SamChunDang Pharm. Co. Ltd.
SCD411-CP101

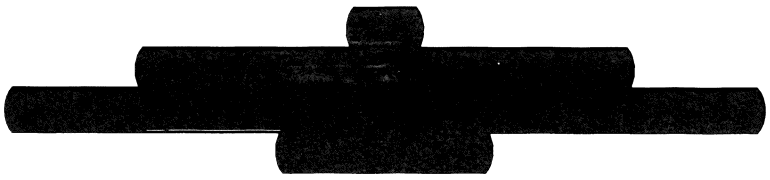
A Phase III Randomized, Double-Masked, Parallel Group, Multicenter Study to Compare the Efficacy, Safety, Tolerability, Pharmacokinetics, and Immunogenicity between SCD411 and Eylea® in Subjects with Neovascular Age-related Macular Degeneration

25May2022

Statistical Analysis Plan

Version *2.0*

Prepared by:



Confidential

SAP Version History

Version no.	Approved date	Changed part and short reason	For which event
Version 1.0	14DEC2021		IDMC 2nd meeting
Version 2.0	25MAY2022	Changed per protocol version 3.0: 1. Updated reference to 'DHHS 2011 [Eylea Statistical Review, Appendix Tables A.1 and A.2]' in section 4.1. 2. Updated missing data assumption of tipping point approach in section 4.5.1. 3. Added analysis of 'Relationship to IVT injection procedure' in section 4.5.2 and section 9.1. 4. Added treatment compliance category of '>100' to satisfy the analysis in section 7.2.1. 5. Deleted standard deviation from the description of BCVA and OCT figure in section 8.4.1 and 8.4.2 by referring to Eylea® study. 6. Changed all 'patients' to 'subjects' through whole SAP in order to keep the text uniform. 7. For PK analysis and PK sampling time out of window, changed 'excluded from the calculation' to 'included in the calculation' in section 10.2. 8. In section 10.3: WinNonlin version updated from 8.0 to 8.3; Renamed PK Parameters to be consistent with protocol (T_{max} to t_{max}, AUC_{tau} to $AUC_{0\text{-}tau}$, AUC_{inf} to $AUC_{0\text{-}inf}$); AUC_{last} parameter replaced with $AUC_{0\text{-}t}$ to be consistent with protocol;	Interim Analysis and Final Analysis

		Additional text added to explain the reason for missing parameters “If the number of data points used to calculate λz is less than 3 (not including C_{max}), or the calculated coefficient of determination (R^2) value for λz is < 0.800, λz and the parameters that utilize λz for determination $AUC_{0\text{-}inf}$, $t_{1/2}$ will not be reported”. 9. Updated wording for interim analysis per protocol version 3.0 in section 12. 10. Updated wording for Independent Data Monitoring Committee per protocol version 3.0 in section 13.	

TABLE OF CONTENTS

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}inf}$	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
BLQ	limit of quantification
CI	confidence interval
C_{max}	maximum plasma concentration
CM	concomitant medication
CNV	choroidal neovascularization
CRO	contract research organization
CRT	central retinal thickness
CS	clinically significant.
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end-of-study
EOT	end-of-treatment
ET	early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FAS	full analysis set
FDA	US Food and Drug Administration
FP	fundus photography

FSH	follicle-stimulating hormone
GMT	geometric mean titer
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
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MAR	missing at random
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	modified full analysis set
MI	multiple imputation
MMRM	mixed-effects model for repeated measures
NCS	not clinically significant
NAb	neutralizing antibodies
OCT	optical coherence tomography
PDT	photodynamic therapy
PI	principal investigator
PK	Pharmacokinetic
PlGF	placental growth factor
PMDA	Pharmaceuticals and Medical Devices Agency
PPS	per-protocol set
PT	preferred term
SAE	serious adverse event
SAF	safety set
SD	standard deviation
SOC	standard of care
$t_{1/2}$	elimination half-life
t_{max}	time to reach the maximum plasma concentration

TEAE	treatment-emergent adverse event
TOST	2 one-sided tests
ULOQ	upper limit of quantification
VA	visual acuity
VEGF	vascular endothelial growth factor
WHODD	World Health Organization Drug Dictionary

1. Introduction

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).

Neovascular (wet) age-related macular degeneration (AMD) is characterized by pathological choroidal neovascularization (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).

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.

2. Objectives

2.1. Primary Objective

- 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

- 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

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

3. Investigational Plan

3.1. Overall Study Design and Plan

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 (Appendix 15.1). A schematic of the study design is presented in Figure 1.

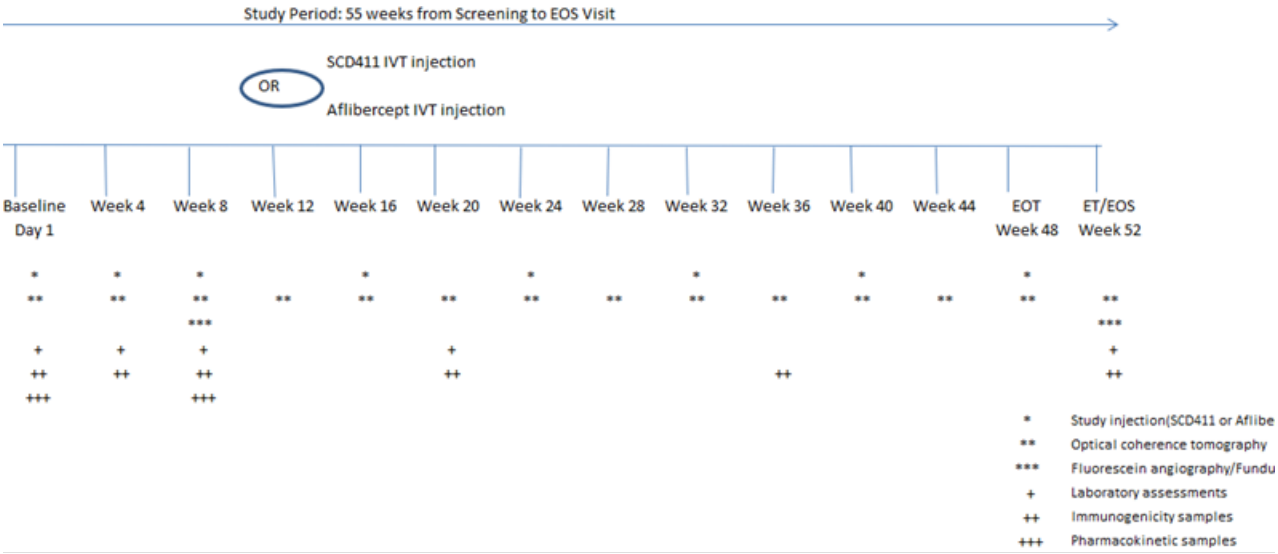
This study includes a screening duration up to 3 weeks, treatment duration up to 48 weeks, and follow-up duration up to 4 weeks; thus, the total duration of study participation is approximately up to 55 weeks.

All subjects will be assessed once every 4 weeks as detailed in the Schedule of Events (Appendix 15.1). 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 adverse event (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 13.

An interim analysis will be performed once approximately 200 subjects complete Week 52 and all subjects complete Week 24 or have discontinued early from the study with details given in Section 12.

Figure 1: Study Schema



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

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. 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.

3.2.3. Exploratory Endpoints

PK 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. Blood samples, for determination of concentrations of SCD411 and aflibercept, will be collected at the timepoints specified in the Schedule of Events (Appendix 15.1). As per the Schedule of Events, additional visits will be arranged for collecting the PK blood samples. 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.

3.3. 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.

Potential intercurrent events to the estimands are listed in Table 1. The relationship between objectives, endpoints and estimands are listed in Table 2-1 and Table 2-2 separately.

Table 1: Intercurrent Event Types

Label	Intercurrent Event Type
IcEv1 (Treatment discontinuation without receipt of rescue therapy)	Discontinuation of study eye treatment with continued participation in study without receipt of rescue therapy
IcEv2 (Rescue therapy)	Receipt of rescue therapy in the study eye
IcEv3 (Study discontinuation)	Discontinuation from study, regardless of reason

Abbreviation: IcEv, intercurrent event.

Table 2-1 Objectives, Endpoints, and Estimands (at Week 8)

Objective	Estimand Label	Endpoint	Estimand Description
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	Primary Estimand	Change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 8	Mean treatment difference in BCVA change from baseline at Week 8 as if subjects do not receive rescue therapy
As above	Secondary Estimand	As above	Mean treatment difference in BCVA change from baseline at Week 8 while allowing for receipt of rescue therapy

Table 2-2: Objectives, Endpoints, and Estimands (at Week 52)

Objective	Estimand Label	Endpoint	Estimand Description
To prove the equivalence of SCD411 as compared to Eylea (aflibercept) in BCVA after 52 weeks of treatment among subjects with wet AMD	Primary Estimand	Change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 52	Mean treatment difference in BCVA change from baseline at Week 52 as if subjects do not receive rescue therapy
As above	Secondary Estimand	As above	Mean treatment difference in BCVA change from baseline at Week 52 while allowing for receipt of rescue therapy

3.4. Treatments

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. The study treatment solution is stored in glass vial. One vial delivers a dose of 2 mg aflibercept or SCD411 in 50 µL. Each vial should only be used for the treatment of a single eye.

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 (WHODD) and this information should be recorded in the eCRF.

Study treatment will be dispensed every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48 as detailed in the Schedule of Events (Appendix 15.1). 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.

3.4.1. 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, intraocular pressure (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.

3.4.2. 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.

3.5. Dose Adjustment/Modifications

Dose reductions will not be allowed.

4. General Statistical Considerations

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

In general, continuous variables will be summarized descriptively using the number of observations (n), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (Min), and maximum (Max). Categorical variables will be summarized using frequency counts and percentages.

Descriptive statistics for continuous variables in summary tables will include the number of subjects in the analysis (n), mean, SD, median, first quartile (Q1), third quartile (Q3) 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.

For summary precision, mean, median, Q1 and Q3 will have one more decimal place than the reported value, SD will have two more decimal places than the reported value, minimum and maximum will have the same decimal place as the reported value. Percentages and 95% CI will have one decimal place. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values.

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

Subgroup analyses will be performed by region/country (Japan, non-Japan). Demographics and baseline characteristics, safety, efficacy and immunogenicity endpoints may be analyzed in

subgroups. Subgroup summaries will be descriptive only with no statistical hypothesis testing performed.

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

4.1. Sample Size

The equivalence margin agreed upon with EMA and PMDA was determined using the data presented from MARINA (and ANCHOR) and VIEW studies. These data were used to estimate the efficacy of aflibercept compared 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 statistical justification of the 3.8 letter equivalence margin is described in Section 4.1.1.

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 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.

4.1.1. Statistical Justification of the 3.8 Letter Equivalence Margin

For all purposes, the clinical equivalence question of 3.8 letters is to demonstrate that 3.8 letters of difference between treatments is immaterial to a clinician in determining the choice of treatment for their patients.

As there is no direct comparison in the literature of Eylea to placebo/sham an indirect comparison is made by first comparing Eylea to Lucentis and then Lucentis to Placebo. The primary efficacy endpoint for the biosimilar comparison will be made at 8 weeks. As the primary efficacy endpoints for the phase III studies for Lucentis (Marina, Anchor) and Eylea (VIEW 1, VIEW 2) were at 52 weeks, there is limited published data for the BCVA mean change from baseline at Week 8.

The Statistical Review from the FDA Summary Basis of Approval for the original Eylea AMD submission contains appendices which provide summary statistics on the ITT observed data for the BCVA mean and BCVA mean change from baseline by study visit, including week 8. This data, along with data from the Lucentis label will be used to estimate a difference between Eylea and Sham at Week 8 from the estimated 95% CI lower limit for the difference between (Lucentis – Sham).

	Eylea			Lucentis			Difference
Study	n	Mean	SD	n	Mean	SD	(Eylea – Lucentis)
VIEW 1	298	7.5	10	293	7.1	9.95	0.4
VIEW 2	305	5.3	9.2	287	6.5	8.6	-1.2
Average			9.6			9.275	-0.4

From VIEW 1 and VIEW 2, the average SD for BCVA change from baseline at 8 weeks for Lucentis is 9.3 letters. From the Lucentis label, at Week 52, the SD for BCVA change from baseline is 17.9 letters for sham and 14.1 for Lucentis, a Sham/Lucentis ratio of ~1.3. The Lucentis average SD for BCVA change from baseline at week 8 of 9.3 letters from VIEW 1 and VIEW 2 studies is inflated by 1.3 to estimate the SD for Sham arm at Week 8 of 12.1 letters.

From the Lucentis label, for AMD-1 study (Marina), the BCVA mean change from baseline at Week 8 shows an approximate 2.5 letters decrease for sham and an approximate 5 letters increase for Lucentis. The Marina study enrolled 229 sham subjects and 230 Lucentis subjects. These numbers with the estimated SD values will be used to estimate the 95% CI lower limit for the difference (Lucentis – Sham) at Week 8.

Study	Lucentis			Sham			Difference (Lucentis – Sham)		Lower 95% CI (z=1.96)
	n	Mean	SD	n	Mean	SD	Estimate	Pooled SE	
Estimate for Marina	230	5.0	9.3	229	-2.5	12.1	7.5	1.0076	5.5249

Adjusting the estimated 95% CI lower limit for (Lucentis – Sham) with the average difference (Eylea – Lucentis) from the View 1 and View 2 studies, the estimate of minimal effect size for Eylea to sham is (5.5 – 0.4) = 5.1 letters for Week 8 which is larger than the proposed margin of 3.8 letters. Based upon the NEI CATT study which compared efficacy across anti-VEGF products, an acceptable non inferiority margin was defined as that which is smaller than the believed smallest effect size for the reference treatment. This further corroborates the case as 3.8 is less than 5.1.

4.2. Randomization, Stratification, and Blinding

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 Interactive Response Technology (IRT). Randomization will be stratified by participation in the PK substudy (yes/no). Subjects in Israel will not participate in the PK substudy. Randomization will also be stratified by subjects enrolled in Japan. 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. Biostatistics will generate the randomization schedule using SAS® software Version 9.4 for the IRT, which will link sequential subject randomization numbers to treatment codes. The randomization schedule will be created by the dedicated randomization team, stored in a separate project area, and will be blinded to the project team with the exception for the unblinded investigator involved in performing the IVT injections.

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

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 unblinded because of a medical emergency, the principal investigator (PI) may unblind 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 unblinded information with the sponsor and monitoring team. The treatment assignment will be unblinded through IRT. Reasons for treatment unblinding 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.

4.3. Analysis Set

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

4.3.1. Full Analysis Set (FAS)

The Full Analysis Set includes all randomized subjects who received at least 1 injection of the study drug. Subjects will be analyzed according to the treatment group to which they were randomized. The primary set for efficacy analysis will be the FAS.

4.3.2. Modified Full Analysis Set (mFAS)

The Modified Full Analysis Set includes all randomized subjects who received at least 1 injection of the study drug and had at least 1 postbaseline BCVA assessment in the study eye. Subjects will be analyzed according to the treatment group to which they were randomized. PMDA requires the efficacy analysis also need to be conducted based on mFAS without multiple imputation as supportive analysis.

4.3.3. Per-Protocol Set (PPS)

The Per-Protocol Set includes all subjects in the FAS, excluding those with significant protocol deviations. Subjects will be analyzed according to the treatment group to which they were randomized. For the EMA submission, the primary efficacy endpoint must also meet equivalence for PPS.

4.3.4. Safety Set (SAF)

The Safety Analysis Set includes all subjects receiving at least 1 injection of the study drug. Subjects will be analyzed according to the treatment group they actually received. The SAF will be the primary analysis set for safety, tolerability, and immunogenicity analyses.

4.3.5. Pharmacokinetic Analysis Set (PK Set)

The Pharmacokinetic Analysis Set is the subset of subjects in FAS who have sufficient evaluable blood samples. A subset of 40 subjects (20 per group) will be selected for collection of PK samples. Subjects will be analyzed according to the treatment group they actually received. The PK set will be used for estimation of PK endpoints.

4.4. Analysis Window/Visit

For non-efficacy analysis, no analysis window mapping will be applied. Any scheduled and unscheduled visits will be reported by the nominal visits reported on the eCRF. As Early Termination (ET) and Week 52 are recorded together as 'Week 52 ET' on the eCRF, they will be separated as 'Week 52' and 'Early Termination' during the analysis.

For efficacy analysis, the analysis visits will be handled in the same way as non-efficacy analysis except for the ET visit. The ET assessments will be summarized based on visit window of when the visit occurred (e.g., if the subject discontinued study at Week 12, the ET assessment will be included in the Week 12 by-visit summaries). Below is the derivation rule:

a. If visit date of ET – visit date of the previous scheduled visit <=14, then the analysis visit window for ET will be the same as the previous scheduled visit. If there are two valid records in a scheduled visit, only the record closer to the target study day will be used for summary statistics and analyses.

b. If visit date of ET – visit date of the previous scheduled visit >14, then the analysis visit window for ET will be the previous scheduled visit + 4 weeks (e.g., the analysis visit for ET will be Week 12 if the previous scheduled visit is Week 8).

4.5. Handling of Missing Data

Data will be presented in the listings as reported. For summaries and analysis, the following conventions apply.

4.5.1. BCVA Data

For the efficacy analysis, missing BCVA data will be imputed using several imputation methods.

- **Multiple Imputation (MI)** is a statistical technique that replaces each missing value with a set of plausible values that represent the uncertainty about the right value. MI has the advantages such as providing results in unbiased estimates, more validity than ad hoc approaches to missing data; using all available data, preserving sample size and statistical power; providing readily interpreted results. The details are described in Section 8.2.1.

- **Tipping point** approach is an alternative strategy for handling missing data. This analysis is under the missing not at random assumption and doesn't involve model uncertainty and assumptions. It can be used to evaluate the robustness of statistical significance when the extent of missing data is reasonable. The details are described in Section 8.2.3.
- **Single imputation** methods (BOCF, LOCF) will be used for the sensitivity analysis.
    - **LOCF**: Last Observation Carried Forward, this analysis type imputes missing data by using a subject's data from their most recent visit.
    - **BOCF**: Baseline Observation Carried Forward, this analysis type imputes missing data by using a subject's baseline result.

4.5.2. Adverse Event Data

Missing information regarding 'Relationship to Study Treatment' or 'Relationship to IVT injection procedure' or 'Severity' will be imputed as related to study treatment and severe, as the worst-case scenario.

Partially missing AE start dates will be imputed as described in Appendix 15.2, but partially missing AE end dates will not be imputed. Completely missing start date will remain missing, with no imputation applied.

In listings of AE data, the partial dates as entered will be displayed.

4.5.3. Prior/Concomitant Medication Data

Partially missing concomitant medication (CM) start or end dates will be imputed as described in Appendix 15.2. Completely missing start or end dates will remain missing, with no imputation applied.

In listings of CM data, the partial dates as entered will be displayed.

5. Subject Disposition

5.1. Disposition

The number of subjects who were randomized and not randomized, the eligibility criteria met/failed will be summarized based on all screened subjects. The number and percentage of screen failure subjects will be summarized for each exclusion criteria met and/or inclusion criteria failed. A listing will be provided for subjects who were randomized.

Disposition of all randomized subjects will be summarized by treatment group including:

- Full Analysis Set

- Modified Full Analysis Set
- Safety Set
- Per-Protocol Set
- Pharmacokinetic Analysis Set
- Number of subjects who completed study treatment
- Number of subjects who prematurely discontinued the study treatment
- Primary reason for treatment discontinuation
- Number of subjects who completed week 8
- Number of subjects who completed study
- Number of subjects who prematurely discontinued the study (early termination)
- Primary reason for study discontinuation

Primary reasons for treatment/study discontinuation collected on the eCRF will be summarized with the following categories separately:

- Death
- Adverse Event
- 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 (e.g., a suspicion of fraud, the subject enrolling in multiple clinical studies, lack of compliance, etc.) other than that of an AE
- 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
- The subject has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal
- The subject withdraws consent

- A subject misses any of first 2 doses (IVT injection of IP at Week 0 [Day 1] or Week 4) after randomization
- 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
- Other

Disposition data will be listed by subjects as collected based on the all randomized subjects.

5.2. 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 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.

Protocol deviations will be summarized in a table and displayed in a listing based on the all randomized subjects.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics data to be analyzed will include age, sex, race, ethnicity, country, weight, height, and body mass index based on the FAS.

Descriptive statistics will be calculated for the following continuous characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) (kg/m^2), derived by Weight in kilograms / (Height in meters)^2

Number and percentage of subjects will be provided for the following categorical variables:

- Sex (Male, Female)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Multiple, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Country

6.2. Baseline Ocular Characteristics

Following baseline ocular characteristics will be summarized for study eye only based on the FAS.

Descriptive statistics will be calculated for the following continuous characteristics:

- BCVA Score (Letters)
- CRT (um)
- Total Lesion Area (mm^2)
- CNV Area (mm^2)
- Leakage Area (mm^2)
- IOP (mmHg)

Number and percentage of subjects will be provided for the following categorical variables:

- Anterior Chamber Flare Grade (0, 1+, 2+, 3+, 4+)
- Anterior Chamber Cells Grade (0, 0.5+, 1+, 2+, 3+, 4+)
- Vitreous Cells Grade (0, Trace, 1, 2, 3, 4)
- Vitreous Haze Grade (0, 1, 2, 3, 4, 5)
- Slit Lamp Examination Overall Assessment (‘Normal’, ‘Abnormal, NCS’, ‘Abnormal, CS’)
- Vitreous Overall Assessment (‘Normal’, ‘Abnormal, NCS’, ‘Abnormal, CS’)
- Macula Overall Assessment (‘Normal’, ‘Abnormal, NCS’, ‘Abnormal, CS’)
- Retina Overall Assessment (‘Normal’, ‘Abnormal, NCS’, ‘Abnormal, CS’)
- Optic Nerve Overall Assessment (‘Normal’, ‘Abnormal, NCS’, ‘Abnormal, CS’)

6.3. Medical History

Medical history will be summarized based on the SAF. Medical history will be coded according to Medical Drug Regulatory Activities (MedDRA) version 23.0 or above and will be summarized

by system organ class (SOC) and preferred term (PT), with SOCs sorted alphabetically and PTs within each SOC in descending order of frequency.

Ocular and non-ocular medical histories are captured separately on the eCRF. Ocular medical history will be summarized separately from non-ocular medical history. Ocular medical history will be summarized for the study eye and fellow eye. Also, a by-subject listing of ocular and non-ocular medical histories will be presented.

6.4. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations noted in the eCRF will be presented for all informed consent subjects in a data listing.

7. Treatments and Medications

7.1. 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 World Health Organization Drug Dictionary (WHODD) during the study. Medications will be summarized based on the SAF, sorted by alphabetical order of Anatomical Therapeutic Chemical (ATC) level, and then descending frequencies of preferred name. Also, a by-subject listing of prior and concomitant medications will be presented.

Partial missing start or end dates will be imputed as described in Appendix 15.2 for medications analysis.

7.1.1. Prior Medications

Prior medications are defined as medications that start before the first dose of study drug, regardless of when the medications stop. Medication with a missing start date will be considered to have a start date before the first dose of study drug.

Ocular prior medications will be summarized separately from non-ocular prior medications. Ocular prior medications will be summarized for the study eye and fellow eye.

7.1.2. Concomitant Medications

Concomitant medications are defined as medications first received at or after the first dose of study drug, medications received before first dose of study drug and continued after first dose, or medications with missing stop date. Medication with a missing stop date will be treated as a continuing medication. 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.

Ocular concomitant medications will be summarized separately from non-ocular concomitant medications. Ocular concomitant medications will be summarized for the study eye and fellow eye.

7.2. Study Treatments

Study treatment will be dispensed every 4 weeks for the first 3 injections and every 8 weeks thereafter until Week 48 as detailed in the Schedule of Events (Appendix 15.1). 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).

7.2.1. Extent of Exposure and Compliance

Extent of exposure will be summarized on study eye only for duration of exposure, planned number of injections, actual number of injections, compliance by treatment group. The number (%) of subjects who have injection interruptions, and the reasons will be summarized. The number (%) of subjects in each compliance category (>100, >= 75 to <=100, >=50 to <75, >=25 to <50, <25, Not Calculable) will also be summarized.

Duration of exposure (days) = end date of study treatment – start date of study treatment + 1.

Treatment Compliance：

Planned number of injections refers to the total planned injections as per the protocol up to the last date of study drug administration.

Actual number of injections refers to the total actual injections administered, over the duration for which the subject is on the study treatment as documented in the Study Drug Injection page of (e)CRF.

Treatment Compliance (%) = actual number of injections / planned number of injections *100.

Subject level listings of all injections administered (including fellow eye treatment) along with injection interruption reasons will be provided.

The SAF will be used for all summaries and listings of study treatment.

8. Efficacy Analysis

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.

Unless otherwise specified, all primary and secondary efficacy analyses with statistical hypothesis testing performed will be analyzed for the study eye only. Assessments collected for the fellow eye will be summarized using descriptive statistics and presented in listings.

8.1. Estimands and Strategies for Managing 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 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 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 therapy 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 after 8 weeks of treatment, 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 therapy 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. The analysis will be assessed for both the FAS and PPS. 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 therapy 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 after 8 weeks of treatment, 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 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 therapy 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.

8.2. Primary Efficacy Endpoint

The primary endpoint is the change from baseline in BCVA as measured by ETDRS letters score or 2702 charts at Week 8.

8.2.1. 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 Mixed-effects Model for Repeated Measures (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. MMRM

analysis will be performed based on multiply imputed data sets. 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. The analysis will be based on both the FAS and PPS.

Primary Estimand (Week 8):

Data after receipt of rescue therapy will be set to missing. Post rescue therapy data or missing data after discontinuation from study will be imputed employing Multiple Imputation (MI) assuming missing at random (MAR) using randomized treatment-based Markov Chain Monte Carlo (MCMC) methodology. Multiple Imputation model impute 50 values for each missing value. The multiply imputed data sets are then analyzed by using MMRM analysis. Rubin's method will be used to pool estimates and standard errors from MMRM across the 50 multiply imputed datasets.

Secondary Estimand (Week 8):

Data post rescue therapy will not be set to missing, others are the same as the analysis for primary estimand.

8.2.2. Assumption Testing

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.

8.2.3. Sensitivity Analysis

The sensitivity analysis will be performed based on the FAS and PPS. Data after receipt of rescue therapy will be set to missing.

An analysis of covariance (ANCOVA) model comparing the change from baseline in BCVA at Week 8 and including the change from baseline as dependent variable, treatment group as fixed effect and baseline BCVA score as a covariate will be performed using multiply imputed data sets.

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 change from baseline as dependent variable, treatment group as fixed effect and baseline BCVA score as a covariate will be performed by imputing the post study discontinuation/rescue therapy BCVA values using LOCF and BOCF approaches.

Additionally, the MMRM analysis will be performed using data from MI including a tipping point approach. 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. The tipping point analysis is used to investigate robustness of results.

8.2.4. Supportive Analysis

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

8.3. Secondary Efficacy Endpoint

The secondary efficacy endpoints include: change from baseline in BCVA at Week 52, change from baseline in CRT at Week 8 and Week 52, change from baseline in CNV area at Week 8 and Week 52, percentage of subjects who gain at least 15 letters in BCVA at Week 8 and Week 52.

8.3.1. Secondary Analysis

The estimated mean treatment difference in the change from baseline in BCVA through 52 weeks along with the corresponding 90% and 95% CIs from the same MMRM model as used in the Week 8 analysis but including data from all weeks through Week 52 will also be presented based on the FAS and PPS.

Primary Estimand (Week 52):

Data after receipt of rescue therapy will be set to missing. Post rescue therapy data or missing data after discontinuation from study will be imputed employing MI. The analysis method will be the same as in primary estimand at Week 8.

The estimated mean change from baseline of BCVA at week 8 and week 52 based on the FAS and PPS will be plotted, with corresponding 95% confidence intervals.

Secondary Estimand (Week 52):

Data post rescue therapy will not be set to missing, others are the same as the analysis for primary estimand.

The analysis of change from baseline in CRT as assessed by OCT or change from baseline in CNV area 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% CIs for the estimates of treatment differences at Week 8 and Week 52 presented. Data after receipt of rescue therapy will be set to missing prior to the MMRM analysis. Multiple imputation will not be performed. The FAS will be used for the analyses.

The percentage of subjects who gain ≥15 letters in BCVA 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. 95% CI for the proportions in each treatment arm will be calculated using Clopper-Pearson method. 95% CI for the difference in proportions between treatment arms is based on exact unconditional confidence interval. 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 (i.e., non-responder imputation). The FAS will be used for the analyses.

The percentage of subjects who gain ≥15 letters in BCVA at week 8 and week 52 based on the FAS will be plotted, with corresponding 95% confidence intervals.

8.3.2. Sensitivity Analysis

The sensitivity analysis will be performed for the analysis of BCVA through Week 52 based on the FAS and PPS. Data after receipt of rescue therapy will be set to missing.

As done for Week 8, the same ANCOVA model comparing the change from baseline in BCVA at Week 52 and including the change from baseline as dependent variable, treatment group as fixed effect and baseline BCVA score as a covariate will be performed using multiply imputed data sets.

Additional 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.

8.4. Efficacy Assessments

BCVA will be measured at sites by certified study staff. All imaging efficacy assessments (OCT, FA/FP) will be interpreted by a central reading center. Efficacy assessments will be performed at the indicated visits in the Schedule of Events (Appendix 15.1).

All efficacy assessments will be summarized and listed with no statistical hypothesis testing performed based on the FAS.

8.4.1. Best Corrected Visual Acuity (BCVA)

BCVA is measured by ETDRS letter score or 2702 charts.

BCVA 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 visual acuity 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.

Raw values of BCVA and change from baseline will be summarized by treatment group using descriptive statistics at each visit for study eye and fellow eye separately. Data after receipt of rescue therapy will be set to missing. A by-subject listing will also be provided for both eyes. The mean change from baseline of BCVA for study eye by visit based on FAS will be plotted.

8.4.2. Optical Coherence Tomography (OCT)

Central Retinal Thickness (CRT) is measured by OCT.

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 must be registered by the central reading center from Screening to Week 52 (EOS visit) or ET Visit

Raw values of CRT and change from baseline will be summarized by treatment group using descriptive statistics at each visit for study eye. Data after receipt of rescue therapy will be set to missing. Other selected assessments performed by OCT may also be summarized using descriptive statistics at each visit for study eye. A by-subject listing will be provided for all the selected assessments performed by OCT.

The mean change from baseline of CRT for study eye by visit based on FAS will be plotted.

8.4.3. Fluorescein Angiography (FA) and Fundus Photography (FP)

Choroidal neovascularization (CNV) area is assessed by FA and FP.

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 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, a subject must use the same FA/FP device consistently from Screening to Week 52 (EOS Visit) or ET Visit.

Raw values of CNV area and change from baseline will be summarized by treatment group using descriptive statistics at each visit for study eye. Data after receipt of rescue therapy will be set to missing. Other selected assessments performed by FA/FP may also be summarized using descriptive statistics at each visit for study eye. A by-subject listing will be provided for study eyes for all the selected assessments performed by FA/FP.

9. Safety Analysis

The purpose of this section is to define the safety endpoints for the study, which consist of incidence of AEs (or Treatment-emergent AEs (TEAEs)), laboratory test results, and vital signs. Other safety parameters include ECG results, slit lamp examination, dilated fundoscopy, IOP and vision check.

All safety analyses will be based on the SAF. No formal statistical analysis of the safety data will be performed.

9.1. Adverse Events

Adverse Events are one of the secondary safety endpoints. Summary of AEs will be based on the SAF.

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.

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.

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or above. Unless otherwise specified, AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), with SOCs sorted in the alphabetical order and PTs within each SOC in descending order of subject incidence. Partial missing AE start dates will be imputed based on Appendix 15.2.

When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if subjects reported multiple events under the same SOC and/or PT.

Ocular TEAEs will be summarized separately from non-ocular TEAEs. Ocular TEAEs will be summarized for the study eye and the fellow eye. Also, by-subject listings of ocular and non-ocular AEs will be presented.

9.1.1. Incidence of Adverse Events

An overall summary of TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any TEAE
- Any TEAE Related to Study Drug
- Any TEAE Related to Injection Procedure
- Any Severe TEAE
- Any Serious TEAE
- Any Serious TEAE Related to Study Drug
- Any Serious TEAE Related to Injection Procedure
- Any TEAE Leading to Dose Interruption
- Any TEAE Leading to Treatment Discontinuation
- Any TEAE Leading to Study Discontinuation

- Any TEAE Leading to Death

Also, separate listings containing individual subject adverse event data for all AEs, SAEs, AEs leading to dose interruption, AEs leading to treatment discontinuation, AEs leading to study discontinuation, and AEs leading to death will be provided separately.

In addition, any treatment-emergent AE of Special Interest (AESI) may also be summarized.

9.1.2. Relationship of Adverse Events to Study Drug or IVT Injection Procedure

Study drug or injection procedure related TEAEs will be summarized by SOC and PT. Study drug or injection procedure related AEs are those with a relationship to study drug or injection procedure of 'Related' based on the eCRF page. AEs assessed as 'Not Related' will be considered unrelated for reporting purpose. Missing relationship will be counted as related to study drug or injection procedure.

9.1.3. Severity of Adverse Event

TEAEs will be rated as Mild, Moderate, or Severe based on 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.

The adverse events with missing severity grade will be imputed as 'Severe'. In the TEAE severity table, if a subject reports multiple occurrences of the same TEAE, only the most severe (mild < moderate < severe) occurrence will be presented.

9.1.4. Serious Adverse Events

Serious AEs are those identified on the eCRF as meeting the protocol defined serious criteria. Serious TEAEs will be summarized by SOC and PT. A by-subject listing will also be provided for all SAEs.

9.1.5. Adverse Events Leading to Treatment Discontinuation

TEAEs with a study treatment action taken of 'Drug Withdrawn' will be summarized by SOC and PT. A by-subject listing will also be provided for all adverse events leading to treatment discontinuation.

9.1.6. Adverse Events Leading to Study Discontinuation

TEAEs leading to study discontinuation (the primary reason for subject terminated study early recorded as 'Adverse Event' on the eCRF) will be summarized by SOC and PT. A by-subject listing will also be provided for all adverse events leading to study discontinuation.

9.1.7. Death

TEAEs with AE outcome as 'Fatal' (recorded as 'Death Related to Adverse Event' on the eCRF) will be summarized by SOC and PT. A by-subject listing will also be provided for all adverse events leading to death.

9.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations are one of the secondary safety endpoints. Summary of laboratory results will be based on the SAF.

Clinical laboratory assessments (chemistry, hematology, urinalysis, pregnancy tests) will be performed as indicated in the Schedule of Events (Appendix 15.1). Collection of blood and urine will occur at the study site and the samples will be shipped to a central laboratory for analysis. On injection visits, 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.

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/EOS Visits; the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels to be measured at screening for women of child-bearing potential.

Table 3 presents the laboratory analyses that will be performed during the study.

Table 3: 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.

If any laboratory value falls below the lower limit of quantification (LLOQ), the value of half of the LLOQ will be taken (e.g. <0.5 will become 0.25); if any laboratory value falls above the upper limit of quantification (ULOQ), the value of the ULOQ will be taken (e.g. >1000 will become 1000). The imputed values will be used for summaries but left as recorded in the listing.

Laboratory test variables will be summarized by treatment group and visits using descriptive statistics and 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.

9.3. Vital Sign Measurements

Vital sign measurements are one of the secondary safety endpoints. Summary of vital signs will be based on the SAF.

Vital signs consist of body temperature, respiratory rate, blood pressure (systolic and diastolic), and heart rate measurement. Vital sign measurements will be performed on all the scheduled visits. 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.

Vital sign measurements will be summarized using descriptive statistics for reported values and change from baseline at each scheduled visit by treatment group. Vital signs data for all safety subjects will also be presented in a listing.

9.4. Electrocardiogram

An ECG could be assessed by the investigator only at Screening, Week 8, and at the EOS/ET Visit. Interpretation results include 'Normal', 'Abnormal, Not Clinically Significant' and 'Abnormal, Clinically Significant'.

The ECG interpretations will be summarized using descriptive statistics at each visit based on the SAF. Electrocardiogram data for all safety subjects will also be presented in a listing.

9.5. Ophthalmological assessments

Routine ophthalmological examinations will be performed at indicated visits in the Schedule of Events (Appendix 15.1). Summary of ophthalmological examinations will be based on the SAF.

9.5.1. Slit Lamp Biomicroscopy

Slit lamp examination (anterior chamber flare, anterior chamber cells, vitreous cells opacities and haze, overall assessment) will be performed on both eyes at all the planned scheduled visits during the study 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. The grading scales can be found from protocol Section 13.1 (Appendix 1) and Section 13.2 (Appendix 2).

The results of slit lamp examination will be summarized using descriptive statistics at each visit for study eye and fellow eye separately. A by-subject listing will also be provided.

9.5.2. Dilated Fundoscopy

Dilated fundoscopy includes evaluation of retina and vitreous (vitreal overall assessment; macular overall assessment; retina overall assessment; and optic nerve overall assessment). 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.

The results of slit lamp examination will be summarized using descriptive statistics at each visit and applicable time point for study eye. A by-subject listing will also be provided.

9.5.3. Intraocular Pressure (IOP) and Vision Check

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 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). 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. IOP will also be performed at any time during the ET/EOS Visit.

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

The results of IOP will be summarized using descriptive statistics at each visit and applicable time point for study eye. A by-subject listing will be provided for study eyes including IOP and vision check results.

10. Pharmacokinetics

10.1. Data Handling

Data rounding specifications for PK data are documented in the PK TLF shells.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics. For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing.

10.2. Plasma Concentrations

Serial blood samples will be collected at the following time points for PK assessment:

- *Day 1 (week 1, First dose/injection): Pre-dose, Days 1, 3, 7, 14 and 28 post first dose*
- *Day 57 (week 8, Third dose/injection): Pre-dose, Days 1, 3, 7, 14 and 28 post third dose*

The permitted windows for PK sample collection are as follows:

Pharmacokinetic time points	**Window**
+1 day	± 1 hour
+ 3 days	± 2 hours
+ 7 days	± 6 hours
+ 14 days	± 1 day
+28 days	± 2 days

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings and included in the calculation of concentration summary statistics.

Individual free and bound plasma concentrations will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, median, minimum, and maximum) by treatment, injection and time point.

Individual free and bound plasma concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Mean free and bound plasma concentrations will be plotted by injection and nominal time on both linear and semi-logarithmic scales with both treatments overlaid on the same plots. All concentration listings and individual concentration-time profiles will be presented using the PK set.

10.3. Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ). The following PK parameters will be calculated for SCD411 and Aflibercept, where data permit:

C_{max}	Maximum plasma concentration.
t_{max}	Time to reach the maximum plasma concentration.
AUC_{0-t}	area under the concentration-time curve from time zero to last quantifiable time point, calculated using the linear up/log down trapezoidal rule.
AUC_{0-tau}	area under the concentration-time curve within a dosing interval, calculated using the linear up/log down trapezoidal rule.
AUC_{0-inf}	area under the concentration-time curve from zero to an infinite time, calculated as $[AUC_{0-t} + (C_{last} / \lambda_z)]$ where C_{last} is the last observed measurable concentration.
$t_{1/2}$	elimination half-life, calculated as: ln (2) / λ_z.

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed to document the selection of data points used to estimate t1/2 using non-compartmental procedures:

λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included.
λ_z lower	Lower bound used for the estimation of λ_z.
λ_z upper	Upper bound used for the estimation of λ_z.
Rsq	r^2, the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$.
$\%AUC_{ext}$	Percentage of AUC_{0-inf} due to extrapolation; AUC_{0-inf} values will be flagged and excluded from summary statistics where $\%AUC_{ext} > 20\%$.

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows). All PK tables, mean figures and all statistical analyses will be presented using the PK set.

Free and bound plasma PK parameters will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by treatment, injection and study day. t_{max} will be summarized using number of observations, median, minimum, and maximum only.

If the number of data points used to calculate λz is less than 3 (not including C_{max}), or the calculated coefficient of determination (R^2) value for λz is < 0.800, λz and the parameters that utilize λz for determination $AUC_{0\text{-}inf}$, $t_{1/2}$ will not be reported. In addition, free and bound plasma PK parameters will be presented in data listings and summarized by ADA status (positive/negative).

A simple comparison of summary statistics of PK parameters (C_{max} and AUC) will be performed between the treatments to understand PK similarity.

11. Immunogenicity Analysis

Immunogenicity analysis is one of the secondary safety endpoints. Summary of immunogenicity results will be based on the SAF.

Immunogenicity 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 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 (NAb) will be tested when Anti-drug antibodies (ADA) results are confirmed to be positive. ADA concentration with signal above cut point of 10.0 ng/mL is defined as ADA - positive.

The analysis on immunogenicity will be descriptive. Geometric mean titer (GMT) and other descriptive statistics (number of subjects (n), median, minimum and maximum) will be provided at each time point by treatment group. The descriptive statistics will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. The number and proportion of ADA-positive subjects and ADA-negative subjects will be summarized by treatment group for each assessment time point. The number and proportion of NAb subjects will be summarized by treatment group for each assessment time point. Also, a by-subject listing will be provided.

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

12. Interim Analysis

The primary analysis of efficacy and all other efficacy and safety analyses will be conducted at the Week 8 database lock; i.e., 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 Week 52 and all subjects complete Week 24 or have early discontinued 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 included 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 at 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.

13. 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 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 held approximately 6 months after the IDMC organizational meeting and second safety meeting will be held after all subjects have completed the Week 8 Visit. After each of these meetings, 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.

14. References

Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. Retina (Philadelphia, Pa). 2017;37(10):1847-58.

Eylea® (aflibercept) Injection, for Intravitreal Use. Full Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. Available from: https://www.regeneron.com/sites/default/files/EYLEA_FPI.pdf

Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis. 2012;15(2):171-85.

Schneider U, Gelisken F, Inhoffen W. Natural course of occult choroidal neovascularization in age-related macular degeneration: development of classic lesions in fluorescein angiography. Acta Ophthalmol Scand. 2005;83(2):141-7.

15. Appendices

15.1. 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
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; 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; NAb, neutralizing antibodies; OCT, optical coherence tomography; PDT, photodynamic therapy; PK, pharmacokinetics; 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, 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: visual acuity 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, 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.

[j] Best corrected 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. BCVA will also be performed at any time during the visit at ET/EOS Visit. A decrease in visual acuity 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. V/S will also be performed at any time during the visit at 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. NAb will be tested when ADA 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).

15.2. Guideline of Missing Date Imputation for Safety Analysis

Impute Missing Date of Adverse Events/ Prior or Concomitant Medications

Incomplete Start Date: If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields
- If the year is **prior to** the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of the first dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are **same** as the month and year of the first dosing date, then the first doing date will be assigned to the missing day.
- If the month and year are **before** the month and year of the first dosing date, then the last day of the month will be assigned to the missing day.
- If the month and year are **after** the month and year of the first dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding AE will be included as TEAE if the AE end date is after the first dosing date or the end date is also missing. The corresponding medication will be considered to have a start date before the first dose of study drug.

Incomplete Stop Date: If the imputed stop date is before the start date then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.

- If the year of the incomplete stop date is **prior to** the year of the last dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the **same** as the month and year of the last dosing date, then the last dosing date will be assigned to the missing day.
- If the month and year of the incomplete stop date are **before** the month and year of the last dosing date, then the last day of the month will be assigned to the missing day.
- If the month and year of the incomplete stop date are **after** the month and year of the last dosing date, then the first day of the month will be assigned to the missing day.

Missing day, month, and year

- No imputation is needed. The corresponding medication will be treated as a continuing medication.