CLINICAL STUDY PROTOCOL

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

SCD411-CP101

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CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase III Randomized, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration
Protocol Number	SCD411-CP101
Protocol Date	24 January 2022

Protocol accepted and approved by:

Director of Bio Research Center

[redacted]

SamChunDang Pharm. Co. Ltd.

[redacted] [redacted]

Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase III Randomized, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, dated 24 Jan 2022, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with SamChunDang Pharm. Co. Ltd. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from SamChunDang Pharm. Co. Ltd.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Name of Institution/Organization of Principal Investigator

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Protocol Synopsis

Protocol Number:	SCD411-CP101
Title:	A Phase III Randomized, Double-Masked, Parallel-Group, Multicenter Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration
Sponsor:	SamChunDang Pharm. Co. Ltd. 351, Hyoryeong-ro, Seocho-gu, Seoul 06643, Republic of Korea
Study Phase:	Phase III
Study Sites:	Approximately 155 study sites and 14 countries
Indication:	Neovascular Age-related Macular Degeneration
Rationale:	SCD411 is being developed as a biosimilar to the reference product Eylea® (aflibercept). Based on the proposed extensive analytical comparability testing, comparative nonclinical testing, and comparative clinical studies using the same licensed reference product, the current study is designed to evaluate comparability between SCD411 and aflibercept. Based on the data from aflibercept clinical studies VIEW 1, VIEW 2, COPERNICUS, GALILEO, VIBRANT, VIVID, VISTA, and MYRROR, wet age-related macular degeneration (AMD) is considered as the most suitable condition to prove similarity between SCD411 and aflibercept as the reference product. The available data regarding the pharmacokinetics (PK) of the reference product suggests that a proper PK characterization will not be possible after single intravitreal (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 is evident that in some cases no measurable systemic levels of free aflibercept were registered after IVT administration. Hence, a comparative PK evaluation in patients with AMD will likely not provide any information of relevance to support biosimilarity. Although the systemic exposure of SCD411 is expected to also be very low at steady state, there is no previous human data on SCD411, and thus this assumption requires experimental support. Hence, PK assessment will be performed in the current study following the first and the third doses of SCD411.

As aflibercept is a therapeutic protein, there is a potential for immunogenicity. No cases of active neutralizing antibodies (NAb) were observed after administration of Eylea. It is evident that immunogenicity is not presenting a substantial safety concern in patients treated with aflibercept injections. There was no substantial difference in the proportion of patients testing positive for anti-drug antibodies (ADA) in different indications, including wet AMD. Based on this observation, the indication chosen for this study is expected to provide sound data for comparing the immunogenicity of the test product (SCD411) with that of Eylea.

The clinical part of the comparison will be based on clinical efficacy and safety data obtained after IVT administration to subjects with wet AMD in the current pivotal study.

Objectives:

The primary objective of this study is:

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

The secondary objectives of this study are:

- To compare the safety and tolerability of SCD411 and aflibercept
- To compare the efficacy of SCD411 and aflibercept after 8 weeks and 52 weeks of treatment demonstrated by BCVA, central retinal thickness (CRT), and choroidal neovascularization (CNV)
- To compare the immunogenicity of SCD411 and aflibercept by presenting information of the development of anti-SCD411 antibodies.

The exploratory objectives of this study are:

- To compare PK parameters of SCD411 and aflibercept
- To quantify free and bound aflibercept and SCD411.

Estimands:

The primary estimand for the primary objective is the mean treatment difference in BCVA change from baseline at Week 8. At Week 52, the primary estimand of interest is the mean treatment difference in BCVA change from baseline at Week 52. For the primary estimand, any observations post receipt of rescue therapy in the study eye will be set to missing, thereby estimating the treatment effect as though subjects do not receive rescue therapy. For each of the Week 8 and Week 52 analyses, the secondary estimand will be presented where post rescue will not be set to missing but will be included in the mixed-effects model for repeated measures

(MMRM) analysis. The secondary estimands are constructed to estimate the treatment effect while including the impact of rescue therapy, which may better reflect actual real-world outcomes, where rescue therapy would likely be given when lack of efficacy is seen.

Study Population: Each subject must meet all of the following inclusion criteria to be enrolled in this study:

1. Capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees 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 center
4. The 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 at Week 0 (Day 1) prior to randomization. In addition, fellow eye should not be less than 35 letter score using the ETDRS chart or 2702 series number chart
5. Women of child-bearing potential with a negative serum pregnancy test at screening must agree to use protocol-defined methods of contraception throughout the study until 3 months after the last injection of aflibercept/SCD411
6. Males with female partners of child-bearing potential must 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 aflibercept/SCD411.
7. The area of CNV making up either 50% or more of the total lesion area and confirmed by the central reading center

Subjects meeting any of the following criteria at the Screening Visit will be excluded from the study:

1. Any prior ocular (in the study eye and fellow eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins

3. Fellow eye shows signs of AMD that, in investigator's medical opinion, may need any treatment during study period

4. Any prior treatment with anti-vascular endothelial growth factor (VEGF) agents in the both eyes (ie, completely treatment naïve subjects only to be included)

5. Total lesion size >30.5 mm^2, including blood, scars, atrophy, fibrosis, and neovascularization as assessed by FA in the study eye and confirmed by the central reading center

6. Central retina thickness of <300 μm in the study eye and confirmed by the central reading center

7. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye and confirmed by the central reading center. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)

8. Scar or fibrosis, making up >50% of the total lesion in the study eye and confirmed by the central reading center

9. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye and confirmed by the central reading center

10. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye and confirmed by the central reading center

11. Lens Opacity Classification System II (LOCS II) grade IV cataract in the study eye, or other significant cataract in the study eye that in the Investigator's opinion interferes with visualization of retina or interferes with retinal imaging

12. Active intraocular/periocular infection and inflammation in either eye

13. History of any vitreous hemorrhage in the study eye within 4 weeks prior to the Screening Visit

14. Presence of other causes of CNV in the study eye as confirmed by central reading center

15. History or clinical evidence of diabetic retinopathy, diabetic macular edema, or any other vascular disease affecting the retina, other than AMD, in either eye

16. Prior vitrectomy in the study eye

17. History of retinal detachment, treatment, or surgery for retinal detachment in the study eye

18. History of macular hole of Stage 2 and above in the study eye as confirmed by central reading center

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

Note: A subject with uncomplicated neodymium yttrium aluminum garnet (Nd:YAG) laser capsulotomy performed for secondary opacification of the posterior capsule in intraocular lens implanted eye within 3 months prior to Day 1 in the study eye will be considered as eligible.

20. Presence of aphakia in the study eye.

21. History of glaucoma-filtering surgery within 3 months of Day 1 in the study eye. Anti-glaucoma laser surgeries will not be considered exclusionary.

22. History of corneal transplant in the study eye.

23. History or evidence of any other clinically significant disorder, condition or disease (eg, co-existence of retinal vein occlusion, 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 (BP) >160 mmHg or diastolic BP >100 mmHg under appropriate antihypertensive treatment

25. Hypersensitivity to aflibercept or medications used in this study (fluorescein, mydriatic eye drops, etc.)

26. Pregnancy or lactation at the Screening Visit and/or at baseline for women of child-bearing potential

27. Any 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 on 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. Any 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

Note: For IVT corticosteroid implant, the exclusion period would be 36 months from the date of the procedure to the date of screening

32. Any prior or concomitant treatment involving the macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (eg, focal laser photocoagulation) in the study eye

33. Any prior or concomitant treatment with pan-retinal photocoagulation 90 days in the study eye before the Screening Visit

34. Any 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. Any 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 ≥25 mmHg in spite of anti-glaucoma treatment

37. Any prior or ongoing systemic medical condition (including but not limited to infectious, inflammatory, psychiatric, neurological, renal, hepatic, respiratory conditions or malignancies) or clinically significant screening laboratory value that in the opinion of the investigator may present a safety risk, interfere with study compliance and follow-up, or confound data interpretation throughout the study period.

Study Design: This is a Phase III, randomized, double-masked, parallel-group, multicenter study to demonstrate biosimilarity of SCD411 compared to Eylea (aflibercept) among adult subjects with neovascular (wet) AMD. Subjects will be randomly assigned in 1:1 ratio using Interactive Response Technology to receive either SCD411 or aflibercept injections. Subjects will receive their randomized first IVT injection on Day 1 and subsequent IVT injection on Weeks 4, 8, 16, 24, 32, 40, and 48. The End-of-Treatment (EOT) Visit will be scheduled for Week 48. Subjects who discontinue the study treatment early should have the reasons for treatment discontinuation documented on the Treatment Discontinuation page of the electronic case report form (eCRF). Treatment discontinuation in the study is defined as subjects discontinuing the

	study treatment due to adverse event/lack of efficacy/rescue treatment but not limited to these conditions. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the Early Termination (ET) Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation. The End-of-Study (EOS) Visit will occur 28 days after the EOT at Week 52. Subjects and study site staff involved in subject management and study assessments will be masked to study treatment assignment. The investigator involved in performing the IVT injections will be unmasked to study treatment.
Estimated Study Duration:	The total study duration is approximately 55 weeks, including a screening duration up to 3 weeks, treatment duration up to 48 weeks, and a follow-up duration up to 4 weeks.
Efficacy Assessments:	Efficacy will be summarized for the study eye only. Primary endpoint: • Change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 8. Secondary endpoints: • Change from baseline in BCVA as measured by ETDRS letter score or 2702 charts at Week 52 • Change from baseline in CRT at Week 8 as assessed by optical coherence tomography (OCT) • Change from baseline in CRT at Week 52 as assessed by OCT • Change from baseline in CNV area at Week 8 • Change from baseline in CNV area at Week 52 • Percentage of subjects who gain at least 15 letters in BCVA as measured by ETDRS letter score or 2702 charts compared with baseline at Week 8 • Percentage of subjects who gain at least 15 letters in BCVA as measured by ETDRS letter score or 2702 charts compared with baseline at Week 52.
Pharmacokinetic Assessments:	Pharmacokinetic parameters include area under the concentration-time curve from time zero to the last quantifiable time point (AUC_{0-t}), AUC from zero to the end of the dosing period (AUC_{0-tau}), AUC from zero to infinite time (AUC_{0-inf}), C_{max}, time to reach maximum

	plasma concentration (t_{max}), and elimination half-life ($t_{1/2}$), of SCD411 and aflibercept. Quantification of free and bound aflibercept and SCD411 in plasma will be performed using blood samples at predose and at +1 day, +3 days, +7 days, +14 days, and +28 days after the first (Day 1) and third (Week 8) doses.
Immunogenicity Assessments:	Immunogenicity assessments and endpoints include the evaluation of development of anti-SCD411 or anti-aflibercept antibodies using blood samples taken at Baseline, at Weeks 4, 8, 20, 36, and 52. The samples will be evaluated for titer of anti-SCD411 or anti-aflibercept antibodies. Neutralizing antibodies will be tested when ADA results are confirmed to be positive.
Safety Assessments:	Safety endpoints include adverse events (AEs), vital signs, and laboratory assessments up to Week 52. Safety is also evaluated during follow-up (4 weeks after EOT). If a subject is discontinued from the study, all the ET Visit procedures should be performed even if they are outside the allowed study window.
Study Drug, Dosage, and Route of Administration:	One IVT injection containing 2 mg dose of either SCD411 or aflibercept (as per randomization) every 4 weeks for 3 consecutive doses, followed by 1 injection every 8 weeks.
Rescue Treatment	In the study eye, rescue treatment for neovascular AMD is not permitted at any point in time. If it is observed that efficacy is not achieved by the study treatment, as determined by the investigator, subjects can be considered for rescue treatment after Week 4 if any 1 of the following conditions are met as assessed by the masked investigators: • Decrease of visual acuity letter score of 15 letters or more from the last assessment and/or • An increase in intraretinal fluid, subretinal fluid, or subretinal hyper-reflective material, that in the investigator's opinion is related to progression of the subject's neovascular AMD. Subjects who will receive rescue treatment need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the ET Visit should be completed as

soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.

Sample Size:

The equivalence margin agreed upon with European Medicines Agency (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) was determined using the data presented from MARINA (and ANCHOR) and VIEW studies. The data were used to estimate the efficacy of aflibercept compared to the placebo treatment in subjects with wet AMD. It was shown that in MARINA, subjects on average lost 2.5 BCVA letters over 2 months in the sham-treated control arm and gained 5 letters in the treatment arm of 2 mg dose, 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 to the placebo would be estimated as approximately 9.3 to 10 letters. A margin of 3.8 letters would be translated to a preservation of 59% to 62% of the difference between Eylea and sham and is less than a 1 line change in visual acuity. Equivalence discussions for EMA and PMDA were based upon a 95% confidence interval (CI) approach or 2 one-sided tests (TOST) at the α=0.025 level.

The US Food and Drug Administration (FDA) requested a tighter equivalence margin of 3 letters but agreed equivalence can be determined from a 90% CI approach (equivalent to TOST at the α=0.05 level).

Standard deviation (SD) for the mean change from baseline at early visits (Weeks 4 to 12) based on observed data for the full analysis set (FAS) ranged from and 8.73 to 11.99 considering all treatment groups from VIEW1 and from 7.4 to 11.0 letters for the VIEW2 study. For power calculations, a range of SD between 10.4 and 11.8 was assumed to be conservative and cover the majority of larger SD values seen in the observed data.

A sample size of 266 subjects per treatment arm was selected as it provides at least 80% power for the FDA, EMA, and PMDA analyses for the range of SD considered when using TOST on data from a parallel-group design. For the FDA analysis based on equivalence limits of -3.0 and 3.0 letters, α=0.05 significance level (90% CI), assuming the true difference between the means is 0.0, power of 91% is achieved for SD of 10.4 letters and power of 80% is achieved for SD of 11.8 letters. For the EMA and PMDA analyses based on equivalence limits of -3.8 and 3.8 letters, α=0.025 significance level (95% CI), assuming the true difference between the means is 0.0, power of 98% is achieved for SD of 10.4 letters and power of 92% is achieved for SD of 11.8 letters when sample

	size is 266 per treatment arm. Considering approximately 5% loss from randomization through Week 8, the total sample size required is 560. A subset of 40 subjects (20 per group) will be selected for collection of PK samples. The sample size is not test-driven since no equivalence test will be performed for PK parameters.
Analysis Sets	The following analysis sets will be used in the statistical analyses: **Full Analysis Set (FAS):** All randomized subjects who received at least 1 injection of the study drug. **Modified FAS (mFAS)**: 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. **Per-protocol Set (PPS):** All subjects in the FAS, excluding those with significant protocol violations. **Safety Set (SAF):** All subjects receiving at least 1 injection of the study drug. **Pharmacokinetic Analysis Set (PK Set):** The subset of subjects in FAS who have sufficient evaluable blood samples to be included in the PK Set. The primary set for efficacy analysis will be the FAS; however, for the EMA submission, the primary efficacy endpoint must meet equivalence for both the FAS and PPS. PMDA also requires an efficacy analysis to be conducted based on the mFAS without multiple imputation (MI) as a supportive analysis. The SAF will be the primary analysis set for safety, tolerability, and immunogenicity analyses. Efficacy will be assessed for the study eye only.
Statistical Methods:	**Primary Analysis:** The primary analysis of the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 8 weeks of treatment will be performed via MMRM including data for the Week 4 and Week 8 visits. The model will include the change from baseline as the dependent variable; treatment, visit, and visit-by-treatment as fixed effects, and baseline BCVA as a covariate. Equivalence will be determined if the upper and lower CI limits for the difference between treatments are within the equivalence margins. The primary null hypothesis (H0) and alternative hypothesis (H1) are: H0: $\Delta \geq M$ or $\Delta \leq -M$

H1: $-M < \Delta < M$

where Δ indicates the mean difference between the 2 treatment groups in the change from baseline in ETDRS letter score or 2702 charts at Week 8 and M represents the equivalence margin.

Based on discussions with regulatory agencies, separate equivalence CIs and equivalence margins will be used for FDA submissions and other regulatory agencies versus submissions to EMA and PMDA.

For the FDA submission and other regulatory agencies, a 90% CI (equivalent to TOST evaluated at an α of 0.05) will be assessed using an equivalence margin of 3 letters. For the EMA and PMDA, a 95% CI (equivalent to TOST evaluated at an α of 0.025) will be assessed using an equivalence margin of 3.8 letters. Other regulatory submissions are assumed to follow the FDA guidance.

Estimates of the treatment difference and corresponding 90% (FDA and other countries) and 95% (EMA/PMDA) CIs will be provided. The primary analysis set for the FDA, PMDA, and any other submissions will be the FAS. For the EMA submission, both the FAS and PPS are considered primary analysis and equivalence will need to be shown for both analysis sets. The analysis will be performed using multiple imputed data under the missing at random (MAR) assumption. The primary analysis will set post rescue assessments to missing prior to the MI procedure.

Secondary Analyses:

The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented for the FAS and PPS. As done for Week 8, analysis will be performed using multiple imputed data, where post rescue assessments have been set to missing while including the post rescue assessments in the imputation model. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics for each visit.

The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV will be based on the MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI for the estimates of treatment differences at Week 8 and Week 52 presented. Raw values and changes from baseline will be summarized by treatment group

using descriptive statistics. Data after the receipt of rescue therapy will be set to missing prior to the MMRM analysis. Multiple imputation will not be performed, and no sensitivity analyses will be performed.

The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score or 2702 charts at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented. For subjects who have missing assessments at corresponding postbaseline visits or who received rescue therapy prior to a visit will be assumed to have a gain of <15 letters in BCVA (eg, nonresponder imputation). No sensitivity analyses will be performed.

Safety Analyses

An overall summary of AEs will be presented, and treatment-emergent AEs will be summarized by system organ class and preferred term. Results of the following safety evaluations will be summarized with observed values and change from baseline: vital signs, ECGs, laboratory examinations including chemistry, hematology, and urinalysis. The results of slit lamp examination, dilated fundoscopy, intraocular pressure, and vision check will be summarized using descriptive statistics at each visit and applicable time point, as applicable.

Pharmacokinetic Analysis

The PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, $t_{1/2}$) from the 2 treatment groups will be summarized using n, arithmetic mean, percent coefficient of variation (% CV), geometric mean, geometric %CV, SD, median, minimum and maximum values in the PK analysis set.

Immunogenicity Analysis

The analysis on immunogenicity will be descriptive. Results will be summarized with observed values and change from baseline for ADA titers (in log scale) by treatment group in the SAF. The number and proportion of ADA-positive subjects and ADA-negative subjects will be summarized by treatment group for each assessment time point. NAb will be tested when ADA results are confirmed to

	be positive. The number and proportion of NAb subjects will be summarized by treatment group for each assessment time point. **Interim Analyses** An interim analysis of safety, secondary efficacy endpoints, and PK parameters will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study. The Week 8 analysis and interim analysis will be performed by an independent biostatistics group and results will be 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 may coincide depending on subject enrollment and data cleaning/programming activities.
Version and Date of Protocol:	Version 3.0 24 January 2022

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
$AUC_{0\text{-}inf}$	area under the concentration-time curve from zero to an infinite time
$AUC_{0\text{-}t}$	area under the concentration-time curve from zero to last quantifiable time point
$AUC_{0\text{-}tau}$	area under the concentration-time curve from zero to the end of the dosing period
BCVA	best corrected visual acuity
BOCF	baseline observation carried forward
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
CNV	choroidal neovascularization
CRO	contract research organization
CRT	central retinal thickness
CV	coefficient of variation
DME	diabetic macular edema
ECG	electrocardiogram
EDC	Electronic Data Capture
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end-of-study
EOT	end-of-treatment
ET	early termination
EU	European Union
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
FDA	US Food and Drug Administration

Abbreviation	Definition
FP	fundus photography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IOP	intraocular pressure
IP	investigational product
IRB	institutional review board
IRT	Interactive Response Technology
IVT	intravitreal
LH	luteinizing hormone
LOCF	last observation carried forward
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
NAb	neutralizing antibodies
OCT	optical coherence tomography
OTC	over-the-counter
PDT	photodynamic therapy
PI	principal investigator
PK	pharmacokinetic(s)
PlGF	placental growth factor
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per-protocol set
RVO	retinal vein occlusion
SAE	serious adverse event
SAF	safety set
SAP	statistical analysis plan

Abbreviation	Definition
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
t_{max}	time to reach the maximum plasma concentration
TEAE	treatment-emergent adverse event
TOST	2 one-sided tests
VA	visual acuity
VEGF	vascular endothelial growth factor
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

1.1 Background

SCD411 is a proposed biosimilar of Eylea® having aflibercept as the active substance that binds to vascular endothelial growth factor A (VEGF-A) and produced in Chinese hamster ovary cells by recombinant DNA technology. Aflibercept, the drug substance of Eylea, is a recombinant fusion protein consisting of 2 identical polypeptide chains, each comprising the second Ig domain of the human vascular endothelial growth factor (VEGF) receptor 1 and the third Ig domain of the human VEGF receptor 2, with both polypeptide chains fused to the Fc domain of human IgG1 (Avery et al 2017).

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and Placental Growth Factor (PlGF) with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors (Papadopoulos et al 2012). SCD411 is under development for the same indications approved for Eylea in United States of America (USA), European Union (EU), and Japan which are neovascular (wet) age-related macular degeneration (AMD), diabetic macular edema (DME), diabetic retinopathy, macular edema following retinal vein occlusion (RVO), and AMD with subfoveal choroidal neovascularization (CNV) (Eylea® 2019; European Medicines Agency 2018; Santen 2012).

Neovascular (wet) AMD is characterized by pathological CNV. Leakage of blood and fluid from CNV may cause retinal thickening or edema and/or sub-/intra-retinal hemorrhage, resulting in loss of visual acuity (VA) (Schneider et al 2005).

Other drugs of this class include ranibizumab (Lucentis®) and pegaptanib sodium (Macugen®). However, aflibercept shows some differences over other VEGF blockers, enabling prolongation of the interval between 2 intravitreal (IVT) injections and a decrease of the number of injections needed by year compared to the other drugs due to the following reasons:

- A higher affinity (~0.5 pM dissociation constant for VEGF165 and ~0.36 pM for VEGF121) than a humanized monoclonal antibody (Papadopoulos et al 2012; García-Quintanilla et al 2019)
- A longer circulating half-life compared to soluble receptor constructs which have been studied in animals (García-Quintanilla et al 2019)

- A binding to the related angiogenic factors such as PlGF1 and PlGF2 (Dixon et al 2009) and Galectin-1 (Kanda et al 2015), thought to be advantageous in certain disease situations, including retinal neovascularizations.

The development of SCD411 involves stepwise similarity exercises starting with comparison of the structural characteristics, physicochemical properties, and biological activities, followed by a series of in vitro and in vivo nonclinical studies, followed by a Phase III equivalence study to demonstrate biosimilarity between SCD411 and Eylea.

1.2 Nonclinical Studies

A series of in vivo nonclinical studies were performed using the test articles of 500 L and 2000 L batches to demonstrate similarity between SCD411 and Eylea, as follows:

- In vivo repeated-dose toxicity study in cynomolgus monkeys of 13 weeks with a 4-week recovery period was conducted. No SCD411-related mortality occurred. No SCD411- or Eylea-related macroscopic or microscopic observations or effects on organ weight parameters were noted.
- A single-dose pharmacokinetic (PK) study in pigmented rabbits using the formulated 500 L batch drug product. After the first rabbit study wherein, the investigational product (IP) was injected at the first stage followed by method development in that study, a single-dose PK study was repeated in pigmented rabbits using the formulated 2000 L batch drug product. Eylea and SCD411 (free) exposure is relatively similar in serum and vitreous humor. There were no measurable concentrations of Eylea-VEGF complex in vitreous humor (right eye). Furthermore, there were no measurable concentrations of Eylea-VEGF complex or SCD411-VEGF complex in serum and no analytes measurable in vitreous humor left (eye not dosed). In order to secure safety in clinical studies, animal tests were conducted using 2000 L, a scale used for clinical studies.

1.3 Study Rationale

SCD411 is being developed as a biosimilar to the reference product Eylea® (aflibercept). Based on the proposed extensive analytical comparability testing, comparative nonclinical testing, and comparative clinical studies using the same licensed reference product, the current study is designed to evaluate comparability between SCD411 and aflibercept. Based

on the data from aflibercept clinical studies VIEW 1, VIEW 2, COPERNICUS, GALILEO, VIBRANT, VIVID, VISTA, and MYRROR, wet AMD is considered as the most suitable condition to prove similarity between SCD411 and aflibercept as the reference product.

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 (Eylea® 2019). It is evident that in some cases no measurable systemic levels of free aflibercept were registered after IVT administration. Hence, a comparative PK evaluation in patients with AMD will likely not provide any information of relevance to support biosimilarity. Although the systemic exposure of SCD411 is expected to also be very low at steady state, there is no previous human data on SCD411, and thus this assumption requires experimental support. Hence, PK assessment will be performed in the current study following the first and the third doses of SCD411.

As aflibercept is a therapeutic protein, there is a potential for immunogenicity. No cases of active neutralizing antibodies (NAb) were observed after administration of Eylea. It is evident that immunogenicity is not presenting a substantial safety concern in patients treated with aflibercept injections. There was no substantial difference in the proportion of patients testing positive for anti-drug antibodies (ADA) in different indications, including wet AMD (Eylea® 2019). Based on this observation, the indication chosen for this study is expected to provide sound data for comparing the immunogenicity of the test product (SCD411) with that of Eylea.

The clinical part of the comparison will be based on clinical efficacy and safety data obtained after IVT administration to subjects with wet AMD in the current pivotal study.

1.4 Benefit-risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SCD411 may be found in the investigator's brochure.

2 Study Objectives, Estimands, and Endpoints

2.1 Primary Objective

The primary objective of this study is:

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

2.2 Secondary Objectives

The secondary objectives of this study are:

- To compare the safety and tolerability of SCD411 and aflibercept
- To compare the efficacy of SCD411 and aflibercept after 8 weeks and 52 weeks of treatment demonstrated by BCVA, central retinal thickness (CRT), and CNV
- To compare the immunogenicity of SCD411 and aflibercept by presenting information of the development of anti-SCD411 antibodies

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To compare PK parameters of SCD411 and aflibercept
- To quantify free and bound aflibercept and SCD411.

2.4 Endpoints

Efficacy will be summarized for the study eye only.

2.4.1 Primary Endpoint

- Change from baseline in BCVA as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters score or 2702 charts at Week 8

2.4.2 Secondary Endpoints

- Safety endpoints include AEs, vital signs, and laboratory assessments up to Week 52.

- Efficacy endpoints are:
    - Change from baseline in BCVA as measured by ETDRS letter score or 2702 charts at Week 52.
    - Change from baseline in CRT at Week 8 as assessed by optical coherence tomography (OCT).
    - Change from baseline in CRT at Week 52 as assessed by OCT.
    - Change from baseline in CNV area at Week 8.
    - Change from baseline in CNV area at Week 52.
    - Percentage of subjects who gain at least 15 letters in BCVA as measured by ETDRS letter score or 2702 charts compared with baseline at Week 8.
    - Percentage of subjects who gain at least 15 letters in BCVA as measured by ETDRS letter score or 2702 charts compared with baseline at Week 52.
- Immunogenicity endpoints include the evaluation of development of anti-SCD411 or anti-aflibercept antibodies using blood samples taken at Baseline, at Weeks 4, 8, 20, 36, and 52. Neutralizing antibodies will be tested when ADA results are confirmed to be positive.

2.4.3 Exploratory Endpoints

PK parameters include area under the concentration-time curve from time zero to the last quantifiable time point ($AUC_{0\text{-}t}$), AUC from zero to the end of the dosing period ($AUC_{0\text{-}tau}$), AUC from zero to infinite time ($AUC_{0\text{-}inf}$), C_{max}, time to reach maximum plasma concentration (t_{max}), and elimination half-life ($t_{1/2}$), of SCD411 and aflibercept. Quantification of free and bound aflibercept and SCD411 in plasma will be performed using blood samples at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first dose. At Week 8, PK samples will be taken predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the third (Week 8) dose (Table 6-3).

2.5 Estimands

The primary estimand for the primary objective is the mean treatment difference in BCVA change from baseline at Week 8. At Week 52, the primary estimand of interest is the mean treatment difference in BCVA change from baseline at Week 52. For the primary estimand,

any observations post receipt of rescue therapy in the study eye will be set to missing, thereby estimating the treatment effect as though subjects do not receive rescue therapy. For each of the Week 8 and Week 52 analyses, the secondary estimand will be presented where post rescue will not be set to missing but will be included in the mixed-effects model for repeated measures (MMRM) analysis. The secondary estimands are constructed to estimate the treatment effect while including the impact of rescue therapy, which may better reflect actual real-world outcomes, where rescue therapy would likely be given when lack of efficacy is seen.

3 Investigational Plan

3.1 Study Design

This is a Phase III, randomized, double-masked, parallel-group, multicenter study to demonstrate biosimilarity of SCD411 compared to Eylea (aflibercept) among adult subjects with neovascular (wet) AMD.

Approximately 560 subjects with wet AMD will be enrolled in this study across approximately 155 sites in 14 countries. Upon entry into the study, subjects will be assigned a screening number. Subjects who meet all inclusion and none of the exclusion criteria will return to the clinic on Day 1 for further evaluation. Subjects who continue to meet all inclusion and none of the exclusion criteria will be randomly assigned and treated on Day 1. At this visit, the subjects will be randomly assigned in 1:1 ratio to receive IVT SCD411 or aflibercept injections. Randomization will be stratified by subject participation in the PK substudy. Subjects in Israel will not participate in the PK substudy. Randomization will also be stratified by subjects enrolled in Japan. Subjects will be treated with study treatment every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48 as detailed in the Schedule of Events (Table 6-1). A schematic of the study design is presented in Figure 3-1. The details of the implementation in Interactive Response Technology (IRT) will be provided in the IRT manual and the randomization specification form.

This study includes a screening duration up to 3 weeks, treatment duration up to 48 weeks, and follow-up duration up to 4 weeks; thus, the total duration of study participation is approximately up to 55 weeks.

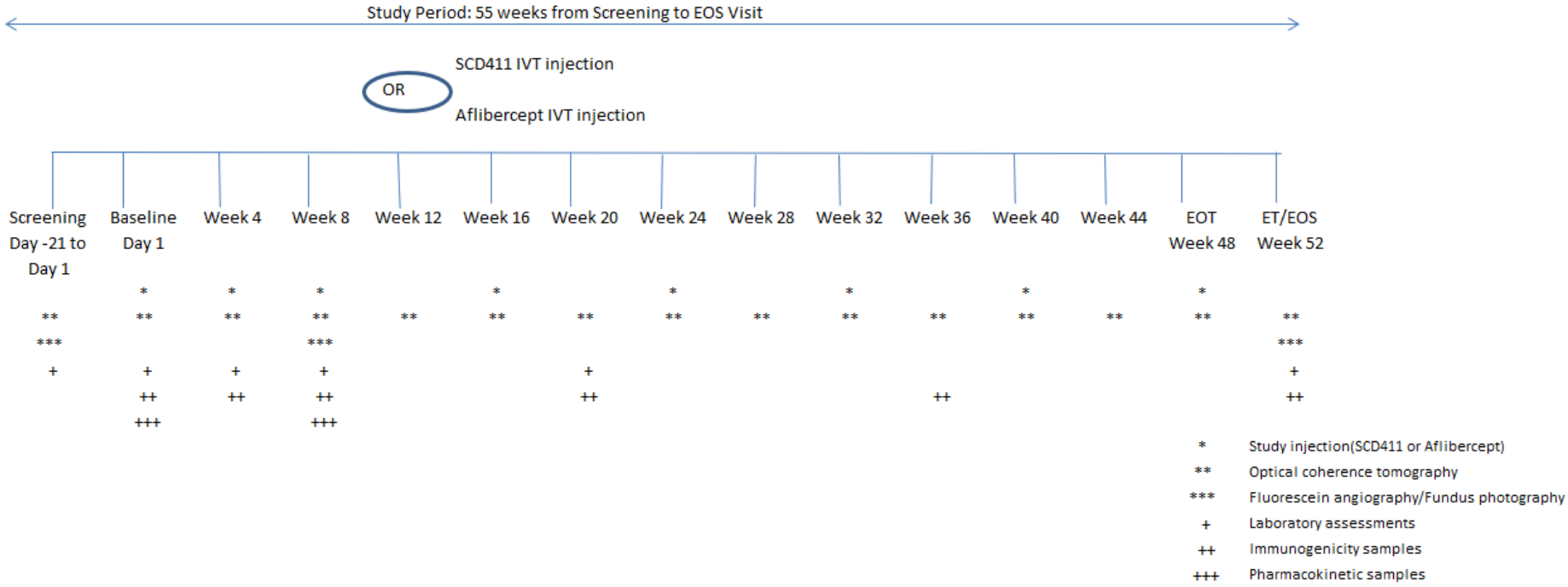
All subjects will be assessed once every 4 weeks as detailed in the Schedule of Events (Table 6-1). The End-of-Treatment (EOT) Visit will be scheduled for Week 48. Subjects who discontinue the study treatment early should have the reasons for treatment discontinuation documented on the Treatment Discontinuation page of the electronic case report form (eCRF). Treatment discontinuation in the study is defined as subjects discontinuing the study treatment due to AE/lack of efficacy/rescue treatment but not limited to these conditions. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the Early

Termination (ET) Visit should be completed as soon as possible after discontinuing the treatment but no later than 28 days after discontinuation. The End-of-Study (EOS) Visit will occur 28 days after the EOT at Week 52. The end of the study is defined as the date of the last visit of the last subject in the study.

The study design incorporates an Independent Data Monitoring Committee (IDMC) that will review ongoing safety and will also make recommendations to the sponsor as described in the IDMC Charter. Details of the IDMC are given in Section 6.6.

An interim analysis will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study. Details of the interim analysis are given in Section 7.5.6.

Figure 3-1: Study Schema



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

3.1.1 Rationale of Study Design

The current study design and choice of endpoints are mainly based on the data from aflibercept clinical studies VIEW 1, VIEW 2, COPERNICUS, GALILEO, VIBRANT, VIVID, VISTA, and MYRROR, which indicates that the model of wet AMD can be regarded as representative of approved therapeutic indications of the reference product and sensitive for detecting potential differences between the biosimilar, SCD411 and the reference product, aflibercept.

Selection of Doses in the 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 the first 3 months, followed by 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.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 560 subjects will be enrolled at 155 sites in 14 countries. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed as they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. Capable of understanding the written informed consent, provides signed and witnessed written informed consent, and agrees 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 center.
4. The BCVA letter score of 73 to 35 using original series ETDRS charts or 2702 series number charts in the study eye at screening and at Week 0 (Day 1) prior to randomization. In addition, fellow eye should not be less than 35 letter score using the ETDRS chart or 2702 series number chart
5. Women of child-bearing potential with a negative serum pregnancy test at screening must agree to use protocol-defined methods of contraception throughout the study until 3 months after the last injection of aflibercept/SCD411 (Section 4.1.3 and Section 4.1.4).
6. Males with female partners of child-bearing potential must 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 aflibercept/SCD411.

7. The area of CNV making up either 50% or more of the total lesion area and confirmed by the central reading center.

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria at the Screening Visit will be excluded from the study:

1. Any prior ocular (in the study eye and fellow eye) or systemic treatment or surgery for neovascular AMD except dietary supplements or vitamins
2. Any prior or concomitant therapy with another investigational agent to treat neovascular AMD in the study eye, except dietary supplements or vitamins
3. Fellow eye shows signs of AMD that, in investigator's medical opinion, may need any treatment during study period
4. Any prior treatment with anti-VEGF agents in the both eyes (ie, completely treatment naïve subjects only to be included)
5. Total lesion size >30.5 mm^2, including blood, scars, atrophy, fibrosis, and neovascularization as assessed by FA in the study eye and confirmed by the central reading center
6. Central retina thickness of <300 μm in the study eye and confirmed by the central reading center
7. Subretinal hemorrhage that is either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye and confirmed by the central reading center. (If the blood is under the fovea, then the fovea must be surrounded 270 degrees by visible CNV.)
8. Scar or fibrosis, making up >50% of the total lesion in the study eye and confirmed by the central reading center
9. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye and confirmed by the central reading center
10. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye and confirmed by the central reading center

11. Lens Opacity Classification System II (LOCS II) grade IV cataract in the study eye, or other significant cataract in the study eye that in the Investigator's opinion interferes with visualization of retina or interferes with retinal imaging
12. Active intraocular/periocular infection and inflammation in either eye
13. History of any vitreous hemorrhage in the study eye within 4 weeks prior to the Screening Visit
14. Presence of other causes of CNV in the study eye as confirmed by central reading center
15. 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 in the study eye
17. History of retinal detachment, treatment, or surgery for retinal detachment in the study eye
18. History of macular hole of Stage 2 and above in the study eye as confirmed by central reading center
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

    Note: A subject with uncomplicated neodymium yttrium aluminum garnet (Nd:YAG) laser capsulotomy performed for secondary opacification of the posterior capsule in intraocular lens implanted eye within 3 months prior to Day 1 in the study eye will be considered as eligible.
20. Presence of aphakia in the study eye
21. History of glaucoma-filtering surgery within 3 months of Day 1 in the study eye. Anti-glaucoma laser surgeries will not be considered exclusionary.
22. History of corneal transplant in the study eye
23. History or evidence of any other clinically significant disorder, condition or disease (eg, 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 (BP) >160 mmHg or diastolic BP >100 mmHg under appropriate antihypertensive treatment
25. Hypersensitivity to aflibercept or medications used in this study (fluorescein, mydriatic eye drops, etc.)
26. Pregnancy or lactation at the Screening Visit and/or at baseline for women of child-bearing potential
27. Any 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 on 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. Any 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

    Note: For IVT corticosteroid implant, the exclusion period would be 36 months from the date of the procedure to the date of screening.
32. Any prior or concomitant treatment involving the macula with photodynamic therapy (PDT) with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (eg, focal laser photocoagulation) in the study eye
33. Any prior or concomitant treatment with pan-retinal photocoagulation 90 days in the study eye before the Screening Visit
34. Any 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. Any IP 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 ≥25 mmHg in spite of anti-glaucoma treatment
37. Any prior or ongoing systemic medical condition (including but not limited to infectious, inflammatory, psychiatric, neurological, renal, hepatic, respiratory conditions or malignancies) or clinically significant screening laboratory value that in the opinion of the investigator may present a safety risk, interfere with study compliance and follow-up, or confound data interpretation throughout the study period.

4.1.3 Women of Child-bearing Potential

Women of child-bearing potential are defined as premenopausal women physiologically capable of becoming pregnant.

Women of non-child-bearing potential are defined as women meeting any of the following criteria:

- Older than 50 years with amenorrhea for >2 years or older than 60 years with amenorrhea for >1 year. In both cases, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels are performed at screening to ensure these subjects are not pregnant.
- Has undergone hysterectomy.
- Has undergone bilateral oophorectomy.
- Has undergone bilateral salpingectomy.

4.1.4 Approved Methods of Contraception

Approved methods of contraception include oral contraceptives, intrauterine device, medically acceptable barrier methods (diaphragm or condom), implantable or injectable contraceptives or removable birth control device, and/or sterilization. Subjects practicing abstinence and coitus interruptus (pull out method) must agree to use an approved method of contraception during the study and until 3 months after their last injection.

4.2 Selection of Study Eye

Only one eye (study eye) must meet all the inclusion criteria and none of the exclusion criteria.

Fellow eye should not show any signs of AMD that, in the investigator's medical opinion, may need any treatment during study period.

4.3 Withdrawal of Subjects From Study Treatment and/or the Study

The duration of the study for each subject is defined as the date the subject signs the written informed consent form (ICF) up to the last EOS Visit, which is 28 days after the End-of-Treatment (EOT) Visit.

Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator and/or sponsor for safety, behavioral, or administrative reasons. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

4.3.1 Discontinuation From Study Treatment

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study treatment. If the IP is definitively discontinued, the Treatment Discontinuation page of the eCRF should be completed. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the subject should undergo ET Visit assessments as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation, as described in the Schedule of Events (Table 6-1).

A subject may discontinue from the study treatment for any of the following reasons:

- Subject has a serious or intolerable AE that, in the investigator's opinion, requires discontinuation from the study treatment.

- Decision by the investigator that the subject requires alternate treatment for neovascular AMD in the study eye.
- Pregnancy.
- A subject misses either of the first 2 doses (IVT injection of IP at Week 0 [Day 1] or Week 4) after randomization.
- Decision by the Sponsor or administrative decision for a reason (eg, a suspicion of fraud, the subject enrolling in multiple clinical studies, lack of compliance) other than that of an AE.
- Certain specific criteria for treatment discontinuation include:
- Development of rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- A decrease in BCVA of ≥30 letters compared with the last assessment of VA.
- A subretinal hemorrhage involving the center of the fovea or if the size of the hemorrhage is ≥50% of the total lesion area.
- Clinical signs of irreversible ischemic visual function loss.

4.3.2 Withdrawal From the Study

A subject may withdraw from the study for any of the following reasons:

- Death.
- Lost to follow-up.
- Protocol deviation which may adversely affect the subject's safety and/or integrity of data as agreed by the investigator and/or upon request from the Sponsor.
- The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal.
- The subject withdraws consent.
- If a subject withdraws his/her consent, the investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (eg, documented lack of efficacy, AE or pregnancy); however, the subject may refuse to provide such reason.

4.3.3 Handling of Withdrawals

Subjects are free to withdraw from the study or study treatment at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF.

Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration after discontinuation of the study treatment unless the subjects withdraw consent. All subjects who withdraw from the study prematurely will be asked to complete the ET Visit procedures as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation. If a subject discontinues the study treatment due to an AE/serious AE (SAE) or if AEs/SAEs were ongoing at the time of discontinuation, the subject will be followed-up until resolution or stabilization.

4.3.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized to the study treatments. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Subjects who do not meet the criteria for participation in this study may not be rescreened. Image retransmission requested from the central image center due to any possible technical issues is not considered to be rescreening.

4.3.5 Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.3.6 Study Termination

The sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents, study supplies have been collected (if required), and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects
- Cancellation of drug development.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the institutional review board (IRB)/ independent ethics committee (IEC) or local health authorities, the sponsor's procedures, or Good Clinical Practice (GCP) guidelines
- Inadequate recruitment of participants by the investigator.

4.3.7 Replacements

Dropout subjects will not be replaced in the study.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

All subjects will be centrally randomized in a 1:1 ratio to receive SCD411 or aflibercept IVT injections at the baseline/randomization visit (Day 1) using IRT. Randomization will be stratified by participation in the PK substudy (yes/no). Before the study is initiated, the log in information and directions for the IRT will be provided to each site. Only qualified study staff and those delegated the responsibility of study drug administration should administer the study drug injections.

If a subject visits the site outside of the visit window for a dosing visit until Week 8:

- During the 4-week intervals dosing: assessment and dosing can be done within a window of ±2 days. In this case, the interval between the 2 doses should not be less than 24 days and more than 32 days. If the subject IP dosing window is out of the allowed window interval, dosing should be skipped.
- During the 8-week intervals dosing: assessment and dosing should be done within the window of ±7 days. In this case, the interval between the 2 doses should not be less than 49 days and not more than 63 days.

Study treatment will be dispensed at the study visits summarized in the Schedule of Events (Table 6-1).

5.2 Treatments Administered

Subjects who complete the study screening and baseline assessments and meet all the eligibility criteria will enter the study and will be randomly assigned in a 1:1 ratio on Day 1 to receive SCD411 or aflibercept. Details of study treatments that will be administered during the study are provided below in Section 5.3.

Subjects will receive their randomized study treatment injections as per the Schedule of Events (Table 6-1) and according to the procedure manual. Clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to minimize the risk of potential AEs associated with IVT injections. If the pre-procedure IOP is equal to or greater than 30 mmHg, the IVT

injection will not be administered (either withheld or delayed) until the IOP is decreased to acceptable safety levels as per the investigator's medical judgment.

The IVT injection procedure should be carried out under controlled aseptic conditions. Adequate anesthesia and a topical broad-spectrum microbicide and antibiotics can be given as per the system organ class in World Health Organization Drug Dictionary (WHODRUG) and this information should be recorded in the eCRF.

Immediately following the IVT injection, subjects should be checked by the unmasked staff for hand movement/finger counting vision for subject safety. The information will not be captured in the eCRF. If subjects can recognize hand movement/finger counting vision immediately following the IVT injection, then the subjects should be transferred from the unmasked staff to the masked staff. If subjects cannot recognize hand movement/finger counting vision immediately following the IVT injection, then the unmasked staff should further investigate the reason. If required, a sterile paracentesis needle should be available for the injecting physician to ensure control of excessive IOP elevation.

The safety data for IOP and dilated fundoscopy after administration of the study treatment will be collected by the masked staff. The information will be captured in the eCRF.

Following the injection, the masked team will measure IOP and evaluate subjects for any injection-related ophthalmic changes and AEs.

Subjects should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (eg, eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Dosing visits will be allowed within ±2 days for the second and third injections and within ±7 days for the fourth injection onwards of the scheduled dosing visit date (except Week 0 [Day 1], visit window not allowed). All applications outside of the specified windows will be captured a protocol deviation.

5.2.1 Treatment of Fellow Eye

Treatment of fellow eye will be allowed at any time during the study if a subject is newly diagnosed with neovascular AMD or has worsening neovascular AMD in the fellow eye. The fellow eye should be treated only with Eylea as per investigator's discretion. In this case,

fellow eye data of dilated fundoscopy, IOP, fellow eye treatment date and medication name will be collected via eCRF. Also, the fellow eye treatment injection is not permitted on the same day as the study eye treatment.

The cost of the fellow eye treatment will be covered by the sponsor in terms of either providing open-label Eylea or reimbursement after the site stock of Eylea is used up.

5.2.2 Dose Modification

Dose reductions will not be allowed.

5.3 Identity of Investigational Product

The study treatment solution is colorless to pale yellow. If particulates, cloudiness, or discoloration are visible, the vial must not be used. The glass vial is for a single-use only. The study injections should be inspected visually prior to administration.

The active substances are aflibercept and SCD411. One vial contains 100 µL, equivalent to 4 mg aflibercept. One vial delivers a dose of 2 mg aflibercept in 50 µL. [redacted]

Each vial should only be used for the treatment of a single eye. After injection, the used vial should be placed back within the box and resealed at the site to prevent unintentional unmasking.

Manufacturer details of the study treatment and Eylea will be provided in the pharmacy manual.

The following drug supplies will be used in the study:

Study Treatment Name:	SCD411	Eylea (Aflibercept)
Dosage Formulation:	Solution for intravitreal injection	Solution for intravitreal injection
Unit Dose Strength(s)/ Dosage Level(s):	Single-use vial containing 0.1 mL (40 mg/mL) aflibercept biosimilar solution	Single-use vial containing 0.1 mL (40 mg/mL) aflibercept solution
Route of Administration:	Intravitreal injection	Intravitreal injection
Dosing Instructions:	0.05 mL of solution containing 2 mg	0.05 mL of solution containing 2 mg
Packaging and Labeling:	Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.	The current study will use EU-licensed Eylea as comparator drug. Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Study treatment products should be stored in a refrigerator (2ºC to 8ºC) and should not be frozen. The vial should be kept in its outer carton in order to protect from light.

5.4.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

5.5 Overdose Management

An overdose is any dose of study treatment given to a subject or taken by a subject that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the PPD Drug Safety Center. Overdoses without signs or symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE/SAE sections in the eCRF.

Currently there is no information available on the overdose effects of the study drug in humans.

5.5.1 Medication Errors

Medication errors include overdose, incorrect dose, incorrect drug, incorrect administration or incorrect kit used in the study. Usually, an overdose or incorrect administration of study treatments is not itself an AE, but it may result in an AE. Medication errors will be reported by the unmasked investigator in a masked manner to the masked investigator.

5.6 Masking

This is a double-masked study. To prevent bias in treatment assignment, eligible subjects will be randomly assigned using the IRT.

Subjects and study site staff involved in subject management and study assessments will be masked to study treatment assignment. The sponsor, the delegated contract research organization (CRO), and imaging teams will also be masked to the study treatment. Only the unmasked investigator involved in performing the IVT injections will be unmasked to study treatment. These individuals are not allowed to discuss treatment and/or subject outcome with masked study staff, including the evaluating investigator.

5.6.1 Unmasking

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the treatment assignment needs to be unmasked because of a medical emergency, the PI may unmask an individual subject's treatment allocation.

The PI is encouraged to first contact the sponsor representatives to discuss the medical emergency and the reason for revealing the actual treatment received by that subject as soon as possible. The investigator should not share any unmasked information with the sponsor and monitoring team. The treatment assignment will be unmasked through IRT. Reasons for treatment unmasking must be clearly explained and justified in the eCRF. The date on which the code was broken along with the identity of the person responsible for breaking the code, must also be documented in the eCRF.

5.7 Treatment Compliance

Study procedures at the study center are to be performed under the direct supervision of the investigator and qualified study center personnel. All injections must be taken in accordance with the original schedule outlined at subject's Day 1 Visit with the first dose.

The study drug is administered as an IVT injection at the study site, so it is not necessary to monitor subject compliance with the study drug regimen.

5.8 Prior and Concomitant Therapy

Use of all concomitant medications will be recorded in the subject's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter (OTC) medications. Any changes in concomitant medications also will be recorded in the subject's eCRF.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF. Information on prior and concomitant medications is collected within 30 days prior to signing the ICF or longer if the investigator considers relevant. Prohibited medications are collected from prior to duration of prohibition of use for this study (Table 5-1).

5.8.1 Rescue Treatment

In the study eye, rescue treatment for neovascular AMD is not permitted at any point in time. If it is observed that efficacy is not achieved by the study treatment, as determined by the investigator, subjects can be considered for rescue treatment after Week 4 if any 1 of the following conditions are met as assessed by the masked investigators:

- Decrease of VA letter score of 15 letters or more from the last assessment and/or
- An increase in intraretinal fluid, subretinal fluid, or subretinal hyper-reflective material that, in the investigator's opinion, is related to progression of the subject's neovascular AMD

Subjects who will receive rescue treatment need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.

5.8.2 Prohibited Medications

The details of the prohibited medications during the study are presented in Table 5-1. Concurrent use of systemic or IVT anti-VEGF agents; IVT, subtenon, or peribulbar corticosteroids in study eye are not permitted, except as required to treat AEs.

In addition, the use of photocoagulation or PDT with verteporfin are prohibited during the study. Antimicrobial drops can be used at the discretion of the investigator.

Table 5-1: Prohibited Medications

Medication/Therapy	Eye (Study Eye or Study Eye and Fellow Eye or Either)	Duration of Prohibition
Ocular therapy/treatment list		
IVT anti-VEGF treatment to treat neovascular AMD	Study eye Note: Treatment of fellow eye will be allowed at any time during the study if a subject has newly diagnosed neovascular AMD or worsening neovascular AMD in fellow eye. The fellow eye should be treated only with Eylea as per investigator's discretion.	Ever before and to EOS/ET Visit
IVT injection of corticosteroids (eg, triamcinolone acetonide) or intravitreal - Corticosteroid implant -Subtenon corticosteroids -Peribulbar corticosteroids	Study eye	6 months before screening and throughout the study period For IVT corticosteroid implant, the exclusion period would be 36 months from the date of the procedure to the date of screening
Treatment involving macula with PDT with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (eg, focal laser photocoagulation)	Study eye	Prior to screening and throughout the study period
Treatment with pan-retinal photocoagulation	Study eye	90 days prior to screening and throughout the study period
Systemic medications		
Systemic anti-VEGF agents	NA	Within 90 days prior to randomization and throughout the study
Deferoxamine	NA	4 weeks prior to randomization and throughout the study period
Tamoxifen	NA	8 weeks before randomization and throughout the study period
Hydroxychloroquine, Chloroquine	NA	8 weeks before randomization and throughout the study period

Medication/Therapy	Eye (Study Eye or Study Eye and Fellow Eye or Either)	Duration of Prohibition
Vigabatrin	NA	8 weeks before randomization and throughout the study period
Ethambutol	NA	2 weeks before randomization and throughout the study period
Topiramate	NA	4 weeks prior to randomization and throughout the study period
Amiodarone	NA	12 weeks prior to randomization and throughout the study period
Other investigational products		
Systemic IP to treat neovascular AMD	NA	Prior to screening and throughout the study period
Ocular IP to treat neovascular AMD	Study eye and fellow eye	Prior to screening and throughout the study period
Ocular IP to treat any ocular disease	Study eye and fellow eye	30 days or 5 half-lives prior to randomization (whichever is longer), and throughout the study period
Systemic IP (excluding dietary supplements, vitamins and minerals) to treat systemic diseases	NA	30 days or 5 half-lives prior to randomization (whichever is longer), and throughout the study period

Abbreviations: AE, adverse event; AMD, age-related macular degeneration; EOS, end-of-study; ET, early termination; IP, investigational product; IVT, intravitreal; NA, not applicable; PDT, photodynamic therapy; VEGF, vascular endothelial growth factor.

6 Study Assessments and Procedures

Before performing any study procedures, all potential subjects will sign an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign the ICF.

The Schedule of Events is presented in Table 6-1.

Table 6-1: Schedule of Events

Assessment	Screening	Treatment													ET[a]/EOS[b]
Study Day	**–21 to 0**	**Baseline/1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**EOT/337**	**365**
Study Week	**-3**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Time Window (days)			**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent	X														
Demographic information (incl. height and weight)	X														
Inclusion/exclusion criteria	X	X													
Ocular and systemic medical history	X														
Slit lamp examination[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopy[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[e]	X	X													X
Prior and concomitant ocular and systemic medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[g]		X													
SCD411 or aflibercept injection [h]		X	X	X		X		X		X		X		X	
Pre-injection IOP[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-injection IOP and vision check[i]		X	X	X		X		X		X		X		X	
BCVA[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OCT[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FA and FP[l]	X			X											X
Laboratory assessments[m]	X	X	X	X			X								X
Vital signs[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X			X											X

Assessment	Screening	Treatment													ET[a]/EOS[b]
Study Day	**–21 to 0**	**Baseline/1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**EOT/337**	**365**
Study Week	**-3**	**1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Visit Time Window (days)			**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity samples[o]		X	X	X			X				X				X
PK samples[p]		X		X											

Abbreviations: AEs, adverse events; BCVA, best corrected visual acuity; ECG, electrocardiogram; EOS, end-of-study; EOT, end-of-treatment; ET, early termination; FA, fluorescein angiography; FP, fundus photography; FSH, follicle-stimulating hormone; IOP, intraocular pressure; IVT, intravitreal; LH, luteinizing hormone; OCT, optical coherence tomography; PDT, photodynamic therapy; PK, pharmacokinetics; SAE, serious adverse event; VA, visual acuity; VEGF, vascular endothelial growth factor.

[a] For subjects who discontinue study treatment and choose to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, ET Visit assessments are to be performed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.

[b] End-of-study assessments are to be performed 28 days after the EOT.

[c] Slit lamp examination will be performed on both eyes at all the planned scheduled visits during the study.

[d] Dilated fundoscopy will be performed on the study eye at all the planned scheduled visits during the study, including the time prior to IVT injection of the study drug, and within 60±30 minutes after IVT injection of the study drug, and at any time during the visit at ET/EOS Visit.

[e] Serum pregnancy test will be done at screening, and urine pregnancy test at baseline, ET, and EOS Visits for female subjects of child-bearing potential. If urine pregnancy test is positive, serum pregnancy test should be performed; if found positive, study treatment will be discontinued, and the subject should continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. Pregnancy cases should be followed until resolution of the pregnancy.

[f] Concurrent use of systemic or intravitreal anti-VEGF agents, IVT, subtenon, or peribulbar corticosteroids in study eye, except as required to treat AEs, and use of photocoagulation or PDT with verteporfin are prohibited during the study. Antimicrobial drops can be used at the discretion of the investigator. For IVT corticosteroid implant, the exclusion period would be 36 months from the date of the procedure to the date of screening.

[g] The investigator must confirm that the subject meets all inclusion and none of the exclusion criteria at both screening and Day 1. This is inclusive of BCVA scoring.

[h] Rescue treatment for the study eye is not permitted at any point in time. Subjects can be considered for rescue treatment after Week 4 if the following conditions are met as assessed by the masked investigator: VA letter score decrease of 15 letters or more from the last assessment, an increase in intraretinal fluid, subretinal fluid, or subretinal hyper-reflective material, that in the investigator's opinion is related to progression of the subject's neovascular AMD. Subjects who will receive rescue treatment need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with all their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.

[i] Intraocular pressure will be measured on both eyes at screening, and on the study eye prior to IVT injection of the study drug, and 60±30 mins after IVT injection of the study drug at each visit from baseline/Day 1 to EOT (48 weeks). If the pre-procedure IOP is equal to or greater than 30 mmHg, IVT injection will not be administered (either withheld or delayed) until IOP is decreased to acceptable safety levels as per investigator's medical judgment. IOP should be measured after OCT and FA are completed to avoid corneal erosion. Finger counting test to be performed immediately after the IVT injection of the study drug. IOP will also be performed at any time during the ET/EOS Visit.

[j] Best corrected VA testing will be done for both eyes and should be performed prior to the dilation of pupils, FA, and OCT assessments, and prior to the IVT injection of the study drug. BCVA will also be performed at any time during the visit at ET/EOS Visit. A decrease in VA of ≥15 letters from the last assessment of VA should be reported as AEs/SAEs as appropriate. If there is a decrease in VA of ≥30 letters from the last assessment of VA or if there is a decrease in VA to the level of Light Perception or worse, it should be reported as SAE.

[k] OCT imaging should be performed on the study eye prior to the IVT injection of the study drug. Those images will be sent to the central reading center. Site staff who will perform OCT scans in this study must be certified by the central reading center before study starts. OCT devices registered in an investigational site should be all from the same manufacturer and meet the minimum software requirement. The subject should use the OCT device registered by the central reading center from Screening to Week 52 (EOS visit) or ET Visit.

[l] At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS, FA and FP will be performed on the study eye (prior to IVT injection of the study drug at Week 8). Those images will be sent to the central reading center. Site staff who will perform FA and FP in this study must be certified by the central reading center before study starts. Only FP/FA devices certified by central reading center are allowed to be used in this study. If 1 or more FP/FA devices are certified at an investigational site, a subject must use the same FP/FA device consistently from Screening to Week 52 (EOS Visit) or ET Visit.

[m] Hematology, chemistry, and urinalysis samples will be collected prior to IVT injection of the study drug. Urine samples will be collected prior to performing FA to avoid false elevations in urine protein values. No pregnancy test is required for women of non-child-bearing potential. For women of child-bearing potential, serum pregnancy test will be performed at screening and in case of a positive urine test during the study; urine pregnancy test will be performed at the Baseline, ET and EOS Visits; the FSH and LH levels to be measured at screening for women of child-bearing potential. Hematology, chemistry, and urinalysis samples will also be performed at any time during the visit at ET/EOS Visit.

[n] Includes blood pressure, respiratory rate, heart rate, and temperature. On days when study injections will be administered, vital signs should be measured prior to IVT injection of the study drug. Vital signs will also be performed at any time during the ET/EOS Visit.

[o] Immunogenicity samples should be collected prior to IVT injection of the study drug and prior to FA assessment when performed on the same day. Immunogenicity will also be performed at any time during the visit at ET/EOS Visit. Neutralizing antibodies will be tested when anti-drug antibodies results are confirmed to be positive.

[p] Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection (Week 8).

6.1 Study Visits

6.1.1 Screening Phase

Subjects will sign the ICF prior to any screening procedures. Screening will take place within 21 days before the baseline/study treatment. The following information will be recorded and procedures will be performed at the Screening Visit:

- Eligibility (inclusion/exclusion) criteria
- Demographic information including height and weight
- Ocular and systemic medical history
- Prior and concomitant ocular and systemic medications
- Vital signs
- ECG
- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP of both eyes
- Dilated fundoscopy
- OCT
- FA
- Fundus photography (FP)
- Laboratory assessments including hematology, chemistry, and urinalysis
- Serum pregnancy test, FSH, and LH levels will be measured for women of child-bearing potential
- AEs

6.1.2 Treatment Phase

6.1.2.1 Baseline (Day 1)

During the Day 1 Visit at baseline, all inclusion/exclusion criteria should be reviewed prior to randomization and study treatment injection. Subjects will be randomly assigned to 1 of the study treatments, SCD411 or aflibercept. Randomized subjects will receive their first treatment injection on Day 1.

Assessments on Day 1 include the following:

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT
- Post-injection IOP and vision check

The IOP is measured on both eyes at screening, and on the study eye prior to IVT injection of the study drug, and 60±30 mins after IVT injection of the study drug at each visit from baseline/Day 1 to EOT (48 weeks). The IOP is to be measured after OCT and FA are completed to avoid corneal erosion.

Dilated fundoscopy is measured on the study eye prior to IVT injection of the study drug and within 60±30 minutes after IVT injection of the study drug.

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- Urine pregnancy test for female subjects of child-bearing potential
- Laboratory assessments including hematology, chemistry, and urinalysis

- AEs
- Immunogenicity sample collection
- PK sample collection.

Other baseline assessments will be same as that for other visits as detailed in Section 6.1.2.2.

6.1.2.2 Subsequent Treatment Period (Week 4, Week 8, Week 12, Week 16, Week 24, Week 28, Week 32, Week 40, Week 44, and Week 48)

All study procedures should be performed on the same day. Following completion of the evaluations, the IVT injection will be administered on the same day of every visit. Only in rare circumstances with reason well documented on the eCRF, the IVT injection may be administered the next day.

Study treatment will be injected on Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48.

Week 8 is the most critical visit for assessment of the primary endpoint assessment for US Food and Drug Administration (FDA), Japan Pharmaceuticals and Medical Devices Agency (PMDA), and European Medicines Agency (EMA) Committee on Human Medicinal Products submissions. Thus, every effort should be made to adhere to the visit schedule for the subjects.

The following procedures/assessments will be performed and information will be recorded during the treatment period:

Week 4

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy

- OCT
- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- Laboratory assessments including hematology, chemistry, and urinalysis
- AEs
- Immunogenicity sample collection

Week 8

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT
- FA
- FP
- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- Laboratory assessments including hematology, chemistry, and urinalysis
- ECG
- AEs

- Immunogenicity sample collection
- PK sample collection

Week 12

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 16

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT
- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications

- Vital signs
- AEs

Week 20:

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- Laboratory assessments including hematology, chemistry, and urinalysis
- AEs
- Immunogenicity sample collection

Week 24

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT
- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 28

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 32

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT
- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 36

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs
- Immunogenicity sample collection

Week 40

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 44

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Week 48

Ocular:

- BCVA measured by ETDRS letter score or 2702 charts
- Slit lamp examination
- Pre-injection IOP
- Dilated fundoscopy
- OCT

- Post-injection IOP and vision check

Nonocular:

- Concomitant ocular and systemic medications
- Vital signs
- AEs

Note: PK samples will be collected on the first and the third injection on Day 1 and Week 8 at the following time points: predose, +1 day, +3 days, +7 days, +14 days, and +28 days after the study treatment injections.

6.1.3 Early Termination/End-of-Study

The end of the study is defined as the date of the last visit of the last subject in the study.

For subjects who discontinue study treatment, the Treatment Discontinuation page of the eCRF should be completed. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn from the study, then the subject should return for the ET Visit as soon as possible after the discontinuation but no later than 28 days after discontinuation. End-of-Study Visit assessments will be conducted 28 days after the EOT at Week 52.

The following procedures/assessments will be performed at the ET/EOS Visit:

Ocular:

- Slit lamp examination
- Dilated fundoscopy
- IOP
- BCVA measured by ETDRS letter score or 2702 charts
- OCT
- FA (at ET/EOS)

- FP (at ET/EOS)

Nonocular:

- Urine pregnancy test for female subjects of child-bearing potential (at ET/EOS)
- Concomitant ocular and systemic medications
- Laboratory assessments (at ET/EOS)
- Vital signs
- ECG (at ET and EOS Visits)
- AEs
- Immunogenicity samples (at ET and EOS Visits)

If a subject is discontinued from the study, all the ET Visit procedures should be performed even if they are outside the allowed study window.

6.2 Efficacy Assessments

In this study, efficacy is assessed using BCVA by ETDRS letter score or 2702 charts, OCT measures CRT, and CNV area is assessed using FA and FP.

6.2.1 Best Corrected Visual Acuity

Best corrected visual acuity will be measured at the scheduled visits as indicated in the Schedule of Events (Table 6-1) by certified study staff. BCVA will also be performed at any time during the visit at ET/EOS Visit. If the light bulbs are not changed yearly or burned in properly, it will be considered a deviation. The VA examiners are masked to study arm assignments. Visual acuity testing will be done for both eyes and should be performed prior to the dilation of pupils, FA, and OCT assessments and prior to the IVT injection of the study drug. Visual acuity testing will be consistently assessed from Screening to Week 52 (EOS visit) or ET Visit using either original series ETDRS charts or 2702 charts at a starting distance of 4 meters, performed by a certified VA examiner. The same method of BCVA must be used in each subject from Screening to Week 52 (EOS Visit) or ET Visit.

A Visual Acuity Specifications Procedure Manual and training materials will be provided to all sites. All examiners will require certification prior to performing this assessment as part of the study.

A decrease in VA of ≥15 letters from the last assessment of VA should be reported as AEs/SAE as appropriate. If there is a decrease in VA of ≥ 30 letters from the last assessment of VA or if there is a decrease in VA to the level of Light Perception or worse, it should be reported as an SAE.

6.2.2 Ocular Imaging

Central retinal thickness will be measured using OCT and FA/FP will be used to measure CNV.

6.2.2.1 Optical Coherence Tomography

A reading center manual along with training materials will be provided to all sites which will provide information on standardized procedures for the collection, storage, and transmission of the images. Prior to any study images being taken at the sites, site personnel and equipment must be assessed and certified through test images using instruments and software approved by the central reading center. Only trained and certified site staff delegated with the responsibility of image collection should perform this test. The OCT imaging should be performed on the study eye prior to the IVT injection of the study drug. Those images will be sent to the central reading center.

All OCT devices must be registered in an investigational site by the central reading center and meet the minimum software requirement. The subject should consistently use the same OCT device from Screening to Week 52 (EOS Visit) or ET Visit. The devices should be registered by the central reading center from Screening to Week 52 (EOS Visit) or ET Visit and OCT images will be sent to the central reading center.

If a subject misses a visit during which ocular images should be taken, the images should be collected at the next scheduled visit.

6.2.2.2 Fluorescein Angiography and Fundus Photography

At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS Visit, FA and FP will be performed on the study eye (prior to IVT injection of the study drug at Week 8) and those images will be sent to the central reading center. Site staff who will perform FA and FP in this study must be certified by the central reading center before the start of the study. Only FA/FP devices certified by central reading center are allowed to be used in this study. If 1 or more FA/FP devices are certified at an investigational site, the same FA/FP device should be consistently used from Screening to Week 52 (EOS Visit) or ET Visit in each subject.

In the event a subject is suspected to have a new active CNV in the study eye, an OCT should be performed to confirm the diagnosis. An optional FA will be performed.

6.3 Safety Assessments

Safety endpoints include AEs, vital signs, ECGs, ophthalmological examinations, and laboratory assessments up to Week 52. Safety is also evaluated during follow-up (4 weeks after EOT).

6.3.1 Medical History and Concomitant Medications

All significant ocular and systemic medical conditions and surgeries within the past 5 years should be captured for all subjects. Any significant previous ocular surgeries, procedures and/or medications or treatments used for these conditions should be recorded. History of thrombotic events, IVT anti-VEGF treatment, treatment involving macula with PDT with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment should be reviewed in detail.

6.3.2 Ophthalmic Examinations

Routine ophthalmological examinations will be performed at indicated visits in the Schedule of Events (Table 6-1) and include the following:

- Biomicroscopy slit lamp examination (anterior chamber flare, anterior chamber cells, vitreous cells opacities and haze) will be performed on both eyes at screening and prior to IVT injection of the study drug. Slit lamp will also be performed at any time during the visit at ET/EOS Visit. Please see Section 13.1 (Appendix 1) and Section 13.2 (Appendix 2) for grading scales.
- Dilated fundoscopy includes evaluation of retina and vitreous (vitreal overall assessment; macular overall assessment; retina overall assessment; and optic nerve overall assessment). A standard method of indirect ophthalmoscopy (ie, using a head-mounted light source and a 20-30 lens) will be performed by the masked team/study staff on the study eye prior to IVT injection of the study drug and within 60±30 minutes after IVT injection of the study drug. Dilated fundoscopy will also be performed at any time during the visit at ET/EOS Visit. Dilated fundoscopy assessments should be performed at all assessment visits as mentioned in Table 6-1.

Intraocular pressure is a part of routine study assessment. A measurement of IOP will be conducted using either Goldmann applanation tonometer or Tono-pen.

The same method of IOP measurement must be used in each subject from Screening to Week 52 (EOS Visit) or ET Visit. Intraocular pressure will be measured by the masked team/study staff on both eyes at screening, and on the study eye prior to IVT injection of the study drug, and 60±30 minutes after IVT injection of the study drug at each visit from baseline/Day 1 to EOT (48 weeks). When IOP is measured prior to IVT injection of the study drug, IOP should be measured after OCT and FA are completed to avoid corneal erosion. IOP will also be performed at any time during the visit at ET/EOS Visit.

Finger counting test is a part of post-injection procedures and is to be performed by the unmasked investigator immediately after the IVT injection of the study drug.

6.3.3 Adverse Events

6.3.3.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or to IVT injection procedure or their clinical significance.

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug or to IVT injection procedure. Subjects will be instructed to contact the investigator at any time if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

6.3.3.2 Serious Adverse Events

An SAE is defined as any event that:

- results in death
- is immediately life threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Simple emergency room visits (excluding hospital stay that crosses midnight) are not reported as an SAE.

In addition to the above criteria, the following criteria would be considered as SAEs and are to be reported as SAEs:

- Development of rhegmatogenous retinal detachment or stage 3 or 4 macular holes.
- A decrease in BCVA of ≥30 letters compared with the last assessment of VA.

A decrease in VA of ≥15 letters from the last assessment of VA should be reported as AEs/SAE as appropriate. If there is a decrease in VA of ≥30 letters from the last assessment of VA or if there is a decrease in VA to the level of Light Perception or worse, it should be reported as an SAE.

6.3.3.3 Eliciting and Documenting Adverse Events

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

Serious AEs that occur more than 28 days after the last dose of study drug need not be reported unless the investigator considers them related to study drug.

At every study visit, subjects will be asked a standard nonleading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs identified from any study data (eg, laboratory values, electrocardiogram [ECG] changes, etc.) or identified from review of other documents (eg, subject diaries) that are relevant to subject safety will be documented on the AE page in the eCRF.

6.3.3.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes the following:

- drug treatment
- dose
- event term

- time of onset
- investigator-specified assessment of severity and relationship to study drug and to IVT injection procedure
- time of resolution of the event
- seriousness
- any required treatment or evaluations
- outcome

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

A decrease in VA of ≥15 letters from the last assessment of VA should be reported as an AE/SAE, as appropriate. If there is a decrease in VA of ≥30 letters from the last assessment of VA or if there is a decrease in VA to the level of Light Perception or worse, it should be reported as an SAE.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs or vital sign measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be worse than the subject's baseline condition, are **not** to be reported as AEs or SAEs.

6.3.3.5 Reporting Serious Adverse Events

Any AE that meets SAE criteria (Section 6.3.3.2) must be reported by the investigator to PPD, Inc immediately (ie, within 24 hours) after the time site personnel first learn about the

event through the Electronic Data Capture (EDC) system, or if unable to do so due to technical issues, by 1 of the back-up mechanisms provided (eg, fax). The following contact information is to be used for SAE reporting:

PPD, Inc, Pharmacovigilance

SAE NA Safety Hotline - [redacted]

SAE NA Fax line- [redacted]

SAE EMEA/APAC Safety Hotline - [redacted]

SAE EMEA/APAC Fax line- [redacted]

6.3.3.6 Suspected Unexpected Serious Adverse Reactions

The sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the sponsor will assess the expectedness of these events using the investigator's brochure.

The sponsor will compare the severity of each SUSAR and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

6.3.3.7 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	These events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate:	These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
Severe:	These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed.

6.3.3.8 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug and IVT injection procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated:	This relationship suggests that there is no association between the study drug or the IVT injection procedure and the reported event.
Related:	This relationship suggests that there is an association between the study drug or the IVT injection procedure and the reported event.

6.3.3.9 Follow-Up of Subjects Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the subject is considered to be stable.

6.3.4 Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed as indicated in Table 6-1. Collection of blood and urine will occur at the study site and the samples will be shipped to a central laboratory for analysis. All samples (including urine) should be collected prior to IVT

injection of the study drug; urine samples will be collected prior to FA assessment to avoid false elevations in urine protein values. Hematology, chemistry, and urinalysis samples will also be performed at any time during the visit at ET/EOS Visit. Procedures for collection and processing of blood and urine are provided in the laboratory manual.

Table 6-2 presents the laboratory analyses that will be performed during the study.

Table 6-2: Clinical Laboratory Evaluations

Clinical Chemistry	Hematology	Urinalysis	For Women
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Creatinine Creatine kinase Total and direct bilirubin	Basophils Eosinophils Hematocrit Hemoglobin Lymphocytes MCV Monocytes Neutrophils Platelet count RBC count RBC morphology WBC count	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Serum pregnancy test: At Screening Visit for women of child-bearing potential (serum β-hCG, follicle-stimulating hormone, luteinizing hormone) Urine pregnancy test: At baseline, ET, and EOS visits for women of child-bearing potential[a]

Abbreviations: EOS, end-of-study; ET, early termination; hCG, human chorionic gonadotropin; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

a. If urine pregnancy test is positive, serum pregnancy test should be performed; if found positive, study treatment will be discontinued.

6.3.5 Vital Signs

Vital signs consist of body temperature, respiratory rate, blood pressure (systolic and diastolic), and heart rate measurement.

On injection visits, vital signs will be measured prior to IVT injection of the study drug. Vital signs will also be performed at any time during the ET/EOS Visit. Vital signs should be taken with the subject in a seated position after resting for 5 minutes. Vital signs will be measured before venipuncture.

6.3.6 Electrocardiograms

An ECG could be done for safety and assessed by the investigator only at Screening, Week 8, and at the EOS/ET Visit.

6.4 Pharmacokinetic Assessments

Blood samples, for determination of concentrations of SCD411 and aflibercept, will be collected at the time points specified in the Schedule of Events (Table 6-1) and detailed sampling window is provided in Table 6-3. As per the Schedule of Events, additional visits will be arranged for collecting the PK blood samples. Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples drawn at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection (Week 8). Samples should be collected before performing FA, when performed on the same day. Plasma concentrations of SCD411 and aflibercept will be determined using validated analytical procedures. PK parameters assessed in the study include $AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, and $t_{1/2}$.

Additional details of PK analysis are available in the PK manual.

Table 6-3: Sampling Window

Study Day/Week	Time (Relative to Dosing)	Time in Hours (Visit Window)	PK	Immunogenicity
Day 1	0 (Predose)	0	X	X
	+1 day	24 (±1 hour)	X	
	+ 3 days	72 (±2 hours)	X	
	+7 days	168 (±6 hours)	X	
	+14 days	336 (±1 day)	X	
	+28 days (Week 4)[1]	672 (±2 days)	X	X
Week 8	0 (Predose)	0	X	X
	+1 day	24 (±1 hour)	X	
	+ 3 days	72 (±2 hours)	X	
	+7 days	168 (±6 hours)	X	
	+14 days	336 (±1 day)	X	
	+28 days	672 (±2 days)	X	
Week 20				X
Week 36				X
Week 52/End-of-Study				X

[1] This blood sample should be collected before Week 4 injection.

6.5 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected at Baseline (predose), at Weeks 4, 8, 20, 36, and 52 as indicated in the Schedule of Events (Table 6-1). Detailed sampling window is provided in Table 6-3. Samples should be collected before the IVT injection of the study drug and prior to FA assessment when performed on the same day. The samples will be evaluated for anti-SCD411 or anti-aflibercept antibodies.

Neutralizing antibodies (NAb) will also be evaluated only if ADA test positive.

6.6 Independent Data Monitoring Committee

An IDMC will be established for the study. The IDMC and associated parties (CRO Pharmacovigilance, Data management, sponsor as well as the CRO for IDMC management) will function under the terms of an IDMC Charter. The IDMC will comprise 3 voting members (including 1 independent [unmasked] biostatistician) and 2 clinicians with significant experience in wet AMD and who are not involved in the study. The duty of this IDMC is to protect the safety interests of subjects and all others who may possibly be exposed to the study drug and to make recommendations to the sponsor. The IDMC (without the sponsor or CRO personnel involved in the conduct of the study) will review efficacy and safety data in an unmasked manner.

The voting members of the IDMC will participate in a closed, unmasked session, following the blinded presentation of data to discuss recommendations. During these sessions, the IDMC members will be able to review unmasked safety data and efficacy data. Only the voting members, unblinded independent biostatistician, and the PPD Data Monitoring Coordinators will be present in the closed meetings.

Two IDMC meetings will be held: one safety meeting will be held approximately 6 months after the IDMC organizational meeting and the second safety meeting will be held after all subjects have completed the Week 8 Visit. After each meeting, the IDMC members will make a decision to continue the study without change, modify the study or enrollment to be placed on hold, or study termination. Any decision to terminate the study will be based on clinical judgment only and no formal stopping rules are defined. The sponsor is obligated to inform the study sites, IRB/IEC and Competent Authorities of the IDMC recommendations according to country-specific requirements.

6.7 Pregnancy

Pregnancy is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using the same procedures as an SAE (Section 6.3.3.5) eg, a clinical study pregnancy form. To ensure subject safety, each pregnancy must be reported to the sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the subject was discontinued from the study. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE. Pregnancy outcomes can be collected for the female partners of any male subjects who participated in this study, provided their verbal consent is obtained prior to collecting this information.

Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study, and considered by the investigator as possibly related to the study treatment, must be promptly reported to the sponsor.

No pregnancy test is required for women of non-child-bearing potential. Serum pregnancy test will be performed for women of child-bearing potential at the Screening Visit. At Baseline, ET, and EOS Visits, a urine pregnancy test will be performed and if found positive, then the serum pregnancy test should be performed. If serum pregnancy test results are positive, the study treatment should be discontinued, and the subjects should continue with regularly scheduled visits and assessments until Week 52 after discontinuation, unless the subjects withdraw consent, in which circumstance ET Visit procedures should be conducted; the subject or the female partner of any male subject should be followed for safety until the outcome of the pregnancy is known.

6.8 Sample Collections

Sample collection, processing, and shipping should be performed according to the local laboratory requirements. The amount of blood to be collected per subject during the study for PK, immunogenicity, and safety evaluations will be provided in the laboratory manual.

7 Statistical and Analytical Plan

The objectives and endpoints for this study are described in Section 2. This section focuses on key aspects for the analysis and reporting of efficacy and safety endpoints. Details for all endpoint analyses will be provided in the final statistical analysis plan (SAP), which will be finalized prior to the Week 8 and interim database lock.

Based on discussions with regulatory agencies which resulted in acceptance of different equivalence margins, different efficacy analyses will be performed for FDA submissions and other regulatory agencies versus submissions to EMA and PMDA. As the agencies will independently assesses efficacy based on their specific criteria, no adjustment for multiple comparisons will be required.

7.1 Estimands and Intercurrent Events

Week 8

Primary Estimand: The primary estimand is the mean treatment difference in BCVA change from baseline at Week 8. For the EMA, the primary analysis will be assessed for both the full analysis set (FAS) and per-protocol set (PPS). For the FDA, PMDA, and any other submissions, the primary analysis will be performed for the FAS. The primary estimand treats subjects in the analysis as if subjects do not receive rescue therapy.

Target Population: Subjects with wet AMD as defined in the enrollment criteria.

Endpoint: Change from baseline in BCVA at Week 8.

Treatment Condition(s): Dosing at Day 1, Week 4, and Week 8 with one of the following: SCD411 or aflibercept, both without rescue therapy.

Population-level Summary: The difference in mean change from baseline in BCVA at Week 8 between SCD411 and aflibercept and the corresponding confidence interval (CI) for the mean difference.

Intercurrent Events and Strategies to Address Intercurrent Events

- Discontinuation of study eye study treatment with continued participation in study without receipt of rescue therapy

  - Treatment Policy – no imputation; use observed data

- Receipt of rescue therapy in the study eye
  - Hypothetical approach – data after receipt of rescue will be set to missing and post rescue data will be imputed employing multiple imputation (MI) assuming missing at random (MAR) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology.

- Discontinuation from study, regardless of reason
  - Hypothetical approach – missing data after discontinuation will be imputed via MI assuming MAR using randomized treatment-based MCMC methodology.

Rationale for Strategy: As the primary objective of this study is to show biosimilar equivalence between SCD411 and aflibercept, the primary estimand is constructed to estimate the treatment effect under the assumption that all subjects take study treatments without the use of rescue therapy while allowing for subjects to discontinue study treatment. Multiple imputation under MAR assumptions results in treatment estimates as if subjects continued as on their original treatment. Treating discontinuation as MAR and setting the post rescue assessment to missing prior to performing MI was chosen to avoid inflation of the SCD411 treatment effect. Subjects who receive rescue therapy or discontinue will have shown lack of efficacy in assessments, so the MAR approach should be conservative if the test treatment is not equivalent to or less efficacious than the reference product.

Secondary Estimand: A secondary estimand for the primary efficacy endpoint is the mean treatment difference in BCVA change from baseline at Week 8 while allowing for receipt of rescue therapy. The estimand will be constructed as above, but the intercurrent event of rescue therapy use will be handled using the treatment policy approach. Data post rescue will not be set to missing. This estimand is constructed to estimate the treatment effect including the impact of rescue therapy, which may better reflect actual real-world outcomes, where rescue would likely be given when lack of efficacy is seen.

Week 52

Primary Estimand: The primary estimand is the mean treatment difference in BCVA change from baseline at Week 52. For the EMA, the primary analysis will be assessed for both the FAS and PPS. For the FDA, PMDA, and any other submissions, the primary analysis will be

performed for the FAS. The primary estimand treats subjects in the analysis as if subjects do not receive rescue therapy.

Target Population: Subjects with wet AMD as defined in the enrollment criteria.

Endpoint: Change from baseline in BCVA at Week 52

Treatment Condition(s): Dosing at Day 1, Week 4, Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 with one of the following: SCD411 or aflibercept, both without rescue therapy.

Population-level Summary: The difference in mean change from baseline in BCVA at Week 52 between SCD411 and aflibercept and the corresponding CI for the mean difference.

Intercurrent Events and Strategies to Address Intercurrent Events

- Discontinuation of study eye study treatment with continued participation in study without receipt of rescue therapy
  - Treatment Policy – no imputation; use observed data
- Receipt of rescue therapy in the study eye
  - Hypothetical approach – Data after receipt of rescue will be set to missing and post rescue data will be imputed employing MI assuming MAR using randomized treatment-based MCMC methodology.
- Discontinuation from study, regardless of reason
  - Hypothetical approach – Missing data after discontinuation will be imputed via MI assuming MAR using randomized treatment-based MCMC methodology.

Rationale for Strategy: As the primary objective of this study is to show biosimilar equivalence between SCD411 and aflibercept, the primary estimand is constructed to estimate the treatment effect under assumption that all subjects take study treatments without the use of rescue therapy while allowing for subjects to discontinue study treatment. Multiple imputation under MAR assumptions results in treatment estimates as if subjects continued on their original treatment. Treating discontinuation as MAR and setting the post rescue assessment to missing prior to performing MI was chosen to avoid inflation of the SCD411 treatment effect. Subjects who receive rescue therapy or discontinue will have shown lack of

efficacy in assessments, so the MAR approach should be conservative if the test treatment is not equivalent to or less efficacious than the reference product.

Secondary Estimand: A secondary estimand for the secondary efficacy endpoint is the mean treatment difference in BCVA change from baseline at Week 52 while allowing for receipt of rescue therapy. The estimand will be constructed as above, but the intercurrent event of rescue therapy use will be handled using the treatment policy approach. Data post rescue will not be set to missing. This estimand is constructed to estimate the treatment effect including the impact of rescue therapy, which may better reflect actual real-world outcomes, where rescue would likely be given when lack of efficacy is seen.

7.2 Sample Size Determination

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 to the placebo treatment in subjects with wet AMD. It was shown that in MARINA, subjects on average 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 dose, 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 to the placebo would be estimated as approximately 9.3 to 10 letters. A margin of 3.8 letters would be translated to a preservation of 59% to 62% of the difference between Eylea and sham and is 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.

Given that the statistical justification of the 3.8 letter equivalence margin is not included in the current version of the protocol, this will be added in the SAP and provided to the regulatory agencies upon request.

The FDA requested a tighter equivalence margin of 3 letters but agreed equivalence can be determined from a 90% CI approach (equivalent to TOST at the α=0.05 level).

Standard deviation (SD) for the mean change from baseline at early visits (Weeks 4 to 12) based on observed data for the FAS ranged from and 8.73 to 11.99 considering all treatment groups from VIEW1 and from 7.4 to 11.0 letters for the VIEW2 study (DHHS 2011 [Eylea

Statistical Review, Appendix Tables A.1 and A.2]). For power calculations, a range of SD between 10.4 and 11.8 was assumed to be conservative and cover the majority of larger SD values seen in the observed data.

A sample size of 266 subjects per treatment arm was selected as it provides at least 80% power for the FDA, EMA, and PMDA analyses for the range of SD considered when using TOST on data from a parallel-group design. For the FDA analysis based on equivalence limits of -3.0 and 3.0 letters, α=0.05 significance level (90% CI), assuming the true difference between the means is 0.0, power of 91% is achieved for SD of 10.4 letters and power of 80% is achieved for SD of 11.8 letters. For the EMA and PMDA analyses based on equivalence limits of -3.8 and 3.8 letters, α=0.025 significance level (95% CI), assuming the true difference between the means is 0.0, power of 98% is achieved for SD of 10.4 letters and power of 92% is achieved for SD of 11.8 letters when sample size is 266 per treatment arm. Considering approximately 5% loss from randomization through Week 8, the total sample size required is 560.

A subset of 40 subjects (20 per group) will be selected for collection of PK samples. The sample size is not test-driven since no equivalence test will be performed for PK parameters.

7.3 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Full Analysis Set (FAS): All randomized subjects who received at least 1 injection of the study drug.

Modified FAS (mFAS): 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.

Per-protocol Set (PPS): All subjects in the FAS, excluding those with significant protocol violations.

Safety Set (SAF): All subjects receiving at least 1 injection of the study drug.

Pharmacokinetic Analysis Set (PK Set): The subset of subjects in FAS who have sufficient evaluable blood samples to be included in the PK Set.

The primary set for efficacy analysis will be the FAS; however, for the EMA submission, the primary efficacy endpoint must meet equivalence for both the FAS and PPS. PMDA also requires an efficacy analysis to be conducted based on the mFAS without MI as a supportive analysis. The SAF will be the primary analysis set for safety, tolerability, and immunogenicity analyses.

7.4 Description of Subgroups to be Analyzed

Subgroup analyses will be performed by region/country and important demographic/baseline characteristics; however, the study is not powered for treatment comparisons within subgroups. Details of subgroups analyses will be provided in the SAP.

7.5 Statistical Analysis Methodology

The data will be analyzed by the sponsor and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed with SAS® software, version 9.4 or higher.

Descriptive statistics for continuous variables in summary tables will include the number of subjects in the analysis (n), mean, SD, median, and range (minimum, maximum). Descriptive statistics for categorical variables in summary tables will include counts and percentages. Graphical summaries of the data may be presented.

The most recent nonmissing measurement collected prior to the first administration of study drug will be used as the baseline value.

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

Unless otherwise specified, the missing data will not be imputed.

7.5.1 Efficacy Analyses

Efficacy analyses will be based on the study eye only.

7.5.1.1 Primary Efficacy Outcome Measures

The pre-postchange in BCVA as measured by ETDRS letter score or 2702 charts provides direct information regarding the primary clinical effect of a product intended to preserve or improve VA. This endpoint was used as a primary endpoint in most of the clinical studies performed for Eylea: GALILEO, COPERNICUS, VISTA, VIVID, and MYRROR and was also assessed as a secondary endpoint in the clinical studies VIEW 1 and VIEW 2. The increase in BCVA under treatment with aflibercept generally reaches a plateau within the first 24 weeks of treatment in all therapeutic indications studied. Evaluating the effect after 8 weeks of treatment allows a comparison at a time when a substantial proportion of the maximum effect is achieved but before the plateau of the effect is reached. This makes a comparison between 2 similar products after 8 weeks of treatment more sensitive as compared to an endpoint after 52 weeks of treatment.

The primary analysis of the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 8 weeks of treatment will be performed via MMRM including data for the Week 4 and Week 8 visits. The model will include the change from baseline as the dependent variable; treatment, visit, and visit-by-treatment as fixed effects, and baseline BCVA as a covariate. An unstructured covariance matrix will be used. In the event of convergence issues, compound-symmetry will be used instead. Rubin's rules will be used to combine the estimates from the MMRM analyses and the estimated mean treatment difference at Week 8 along with the corresponding 90% and 95% CIs will be presented. Equivalence will be determined if the upper and lower CI limits for the difference between treatments are within the equivalence margins. Raw values and changes from baseline at Week 4 and Week 8 will be summarized by treatment group using descriptive statistics based on observed data.

The primary null hypothesis (H0) and alternative hypothesis (H1) are:

H0: $\Delta \geq M$ or $\Delta \leq -M$

H1: $-M < \Delta < M$

where Δ indicates the mean difference between the 2 treatment groups in the change from baseline in ETDRS letter score or 2702 charts at Week 8 and M represents the equivalence margin.

Based on discussions with regulatory agencies, separate equivalence CIs and equivalence margins will be used for FDA submissions and other regulatory agencies versus submissions to EMA and PMDA. Submissions to other regulatory agencies will be assumed to follow FDA guidance.

For the FDA submission and other countries submission, a 90% CI (equivalent to TOST evaluated at an α of 0.05) will be assessed using an equivalence margin of 3 letters. If the upper bound of the 90% CI is less than 3 and the lower bound is greater than -3, then study success will be claimed. For the EMA and PMDA, a 95% CI (equivalent to TOST evaluated at an α of 0.025) will be assessed using an equivalence margin of 3.8 letters. If the upper bound of the 95% CI is less than 3.8 and the lower bound is greater than -3.8, then study success will be claimed.

The least squares mean estimate of treatment difference and corresponding 90% (FDA and other countries) and 95% (EMA/PMDA) CIs will be provided. The primary analysis set for the FDA, PMDA, and any other submissions will be the FAS. For the EMA submission, both the FAS and PPS are considered primary analysis and equivalence will need to be shown for both analysis sets.

As a sensitivity analysis, an analysis of covariance (ANCOVA) model comparing the change from baseline in BCVA at Week 8 and including the baseline BCVA value as a covariate will be performed using multiple imputed data.

Additional sensitivity analyses to the primary analysis will be performed using single imputation approaches for post study discontinuation/rescue therapy BCVA scores using the LOCF and BOCF prior to MMRM analysis (intermittent missing data will be considered MAR and not imputed) for both the FAS and PPS. In addition, an ANCOVA model comparing the change from baseline in BCVA at Week 8 and including the baseline BCVA value as a covariate will be performed by imputing the post study discontinuation/rescue therapy BCVA values using LOCF and BOCF approaches for the FAS and PPS.

Additionally, the MMRM analysis will be performed using data from MI including a tipping point approach. Observations after receipt of rescue therapy will be set to missing prior to the MI. Multiple imputation assuming MAR will be applied to all missing data. After conclusion of MI, post study discontinuation/rescue therapy observations for the SCD411 arm will have fixed value C added to the imputed values. The imputed data, including the fixed penalty,

will be analyzed by the same MMRM model as for the primary analysis. A range of values for C will be considered to identify the point at which equivalence can no longer be claimed. Details will be provided in SAP.

Supportive analysis for the primary endpoint will be performed based on the mFAS per the PMDA's request. Data after receipt of rescue therapy will be set to missing without employing MI. Both the MMRM and ANCOVA analyses will be performed using the non-imputed data.

7.5.1.2 Secondary Efficacy Outcome Measures

The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented for the FAS and PPS.

The estimated mean treatment difference at Week 52 along with the corresponding 90% and 95% CIs will also be presented using the same MMRM and ANCOVA models as used in the Week 8 analysis. As done for Week 8, analysis will be performed using MI data, where post rescue assessments have been set to missing while including the post rescue assessments in the imputation model. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics for each visit.

Sensitivity analyses will be performed using LOCF and BOCF for post study discontinuation assessments or after receipt of rescue therapy prior to performing the MMRM and ANCOVA analysis (intermittent missing data will be considered MAR and not imputed). Additionally, the MMRM analysis will be performed using data from MI including a tipping point approach.

The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV are will be based on the MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI for the estimates of treatment differences at Week 8 and Week 52 presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Data after receipt of rescue therapy will be set to missing prior to the MMRM analysis. Multiple imputation will not be performed, and no sensitivity analyses will be performed.

The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score or 2702 charts at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented. For subjects who have missing assessments at corresponding postbaseline visits or who received rescue therapy prior to a visit will be assumed to have a gain of <15 letters in BCVA (eg, nonresponder imputation). No sensitivity analyses will be performed.

7.5.2 Pharmacokinetic Analyses

The PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, $t_{1/2}$,) from the 2 treatment groups will be summarized using n, arithmetic mean, percent coefficient of variation (% CV), geometric mean, geometric %CV, SD, median, minimum and maximum values in the PK analysis set.

7.5.3 Immunogenicity Analyses

The analysis on immunogenicity will be descriptive. Results will be summarized with observed values and change from baseline for ADA titers (in log scale) by treatment group in the SAF. The number and proportion of ADA-positive subjects and ADA-negative subjects will be summarized by treatment group for each assessment time point. NAb will be tested when ADA results are confirmed to be positive. The number and proportion of NAb subjects will be summarized by treatment group for each assessment time point.

7.5.4 Safety Analyses

Safety variables include incidence of AEs (or TEAEs), laboratory test results, ECG results, and vital signs. All safety analyses will be based on the SAF. No formal statistical analysis of the safety data will be performed.

Adverse events will be coded according to the MedDRA in the study. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA system organ class and preferred term. AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that are reported or worsened after signing the ICF up to the first dose date of study drug.

Treatment-emergent AEs are defined as AEs that are reported or worsened on or after the first dose date of study drug through 28 days after the last dose date of study drug.

Only TEAEs will be summarized in tables. The AE summary tables will include counts of subjects. Therefore, if a subject experiences more than 1 episode of a particular AE, the subject will be counted only once for that event. If a subject has more than 1 AE that is coded to the same preferred term, the subject will be counted only once for that preferred term. Only the maximum severity level will be presented in the severity summary, and only the worst relationship level will be presented in the relationship summary. Adverse events leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the EOS, including pretreatment AEs, will be listed in a data listing. Ocular AEs will be summarized separately for the study and fellow eyes.

Laboratory test variables will be summarized by treatment group and visit using descriptive statistics (number of subjects, mean, SD, minimum, maximum, and mean change from baseline). Shift tables (low, normal, high) between baseline and postbaseline time points will be presented by laboratory test and treatment group. Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized but will be listed.

The results of slit lamp examination, dilated fundoscopy, IOP, and vision check will be summarized using descriptive statistics at each visit and applicable time point, as applicable. Separate summaries will be presented.

Descriptive statistics of vital signs and change from baseline at each visit will be presented by treatment group.

Descriptive statistics of ECG parameters and change from baseline at each visit will be presented by treatment group.

7.5.5 Other Analyses

7.5.5.1 Background Characteristics

7.5.5.1.1 Subject Disposition

The number and percentage of subjects who are included in each analysis set and who complete and discontinue the study will be summarized by treatment group and overall.

7.5.5.1.2 Demographics and Baseline Characteristics

Demographic information: age, sex, ethnicity, height, weight, body mass index, and other baseline measures such as ETDRS letter score or 2702 chart, CRT and CNV, will be summarized by treatment group and overall, using descriptive statistics. Ocular measures will be summarized for the study eye only.

7.5.5.1.3 Prior and Concomitant Medications

Medications taken from the informed consent date up to 28 days after the EOT will be coded using the latest version of WHODRUG Enhanced during the study, and tabulated by treatment group and overall in the SAF, using counts and percentages, separately for:

- Prior medication: medication that starts before the first dose of study drug, regardless of when the medication stops.
- Concomitant medication: medication first received at or after the first dose of study drug, medication received before first dose of study drug and continued after first dose, or medication with missing stop date.

Medication that starts before the first dose of study drug and continued after the first dose will be classified as both prior and concomitant medication. Medications with a missing start date will be considered to have a start date before the first dose of study drug. Ocular medications will be summarized separately for the study eye and fellow eye.

7.5.5.1.4 Medical History

Systemic and ocular medical history data will be listed by subject.

7.5.5.1.5 Study Drug Exposure and Compliance

Exposure to study drug and dosing compliance will be summarized for the SAF using summary statistics.

The compliance will be summarized by treatment group for the SAF and is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions.

7.5.6 Interim Analyses

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

An interim analysis of safety, secondary efficacy endpoints, and PK parameters will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study.

The Week 8 analysis and interim analysis will be performed by an independent biostatistics group and results will be 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 may coincide depending on subject enrollment and data cleaning/programming activities.

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

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain accurate eCRFs and source documentation as adequate case histories for the subjects treated as part of the research under this protocol. These source documents may include laboratory reports, ECG strips, etc.

Investigative site personnel will enter subject data into an EDC system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA, an internal validated medical dictionary, and concomitant medications will be coded using WHODRUG.

After database lock, each study site will receive a CDROM containing all of their site specific eCRF data.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance with regulatory authority regulations (eg, US Title 21 Code of Federal Regulations [CFR] Part 50) shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before the investigator submits it to the IRB/IEC for review and approval prior to the start of

the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring, inspection by regulatory agencies, and auditing by the sponsor, its designee, the FDA, other countries regulatory agencies, or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing all essential documents.

10.4 Study Conduct

The investigator agrees to conduct the study as outlined in this protocol in accordance with the principles of ICH E6(R2) and all applicable national, state, and local laws, guidelines, or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adverse Events and Study Report Requirements

By participating in this study the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.6 Records Retention

Essential documents should be retained until at least 3 years after the last approval of a marketing application in an ICH region or after the completion or formal discontinuation of clinical development of the IP, whichever is the longer period. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.7 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

An IDMC will be established for the study. Two IDMC meetings will be held: one safety meeting will be held approximately 6 months after the IDMC organizational meeting and the second safety meeting will be held after all subjects have completed the Week 8 Visit. After each meeting, the IDMC will make a recommendation to the sponsor regarding the study to continue without change, modify the study or enrollment to be placed on hold, or study termination. The sponsor is obligated to inform the study sites, IRB/IEC, and regulatory agency of the IDMC recommendations according to country-specific requirements (Section 6.6).

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit or inspection, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency (eg, FDA) access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits or inspections scheduled by any regulatory authorities and promptly forward copies of any audit or inspection reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Protocol Amendments

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.3). Significant protocol deviations may include below but not limited to the following deviations:

- ICH/GCP deviation
- Deviation from inclusion/exclusion criteria
- Deviation on study treatment randomization

The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit.

11.4 Final Report

Upon completion of the interim and final analyses of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary report of the study's outcome and the sponsor and regulatory authorities with any reports required.

The sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agencies as required by the applicable regulatory requirements. The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study reports.

Upon completion of the clinical study reports, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

12 Reference List

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13 Appendices

13.1 Appendix 1: Slit Lamp Examination - Grading Scale

Grading Scheme for Anterior Chamber Flare

Grade	Description
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Source: Jabs DA, Nussenblatt RB, Rosenbaum JT, et al., Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop, Am J Ophthalmol, 2005;140:509–16.

Grading Scheme for Anterior Chamber Cells

Grade	Number of Cells
0	<1
0.5+	1-5
1+	6–15
2+	16–25
3+	26–50
4+	>50

Source: Jabs DA, Nussenblatt RB, Rosenbaum JT, et al., Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop, Am J Ophthalmol, 2005;140:509–16.

13.2 Appendix 2: Assessment of Vitreous Cells - Grading Scale

Grade	Description
0	Clear
Trace	Few opacities
1	Scattered opacities
2	Moderate opacities
3	Many opacities
4	Dense opacities

Source: Nussenblatt RB, Whitcup SM, Palestine AG. Uveitis: fundamentals and clinical practice. 2nd rev. ed. New York:Mosby, 1996, p. 64.

Grading Scheme for Vitreous Haze

Grade	Description	Cells in Retro-Illuminated Field
0	Nil	None
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details slightly hazy
3	Moderate	Posterior pole details very hazy
4	Marked	Posterior pole details barely visible
5	Severe	Fundal details not visible

Source: Nussenblatt RB, Palestine AG, Chan CC, et al., Standardization of vitreal inflammatory activity in intermediate and posterior uveitis, Ophthalmology, 1985;92:467–71.

14 Protocol Amendment

14.1 Protocol Amendment, Version 3.0, 24 January 2022

This global protocol amendment is considered substantial for the following reasons because they represent significant changes to the study conduct:

1. An interim analysis is planned to be performed once approximately 200 subjects complete the Week 52 Visit and once all planned (approximately 560) treated subjects complete Week 24 Visit or discontinue early from the study. The purpose of the interim analysis is to support regulatory filing to the PMDA.
2. Text regarding the IDMC analyses has been updated to reflect that the IDMC will meet throughout the study and not only when all subjects complete the Week 8 Visit.

The amendment also incorporates the changes that were explained in protocol clarification letters dated 18 December 2020 and 29 April 2021, and the details to include the causality assessment of AEs for an IVT injection procedure.

Additions to the protocol text are shown in bold and deletions are shown in strikethrough text. Minor editorial and administrative changes and grammatical corrections are not specified.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
Synopsis (Exclusion Criteria); 4.1.2 Exclusion Criteria	29. History or evidence of cardiac conditions including congestive cardiac failure leading to marked limitation on physical activity, or inability to perform any physical activity without discomfort, ventricular arrhythmia requiring ongoing treatment, and atrial fibrillation	29. History or evidence of cardiac conditions ~~including~~ **with** congestive cardiac failure ~~leading to~~ **resulting in** marked limitation on physical activity~~,~~ or inability to perform any physical activity without discomfort~~,~~**; subjects with** ventricular arrhythmia requiring ongoing treatment~~, and~~**; or subjects with** atrial fibrillation	To clarify the exclusion criterion for subjects with a history or evidence of cardiac conditions.
Synopsis (Study Design)	This is a Phase III, randomized, parallel-group, double-masked, multicenter	This is a Phase III, randomized, **double-masked,** parallel-group, ~~double-masked,~~ multicenter study ~~in~~ **to demonstrate biosimilarity of SCD411**	To be consistent with Section 3.1.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	study in adult subjects with neovascular (wet) AMD	**compared to Eylea (aflibercept) among** adult subjects with neovascular (wet) AMD	
Synopsis (Immunogenicity Assessments); 2.4.2 Secondary Endpoints	Immunogenicity assessments and endpoints include the evaluation of development of anti-SCD411 antibodies using blood samples taken at Baseline, at Weeks 4, 8, 20, 36, and 52.	Immunogenicity assessments and endpoints include the evaluation of development of anti-SCD411 **or anti-aflibercept** antibodies using blood samples taken at Baseline, at Weeks 4, 8, 20, 36, and 52.	To be consistent with Section 6.5.
Synopsis (Rescue Treatment)	Subjects who will receive rescue treatment need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with their regularly scheduled visits.	Subjects who will receive rescue treatment need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with their regularly scheduled visits **and assessments until Week 52 except for study treatment administration**.	To be consistent with other protocol sections.
Synopsis (Sample Size)	Considering approximately 5% loss from Day 1 through Week 8, the total sample size required is 560.	Considering approximately 5% loss from ~~Day 1~~**randomization** through Week 8, the total sample size required is 560.	To be consistent with Section 7.2.
Synopsis (Analysis Sets); 7.3 Analysis Sets	-	**Modified FAS (mFAS): 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.**	To be in line with the SAP.
	The primary set for efficacy analysis will be the FAS; however, for the EMA submission, the primary efficacy endpoint must meet equivalence for both the FAS and PPS sets.	The primary set for efficacy analysis will be the FAS; however, for the EMA submission, the primary efficacy endpoint must meet equivalence for both the FAS and PPS ~~sets~~. **PMDA also requires an efficacy analysis to be conducted based on the mFAS without multiple imputation (MI) as a supportive analysis.**	

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
Synopsis (Statistical Methods); 7.5.1.1 Primary Efficacy Outcome Measures	The model will include the change from baseline as the dependent variable; treatment and visit as fixed effects, and baseline BCVA as a covariate.	The model will include the change from baseline as the dependent variable; treatment**, visit,** and visit**-by-treatment** as fixed effects, and baseline BCVA as a covariate.	To be in line with the SAP.
Synopsis (Statistical Methods)	**Secondary Analyses:** The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis will be presented for the FAS and PPS. As per the Week 8 analyses, the primary analysis will be performed using multiple imputed data under the MAR assumptions with post rescue assessments set to missing prior to imputation. The estimated mean treatment difference at each visit along with the corresponding 90% and 95% CIs will also be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV will be based on a MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI for the estimates of treatment	**Secondary Analyses:** The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis **but including data from all weeks through Week 52** will **also** be presented for the FAS and PPS. As ~~per the~~ **done for** Week 8 ~~analyses, the primary~~**,** analysis will be performed using multiple imputed data ~~under the MAR assumptions with~~**, where** post rescue assessments **have been** set to missing ~~prior to~~ **while including the post rescue assessments in the** imputation~~. The estimated mean treatment difference at each visit along with the corresponding 90% and 95% CIs will also be presented~~ **model**. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics **for each visit**. The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV will be based on ~~a~~ **the** MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI	To be consistent with Section 7.5.1.2.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	differences at Week 8 and Week 52 will be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Multiple imputation will not be performed. Data after the receipt of rescue therapy will be set to missing prior to analysis. The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score or 2702 charts at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented. For subjects who have missing assessments at corresponding postbaseline visits or received rescue therapy prior to visit, will be assumed to have a gain <15 letters in BCVA (eg, nonresponder imputation).	for the estimates of treatment differences at Week 8 and Week 52 ~~will be~~ presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. ~~Multiple imputation will not be performed.~~ Data after the receipt of rescue therapy will be set to missing prior to **the MMRM** analysis**. Multiple imputation will not be performed and no sensitivity analyses will be performed**. The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score or 2702 charts at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented. For subjects who have missing assessments at corresponding postbaseline visits or **who** received rescue therapy prior to **a** visit~~,~~ will be assumed to have a gain **of** <15 letters in BCVA (eg, nonresponder imputation). **No sensitivity analyses will be performed.**	
Synopsis (Statistical Methods)	Immunogenicity Analysis The analysis on immunogenicity will be descriptive. Results will be summarized with observed values and change from baseline for titers (in log scale) ADA for the SAF. The number and proportion of ADA-positive subjects and ADA-negative subjects will be summarized for each assessment time point. NAb will be tested when ADA	Immunogenicity Analysis The analysis on immunogenicity will be descriptive. Results will be summarized with observed values and change from baseline for **ADA** titers (in log scale) ~~ADA for~~ **by treatment group in** the SAF. The number and proportion of ADA-positive subjects and ADA-negative subjects will be summarized **by treatment group** for each assessment time point. NAb will be tested when ADA results are	To be consistent with text elsewhere in the protocol.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	results are confirmed to be positive. The number and proportion of NAb subjects will be summarized by treatment group for each assessment time point.	confirmed to be positive. The number and proportion of NAb subjects will be summarized by treatment group for each assessment time point.	
Synopsis (Statistical Methods)	-	**Interim Analyses** **An interim analysis of safety, secondary efficacy endpoints, and PK parameters will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study.** **The Week 8 analysis and interim analysis will be performed by an independent biostatistics group and results will be 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 may coincide depending on subject enrollment and data cleaning/programming activities.**	To add an interim analysis to support regulatory filing to the PMDA.
1.1 Background	• A higher affinity (~ 0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody (Papadopoulos et al 2012; García-Quintanilla et al 2019)	• A higher affinity (~0.5 pM dissociation constant for VEGF165 and ~**0.36 pM for** VEGF121) than a humanized monoclonal antibody (Papadopoulos et al 2012; García-Quintanilla et al 2019)	To be consistent with the investigator brochure, version 3.0.
3.1 Study Design	This is a Phase III, randomized, double-masked, parallel-group, multicenter study to demonstrate biosimilarity of SCD411	This is a Phase III, randomized, double-masked, parallel-group, multicenter study to demonstrate biosimilarity of SCD411 compared to Eylea (aflibercept)	To be consistent with synopsis.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	compared to Eylea (aflibercept) among adult subjects with wet AMD.	among adult subjects with **neovascular (**wet**)** AMD.	
	The study design incorporates an Independent Data Monitoring Committee (IDMC) that will review ongoing safety and will also make recommendations to the sponsor as described in the IDMC Charter. Details of the IDMC are given in Section 6.6.	The study design incorporates an Independent Data Monitoring Committee (IDMC) that will review ongoing safety and will also make recommendations to the sponsor as described in the IDMC Charter. Details of the IDMC are given in Section 6.6. **An interim analysis will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study. Details of the interim analysis are given in Section 7.5.6.**	To add an interim analysis to support regulatory filing to the PMDA.
5.1 Method of Assigning Subjects to Treatment Groups	• During the 4-week intervals dosing: assessment and dosing can be done within a window of ±2 days. In this case, the interval between the 2 doses should not be less than 24 days and more than 32 days. If the subject visit window is out of the allowed window interval, dosing should be skipped.	• During the 4-week intervals dosing: assessment and dosing can be done within a window of ±2 days. In this case, the interval between the 2 doses should not be less than 24 days and more than 32 days. If the subject **IP dosing** ~~visit~~ window is out of the allowed window interval, dosing should be skipped.	To clarify the text in alignment with the specification of IP dosing.
5.8.1 Rescue Treatment	If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.	If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn **from the study**, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.	To clarify the text throughout.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
5.8.2 Prohibited Medications	Concurrent use of systemic or IVT anti-VEGF agents; IVT, subtenon, or peribulbar corticosteroids in study eye, except as required to treat AEs.	Concurrent use of systemic or IVT anti-VEGF agents; IVT, subtenon, or peribulbar corticosteroids in study eye **are not permitted**, except as required to treat AEs.	To clarify the text.
Table 5-1: Prohibited Medications	Topiramate (duration of prohibition): 4 weeks prior to screening and throughout the study period Amiodarone (duration of prohibition): 12 weeks prior to screening and throughout the study period	Topiramate (duration of prohibition): 4 weeks prior to ~~screening~~ **randomization** and throughout the study period Amiodarone (duration of prohibition): 12 weeks prior to ~~screening~~ **randomization** and throughout the study period	To be consistent with exclusion criterion 34.
Table 6-1: Schedule of Events	Study Day: 199	Study Day: ~~199~~**197**	Per calculation, a correction was made for the study day of the Week 28 Visit.
	[1] At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS, FA and FP will be performed on the study eye prior to IVT injection of the study drug.	[1] At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS, FA and FP will be performed on the study eye **(**prior to IVT injection of the study drug **at Week 8).**	To clarify the time point.
6.1.3 Early Termination/End-of-Study	End-of-Study Visit assessments will be conducted 28 days after the end of treatment for Week 52.	End of Study Visit assessments will be conducted 28 days after the **EOT at** ~~end of treatment for~~ Week 52.	To clarify the text throughout.
6.2.2.2 Fluorescein Angiography and Fundus Photography	At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS Visit, FA and FP will be performed on the study eye prior to IVT injection of the study drug and those images will be sent to the central reading center.	At screening, FA and FP will be performed on both eyes and those images will be sent to the central reading center. At Week 8 and ET/EOS Visit, FA and FP will be performed on the study eye **(**prior to IVT injection of the study drug **at Week 8)** and those images will be sent to the central reading center.	To clarify the time point.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
6.3.3.1 Definitions of Adverse Events	The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.	The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug **or to IVT injection procedure** or their clinical significance.	To include an assessment of AEs for IVT injection procedure.
	An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug.	An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug **or to IVT injection procedure**.	
6.3.3.4 Reporting Adverse Events	• investigator-specified assessment of severity and relationship to study drug	• investigator-specified assessment of severity and relationship to study drug **and to IVT injection procedure**	To include an assessment of AEs for IVT injection procedure.
6.3.3.8 Assessment of Causality	The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study.	The investigator's assessment of an AE's relationship to study drug **and IVT injection procedure** is part of the documentation process, but it is not a factor in determining what is or is not reported in the study.	To include an assessment of AEs for IVT injection procedure.
	Unrelated: This relationship suggests that there is no association between the study drug and the reported event. Related: This relationship suggests that there is an association between the study drug and the reported event.	Unrelated: This relationship suggests that there is no association between the study drug **or the IVT injection procedure** and the reported event. Related: This relationship suggests that there is an association between the study drug **or the IVT injection procedure** and the reported event.	
6.3.5 Vital Signs	On injection visits, vital signs will be measured prior to IVT injection of the study drug.	On injection visits, vital signs will be measured prior to IVT injection of the study drug. **Vital signs will also be performed at any time during the ET/EOS Visit.**	To be consistent with footnote n of the Table 6-1.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
6.4 Pharmacokinetic Assessments	Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples drawn at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection.	Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples drawn at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection **(Week 8)**.	To be consistent with footnote p of the Table 6-1.
6.6 Independent Data Monitoring Committee	An IDMC meeting will be held after all subjects have completed Week 8 Visit. From this meeting, the IDMC members will make a decision to continue the study without change, modify study, or study termination. Any decision to terminate the study will be based on clinical judgment only and no formal stopping rules are defined. The sponsor is obligated to inform the study sites, IRB/IEC and Competent Authorities of the IDMC recommendations according to country specific requirements.	~~An~~ **Two** IDMC ~~meeting~~ **meetings** will be held**: one safety meeting will be held approximately 6 months after the IDMC organizational meeting and the second safety** meeting will be held after all subjects have completed **the** Week 8 Visit. ~~From this meeting~~ **After each meeting**, the IDMC members will make a decision to continue the study without change, modify **the** study **or enrollment to be placed on hold**, or study termination. Any decision to terminate the study will be based on clinical judgment only and no formal stopping rules are defined. The sponsor is obligated to inform the study sites, IRB/IEC and Competent Authorities of the IDMC recommendations according to country-specific requirements.	To reflect the addition of an interim analysis.
7 Statistical and Analytical Plan	Details for all endpoint analyses will be provided in the final statistical analysis plan (SAP), which will be finalized prior to the database lock.	Details for all endpoint analyses will be provided in the final statistical analysis plan (SAP), which will be finalized prior to the **Week 8 and interim** database lock.	To add an interim analysis to support regulatory filing to the PMDA.
7.2 Sample Size Determination	Standard deviation (SD) for the mean change from baseline at early visits (Weeks 4 to 12) based on observed data for the FAS	Standard deviation (SD) for the mean change from baseline at early visits (Weeks 4 to 12) based on observed data for the FAS ranged from and 8.73 to	To insert the correct reference.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	ranged from and 8.73 to 11.99 considering all treatment groups from VIEW1 and from 7.4 to 11.0 letters for the VIEW2 study (Eylea Statistical Review, Appendix Tables A.1 and A.2).	11.99 considering all treatment groups from VIEW1 and from 7.4 to 11.0 letters for the VIEW2 study (**DHHS 2011 [**Eylea Statistical Review, Appendix Tables A.1 and A.2**]**).	
7.5.1.1 Primary Efficacy Outcome Measures	-	**Supportive analysis for the primary endpoint will be performed based on the mFAS per the PMDA's request. Data after receipt of rescue therapy will be set to missing without employing MI. Both the MMRM and ANCOVA analyses will be performed using the non-imputed data.**	To be in line with the SAP.
7.5.1.2 Secondary Efficacy Outcome Measures	The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented.	The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score **or 2702 charts** through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented **for the FAS and PPS**.	To be consistent with the text in the synopsis.
	The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented.	The percentage of subjects who gain ≥15 letters in BCVA as measured by ETDRS letter score **or 2702 charts** at postbaseline visits (Week 8 and Week 52) compared with baseline will be summarized and 95% CI for the proportions in each treatment arm and difference in proportions between treatment arms will be presented.	
7.5.6 Interim Analyses	No interim analyses are planned for this study. The primary analysis of efficacy and all other efficacy and	~~No interim analyses are planned for this study.~~ The primary analysis of efficacy and all other efficacy and safety analyses will	To add an interim analysis to support regulatory filing to the PMDA.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
	safety analyses will be conducted at the Week 8 database lock; ie, after all subjects have completed the Week 8 Visit or have been discontinued from the study prior to this visit. Distribution of the Week 8 analysis will be restricted only to the IDMC members in order to minimize bias through the end of the study.	be conducted at the Week 8 database lock; ie, after all subjects have completed the Week 8 Visit or have been discontinued from the study prior to this visit. Distribution of the Week 8 analysis will be restricted only to the IDMC members in order to minimize bias through the end of the study. **An interim analysis of safety, secondary efficacy endpoints, and PK parameters will be performed once approximately 200 subjects complete the Week 52 Visit and all subjects complete the Week 24 Visit or discontinue early from the study.** **The Week 8 analysis and interim analysis will be performed by an independent biostatistics group and results will be 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 may coincide depending on subject enrollment and data cleaning/programming activities.** **As the primary study endpoint is the bioequivalence comparison at Week 8, no type I error adjustments are required as the analysis performed after the Week 8 database lock are considered final for the primary efficacy endpoint. No type I error adjustments are planned for the secondary efficacy endpoints; therefore, no error adjustments will be performed**	

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
		due to the interim analysis as all analyses after the primary analysis at the Week 8 database lock are considered secondary analyses.	
11.1.1 External Data Monitoring Committee	An IDMC will be established for the study. An IDMC meeting will be held after all subjects have completed Week 8 Visit. From this meeting, the IDMC will make a recommendation to the sponsor regarding the study to continue without change, modify study or enrollment to be placed on hold, or study termination.	An IDMC will be established for the study. ~~An~~ **Two** IDMC ~~meeting~~ **meetings** will be held**: one safety meeting will be held approximately 6 months after the IDMC organizational meeting and the second safety** meeting will be held after all subjects have completed **the** Week 8 Visit. ~~From this meeting~~ **After each meeting**, the IDMC will make a recommendation to the sponsor regarding the study to continue without change, modify **the** study or enrollment to be placed on hold, or study termination.	To reflect the addition of an interim analysis.
11.4 Final Report	Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary report of the study's outcome and the sponsor and regulatory authorities with any reports required.	Upon completion of **the interim and final analyses of** the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary report of the study's outcome and the sponsor and regulatory authorities with any reports required.	To reflect the addition of an interim analysis.
12 Reference List	-	**Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics (US). Statistical Review and Evaluation. Aflibercept ophthalmic solution (VEGF Trap-Eye). 2011 [cited 2022 Jan 24] [application number 125387Orig1s000]. Available**	To insert the correct reference.

Chapter/Section	Initial Wording	Amended or New Wording	Reason/Justification for Change
		from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125387Orig1s000StatR.pdf	
Throughout	-	*Editorial and administrative changes, typographical error corrections, and document formatting revisions.*	To improve the readability and overall quality of the document.

14.2 Protocol Amendment, Version 2.0, 24 November 2020

This global protocol amendment is considered substantial mainly for the following reasons. The amendment incorporated the changes that had been updated in the country-specific protocol amendments, including the Slovakia- and Korea-specific protocol amendments, as per the requests from the regulatory agencies in both countries. Additionally, the amendment incorporated the recommendations from the US FDA to 1) change the FAS population and 2) keep subjects in the study to continue with their regularly scheduled visits and assessments until Week 52 after study treatment discontinuation. To meet these recommendations, the analysis sets and statistical methods were changed. In addition, treatment of fellow eye was allowed during the whole duration of the study. These revisions are considered substantial because they represent significant changes to the study conduct. Additional non-substantial changes were made for clarity.

Additions to the protocol text are shown in bold, and deletions are shown in strikethrough text. Minor editorial and grammatical corrections are not specified. Any notes for the section are included in brackets.

Initial Wording	Amended or New Wording	Reason/Justification for Change
Chapter/section concerned Section 2.5 Estimands The estimand for the primary objective is the mean treatment difference for BCVA change from baseline at Week 8. At Week 52, the estimand of interest is the mean treatment difference for BCVA change from baseline at Week 52.	The **primary** estimand for the primary objective is the mean treatment difference ~~for~~ **in** BCVA change from baseline at Week 8. At Week 52, the **primary** estimand of interest is the mean treatment difference for BCVA change from baseline at Week 52. **For the primary estimands, any observations post receipt of rescue therapy in the study eye will be set to missing, thereby**	The section of estimands has been revised as per the US FDA requirement of changing the FAS population and the recommendation to not discontinue subjects from the study when they discontinue study treatment.

	estimating treatment effect as though subjects do not receive rescue therapy. For each of the Week 8 and Week 52 analyses, the secondary estimand will be presented where post rescue will not be set to missing but will be included in the mixed-effects model for repeated measures (MMRM) analysis. The secondary estimands are constructed to estimate the treatment effect while including the impact of rescue therapy, which may better reflect actual real-world outcomes where rescue would likely be given when lack of efficacy is seen.	
Chapter/section concerned Section 3.1 Study Design ... Approximately 560 subjects with wet AMD will be enrolled in this study across approximately 155 sites in 14 countries. Upon entry into the study, subjects will be assigned a screening number. Subjects who meet all inclusion and none of the exclusion criteria will return to the clinic on Day 1 for further evaluation. Subjects who continue to meet all inclusion and none of the exclusion criteria will be randomly assigned and treated on Day 1. At this visit, the subjects will be randomly assigned in 1:1 ratio to receive IVT SCD411 or aflibercept injections. Randomization will be stratified by subject participation in the PK substudy. Subjects will be treated with study treatment every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48 as detailed in the Schedule of Events (Table 6-1). A schematic of the study design is presented in Figure 3-1. The details of the implementation in Interactive	... Approximately 560 subjects with wet AMD will be enrolled in this study across approximately 155 sites in 14 countries. Upon entry into the study, subjects will be assigned a screening number. Subjects who meet all inclusion and none of the exclusion criteria will return to the clinic on Day 1 for further evaluation. Subjects who continue to meet all inclusion and none of the exclusion criteria will be randomly assigned and treated on Day 1. At this visit, the subjects will be randomly assigned in 1:1 ratio to receive IVT SCD411 or aflibercept injections. Randomization will be stratified by subject participation in the PK substudy. **Subjects in Israel will not participate in the PK substudy. Randomization will also be stratified by subjects enrolled in Japan.** ... ... All subjects will be assessed once every 4 weeks as detailed in the Schedule of Events (Table 6-1). **The End-of-Treatment (EOT) Visit will be scheduled for Week 48.** Subjects who	The PK substudy in Israel was clarified as per the request from the Israel regulatory agency. Stratification by subjects in Japan has been added to the protocol as per sponsor's decision. The paragraph on study treatment discontinuation has been 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 can be collected to support sensitivity analyses.

Response Technology (IRT) will be provided in the IRT manual and the randomization specification form. ... All subjects will be assessed once every 4 weeks as detailed in the Schedule of Events (Table 6 1). Subjects who discontinue the study treatment should be encouraged to return for the Early Termination (ET) Visit as soon as possible after discontinuing the treatment but no later than 28 days after discontinuation. The End-of-Study (EOS) Visit will occur 28 days after the end of treatment. The end of the study is defined as the date of the last visit of the last subject in the study.	discontinue the study treatment **early** should **have the reasons for treatment discontinuation documented on the Treatment Discontinuation page of the electronic case report form (eCRF). Treatment discontinuation in the study was defined as subjects discontinuing the study treatment due to adverse event/lack of efficacy/rescue treatment but not limited to these conditions. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator the subject should be prematurely withdrawn, then** ~~should be encouraged to return for~~ the Early Termination (ET) Visit **should be completed** as soon as possible after discontinuing the treatment but no later than 28 days after discontinuation. The End-of-Study (EOS) Visit will occur 28 days after the end of treatment **for Week 52**. The end of the study is defined as the date of the last visit of the last subject in the study.	
Chapter/section concerned Section 4.1.1 Inclusion Criteria 3. Active choroidal neovascularization lesions secondary to AMD evidenced by fluorescein angiography (FA) in the study eye at screening and confirmed by the central reading center. ...	... 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 center ... 7. **The area of CNV making up either 50% or more of the total lesion area and confirmed by the central reading center.**	Inclusion criterion (IC) #3 has been updated by adding the range of choroidal neovascular lesions as per the request from the Korean Ministry of Food and Drug Safety (MFDS), which has been incorporated into the Korea-specific protocol amendment. IC#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 criteria. This change has been applied to the Korea-specific protocol amendment.
Chapter/section concerned Section 4.1.2 Exclusion Criteria 12. Active extraocular inflammation in either eye or intraocular inflammation in study eye ... 24. Uncontrolled hypertension defined as systolic blood pressure (BP) >180 mmHg or diastolic BP >100 mmHg under appropriate antihypertensive treatment	... 12. Active ~~extraocular inflammation in either eye or intraocular~~ **intraocular/periocular infection and** inflammation in either eye ... 24. Uncontrolled hypertension defined as systolic blood pressure (BP) >~~180~~ **160** mmHg or diastolic BP >100 mmHg under appropriate antihypertensive treatment ... **36. Intraocular pressure ≥25 mmHg in spite of anti-glaucoma treatment** **37. Any prior or ongoing systemic medical condition (including but not limited to infectious, inflammatory, psychiatric, neurological, renal, hepatic, respiratory conditions or malignancies) or clinically significant screening laboratory value that in the opinion of the investigator may present a safety risk, interfere with study compliance and follow-up, or confound data interpretation throughout the study period.**	Exclusion criterion (EC) #12 was updated to clarify that subjects with the conditions of intraocular/periocular infection and inflammation in either eye should be excluded at screening. This change has been applied to the Korea-specific protocol amendment. The limit of systolic blood pressure was decreased from 180 to 160 mmHg in EC#24, as per the request from the Slovakia regulatory agency. The change has been applied to the Slovakia-specific protocol amendment. As per the requests from the Slovakia regulatory agency and the Korean MFDS, EC#36 regarding the IOP condition in spite of anti-glaucoma treatment was added according to the SmPC with the IOP. The change has 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 should be excluded from the study; therefore, EC#37 was added.
Chapter/section concerned Section 4.2 Selection of Study Eye The section does not exist in the original protocol (version 1.0).	**Only one eye (study eye) must meet all the inclusion criteria and none of the exclusion criteria.** **Fellow eye should not show any signs of AMD that, in the investigator's medical opinion, may need any treatment during study period.**	The section of selection of study eye was added as per the US FDA requirement to clearly define study eye in the protocol.

Chapter/section concerned Section 4.3.1 Discontinuation From Study Treatment Section 4.3.2 Withdrawal From the Study Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator and/or sponsor for safety, behavioral, or administrative reasons. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Subjects should undergo ET Visit assessments as soon as possible after discontinuing the study treatment, but no later than 28 days after discontinuation, as described in the Schedule of Events (Table 6-1). General reasons for discontinuation can include, but are not limited to: • Death. • Subject has a serious or intolerable AEs that in the Investigator's opinion requires withdrawal from the study. • Lost to follow-up. • Decision by the investigator that the subject requires alternate treatment for neovascular AMD in the study eye. • Decision by the Sponsor or administrative decision for a reason (eg, a suspicion of fraud, the subject enrolling in multiple clinical studies, lack of compliance, etc.) other than that of an AE.	**Section 4.3.1 Discontinuation From Study Treatment** ~~Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator and/or sponsor for safety, behavioral, or administrative reasons. If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.~~ **In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study treatment. If the investigational product is definitively discontinued, the Treatment Discontinuation page of the eCRF should be completed. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn, then the** ~~S~~subjects should undergo ET Visit assessments as soon as possible after discontinuing the study treatment, but no later than 28 days after discontinuation, as described in the Schedule of Events (Table 6-1). **A subject may discontinue from the study treatment for any of the following reasons:** • Subject has a serious or intolerable AEs that in the	As per the US FDA recommendation to keep subjects who discontinue study treatment in the study to continue with their regularly scheduled visits, the reasons for withdrawal/discontinuation need to be introduced separately. As per the latest PPD protocol template, the above reasons were placed in the corresponding sections (The Section 4.2.1 Reason for Withdrawal/Discontinuation in the original protocol was divided into two sections: Discontinuation From Study Treatment, and Withdrawal From the Study). For clarity, certain specific criteria for treatment discontinuation were moved to the section of discontinuation of study treatment.

• Pregnancy. • Protocol deviation which may adversely affect the subject's safety and/or integrity of data as agreed by the Investigator and/or upon request from the Sponsor. • New diagnosis or worsening neovascular AMD in the fellow eye at any point during the study. o Before 8 weeks of the study: Study treatment is continued till 8 weeks and then discontinued. o After 8 weeks of the study: Study treatment is immediately discontinued. • The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal. • The subject withdraws consent. • If a subject withdraws his/her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (eg, documented lack of efficacy, AE or pregnancy); however, the subject may refuse to provide such reason. • A subject misses any of first 2 doses (IVT injection of IP at Week 0 [Day 1] or Week 4) after randomization. Certain specific criteria for treatment discontinuation include: • Development of rhegmatogenous retinal detachment or stage 3 or 4 macular holes • A decrease in BCVA of ≥30 letters compared with the last	Investigator's opinion requires withdrawal from the study. • Decision by the investigator that the subject requires alternate treatment for neovascular AMD in the study eye. • Pregnancy. • ~~New diagnosis or worsening neovascular AMD in the fellow eye at any point during the study.~~ o ~~Before 8 weeks of the study: Study treatment is continued till 8 weeks and then discontinued.~~ o ~~After 8 weeks of the study: Study treatment is immediately discontinued.~~ • A subject misses **either** ~~any~~ of **the** first 2 doses (IVT injection of IP at Week 0 [Day 1] or Week 4) after randomization. • Decision by the Sponsor or administrative decision for a reason (eg, a suspicion of fraud, the subject enrolling in multiple clinical studies, lack of compliance, etc.) other than that of an AE. Certain specific criteria for treatment discontinuation include: • Development of rhegmatogenous retinal detachment or stage 3 or 4 macular holes • A decrease in BCVA of ≥30 letters compared with the last assessment of VA • A subretinal hemorrhage involving the center of the fovea or, if the size of the hemorrhage is ≥50% of the	

assessment of VA • A subretinal hemorrhage involving the center of the fovea or, if the size of the hemorrhage is ≥50% of the total lesion area • Clinical signs of irreversible ischemic visual function loss.	total lesion area • Clinical signs of irreversible ischemic visual function loss. **Section 4.3.2 Withdrawal From the Study** **A subject may withdraw from the study for any of the following reasons:** • Death. • Lost to follow-up. • Protocol deviation which may adversely affect the subject's safety and/or integrity of data as agreed by the ~~I~~investigator and/or upon request from the Sponsor. • The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal. • The subject withdraws consent. • If a subject withdraws his/her consent, the ~~I~~investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (eg, documented lack of efficacy, AE or pregnancy); however, the subject may refuse to provide such reason.	
Chapter/section concerned Section 4.3.3 Handling of Withdrawals Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by	... ~~Subjects who discontinue study treatment or active participation in the study will no longer receive study drug. When a subject withdraws from the study treatment or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF).~~ **Every effort**	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.

the investigator on the relevant page of the electronic case report form (eCRF). All subjects who discontinue study treatment or withdraw from the study prematurely will be asked to complete the ET Visit procedures as soon as possible after discontinuing the study treatment, but no later than 28 days after discontinuation. If a subject discontinues the study treatment due to an AE/serious adverse event (SAE) or if AEs/SAEs were ongoing at the time of discontinuation, the subject will be followed-up until resolution or stabilization.	**should be made to have such subjects continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration after discontinuation of the study treatment, unless the subjects withdraw consent.** All subjects who ~~discontinue study treatment or~~ withdraw from the study prematurely will be asked to complete the ET Visit procedures as soon as possible after discontinuing the study treatment, but no later than 28 days after discontinuation. If a subject discontinues the study treatment due to an AE/serious adverse event (SAE) or if AEs/SAEs were ongoing at the time of discontinuation, the subject will be followed-up until resolution or stabilization.	
Chapter/section concerned Section 4.3.4 Screen Failures ... Subjects who do not meet the criteria for participation in this study may not be rescreened unless an image retransmission is requested from the central image vendor due to any possible technical issues. However, this is not considered to be rescreening.	... Subjects who do not meet the criteria for participation in this study may not be rescreened**.** ~~unless an image~~ **Image** retransmission is requested from the central image **center** ~~vendor~~ due to any possible technical issues~~. However, this~~ is not considered to be rescreening.	The text was revised for clarity.
Chapter/section concerned Section 5.2 Treatments Administered ... Subjects will receive their randomized study treatment injections as per the Schedule of Events (Table 6 1) and according to the procedure manual. Clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to	... Subjects will receive their randomized study treatment injections as per the Schedule of Events (Table 6-1) and according to the procedure manual. Clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration will follow appropriate aseptic techniques to minimize the risk of potential AEs associated with IVT injections. **If the pre-procedure IOP is equal to or greater than 30 mmHg, the**	To further ensure 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 will only be conducted by the masked staff. The sponsor

minimize the risk of potential AEs associated with IVT injections. ... Immediately following the IVT injection, subjects should be checked for presence of optic nerve perfusion, formed vision, and excessive level of intraocular pressure (IOP) elevation or decrease. Appropriate monitoring consists of a fundoscopy check for perfusion of the optic nerve head, hand movement/finger counting vision and tonometry. If required, a sterile paracentesis needle should be available for the injecting physician to ensure control of excessive IOP elevation. Assessment of perfusion and presence of formed vision and hard globe due to excessive pressure is done immediately following the injection by the physician who injects the subject. There is technological time between the subject leaving the injecting room and going to the room where the IOP will be followed until safe to let the subject go home.	**IVT injection will not be administered (either withheld or delayed) until the IOP is decreased to acceptable safety levels as per the investigator's medical judgement.** ... Immediately following the IVT injection, subjects should be checked **by the unmasked staff** for ~~presence of optic nerve perfusion, formed vision, and excessive level of intraocular pressure (IOP) elevation or decrease. Appropriate monitoring consists of a fundoscopy check for perfusion of the optic nerve head,~~ hand movement/finger counting vision ~~and tonometry~~ **for subject safety. The information will not be captured in the eCRF. If subjects can recognize hand movement/finger counting vision immediately following the IVT injection, then the subjects should be transferred from the unmasked staff to the masked staff. If subjects cannot recognize hand movement/finger counting vision immediately following the IVT injection, then the unmasked staff should further investigate the reason**. If required, a sterile paracentesis needle should be available for the injecting physician to ensure control of excessive IOP elevation. ~~Assessment of perfusion and presence of formed vision and hard globe due to excessive pressure is done immediately following the injection by the physician who injects the subject. There is technological time between the subject leaving the injecting room and going to the room where the IOP will be followed until safe to let the~~	confirmed that the hand movement/finger counting checks by the unmasked team are sufficient for safety assessment.

	~~subject go home.~~ **The safety data after administration of the study treatment is collected by the masked staff for IOP and dilated fundoscopy. The information will be captured in the eCRF.**	
Chapter/section concerned Section 5.2.1 Treatment of Fellow Eye If a subject is newly diagnosed with neovascular AMD or has worsening neovascular AMD in the fellow eye before completion of 8 weeks of treatment, the same schedule is followed until Week 8. Fellow eye treatment with Eylea is allowed and the cost of this treatment will be covered by the sponsor until Week 8. The subject should perform ET Visit assessments after Week 8. In this case, fellow eye data of dilated fundoscopy, IOP, fellow eye treatment date and medication name will be collected via eCRF. Also, the fellow eye treatment injection is not permitted on the same day as the study eye treatment. If the subject is newly diagnosed with neovascular AMD or has worsening neovascular AMD in fellow eye after Week 8, the principal investigator (PI) will perform ET/EOS Visits, discontinue the subject from the study, and will continue treatment of neovascular AMD in both eyes as per PI's standard of care (SOC) and his/her discretion.	**Treatment of fellow eye will be allowed at any time during the study if** ~~If~~ a subject is newly diagnosed with neovascular AMD or has worsening neovascular AMD in the fellow eye. **The fellow eye should be treated only with Eylea as per investigator's discretion.** ~~before completion of 8 weeks of treatment, the same schedule is followed until Week 8. Fellow eye treatment with Eylea is allowed and the cost of this treatment will be covered by the sponsor until Week 8. The subject should perform ET Visit assessments after Week 8.~~ In this case, fellow eye data of dilated fundoscopy, IOP, fellow eye treatment date and medication name will be collected via eCRF. Also, the fellow eye treatment injection is not permitted on the same day as the study eye treatment. **The cost of the fellow eye treatment will be covered by the sponsor in terms of either providing open-label Eylea or reimbursement after the site stock of Eylea is used up.** ~~If the subject is newly diagnosed with neovascular AMD or has worsening neovascular AMD in fellow eye after Week 8, the principal investigator (PI) will perform ET/EOS Visits, discontinue the subject from the study, and will continue treatment of neovascular AMD in both eyes~~	The 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.

	~~as per PI's standard of care (SOC) and his/her discretion.~~	
Section 5.8.1 Rescue Treatment ... Subjects who will receive rescue treatment will need to perform ET/EOS Visits and discontinue from the study.	... In the study eye, rescue treatment for neovascular AMD is not permitted at any point in time. If it is observed that efficacy is not achieved by the study treatment, as determined by the investigator, subjects can be considered for rescue treatment after Week 4 if any 1 of the following conditions are met as assessed by the masked investigators: • Decrease of VA letter score of 15 letters or more from the last assessment and/or • ~~Increase in the central subfield thickness of 100 µm compared to the latest assessment (OCT) by the investigator,~~ ~~an~~ **An** increase in intraretinal fluid, subretinal fluid, or subretinal hyper-reflective material, that in the investigator's opinion is related to progression of the subject's neovascular AMD Subjects who will receive rescue treatment **need to discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after**	The section was updated as per the US FDA recommendation to remain subjects who discontinue study treatment due to receipt of rescue treatment in the study continuing with their regularly scheduled visits. Due to SCD'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 to the latest assessment (OCT) by the investigator was removed.

	discontinuation ~~will need to perform ET/EOS Visits and discontinue from the study~~.	
Chapter/section concerned Section 5.8.2 Prohibited Medications The details of the prohibited medications during the study are presented in Table 5-1. Concurrent use of systemic or IVT anti-VEGF agents; IVT, subtenon, or peribulbar corticosteroids in either eye, except as required to treat AEs. ...	The details of the prohibited medications during the study are presented in Table 5-1. Concurrent use of systemic or IVT anti-VEGF agents; IVT, subtenon, or peribulbar corticosteroids in ~~either~~ **study** eye, except as required to treat AEs. ...	Prohibited medications applied to the fellow eye have been removed, as per sponsor's decision to allow fellow eye treatment only with Eylea for the whole duration of the study.
Chapter/section concerned Section 6.1.3 Early Termination/End-of-Study All subjects who discontinue study treatment should return for the ET Visit as soon as possible after the discontinuation but no later than 28 days after discontinuation. End-of-study Visit assessments will be conducted 28 days after the end of treatment. ...	**The end of the study is defined as the date of the last visit of the last subject in the study.** ~~All~~ **For** subjects who discontinue study treatment, **the Treatment Discontinuation page of the eCRF should be completed. Every effort should be made to have such subjects remain in the study and continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn, then the subject** should return for the ET Visit as soon as possible after the discontinuation but no later than 28 days after discontinuation. End of **S**~~s~~tudy Visit assessments will be conducted 28 days after the end of treatment **for Week 52**. ...	The section was updated as per the US FDA request to keep subjects who discontinue study treatment in the study to continue with their regularly scheduled visits.
Chapter/section concerned Section 6.3.3.6 Suspected Unexpected Serious Adverse Reactions and Nonserious	Section 6.3.3.6 Suspected Unexpected Serious Adverse Reactions~~ and Nonserious Adverse Events of Special Interest~~	The title of the section and the body text on nonserious adverse events of special interest (AESIs) were removed because there is no

Adverse Events of Special Interest The sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) and nonserious AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation. ...	The sponsor will promptly evaluate all suspected unexpected serious adverse reactions (SUSARs) ~~and nonserious AEs of special interest~~ against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation. ,,,	definition of AESI in the protocol.
Chapter/section concerned Section 6.4 Pharmacokinetic Assessments Blood samples, for determination of concentrations of SCD411 and aflibercept, will be collected at the timepoints specified in the Schedule of Events (Table 6 1) and detailed sampling window is provided in Table 6 3. Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples drawn at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection. Samples should be collected before performing FA, when performed on the same day. Plasma concentrations of SCD411 and aflibercept will be determined using validated analytical procedures. PK parameters assessed in the study include AUC0-t, AUC0-tau, AUC0-inf, Cmax, tmax, and t1/2. …	Blood samples, for determination of concentrations of SCD411 and aflibercept, will be collected at the timepoints specified in the Schedule of Events (Table 6 1) and detailed sampling window is provided in Table 6 3. **As per the Schedule of Events, additional visits will be arranged for collecting the PK blood samples.** Quantification of free and bound SCD411 and aflibercept will be performed for subjects who agree to participate in the PK substudy using blood samples drawn at predose, and at +1 day, +3 days, +7 days, +14 days, and +28 days following the first and the third injection. Samples should be collected before performing FA, when performed on the same day. Plasma concentrations of SCD411 and aflibercept will be determined using validated analytical procedures. PK parameters assessed in the study include AUC0-t, AUC0-tau, AUC0-inf, Cmax, tmax, and t1/2. …	For clarity, the sentence on the additional visits to be arranged for collecting the PK blood samples was added.
Chapter/section concerned Section 6.7 Pregnancy …	**No pregnancy test is required for women of non-child-bearing potential.** Serum pregnancy test will be performed for **women of child-bearing potential** at the	The section was updated to clarify that the serum pregnancy test will be only administered to women of child-bearing potential and to implement the change to keep

Serum pregnancy test will be performed at the Screening Visit. At Baseline, ET, and EOS Visits, a urine pregnancy test will be performed and if found positive, then the serum pregnancy test should be performed. If serum pregnancy test results are positive, the study treatment should be discontinued and ET Visit procedures should be conducted.	Screening Visit. At Baseline, ET, and EOS Visits, a urine pregnancy test will be performed and if found positive, then the serum pregnancy test should be performed. If serum pregnancy test results are positive, the study treatment should be discontinued**, and the subjects should continue with regularly scheduled visits and assessments until Week 52 after discontinuation, unless the subjects withdraw consent, in which circumstance** ET Visit procedures should be conducted, **the subject or the female partner of any male subject should be followed for safety until the outcome of the pregnancy is known.**	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 is known was emphasized.
Chapter/section concerned Section 7.1 Estimands and Intercurrent Events Intercurrent events of interest are receipt of rescue therapy and treatment/study discontinuation. Subjects who discontinue treatment are to discontinue the study. Week 8 The estimand is the mean treatment difference for BCVA change from baseline at Week 8. For the EMA, the primary analysis will be assessed for both the full analysis set (FAS) and per-protocol set (PPS). For the FDA, PMDA, and any other submissions, the primary analysis will be performed for the FAS. The primary analysis will be based on a mixed model for repeated measures (MMRM)	~~Intercurrent events of interest are receipt of rescue therapy and treatment/study discontinuation. Subjects who discontinue treatment are to discontinue the study~~. Week 8 ~~The estimand is the mean treatment difference for BCVA change from baseline at Week 8. For the EMA, the primary analysis will be assessed for both the full analysis set (FAS) and per-protocol set (PPS). For the FDA, PMDA, and any other submissions, the primary analysis will be performed for the FAS. The primary analysis will be based on a mixed model for repeated measures (MMRM) including data for Week 4 and Week 8 based on observed data and baseline BCVA value as a covariate. Subjects who discontinue treatment are to discontinue the study and~~	The section on estimands and intercurrent events have been updated as per the US FDA request to change the FAS population and to not discontinue subjects from the study when they discontinue study treatment due to AE/lack of efficacy/rescue treatment.

including data for Week 4 and Week 8 based on observed data and baseline BCVA value as a covariate. Subjects who discontinue treatment are to discontinue the study and observations after receipt of rescue therapy should be missing; however, in the event the subject continues follow-up, BCVA values after treatment discontinuation or receipt of rescue therapy will be set to missing prior to performing the MMRM. The MMRM approach assumes data is missing at random (MAR) and treatment estimates are as if subjects continued as on their original treatment. Sensitivity analyses will be performed using single imputation approaches of last observation carried forward (LOCF) and baseline observation carried forward (BOCF) approaches for observations after treatment discontinuation/receipt of rescue therapy prior to performing the MMRM analysis (intermittent missing data will be considered MAR and not imputed). An ANCOVA model comparing the Week 8 BCVA change from baseline and including baseline BCVA value as covariate will be performed based on observed data, using LOCF, and BOCF approaches. As with the MMRM analysis, for the ANCOVA, intermittent missing data at Week 8 will be considered MAR and observations after treatment discontinuation/receipt of rescue therapy will be set to missing. LOCF also approaches treatment estimates as if subjects who discontinue had continued on their original treatments and BOCF approaches treatment estimates as if subjects who discontinue received no treatment or returned to their original	~~observations after receipt of rescue therapy should be missing; however, in the event the subject continues follow-up, BCVA values after treatment discontinuation or receipt of rescue therapy will be set to missing prior to performing the MMRM. The MMRM approach assumes data is missing at random (MAR) and treatment estimates are as if subjects continued as on their original treatment. Sensitivity analyses will be performed using single imputation approaches of last observation carried forward (LOCF) and baseline observation carried forward (BOCF) approaches for observations after treatment discontinuation/receipt of rescue therapy prior to performing the MMRM analysis (intermittent missing data will be considered MAR and not imputed). An ANCOVA model comparing the Week 8 BCVA change from baseline and including baseline BCVA value as covariate will be performed based on observed data, using LOCF, and BOCF approaches. As with the MMRM analysis, for the ANCOVA, intermittent missing data at Week 8 will be considered MAR and observations after treatment discontinuation/receipt of rescue therapy will be set to missing. LOCF also approaches treatment estimates as if subjects who discontinue had continued on their original treatments and BOCF approaches treatment estimates as if subjects who discontinue received no treatment or returned to their original condition. Multiple imputation approached including tipping point analyses will also be performed for sensitivity.~~ **Primary Estimand: The**	

condition. Multiple imputation approached including tipping point analyses will also be performed for sensitivity. Week 52 The estimand is the mean treatment difference for BCVA change from baseline at Week 52. For the FDA, PMDA and any other submissions, the primary analysis will be performed for FAS. For the EMA, the primary analysis will be assessed for both the FAS and PPS. The primary analysis will be based on an MMRM including data from all study visits through Week 52 and baseline BCVA value as a covariate. As in the Week 8 analysis, observations after treatment discontinuation or receipt of rescue therapy will be set to missing prior to analysis. Sensitivity analyses will be performed using single imputation LOCF and BOCF approaches for post-treatment discontinuation/rescue therapy assessments prior to performing the MMRM analysis (intermittent missing data will be considered MAR and not imputed). An ANCOVA model comparison the Week 52 BCVA change from baseline and including baseline BCVA value as covariate will be performed using observed data with LOCF, and BOCF approaches for post-treatment discontinuation/rescue therapy observations. Multiple imputation approached including tipping point analyses will also be performed for sensitivity. Data imputation/analysis methods which generate treatment estimates as if subjects continued original treatment are considered	**primary estimand is the mean treatment difference in BCVA change from baseline at Week 8. For the EMA, the primary analysis will be assessed for both the full analysis set (FAS) and per-protocol set (PPS). For the FDA, PMDA, and any other submissions, the primary analysis will be performed for the FAS. The primary estimand treats subjects in the analysis as if subjects do not receive rescue therapy.** **Target Population: Subjects with wet AMD as defined in the enrollment criteria.** **Endpoint: Change from baseline in BCVA at Week 8.** **Treatment Condition(s): Dosing at Day 1, Week 4 and Week 8 with one of the following: SCD411 or aflibercept, both without rescue therapy.** **Population-level Summary: The difference in mean change from baseline in BCVA at Week 8 between SCD411 and aflibercept and the corresponding confidence interval for the mean difference.** **Intercurrent Events and Strategies to Address Intercurrent Events** • **Discontinuation of study eye study treatment with continued participation in study without receipt of rescue therapy** ○ **Treatment Policy – no imputation; use observed data** • **Receipt of rescue therapy**	

appropriate for the primary estimand methodology as the goal of the study is to show treatment equivalence. Subjects which receive rescue therapy will have shown lack of efficacy in assessments prior to rescue, so carrying forward their data should be conservative if the test treatment is not equivalent/less efficacious to the reference product. Sample Size Determination 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 to the placebo treatment in subjects with wet AMD. It was shown that in MARINA, subjects on average 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 to the placebo would be estimated as approximately 9.3 to 10 letters. A margin of 3.8 letters would be translated to a preservation of 59% to 62% of the difference between Eylea and sham and is 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. The FDA requested a tighter equivalence margin of 3 letters but agreed equivalence can be determined from a 90% CI approach (equivalent to TOST at	**in the study eye** ○ **Hypothetical approach – data after receipt of rescue will be set to missing and post rescue data will be imputed employing multiple imputation (MI) assuming missing at random (MAR) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology.** • **Discontinuation from study, regardless of reason** ○ **Hypothetical approach - missing data after discontinuation will be imputed via MI assuming MAR using randomized treatment based MCMC methodology.** **Rationale for Strategy: As the primary objective of this study is to show biosimilar equivalence between SCD411 and aflibercept, the primary estimand is constructed to estimate the treatment effect under the assumption that all subjects take study treatments without the use of rescue therapy while allowing for subjects to discontinue study treatment. Multiple imputation under MAR assumptions results in treatment estimates as if subjects continued as on their original treatment. Treating discontinuation as MAR and setting the post rescue assessment to missing prior to performing MI was chosen to avoid inflation of the SCD411 treatment effect. Subjects who receive rescue therapy or discontinue will have shown**	

the α=0.05 level). Standard deviation (SD) for the mean change from baseline at early visits (Weeks 4 to 12) based on observed data for the FAS ranged from and 8.73 to 11.99 considering all treatment groups from VIEW1 and from 7.4 to 11.0 letters for the VIEW2 study (Eylea Statistical Review, Appendix Tables A.1 and A.2). For power calculations, a range of SD of between 10.4 and 11.8 was assumed to be conservative and cover the majority of larger SD values seen in the observed data. A sample size of 266 subjects per treatment arm was selected as it provides at least 80% power for the FDA, EMA, and PMDA analyses for the range of SD considered when using 2 one-sided t-tests on data from a parallel-group design. For the FDA analysis based on equivalence limits of -3.0 and 3.0 letters, α=0.05 significance level (90% CI), assuming the true difference between the means is 0.0, power of 91% is achieved for SD is 10.4 letters and power of 80% is achieved for SD of 11.8 letters. For the EMA and PMDA analyses based on equivalence limits of -3.8 and 3.8 letters, α=0.025 significance level (95% CI), assuming the true difference between the means is 0.0, power of 98% is achieved for SD is 10.4 letters and power of 92% is achieved for SD of 11.8 letters when sample size is 266 per treatment arm. Considering approximately 5% loss from randomization through Week 8, the total sample size required is 560. A subset of 40 subjects (20 per	**lack of efficacy in assessments, so the MAR approach should be conservative if the test treatment is not equivalent to or less efficacious than the reference product.** **Secondary Estimand: A secondary estimand for the primary efficacy endpoint is the mean treatment difference in BCVA change from baseline at Week 8 while allowing for receipt of rescue therapy. The estimand will be constructed as above, but the intercurrent event of rescue therapy use will be handled using the treatment policy approach. Data post rescue will not be set to missing. This estimand is constructed to estimate the treatment effect including the impact of rescue therapy, which may better reflect actual real-world outcomes, where rescue would likely be given when lack of efficacy is seen.** Week 52 **Primary Estimand: The primary estimand is the mean treatment difference in BCVA change from baseline at Week 52. For the EMA, the primary analysis will be assessed for both the FAS and PPS. For the FDA, PMDA, and any other submissions, the primary analysis will be performed for the FAS. The primary estimand treats subjects in the analysis as if subjects do not receive rescue therapy.** **Target Population: Subjects with wet AMD as defined in the enrollment criteria.**	

group) will be selected for collection of PK samples. The sample size is not test-driven since no equivalence test will be performed for PK parameters.	**Endpoint: Change from baseline in BCVA at Week 52** **Treatment Condition(s): Dosing at Day 1, Week 4 and Week 8, Week 16, Week 24, Week 32, Week 40, and Week 48 with one of the following: SCD411 or aflibercept, both without rescue therapy.** **Population-level Summary: The difference in mean change from baseline in BCVA at Week 52 between SCD411 and aflibercept and the corresponding confidence interval for the mean difference.** **Intercurrent Events and Strategies to Address Intercurrent Events** • **Discontinuation of study eye study treatment with continued participation in study without receipt of rescue therapy** o **Treatment Policy – no imputation; use observed data** • **Receipt of rescue therapy in the study eye** o **Hypothetical approach – Data after receipt of rescue will be set to missing and post rescue data will be imputed employing MI assuming MAR using randomized treatment-based MCMC methodology.** • **Discontinuation from study, regardless of reason** o **Hypothetical approach - Missing data after discontinuation will be imputed via MI assuming MAR using randomized treatment-**	

	based MCMC methodology. **Rationale for Strategy: As the primary objective of this study is to show biosimilar equivalence between SCD411 and aflibercept, the primary estimand is constructed to estimate the treatment effect under assumption that all subjects take study treatments without the use of rescue therapy while allowing for subjects to discontinue study treatment. Multiple imputation under MAR assumptions results in treatment estimates as if subjects continued as on their original treatment. Treating discontinuation as MAR and setting the post rescue assessment to missing prior to performing MI was chosen to avoid inflation of the SCD411 treatment effect. Subjects who receive rescue therapy or discontinue will have shown lack of efficacy in assessments, so the MAR approach should be conservative if the test treatment is not equivalent to or less efficacious than the reference product.** **Secondary Estimand: A secondary estimand for the secondary efficacy endpoint is the mean treatment difference for BCVA change from baseline at Week 52 while allowing for receipt of rescue therapy. The estimand will be constructed as above, but the intercurrent event of rescue therapy use will be handled using the treatment policy approach. Data post rescue will not be set to missing. This estimand is constructed to estimate the treatment effect**	

	including the impact of rescue therapy, which may better reflect actual real-world outcomes where rescue would likely be given when lack of efficacy is seen.	
Chapter/section concerned Section 7.2 Sample Size Determination 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 to the placebo treatment in subjects with wet AMD. It was shown that in MARINA, subjects on average 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 to the placebo would be estimated as approximately 9.3 to 10 letters. A margin of 3.8 letters would be translated to a preservation of 59% to 62% of the difference between Eylea and sham and is 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.	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 to the placebo treatment in subjects with wet AMD. It was shown that in MARINA, subjects on average 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 to the placebo would be estimated as approximately 9.3 to 10 letters. A margin of 3.8 letters would be translated to a preservation of 59% to 62% of the difference between Eylea and sham and is 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. **Given that the statistical justification of the 3.8 letter equivalence margin is not included in the current version of the protocol, this will be added in the SAP and provided to the regulatory agencies upon request.**	Upon agreement within the internal PPD team, justification for the 3.8 letter margin was briefly mentioned in the protocol amendment.
Chapter/section concerned Section 7.3 Analysis Sets	... **Full Analysis Set (FAS)**: ~~a~~**A**ll randomized subjects who received	The definition of FAS has been updated as per the request from US FDA.

Full Analysis Set (FAS): 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. ... **Safety Set (SAF)**: all randomized subjects receiving at least 1 injection of the study drug. **Pharmacokinetic Analysis Set (PK Set)**: the subset of subjects in SAF who have sufficient evaluable blood samples to be included in the PK Set.	at least 1 injection of the study drug ~~and had at least 1 postbaseline BCVA assessment in the study eye.~~ **Per-protocol Set (PPS)**: ~~a~~**A**ll subjects in the FAS, excluding those with significant protocol violations. **Safety Set (SAF)**: ~~a~~**A**ll ~~randomized~~ subjects receiving at least 1 injection of the study drug. **Pharmacokinetic Analysis Set (PK Set)**: ~~t~~**T**he subset of subjects in ~~SAF~~ **FAS** who have sufficient evaluable blood samples to be included in the PK Set.	The definitions of SAF and PK set were updated for clarity.
Chapter/section concerned Section 7.5.1.1 Primary Efficacy Outcome Measures ... The primary analysis of the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 8 weeks of treatment will be performed via MMRM including data for the Week 4 and Week 8 visits. The model will include the change from baseline as the dependent variable; treatment and visit as fixed effects, and baseline BCVA as a covariate. An appropriate covariance matrix will be selected, and details will be provided in the SAP. The estimated mean treatment difference at Week 8 along with the corresponding 90% and 95% CIs will also be presented. Equivalence will be determined if the upper and lower CI limits for the difference between treatments are within the equivalence margins. Raw values and changes from baseline at Week 4 and Week 8 will be summarized by treatment group	... The primary analysis of the change from baseline in BCVA as measured by ETDRS letter score or 2702 charts through 8 weeks of treatment will be performed via MMRM including data for the Week 4 and Week 8 visits. The model will include the change from baseline as the dependent variable; treatment and visit as fixed effects, and baseline BCVA as a covariate. An ~~appropriate~~ **unstructrued** covariance matrix will be ~~selected~~ **used. In the event of convergence issues, compound-symmetry will be used instead. Rubin's rules will be used to combine the estimates from the MMRM analyses and the** ~~and details will be provided in the SAP. The~~ estimated mean treatment difference at Week 8 along with the corresponding 90% and 95% CIs will ~~also~~ be presented. Equivalence will be determined if the upper and lower CI limits for the difference between treatments are within the equivalence	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 discontinue study treatment due to AE/lack of efficacy/rescue treatment. The covariance structure was specified as per the request from US FDA.

using descriptive statistics. ... For the FDA submission and other countries submission, a 90% CI (equivalent to 2 one-sided tests evaluated at an α of 0.05) will be assessed using an equivalence margin of 3 letters. If the upper bound of the 90% CI from the MMRM model is less than 3 and the lower bound is greater than -3, then study success will be claimed. For the EMA and PMDA, a 95% CI (equivalent to 2 one-sided tests evaluated at an α of 0.025) will be assessed using an equivalence margin of 3.8 letters. If the upper bound of the 95% CI from the MMRM model is less than 3.8 and the lower bound is greater than -3.8, then study success will be claimed. The least squares mean estimate of treatment difference and corresponding 90% (FDA and other countries) and 95% (EMA/PMDA) CIs will be provided. The primary analysis set for the FDA, PMDA, and any other submissions will be the FAS. For the EMA submission, both the FAS and PPS are considered primary analysis and equivalence will need to be shown for both analysis sets. As the extent of missing data and/or treatment discontinuation/rescue therapy is expected to be less than 5%, the primary analysis will be based on observed data assuming data is missing at random. Non-missing observations after treatment discontinuation/receipt of rescue therapy will be set to missing prior to analysis. Sensitivity analyses to the primary analysis will be performed by imputing the post treatment discontinuation/rescue therapy BCVA scores using the	margins. Raw values and changes from baseline at Week 4 and Week 8 will be summarized by treatment group using descriptive statistics **based on observed data**. ... For the FDA submission and other countries submission, a 90% CI (equivalent to 2 one-sided tests evaluated at an α of 0.05) will be assessed using an equivalence margin of 3 letters. If the upper bound of the 90% CI ~~from the MMRM model~~ is less than 3 and the lower bound is greater than -3, then study success will be claimed. For the EMA and PMDA, a 95% CI (equivalent to 2 one-sided tests evaluated at an α of 0.025) will be assessed using an equivalence margin of 3.8 letters. If the upper bound of the 95% CI ~~from the MMRM model~~ is less than 3.8 and the lower bound is greater than -3.8, then study success will be claimed. The least squares mean estimate of treatment difference and corresponding 90% (FDA and other countries) and 95% (EMA/PMDA) CIs will be provided. The primary analysis set for the FDA, PMDA, and any other submissions will be the FAS. For the EMA submission, both the FAS and PPS are considered primary analysis and equivalence will need to be shown for both analysis sets. ~~As the extent of missing data and/or treatment discontinuation/rescue therapy is expected to be less than 5%, the primary analysis will be based on observed data assuming data is missing at random. Nonmissing observations after treatment discontinuation/receipt of rescue therapy will be set to~~	

LOCF and BOCF prior to the MMRM analysis (intermittent missing data will be considered MAR and not imputed). In addition, analyses will also be repeated for the PPS using observed data as well as imputing missing data using the LOCF and BOCF approaches. An ANCOVA model comparing the change from baseline in BCVA at Week 8 and including baseline BCVA value as covariate will be performed based on observed data with nonmissing observations after treatment discontinuation/receipt of rescue therapy being set to missing prior to analysis. The ANCOVA model will also be performed by imputing the post-treatment discontinuation/rescue therapy BCVA values using LOCF and BOCF approaches. Additionally, the MMRM analysis will be performed using data from multiple imputation (MI) including a tipping point approach. Observations after treatment discontinuation/receipt of rescue therapy will be set to missing prior to the MI. Multiple imputation assuming MAR will be applied to all missing data. After conclusion of MI, post treatment discontinuation/rescue therapy observations for the SCD411 arm will have fixed value C added to the imputed values. The imputed data included the fixed penalty will be analyzed by the same MMRM model as for the primary analysis. A range of values for C will be considered to identify the point at which equivalence can no longer be claimed. Details will be provided in SAP.	~~missing prior to analysis.~~ **As a senstitivity analysis an ANCOVA model comparing the change from the baseline in BCVA at Week 8 and including baseline BCVA value as a covariate will be performed using the multiple imputed data.** Additional ~~Sensitivity~~ sensitivity analyses to the primary analysis will be performed ~~by imputing the~~ **using single imputation approaches for** post **study** ~~treatment~~ discontinuation/rescue therapy BCVA scores using the LOCF and BOCF prior to the MMRM analysis (intermittent missing data will be considered MAR and not imputed) **for both the FAS and PPS**. In addition, ~~analyses will also be repeated for the PPS using observed data as well as imputing missing data using the LOCF and BOCF approaches. An~~ **an** ANCOVA model comparing the change from baseline in BCVA at Week 8 and including **the** baseline BCVA value as **a** covariate will be performed ~~based on observed data with nonmissing observations after treatment discontinuation/receipt of rescue therapy being set to missing prior to analysis. The ANCOVA model will also be performed~~ by imputing the post **study** ~~treatment~~ discontinuation/rescue therapy BCVA values using LOCF and BOCF approaches **for the FAS and PPS**. Additionally, the MMRM analysis will be performed using data from ~~multiple imputation (~~**MI~~)~~ including a tipping point approach. Observations after	

	treatment discontinuation/receipt of rescue therapy will be set to missing prior to the MI. Multiple imputation assuming MAR will be applied to all missing data. After conclusion of MI, post **study** ~~treatment~~ discontinuation/rescue therapy observations for the SCD411 arm will have fixed value C added to the imputed values. The imputed data included the fixed penalty will be analyzed by the same MMRM model as for the primary analysis. A range of values for C will be considered to identify the point at which equivalence can no longer be claimed. Details will be provided in SAP.	
Chapter/section concerned Section 7.5.1.2 Secondary Efficacy Outcome Measures The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented. Data after the treatment discontinuation or receipt of rescue therapy will be set to missing prior to analysis. The estimated mean treatment difference at Week 52 along with the corresponding 90% and 95% CIs will also be presented using the same MMRM and ANCOVA models as used in the Week 8 analysis. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics for each visit. Sensitivity analyses will be performed using LOCF and BOCF	The estimated mean treatment difference in the change from baseline in BCVA as measured by ETDRS letter score through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the primary analysis but including data from all weeks through Week 52 will also be presented. ~~Data after the treatment discontinuation or receipt of rescue therapy will be set to missing prior to analysis.~~ The estimated mean treatment difference at Week 52 along with the corresponding 90% and 95% CIs will also be presented using the same MMRM and ANCOVA models as used in the Week 8 analysis. **As done for the Week 8, analysis will be performed using MI data, where post rescue assessments have been set to missing while including the post rescue assessments in the imputation model**. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics	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 discontinue study treatment due to AE/lack of efficacy/rescue treatment.

for post-treatment discontinuation assessments or after receipt of rescue therapy prior to performing the MMRM and ANCOVA analysis (intermittent missing data will be considered MAR and not imputed). Additionally, the MMRM analysis will be performed using data from multiple imputation (MI) including a tipping point approach. The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV are will be based on a MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI for the estimates of treatment differences at Week 8 and Week 52 will be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Data post treatment discontinuation or after receipt of rescue therapy will be set to missing prior to the MMRM analysis. No sensitivity analyses will be performed.	for each visit. Sensitivity analyses will be performed using LOCF and BOCF for post~~-treatment~~ **study** discontinuation assessments or after receipt of rescue therapy prior to performing the MMRM and ANCOVA analysis (intermittent missing data will be considered MAR and not imputed). Additionally, the MMRM analysis will be performed using data from ~~multiple imputation (~~MI~~)~~ including a tipping point approach. The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV are will be based on a MMRM model similar to the one used for the analysis of change from baseline in BCVA, with the corresponding 95% CI for the estimates of treatment differences at Week 8 and Week 52 will be presented. Raw values and changes from baseline will be summarized by treatment group using descriptive statistics. Data ~~post treatment discontinuation or~~ after receipt of rescue therapy will be set to missing prior to the MMRM analysis. **Multiple imputation will not be performed and no** ~~No~~ sensitivity analyses will be performed.	
Chapter/section concerned Section 11.2.2 Protocol Deviations ... A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is	... A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a	Section 11.2.2 was updated as per the request from the Korean MFDS to list serious protocol violations in the protocol. The update has been applied to the Korea-specific protocol amendments.

nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).	significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2). **Significant protocol deviations may include below but not limited to the following deviations:** • **ICH/GCP deviation** • **Deviation from inclusion/exclusion criteria** • **Deviation on study treatment randomization** ...	
Chapter/section concerned Section 12 Reference List The reference does not exist in version 1.0.	... **European Medicines Agency (EMA). Eylea (aflibercept). An overview of Eylea and why it is authorised in the EU. EMA/481361/2018. [cited 2020 Jul 23] Available from: https://www.ema.europa.eu/en/documents/overview/eylea-epar-medicine-overview_en.pdf**	The reference was added as it was missing in the original protocol.

Chapter/section concerned

Section 5.3 Identity of Investigational Product

Initial wording

Study Treatment Name:	SCD411	Eylea (Aflibercept)
Dosage Formulation:	Solution for intravitreal injection	Solution for intravitreal injection
Unit Dose Strength(s)/ Dosage Level(s):	Single use vial containing 0.1 mL (40 mg/mL) aflibercept biosimilar solution	Single-use vial containing 0.1 mL (40 mg/mL) aflibercept solution
Route of Administration:	Intravitreal injection	Intravitreal injection
Dosing Instructions:	0.05 mL of solution containing 2 mg	0.05 mL of solution containing 2 mg
Packaging and Labeling:	Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.	Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.

Amended or new wording

Study Treatment Name:	SCD411	Eylea (Aflibercept)
Dosage Formulation:	Solution for intravitreal injection	Solution for intravitreal injection
Unit Dose Strength(s)/ Dosage Level(s):	Single use vial containing 0.1 mL (40 mg/mL) aflibercept biosimilar solution	Single-use vial containing 0.1 mL (40 mg/mL) aflibercept solution
Route of Administration:	Intravitreal injection	Intravitreal injection
Dosing Instructions:	0.05 mL of solution containing 2 mg	0.05 mL of solution containing 2 mg
Packaging and Labeling:	Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.	**The current study will use EU-licensed Eylea as comparator drug.** Study injection formulations will be provided in vials in cartons. Each carton and vial will have the multi-country booklet label along with them which follows regulatory requirements.

Reason/Justification for Change

As per the US FDA request, the column regarding the treatment of Eylea (aflibercept) was updated to clarify the source of Eylea.

Table concerned

Table 5-1 Prohibited Medications

Initial wording

Table 5-1: Prohibited Medications

Medication/Therapy	Eye (Study Eye or Study Eye and Fellow Eye or Either)	Duration of Prohibition
Ocular therapy/treatment list		
IVT anti-VEGF treatment to treat neovascular AMD	Either eye Note: If a subject has newly diagnosed neovascular AMD or worsening neovascular AMD in fellow eye before Week 8, the same schedule is followed until Week 8 and fellow eye treatment with an anti-VEGF drug is allowed until Week 8. If a subject has newly diagnosed AMD or worsening neovascular AMD in the fellow eye after Week 8, the PI will perform ET/EOS Visits, discontinue the subject from the study, and will continue treatment of neovascular AMD in both eyes as per PI's SOC and his/her discretion.	Ever before and to EOS/ET Visit

…

Abbreviations: AE, adverse event; AMD, age-related macular degeneration; EOS, end-of-study; ET, early termination; IP, investigational product; IVT, intravitreal; NA, not applicable; PDT, photodynamic therapy; SOC, standard of care; VEGF, vascular endothelial growth factor.

Amended or new wording

Table 5-1: Prohibited Medications

Medication/Therapy	Eye (Study Eye or Study Eye and Fellow Eye or Either)	Duration of Prohibition
Ocular therapy/treatment list		
IVT anti-VEGF treatment to treat neovascular AMD	~~Either~~ **Study** eye Note: **Treatment of fellow eye will be allowed at any time during the study if** ~~If~~ a subject has newly diagnosed neovascular AMD or worsening neovascular AMD in fellow eye ~~before Week 8, the same schedule is followed until Week 8 and fellow eye treatment with an anti-VEGF drug is allowed until Week 8~~. ~~If a subject has newly diagnosed AMD or worsening neovascular AMD in the fellow eye after Week 8, the PI will perform ET/EOS Visits, discontinue the subject from the study, and will continue treatment of neovascular AMD in both eyes~~ **The fellow eye should be treated only with Eylea** as per ~~PI~~ **investigator**'s ~~SOC and his/her~~ discretion.	Ever before and to EOS/ET Visit

…

Abbreviations: AE, adverse event; AMD, age-related macular degeneration; EOS, end-of-study; ET, early termination; IP, investigational product; IVT, intravitreal; NA, not applicable; PDT, photodynamic therapy; ~~SOC, standard of care;~~ VEGF, vascular endothelial growth factor.

Reason/Justification for Change

Due to the sponsor's decision to allow treatment of fellow eye only with Eylea for the whole duration of the study, 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.

Table concerned

Table 6-1 Schedule of Events

Amended or new wording

Footnote:

a. For subjects who discontinue study treatment **and choose to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn**, ET Visit assessments are to be performed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation

c. Slit lamp examination will be performed on both eyes at ~~screening and prior to IVT injection of the study drug. Slit lamp will also be performed at any time during the visit at ET/EOS Visit~~ **all the planned scheduled visits during the study**.

d. Dilated fundoscopy will be performed on the study eye **at all the planned scheduled visits during the study, including the time** prior to IVT injection of the study drug, and within 60±30 minutes after IVT injection of the study drug~~,. Dilated fundoscopy will also be performed~~ **and** at any time during the visit at ET/EOS Visit.

e. Serum pregnancy test will be done at screening, and urine pregnancy test at baseline, ET, and EOS Visits for female subjects of child-bearing potential. If urine pregnancy test is positive, serum pregnancy test should be performed; ~~and~~ if found positive, study treatment will be discontinued and the subject should ~~complete ET Visit procedures~~ **continue with their regularly scheduled visits and assessments until Week 52 except for study treatment administration. Pregnancy cases should be followed until resolution of the pregnancy.**

f. Concurrent use of systemic or intravitreal anti-VEGF agents, IVT, subtenon, or peribulbar corticosteroids in ~~either~~ **study** eye, except as required to treat AEs, and use of photocoagulation or PDT with verteporfin are prohibited during the study. Antimicrobial drops can be used at the discretion of the investigator. For IVT corticosteroid implant, the exclusion period would be 36 months from the date of the procedure to the date of screening.

h. Rescue treatment for the study eye is not permitted at any point in time ~~if it observed that efficacy is not achieved by the study treatment, as determined by the investigator~~. Subjects can be considered for rescue treatment after Week 4 if the following conditions are met as assessed by the masked investigator: visual acuity letter score decrease of 15 letters or more from the last assessment ~~and/or increase in the central subfield thickness of 100 µm compared to the latest assessment (OCT) by the investigator~~, an increase in intraretinal fluid, subretinal fluid, or subretinal hyper-reflective material, that in the investigator's opinion is related to progression of the subject's neovascular AMD. Subjects who will receive rescue treatment need to ~~perform ET/EOS Visits and discontinue from the study~~ **discontinue the study treatment and should have the reason for treatment discontinuation documented on the Treatment Discontinuation page of the eCRF and continue with all their regularly scheduled visits and assessments until Week 52 except for study treatment administration. If a subject chooses to withdraw from the study or if, in the opinion of the investigator, the subject should be prematurely withdrawn, then the ET Visit should be completed as soon as possible after discontinuing the study treatment but no later than 28 days after discontinuation.**

i. Intraocular pressure will be measured on both eyes at screening, and on the study eye prior to IVT injection of the study drug, and 60±30 mins after IVT injection of the study drug at each visit from baseline/Day 1 to EOT (48 weeks). **If the pre-procedure IOP is equal to or greater than 30 mmHg, IVT injection will not be administered (either withheld or delayed) until IOP is decreased to acceptable safety levels as per investigator's medical judgement.** IOP should be measured after OCT and FA are completed to avoid corneal erosion. Finger counting test to be performed immediately after the IVT injection of the study drug. IOP will also be performed at any time during the ET/EOS Visit.

…

m. Hematology, chemistry, and urinalysis samples will be collected prior to IVT injection of the study drug. Urine samples will be collected prior to performing FA to avoid false elevations in urine protein values. **No pregnancy test is required for women of non-child-bearing potential. For women of child-**

bearing potential, serum pregnancy test will be performed at screening and in case of a positive urine test during the study; urine pregnancy test will be performed at the Baseline, ET and EOS Visits; T~~t~~he FSH and LH levels to be measured at screening for women of child-bearing potential. Hematology, chemistry, and urinalysis samples will also be performed at any time during the visit at ET/EOS Visit.

Reason/Justification for Change

The following changes were made to the footnotes of Table 6-1.

- Footnote a: As per the US FDA request to keep subjects in the study to continue with their regularly scheduled visits after study treatment discontinuation, the relevant text has been updated.
- Footnote c: For clarity, the timing of slit lamp examination has been updated to all planned scheduled visits during the study.
- Footnote d: For clarity, the timing of dilated fundoscopy has been updated to all planned scheduled visits during the study.
- Footnote e: As per the US FDA recommendation on collecting data after study treatment discontinuation, women who have a positive serum pregnancy test will continue with their regularly scheduled visits after study treatment discontinuation and should be followed-up until the resolution of pregnancy.
- Footnote f: As per the sponsor's decision to allow treatment of fellow eye for the whole duration of the study, prohibited medications that were initially applied to both eyes have been changed to only study eye.
- Footnote h: Part of the text on rescue treatment was updated due to the US FDA recommendation of collecting data after study treatment discontinuation due to receiving rescue treatment. Additionally, the condition for rescue treatment of an increase in the central subfield thickness of 100 μm compared to the latest assessment (OCT) by the investigator was removed.
- Footnote i: The pre-injection IOP pressure was added as per the request from the Russian regulatory agency to add this condition to ensure participant safety.
- Footnote m: The pregnancy tests were specified for women of non-child-bearing potential and women of child-bearing potential.

Table concerned

Table 6-2 Clinical Laboratory Evaluations

Initial wording

Table 6-2: Clinical Laboratory Evaluations

Clinical Chemistry	Hematology	Urinalysis	For Women
Alanine aminotransferase	Hematocrit	Bilirubin	Serum pregnancy test: All women
Albumin	Hemoglobin	Glucose	Urine pregnancy test: Women of child-bearing potential
Alkaline phosphatase	Platelet count	Ketones	
Aspartate aminotransferase	Red blood cell count	Leukocytes	
Blood urea nitrogen	White blood cell count	Nitrite	
Creatinine		Occult blood	
Creatine Kinase		pH	
Total and direct bilirubin		Protein	
		Specific gravity	
		Urobilinogen	

Amended or new wording

Table 6-2: Clinical Laboratory Evaluations

Clinical Chemistry	Hematology	Urinalysis	For Women
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Creatinine Creatine ~~K-~~kinase Total and direct bilirubin	**Basophils** **Eosinophils** Hematocrit Hemoglobin **Lymphocytes** **MCV** **Monocytes** **Neutrophils** Platelet count ~~Red blood cell~~ **RBC** count **RBC morphology** ~~White blood cell~~ **WBC** count	Bilirubin **Blood** Glucose Ketones Leukocytes **Esterase** Nitrite Occult blood pH Protein Specific gravity Urobilinogen	Serum pregnancy test: **At screening visit for** ~~All~~ women **of child-bearing potential (serum β-HCG, follicle stimulating hormone, luteinizing hormone)** Urine pregnancy test: **At baseline, ET, and EOS visits for** ~~W~~women of child-bearing potential[a]

Abbreviations: EOS, end of study; ET, early termination; HCG, human chorionic gonadotropin; MCV, mean corpuscular volume; RBC, red blood cell; WBC, white blood cell.

a. If urine pregnancy test is positive, serum pregnancy test should be performed; if found positive, study treatment will be discontinued.

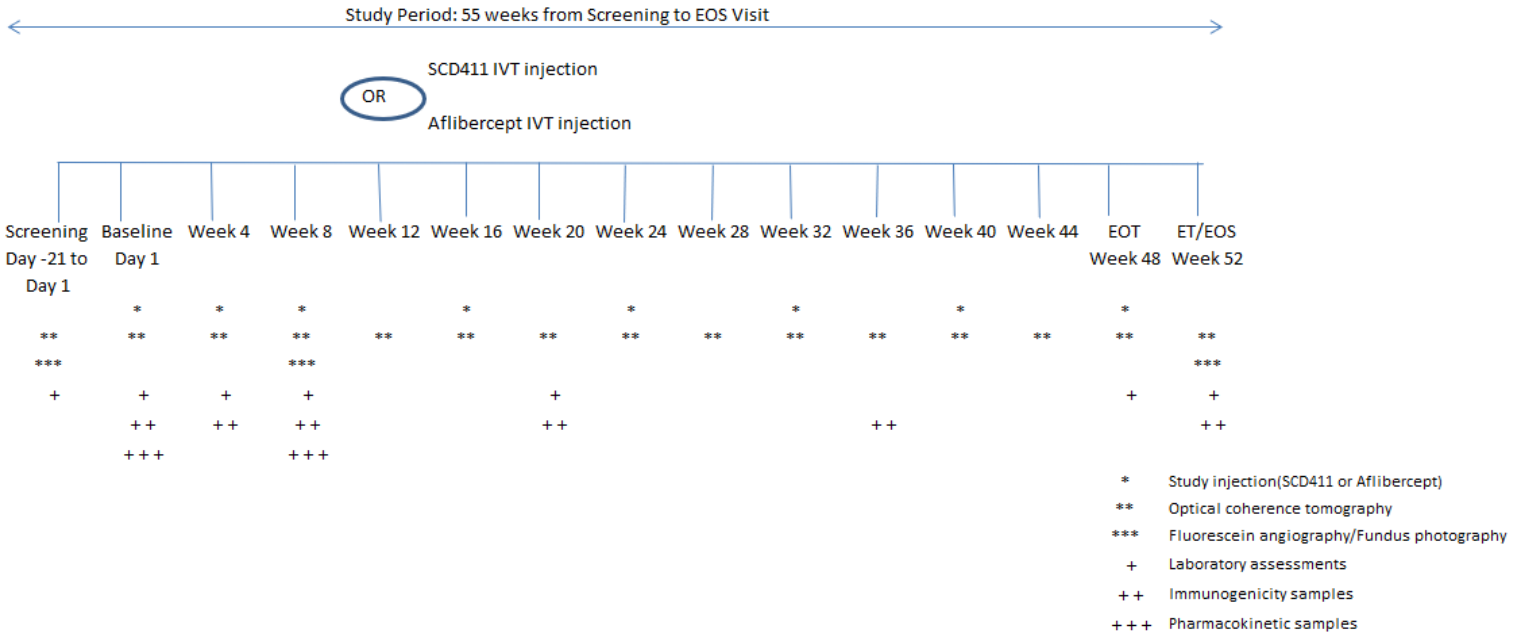
Reason/Justification for Change

The table of clinical laboratory evaluations was updated to include all the laboratory tests provided by Covance.

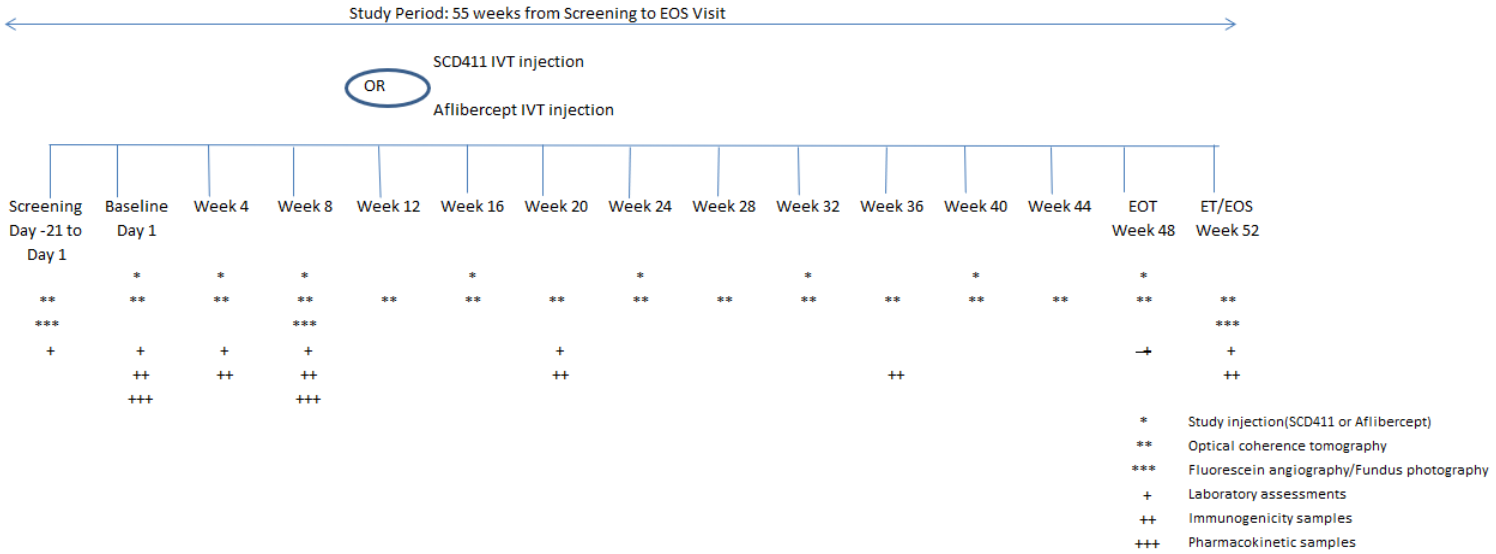
Figure concerned

Figure 3-1 Study Schema

Initial wording



Amended or new wording



Reason/Justification for Change

In Figure 3-1 Study Schema, the laboratory assessments at the Week 48 EOT Visit have been removed.