available from 2 subjects) for free SCD411 following the third IVT injection on Week 8, while $t_{1/2}$ values not determined for free Eylea. Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1, peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were comparable, when accounting for inter-subject variability. Geometric mean values of C_{max} were 58.9 ng/mL and 49.3 ng/mL for free SCD411 and Eylea, respectively, with values ranging from 26.3 to 286 ng/mL for free SCD411 and from 23.5 to 164 ng/mL for free Eylea. Geometric mean values of AUC_{0-t} were 250 day x ng/mL free SCD411 and Eylea, respectively, with values ranging from 155 to 581 day × ng/mL for free SCD411 and from 257 to 662 day × ng/mL for free Eylea.

Peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were similarly comparable following the third IVT injection on Week 8 (third injection). Geometric mean values of C_{max} were 50.7 ng/mL and 43.0 ng/mL for free SCD411 and Eylea, respectively, with values ranging from 22.6 to 105 ng/mL for free SCD411 and from 33.3 to 83.3 ng/mL for free Eylea. Geometric mean values of AUC_{0-t} were 401 day × ng/mL and 200 day × ng/mL for free SCD411 and Eylea, respectively, with values

ranging from 169 to 946 day × ng/mL for free SCD411 and from 186 to 217 day × ng/mL for free Eylea.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), the mean bound SCD411 and Eylea concentration versus time profiles were similarly characterized by a slower absorption phase compared to free SCD411 and Eylea, with concentrations remaining constant up to the end of the sampling period (28 days). Peak concentrations (C_{max}) were attained later following the first IVT injection; median t_{max} estimates were 14 days for bound SCD411 and Eylea on Day 1 (first injection) and were 7 days on Week 8 (third injection).

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection), peak (C_{max}) and total (AUC_{0-t} and AUC_{0-tau}) exposure to bound SCD411 and Eylea were comparable, when accounting for inter-subject variability. Geometric mean values of C_{max} were 48.7 ng/mL and 55.2 ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 28.2 to 86.1 ng/mL for bound SCD411 and from 36.2 to 108 ng/mL for bound Eylea. Geometric mean values of AUC_{0-t} were 1030 day × ng/mL and 1260 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 580 to 2040 day × ng/mL for bound SCD411 and from 836 to 2560 day × ng/mL for bound Eylea. Geometric mean values of AUC0-tau were 996 day × ng/mL and 1160 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 718 to 1250 day × ng/mL for bound SCD411 and from 919 to 1410 day × ng/mL for bound Eylea.

Peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were similarly comparable following the third IVT injection on Week 8. Geometric mean values of C_{max} were 87.8 ng/mL and 94.7 ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 43.6 to 210 ng/mL for bound SCD411 and from 56.3 to 149 ng/mL for bound Eylea. Geometric mean values of AUC_{0-t} were 1930 day × ng/mL and 2080 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 938 to 4900 day × ng/mL for bound SCD411 and from 492 to 3190 day × ng/mL for bound Eylea. Geometric mean values of AUC_{0-tau} were 1680 day × ng/mL and 1960 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 1280 to 2570 day × ng/mL for bound SCD411 and from 656 to 2980 day × ng/mL for bound Eylea.

Immunogenicity results

Observed levels of immunogenicity were similar between the SCD411 and Eylea groups with low incidence of NAb positivity at postbaseline, in the total population as well as Japanese and non-Japanese subgroups.

Discussion of study design and conduct of clinical study

The randomized, double-masked, active-controlled trial design was appropriate and adhered to regulatory requirements. The 52-week duration is sufficient for initial efficacy and safety assessments. The study's dosing frequency for SCD411 was every 4 weeks for the first 3 injections, followed by every 8 weeks thereafter until Week 48. Given its established efficacy, the use of Eylea as a comparator is relevant and justified. The study was conducted in accordance with Good Clinical Practice (GCP) and adhered to all relevant legal and regulatory guidelines applied for the EU/EEA region.

The Phase III study enrolled 576 patients, 288 of whom received SCD411 and 288 of whom received Eylea. The inclusion and exclusion criteria were comprehensive, ensuring a representative patient population was selected. Key inclusion criteria were subjects aged 50 years or older, having active choroidal neovascularization lesions secondary to AMD, and having a best corrected visual acuity (BCVA) letter score of 73 to 35 using ETDRS charts. There were no major age-related exclusions. Significant protocol deviations occurred in 27.4% of subjects, mostly related to visit scheduling and study procedures. Findings regarding dropouts or deviations included 54 subjects (9.4%) prematurely

discontinuing the study, with reasons including adverse events (16.7%), loss to follow-up (13.0%), and withdrawal of consent (25.9%).

The choice of BCVA and CRT as primary and secondary endpoints is appropriate and aligns with regulatory guidelines. These endpoints are valid surrogate markers for visual function and retinal health in neovascular wet AMD.

The statistical methods used, including MMRM and ANCOVA, were robust and appropriate for the data. Sensitivity analyses and subgroup analyses were also conducted to ensure the reliability of the findings.

The study design adhered to regulatory requirements set by EMA, including those of the US FDA and PMDA (Japan). The equivalence margins and statistical methods used align with regulatory guidelines. The study incorporated feedback from SA, ensuring the study design's robustness and the endpoints' relevance. Also, the applicant has adhered to the scientific advice provided by CHMP (specifically the follow-up scientific advice EMEA/H/SA/3594/1/FU/1/2019/II) regarding the equivalence margins for demonstrating biosimilarity between SCD411 and Eylea. The applicant's documentation and analysis demonstrate a thorough and compliant approach to establishing biosimilarity as advised by CHMP.

Results

At Week 8, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.4 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. The primary analysis results showed that the 95% CIs for the difference in BCVA scores were within the specified equivalence margins of ±3.8 letters, indicating that SCD411 is equivalent to Eylea in terms of clinical efficacy. SCD411 demonstrated similar efficacy to Eylea, with comparable changes in BCVA and CRT at Weeks 8 and 52. The mean differences between the two treatments were within the predefined equivalence margins, supporting the hypothesis of biosimilarity.

Some variability in the efficacy outcomes across different subgroups was noted. E.g., the least square mean difference in best corrected visual acuity (BCVA) between SCD411 and Eylea was 0.9 (±2.79) letters in Japanese subjects compared to 1.2 (±1.09) letters in non-Japanese subjects. This difference's 95% confidence interval ranged from -4.6 to 6.3 in Japanese subjects and -0.9 to 3.4 in non-Japanese subjects, indicating slightly higher variability in the Japanese subgroup. Additionally, the proportion of subjects who gained ≥15 letters in BCVA score varied, with 28.6% of Japanese subjects on SCD411 achieving this improvement compared to 24.8% of non-Japanese subjects. Central retinal thickness (CRT) changes also showed variability, with mean reductions of 95.1 µm in Japanese subjects and 92.3 µm in non-Japanese subjects. These differences highlight the demographic variations in clinical efficacy assessments. However, these demographic variations do not question the overall efficacy for the population intended on the EU market.

The impact of rescue therapy on efficacy outcomes was considered, but further clarity on how it influenced the overall results is needed. A summary of the use of previous and concurrent prohibited medication was not found in the documentation. The applicant is invited to provide this data. The number of intercurrent events till Week 8 (treatment discontinuation, rescue medication) should be compared between treatment arms. In addition, subgroup analyses for the patients with and without fellow eye Eylea treatment should be performed.

The applicant's clinical overview, summary of clinical efficacy, and other relevant documents submitted in M5 provide detailed results of the studies that were conducted to assess biosimilarity.

The subgroup analyses

In the Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -2.5 letters with 90% CI = -5.6 to 0.6 and

95% CI = -6.2 to 1.2. In the non-Japanese subgroup, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.1 letters with 90% CI = -1.4 to 1.2 and 95% CI = -1.7 to 1.5.

The differences in efficacy outcomes between Japanese and non-Japanese subgroups suggest potential variability based on race. There were observed differences in the change from baseline in CRT between Japanese and non-Japanese subgroups, with Japanese participants showing a more substantial decrease at Week 52. The primary endpoint, change from baseline in BCVA score at Week 8, showed some differences between the two subgroups, but these were not statistically significant. The observed variability in efficacy between subgroups (e.g., Japanese vs. non-Japanese) raises uncertainty about the generalizability of the results. Possible coping strategies include conducting additional subgroup-specific analyses and considering further studies to confirm these findings.

Immunogenicity

The incidence of ADA-positive subjects was relatively high during the study, but no clear impact on efficacy endpoints was observed. Approximately 20% to 40% of subjects in the SCD411 group and 19% to 52% in the Eylea group were ADA positive at postbaseline timepoints through Week 52.

The incidence of NAb-positive subjects was low, and there was no clear impact on efficacy. Of the subjects who provided blood samples for immunogenicity assessment at Baseline, 1.1% of subjects in the SCD411 group and 2.2% of subjects in the Eylea group were NAb positive at Baseline. Postbaseline, the incidence of NAb positive subjects remained below 3% in the SCD411 group and mostly below 4% in the Eylea group. For more information, see section Discussion on clinical safety.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

Not applicable.

Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances

Not applicable.

2.4.7. Conclusions on the clinical efficacy

SCD411 (Vgenfli) is shown to be equivalent to Eylea with respect to the change from baseline in BCVA score for study eye at Week 8. SCD411 also shows comparable efficacy to Eylea with respect to BCVA change from baseline; change from baseline in CRT and CNV area; and proportion of subjects who gain ≥15 letters in BCVA over 52 weeks of treatment. SCD411 is well-tolerated with a favourable safety profile that is comparable with Eylea. Immunogenicity of SCD411 and Eylea is low and PK profile is comparable.

The submitted data support the biosimilarity of VGENFLI (SCD411) to EU-EYLEA.

2.4.8. Clinical safety

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

The sponsor has conducted 1 clinical study, the first-in-human study with SCD411. This was a Phase 3, randomized, double-masked, parallel-group, multicentre study (Study SCD411-CP101) to compare the efficacy, safety, tolerability, pharmacokinetics (PK), and immunogenicity between the SCD411 and Eylea® in subjects with neovascular age-related macular degeneration (AMD). The study is complete and final analysis results are presented by the applicant.

Safety endpoints in this study included adverse events (AEs), vital signs, electrocardiograms (ECGs), ophthalmological examinations, and laboratory assessments up to Week 52. Safety was also evaluated during post-treatment follow-up (4 weeks after End-of-Treatment [EOT] visit). The interim analysis was performed when approximately 200 subjects completed the Week 52 Visit and all subjects who completed the Week 24 Visit or discontinued early from the study.

2.4.8.1. Patient exposure

Table 37: Patient exposure (cut off)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled)	NA	NA	NA	NA
Blinded studies (active -controlled)	576	287 (reference 286)*	287 (reference 286)*	Not provided
Open studies	NA	NA	NA	NA
Post marketing	NA	NA	NA	NA
Compassionate use	NA	NA	NA	NA

* Received at least 1 dose of active treatment

** In general, this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

The median duration of exposure was 337.0 days in each of the SCD411 and Eylea group and overall ranged from 1 to 372 days. Median compliance was 100.0% in each of the SCD411 and Eylea group and overall ranged from 66.7 to 100.0%. Most subjects (99.8%) were ⩾75 to ⩽100% compliant to study treatment.

2.4.8.2. Adverse events

Table 38: Overview of treatment emergent adverse events

	SCD411 (N=287) n (%)	Eylea (N=286) n (%)	Total (N=573) n (%)
Ocular TEAE			
Study eye			
Any TEAE	69 (24.0)	71 (24.8)	140 (24.4)
Any TEAE related to study drug	15 (5.2)	12 (4.2)	27 (4.7)
Any TEAE related to injection procedure	20 (7.0)	19 (6.6)	39 (6.8)
Any severe TEAE	2 (0.7)	2 (0.7)	4 (0.7)
Any serious TEAE	5 (1.7)	3 (1.0)	8 (1.4)
Any serious TEAE related to study drug	2 (0.7)	0	2 (0.3)
Any serious TEAE related to injection procedure	2 (0.7)	0	2 (0.3)
Any TEAE leading to dose interruption	0	0	0
Any TEAE leading to treatment discontinuation	4 (1.4)	5 (1.7)	9 (1.6)
Any TEAE leading to study discontinuation	2 (0.7)	2 (0.7)	4 (0.7)
Any TEAE leading to death	0	0	0
Any AESI	17 (5.9)	15 (5.2)	32 (5.6)
Fellow eye			
Any TEAE	54 (18.8)	48 (16.8)	102 (17.8)
Any TEAE related to study drug	1 (0.3)	0	1 (0.2)
Any TEAE related to injection procedure	2 (0.7)	1 (0.3)	3 (0.5)
Any severe TEAE	1 (0.3)	1 (0.3)	2 (0.3)
Any serious TEAE	0	1 (0.3)	1 (0.2)
Any serious TEAE related to study drug	0	0	0
Any serious TEAE related to Injection procedure	0	0	0
Any TEAE leading to dose interruption	1 (0.3)	0	1 (0.2)
Any TEAE leading to treatment discontinuation	0	0	0
Any TEAE leading to study discontinuation	0	0	0
Any TEAE leading to death	0	0	0
Any AESI	9 (3.1)	9 (3.1)	18 (3.1)
	SCD411 (N=287) n (%)	**Eylea (N=286) n (%)**	**Total (N=573) n (%)**

Non-ocular TEAE			
Any TEAE			
	128 (44.6)	130 (45.5)	258 (45.0)
Any TEAE related to study drug	0	2 (0.7)	2 (0.3)
Any TEAE related to injection procedure	1 (0.3)	0	1 (0.2)
Any severe TEAE	18 (6.3)	22 (7.7)	40 (7.0)
Any serious TEAE	27 (9.4)	27 (9.4)	54 (9.4)
Any serious TEAE related to study drug	0	2 (0.7)	2 (0.3)
Any serious TEAE related to injection procedure	0	0	0
Any TEAE leading to dose interruption	4 (1.4)	4 (1.4)	8 (1.4)
Any TEAE leading to treatment discontinuation	3 (1.0)	4 (1.4)	7 (1.2)
Any TEAE leading to study discontinuation	2 (0.7)	1 (0.3)	3 (0.5)
Any TEAE leading to death	0	0	0
Any AESI	5 (1.7)	10 (3.5)	15 (2.6)
	SCD411 (N=287)	**Eylea (N=286)**	**Total (N=573)**
	n (%)	**n (%)**	**n (%)**

AE in the study eye

Overall, TEAEs of the study eye were reported in 140 subjects (24.4%). There were no ocular TEAE-related deaths. Treatment-emergent AEs related to study drug and injection procedure were reported in 27 subjects (4.7%) and 39 subjects (6.8%), respectively. Non-fatal ocular serious TEAEs of the study eye were reported in 8 subjects (1.4%) and serious TEAEs in 2 subjects (0.3%) each were related to the study drug and injection procedure. None of the TEAEs in the study eye led to dose interruption. Treatment-emergent AEs of the study eye leading to treatment discontinuation were reported in 9 subjects (1.6%) and leading to study discontinuation were reported in 4 subjects (0.7%). Most TEAEs of the study eye were mild or moderate in intensity and severe TEAEs were reported in 4 subjects (0.7%). Adverse events of special interest (AESIs) were reported in 32 subjects (5.6%).

AE in the fellow eye

Overall, TEAEs of the fellow eye were reported in 102 subjects (17.8%). In the fellow eye, there were no fatal TEAEs or TEAEs that led to treatment or study discontinuation. Treatment-emergent AEs related to study drug and injection procedure were reported in 1 subject (0.2%) and 3 subjects (0.5%), respectively. A non-fatal ocular serious TEAE of the fellow eye was reported in 1 subject (0.2%). Treatment-emergent AE of the fellow eye leading to dose interruption were reported in 1 subject (0.2%). Almost all TEAEs of the fellow eye were mild or moderate in intensity and severe TEAEs were reported in 2 subjects (0.3%). Adverse events of special interest were reported in 18 subjects (3.1%).

Non – ocular TEAEs

Overall, non-ocular TEAEs were reported in 258 subjects (45.0%). Treatment-emergent AEs related to study drug and injection procedure were reported in 2 subjects (0.3%) and 1 subject (0.2%), respectively. There were no non-ocular TEAE-related deaths. Non-fatal non-ocular serious TEAEs were reported in 54 subjects (9.4%), and serious TEAEs in 2 subjects (0.3%) were related to the study drug. Non-ocular TEAEs leading to dose interruption were reported in 8 subjects (1.4%). Non-ocular TEAEs leading to treatment discontinuation were reported in 7 subjects (1.2%) and leading to study discontinuation were reported in 3 subjects (0.5%). Most non-ocular TEAEs were mild in intensity and severe TEAEs were reported in 40 subjects (7.0%). Adverse events of special interest were reported in 15 subjects (2.6%).

Japanese and Non-Japanese Subgroups

Overall, there was no difference between the Japanese and non-Japanese subgroups with respect to the incidence of any ocular and non-ocular TEAEs. Within the Japanese and non-Japanese subgroups, the incidence of ocular and non-ocular TEAEs was comparable between the treatment groups.

Overall, TEAEs of the study eye were reported in 16 subjects (26.7%) and 124 subjects (24.2%) in the Japanese and non-Japanese subgroups, respectively. The TEAEs of the fellow eye were reported in 13 subjects (21.7%) and 89 subjects (17.3%) in the Japanese and non-Japanese subgroups, respectively. Non-ocular TEAEs were reported in 35 subjects (58.3%) and 223 subjects (43.5%) in the Japanese and non-Japanese subgroups, respectively.

Most common AE

The most common reported TEAE are presented in the following table:

Table 39: Ocular Treatment-Emergent Adverse Events Reported in ⩾1% of Subjects in Any Treatment Group (Safety Set)

	SCD411	**Eylea**	**Total**
System Organ Class	**(N=287)**	**(N=286)**	**(N=573)**
Preferred Term [a]	**n (%)**	**n (%)**	**n (%)**
Study eye			
Subjects with at least one TEAE	69 (24.0	71 (24.8)	140 (24.4)
Eye disorders	60 (20.9)	66 (23.1)	126 (22.0)
Visual acuity reduced	13 (4.5	13 (4.5)	26 (4.5)
Conjunctival haemorrhage	8 (2.8)	6 (2.1)	14 (2.4)
Cataract	5 (1.7)	4 (1.4)	9 (1.6)
Dry eye	5 (1.7)	4 (1.4)	9 (1.6)
Neovascular age-related macular degeneration	5 (1.7)	4 (1.4)	9 (1.6)
Vitreous floaters	5 (1.7)	3 (1.0)	8 (1.4)
Eye pain	3 (1.0)	3 (1.0)	6 (1.0)
Retinal haemorrhage	1 (0.3)	5 (1.7)	6 (1.0)
Posterior capsule opacification	4 (1.4)	1 (0.3)	5 (0.9)

Punctate keratitis	3 (1.0)	2 (0.7)	5 (0.9)
Retinal pigment epithelial tear	3 (1.0)	2 (0.7)	5 (0.9)
Visual impairment	4 (1.4)	1 (0.3)	5 (0.9)
Blepharitis	1 (0.3)	3 (1.0)	4 (0.7)
Corneal erosion	0	4 (1.4)	4 (0.7)
Lacrimation increased	3 (1.0)	1 (0.3)	4 (0.7)
Subretinal fluid	3 (1.0)	1 (0.3)	4 (0.7)
Vitreous detachment	0	4 (1.4)	4 (0.7)
Ocular hypertension	0	3 (1.0)	3 (0.5)
Infections and infestations	5 (1.7)	6 (2.1)	11 (1.9)
Conjunctivitis	3 (1.0)	3 (1.0)	6 (1.0)
Investigations	5 (1.7)	3 (1.0)	8 (1.4)
Intraocular pressure increased	5 (1.7)	3 (1.0)	8 (1.4)
Fellow Eye			
Subjects with at least one TEAE	54 (18.8)	48 (16.8)	102 (17.8)
Eye disorders	48 (16.7)	45 (15.7)	93 (16.2)
Neovascular age-related macular degeneration	20 (7.0)	13 (4.5)	33 (5.8)
Dry eye	5 (1.7)	4 (1.4)	9 (1.6)
Cataract	3 (1.0)	3 (1.0)	6 (1.0)
Age-related macular degeneration	2 (0.7)	3 (1.0)	5 (0.9)
Visual acuity reduced	2 (0.7)	3 (1.0)	5 (0.9)
Blepharitis	1 (0.3)	3 (1.0)	4 (0.7)
Conjunctival haemorrhage	3 (1.0)	1 (0.3)	4 (0.7)
Visual impairment	3 (1.0)	0	3 (0.5)
Infections and infestations	7 (2.4)	4 (1.4)	11 (1.9)
Conjunctivitis	7 (2.4)	2 (0.7)	9 (1.6)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects in the analysis; N, number of subjects in the analysis set for each treatment group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: Percentages were based on the number of subjects in Safety Set for each treatment group. The TEAEs were sorted by alphabetical order of SOC, and then descending frequencies of PT based on total group.

[a] The SOC and PT were coded using the MedDRA Version 23.0. A subject with multiple occurrences within the SOC and PT was counted once for that SOC and PT.

Japanese and Non-Japanese Subgroups:

Ocular TEAEs reported in ⩾5% of subjects in any treatment group are summarized by eye, SOC, and PT in Japanese and non-Japanese subgroups in Table 43. Overall, there was no difference between SCD411 and Eylea groups with respect to the incidence of any ocular TEAE in the study eye in the Japanese and non-Japanese subgroups. In the Japanese subgroup, the most common ocular TEAEs in the study eye included punctate keratitis (2 subjects [6.7%] in the SCD411 group) and visual acuity reduced (2 subjects [6.7%] in the Eylea group). The most common ocular TEAEs in the fellow eye included conjunctivitis allergic (2 subjects [6.7%] in the SCD411 group).

In the non-Japanese subgroup, the most common ocular TEAEs in the study eye included visual acuity reduced (13 subjects [5.1%] in the SCD411 group and 11 subjects [4.3%] in the Eylea group). The most common ocular TEAEs in the fellow eye included, neovascular AMD (19 subjects [7.4%] in the SCD411 group and 13 subjects [5.1%] in the Eylea group).

Table 40: Ocular Treatment-Emergent Adverse Events Reported by ⩾5% of subjects in Japanese and Non-Japanese Subgroups in Any Treatment Group (Safety Set)

System Organ Class **Preferred Term [a]**	**SCD411** **n (%)**	**Eylea** **n (%)**	**Total** **n (%)**
Japanese Subjects	**N=30**	**N=30**	**N=60**
Study Eye			
Subjects with at least one TEAE	8 (26.7)	8 (26.7)	16 (26.7)
Eye disorders	7 (23.3)	7 (23.3)	14 (23.3)
Punctate keratitis	2 (6.7)	0	2 (3.3)
Visual acuity reduced	0	2 (6.7)	2 (3.3)
Fellow Eye			
Subjects with at least one TEAE	8 (26.7)	5 (16.7)	13 (21.7)
Eye disorders	8 (26.7)	4 (13.3)	12 (20.0)
Conjunctivitis allergic	2 (6.7)	0	2 (3.3)
Non-Japanese Subjects	**N=257**	**N=256**	**N=513**
Study Eye			
Subjects with at least one TEAE	61 (23.7)	63 (24.6)	124 (24.2)
Eye disorders	53 (20.6)	59 (23.0)	112 (21.8)
Visual acuity reduced	13 (5.1)	11 (4.3)	24 (4.7)
Fellow Eye	46 (17.9)		
Subjects with at least one TEAE		43 (16.8)	89 (17.3)
Eye disorders	40 (15.6)	41 (16.0)	81 (15.8)
Neovascular age-related macular	19 (7.4)	13 (5.1)	32 (6.2)

degeneration

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects in the analysis; N, number of subjects in the analysis set for each treatment group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: Percentages were based on the number of subjects in Safety Set for each treatment group. The TEAEs were sorted by alphabetical order of SOC, and then descending frequencies of PT based on total group.

[a] The SOC and PT were coded using the MedDRA Version 23.0. A subject with multiple occurrences within the SOC and PT was counted once for that SOC and PT.

Source: Table 14.3.1.2.1.1 in CTD 5.3.5.1-2

Non – ocular TEAEs

Non-ocular TEAEs reported in ⩾2% of subjects in any treatment group are summarized by SOC and PT. Overall, there was no difference between the SCD411 and Eylea treatment groups with respect to the incidence of any non-ocular TEAE.

The most common non-ocular TEAEs included coronavirus disease 2019 (COVID-19) (18 subjects [6.3%] in the SCD411 group and 21 subjects [7.3%] in the Eylea group); back pain (9 subjects [3.1%] in the SCD411 group and 10 subjects [3.5%] in the Eylea group); urinary tract infection (10 subjects [3.5%] in the SCD411 group and 7 subjects [2.4%] in the Eylea group); hypertension (12 subjects [4.2%] in the SCD411 group and 4 subjects [1.4%] in the Eylea group); arthralgia (3 subjects [1.0%] in the SCD411 group and 6 subjects [2.1%] in the Eylea group); nasopharyngitis (6 subjects [2.1%] in the SCD411 group and 1 subject [0.3%] in the Eylea group); and osteoarthritis (6 subjects [2.1%] in the SCD411 group and 1 subject [0.3%] in the Eylea group).

Japanese and Non-Japanese Subgroups:

Non-ocular TEAEs reported in ⩾5% subjects in any treatment group in the Japanese and non-Japanese subgroups are summarized by SOC and PT Overall, there was no difference between SCD411 and Eylea groups with respect to the incidence of any ocular TEAE in the study eye in the Japanese and non-Japanese subgroups. In the Japanese subgroup, non-ocular TEAEs were reported in 20 subjects (66.7%) in the SCD411 group and 15 subjects (50.0%) in the Eylea group. The most common non-ocular TEAEs in Japanese subgroup included: nasopharyngitis (3 subjects [10.0%] in the SCD411 group), back pain (2 subjects [6.7%], each in the SCD411 and Eylea groups), and nausea, vomiting, and osteoporosis (each reported in 2 subjects [6.7%] in the Eylea group).

In the non-Japanese subgroup, the incidence of non-ocular TEAEs was similar between the SCD411 and Eylea groups (108 subjects [42.0%] versus 115 subjects [44.9%], respectively). The most common non-ocular TEAE in non-Japanese subgroup was COVID-19 (18 subjects [7.0%] in the SCD411 group and 20 subjects [7.8%] in the Eylea group).

TEAEs categorized by maximal severity of event

Ocular TEAEs

Overall, there was no difference between the SCD411 and Eylea treatment groups with respect to the severity of ocular TEAEs.

Most TEAEs of the study eye were of mild or moderate intensity, and severe TEAEs were reported in 4 subjects (0.7%) overall: 2 subjects (0.7%) each in the SCD411 group and the Eylea group. Severe TEAEs in the study eye included visual acuity reduced and AMD (1 subject [0.3%] each in the Eylea group), retinal pigment epithelial tear and endophthalmitis (1 subject [0.3%] each in the SCD411 group). The severe TEAE of retinal pigment epithelial tear was considered related to the study drug and injection procedure.

Almost all TEAEs of the fellow eye were mild or moderate in intensity, and severe TEAEs were reported in 2 subjects (0.3%) overall: 1 subject (0.3%) with neovascular AMD in the SCD411 group and 1 subject (0.3%) with CNV in the Eylea group.

Japanese and Non-Japanese Subgroups:

In the Japanese subgroup, all ocular TEAEs were of mild or moderate intensity, and no severe ocular TEAEs were reported in the study eye or the fellow eye. In the non-Japanese subgroup, most ocular TEAEs were of mild or moderate intensity, and severe TEAEs were reported in 4 subjects (0.8%) in the study eye and 2 subjects (0.4%) in the fellow eye.

Non- ocular TEAEs

Overall, there was no difference between the SCD411 and Eylea treatment groups with respect to the severity of non-ocular TEAEs.

Most non-ocular TEAEs were of mild or moderate intensity, and severe non-ocular TEAEs were reported in 40 subjects (7.0%), overall: 18 subjects (6.3%) in the SCD411 group and 22 subjects (7.7%) in the Eylea group. Each of the severe TEAE was reported in 1 subject only. The non-ocular severe TEAEs of cerebrovascular accident in 1 subject (0.3%) and angina pectoris in another subject (0.3%) in the Eylea group were considered related to the study drug.

Japanese and Non-Japanese Subgroups:

In Japanese subgroup, most non-ocular TEAEs were of mild or moderate intensity, and severe TEAEs were reported in 5 subjects (8.3%): 2 subjects (6.7%) in the SCD411 group and 3 subjects (10.0%) in the Eylea group. In the non-Japanese subgroup, most non-ocular TEAEs were of mild or moderate intensity, and severe TEAEs were reported in 35 subjects (6.8%): 16 subjects (6.2%) in the SCD411 group and 19 subjects (7.4%) in the Eylea group.

Serious AE

Death

No TEAEs leading to death were reported in the study

Other serious AE

Ocular SAE

Non-fatal ocular serious TEAEs of the study eye were reported in 8 subjects (1.4%) overall: 5 subjects (1.7%) in the SCD411 group and 3 subjects (1.0%) in the Eylea group. Ocular serious TEAEs in the SCD411 group included visual acuity reduced and retinal pigment epithelial tear (each reported in 2 subjects [0.7%]), and endophthalmitis (1 subject [0.3%]). Ocular serious TEAEs in the Eylea group included visual acuity reduced, amaurosis fugax, and retinal hemorrhage (each reported in 1 subject [0.3%]). The ocular serious TEAEs of retinal pigment epithelial tear in 2 subjects (0.7%) in the SCD411 group were considered related to the study drug. The ocular serious TEAEs of retinal pigment epithelial tear and endophthalmitis, each reported in 1 subject (0.3%) in the SCD411 group were considered related to the injection procedure (see Table 45).

A non-fatal ocular serious TEAE of the fellow eye was reported in 1 subject (0.3%) in the Eylea group.

Table 41: Non-fatal ocular serious TEAEs in SCD411 and Eylea groups.

System Organ Class Preferred Term[a]	SCD411 (N=287) n (%)	Eylea (N=286) n (%)	Total (N=573) n (%)
Subjects with at least one serious TEAE in the study eye	5 (1.7)	3 (1.0)	8 (1.4)
Eye disorders	4 (1.4)	3 (1.0)	7 (1.2)
Visual acuity reduced	2 (0.7)	1 (0.3)	3 (0.5)
Retinal pigment epithelial tear	2 (0.7)	0	2 (0.3)
Amaurosis fugax	0	1 (0.3)	1 (0.2)
Retinal haemorrhage	0	1 (0.3)	1 (0.2)
Infections and Infestations	1 (0.3)	0	1 (0.2)
Endophthalmitis	1 (0.3)	0	1 (0.2)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; n, number of subjects in the analysis; N, number of subjects in the analysis set for each treatment group; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: Percentages were based on the number of subjects in Safety Set for each treatment group. The TEAEs were sorted by alphabetical order of SOC, and then descending frequencies of PT based on total group.

[a]The SOC and PT were coded using the MedDRA Version 23.0. A subject with multiple occurrences within the SOC and PT was counted once for that SOC and PT.

Japanese and Non-Japanese Subgroups:

No ocular serious TEAEs were reported in the Japanese subjects. All ocular serious TEAEs of the study eye were reported in 8 non-Japanese subjects (1.6%): 5 subjects (1.9%) in the SCD411 group and 3 subjects (1.2%) in the Eylea group.

Non – ocular SAE

Non-ocular serious TEAEs are summarized by SOC and PT in Table 45 (see below).

Non-fatal non-ocular serious TEAEs were reported in 54 subjects (9.4%) overall: 27 subjects (9.4%) each in the SCD411 and the Eylea groups.

Non-fatal non-ocular serious TEAEs (reported in >1 subject in any treatment group) were: COVID-19 (2 subjects [0.7%] in the SCD411 group and 1 subject [0.3%] in the Eylea group), angina pectoris (2 subjects [0.7%] in the Eylea group), and pneumonia, and sleep apnoea syndrome (each reported in 2 subjects [0.7%] in the SCD411 group).

Non-fatal non-ocular serious TEAEs considered related to the study drug included angina pectoris and cerebrovascular accident (each reported in 1 subject [0.3%] in the Eylea group). No non-ocular serious TEAEs related to injection procedure were not reported.

Table 42: Non – ocular SAE treatment emergent (Safety set)

System Organ Class Preferred Term[a]	SCD411 (N=287) n (%)	Eylea (N=286) n (%)	Total (N=573) n (%)
Subjects with at least one serious TEAE	27 (9.4)	27 (9.4)	54 (9.4)
Blood and lymphatic system disorders	0	1 (0.3)	1 (0.2)
Autoimmune haemolytic anaemia	0	1 (0.3)	1 (0.2)
Cardiac disorders	1 (0.3)	6 (2.1)	7 (1.2)
Angina pectoris	0	2 (0.7)	2 (0.3)
Acute myocardial infarction	0	1 (0.3)	1 (0.2)
Arrhythmia supraventricular	0	1 (0.3)	1 (0.2)
Cardiac failure	1 (0.3)	0	1 (0.2)
Cardiac ventricular thrombosis	0	1 (0.3)	1 (0.2)
Myocardial ischaemia	0	1 (0.3)	1 (0.2)
Gastrointestinal disorders	3 (1.0)	0	3 (0.5)
Abdominal hernia	1 (0.3)	0	1 (0.2)
Gastritis	1 (0.3)	0	1 (0.2)
Large intestine polyp	1 (0.3)	0	1 (0.2)
General disorders and administration site conditions	0	1 (0.3)	1 (0.2)
Asthenia	0	1 (0.3)	1 (0.2)
Pyrexia	0	1 (0.3)	1 (0.2)
Hepatobiliary disorders	2 (0.7)	0	2 (0.3)
Bile duct stone	1 (0.3)	0	1 (0.2)
System Organ Class **Preferred Term [a]**	**SCD 411 (N=287) n (%)**	**Eyela (N=286) n (%)**	**Total (N=573) n (%)**
Immune system disorders	1 (0.3)	0	1 (0.2)
Anaphylactic shock	1 (0.3)	0	1 (0.2)

Infections and infestations	8 (2.8)	5 (1.7)	13 (2.3)
COVID-19	2 (0.7)	1 (0.3)	3 (0.5)
Pneumonia	2 (0.7)	0	2 (0.3)
Aspergilloma	0	1 (0.3)	1 (0.2)
Bone tuberculosis	1 (0.3)	0	1 (0.2)
Bronchitis	1 (0.3)	0	1 (0.2)
COVID-19 pneumonia	1 (0.3)	0	1 (0.2)
Diverticulitis	1 (0.3)	0	1 (0.2)
Influenza	1 (0.3)	0	1 (0.2)
Pyelonephritis acute	0	1 (0.3)	1 (0.2)
Staphylococcal bacteraemia	0	1 (0.3)	1 (0.2)
Urinary tract infection	0	1 (0.3)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.3)	6 (2.1)	7 (1.2)
Femoral neck fracture	1 (0.3)	1 (0.3)	2 (0.3)
Foot fracture	0	1 (0.3)	1 (0.2)
Joint dislocation	0	1 (0.3)	1 (0.2)
Limb injury	0	1 (0.3)	1 (0.2)
Spinal compression fracture	0	1 (0.3)	1 (0.2)
Venom poisoning	0	1 (0.3)	1 (0.2)
Metabolism and nutrition disorders	1 (0.3)	1 (0.3)	2 (0.3)
Hyperkalaemia	0	1 (0.3)	1 (0.2)
Hyponatraemia	1 (0.3)	0	1 (0.2)
Musculoskeletal and connective tissue Disorders	2 (0.7)	3 (1.0)	5 (0.9)
Back pain	0	1 (0.3)	1 (0.2)
Osteoarthritis	1 (0.3)	0	1 (0.2)
Spinal stenosis	0	1 (0.3)	1 (0.2)
Spondylolisthesis	0	1 (0.3)	1 (0.2)
Tenosynovitis	1 (0.3)	0	1 (0.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3 (1.0)	3 (1.0)	6 (1.0)
Diffuse large B-cell lymphoma	0	1 (0.3)	1 (0.2)

Fibroadenoma of breast	0	1 (0.3)	1 (0.2)
High-grade B-cell lymphoma	0	1 (0.3)	1 (0.2)
Lung adenocarcinoma Stage 0	1 (0.3)	0	1 (0.2)
Prostate cancer	1 (0.3)	0	1 (0.2)
Squamous cell carcinoma of lung	1 (0.3)	0	1 (0.2)
Nervous system disorders	3 (1.0)	2 (0.7)	5 (0.9)
Transient ischaemic attack	1 (0.3)	1 (0.3)	2 (0.3)
Cerebrovascular accident	0	1 (0.3)	1 (0.2)
Intracranial mass	1 (0.3)	0	1 (0.2)
Syncope	1 (0.3)	0	1 (0.2)
Product issues	0	1 (0.3)	1 (0.2)
Device dislocation	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	0	1 (0.3)	1 (0.2)
Haematuria	0	1 (0.3)	1 (0.2)
Reproductive system and breast disorders	0	1 (0.3)	1 (0.2)
Benign prostatic hyperplasia	0	1 (0.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	3 (1.0)	3 (1.0)	6 (1.0)
Sleep apnoea syndrome	2 (0.7)	0	2 (0.3)
Bronchiectasis	0	1 (0.3)	1 (0.2)
Chronic obstructive pulmonary disease	0	1 (0.3)	1 (0.2)
Idiopathic pulmonary fibrosis	0	1 (0.3)	1 (0.2)
Pulmonary mass	1 (0.3)	0	1 (0.2)
Vascular disorders	1 (0.3)	0	1 (0.2)
Hypertension	1 (0.3)	0	1 (0.2)
System Organ Class **Preferred Term a**	**SCD 411** **(N=287)** **n (%)**	**Eyela** **(N=286)** **n (%)**	**Total** **(N=573)** **n (%)**

Drug related adverse events

TEAEs in relation to study drug

Ocular TEAEs

Overall, the incidence of ocular TEAEs in the study eye considered related to the study drug was comparable between the SCD411 and Eylea treatment groups.

Ocular TEAEs (reported in ⩾1% of subjects in any treatment group) in the study eye considered related to the study drug included: retinal pigment epithelial tear (3 subjects [1.0%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), visual acuity reduced (3 subjects [1.0%] in the Eylea group), and IOP increased (3 subjects [1.0%] in the SCD411 group and 1 subject [0.3%] in the Eylea group). Ocular TEAE in the fellow eye considered related to the study drug included: uveitis (1 subject [0.3%] in the SCD411 group).

Japanese and Non-Japanese Subgroups:

Ocular TEAEs in the study eye and fellow eye considered related to the study drug by SOC and PT in Japanese and non-Japanese subgroups are summarized in the related table. In both the Japanese and non-Japanese subgroups, the incidence of ocular TEAEs considered related to the study drug in the study eye was comparable between the SCD411 and Eylea groups (3 subjects [10.0%] in the SCD411 group and 2 subjects [6.7%] in the Eylea group in the Japanese subgroup; 12 subjects [4.7%] in the SCD411 group and 10 subjects [3.9%] in the Eylea group in the non-Japanese subgroup).

Ocular TEAE in the fellow eye considered related to the study drug included: uveitis (1 subject [0.4%]) in the SCD411 group in the non-Japanese group.

Non – ocular TAEAs

Two subjects (0.7%) in the Eylea group reported non-ocular TEAEs related to the study drug; 1 subject (0.3%) had angina pectoris and another subject (0.3%) had cerebrovascular accident.

Japanese and Non-Japanese Subgroups:

One Japanese subject (3.3%) in the Eylea group experienced a study drug-related TEAE of angina pectoris and 1 non-Japanese subject (0.4%) in the Eylea group experienced a study drug-related TEAE of cerebrovascular accident.

Ocular TEAEs related to injection procedure

Overall, the incidence of ocular TEAEs in the study eye considered related to the injection procedure was comparable between SCD411 and Eylea groups.

Ocular TEAEs (reported in ⩾1% of subjects in any treatment group) in the study eye considered related to the injection procedure included: conjunctival haemorrhage (7 subjects [2.4%] in the SCD411 group and 6 subjects [2.1%] in the Eylea group), intraocular pressure increased (5 subjects [1.7%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), vitreous floaters (3 subjects [1.0%] in the SCD411 group and 1 subject [0.3%] in the Eylea group), and visual acuity reduced (3 subjects [1.0%] in the Eylea group).

Ocular TEAEs in the fellow eye considered related to the injection procedure included: conjunctival haemorrhage (1 subject [0.3%] in the Eylea group) and eye disorder and eye pain (each reported in 1 subject [0.3%] in the SCD411 group).

Japanese and Non-Japanese Subgroups:

In both Japanese and non-Japanese subgroups, the incidence of ocular TEAEs considered related to the injection procedure in the study eye was similar between SCD411 and Eylea groups (3 subjects [10.0%] in the SCD411 group and 3 subjects [10.0%] in the Eylea group in the Japanese subgroup; 17 subjects [6.6%] in the SCD411 group and 16 subjects [6.3%] in the Eylea group in the non-Japanese subgroup).

All ocular TEAEs considered related to the injection procedure in the fellow eye were reported in 3 non-Japanese subjects (0.6%): 2 subjects (0.8%) in the SCD411 group and 1 subject (0.4%) in the Eylea group and have been described for the total population before.

Non – ocular TEAEs related to injection procedure

The injection procedure-related TEAE of headache was reported by 1 non-Japanese subject (0.4%) in the SCD411 group.

Japanese and Non-Japanese Subgroups:

In Japanese and non-Japanese subgroups, no apparent treatment-related trend and no clinically relevant changes were seen in haematology, clinical chemistry, or urinalysis parameters. Shifts in haematology, clinical chemistry, or urinalysis parameters from normal at baseline to low or high at postbaseline timepoints were noted in very few subjects and were balanced among treatment groups.

2.4.8.3. Serious adverse events, deaths, and other significant events

Serious AE

Death

No TEAEs leading to death were reported in the study

Other serious AE

Ocular SAE

Non-fatal ocular serious TEAEs of the study eye were reported in 8 subjects (1.4%) overall: 5 subjects (1.7%) in the SCD411 group and 3 subjects (1.0%) in the Eylea group. Ocular serious TEAEs in the SCD411 group included visual acuity reduced and retinal pigment epithelial tear (each reported in 2 subjects [0.7%]), and endophthalmitis (1 subject [0.3%]). Ocular serious TEAEs in the Eylea group included visual acuity reduced, amaurosis fugax, and retinal hemorrhage (each reported in 1 subject [0.3%]). The ocular serious TEAEs of retinal pigment epithelial tear in 2 subjects (0.7%) in the SCD411 group were considered related to the study drug. The ocular serious TEAEs of retinal pigment epithelial tear and endophthalmitis, each reported in 1 subject (0.3%) in the SCD411 group were considered related to the injection procedure.

A non-fatal ocular serious TEAE of the fellow eye was reported in 1 subject (0.3%) in the Eylea group

2.4.8.4. Laboratory findings

Overall, no apparent treatment-related trend and no clinically relevant changes were seen in haematology, clinical chemistry, or urinalysis parameters. No abnormalities of potential clinical concern were reported for any laboratory test parameters.

Shifts in haematology, clinical chemistry, or urinalysis parameters from normal at baseline to low or high at postbaseline timepoints were noted in very few subjects and were balanced among treatment groups.

The abnormal laboratory parameters that were reported as TEAEs in the SCD411 group included blood creatine phosphokinase increased (2 subjects [0.7%]) and glucose urine present, blood creatinine increased, blood uric acid increased, protein urine present, blood urine present, platelet count increased, hyperkalaemia, hyponatremia, and haematuria (each reported in 1 subject [0.3%]).

The abnormal laboratory parameters that were reported as TEAEs in the Eylea group included glucose urine present and blood urea increased (each reported in 2 subjects [0.7%]) and blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, hyperkalaemia, haematuria, and ketonuria (each reported in 1 subject [0.3%]).

Japanese and Non-Japanese Subgroups:

In Japanese and non-Japanese subgroups, no apparent treatment-related trend and no clinically relevant changes were seen in hematology, clinical chemistry, or urinalysis parameters. Shifts in hematology, clinical chemistry, or urinalysis parameters from normal at baseline to low or high at postbaseline timepoints were noted in very few subjects and were balanced among treatment groups.

2.4.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.4.8.6. Safety in special populations

Not applicable.

2.4.8.7. Immunological events

See section 2.4.10

2.4.8.8. Safety related to drug-drug interactions and other interactions

Not applicable.

2.4.8.9. Discontinuation due to adverse events

Ocular TEAEs Leading to Treatment Discontinuation:

All ocular TEAEs leading to treatment discontinuation were reported in the study eye (4 subjects [1.4%] in the SCD411 group and 5 subjects [1.7%] in the Eylea group) and included retinal haemorrhage (1 subject [0.3%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), retinal pigment epithelial tear (2 subjects [0.7%] in the SCD411 group), neovascular AMD (1 subject [0.3%] each in the SCD411 and Eylea groups), and AMD and visual acuity reduced (1 subject [0.3%] each in the Eylea group).

Japanese and Non-Japanese Subgroups:

Ocular TEAEs in the study eye leading to treatment discontinuation in Japanese and non-Japanese subgroups are summarized by SOC and PT in Table 43.

One Japanese subject (3.3%) in the SCD411 group reported an ocular TEAE of retinal haemorrhage leading to treatment discontinuation. All other ocular TEAEs leading to treatment discontinuation were reported in the non-Japanese subgroup in 8 subjects (1.6%): 3 subjects (1.2%) in the SCD411 group and 5 subjects (2.0%) in the Eylea group.

Table 43: Ocular Treatment-Emergent Adverse Events in the Study Eye Leading to Treatment Discontinuation (Safety Set)

System Organ Class Preferred Term[a]	SCD411 (N=287) n (%)	Eylea (N=286) n (%)	Total (N=573) n (%)
Subjects with at least one TEAE leading to treatment discontinuation	4 (1.4)	5 (1.7)	9 (1.6)
Eye disorders	4 (1.4)	5 (1.7)	9 (1.6)
Retinal haemorrhage	1 (0.3)	2 (0.7)	3 (0.5)
Neovascular age-related macular degeneration	1 (0.3)	1 (0.3)	2 (0.3)
Retinal pigment epithelial tear	2 (0.7)	0	2 (0.3)
Age-related macular degeneration	0	1 (0.3)	1 (0.2)
Visual acuity reduced	0	1 (0.3)	1 (0.2)

Non-ocular TEAEs Leading to Treatment Discontinuation:

Non-ocular TEAEs leading to treatment discontinuation are summarized by SOC and PT in Table 48. Non-ocular TEAEs leading to treatment discontinuation were reported in 7 subjects (1.2%) overall: 3 subjects (1.0%) in the SCD411 group and 4 subjects (1.4%) in the Eylea group and included asthenia, bone tuberculosis, and transient ischemic attack, each reported in 1 subject (0.3%) in the SCD411 group and angina pectoris, cerebrovascular accident, chronic obstructive pulmonary disease, and COVID-19, each reported in 1 subject (0.3%) in the Eylea group.

Table 44: Non – ocular TAES leading to treatment discontinuation (Safety set)

System Organ Class Preferred Term[a]	SCD411 (N=287) n (%)	Eylea (N=286) n (%)	Total (N=573) n (%)
Subjects with at least one TEAE leading to treatment discontinuation	3 (1.0)	4 (1.4)	7 (1.2)
Cardiac disorders	0	1 (0.3)	1 (0.2)
Angina pectoris	0	1 (0.3)	1 (0.2)
General disorders and administration site conditions	1 (0.3)	0	1 (0.2)
Asthenia	1 (0.3)	0	1 (0.2)
Infections and infestations	1 (0.3)	1 (0.3)	2 (0.3)
Bone tuberculosis	1 (0.3)	0	1 (0.2)
COVID-19	0	1 (0.3)	1 (0.2)
Nervous system disorders	1 (0.3)	1 (0.3)	2 (0.3)
Cerebrovascular accident	0	1 (0.3)	1 (0.2)
Transient ischaemic attack	1 (0.3)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	1 (0.2)
Chronic obstructive pulmonary disease	0	1 (0.3)	1 (0.2)

Japanese and Non-Japanese Subgroups:

In Japanese subgroup, non-ocular TEAE of angina pectoris leading to treatment discontinuation was reported in 1 subject (3.3%) in the Eylea group. All other non-ocular TEAEs leading to treatment discontinuation were reported in the non-Japanese subgroup.

Ocular TEAEs Leading to Dose Interruption:

None of the TEAEs in the study eye caused dose interruption of study treatment. One subject (0.3%) in the SCD411 group experienced an ocular TEAE of conjunctivitis in the fellow eye that led to dose interruption of study treatment. The TEAE of conjunctivitis was considered to be mild in intensity, not related to study drug/injection procedure, and resolved with concomitant treatment.

Japanese and Non-Japanese Subgroups:

None of the ocular TEAEs caused dose interruption of study treatment in the Japanese subgroup. The one TEAE of conjunctivitis in the fellow eye that led to dose interruption was reported in the non-Japanese subgroup.

Non-Ocular TEAEs Leading to Dose Interruption:

Non-ocular TEAEs leading to dose interruption were reported in 8 subjects (1.4%) overall: 4 subjects (1.4%) each in the SCD411 and Eylea groups. Non-ocular TEAEs leading to dose interruption in the SCD411 group included atrial fibrillation, COVID-19, syncope, and hypertension, each reported in 1 subject (0.3%). Non-ocular TEAEs leading to dose interruption in the Eylea group included COVID-19 (3 subjects [1.0%]) and foot fracture (1 subject [0.3%]).

Japanese and Non-Japanese Subgroups:

In the Japanese subgroup, non-ocular TEAEs leading to dose interruption were reported in 2 subjects (3.3%) and included atrial fibrillation (SCD411 group) and COVID-19 (Eylea group), each reported in 1 subject (3.3%). All other non-ocular TEAEs leading to dose interruption were reported in the non-Japanese subgroup in 6 subjects (1.2%): 3 subjects (1.2%) each in the SCD411 and Eylea groups

2.4.8.10. Post marketing experience

Not applicable.

2.4.9. Discussion on clinical safety

In Study SCD411-CP101, safety assessments consisted of collecting all AEs, SAEs, including their severity and relationship to study treatment or study procedure. Safety assessments also included the regular monitoring of haematology, blood chemistry, coagulation, and urinalysis. Safety assessments additionally included immunogenicity testing, and regular assessments of vital signs, physical condition, and body weight. Furthermore, a complete ophthalmic examination consisting of slit-lamp examination, IOP measurement, and fundus exam/ophthalmoscopy was performed. Development of binding and neutralizing antidrug antibodies (ADAs) up to Week 52 was assessed too.

SCD411 (Vgenfli) was well-tolerated with a favourable safety profile that was comparable with Eylea in the total population as well as Japanese and non-Japanese subgroups. 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.

Safety results

Overall, SCD411 was well-tolerated with a favourable safety profile that was comparable with Eylea in the total population as well as Japanese and non-Japanese subgroups. 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.

Ocular TEAE's in the study eye

Approximately 24% subjects in each treatment group reported at least 1 ocular TEAE in the study eye.

The most common ocular TEAEs in the study eye included visual acuity reduced (13 subjects [4.5%], each in the SCD411 and Eylea groups) and conjunctival haemorrhage (8 subjects [2.8%] in the SCD411 group and 6 subjects [2.1%] in the Eylea group).

Most ocular TEAEs in the study eye were of mild or moderate intensity, and severe TEAEs were reported in 4 subjects (0.7%) overall: 2 subjects (0.7%) in the SCD411 group and 2 subjects (0.7%)

in the Eylea group. Severe TEAEs in the SCD411 group included retinal pigment epithelial tear (1 subject [0.3%]) and endophthalmitis (1 subject [0.3%]) and in the Eylea group included visual acuity reduced (1 subject [0.3%]) and AMD (1 subject [0.3%]). The severe TEAEs of retinal pigment epithelial tear was considered related to the study drug and injection procedure.

Most ocular TEAEs in the study eye were considered unrelated to study drug.

The most common ocular TEAEs (reported in ⩾1% of subjects in any treatment group) considered related to the study drug included: retinal pigment epithelial tear (3 subjects [1.0%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), visual acuity reduced (3 subjects [1.0%] in the Eylea group), and intraocular pressure increased (3 subjects [1.0%] in the SCD411 group and 1 subject [0.3%] in the Eylea group).

Ocular TEAEs (reported in ⩾1% of subjects in any treatment group) in the study eye considered related to the injection procedure included: conjunctival haemorrhage (7 subjects [2.4%] in the SCD411 group and 6 subjects [2.1%] in the Eylea group), intraocular pressure increased (5 subjects [1.7%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), vitreous floaters (3 subjects [1.0%] in the SCD411 group and 1 subject [0.3%] in the Eylea group), and visual acuity reduced (3 subjects [1.0%] in the Eylea group).

Ocular TEAEs that led to treatment or study discontinuation were reported only in the study eye and their incidence was low (<2.0% in any treatment group).

Non-fatal ocular serious TEAEs of the study eye were reported in 8 subjects (1.4%) overall: 5 subjects (1.7%) in the SCD411 group and 3 subjects (1.0%) in the Eylea group.

Ocular serious TEAEs in the SCD411 group included visual acuity reduced and retinal pigment epithelial tear (each reported in 2 subjects [0.7%]), and endophthalmitis (1 subject [0.3%]).

Ocular serious TEAEs in the Eylea group included visual acuity reduced, amaurosis fugax, and retinal haemorrhage (each reported in 1 subject [0.3%]). The ocular serious TEAEs of retinal pigment epithelial tear in 2 subjects (0.7%) in the SCD411 group were considered related to the study drug. The ocular serious TEAEs of retinal pigment epithelial tear and endophthalmitis, each reported in 1 subject (0.3%) in the SCD411 group were considered related to the injection procedure.

The events of retinal pigment epithelial tear were reported in 5 subjects (0.9%) overall: 3 subjects (1.0%) in the SCD411 group and 2 subjects (0.7%) in the Eylea group. Of these, all events were considered related to the study drug and one event each in SCD411 and Eylea groups was considered related to the injection procedure. All events were of mild or moderate intensity, except one event in the SCD411 group was severe. Serious TEAEs of retinal pigment epithelial tear were reported in 2 subjects (0.7%) in the SCD411 group.

Ocular TEAE's in the fellow eye

Approximately 18% subjects in each treatment group reported at least 1 ocular TEAE in the fellow eye.

The most common ocular TEAEs in the fellow eye included neovascular AMD (20 subjects [7.0%] in the SCD411 group and 13 subjects [4.5%] in the Eylea group).

Almost all ocular TEAEs of the fellow eye were mild or moderate in intensity, and severe TEAEs were reported in 2 subjects (0.3%) overall: 1 subject (0.3%) with neovascular AMD in the SCD411 group and 1 subject (0.3%) with CNV in the Eylea group.

Ocular TEAE in the fellow eye considered related to the study drug included: uveitis (1 subject [0.3%] in the SCD411 group). Ocular TEAEs in the fellow eye considered related to the injection procedure included: conjunctival haemorrhage (1 subject [0.3%] in the Eylea group) and eye disorder and eye

pain (each reported in 1 subject [0.3%] in the SCD411 group). A non-fatal ocular serious TEAE of the fellow eye was reported in 1 subject (0.3%) in the Eylea group.

Non-ocular TEAE's

Approximately 45% subjects in each treatment group reported at least 1 non-ocular TEAE.

The most common non-ocular TEAEs included coronavirus disease-2019 (COVID-19; 18 subjects [6.3%] in the SCD411 group and 21 subjects [7.3%] in the Eylea group), back pain (9 subjects [3.1%] in the SCD411 group and 10 subjects [3.5%] in the Eylea group), urinary tract infection (10 subjects [3.5%] in the SCD411 group and 7 subjects [2.4%] in the Eylea group), hypertension (12 subjects [4.2%] in the SCD411 group and 4 subjects [1.4%] in the Eylea group), arthralgia (3 subjects [1.0%] in the SCD411 group and 6 subjects [2.1%] in the Eylea group), nasopharyngitis (6 subjects [2.1%] in the SCD411 group and 1 subject [0.3%] in the Eylea group), and osteoarthritis (6 subjects [2.1%] in the SCD411 group and 1 subject [0.3%] in the Eylea group).

Most non-ocular TEAEs were of mild or moderate intensity, and severe non-ocular TEAEs were reported in 40 subjects (7.0%) overall: 18 subjects (6.3%) in the SCD411 group and 22 subjects (7.7%) in the Eylea group. Each of the severe TEAEs was reported in 1 subject only. The non-ocular severe TEAEs of cerebrovascular accident in 1 subject (0.3%) and angina pectoris in another subject (0.3%) in the Eylea group were considered related to the study drug.

The injection procedure-related TEAE of headache was reported by 1 non-Japanese subject (0.4%) in the SCD411 group.

The incidence of non-ocular TEAEs that led to treatment or study discontinuation was low (⩽2.0% in any treatment group).

Non-fatal non-ocular serious TEAEs were reported in 54 subjects (9.4%) overall: 27 subjects (9.4%) each in the SCD411 group and the Eylea group. The most common non-fatal non-ocular serious TEAEs (reported in >1 subject in any treatment group) were: COVID-19 (2 subjects [0.7%] in the SCD411 group and 1 subject [0.3%] in the Eylea group), angina pectoris (2 subjects [0.7%] in the Eylea group), and pneumonia and sleep apnoea syndrome (each reported in 2 subjects [0.7%] in the SCD411 group). Non-fatal non-ocular serious TEAEs considered related to the study drug included angina pectoris and cerebrovascular accident (each reported in 1 subject [0.3%] in the Eylea group).

Other evaluations did not demonstrate any other safety concerns. Ophthalmologic safety evaluations (slit lamp examination, dilated fundoscopy, IOP measurement, and vision check) were reported as normal in most subjects.

No apparent treatment-related trend and no clinically relevant changes were seen in haematology, clinical chemistry, and urinalysis parameters; vital signs; or ECG parameters.

The application for VGENFLI is in the treatment of neovascular (wet) age-related macular degeneration (AMD); visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO); visual impairment due to diabetic macular oedema (DME); visual impairment due to myopic choroidal neovascularisation (myopic CNV).

2.4.10. Conclusions on the clinical safety

The overall safety profile of SCD411 (Vgenfli) is in line with the safety profile of Eylea EU.

The summary of safety concerns presented is aligned with the summary of safety concerns for EU Eylea, the originator product.

The submitted safety data support the biosimilarity of SCD411 to Eylea. The adverse events, serious adverse events, and immunogenicity profiles were comparable between the two products. There were

no new safety signals or significant differences in adverse event incidence that would suggest a lack of biosimilarity. The immunogenicity profile is consistent with Eylea, with no unexpected immune responses observed.

In conclusion, the clinical safety documentation supports the biosimilarity of SCD411 to Eylea. The tested product has comparable adverse drug reactions and immunogenicity profiles and no significant safety concerns that would preclude its use as a biosimilar.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns

Table 45: Summary of safety concerns in proposed RMP

Summary of safety concerns	
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

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Endophthalmitis (likely infectious origin)	**Routine risk minimisation measures**: SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities**: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Intraocular inflammation	**Routine risk minimisation measures:** SmPC sections 4.2, 4.3, 4.4, and 4.8 Package Leaflet section 2, 3 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections, **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for endophthalmitis and intraocular inflammation (see **Annex 4.1**). **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Transient intraocular pressure increase	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4, 4.8, and 4.9 Package Leaflet sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific questionnaire to be used for any post-marketing or study reports suspicious for intraocular pressure increase (see **Annex 4.2**). **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Retinal pigment epithelial tears	**Routine risk minimisation measures:** SmPC sections 4.4 and 4.8 Package Leaflet sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cataract (especially of traumatic origin)	**Routine risk minimisation measures:** SmPC sections 4.2, 4.4 and 4.8 Package Leaflet sections 2, 3, and 4. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on identified and potential risks (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Medication errors	**Routine risk minimisation measures:** SmPC sections 4.2, 4.9 and 6.6 Package Leaflet sections 1 and 3. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on medication error (prescriber guide and video; in additionpatient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Off-label use and misuse	**Routine risk minimisation measures:** SmPC sections 4.1, 4.3, 4.4 and 4.6 Package Leaflet sections 1, 2 and 3. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on off-label use (prescriber guide and video; in addition, patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Embryo-fetotoxicity	**Routine risk minimisation measures:** SmPC sections 4.4, 4.6 and 5.3 Package Leaflet section 2. **Other routine risk minimization measures beyond the Product Information:** Medicinal product subject to restricted medical prescription. Vgenfli must only be administered by a qualified physician experienced in administering intravitreal injections. **Additional risk minimization measures:** Educational program: Beyond routine minimization activities, additional measures are currently needed to raise patients´ and physicians´ awareness on the potential risk of embryo-toxicity and to underline information on treatment of women of child-bearing potential, and the need for appropriate contraception in women of childbearing potential (prescriber guide and video; in addition patient guide "Your guide to Vgenfli", and its audio version).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Not applicable. **Additional pharmacovigilance activities:** None

2.5.4. Conclusion

The CHMP considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Eylea. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vgenfli (Aflibercept) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Biosimilarity assessment

3.1. Comparability exercise and indications claimed

Vgenfli (SDC411) has been developed as a biosimilar to aflibercept using EU Eylea as a reference product and was intended to be used in the same indications as the reference product with only the exception of retinopathy of prematurity (ROP):

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

A comprehensive analytical exercise was performed to evaluate SCD411 similarity with EU-Eylea reference medicinal product in all relevant physical and chemical attributes and functional characteristics. Moreover, comparative stability studies were conducted under accelerated conditions as well as forced degradation conditions. The studies were intended to reveal any potential differences in degradation behaviour between SCD411 and the reference product EU-Eylea.

Eylea 40 mg/mL solution for injection in pre-filled syringe is indicated for adults for the treatment of:

• neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),

• visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),

• visual impairment due to diabetic macular oedema (DME) (see section 5.1),

• visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

EYLEA is also indicated in preterm infants for the treatment of

• retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 2+ or 3+) or AP-ROP (aggressive posterior ROP) disease.

Eylea obtained the preterm infants indication in December 2022 via a type II variation.

The stepwise development of VGENFLI (SCD411) gives the evidence for similarity of structural characteristics, physiochemical characteristics, and biological activities to Eylea. This similarity directly implies that VGENFLI (SCD411) has the same mechanism of action as Eylea. Therefore, VGENFLI (SCD411) is expected to be efficacious in the other indications approved for Eylea: macular oedema secondary to CRVO, macular oedema secondary to BRVO, DME, and myopic CNV.

VGENFLI (SCD411) has the same dosage as EU-Eylea. The recommended dose is 2 mg aflibercept, in a 0.05 ml solution administered as a single ophthalmic intravitreal (IVT) injection. After the initial injection additional doses may be administered depending on the therapeutic indication.

The clinical development consisted of one pivotal phase III clinical study (SDC411-CP101), a multicentre, randomised, double-masked, 2-arm parallel study to compare efficacy, safety and immunogenicity of SDC411 to EU - Eylea, administered intravitreally, in patients with neovascular age-related macular degeneration. The design of the clinical study has been discussed with EMA, FDA and Pharmaceuticals and Medical Devices Agency (Japan).

3.2. Results supporting biosimilarity

Quality

Results of the comprehensive analytical comparability exercise of SCD411 and EU-Eylea reference medicinal product overall support similarity with respect to primary and higher order structure, molecular weight and apparent molecular weight. The profile of N-linked glycans is comparable at qualitative level with no new structures occurring. Functional characterisation by the large panel of binding assays as well as by cell-based assays overall supports similarity. Absence of Fc-mediated effector functions was confirmed.

Forced degradation studies revealed similar degradation pathways at qualitative level.

Pharmacokinetic

The exploratory objectives of the pivotal phase III study were to:

- Compare the PK parameters of SCD411 and Eylea
- Quantify the free and bound Eylea and SCD411.

The exploratory endpoints were:

- Pharmacokinetic parameters of SCD411 and Eylea including: $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, and $t_{1/2}$.
- Quantification of free a d bound Eylea and SCD411 in plasma at predefined time points.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), peak free SCD411 and Eylea concentrations were attained at a median tmax of 1 day, ranging from 0.91 to 7 days across both treatment groups. Lambda_z and all associated parameters were only reported where a minimum of 3 data points were used (C_{max} was not to be included) and

where r2 $\geqslant$0.80. Based on these criteria, characterization of the terminal elimination phase was limited for both free SCD411 and Eylea, with geometric mean $t_{1/2}$ of 6.58 days (based on data available from 2 subjects) for free SCD411 following the third IVT injection on Week 8, while $t_{1/2}$ values not determined for free Eylea. Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1, peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were comparable, when accounting for inter-subject variability. Geometric mean values of C_{max} were 58.9 ng/mL and 49.3 ng/mL for free SCD411 and Eylea, respectively, with values ranging from 26.3 to 286 ng/mL for free SCD411 and from 23.5 to 164 ng/mL for free Eylea. Geometric mean values of AUC_{0-t} were 250 day x ng/mL free SCD411 and Eylea, respectively, with values ranging from 155 to 581 day × ng/mL for free SCD411 and from 257 to 662 day × ng/mL for free Eylea.

Peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were similarly comparable following the third IVT injection on Week 8 (third injection). Geometric mean values of C_{max} were 50.7 ng/mL and 43.0 ng/mL for free SCD411 and Eylea, respectively, with values ranging from 22.6 to 105 ng/mL for free SCD411 and from 33.3 to 83.3 ng/mL for free Eylea. Geometric mean values of AUC_{0-t} were 401 day × ng/mL and 200 day × ng/mL for free SCD411 and Eylea, respectively, with values ranging from 169 to 946 day × ng/mL for free SCD411 and from 186 to 217 day × ng/mL for free Eylea.

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection) and Week 8 (third injection), the mean bound SCD411 and Eylea concentration versus time profiles were similarly characterized by a slower absorption phase compared to free SCD411 and Eylea, with concentrations remaining constant up to the end of the sampling period (28 days). Peak concentrations (C_{max}) were attained later following the first IVT injection; median t_{max} estimates were 14 days for bound SCD411 and Eylea on Day 1 (first injection) and were 7 days on Week 8 (third injection).

Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 (first injection), peak (C_{max}) and total (AUC_{0-t} and AUC_{0-tau}) exposure to bound SCD411 and Eylea were comparable, when accounting for inter-subject variability. Geometric mean values of C_{max} were 48.7 ng/mL and 55.2 ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 28.2 to 86.1 ng/mL for bound SCD411 and from 36.2 to 108 ng/mL for bound Eylea. Geometric mean values of AUC_{0-t} were 1030 day × ng/mL and 1260 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 580 to 2040 day × ng/mL for bound SCD411 and from 836 to 2560 day × ng/mL for bound Eylea. Geometric mean values of AUC0-tau were 996 day × ng/mL and 1160 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 718 to 1250 day × ng/mL for bound SCD411 and from 919 to 1410 day × ng/mL for bound Eylea.

Peak (C_{max}) and total (AUC_{0-t}) exposure to free SCD411 and Eylea were similarly comparable following the third IVT injection on Week 8. Geometric mean values of C_{max} were 87.8 ng/mL and 94.7 ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 43.6 to 210 ng/mL for bound SCD411 and from 56.3 to 149 ng/mL for bound Eylea. Geometric mean values of AUC_{0-t} were 1930 day × ng/mL and 2080 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 938 to 4900 day × ng/mL for bound SCD411 and from 492 to 3190 day × ng/mL for bound Eylea. Geometric mean values of AUC_{0-tau} were 1680 day × ng/mL and 1960 day × ng/mL for bound SCD411 and Eylea, respectively, with values ranging from 1280 to 2570 day × ng/mL for bound SCD411 and from 656 to 2980 day × ng/mL for bound Eylea.

Immunogenicity

Observed levels of immunogenicity were similar between the SCD411 and Eylea groups with low incidence of NAb positivity at postbaseline, in the total population as well as Japanese and non-Japanese subgroups.

Efficacy

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 5.8 letters in the SCD411 and Eylea groups, respectively. The LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.3 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.

Overall, based on the results of the primary endpoint analysis (primary estimand: change from baseline in BCVA score for study eye at Week 8, without rescue therapy) for the FAS, SCD411 was found to be equivalent to Eylea. At Week 8, the LS mean difference between the treatment groups (SCD411-Eylea) for estimated mean change from baseline in BCVA score was -0.4 letters with 90% CI = -1.6 to 0.9 and 95% CI = -1.8 to 1.1. The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups.

Safety

In Study SCD411-CP101, safety assessments consisted of collecting all AEs, SAEs, including their severity and relationship to study treatment or study procedure. Safety assessments also included the regular monitoring of haematology, blood chemistry, coagulation, and urinalysis. Safety assessments additionally included immunogenicity testing, and regular assessments of vital signs, physical condition, and body weight. Furthermore, a complete ophthalmic examination consisting of slit-lamp examination, IOP measurement, and fundus exam/ophthalmoscopy was performed. Development of binding and neutralizing antidrug antibodies (ADAs) up to Week 52 was assessed too.

Ocular TEAE's in the study eye

Most ocular TEAEs in the study eye were considered unrelated to study drug.

The most common ocular TEAEs (reported in $\geqslant$1% of subjects in any treatment group) considered related to the study drug included: retinal pigment epithelial tear (3 subjects [1.0%] in the SCD411 group and 2 subjects [0.7%] in the Eylea group), visual acuity reduced (3 subjects [1.0%] in the Eylea group), and intraocular pressure increased (3 subjects [1.0%] in the SCD411 group and 1 subject [0.3%] in the Eylea group).

Ocular TEAEs that led to treatment or study discontinuation were reported only in the study eye and their incidence was low (<2.0% in any treatment group).

Non-fatal ocular serious TEAEs of the study eye were reported in 8 subjects (1.4%) overall: 5 subjects (1.7%) in the SCD411 group and 3 subjects (1.0%) in the Eylea group.

Ocular serious TEAEs in the SCD411 group included visual acuity reduced and retinal pigment epithelial tear (each reported in 2 subjects [0.7%]), and endophthalmitis (1 subject [0.3%]).

Other evaluations did not demonstrate any other safety concerns. Ophthalmologic safety evaluations (slit lamp examination, dilated fundoscopy, IOP measurement, and vision check) were reported as normal in most subjects.

No apparent treatment-related trend and no clinically relevant changes were seen in haematology, clinical chemistry, and urinalysis parameters; vital signs; or ECG parameters.

SCD411 (Vgenfli) was well-tolerated with a favourable safety profile that was comparable with Eylea in the total population as well as Japanese and non-Japanese subgroups. 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.

The submitted data support the biosimilarity of VGENFLI (SCD411) to EU-EYLEA.

3.3. Uncertainties and limitations about biosimilarity

Quality

Structural differences identified between SCD411 and EU-Eylea reference product comprise levels of oxidated (higher for test product) and deamidated (lower for the test product) Met and Asn residues of the polypeptide backbone and differences of N-glycosylation profile at quantitative level. Considering the inherent variability of glycosylation, differences beyond this variability were observed with respect to the level of fucosylation, galactosylation and sialylation. In the test product higher levels of fucosylated N-glycans are accompanied by lower levels of galactosylated and sialylated N-glycans as compared to the reference product.

A large number of biological and biofunctional assays were performed to evaluate any potential impact of structural differences on potency. Of these, the binding assay to FcgRIIIA showed binding affinity of test product outside the established ranges of binding affinity of reference product. However, since aflibercept does not show effector functions (as assayed by ADCC and CDC cell-based assays), the conclusion on similarity is not affected by the differing binding affinity results to FcgRIIIA.

By forced degradation studies, the reference product showed a higher deamidation rate while the test product showed a higher oxidation rate. The company presented a detailed and comprehensive set of studies revealing that the potential root cause of this difference in susceptibility to oxidative stress is the residual presence of reactive oxygen species (ROS) from the cell culture process. Since these ROS are unrelated to structural attributes of aflibercept the conclusion on biosimilarity is not affected.

The applicant provided a complete validation report for the bioanalytical method concerning an Electrochemiluminescence (ECL) Assay for the Quantification of Complex VEGF: SCD411 DP and Complex VEGF: EYLEA in Human Plasma. A summary but sufficient description of the method is presented.

The applicant provided a Final Bioanalytical Sample Analysis Report for the Determination of Free SCD411 and free Eylea DP in Human Plasma as well as for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma using Electrochemiluminescence (ECL) for Protocol Number SCD411-CP101.

A validation of an Immunoassay for Detection of Neutralizing Antibodies to SCD411 in Human Serum is presented, including a Negative Control (NC), LPC Determination Assessment description, Assay Sensitivity and Intra/Inter-assay Titer description and Assessment as well as Intra/Inter-assay Precision and System Suitability Ranges. Selectivity for Normal, Disease State (Age-related Macular Degeneration), Hemolyzed and Lipemic Matrices were also included as well as Freeze/Thaw, Refrigerator and Bench Top Stability.

Results are presented in a summary table and show compliance with the established standards.

Tables for Intra and Inter-Assay Precision for Screening and Confirmation Assays for Anti-SCD and anti-Eylea in Human Serum LPC, MPC and HPC controls are also included in this AR. All titer determinants were within the range of the median target titer, which supported the intra and inter-assay precision criteria was achievable within the assay. Some validation runs were excluded.

Pharmacokinetic assessments were performed in the Phase 3 SCD411 – CP101 study following the first and the third doses of SCD411. Following a single SCD411 or Eylea IVT injection at 2 mg on Day 1 and

Week 8, the mean free SCD411 and aflibercept concentration versus time profiles were similarly characterized by an absorption phase where peak concentrations were observed at the first postdose sampling timepoint, with measurable concentrations observed up to 7 to 14 days postdose on Day 1 and Week 8.

For clinical efficacy, the pivotal study SCD411-CP101 was a Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration.

3.4. Discussion on biosimilarity

Quality

Results of the comprehensive analytical comparability exercise of SCD411 and EU-Eylea reference medicinal product overall support similarity with respect to primary and higher order structure, molecular weight, and apparent molecular weight. The differences observed for profile of N-linked glycans at quantitative were addressed by functional characterisation tests. Of the large panel of binding assays as well as by cell-based assays only binding to the FcgRIIIA showed results for the test product totally outside the established ranges of binding affinity of reference product. However, since absence of Fc-mediated effector functions was confirmed by ADCC and CDC-testing this difference does not affect the conclusion on similarity.

Forced degradation studies revealed similar degradation pathways at qualitative level, however a higher susceptibility of test product to oxidative stress was revealed at quantitative level. The company revealed the structural root causes for this different susceptibility to oxidative stress as residual reactive oxygen species from the cell culture process. Since ROS are unrelated to structural quality attributes of aflibercept a conclusion on similarity at "totality of evidence" level is not compromised.

The applicant provided a complete validation report for the bioanalytical method concerning an Electrochemiluminescence (ECL) Assay for the Quantification of Complex VEGF: SCD411 DP and Complex VEGF: EYLEA in Human Plasma.

The applicant also provided a Final Bioanalytical Sample Analysis Report for the Determination of Free SCD411 and free Eylea DP in Human Plasma as well as for Complex VEGF: SCD411 and Complex VEGF: EYLEA in Human Plasma using Electrochemiluminescence (ECL) for Protocol Number SCD411-CP101.

A validation of an Immunoassay for Detection of Neutralizing Antibodies to SCD411 in Human Serum was presented.

For clinical efficacy, the pivotal study SCD411-CP101 was a Phase III Randomized Double Masked Parallel – Group, Multicentre Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration.

The results from the pivotal study SCD411-CP101 were comparable for the two treatment groups (SCD411 and Eylea). It can be agreed that the analysis of the primary endpoint based on the PPS yielded results similar to those of the FAS in the total population as well as the Japanese and non-Japanese subgroups.

The BCVA score was comparable at Baseline among the treatment groups in the FAS. The 90% CI was within the limit required for US FDA (-3.0 and 3.0 letters) and the 95% CI was within the limit required for EMA and PMDA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.

For the BCVA score in the PPS, the 95% CI was within the limit required for EMA (-3.8 and 3.8 letters) for claiming equivalence between the treatment groups, indicating that SCD411 was equivalent to Eylea.

The sensitivity and supportive analyses supported the primary analyses of the primary endpoint for the total population as well as the Japanese and non-Japanese subgroups.

The pivotal Study SDC411-CP101 demonstrated the biosimilarity of the study drug and the reference product regarding efficacy and safety.

3.5. Extrapolation of safety and efficacy

In the EU, the reference product Eylea is approved for the treatment of nAMD, RVO, DME and myopic CNV in adults and for the treatment of ROP in preterm infants. The clinical development program for the biosimilar SCD411 comprised a single pivotal Phase III study (study CP101) to investigate Eylea and SCD411 regarding efficacy, safety, pharmacokinetics and immunogenicity in the treatment of subjects with nAMD.

The applicant's intention is the approval for nAMD and all other indications of Eylea in adults, based on the common mechanism of action across all indications and comparable PK, safety, and immunogenicity profiles of aflibercept (Eylea) across the approved indications. The pathogenesis of all approved indications involves angiogenesis mediated by the members of the VEGF family of angiogenic factors, and the mechanism of action of aflibercept in nAMD is considered representative of the mechanism of action of aflibercept in all other approved indications for Eylea.

3.6. Additional considerations

None.

3.7. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Vgenfli is considered biosimilar to EYLEA. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Vgenfli is favourable in the following indication(s):

- neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
- visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) (see section 5.1),
- visual impairment due to diabetic macular oedema (DME) (see section 5.1),
- visual impairment due to myopic choroidal neovascularisation (myopic CNV) (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH has agreed to provide EU educational material for Vgenfli. Prior to launch and during the product's lifecycle in each Member State the MAH will agree the final educational material with the National Competent Authority.

The MAH ensures that, following discussions and agreement with the National Competent Authorities in each Member State where Vgenfli is marketed, ophthalmological clinics where Vgenfli is expected to be used are provided with an updated physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs.

The physician information in the educational material contains the following key elements:

- Techniques for the intravitreal injection including use of a 30 G needle, and angle of injection
- Confirmation that the pre-filled syringe and the vial are for single use only
- The need to expel excess volume of the syringe before injecting Vgenfli to avoid overdose
- Patient monitoring after intravitreal injection including monitoring for visual acuity and increase of intraocular pressure post-injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Vgenfli.

The patient information pack of the educational material includes a patient information guide and its audio version. The patient information guide contains following key elements:

- Patient information leaflet

- Who should be treated with Vgenfli
- How to prepare for Vgenfli treatment
- What are the steps following treatment with Vgenfli
- Key signs and symptoms of serious adverse events including endophthalmitis, intraocular inflammation, intraocular pressure increased, retinal pigment epithelial tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Vgenfli.