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Clinical Study Protocol

A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics, and Immunogenicity between SB15 (proposed aflibercept biosimilar) and Eylea® in Subjects with Neovascular Age-related Macular Degeneration

Product	SB15 (proposed aflibercept biosimilar)	
EudraCT Number	2019-003883-28	
US IND Number (if applicable)	N/A	
Protocol Number	SB15-3001	
Study Phase	Phase III	
Version and Effective Date	Version 1.0	Oct 30, 2019

Sponsor

Samsung Bioepis Co., Ltd.

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SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.	
Name of Finished Product:	SB15 (proposed aflibercept biosimilar)	
Name of Active Ingredient:	Aflibercept	
Title of Study: A Phase III randomised, double-masked, parallel group, multicentre study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB15 (proposed aflibercept biosimilar) and Eylea® in subjects with neovascular age-related macular degeneration		
Protocol No:	SB15-3001	**Phase:** III
Investigator sites:	Approximately 60 Investigator sites globally	
Planned Study Period: Approximately 59 weeks per subject Screening period will be 3 weeks. Investigational product (IP; SB15 or Eylea®) will be given for 48 weeks and the last assessment will be done at Week 56.		
Objectives: Primary objective The primary objective of this study is to demonstrate the equivalence in efficacy of SB15 compared to Eylea® in subjects with neovascular age-related macular degeneration (AMD). Secondary objective(s) The secondary objectives are: • To evaluate the safety of SB15 compared to Eylea® • To evaluate the systemic exposure of SB15 compared to Eylea® in subjects participating in pharmacokinetics (PK) evaluation • To evaluate the immunogenicity of SB15 compared to Eylea®		
Study Design: This is a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of SB15 compared to Eylea® in subjects with neovascular AMD. Subjects will be randomised in a 1:1 ratio to receive either SB15 or Eylea® (administered via intravitreal [IVT] injection 2 mg [0.05 mL] every 4 weeks for the first 3 months (i.e., at Weeks 0, 4, and 8), followed by 2 mg [0.05 mL] once every 8 weeks). At Week 32, subjects in Eylea® treatment group will be randomised again in a 1:1 ratio to either continue on Eylea® treatment or be transitioned to SB15 treatment. In the 8-week treatment cycle, IPs (SB15 or Eylea®) will be administered up to Week 48, and the last assessment will be done at Week 56, corresponding to the end of follow-up for all subjects.		
Number of Subjects: Approximately a total of 446 subjects will be randomised in this study.		
Target Population: Subjects with neovascular AMD		
Eligibility Criteria: Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the eye with the worse visual acuity will be selected as the study eye. If both eyes have equal visual acuity, the eye		

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with clearer lens and ocular media will be selected at the Investigator's discretion. If there is no objective basis for selecting the study eye, factor such as ocular dominance, other ocular pathology, and subject preference should be considered by the Investigator in making the selection. Subject with only one functional eye (defined as Best Corrected Visual Acuity (BCVA) of counting finger or less on the eye with worse vision) cannot be enrolled, even if otherwise eligible for the study.

Inclusion criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Age ≥ 50 years at Screening
2. Treatment naïve, *active subfoveal choroidal neovascularisation (CNV) lesion secondary to AMD in the study eye

   * Active CNV indicates presence of leakage and intra- or sub-retinal fluid which should be confirmed by the central reading centre during Screening.
3. The area of CNV must occupy at least 50% of total lesion in the study eye (confirmed by the central reading centre during Screening)
4. Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars, and neovascularisation) in the study eye (confirmed by the central reading centre during Screening)
5. BCVA of 20/40 to 20/200 (letter score of 73 to 34, inclusive) using original series Early Treatment Diabetic Retinopathy Study (ETDRS) charts or 2702 series Number charts in the study eye at Screening and at Week 0 (Day 1) prior to randomisation
6. Non-childbearing potential female (e.g., permanently sterilized, postmenopausal [defined as 12 months with no menses without an alternative medical cause prior to Screening]), OR childbearing potential female subjects or male subjects with their (respectively male or female) partners who agree to use at least two forms of appropriate contraception method that can achieve a failure rate of less than 1% per year (e.g., established use of oral, injected, intravaginal, transdermal, or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, physical barrier, sexual abstinence) from Screening until 3 months after the last IVT injection of IP
7. Written informed consent form (ICF) must be obtained from the subject prior to any study related procedure (if the subject is legal blindness or illiterate, an impartial witness should be present during the entire informed consent discussion)
8. Willingness and ability to undertake all scheduled visits and assessments

Exclusion criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Study eye: Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion or presence of blood with the size of 1 DA or more involving the centre of fovea (confirmed by the central reading centre during Screening)
2. Study eye: Scar, fibrosis, or atrophy involving the centre of the fovea (confirmed by the central reading centre during Screening)
3. Study eye: Presence of CNV due to other causes, such as ocular histoplasmosis, trauma, multifocal

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choroiditis, angioid streaks, history of choroidal rupture, or pathologic myopia (confirmed by the central reading centre during Screening)

4. Study eye: Presence of retinal pigment epithelial tears or rips involving the macula (confirmed by the central reading centre during Screening)
5. Study eye: Presence of macular hole at any stage (confirmed by the central reading centre during Screening)
6. Study eye: Any concurrent macular abnormality other than AMD which could affect central vision or the efficacy of IP including but not limited to epiretinal membrane, vitreomacular traction, macular telangiectasia, retinal vascular abnormality, etc. (confirmed by the central reading centre during Screening)
7. Study eye: Any concurrent ocular condition which, in the opinion of the Investigator, could either confound the interpretation of efficacy and safety of IP (e.g., ocular media opacities such as significant cataract, optic neuropathy etc.) or require medical or surgical intervention during the study period
8. Either eye: History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy) or diabetic macular oedema (DME)
9. Study eye: Current vitreous haemorrhage
10. Either eye: Any previous IVT anti-vascular endothelial growth factor (VEGF) treatment (e.g., bevacizumab, ranibizumab, aflibercept, pegaptanib, etc.)
11. Any previous systemic anti-VEGF treatment
12. Study eye: History of treatment involving macula such as macular laser photocoagulation, photodynamic therapy (PDT), transpupillary thermotherapy (TTT), radiation therapy, or any ocular treatment for neovascular AMD
13. Any systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD within 30 days prior to randomisation, and such treatment or therapy will not be allowed during the study period. However, dietary supplements, vitamins, or minerals will be allowed.
14. Study eye: History of vitrectomy, scleral bucking (encircling), glaucoma filtration surgery, corneal transplantation, or pan-retinal photocoagulation
15. Study eye: Previous ocular (intraocular and peribulbar) corticosteroids injection/implant within 1 year prior to randomisation
16. Study eye: Topical ocular corticosteroids administered for ≥ 30 consecutive days or for ≥ 60 non-consecutive days within 90 days prior to randomisation
17. Use of systemic corticosteroids for 30 or more consecutive days within 90 days prior to randomisation (inhaled steroid is permitted).
18. Study eye: Any other intraocular surgery (including cataract surgery or Yttrium Aluminium Garnet [YAG] laser posterior capsulotomy in association with prior posterior chamber intraocular lens [IOL] implantation) or periocular surgery within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation.
19. Current use of medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, ethambutol,

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at Screening and such medications will not be allowed during the study period.

20. Study eye: Previous radiation therapy near the region of the study eye
21. Previous participation in clinical studies with IP to treat neovascular AMD in either eye.
22. Previous participation in clinical studies with IP to treat disease other than neovascular AMD within 90 days prior to randomisation (excluding dietary supplementary, vitamins, and minerals). Such participation will not be allowed during the study period even if the IP is dietary supplementary, vitamins, or minerals.
23. Subject with only one functional eye (defined as BCVA of counting finger or less on the eye with worse vision)
24. Study eye: Spherical equivalent of the refractive error demonstrating more than 6 diopters of myopia. For subjects who have undergone previous refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 6 diopters of myopia.
25. Study eye: Aphakia or absence of the posterior capsule (unless it occurred as a result of a YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation)
26. Either eye: Active or suspected ocular and periocular infection at Screening or at randomisation (e.g., infectious blepharitis, infectious conjunctivitis, infection in eyelid)
27. Either eye: Active intraocular inflammation including scleritis at Screening or at randomisation
28. Either eye: History of idiopathic or autoimmune-associated uveitis
29. Study eye: Uncontrolled ocular hypertension (defined as intraocular pressure [IOP] ≥ 25 mmHg despite treatment with anti-glaucoma medication) at Screening
30. Known allergic reactions and/or hypersensitivity to any component of Eylea® or SB15
31. History of allergy to the fluorescein sodium for injection in angiography
32. History of a medical condition that would preclude scheduled study visits or safe use of IP in the opinion of the Investigator (e.g., history of organ transplant, immunocompromised subject, etc.)
33. Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus (in the opinion of the Investigator), uncontrolled systemic hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg on optimal medical regimen), or uncontrolled atrial fibrillation (resting heart rate ≥ 110 beats per minutes) at Screening
34. Stroke, transient ischaemic attacks, or myocardial infarction within 180 days prior to randomisation
35. History of recurrent significant infections and/or current treatment for systemic infection
36. Severe renal impairment with dialysis or a history of renal transplant
37. Malignancy (other than non-melanoma skin cancer) under treatment or with history of metastatic disease
38. Women of childbearing potential who are pregnant, planning to become pregnant, lactating, or not using adequate birth control, as specified in protocol. For women of childbearing potential, a serum pregnancy test must result negative at Screening.
39. Employees of investigational sites, individuals directly involved with the conduct of the study,

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prisoners, and persons who are legally institutionalized

Investigational Products:

- Test IP: SB15 (proposed aflibercept biosimilar)
- Reference IP: Eylea® (aflibercept)
- Formulation: Solution for injection
- Route of administration: IVT injection
- Dose regimen: 2 mg (0.05 mL) every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks

Study Endpoints

Primary efficacy endpoint

- Change from baseline in BCVA at Week 8

Secondary efficacy endpoints

The secondary efficacy endpoints are:

- Change from baseline in BCVA over time up to Week 32 and up to Week 56
- Proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32 and Week 56 (proportion of subjects who maintained BCVA)
- Proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 32 and Week 56
- Change from baseline in central subfield thickness (CST) and total retinal thickness (TRT) at Week 4, and over time up to Week 32 and up to Week 56 (based on assessment by the central reading centre)
  - CST measured from internal limiting membrane (ILM) to retinal pigment epithelium (RPE) in 1-mm central subfield
  - TRT measured from ILM to Bruch's membrane (BM) in 1-mm central subfield
- Proportion of subjects with intra- or sub-retinal fluid on optical coherence tomography (OCT) at Week 32 and Week 56 (based on assessment by the central reading centre)
- Change from baseline in CNV area at Week 32 and Week 56 (based on assessment by the central reading centre)
- Proportion of subjects with active CNV leakage at Week 32 and Week 56 (based on assessment by the central reading centre)

Safety endpoints

- Incidence of ocular adverse events (AEs) or serious ocular AEs
- Incidence of non-ocular AEs and serious non-ocular AEs

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- Incidence of intraocular inflammation and IOP increase
- Changes in vital signs and clinical laboratory parameters

PK endpoints

Blood samples for PK assessment will be collected in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1]).

- Pre-dose (trough serum concentration [C_{trough}])
  - Systemic exposure measured pre-dose at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40
- Post-dose (close to maximum serum concentration [C_{max}])
  - Systemic exposure measured once between 24 hours and 72 hours after IVT injection of IP at Week 0 (Day 1)
  - Systemic exposure measured on 1 day, 2 days, and 3 days after the date of IVT injection of IP at Week 24 (total 3 times of PK sample collection for 3 consecutive days)
- Systemic exposure measured during the visit at Week 56 (end of study [EOS] visit)

Immunogenicity endpoints

Blood samples for immunogenicity assessment will be collected pre-dose at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for immunogenicity assessment will also be collected during the visit at Week 56 (EOS visit) or early termination (ET) visit

- Incidence of anti-drug antibodies (ADAs) to aflibercept
- Incidence of neutralising antibodies (NAbs) to aflibercept

Exploratory endpoint

- Proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56 (based on assessment by the central reading centre)

The quality of life (QOL) is assessed using National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

- Change from baseline in subscale scores and composite scores of NEI VFQ-25 at Week 32 and Week 56

Statistical Methods

Analysis sets for efficacy analyses

The Full Analysis Set (FAS) consists of all randomised subjects. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are assigned to at randomisation. However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from FAS.

Per-Protocol Set (PPS) consists of all FAS subjects who have BCVA assessment result at baseline and at Week 8 without any major protocol deviations (PDs) that have impact on the BCVA assessment. Major PDs that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment group

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assignment for analyses.

Efficacy analyses

The primary efficacy analysis will aim to demonstrate equivalence in terms of change from baseline in BCVA at Week 8 between SB15 and Eylea®.

The equivalence between the two treatment groups will be declared if the 90% confidence interval (CI) of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The 90% CI of the difference between the two treatment groups in relation to the change from baseline in BCVA at Week 8 will be estimated for the FAS. The same analysis will be performed for the PPS as a sensitivity analysis.

For the European Medicines Agency (EMA) submission, equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The 95% CI of the difference between the two treatment groups in relation to the change from baseline in BCVA at Week 8 will be estimated for the FAS. The same analysis will be performed for the PPS as a sensitivity analysis. For those subjects who drop out of the study prematurely, a multiple imputation will be used under the missing at random assumption. The 95% CI of the difference between the two treatment groups will also be estimated for the FAS as supportive analysis.

As the secondary efficacy endpoints, change from baseline in BCVA, CST, TRT, and CNV area will be summarised descriptively by treatment group and visit.

Proportion of subjects who lost fewer than 15 letters and gained 15 letters or more in BCVA compared to baseline, subjects with intra- or sub-retinal fluid, and subjects with active CNV leakage will be summarised descriptively by treatment group and visit.

The two-sided 95% CI of the Least Square mean (LSMean) difference of change from baseline in secondary efficacy endpoints between the two treatment groups will be estimated.

Safety analyses

All reported terms for AEs (ocular or non-ocular) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). AEs including ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs will be summarised descriptively by treatment group.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment group and visit. All other safety variables will be summarised descriptively by treatment group and visit unless specified otherwise.

PK analyses

Blood samples for PK assessment will be collected in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1]). The systemic exposure will be summarised descriptively by treatment group and visit.

Immunogenicity analyses

The number and proportion of subjects with ADA and NAb results (e.g., ‘positive’ or ‘negative’) will be summarised descriptively by treatment group and visit.

Exploratory analyses

Proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56 will be summarised descriptively

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by treatment group and visit.

For NEI VFQ-25 as a measurement of QOL, subscale scores (general health, general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, colour vision, and peripheral vision) and the composite score, which represent overall visual function, will be calculated, and the change from baseline will be summarised descriptively by treatment group and visit.

Sample size calculation

For the calculation of the equivalence margin for BCVA, the mean changes in BCVA were referred from VIEW1 study of Eylea® in subjects with neovascular AMD.

In the VIEW1 study, as reported in the Summary of Product Characteristics (SmPC) of Eylea®, the mean change of BCVA at Month 12 (standard deviation [SD]) was 10.9 (13.8) letters for the dosing of 2 mg every 4 weeks in the Eylea® treatment group and the LSMean difference between Eylea® and Lucentis® (ranibizumab) with its 95% CI was 3.15 (0.92, 5.37) letters.

The United States of America (US) Food and Drug Administration (FDA) Guidance describes that if the active control (Eylea® in this study) has shown superiority to other active treatments (Lucentis® in VIEW1) in the past, the difference demonstrated (3.15 letters) represents a conservative estimate of historical evidence of sensitivity to drug-effects, one that could serve as a basis for choosing M1. Therefore, the equivalence margin of 3 letters was chosen as it would be less than the LSMean difference in VIEW1 study, which proved statistical superiority to ranibizumab.

The ETDRS chart has 5 letters in one line (that is the minimum limit, in terms of number of letters, for detecting a visual acuity change); thus, the difference of more than 5 letters in BCVA could be considered as a minimal clinically important difference. In addition, most of the anti-VEGF non-inferiority clinical trials on AMD also used a non-inferiority margin of 5 letters. Therefore, the equivalence margin of [−3 letters, 3 letters] is considered to be a conservative margin to test the clinical equivalence between SB15 and Eylea®.

With the equivalence limit of [−3 letters, 3 letters], a sample size of 216 subjects per treatment group was calculated with the assumptions of the mean difference of 0.5 letters and SD of 9.0 at the overall 5% significance level, providing 80% power to reject the null hypothesis. Overall 446 subjects (223 per treatment group) will be randomised into the study, allowing 3% loss from the randomised subjects, if any.

GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES

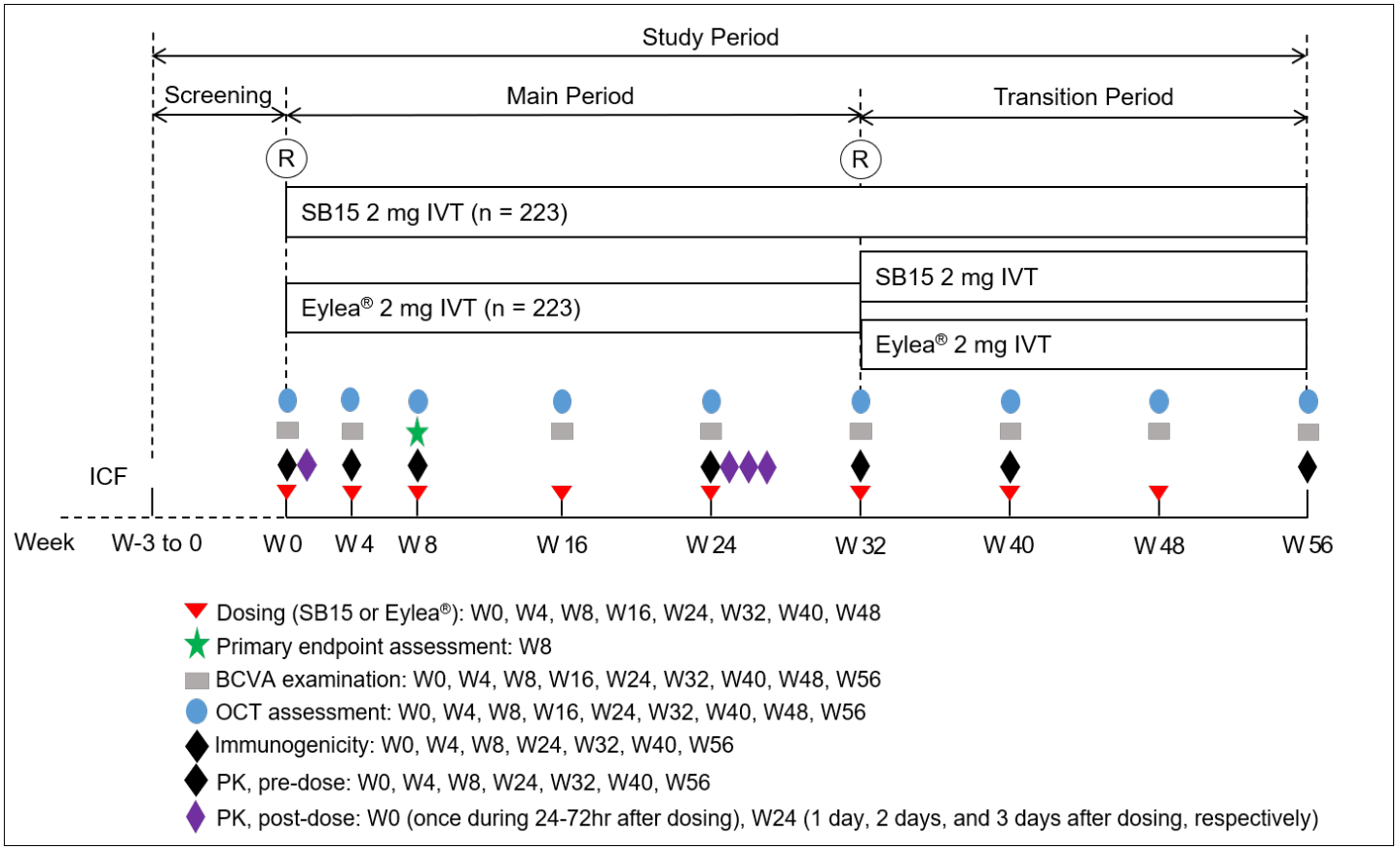

Figure 1. Graphical Study Design

ICF = informed consent form; ® = randomisation; IVT = intravitreal; OCT = optical coherence tomography; BCVA = best corrected visual acuity; PK = pharmacokinetics; W = week

Table 1. Schedule of Activities

Procedures	Study Period									
W: Week	**Screening[25]**	**W0**	**W4**	**W8**	**W16**	**W24**	**W32**	**W40**	**W48 EOT[26]**	**W56 EOS[27]/ET[28]**
D: Day (± Visit Window)	**D-21 to D-1**	**D1**	**D29 (± 7)**	**D57 (± 7)**	**D113 (± 7)**	**D169 (± 7)**	**D225 (± 7)**	**D281 (± 7)**	**D337 (± 7)**	**D393 (± 7)**
V: Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Written informed consent[1]	X									
Inclusion/exclusion criteria	X	X								
Demographic data[2]	X									
Medical/ophthalmic history	X									
Physical examination[3]	X									X
Randomisation[4]		X					X[5]			
Vital signs[6]	X	X	X	X	X	X	X	X	X	X
BCVA examination[7]	X	X[8]	X	X[9] (Primary)	X	X	X	X	X	X
OCT[10]	X	X	X	X	X	X	X	X	X	X
FP/FA[11]	X						X			X
Indirect ophthalmoscopy[12] (pre- and post-dose)	X	X	X	X	X	X	X	X	X	X
Slit lamp examination[13]	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[14] (pre- and post-dose)	X	X	X	X	X	X	X	X	X	X
NEI VFQ-25[15]		X					X			X
Clinical laboratory test[16]	X			X			X	X		X
Blood sampling for immunogenicity[17]		X	X	X		X	X	X		X
Blood sampling for PK[18]		X	X	X		X	X	X		X[19]
Pregnancy test[20]	X	X	X	X	X	X	X	X	X	X
IP injection[21]		X[22]	X	X	X	X	X	X	X	

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D: Day (± Visit Window)	**D-21 to D-1**	**D1**	**D29 (± 7)**	**D57 (± 7)**	**D113 (± 7)**	**D169 (± 7)**	**D225 (± 7)**	**D281 (± 7)**	**D337 (± 7)**	**D393 (± 7)**
V: Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
AE monitoring[23]	Continuously									
Prior or concomitant medication or therapy[24]	Continuously									

AE = adverse event; BCVA = best corrected visual acuity; EOS = end of study; EOT = end of treatment; ET = early termination; FA = fluorescein angiography; FP = fundus photography; IP = investigational product; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; OCT = optical coherence tomography; PK = pharmacokinetics.

1. Written informed consent must be obtained from the subject prior to any study related procedures.
2. Demographic data includes the date of birth (year of birth is required), gender, race, and ethnicity.
3. Physical examination will be performed at Screening and Week 56 (EOS visit) or ET visit. Body weight will be measured and recorded at Screening and Week 56 (EOS visit) or ET visit, whereas height will be measured and recorded only at Screening.
4. All subjects' eligibility should be confirmed by the central reading centre and the Investigator prior to randomisation.
5. At Week 32, subjects in Eylea® treatment group will be randomised in a 1:1 ratio to either continue on Eylea® treatment or be transitioned to SB15 treatment. Subjects receiving SB15 will continue to receive SB15 up to Week 48, but they will also follow the randomisation procedure in order to maintain masking.
6. Vital signs include blood pressure, pulse rate, and body temperature. Vital signs will be assessed at Screening and prior to intravitreal (IVT) injection of IP at each visit until Week 48. Vital signs will also be assessed at Week 56 (EOS visit) or ET visit.
7. Visual acuity will be assessed in both the study eye and fellow (non-study) eye at Screening and prior to IVT injection of IP at each visit until Week 48. Visual acuity will also be assessed during the final visit at Week 56 (EOS visit) or ET visit. Subject must use either original series Early Treatment Diabetic Retinopathy Study (ETDRS) chart or 2702 series Number chart (at a starting distance of 4 meters) consistently from Screening to Week 56 (EOS visit) or ET visit. Visual acuity testing must be performed before dilation of pupils and other ophthalmic procedures including FA/FP and OCT assessment. A decrease in visual acuity of ≥ 15 letters from the last assessment of VA should be reported as AEs/serious AEs (SAEs) as appropriate. If there is a decrease in visual acuity of ≥ 30 letters from the last assessment of visual acuity or if there is a decrease in visual acuity to the level of light perception or worse, it should be reported as SAE.
8. The Investigator must confirm that the subject can read between 73 letters and 34 letters, inclusive, in the study eye using original series ETDRS chart or 2702 series Number chart at Week 0 (Day1) prior to randomisation.
9. Visit at Week 8 is the most critical as this is the visit scheduled for the primary endpoint assessment. Thus, every effort should be made to adhere to the visit schedule for the subjects.
10. OCT will be performed on both eyes at Screening and those images taken from both eyes will be sent to the central reading centre. OCT will be performed on the study eye prior to IVT injection of IP at each visit until Week 48. OCT will also be performed on the study eye at Week 56 (EOS visit) or ET visit. OCT images taken from the study eye will be sent to the central reading centre. Only OCT devices certified by the central reading centre are allowed to be used in this study. If one or more OCT devices are certified in an investigational site, a subject must use the same OCT system from the same manufacture consistently from Screening to Week 56 (EOS visit) or ET visit.
11. FP/FA will be performed on both eyes at Screening and those images taken from both eyes will be sent to the central reading centre. FP/FA will also be performed on the study eye prior to IVT injection of IP at Week 32 and at Week 56 (EOS visit) or ET visit. Those images taken from the study eye at Week 32 and Week 56 (EOS visit) or ET visit will be sent to the central

reading centre. Only FP/FA devices certified by the central reading centre are allowed to be used in this study. If one or more FP/FA devices are certified in an investigational site, a subject must use the same FP/FA system from the same manufacture consistently from Screening to Week 56 (EOS visit) or ET visit.

12. Indirect ophthalmoscopy using a standard way (i.e., usually using a head-mounted light source and a 20-30 lens) will be performed on the study eye at Screening and prior to IVT injection of IP and 0-15 minutes after IVT injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at Week 56 (EOS visit) or ET visit.
13. Slit lamp examination will be performed on both the study eye and fellow eye (non-study eye) at Screening and prior to IVT injection of IP at each visit until Week 48. Slit lamp examination will also be performed at Week 56 (EOS visit) or ET visit.
14. Intraocular pressure (IOP) should be measured using Goldmann applanation tonometry. The same method of IOP measurement must be used in each subject from Screening to Week 56 (EOS visit) or ET visit. IOP will be measured on the study eye at Screening as well as prior to each IVT injection of IP and 30-60 minutes after IVT injection of IP at each visit until Week 48. IOP will also be measured at Week 56 (EOS visit) or ET visit. If IOP is measured prior to OCT and FP/FA, IOP should be carefully measured not to cause corneal erosion, which might affect the quality of OCT/FP/FA images.
15. NEI VFQ-25 will be performed at Week 0 (Day1) after randomisation. Subsequently, NEI VFQ-25 should be performed before dilation of pupils at Week 32 and at Week 56 (EOS visit) or ET visit.
16. Blood and urine samples for clinical laboratory test will be collected at Screening and prior to IVT injection of IP at Week 8, Week 32, and Week 40. Blood and urine samples will also be collected at Week 56 (EOS visit) or ET visit. Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.
    - Haematology: Haemoglobin, haematocrit, platelet count, and white blood cell count (total and differential)
    - Chemistry: Sodium, potassium, creatinine, glucose, calcium, phosphorus, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase
    - Urinalysis (dipstick): Protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, and urobilinogen
17. Blood samples for immunogenicity assessment will be collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for immunogenicity assessment will also be collected at Week 56 (EOS visit) or ET visit.
18. Blood samples for PK assessment will be collected only in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1]). Blood samples for pre-dose PK assessment will be collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for post-dose PK assessment will be collected once between 24 hours and 72 hours after IVT injection of IP at Week 0 (Day 1) and on 1 day, 2 days, and 3 days after the date of IVT injection of IP at Week 24 (total 3 times of PK sample collection for 3 consecutive days). Blood samples for PK assessment will also be collected at Week 56 (EOS visit).
19. Blood samples for PK assessment should not be collected at ET visit.
20. Only for women of childbearing potential, a serum pregnancy test must be performed at Screening. A pregnancy test (on serum or urine at the Investigator's discretion) must be repeated and a negative result shall be obtained prior to each IVT injection of IP after randomisation.
21. Subjects will be administered SB15 or Eylea® 2 mg (0.05 mL) via IVT injection into the study eye every 4 weeks for the first 3 months, followed by 2 mg (0.05 mL) once every 8 weeks up to Week 48. Dosing visits will be allowed within ± 7 days of the scheduled dosing visit date (except Week 0 [Day 1], visit window not allowed).
22. The first IVT injection of IP should be performed at the same day of randomisation.
23. Ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs will be recorded after the written informed consent is obtained from the subject until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).
24. Any medications, including prescription drugs, non-prescription drugs, or any therapy received locally (in the study eye and/or fellow eye) or systemically within 180 days prior to Screening will be recorded until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).
25. If the subject is not randomised within 21 days after signing the informed consent form, the subject will be screen failed. Once a subject is screen failed for one eye, he or she should not be re-screened for the same eye. Screening for the other eye is allowed within the screening period.
26. EOT visit is defined as the visit for the last scheduled IVT injection of SB15 or Eylea®. The Sponsor will not provide IP (SB15 or Eylea®) to subjects after they complete the EOT visit.
27. EOS visit is defined as Week 56, corresponding to 8 weeks (± 7 days) after the last scheduled IVT injection of SB15 or Eylea®.
28. ET visit is recommended to be performed at 8 weeks (± 7 days) after the last IVT injection of SB15 or Eylea®. When this schedule is not available (e.g., due to subject not available), the ET visit should still be performed as soon as available and no later than Week 56 from the first IVT injection of IP. If ET visit occurs before 7 weeks after the last IVT injection of IP, a follow-up

visit or telephone interview will be conducted at 8 weeks (± 7 days) after the last IVT injection of IP to collect adverse events and related concomitant medications.

Table 2. Blood Sampling Schedule for PK, Immunogenicity, and Clinical Laboratory Test

Visit	Week (± Visit Window)	Sampling Time	PK Sampling (Only in Subjects Participating PK Evaluation)	Immunogenicity Sampling (in All Randomised Subjects)	Clinical Laboratory Test (in All Randomised Subjects)
V1	Screening	D-21 to D-1	-	-	O*
V2	Week 0	Prior to IVT injection	O	O	-
		24-72 hr after IVT injection	O	-	-
V3	Week 4 (± 7 days)	Prior to IVT injection	O	O	-
V4	Week 8 (± 7 days)	Prior to IVT injection	O	O	O
V6	Week 24 (± 7 days)	Prior to IVT injection	O	O	-
		1 day after IVT injection	O	-	-
		2 days after IVT injection	O	-	-
		3 days after IVT injection	O	-	-
V7	Week 32 (± 7 days)	Prior to IVT injection	O	O	O
V8	Week 40 (± 7 days)	Prior to IVT injection	O	O	O
V10	Week 56 (EOS visit) (± 7 days)	Samples to be collected during the visit	O	O	O
-	ET visit	Samples to be collected during the visit	-	O	O

D = day; EOS = end of study; ET = early termination; hr = hour; IVT = intravitreal; PK = pharmacokinetics; V = visit
* In all subjects who signed written informed consent

LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	AEs of special interests
AMD	Age-related macular degeneration
ATE	Arterial thromboembolic event
AUC	Area under the plasma drug concentration-time curve
BCVA	Best Corrected Visual Acuity
BM	Bruch's membrane
CHO	Chinese Hamster Ovary
CI	Confidence interval
C_{max}	Maximum serum concentration
CNV	Choroidal neovascularisation
CRO	Contract Research Organisation
CRT	Central retinal thickness
CSR	Clinical study report
CST	Central subfield thickness
C_{trough}	Trough serum concentration
DA	Disc Areas
DME	Diabetic macular oedema
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End of study
ET	Early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus photography

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
ILM	Internal limiting membrane
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IVT	Intravitreal
IWRS	Interactive Web Response System
LSMean	Least Square mean
MedDRA®	Medical Dictionary for Regulatory Activities
NAb	Neutralising antibody
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NOAEL	No observed adverse effect level
OCT	Optical coherence tomography
PD	Protocol deviation
PDT	Photodynamic therapy
PI	Prescribing Information
PlGF	Placental growth factor
PK	Pharmacokinetic(s)
PKS	PK Analysis Set
PPS	Per-Protocol Set
QOL	Quality of life
RAN	Randomised Set
RPE	Retinal pigment epithelium
RSI	Reference safety information
RVO	Retinal vein occlusion
SAE	Serious AE
SAF	Safety set

SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard operation procedures
TRT	Total retinal thickness
TTT	Transpupillary thermotherapy
US	The United States of America
VEGF	Vascular endothelial growth factor
WHO-DDE	World Health Organisation-Drug Dictionary Enhanced
YAG	Yttrium Aluminium Garnet

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1. Introduction

1.1. Background

Age-related macular degeneration (AMD) is a disease that affects the macular region of the retina, causing progressive loss of central vision. AMD is the major cause of severe visual loss in older adults if left untreated. Choroidal neovascularisation (CNV) due to neovascular AMD is responsible for most AMD-related severe vision loss. Visual impairment leads to reduced quality of life (QOL), poorer general health, and increased mortality. In the developed world, AMD is known as the most frequent cause of uncorrectable severe vision loss in people older than 55 years of age. As many as 30% of adults aged 75 years or older develop signs of senile retinal degeneration, and the prevalence of AMD is increasing in an aging population.

Pathogenesis of AMD includes drusen genesis, lipofuscin genesis, local inflammatory state genesis, as well as angiogenesis. Angiogenesis is the development of new blood vessels from pre-existing vessels and whilst being a crucial process in normal physiology, it is an important pathogenic process in both benign and malignant disease. Vascular endothelial growth factor (VEGF) is one of the activators of angiogenesis and abnormal angiogenesis is a hallmark of neovascular AMD. CNV represents the growth of new blood vessels from the choroid into the subretinal pigment epithelium. Several proangiogenic factors are consistently upregulated during CNV formation, particularly two members of the VEGF family, VEGF-A and placental growth factor (PlGF). These factors activate quiescent endothelial cells and promote cell proliferation, migration, and vascular permeability. Retinal pigment epithelium (RPE) produces VEGF-A via two major pathways; complement activation and oxidative stress. Overproduction of VEGF-A leads to the breakdown of the blood-retinal barrier and formation of new blood vessels into the retina. Leakage of blood from these abnormal vessels results in oedema and loss of vision if left untreated [1].

Early treatments for CNV including laser ablation or photodynamic therapy (PDT) with verteporfin decreased severe vision loss rather than truly stabilizing vision or resulting in clinically significant improvements in visual acuity. Currently, the most common and effective clinical treatment for neovascular AMD is anti-VEGF therapy. Effective treatment for neovascular AMD is based on inhibition of the angiogenic protein VEGF. The first anti-VEGF drug to be used in trials for neovascular AMD was pegaptanib sodium which is an aptamer that selectively binds to and neutralizes VEGF-A_{165}, but not VEGF-A_{121}. Ranibizumab is a monoclonal humanized antibody fragment that binds all VEGF-A isoforms. In the two pivotal studies, ranibizumab showed gains in vision of patients affected by neovascular AMD that led to widespread use of ranibizumab for treatment of neovascular AMD. Another drug that showed efficacy initially when used systemically and then intravitreally was bevacizumab which is a whole monoclonal antibody and binds all isoforms of VEGF-A. Although bevacizumab is not approved for this specific indication, it was used as an off-label treatment for neovascular AMD. Aflibercept is a recombinant protein that includes binding domains of VEGF receptors 1 and 2 and it blocks all VEGF-A isoforms and VEGF-B, and blocks PlGF. The VIEW 1 and 2 trials demonstrate that aflibercept is an effective treatment for AMD, with the every-2-month regimen after loading dose offering the potential to reduce the risk from monthly intravitreal (IVT) injections and the burden of monthly monitoring. Aflibercept is the most recent major new molecule to be used clinically worldwide [1].

1.2. Overview of SB15

SB15 has been developed as a similar biological medicinal product to Eylea® having aflibercept as the active substance. Eylea® is currently indicated for the treatment of patients with neovascular AMD, macular oedema secondary to retinal vein occlusion (RVO; branch RVO or central RVO), and diabetic

macular oedema (DME) by both European Medicines Agency (EMA) and the United States of America (US) Food and Drug Administration (FDA). In addition, EMA approved Eylea® for the treatment of myopic CNV and the US FDA approved Eylea® for the treatment of diabetic retinopathy [2; 3].

SB15 is produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system and purified by various affinity and ion exchange chromatography steps that include specific viral inactivation and removal procedures.

According to the guideline International Conference on Harmonisation Q6B, characterisation of a biological therapeutic must involve its physicochemical properties, biological activities, purity, impurities, and quantity. The characterisation study will employ the 'state-of-the-art' analytical methods in order to investigate the primary, secondary, higher-order structures, and the post-translational modifications associated the structural heterogeneity, the charge variants, the purity, and the biological activities.

1.2.1. Non-Clinical Studies of SB15

As outlined in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" [4], a risk-based approach was taken to the non-clinical evaluation of SB15. A series of *in vitro* biologic activity studies is to be performed in order to demonstrate non-clinical similarity between SB15 and Eylea®. In line with the guideline, if similarity is to be demonstrated in quality and *in vitro* comparisons to provide non-clinical evidence of similarity between SB15 and Eylea®, *in vivo* studies will not be performed. Moreover, *in vitro* studies are considered to be the more sensitive measurement than with *in vivo* studies. Also, non-clinical safety pharmacology, reproductive and developmental toxicity, and carcinogenicity studies were not performed, as they are not required for non-clinical testing of biosimilars as outlined in the guideline [4].

1.3. Comparator Investigational Product: Eylea®

1.3.1. Non-clinical Data of Reference Product

Effects in non-clinical studies on repeated dose toxicity were observed only at systemic exposures considered substantially in excess of the maximum human exposure after IVT administration at the intended clinical dose indicating little relevance to clinical use. Erosions and ulcerations of the respiratory epithelium in nasal turbinates in monkeys treated with aflibercept intravitreally were observed at systemic exposures in excess of the maximum human exposure. The systemic exposure based on maximum serum concentration (C_{max}) and area under the plasma drug concentration-time curve (AUC) for free aflibercept were approximately 200- and 700-fold higher, respectively, when compared to corresponding values observed in humans after an IVT dose of 2 mg. At the No observed adverse effect level (NOAEL) of 0.5 mg/eye in monkeys the systemic exposure was 42- and 56-fold higher based on C_{max} and AUC, respectively. No studies have been conducted on the mutagenic or carcinogenic potential of aflibercept. An effect of aflibercept on intrauterine development was shown in embryo-foetal development studies in pregnant rabbits with intravenous (3 to 60 mg/kg) as well as subcutaneous (0.1 to 1 mg/kg) administration. The maternal NOAEL was at the dose of 3 mg/kg or 1 mg/kg, respectively. A developmental NOAEL was not identified. At the 0.1 mg/kg dose, the systemic exposures based on C_{max} and cumulative AUC for free aflibercept were approximately 17- and 10-fold higher, respectively, when compared to corresponding values observed in humans after an IVT dose of 2 mg. Effects on male and female fertility were assessed as part of a 6-month study in monkeys with intravenous administration of aflibercept at doses ranging from 3 to 30 mg/kg. Absent or irregular menses associated with alterations in female reproductive hormone levels and changes in sperm

morphology and motility were observed at all dose levels. Based on C_{max} and AUC for free aflibercept observed at the 3 mg/kg intravenous dose, the systemic exposures were approximately 4,900-fold and 1,500-fold higher, respectively, than the exposure observed in humans after an IVT dose of 2 mg. All changes were reversible [2; 3].

1.3.2. Clinical Data of reference product in neovascular AMD

In patients treated with Eylea® (one injection per month for three consecutive months, followed by one injection every 2 months), central retinal thickness (CRT) decreased soon after treatment initiation, and the mean CNV lesion size was reduced, consistent with the results seen with ranibizumab 0.5 mg every month.

In the VIEW1 study there were mean decreases in CRT on optical coherence tomography (OCT) (–130 and –129 microns at week 52 for the Eylea® 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). Also, at the 52-week time point, in the VIEW2 study there were mean decreases in CRT on OCT (–149 and –139 microns for the Eylea® 2 mg every two months and ranibizumab 0.5 mg every month study groups, respectively). The reduction of CNV size and reduction in CRT were generally maintained in the second year of the studies.

The ALTAIR study was conducted in Japanese patients with treatment naïve neovascular AMD, showing similar outcomes to the VIEW studies using 3 initial monthly Eylea® 2 mg injections, followed by one injection after a further 2 months, and then continued with a treat-and-extend regimen with variable treatment intervals (2- or 4-week adjustments) up to a maximum 16-week interval according to pre-specified criteria. At Week 52, there were mean decreases in CRT on OCT of –134.4 and –126.1 microns for the 2-week adjustment group and the 4-week adjustment group, respectively. The proportion of patients without fluid on OCT at Week 52 was 68.3% and 69.1% in the 2- and 4-week adjustment groups, respectively.

In a pharmacokinetic (PK) sub-study in 6 neovascular AMD patients with frequent sampling, maximum plasma concentrations of free aflibercept (systemic C_{max}) 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 intravitreal injection, and were undetectable 2 weeks following dosage in almost all patients. Aflibercept does not accumulate in the plasma when administered intravitreally every 4 weeks [2].

The safety and efficacy of Eylea® were assessed in two randomised, multi-centre, double-masked, active-controlled studies in patients with neovascular AMD (VIEW1 and VIEW2) with a total of 2,412 patients treated and evaluable for efficacy (1,817 with Eylea®). Patient ages ranged from 49 to 99 years with a mean of 76 years. In these clinical studies, approximately 89% (1,616/1,817) of the patients randomised to treatment with Eylea® were 65 years of age or older, and approximately 63% (1,139/1,817) were 75 years of age or older [2; 3].

1.4. Study Rationale

A biosimilar is a biological medicinal product that is highly similar to an already authorised original biological medicinal product (reference medicinal product) in terms of quality, tolerability, and efficacy based on a comprehensive comparability exercise [4; 5]. The EMA and the US FDA have developed specific guidelines for a biologic drug to be approved as a biosimilar [5; 6]. These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological characterisation before initiating clinical studies for the comparison of the efficacy, tolerability, PK properties, and immunogenicity of the biosimilar. The purpose of this study is to demonstrate the equivalence in efficacy of SB15 compared to Eylea® and to evaluate the safety and immunogenicity in subjects with neovascular AMD. In addition, systemic exposure of SB15 to Eylea®

will also be evaluated in subjects participating in PK evaluation.

1.5. Risk and Benefit Assessment

1.5.1. Known Potential Risks

According to Eylea® Prescribing Information (PI) and Summary of Product Characteristics (SmPC), there are IVT injection related risks such as endophthalmitis, intraocular inflammation, retinal break, retinal detachment, iatrogenic traumatic cataract. There is a risk of intraocular pressure (IOP) elevation within 60 minutes of IVT injection. Sustained increased of IOP was also reported. As this is a therapeutic protein, there is a potential for immunogenicity with investigational products (IPs; SB15 or Eylea®). There is a potential risk of non-ocular haemorrhage and arterial thromboembolic events (ATEs) following IVT use of VEGF inhibitors, including Eylea®. There is a risk of retinal pigment epithelial tear after anti-VEGF therapy for neovascular AMD [2; 3].

In order to ensure the safety of subjects who participate in the study, the followings will be performed during the study. Proper aseptic injection techniques must always be used when administering Eylea®. The patient should be instructed to report their symptoms related to these adverse events (AEs) without delay and should be managed appropriately. Special precaution is needed in patients with poorly controlled glaucoma and Eylea® should not be injected while the IOP is ≥ 30 mmHg. In all cases, both the IOP and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g., pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity. There are limited data on safety in the treatment of patients with central RVO, branch RVO, DME, or myopic CNV with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months and caution should be exercised when treating such patients. Caution also should be used in patients with a large and/or high pigment epithelial retinal detachment.

This study will take place at multicentre with accessible medical facilities which will allow immediate treatment of medical emergencies. All study related procedures will be conducted by medical staffs with appropriate level of training and expertise and an understanding of the IPs, its target, and mechanism of action. Subjects will have a safety follow-up at the end of study (EOS) visit, 8 weeks after the last IVT injection of IP. An independent Data and Safety Monitoring Board (DSMB) will convene at pre-specified intervals to conduct interim monitoring of accumulating safety data. Following each data review, the DSMB will make recommendations regarding the conduct of the study, including continuation of the study without modifications, modification of the protocol, pausing of subject enrolment until the resolution of an issue, or termination of the study for safety reasons.

1.5.2. Known Potential Benefits

Neovascular AMD is characterized by growth of abnormal vessel from choroid and retina and vascular leakage from abnormal vessels, leading to eventual damage to tissue in macula. VEGF-A is in excess in the eye of subjects with neovascular AMD and thought to contribute to pathophysiology of neovascular AMD. VEGF acts via two receptor tyrosine kinases; VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularisation and excessive vascular permeability. Eylea® acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors.

Eylea® reduce abnormal growth of new vessels and vascular leakage in retinal diseases. In pooled analysis of two VIEW studies in neovascular AMD, subject treated with 2 mg every 8 weeks after 3

monthly loading doses showed Best Corrected Visual Acuity (BCVA) improvement of 8.4 letters and 7.6 letters at Week 52 and Week 96, respectively. The proportion of patients maintaining visual acuity was 95.3% and 92.4%, and the proportion of patients who gained 15 letters or more was 30.9% and 33.4% at Week 52 and Week 96, respectively. Visual gain was accompanied by decreases in CRTby –139 microns and –133 microns at Week 52 and Week 96, respectively [7; 8].

Although clinical data is currently unavailable, SB15 is expected to have similar clinical outcome to Eylea® based on the physicochemical and biological similarity.

1.5.3. Assessment of Potential Risks and Benefits

If left untreated, neovascular AMD progress overtime resulting in permanent visual loss. Treatment with anti-VEGF agents prevent disease progression and allow maintenance and improvement of vision. Although there have been alternative treatments such as PDT with verteprofin, macular photocoagulation, and transpupillary thermotherapy (TTT), these treatments failed to improve visual acuity and function as shown in anti-VEGF treatments. Benefit of Eylea® treatment including preservation of reading and driving vision, and ability to recognize face outweigh the potential risks of endophthalmitis, intraocular inflammation, retinal tear, retinal detachment, iatrogenic traumatic cataract, development of immunogenicity, and ATEs.

The available data demonstrate a high degree of physicochemical and biological similarity of SB15 with the reference medicinal product (Eylea®). The suitability of the methodology employed to evaluate the similarity of SB15 and Eylea® in a pharmaceutical setting were confirmed by EMA and the US FDA. The known and potential risks of receiving SB15 are expected to be similar to those seen with Eylea®. In conclusion, sufficient evidence exists for the justification of the administration of SB15, as a similar biological medicinal product of Eylea®, to subjects with neovascular AMD.

The study protocol provides adequate instructions for the detection and treatment of AEs arising following the administration of the IP.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is to demonstrate the equivalence in efficacy of SB15 compared to Eylea® in subjects with neovascular AMD.

2.1.2. Secondary Objectives

The secondary objectives are:

- To evaluate the safety of SB15 compared to Eylea®
- To evaluate the systemic exposure of SB15 compared to Eylea® in subjects participating in PK evaluation
- To evaluate the immunogenicity of SB15 compared to Eylea®

2.2. Study Endpoint

2.2.1. Primary Efficacy Endpoint

- Change from baseline in BCVA at Week 8

2.2.2. Secondary Endpoints

Secondary efficacy endpoints

- Change from baseline in BCVA over time up to Week 32 and up to Week 56
- Proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32 and Week 56 (proportion of subjects who maintained BCVA)
- Proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 32 and Week 56
- Change from baseline in central subfield thickness (CST) and total retinal thickness (TRT) at Week 4, and over time up to Week 32 and up to Week 56 (based on assessment by the central reading centre)
    - CST measured from internal limiting membrane (ILM) to RPE in 1-mm central subfield
    - TRT measured from ILM to Bruch's membrane (BM) in 1-mm central subfield
- Proportion of subjects with intra- or sub-retinal fluid on OCT at Week 32 and Week 56 (based on assessment by the central reading centre)
- Change from baseline in CNV area at Week 32 and Week 56 (based on assessment by the central reading centre)
- Proportion of subjects with active CNV leakage at Week 32 and Week 56 (based on assessment by the central reading centre)

Safety endpoints

- Incidence of ocular AEs or serious ocular AEs
- Incidence of non-ocular AEs and serious non-ocular AEs
- Incidence of intraocular inflammation and IOP increase
- Changes in vital signs and clinical laboratory parameters

PK endpoints

Blood samples for PK assessment will be collected in approximately **40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1])**.

- Pre-dose (trough serum concentration [C_{trough}])
    - Systemic exposure measured pre-dose at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40
- Post-dose (close to C_{max})
    - Systemic exposure measured once between 24 hours and 72 hours after IVT injection of IP at Week 0 (Day 1)

- Systemic exposure measured on 1 day, 2 days, and 3 days after the date of IVT injection of IP at Week 24 (total 3 times of PK sample collection for 3 consecutive days)

- Systemic exposure measured during the visit at Week 56 (EOS visit)

Immunogenicity endpoints

Blood samples for immunogenicity assessment will be collected pre-dose at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Immunogenicity sampling will also be collected during the visit at Week 56 (EOS visit) or early termination (ET) visit.

- Incidence of anti-drug antibodies (ADAs) to aflibercept
- Incidence of neutralising antibodies (NAbs) to aflibercept

Exploratory endpoint

- Proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56 (based on assessment by the central reading centre)

The QOL is assessed using National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

- Change from baseline in subscale scores and composite scores of NEI VFQ-25 at Week 32 and Week 56

3. Study Design

3.1. Overview of Study Design

This is a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, PK, and immunogenicity of SB15 compared to Eylea® in subjects with neovascular AMD. Subjects will be randomised in a 1:1 ratio to receive either SB15 or Eylea® (administered via IVT injection 2 mg [0.05 mL] every 4 weeks for the first 3 months, followed by 2 mg [0.05 mL] once every 8 weeks).

At Week 32, subjects in Eylea® treatment group will be randomised again in a 1:1 ratio to either continue on Eylea® treatment or be transitioned to SB15 treatment. IPs (SB15 or Eylea®) will be administered up to Week 48. Subjects receiving SB15 will continue to receive SB15 up to Week 48 but they will also follow the randomisation procedure to maintain masking.

The screening period is 21 days. IP (SB15 or Eylea®) will be given until 48 weeks and the last assessment will be done at Week 56, corresponding to the end of follow-up for all subjects.

3.2. Rationale for Study Design

3.2.1. Scientific Rationale for Study Design

The purpose of this study is to demonstrate the equivalence in clinical efficacy of Eylea® and SB15 in subjects with neovascular AMD.

Neovascular AMD is an indication approved by both EMA and the US FDA. In addition, neovascular AMD typically demonstrates homogeneous disease progressions with fewer compounding factors than DME or RVO. Though DME is one of the major causes of visual impairment in patients with diabetic retinopathy and thus a successful management of glycemia reduces the risk of developing progression

of DME, the disease progression of DME is influenced by numerous factors such as glycemia, hypertension, and lipid level [9]. RVO, involving a central retinal vein or a branch retinal vein, results in various vision loss of visual acuity (moderate to severe) [10]. For example, nonischaemic central RVO may resolve fully with good visual outcomes or may progress to the ischaemic type, while ischaemic central RVO usually presents with a severe visual loss [11].

Left untreated, neovascular AMD shows a common disease progression. For instance, it results in severe visual impairment with an average loss of around 4 lines of visual acuity within 2 years of disease onset [12]. Although this neovascular form accounts for only approximately 10% to 20% of the AMD cases, it is responsible for 80% to 90% of AMD-associated vision loss [13]. Therefore, neovascular AMD subjects with potential serious clinical outcome without an appropriate treatment are the most appropriate population to evaluate the similarity between SB15 and Eylea®.

In the pivotal studies for the treatment of neovascular AMD with Eylea®, the primary efficacy endpoints were the proportion of the subjects losing < 15 letters from baseline in visual acuity. The treatment of ranibizumab or aflibercept prevents the loss of visual acuity in approximately 90% of patients and improves visual acuity over time in terms of gaining letters.

The proportion of subjects losing < 15 letters in the visual acuity indicates the preventive effect of the loss of visual acuity. Thus, the proportion of subjects losing < 15 letters in the visual acuity would not be a sensitive primary endpoint to detect product-specific effect between the proposed biosimilar product and the reference product.

On the other hand, change from baseline in visual acuity could reflect any change (improvement or deterioration) in the disease status and is more sensitive in detecting product-specific effects between the two treatments. Thus, the mean change from baseline in BCVA is an appropriate primary endpoint for the proposed study.

Visual acuity was assessed monthly in neovascular AMD patients during the study period in pivotal studies with Eylea®. The efficacy plateau was reached approximately at Week 12 or Week 16. The most sensitive timing to detect any potential differences between the proposed biosimilar product and the reference product could be the visit before the efficacy plateau is reached.

Thus, to increase sensitivity, the evaluation of equivalence between SB15 and Eylea® is to be conducted at Week 8 before the efficacy plateau is reached.

Transition will be performed at Week 32 to investigate the clinical impact of switching from Eylea® to SB15.

3.2.2. Rationale for Dose Selection

The selection of the aflibercept dose and dosing interval is based on safety and efficacy data obtained from 2 pivotal clinical trials (VIEW 1 and VIEW 2) in neovascular AMD. Aflibercept administration in this study is 2 mg (0.05 mL or 50 microliters) administered by IVT injection every 4 weeks (approximately every 28 days, monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via IVT injection once every 8 weeks (2 months).

3.2.3. Rationale for Pharmacokinetic Assessments

Although a Phase I comparative PK study comparing the proposed biosimilar product to reference product is a fundamental component in supporting a demonstration of biosimilarity, a Phase I comparative PK study has not been necessary to support a demonstration of biosimilarity due to negligible systemic exposure following IVT injection of aflibercept. However, for supporting the

assessment of overall systemic safety of SB15 relative to Eylea®, systemic exposures will be collected and compared in the subgroup population (approximately 40 subjects, 20 subjects per treatment group in initial randomisation at Week 0 [Day 1]) in Phase III comparative efficacy study.

3.2.4. Rationale for Immunogenicity Assessments

Biological/biotechnology-derived proteins can induce an unwanted immune response that is triggered by more than a single factor and the consequence of immunogenicity may vary considerably, ranging from irrelevant to therapy to serious and life-threatening. Immune responses may affect both safety and effectiveness such as altering PK, inducing anaphylaxis, or promoting development of NAbs that neutralise the product as well as its endogenous protein counterpart.

In pivotal clinical studies of Eylea®, the frequency of ADAs has been reported as 1% to 4%. Observed levels of immunogenicity were relatively low and there were no differences in efficacy or safety between patients with or without immunoreactivity.

For subject safety and for demonstrating biosimilarity, immunogenicity will be assessed in this study according to the recommended guideline.

3.3. Duration of Study Participation

After Screening, the duration of study participation will be 56 weeks per subject including 48-week treatment period and 8-week post-treatment follow-up period.

3.4. Number of Subjects

Approximately 446 subjects are planned to be randomised from approximately 60 sites for study duration.

3.5. End of Study Definition

A subject is considered to have completed the study if he or she has completed the last visit or the last scheduled procedure shown in Table 1. The EOS is defined as completion of the last scheduled visit (Week 56) shown in Table 1. The end of this clinical study is defined as completion of the last subject's EOS visit.

4. Study Population

4.1. Overview

Eligibility for participation in this study will be based on the inclusion/exclusion criteria. Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the eye with the worse visual acuity will be selected as the study eye. If both eyes have equal visual acuity, the eye with clearer lens and ocular media will be selected at the Investigator's discretion. If there is no objective basis for selecting the study eye, factor such as ocular dominance, other ocular pathology, and subject preference should be considered by the Investigator in making the selection. Subject with only one functional eye (defined as BCVA of counting finger or less on the eye with worse vision) cannot be enrolled, even if otherwise eligible for the study.

4.2. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for the study:

1. Age ≥ 50 years at Screening

2. Treatment naïve, *active subfoveal CNV lesion secondary to AMD in the study eye

   * Active CNV indicates presence of leakage and intra- or sub-retinal fluid which should be confirmed by the central reading centre during Screening.

3. The area of CNV must occupy at least 50% of total lesion in the study eye (confirmed by the central reading centre during Screening)

4. Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars, and neovascularisation) in the study eye (confirmed by the central reading centre during Screening)

5. BCVA of 20/40 to 20/200 (letter score of 73 to 34, inclusive) using original series Early Treatment Diabetic Retinopathy Study (ETDRS) charts or 2702 series Number charts in the study eye at Screening and at Week 0 (Day 1) prior to randomisation

6. Non-childbearing potential female (e.g., permanently sterilized, postmenopausal [defined as 12 months with no menses without an alternative medical cause prior to Screening]), OR childbearing potential female subjects or male subjects with their (respectively male or female) partners who agree to use at least two forms of appropriate contraception method that can achieve a failure rate of less than 1% per year (e.g., established use of oral, injected, intravaginal, transdermal, or implanted hormonal contraceptive, placement of an intrauterine device or intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, physical barrier, sexual abstinence) from Screening until 3 months after the last IVT injection of IP

7. Written informed consent form (ICF) must be obtained from the subject prior to any study related procedure (if the subject is legal blindness or illiterate, an impartial witness should be present during the entire informed consent discussion)

8. Willingness and ability to undertake all scheduled visits and assessments

4.3. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for the study:

1. Study eye: Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion or presence of blood with the size of 1 DA or more involving the centre of fovea (confirmed by the central reading centre during Screening)

2. Study eye: Scar, fibrosis, or atrophy involving the centre of the fovea (confirmed by the central reading centre during Screening)

3. Study eye: Presence of CNV due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture, or pathologic myopia (confirmed by the central reading centre during Screening)

4. Study eye: Presence of retinal pigment epithelial tears or rips involving the macula (confirmed by the central reading centre during Screening)

5. Study eye: Presence of macular hole at any stage (confirmed by the central reading centre during Screening)

6. Study eye: Any concurrent macular abnormality other than AMD which could affect central vision or the efficacy of IP including but not limited to epiretinal membrane, vitreomacular

traction, macular telangiectasia, retinal vascular abnormality, etc. (confirmed by the central reading centre during Screening)

7. Study eye: Any concurrent ocular condition which, in the opinion of the Investigator, could either confound the interpretation of efficacy and safety of IP (e.g., ocular media opacities such as significant cataract, optic neuropathy etc.) or require medical or surgical intervention during the study period
8. Either eye: History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy) or DME
9. Study eye: Current vitreous haemorrhage
10. Either eye: Any previous IVT anti-VEGF treatment (e.g., bevacizumab, ranibizumab, aflibercept, pegaptanib, etc.)
11. Any previous systemic anti-VEGF treatment
12. Study eye: History of treatment involving macula such as macular laser photocoagulation, PDT, TTT, radiation therapy, or any ocular treatment for neovascular AMD
13. Any systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD within 30 days prior to randomisation, and such treatment or therapy will not be allowed during the study period. However, dietary supplements, vitamins, or minerals will be allowed.
14. Study eye: History of vitrectomy, scleral bucking (encircling), glaucoma filtration surgery, corneal transplantation, or pan-retinal photocoagulation
15. Study eye: Previous ocular (intraocular and peribulbar) corticosteroids injection/implant within 1 year prior to randomisation
16. Study eye: Topical ocular corticosteroids administered for ≥ 30 consecutive days or for ≥ 60 non-consecutive days within 90 days prior to randomisation
17. Use of systemic corticosteroids for 30 or more consecutive days within 90 days prior to randomisation (inhaled steroid is permitted).
18. Study eye: Any other intraocular surgery (including cataract surgery or Yttrium Aluminium Garnet [YAG] laser posterior capsulotomy in association with prior posterior chamber intraocular lens [IOL] implantation) or periocular surgery within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation.
19. Current use of medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, ethambutol, at Screening and such medications will not be allowed during the study period.
20. Study eye: Previous radiation therapy near the region of the study eye
21. Previous participation in clinical studies with IP to treat neovascular AMD in either eye.
22. Previous participation in clinical studies with IP to treat disease other than neovascular AMD within 90 days prior to randomisation (excluding dietary supplementary, vitamins, and minerals). Such participation will not be allowed during the study period even if the IP is dietary supplementary, vitamins, or minerals.

23. Subject with only one functional eye (defined as BCVA of counting finger or less on the eye with worse vision)
24. Study eye: Spherical equivalent of the refractive error demonstrating more than 6 diopters of myopia. For subjects who have undergone previous refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot exceed 6 diopters of myopia.
25. Study eye: Aphakia or absence of the posterior capsule (unless it occurred as a result of a YAG laser posterior capsulotomy in association with prior posterior chamber IOL implantation)
26. Either eye: Active or suspected ocular and periocular infection at Screening or at randomisation (e.g., infectious blepharitis, infectious conjunctivitis, infection in eyelid)
27. Either eye: Active intraocular inflammation including scleritis at Screening or at randomisation
28. Either eye: History of idiopathic or autoimmune-associated uveitis
29. Study eye: Uncontrolled ocular hypertension (defined as IOP ≥ 25 mmHg despite treatment with anti-glaucoma medication) at Screening
30. Known allergic reactions and/or hypersensitivity to any component of Eylea® or SB15
31. History of allergy to the fluorescein sodium for injection in angiography
32. History of a medical condition that would preclude scheduled study visits or safe use of IP in the opinion of the Investigator (e.g., history of organ transplant, immunocompromised subject, etc.)
33. Uncontrolled systemic disease including but not limited to uncontrolled diabetes mellitus (in the opinion of the Investigator), uncontrolled systemic hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 100 mmHg on optimal medical regimen), or uncontrolled atrial fibrillation (resting heart rate ≥ 110 beats per minutes) at Screening
34. Stroke, transient ischaemic attacks, or myocardial infarction within 180 days prior to randomisation
35. History of recurrent significant infections and/or current treatment for systemic infection
36. Severe renal impairment with dialysis or a history of renal transplant
37. Malignancy (other than non-melanoma skin cancer) under treatment or with history of metastatic disease
38. Women of childbearing potential who are pregnant, planning to become pregnant, lactating, or not using adequate birth control, as specified in protocol. For women of childbearing potential, a serum pregnancy test must result negative at Screening.
39. Employees of investigational sites, individuals directly involved with the conduct of the study, prisoners, and persons who are legally institutionalized

4.4. Screen Failures and Re-screening

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet one or more criteria required for participation in the trial during the screening procedures. A minimal set of screen failure information is required. If the subject is not randomised within 21 days after signing

the ICF, the subject should be screen failed.

Once a subject is screen failed for one eye, he or she should not be re-screened for the same eye. Screening for the other eye is allowed within the screening period and the subject will use the same screening number.

4.5. Replacement

Subjects who are discontinued from IP after randomisation will not be replaced.

5. Treatment and Investigational Product

5.1. Treatment of the Subjects

5.1.1. Dosing and Treatment Schedule

Subjects will be administered SB15 or Eylea® 2 mg via IVT injection into the study eye every 4 weeks for the first 3 months, followed by 2 mg once every 8 weeks up to Week 48 (a total of 8 administrations of IP) unless they are early discontinued from IP.

IP injection will be performed by the Investigator according to delegation of study personnel for this study.

Dosing visits will be allowed within ± 7 days of the scheduled dosing date (except Week 0 [Day 1], visit window not allowed). Dosing skip is defined when a subject does not receive the IP within 20 days after scheduled dosing date for Week 0 and/or Week 4 visits and 48 days after scheduled dosing date for the subsequent visits. Next scheduled dosing date and visit window should not be altered even though previous dosing is not performed on the scheduled dosing date or previous dosing is skipped.

5.1.2. Assignment of Subjects to Treatment Group

A unique subject number will be assigned to subjects at Screening. The subject number will be used to register the subject using the Interactive Web Response System (IWRS) and the subject will then be randomised (in a ratio of 1:1) to either SB15 or Eylea®. At Week 32, subjects receiving Eylea® will be randomised again in a 1:1 ratio to either continue on Eylea® treatment or be transitioned to SB15 treatment. Subjects receiving SB15 will continue to receive SB15 but they will also follow the randomisation procedure to maintain masking.

These randomisations will occur according to a computer-generated randomisation scheme which will randomise subjects at a centre-level. If a subject is withdrawn, the randomisation number(s) will not be re-used. At each study visit the Investigator or designee should contact the IWRS and an appropriate number of codes will be provided. These codes will indicate which vials should be dispensed to the subject. Further details on using the IWRS system are presented in the IWRS Manual.

5.1.3. Withholding Investigational Products

If a subject experiences an AE or the subject's safety or well-being could be compromised by IVT injection of IP at the Investigator's discretion, IPs should be withheld until the event has resolved or adequately repaired.

In case of following events in the study eye, IP must be withheld.

- ≥ 30 mmHg in pre-injection IOP measurement
- A retinal break

- Active or suspected ocular and periocular infection
- Active severe intraocular inflammation (e.g., 4+ anterior chamber cell/flare or 4+ vitritis)
- Performed or planned intraocular surgery within the previous or next 28 days

For the following events in the study eye, IP withholding should be considered by the Investigator.

- A decrease in BCVA of ≥ 30 letters compared with the last assessment of visual acuity
- A subretinal haemorrhage involving the centre of the fovea equal to or more than one DA in size or, if the size of the haemorrhage is ≥ 50%, of the total lesion area

In case of following events, IP must be permanently discontinued

- Rhegmatogenous retinal detachment or full-thickness macular hole in the study eye
- A subject misses any of first two doses or two consecutive doses during the study period after randomisation

NOTE: Please refer to the permanent IP discontinuation criteria in Section 7.2.1.

5.1.4. Masking

This study is double-masked. Subjects, Investigators, and other study personnel will remain masked to the treatment group assignment throughout the study period after randomisation.

To ensure the masking of the treatment group assignment, one carton will contain only one IP vial (SB15 or Eylea®). The carton and IP vial will be packed and labelled in identical appearance.

5.1.5. Unmasking

After all subjects complete the procedures at Week 24, or its corresponding visit, a limited number of identified individuals of the Sponsor and/or Contract Research Organisation (CRO) will be unmasked only for the reporting purpose to regulatory agency. Available efficacy and safety data, PK, and immunogenicity data will be analysed and reported in the main clinical study report (CSR). However, subjects, Investigators, and other study personnel will remain masked throughout the whole study period

After the last subject completes the procedures at Week 56 (EOS visit) or the corresponding visit and database is locked, the treatment group assignment will be unmasked and all study data will be analysed and reported in the final CSR.

Emergency and accidental unmasking are referred to in Section 8.1.7.

5.2. Investigational Product

5.2.1. Identity of Investigational Product

The IPs will be supplied to investigational site in one carton containing a single vial.

Details of the IPs are provided in Table 3.

Table 3. Investigational Products

Active Pharmaceutical Ingredient: Aflibercept	
SB15	
Formulation	Solution for intravitreal injection
Contents	One vial of 0.05 mL contains 2 mg aflibercept
Storage conditions	Stored in refrigerator (2-8°C), Do not freeze
US sourced Eylea®	
Formulation	Solution for intravitreal injection
Contents	One vial of 0.05 mL contains 2 mg aflibercept
Storage conditions	Stored in refrigerator (2-8°C), Do not freeze

5.2.2. Preparation and administration of Investigational Product

IPs should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

Using aseptic technique, all of the SB15 and Eylea® vial contents are withdrawn through a filter needle attached to a 1-mL syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for IVT injection. The filter needle should be replaced with a sterile 30-gauge x 1/2-inch needle for the IVT injection of IP. The contents should be expelled until the plunger tip is aligned with the line that marks 0.05 mL on the syringe.

The IVT injection procedure should be carried out under controlled aseptic technique in accordance with local practice.

Each vial should only be used for the treatment of a single eye.

5.2.3. Formulation, Packaging, and Labelling

Aflibercept (SB15 or Eylea®) will be supplied for use as an iso-osmotic solution for IVT injection (2 mg per vial for SB15 or US sourced Eylea®).

These IP vials will be packed and labelled in a double-masked manner for clinical use. The labels for carton and vial will contain the protocol number, unique identifier, Sponsor company name, expiry or retest date, storage condition, and all other details according to the Good Manufacturing Practice (GMP) and other relevant local laws and/or regulations.

The temperature will be monitored properly during the study period. The IP should be stored in a secure area and clearly labelled and stored away from other IP or medication to prevent confusion (for example in a clearly marked box on a separate shelf of the refrigerator).

A detailed guideline for IP preparation, administration, storage, and destruction will be provided in the Pharmacy Manual.

5.2.4. Product Storage and Stability

SB15 and Eylea® should be stored at 2°C to 8°C (36°F to 46°F) in the original carton until time of use to protect from light. The temperature will be monitored properly during the study period. If continuous monitoring is not available then manual temperature logs should be generated and recorded to ensure proper storage conditions. If a temperature deviation occurred, responsible person should contact the Sponsor to determine if the drug is still appropriate for use.

Do not freeze SB15 or Eylea® vials. The IPs must not be used beyond the expiration date.

5.2.5. Treatment Compliance and Investigational Product Accountability

All IP injections will be given by the Investigator or designee to ensure compliance. The exact date and time of IP injection must be recorded in the source documentation and the electronic case report form (eCRF).

The Investigator or designee should maintain the documents of IP accountability and record the IP kit number administered to subjects. IP accountability and dispensing records must be kept and contain the following information:

- The identification of the subjects to whom the drug was dispensed.
- The date(s) and quantity of the drug dispensed and exact package to the subject.
- The dispensing and inventory logs must be available for inspection by the monitor.

The used IP will be destructed at the investigational site according to local regulation after drug accountability done. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction at site is approved by the Sponsor. If destruction is authorised at the investigational site, the Investigator must ensure that the materials are destroyed in compliance with all applicable environmental regulations, institutional policies, and any instructions provided by the Sponsor. Destruction of the IP must be adequately documented.

5.3. Prohibited Medication or Therapy

Prohibited medication and therapy during the study period are presented in Table 4.

Any other medications that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the IP may be given at the Investigator's discretion.

Details of any medications including prescription drugs, non-prescription drugs, or any therapy (except dietary supplements, vitamins, or minerals) received locally (in the study eye and/or fellow eye) or systemically within 180 days prior to Screening will be collected until Week 56 (EOS visit) or early termination (ET) visit (including a follow-up visit or telephone interview). Details to be recorded include name (generic name preferred), dose number and unit, frequency of administration, route of administration, start and stop dates, and the AE it relates to (if applicable).

Table 4. Prohibited Medication and Therapy

Medication or Therapy	Time to be prohibited	Eye to be prohibited
IVT anti-VEGF treatment (e.g., bevacizumab, aflibercept, ranibizumab, pegaptanib, etc.) to treat neovascular AMD	• Prior to randomisation	• Study eye • Fellow eye
IVT anti-VEGF treatment except IP (SB15 or Eylea®)	• From randomisation to EOS/ET visit	• Study eye
IVT anti-VEGF treatment (e.g., bevacizumab, ranibizumab, pegaptanib, etc.) except aflibercept	• From randomisation to EOS/ET visit	• Fellow eye **NOTE:** If a subject has AMD in the fellow eye during the study period after randomisation, ONLY Eylea® (aflibercept) will be allowed to treat AMD.

Medication or Therapy	Time to be prohibited	Eye to be prohibited
Systemic anti-VEGF agents (e.g., bevacizumab, ziv-aflibercept, etc.)	• Prior to randomisation • From randomisation to EOS/ET visit	Not applicable
History of treatment involving macula such as macular laser photocoagulation, PDT, TTT, radiation therapy, or any ocular treatment for neovascular AMD	• Prior to randomisation • From randomisation to EOS/ET visit	• Study eye
Systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD. However, dietary supplements, vitamins, and minerals are allowed.	• Within 30 days prior to randomisation • From randomisation to EOS/ET visit	Not applicable
Vitrectomy, scleral bucking (encircling), glaucoma filtration surgery, corneal transplantation, or pan-retinal photocoagulation	• Prior to randomisation	• Study eye
Intraocular or peribulbar corticosteroid injection/implant	• Within 1 year prior to randomisation • From randomisation to EOS/ET visit	• Study eye
Topical ocular corticosteroids	• ≥ 30 consecutive days or ≥ 60 non-consecutive days within 90 days prior to randomisation	• Study eye
Use of systemic corticosteroids (inhaled steroid is permitted)	• ≥ 30 consecutive days within 90 days prior to randomisation	Not applicable
Any other intraocular surgery (including cataract surgery or YAG laser posterior capsulotomy).	• Within 90 days prior to randomisation • Within the previous 28 days before IP injection or next 28 days after IP injection during the study period	• Study eye
Peribulbar surgery	• Within 90 days prior to randomisation	• Study eye
Lid surgery	• Within 30 days prior to randomisation • Cosmetic lid surgery is not allowed from randomisation to EOS/ET visit	• Study eye
Medications known to be toxic to the lens, retina, or optic nerve including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin, and ethambutol	• From Screening to EOS/ET visit	Not applicable

Medication or Therapy	Time to be prohibited	Eye to be prohibited
Radiation therapy near the region of the study eye	• Prior to randomisation • From randomisation to EOS/ET visit	• Study eye
Ocular IPs to treat neovascular AMD	• Prior to randomisation • From randomisation to EOS/ET visit	• Study eye • Fellow eye
Systemic IPs to treat neovascular AMD	• Prior to randomisation • From randomisation to EOS/ET visit	Not applicable
Ocular IPs to treat diseases other than neovascular AMD	• Within 90 days prior to randomisation • From randomisation to EOS/ET visit	• Study eye • Fellow eye
Non-ocular IPs (excluding dietary supplements, vitamins, and minerals) to treat diseases other than neovascular AMD	• Within 90 days prior to randomisation • From randomisation to EOS/ET visit **NOTE**: During the study period, IPs such as dietary supplements, vitamins and minerals will be prohibited.	Not applicable

AMD = age-related macular degeneration; EOS = end of study; ET = early termination; IP = investigational product; IVT = intravitreal; PDT = photodynamic therapy; TTT = transpupillary thermotherapy; VEGF = vascular endothelial growth factor; YAG = Yttrium Aluminium Garnet

5.4. Fellow Eye Treatment

The fellow eye (non-study eye) will not be considered as an additional study eye. If a subject has AMD in the fellow eye, the subject could receive ONLY Eylea® during the study period and should remain in the study. Eylea® for AMD treatment in the fellow eye will be reimbursed or provided by the Sponsor during the study period after randomisation.

Fellow eye injection will be performed by the Investigator for this study. However, visits for fellow eye injection are not part of study, thus it will be scheduled in accordance with local practice. If a subject has both eyes injected on the same day, fellow eye should be injected after completion of IVT injection of IP on the study eye. Ocular AEs for the fellow eye and non-ocular AEs will be monitored and recorded after the written informed consent is obtained from the subject until Week 56 (EOS visit) or ET visit.

6. Study Assessment

6.1. Efficacy Assessment

6.1.1. Best Corrected Visual Acuity (BCVA)

Visual acuity will be assessed in both the study eye and fellow eye (non-study eye) at Screening and prior to IVT injection of IP at each visit until Week 48. Visual acuity will also be assessed in both the study eye and fellow eye (non-study eye) at Week 56 (EOS visit) or ET visit.

Visual acuity will be assessed using original series ETDRS charts or 2702 series Number charts at a starting distance of 4 meters, and then continue at a distance of 1 meter, if required by ETDRS protocol. Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit. Visual acuity testing must be performed before dilation of pupils and other ophthalmic procedures including FP (fundus photography)/FA (fluorescein angiography) and OCT assessment.

Visual acuity examiners and visual acuity lanes at investigational sites must be certified to ensure consistent measurement of BCVA prior to BCVA test to subjects.

A detailed instruction for conducting visual acuity testing and refraction will be provided in the Visual Acuity Testing Manual.

NOTE (refer to Section 8.4)

- A decrease in visual acuity of ≥ 15 letters from the last assessment of visual acuity should be reported as AE/serious AE (SAE) as appropriate.
- A decrease in visual acuity of ≥ 30 letters from the last assessment of visual acuity should be reported as SAE.
- A decrease in visual acuity to the level of light perception or worse should be reported as SAE.

6.1.2. Anatomical Parameters

The average retinal thickness in the central 1-mm area in the ETDRS grid (CST and TRT), the presence of intra- or sub-retinal fluid and sub-RPE fluid will be evaluated using OCT at Screening and prior to IVT injection of IP until Week 48. OCT will also be performed at Week 56 (EOS visit) or ET visit.

The CNV area and the presence of CNV leakage will also be evaluated using FP/FA at Screening and prior to IVT injection of IP at Week 32. FP/FA will also be performed at Week 56 (EOS visit) or ET visit.

6.2. Safety Assessment

6.2.1. Adverse Events

All AEs including ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs will be recorded from the time when the written informed consent is obtained from the subject to Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview). AEs should be elicited from subjects using non-leading questions such as ‘How are you feeling?’. Further information on AE monitoring and reporting is presented in Section 8.

6.2.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory test will be collected at Screening and prior to IVT injection of IP at Week 8, Week 32, and Week 40. Blood and urine samples for clinical laboratory test will be also collected at Week 56 (EOS visit) or ET visit. Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.

Blood samples will be analysed in central laboratory and urine samples will be tested in each investigational site by using a dipstick which will be provided by the Sponsor. A detailed process for clinical laboratory sampling, handling, storage, and shipping will be provided in the Central Laboratory Manual for safety lab testing.

The parameters for clinical laboratory tests are listed in Table 5.

Table 5. Parameters for Clinical Laboratory Tests

Haematology	Chemistry	Urinalysis[1]
· Haemoglobin · Haematocrit · Platelet count · White blood cell count (total and differential; neutrophils, lymphocytes, monocytes, eosinophils, and basophils)	· Sodium · Potassium · Creatinine · Glucose · Calcium · Phosphorus · Total bilirubin · Albumin · Alanine aminotransferase · Aspartate aminotransferase · Alkaline phosphatase · Lactate dehydrogenase	· Protein · Blood · Leucocytes · Nitrite · Glucose · Ketone · pH · Specific gravity · Bilirubin · Urobilinogen

[1] Urinalysis will be tested using a dipstick which will be provided by the Sponsor.

The Investigator will check any laboratory values which have potential significance in subject's safety during the study period. The Investigator will also evaluate any change in laboratory values. Each out of range result should be assessed as not clinically significant or clinically significant by the Investigator and reported as AE if relevant. All laboratory abnormalities that require intervention (e.g., IP withholding, IP discontinuation, concomitant medication) must be assessed as clinically significant and the clinically significant abnormalities should be recorded as AEs.

Clinical laboratory test including haematology, clinical chemistry, and urinalysis may be repeated during the study period at the Investigator's discretion.

When a scheduled laboratory test result would not be available due to the subject missing the visit or to technical issues (e.g., sampling error, handling error, tube breakage), it is recommended to perform or repeat the test as soon as available (e.g., at the next scheduled visit) at discretion of the Investigator.

For laboratory tests required at Screening, any missing result should be repeated within the screening period.

6.2.3. Physical Examination

Physical examination will be performed at Screening and Week 56 (EOS visit) or ET visit. The physical examination may include an assessment of the subject's general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory systems, and the subject's abdomen. Abnormal findings will be documented on the source document, and any clinically significant abnormality or worsening of a previously noted abnormality should be recorded as an AE.

Body weight will be measured and recorded at Screening and Week 56 (EOS visit) or ET visit, whereas height will be measured and recorded only at Screening.

6.2.4. Vital Signs

Vital signs include blood pressure, pulse rate, and body temperature. Vital signs will be assessed at Screening and prior to IVT injection of IP at each visit until Week 48. Vital signs will also be assessed

at Week 56 (EOS visit) or ET visit.

The Investigator should assess all vital signs and any clinically significant abnormalities should be reported as AE.

6.3. Pregnancy Test

For women of childbearing potential, a serum pregnancy test must be performed at Screening. The serum samples taken at Screening will be analysed in central laboratory.

At each visit during the study, women of childbearing potential must repeat a pregnancy test and a negative result shall be obtained before each IVT injection of IP. After randomisation, pregnancy tests will be performed either on serum or urine at the Investigator's discretion.

Additional unscheduled (serum or urine) pregnancy tests may be performed during the study period when any suspicion of pregnancy arises at the Investigator's discretion.

When a pregnancy test result at Screening would not be available due to technical issues (e.g., handling error, sampling error, tube breakage), the test shall be repeated in all circumstances (missing results at Screening would be considered as screening failure).

6.4. Ophthalmic Assessments

6.4.1. Full Ophthalmic Examinations

The full ophthalmic examination will consist of macroscopic examination of the eye and adnexa (including but not limited to abnormal pupil reaction to light and afferent pupillary defect, etc.), slit lamp biomicroscopy, IOP measurements, and indirect ophthalmoscopy. Abnormal finding should be assessed as not clinically significant or clinically significant by the Investigator and reported as AE if relevant.

During study period, fellow eye will be evaluated according to local practice to determine whether or not AMD develops. If the AMD is diagnosed in the fellow eye during the study period, this event should be also reported as an AE.

Slit lamp biomicroscopy

The slit lamp examination of anterior segment (conjunctiva, cornea, lens, iris, aqueous reaction [flare and cells]) will be performed on both the study eye and fellow eye at Screening and prior to IVT injection of IP at each visit until Week 48**.** Slit lamp examination will also be performed at Week 56 (EOS visit) or ET visit.

Grading scales for anterior chamber flare and cells are provided in APPENDIX A and APPENDIX B.

NOTE

The following events should be reported as AE of special interest (AESI) (Section 8.3):

- Any case of intraocular infection (suspected infection) such as endophthalmitis
- Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis
- Iatrogenic traumatic cataract

IOP measurement

IOP will be measured on the study eye at Screening as well as prior to IVT injection of IP and 30-60 minutes after IVT injection of IP at each visit until Week 48. IOP will also be measured at Week 56 (EOS visit) or ET visit. In case of any abnormalities, relevant immediate intervention and follow up per standard of care should be taken to ensure subjects safety. AEs/SAEs should be reported as appropriate (Section 8).

IOP should be measured using Goldmann applanation tonometry. The same method of IOP measurement must be used in each subject from Screening to Week 56 (EOS visit) or ET visit. In case IOP is measured prior to OCT and FP/FA, IOP should be carefully measured not to cause corneal erosion, which might affect the quality of OCT/FP/FA images.

NOTE

The following events should be reported as AESI (Section 8.3):

- New onset pre-injection IOP of ≥ 25 mmHg
- Post-injection IOP of ≥ 35 mmHg

Indirect ophthalmoscopy

Indirect ophthalmoscopy using a standard way (i.e., usually using a head-mounted light source and a 20-30 lens) will be performed on the study eye to evaluate posterior segment including vitreous, optic nerve, macula, peripheral retina, or retinal vasculature at Screening and prior to IVT injection of IP and 0-15 min after IVT injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at Week 56 (EOS visit) or ET visit.

Vitreous will be assessed for inflammatory response and the grading scale for vitreous haze is provided in APPENDIX C.

NOTE

The events should be reported as AESI (Section 8.3):

- Retinal pigment epithelial tear
- Subretinal haemorrhage with the size of 1 DA or more involving the centre of the fovea, or if the size of the haemorrhage is ≥ 50% of the total lesion area

6.4.2. Optical Coherence Tomography (OCT)

OCT will be performed on both eyes at Screening and those images taken from both eyes will be sent to the central reading centre.

OCT will be performed on the study eye prior to IVT injection of IP at each study visit until Week 48. OCT will also be performed on the study eye at Week 56 (EOS visit) or ET visit. OCT images taken from the study eye will be sent to the central reading centre. Retinal thickness (CST and TRT), the presence of intra- or sub-retinal fluid, and sub-RPE fluid will be evaluated in the central reading centre. The Investigator will evaluate the OCT images sent to the central reading centre in terms of safety assessment.

Site staffs who will perform OCT scans in this study must be certified by the central reading centre before performing study procedure. Only OCT devices certified by the central reading centre are allowed to be used in this study. If one or more OCT devices are certified in an investigational site, a subject must use the same OCT system from the same manufacture consistently from Screening to Week

56 (EOS visit) or ET visit.

All original OCT images will be kept in the investigational site and copies will be sent to the central reading centre for analysis and archiving

A detailed instruction for OCT image acquisition and transmission will be provided in the Image Handbook.

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

FP/FA will be performed on both eyes at Screening and those images taken from both eyes will be sent to the central reading centre.

FP/FA will also be performed on the study eye prior to IVT injection of IP at Week 32 and at Week 56 (EOS visit) or ET visit. FP/FA images taken from the study eye will be sent to the central reading centre. Lesion type, total lesion area, CNV area, haemorrhage, and the presence of CNV leakage will be evaluated in the central reading centre. The Investigator will evaluate the FP/FA images sent to the central reading centre in terms of safety assessment.

Site staffs who will perform FA/FP in this study must be certified by the central reading centre before performing study procedure. Only FP/FA device certified by the central reading centre is allowed to be used in this study. If one or more FP/FA devices are certified in an investigational site, a subject must use the same FP/FA system from the same manufacture consistently from Screening to Week 56 (EOS visit) or ET visit.

All original FP/FA images will be kept in the investigational site and copies will be sent to the central reading centre for analysis and archiving. If any significant change in the posterior pole (e.g., subretinal haemorrhage, macular hole, vitreous haemorrhage or opacity, retinal detachment, etc.) is detected with fundus examination, additional FP and/or FA can be performed at the Investigator's discretion, but the images will not be sent to the central reading centre.

A detailed instruction for FP/FA image acquisition and transmission will be provided in the Image Handbook.

6.5. NEI VFQ-25

Vision-related QOL will be assessed using the NEI VFQ-25 with interviewer administered format (APPENDIX D). NEI VFQ-25 will be performed at Week 0 (Day 1) after randomisation. Then, NEI VFQ-25 should be performed before dilation of pupils at Week 32 and at Week 56 (EOS visit) or ET visit.

All questionnaires will be administered in the local language. The Investigator or delegated site staff will conduct a questionnaire survey with the subject in a quiet room. The responses collected from the subject will be recorded on a paper questionnaire and entered successively into the eCRF.

6.6. Other Assessments

6.6.1. Pharmacokinetic (PK) Assessment

Blood samples for PK assessment will be collected **in approximately 40 subjects (20 subjects per treatment group in initial randomisation at Week 0 [Day 1])** participating in PK evaluation.

The investigational sites which are interested in taking part in PK sub-study and are also fully equipped as per study requirement will be selected before the study starts. The selected investigational sites will

be defined as PK investigational sites which are registered in the IWRS.

Subjects screened at PK investigational sites will be asked to participate in the PK sub-study. Only subjects who consent to the PK blood sampling will be enrolled in this sub-study. Once the threshold of PK subjects is reached, the following subjects enrolled at the PK investigational sites will be 'non-PK subjects' for whom blood sampling for PK assessment will not be performed.

Blood samples for pre-dose PK assessment will be collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for post-dose PK assessment will be collected **once between 24 and 72 hours after IVT injection of IP at Week 0 (Day 1)** and **on 1 day, 2 days, and 3 days after the date of IVT injection of IP at Week 24 (total 3 times of PK sample collection for 3 consecutive days)**. Blood samples for PK assessment will also be collected during the final visit at Week 56 (EOS visit). Blood samples for PK assessment should not be collected at ET visit. Subjects' samples may be used for method validation and/or investigation, only for this study.

A detailed process for PK sampling, handling, storage, and shipping will be provided in the Central Laboratory Manual for PK and Immunogenicity.

6.6.2. Immunogenicity Assessment

Blood samples for immunogenicity assessment will be collected in all randomised subjects.

Blood samples for immunogenicity assessment will be collected prior to IVT injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 24, Week 32, and Week 40. Blood samples for immunogenicity assessment will also be collected at Week 56 (EOS visit) or ET visit. Subjects' samples may be used for method validation and/or investigation, only for this study.

A detailed process for immunogenicity sampling, handling, storage, and shipping will be provided in the Central Laboratory Manual for PK and Immunogenicity.

7. Study Procedures

During this study, efficacy, safety, PK, and immunogenicity assessments will be performed. All results shall be recorded in the source documents along with the date and time the procedures were performed. Such assessments must be performed at the times outlined in Table 1.

7.1. Study Flow and Visit Schedule

NOTE: The most critical assessment will be at Week 8 as this is the visit for primary endpoint assessment. Thus, every effort should be made to adhere to the visit schedule for the subjects.

7.1.1. Screening Visit (Visit 1, D-21 to D-1)

Screening shall be performed within 21 days before randomisation (i.e., excluding the day of randomisation).

- Written informed consent

The Investigator must discuss the study with the subject and obtain written informed consent from the subject prior to any study related procedures. If the subject is not randomised within 21 days after signing the ICF, the subject will be screen failed. Once a subject is screen failed for one eye, he or she shall not be re-screened for the same eye. Screening for the other eye is allowed within the screening period (Section 4.4).

The following procedures should be performed:

- Evaluate subject compliance with all inclusion and exclusion criteria
- Demographic data
- Medical & ophthalmic history
- Physical examination (including body weight and height)
- Vital signs (temperature, blood pressure, and pulse rate)
- Pregnancy test for women of childbearing potential (serum)
- Blood and urine sampling for clinical laboratory tests
  - Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including FP/FA and OCT assessment)
    - The Investigator must confirm that the subject can read between 73 letters and 34 letters, inclusive, in the study eye (Please see inclusion criteria #5). If the subject is not eligible at this point, no further study assessment should be performed, and the subject should be screen failed.
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit.
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT in both eyes (images should be sent to central reading centre)
  - FP & FA in both eyes (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant and previous medication or therapy

Investigators are advised to send for review OCT and FP/FA images to the central reading centre as soon as possible as this could take more time than the other procedures and Investigators should avoid exceeding the allowed 21 days for completing Screening. If the subject is screen failed due to any reasons before the Investigator send OCT and/or FP/FA images to the central reading centre, the Investigator does not have to send the subject's OCT and/or FP/FA images to the central reading centre.

The central reading centre will send central review results confirming the subject's eligibility to the investigational site. If a subject is confirmed as ineligible from the central reading centre due to poor

quality of images, but the investigator still considers the subject eligible for the study, the Investigator may be allowed to send a second set of images to the central reading centre. In this case, only FP/FA or OCT (and not all other screening procedures) will be repeated and the result should be confirmed within the screening period of 21 days. Only in this case, the subject will retain the subject number initially assigned.

Once the subject is confirmed eligible for the study, the subject will be reminded in particular of the study restrictions such as contraception, prohibited medications, and other study requirements. The Investigator shall pay attention to each subject's particular needs in order to provide the necessary training and advice and foster protocol compliance.

7.1.2. Treatment Period

7.1.2.1. Visit 2 (Week 0 [Day 1])

The following procedures should be performed

- Evaluate subject compliance with all inclusion and exclusion criteria
- BCVA examination
  - The Investigator must confirm that the subject can read between 73 letters and 34 letters, inclusive, in the study eye using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment) **prior to randomisation** (Please see inclusion criteria #5).
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit.
- After a subject's eligibility is confirmed by the central reading centre and the Investigator, subject should be randomised to either SB15 or Eylea® treatment group.
- The first IVT injection of IP and all other study procedures (except blood sampling for post-dose PK assessment) should be performed at the same day of randomisation.

✓ **Before IVT injection of IP**

- NEI VFQ-25 (prior to dilation of pupil after randomisation)
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy

- OCT (images should be sent to the central reading centre)
- IOP using Goldmann applanation tonometry

- AE monitoring
- Review of concomitant and previous medication or therapy

✓ **IVT injection of IP**

- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- Blood sampling for PK for subjects participating in PK evaluation (once between 24 hours and 72 hours post-dose)
- AE monitoring

7.1.2.2. Visit 3 (Week 4 ± 7 days)

✓ **Before IVT injection of IP**

- Vital signs (temperature, blood pressure, and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to the central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**
- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**
- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- AE monitoring

7.1.2.3. Visit 4 (Week 8 ± 7 days)

✓ **Before IVT injection of IP**
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood and urine sampling for clinical laboratory tests
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**
- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**
- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)

- IOP using Goldmann applanation tonometry (30-60 min post-dose)

- AE monitoring

7.1.2.4. Visit 5 (Week 16 ± 7 days)

✓ **Before IVT injection of IP**

- Vital signs (temperature, blood pressure, and pulse rate)
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential.
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to the central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**

- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- AE monitoring

7.1.2.5. Visit 6 (Week 24 ± 7 days)

✓ **Before IVT injection of IP**

- Vital signs (temperature, blood pressure, and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing

potential

- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to the central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**

- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- Blood sampling for PK for subjects participating in PK evaluation (on 1 day, 2 days, and 3 days after the date of IVT injection of IP; total 3 times of PK sample collection for 3 consecutive days)
- AE monitoring

7.1.2.6. Visit 7 (Week 32 ± 7 days) – Re-randomisation

✓ **Before IVT injection of IP**

- NEI VFQ-25 (prior to dilation of pupil)
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood and urine sampling for clinical laboratory tests
  - Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation

- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including FP/FA or OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to the central reading centre)
  - FP & FA (images should be sent to the central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**
- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**
- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- AE monitoring

7.1.2.7. Visit 8 (Week 40 ± 7 days)

✓ **Before IVT injection of IP**
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood and urine sampling for clinical laboratory tests
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:

- BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
  - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
- Slit lamp biomicroscopy
- Indirect ophthalmoscopy
- OCT (images should be sent to the central reading centre)
- IOP using Goldmann applanation tonometry

- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**

- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- AE monitoring

7.1.2.8. End of Treatment Visit (Visit 9, Week 48 ± 7 days)

End of treatment (EOT) visit is defined as the visit for the last scheduled IVT injection of SB15 or Eylea®. The Sponsor will not provide IP (SB15 or Eylea®) to subjects after they complete the EOT visit.

✓ **Before IVT injection of IP**

- Vital signs (temperature, blood pressure, and pulse rate)
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy

- OCT (images should be sent to the central reading centre)
- IOP using Goldmann applanation tonometry

- AE monitoring
- Review of concomitant medication or therapy

✓ **IVT injection of IP**

- IP (SB15 or Eylea®) will be given in the study eye.

✓ **After IVT injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)
  - IOP using Goldmann applanation tonometry (30-60 min post-dose)
- AE monitoring

7.1.3. End of Study (EOS) Visit (Visit 10, Week 56 ± 7 days)

EOS visit is defined as 8 weeks (± 7 days) after the last scheduled IVT injection (i.e., Week 48) of IP. All subjects who complete the last scheduled IVT injection at Week 48 will conduct EOS visit.

- NEI VFQ-25 (prior to dilation of pupil)
- Physical examination (including body weight)
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood and urine sampling for clinical laboratory tests
  - Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.
- Blood sampling for immunogenicity
- Blood sampling for PK for subjects participating in PK evaluation
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including FP/FA or OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit
  - Slit lamp biomicroscopy

  - Indirect ophthalmoscopy
  - OCT (images should be sent to the central reading centre)
  - FP & FA (images should be sent to the central reading centre)
  - IOP using Goldmann applanation tonometry
- AE monitoring
- Review of concomitant medication or therapy

7.1.4. Early Termination (ET) Visit

Subjects who discontinue from the study at any time before study termination will be required to attend an ET visit.

The ET visit is recommended to be performed at 8 weeks (± 7 days) after the last IVT injection of IP. When this schedule is not available (e.g., due to subject not available), the ET visit should still be performed as soon as available and no later than Week 56 from the first IVT injection of IP.

In particular, for safety monitoring, if ET visit occurs before 7 weeks after the last IVT injection of IP, a follow-up visit or telephone interview will be pursued at 8 weeks (± 7 days) after the last IVT injection of IP in order to collect AEs and related concomitant medications. If a subject is not available, a follow-up visit or telephone interview will be performed as soon as possible, but no later than Week 56 from the first IVT injection of IP. Every attempt shall be made to contact the subject for safety monitoring unless the subject has withdrawn his/her consent to collect safety-related information (Section 7.2.1).

The following procedures will be performed:

- NEI VFQ-25 (prior to dilation of pupil)
- Physical examination (including body weight)
- Vital signs (temperature, blood pressure, and pulse rate)
- Blood and urine sampling for clinical laboratory tests
  - Urine samples must be collected before performing FA to avoid interference with fluorescein in urinalysis.
- Blood sampling for immunogenicity
- Pregnancy test (serum or urine at the Investigator's discretion) for all women of childbearing potential
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and other ophthalmic procedures including FP/FA or OCT assessment)
    - Subject must use the same type of chart consistently from Screening to Week 56 (EOS visit) or ET visit

- Slit lamp biomicroscopy
- Indirect ophthalmoscopy
- OCT (images should be sent to the central reading centre)
- FP & FA (images should be sent to the central reading centre)
- IOP using Goldmann applanation tonometry

- AE monitoring
- Review of concomitant medication or therapy

If a subject discontinues the study treatment to receive other alternate treatment, ET visit should be performed prior to starting the alternate treatment (Section 7.2.1).

7.1.5. Unscheduled visit

Unscheduled visit is allowed during study period at the discretion of the Investigator, if deemed clinically necessary. Any tests, procedures, or assessments performed at the unscheduled visits will be recorded in the source documents and be entered in the eCRF if entry is available.

7.2. Discontinuation

7.2.1. Subject Discontinuation from Study Treatment

The subject must be permanently discontinued from IPs in the event of any of the following:

- Consent withdrawal by subject
  - If the subject withdraws his/her consent, the Investigator must inquire the reasons for consent withdrawal as to whether it is related to the study (e.g., documented lack of efficacy, AE, or pregnancy); however, the subject could refuse to provide such reason.
  - If the main reason for consent withdrawal is considered related to the study, the Investigator may select the appropriate reason for withdrawal (other than just consent withdrawal) from a pre-defined list as below.
- Any newly developed or aggravated ophthalmic abnormality other than AMD in the study eye which could interfere with evaluation of efficacy or safety of IP (e.g., retinal vascular abnormality, glaucoma, etc.)
- Rhegmatogenous retinal detachment or full-thickness macular hole in the study eye
- AEs in the study eye which in the opinion of the Investigator and/or subject would require IP discontinuation (e.g., intraocular inflammation, subretinal haemorrhage, vitreous haemorrhage, local infection, etc.)
- Decision by the Investigator that the subject requires alternate treatment to treat neovascular AMD (e.g., other anti-VEGF agents, PDT, intravitreal gas injection, vitrectomy, or other surgical intervention) in the study eye

  Note: ET visit should be performed prior to starting the alternate treatment.
- Development of DME in either eye

- Any other AEs and/or interventions considered intolerable as expose the subject to a risk that outweighs the benefits of participating in the study in the opinion of the Investigator and/or subject
- Decision by the Sponsor that IP discontinuation is in the subject's best medical interest
- Protocol deviations 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
- IP non-compliance
  - A subject misses any of first two doses (IVT injection of IP at Week 0 [Day 1] and Week 4) after randomisation
  - A subject misses two consecutive doses during the study period after randomisation
- Administrative decision by the Investigator and/or the Sponsor 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
- Lost to follow-up

  Note: Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject.
- Unmasking (except unmasking for the purpose of regulatory reporting)
- Pregnancy of study subject
- Death of any cause

If a subject is prematurely discontinued from IP due to any of the above described reasons excluding death, the subject will complete the ET procedures (Section 7.1.4) and will be requested if he/she agrees to provide written consent for continuing the follow-up and further data collection subsequent to his or her ET visit.

If a subject who is permanently discontinued from IP agrees to continue follow-up for associated clinical outcome information until Week 56, the consent form for ET subject shall be requested to be signed by the subject for this limited participation in the study, and the subject will continue to be assessed for all study endpoints per protocol until the subject withdraws consent or receives other non-protocol defined treatment, whichever occurs earlier.

If a subject does not agree to continue follow-up of associated clinical outcome information, the subject will be terminated from the study accordingly. The data and blood samples collected on the subject up to ET visit remains in the study database and no further data will be collected.

In all cases, the reason for IP discontinuation must be recorded in the eCRF and in the subject's medical record.

7.2.2. Discontinuation of Study Sites

Investigational site participation may be discontinued if the Sponsor, the Investigator, or the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the investigational site judge it necessary for any reason. Health authorities and IRB/IEC will be informed about the discontinuation of the study sites in accordance with applicable regulations.

7.2.3. Discontinuation of the Study

The Sponsor may terminate this study prematurely for reasonable cause provided that written notice is submitted to the Investigator, IRB/IEC, and relevant authorities in advance of the intended termination:

- Unsatisfactory enrolment with respect to quantity or quality
- Discontinuation of development of the study drug
- The decision by the Sponsor to terminate the study based on medical/ethical, business decision/strategic, or study conduct-related reasons

If the study is terminated or discontinued prematurely, the Sponsor will promptly notify to the Investigator. The Investigator may be informed of additional procedures to be followed in order to assure that adequate consideration is given to the protection of the subject's welfare and best interests.

Health authorities and IRB/IEC will be informed about the discontinuation of the study in accordance with applicable regulations.

8. Safety Monitoring and Reporting

8.1. Adverse Events (AEs)

8.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject, clinical investigation subject administered the medicinal (investigational) product or other protocol-imposed intervention and which does not necessarily have to have a causal relationship with this treatment or intervention. An AE can therefore be an unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of any dose of a medicinal (investigational) product or other protocol-imposed intervention regardless of attribution.

All AEs including ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs will be collected from the time when the written informed consent is obtained from the subject until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).

In particular, if the AMD is diagnosed in the fellow eye during the study period, this event should be also reported as an AE.

Pre-existing conditions and any abnormal findings from assessments at the time of Screening which are not related to protocol-imposed intervention (i.e., before the first IP administration) should not be reported as AEs, but reported among the medical history of the subject. However, pre-existing conditions which worsen (i.e., change in severity) that meet the definition of an AE during the study period are to be reported as AEs.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs assuming that the medical condition for which the procedure was performed is known. The underlying medical condition should be reported as AE accordingly. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

By definition, any event that emerges during IP treatment having been absent pre-treatment, or worsens relative to the pre-treatment state will be considered as a **Treatment-emergent Adverse Event (TEAE)**. For the purposes of safety analysis, TEAEs will be collected and analysed.

8.1.2. Clinically Significant Abnormality

If there are any abnormalities discovered during the laboratory test, physical examination, vital signs, and/or other safety assessments and the abnormality is assessed clinically significant by the Investigator, it should be reported as an AE. This does not apply to pre-existing conditions which have been documented at Screening or if the abnormality is consistent with a current diagnosis (underlying disease or other AEs). If it is not specified or defined elsewhere in the protocol, clinically significant abnormalities may include the events that led to a clinically significant intervention, including withdrawal of the IP treatment, significant additional concomitant medication, and others, upon medical judgement by the Investigator.

If a clinically significant laboratory finding, or any other abnormality emerging from safety assessments, is not associated with a diagnosis of a disease or syndrome, the abnormality itself should be reported as an AE in the eCRF. If the abnormality can be characterised by a precise clinical term, the clinical term should be reported as the AE. For example, an elevated serum potassium concentration of 7.0 mEq/L should be reported as 'hyperkalemia'. Observations of the same clinically significant abnormality from visit to visit should not be repeatedly reported as AEs in the eCRF, unless their severity grade, seriousness, or etiology changes.

8.1.3. Period of Observation for Adverse Events

All AEs (ocular or non-ocular), including SAEs, will be collected from the time of signing the written informed consent until Week 56 (EOS visit). However, if a subject would withdraw from the study prior to Week 56 (EOS visit), AEs and SAEs shall be collected as follows:

- If the subject would withdraw after receiving the first dose of IP, AEs and SAEs should be actively collected up until the latter, either ET visit or a follow-up visit/telephone interview (Section 7.1.4). In addition, if the subject agrees to continue the follow-up of clinical-associated outcomes until Week 56 (Section 7.2.1), data collected until week 56 will be also recorded.
- If the subject would withdraw during the screening period, **before** enrolment, and/or **before** receiving the first dose of IP, AEs and SAEs should be collected up until the time the subject withdraws.

Unresolved AEs should be followed up until Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview), as available and consented to by the subject, and the collected follow-up information will be recorded in the eCRF. The Investigator should observe the AEs for appropriate medical care of the subject until AE resolution or stabilisation up to Week 56 (EOS visit) or ET visit (including a follow-up visit or telephone interview).

8.1.4. Reporting Adverse Events

AEs are to be reported in the eCRF and reviewed by the Investigator. When reporting an AE, a diagnosis (when possible and appropriate), rather than each individual sign and symptom, should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (Section 8.2.1 for SAE definition). If an AE is classified as an SAE, it must be reported to the Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2. For an SAE, a diagnosis corroborated with a description of signs and symptoms as well as other supporting information (e.g., results of exams) that led to the diagnosis should be described in the SAE report form and reported to the Sponsor, or its designated representative, according to the procedures described in Section

8.2.2.

8.1.5. Severity Assessment

The Investigator is responsible for assessing and reporting the severity of AEs.

Following classifications should be used to classify AEs:

- Mild events are usually transient and do not interfere with the subject's daily activities,
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities,
- Severe events interrupt the subject's usual daily activities.

8.1.6. Causality Assessment

The Investigator is responsible for assigning a causal relationship to each AE. The causal relationship between the IP and the AE should be defined as not related (no) or related (yes).

Events should be classified as 'related' if there is a reasonable possibility that the IP caused the AE. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Events should be classified as 'not related' if there is no reasonable possibility that the IP caused the AE.

8.1.7. Emergency Unmasking for Safety Reasons and Accidental Unmasking

During the study period after randomisation, emergency unmasking should be considered only when knowledge of the treatment group assigned to the subject is deemed essential for the subject's safety by the Investigator. In such situations, emergency unmasking may be performed by the Investigator (or designee) through the IWRS system. In case failure of unmasking through IWRS system, the Investigator will follow the manual unmaking process described in IWRS manual.

Overall, the Investigator (or designee) is responsible for 1) identifying clinical courses or situations where the emergency medical care of a study subject requires knowledge of their masked treatment assignment, 2) implementing the emergency unmasking procedures with associated communication pathways, 3) documenting the reasons for unmasking and which parties were unmasked as appropriate, and 4) informing their local IRB/IEC and the Sponsor of all subjects whose assignment was unmasked.

Similarly, in case of accidental unmasking (i.e., accidental in that it occurred but it was not deliberated by the Investigator), as soon as the Investigator becomes aware that the treatment group assigned to a subject is unmasked, the Investigator should promptly document the accidental unmasking and inform the Sponsor and the CRO (within 24 hours) of the unmasking occurrence as well as of possible route causes, if information is available.

In general, pertinent information regarding the circumstances of unmasking of a subject's treatment group must be documented in the subject's source documents. This includes who performed the unmasking, the subject(s) affected, the reason for the unmasking, the date of the unmasking, and the relevant IP information.

Important note: Emergency or accidental unmasking is one of the reasons for subject's discontinuation from study treatment (Section 7.2.1).

8.1.8. Expectedness Assessment

Expectedness of AEs will be assessed by reference safety information (RSI) in the Investigator's Brochure (IB). The latest SmPC of Eylea®, Annex I of EPAR Product Information posted on the EMA website (https://www.ema.europa.eu/en) will be used as reference when assessing the expectedness of AEs for the reference product after database lock and planned unblinding or emergency unblinding.

8.1.9. Withdrawal due to Adverse Events

Subject's withdrawal from the IP due to an AE should be distinguished from withdrawal due to personal reasons. Subjects withdrawn due to an AE are those who are discontinued from IP because, in the opinion of the Investigator, the risks related with the AE may outweigh the potential benefits of continuing the participation in the study. Thus, the decision of withdrawal due to an AE shall be taken by the Investigator in the subject's best interest due to safety reasons. Subjects withdrawn due to an AE should be followed up for safety until the time point specified in Section 8.1.3. If subjects cannot be followed, the reason(s) will be documented by the Investigator (e.g., lost to follow-up, withdrawal of subject's consent to be followed up). When a subject withdraws from the IP due to a SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.

8.2. Serious Adverse Events

8.2.1. Definition of Serious Adverse Event

An SAE is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defects
- Is medically important

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse.

The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning.

In addition, sight-threatening ocular adverse event will be reported as SAE if it meets one or more of the following criteria:

- A decrease in visual acuity of ≥ 30 letters from the last assessment of visual acuity
- A decrease in visual acuity to the level of light perception or worse
- Severe intraocular inflammation (e.g., 4+ anterior chamber cell/flare or 4+ vitritis)
- Requirement of surgical intervention to prevent permanent loss of vision (e.g., vitrectomy, vitreous tap or biopsy with IVT injection of antibiotics, laser treatment, IVT gas injection, or retinal cryopexy)
- In the investigator's opinion, medical intervention may be required to prevent permanent loss of vision

8.2.1.1. Life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.2.1.2. Hospitalisation

AEs reported from clinical studies associated with inpatient hospitalisation or prolongations of hospitalisation are considered serious.

Any admission to a healthcare facility more than 24 hours meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the medical floor to a coronary care unit, neurological floor to a tuberculosis unit). Staying at the observation unit in the emergency room for more than 24 hours qualifies for hospitalisation.

Any events leading to a subsequent emergency room visit or inpatient hospitalisation for less than 24 hours may be regarded as medically important for its seriousness criteria, at the discretion of the Investigator based on medical judgement.

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a pre-existing (prior to ICF signed) condition not associated with the development of a new AE or with a worsening of the pre-existing condition
- Diagnostic admission (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., study subject has no place to sleep)
- Administrative admission (e.g., for a regular check-up)
- Protocol-specified admission during a clinical study (e.g., for a procedure required by the study protocol)
- Elective admission not associated with an AE (e.g., for elective cosmetic surgery)
- Pre-planned treatments or surgical procedures

: Pre-planned treatments or surgical procedures should be noted in the relevant source document for the individual subject.

8.2.2. Reporting Serious Adverse Events

SAEs will be collected as generally specified in Section 8.1.3 and, in case of ET visit, as detailed in Section 7.1.4. All SAEs must be reported to the Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event. A paper SAE form can be used as backup in every case when the electronic form would not be available.

Date and time (wherever possible) of the Investigator becoming aware of the SAE will be recorded in the SAE form and source document as appropriate.

In particular, if the SAE is fatal or life-threatening, the Sponsor must be notified immediately (within 24 hours), irrespective of the extent of available AE information. This timeframe also applies to additional (follow-up) information that becomes available on previously forwarded SAE reports. The Sponsor will then apply expedited reporting procedures according to local and international regulations as appropriate.

The Investigator is obligated to pursue and provide information to the Sponsor on all SAEs in accordance with the required reporting timeframe of 24 hours from the Investigator's awareness. In addition, the Investigator may be requested by the Sponsor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the SAE, which should be provided in sufficient detail so as to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, if an autopsy is performed upon consent from responsible parties, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

Follow-up information for the SAE should be actively sought and submitted by the Investigator as the information becomes available.

8.3. Adverse Events of Special Interest (AESI)

The following AEs in the study eye will be classified as AESIs in this study:

- Intraocular pressure increase
  - New onset pre-injection IOP of ≥ 25 mmHg
  - Post-injection IOP ≥ 35 mmHg
- Any case of intraocular infection (suspected infection) such as endophthalmitis
- Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis
- Iatrogenic traumatic cataract
- Retinal pigment epithelial tear
- Subretinal haemorrhage with the size of 1 DA or more involving the centre of the fovea, or if the size of the haemorrhage is ≥ 50% of the total lesion area

Other, non-ocular, AESIs include the following:

- Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischaemic events
- Non-ocular haemorrhage

8.4. Reporting Visual Acuity-related Adverse Event

- A decrease in visual acuity of ≥ 15 letters from the last assessment of visual acuity should be reported as AE/SAE as appropriate
- A decrease in visual acuity of ≥ 30 letters from the last assessment of visual acuity should be reported as SAE.
- A decrease in visual acuity to the level of light perception or worse should be reported as SAE

8.5. Pregnancy

Any pregnancy, including those of female partners of male subjects treated with the IP, should be reported to the Sponsor. If the female partner of a male subject becomes pregnant, a written consent must be obtained from the female partner before collecting any pregnancy-related information. All pregnancies associated with the subject, from the time the subject receives the first IVT injection of IP until either Week 56 (EOS visit) or ET visit, should be reported to the Sponsor. Pregnancy reports should be submitted to the Sponsor within 24 hours from when the Investigator became aware of the pregnancy, using the pregnancy report form.

Although pregnancy is not an AE, all pregnancies must be followed up every 2 months until 6-8 weeks after the outcome of the pregnancy becomes available, unless the subject is lost to follow-up. The pregnancy outcome should be notified to the Sponsor by submitting a follow-up pregnancy report form. If the outcome of the pregnancy meets SAE criteria then the Investigator should report this case according to the SAE reporting process (Section 8.2.2).

8.6. Independent Data and Safety Monitoring Board

An independent DSMB will be assigned for this study. The DSMB will consist of external experts (e.g., physician, clinical pharmacologists, or biostatisticians) and will review the safety and tolerability data from the study at pre-specified intervals. The details of the safety data and time points for review will be described in the DSMB Charter and in the DSMB statistical analysis plan (SAP).

In addition, an ongoing masked review of AEs, including clinical laboratory data will be continuously undertaken by the Sponsor medical monitor and pharmacovigilance team.

9. Statistical Methods and Data Analysis

Further information on the statistical methods to be used in this study will be provided in the SAP, which will be finalised prior to the database lock for reporting the main CSR.

Statistical analysis and reporting will be performed as follows:

- **Interim safety analysis for independent DSMB meeting:**

  A DSMB SAP, describing the methodology and presentation of results and access to results will be prepared as a separate document. The safety reports for the DSMB data review meetings will be prepared according to the DSMB SAP.

  The statistical analysis will be performed by an independent statistical reporting team and the results will be communicated to the DSMB directly by an independent unmasked statistician.

- **Main CSR:**

The main analysis will take place once all subjects complete the procedures at Week 24, or its corresponding visit. Available efficacy and safety data, PK, and immunogenicity data will be analysed and reported.

At the time of this reporting, a limited number of identified individuals of the Sponsor or CRO will be unmasked for reporting purpose. However, subjects, Investigators, and other study personnel will remain masked throughout the entire study period.

- **Final CSR:**

  The final analysis will take place after the last subject completes the procedures at Week 56 or the corresponding visit. All study data will be analysed and reported for final CSR.

9.1. Statistical Hypotheses

This is a study to demonstrate equivalence in change from baseline in BCVA at Week 8 between SB15 and Eylea®. The null hypothesis tested for the primary efficacy analysis is that either (1) SB15 is inferior to Eylea® or (2) SB15 is superior Eylea® based on a pre-specified equivalence margin.

The equivalence between the two treatment groups will be declared if the 90% confidence interval (CI) of the difference is entirely contained within the pre-defined margin of [-3 letters, 3 letters]. The 90% CI of the difference between the changes from baseline in BCVA at Week 8 of the two treatment groups will be estimated for the Full Analysis Set (FAS).

For the EMA submission, equivalence between the two treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The 95% CI of the difference between the two treatment groups in relation to the change from baseline in BCVA at Week 8 will be estimated for the FAS.

9.2. Analysis Sets

The following sets will be used for the analyses performed in the study:

- Randomised Set (RAN) consists of all subjects who receive a randomisation number at the randomisation visit.
- FAS consists of all randomised subjects. Following the intent-to-treat principle, subjects will be analysed according to the treatment group they are assigned to at randomisation. However, subjects who do not have any efficacy assessment result after randomisation and do not receive IP during the study period will be excluded from FAS.
- Per-Protocol Set (PPS) consists of all FAS subjects who have BCVA assessment result at baseline and Week 8 without any major protocol deviations (PDs) that have impact on the BCVA assessment. Major PDs that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment group assignment for analyses.
- Safety Set 1 (SAF1) consists of all subjects who receive at least one IP during the study period. Subjects will be analysed according to the IP received.
- Safety Set 2 (SAF2) consists of all subjects in the SAF1 who receive at least one IP after re-randomisation at Week 32. Subjects will be analysed according to the IP received.
- PK Analysis Set (PKS) consists of all subjects in the SAF1 who participate in PK evaluation at PK investigational sites (PK subjects) and have at least one serum concentration data.

9.3. Subject Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarised by treatment group for the RAN and PKS. Continuous variables (e.g., age, weight, height) will be summarised with descriptive statistics (n, mean, standard deviation [SD], median, minimum, maximum) and categorical variables (e.g., gender, race, ethnicity) will be summarised with frequency and percentage.

Comparison between treatment groups in baseline characteristics will be performed using the chi-square test or F-test as appropriate. The results of these tests will be provided including the *p*-value only for descriptive purposes and will not be used as a formal basis to determine the factors to be included in primary or secondary efficacy analysis models. If baseline imbalances are detected for any of the factors, additional analyses may be performed to adjust for these baseline differences.

Relevant medical and ophthalmic history will be summarised by treatment group for the RAN.

Duration of exposure to IP and number of injections will be summarised descriptively by treatment group for the SAF1. Prior and concomitant medications will be summarised by treatment group with frequency and percentage.

9.4. Analysis of the Primary Objective

The primary efficacy analysis will aim to demonstrate equivalence in terms of change from baseline in BCVA at Week 8 between SB15 and Eylea®.

The primary efficacy analysis will be performed for the FAS with the change from baseline in BCVA at Week 8 using an analysis of covariance model with the baseline BCVA as a covariate and region (or pooled centres) and treatment group as factors. The equivalence between the two treatment groups will be declared if the two-sided 90% CI of the difference of Least Squares mean (LSMean) of change from baseline in BCVA at Week 8 is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The same analysis will be performed for the PPS as a sensitivity analysis.

For the EMA submission, the primary efficacy analysis will be performed for the FAS with the change from baseline in BCVA at Week 8 using an analysis of covariance model with the baseline BCVA as a covariate and region (or pooled centres) and treatment group as factors. The equivalence between the two treatment groups will be declared if the two-sided 95% CI of the difference of LSMean of change from baseline in BCVA at Week 8 is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters]. The same analysis will be performed for the PPS as a sensitivity analysis. For those subjects who drop out of the study prematurely, a multiple imputation will be used under the missing at random assumption. The 95% CI of the difference between the two treatment groups will also be estimated for the FAS as supportive analysis.

9.5. Analysis of the Secondary Objectives

9.5.1. Efficacy Variable Analyses

As the secondary efficacy endpoints, change from baseline in BCVA, CST, TRT, and CNV area will be summarised descriptively by treatment group and visit.

Proportion of subjects who lost fewer than 15 letters and gained 15 letters or more in BCVA compared to baseline, subjects with intra- or sub-retinal fluid, and subjects with active CNV leakage will be summarised descriptively by treatment group and visit.

The two-sided 95% CI of the LSMean difference of change from baseline in secondary efficacy endpoints between the two treatment groups will be estimated.

9.5.2. Safety Analyses

Safety analyses will be performed for main period, transition period, and overall study period unless specified otherwise. Analyses for main and transition period will be performed in the SAF1 and SAF2 respectively and analyses for the overall study period will be performed in the SAF1.

All reported terms for AEs (ocular or non-ocular) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). AEs including ocular AEs in the study eye and/or fellow eye as well as non-ocular AEs will be summarised descriptively by treatment group. Intraocular inflammation will also be summarised similarly.

Change in intraocular pressure, vital signs, and clinical laboratory parameters will be summarised descriptively by treatment group and visit. All other safety variables will be summarised descriptively by treatment group and visit unless specified otherwise.

9.5.3. Pharmacokinetic Analyses

Blood samples for PK assessment will be collected in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group in initial randomisation at Week 0 [Day 1]). The systemic exposure will be summarised descriptively by treatment group and visit. If fellow eye received Eylea® during the study period after randomisation, the concentration measured after treatment for the fellow eye will be listed, but excluded from the summary statistics.

9.5.4. Immunogenicity Analyses

The number and proportion of subjects with ADA and NAb results (e.g., 'positive' or 'negative') will be summarised by treatment group and visit. If fellow eye received Eylea® during the study period after randomisation, the ADA and NAb results obtained after treatment for the fellow eye will be listed, but excluded from the summary statistics.

9.6. Exploratory analyses

Proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56 will be summarised descriptively by treatment group and visit.

For NEI VFQ-25 as a measurement of QOL, subscale scores (general health, general vision, ocular pain, near activities, distance activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, vision-specific dependency, driving, colour vision, and peripheral vision) and the composite score, which represent overall visual function, will be calculated, and the change from baseline will be summarised by treatment group and visit.

9.7. Sample Size Calculations

For the calculation of the equivalence margin for BCVA, the mean changes in BCVA were referred from VIEW1 study of Eylea® in subjects with neovascular AMD.

In the VIEW1 study of SmPC of Eylea®, the mean change of BCVA at Month 12 (SD) was 10.9 (13.8) letters for the dosing of 2 mg every 4 weeks Eylea® treatment group and the LSMean difference between Eylea® and Lucentis® (ranibizumab) with its 95% CI was 3.15 (0.92, 5.37) letters.

The US FDA Guidance describes that if the active control (Eylea® in this study) has shown superiority to other active treatments (Lucentis® in VIEW1) in the past, the difference demonstrated (3.15 letters) represents a conservative estimate of historical evidence of sensitivity to drug-effects, one that could serve as a basis for choosing M1. Therefore, the equivalence margin of 3 letters, which would be less

than the LSMean difference in VIEW1 study, which proved statistical superiority to ranibizumab.

The ETDRS chart has 5 letters in one line (that is the minimum limit for visual acuity change) and thus the difference more than 5 letters in BCVA could be considered as a minimal clinically important difference. In addition, most of the anti-VEGF non-inferiority clinical trials on AMD also used a non-inferiority margin of 5 letters. Therefore, the equivalence margin of [−3 letters, 3 letters] is considered to be a conservative margin to test the clinical equivalence between SB15 and Eylea®.

With the equivalence limit of [−3 letters, 3 letters], 216 subjects per treatment group was calculated with the assumptions of the mean difference of 0.5 letters and SD of 9.0 at the overall 5% significance level, providing 80% power to reject the null hypothesis. Overall 446 subjects (223 per treatment group) will give 216 completers per treatment group assuming a 3% loss from the randomised subjects.

The nQuery Advisor® option two one-sided equivalence tests (TOST) for two-group design gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each group is 216, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below -3 and the null hypothesis that the test mean minus the standard mean is above 3 i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.5, the common standard deviation is 9 and that each test is made at the 2.5% level.*"

With the equivalence limit of [−3 letters, 3 letters] for the US FDA submission, 173 subjects per treatment group (overall sample size of 346) was calculated with the assumptions of the mean difference of 0.5 letters and SD of 9.0 at the overall 10% significance level, providing 80% power to reject the null hypothesis.

The nQuery Advisor® option two one-sided equivalence tests for two-group design gives the following statement to estimate the n per group to show the equivalence: "*When the sample size in each group is 173, a two group design will have 80% power to reject both the null hypothesis that the test mean minus the standard mean is below -3 and the null hypothesis that the test mean minus the standard mean is above 3 i.e., that the test and standard are not equivalent, in favor of the alternative hypothesis that the means of the two groups are equivalent, assuming that the expected difference in means is 0.5, the common standard deviation is 9 and that each test is made at the 5% level.*"

Therefore, the sample size of 446 allows enough power to detect the equivalence in both situations.

10. Data Collection and Management

10.1. Data Confidentiality

Information about study subjects will be kept confidential. Subject identification information will be labelled with a code number, and will not include the subject's name or other information that could identify them. A list linking the code and the subject's name will be kept in the investigational site files as required by International Council for Harmonisation (ICH) E6 (R2) Good Clinical Practice (GCP) to protect the subject's confidentiality.

The coded information will be sent to the Sponsor (or designee) who will analyse it and report the study results both to regulatory and ethical authorities. The Sponsor may also place data on public websites or publish journal articles based upon these results. Subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes. Care will be taken to prevent subjects being identified through these publications. In addition, data may be shared with other companies or researchers to aid further research into AMD. Such data sharing practices will be covered by confidentiality agreements. No-one outside the investigational site will

have access to subject-identifiable information.

10.2. Monitoring

The Sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. The monitors will work in accordance with the CRO standard operation procedures (SOPs) and have the same rights and responsibilities as monitors from the Sponsor organisation. Monitors will establish and maintain regular contact between the Investigator and the Sponsor.

Monitors will evaluate the competence of each investigational site and inform the Sponsor about any problems relating to facilities, technical equipment, or medical staff. During the study period, monitors will check that written informed consent has been obtained correctly from all subjects and that data are recorded correctly and completely. Monitors will also perform source data verification by comparing entries in the eCRF with corresponding source data and informing the Investigator of any errors or omissions. Monitors will verify adherence to the protocol at the investigational site. All protocol deviations will be reported to the Sponsor via the Monitoring Visit Reports. Monitors will arrange for the supply of IP and ensure appropriate storage conditions are maintained.

Monitoring visits will be conducted at regular intervals according to ICH E6 (R2) GCP. The monitor will provide written reports to the Sponsor on each occasion they make contacts with the Investigator regardless of whether it is by phone or in person.

Further details on the monitoring processes and the level of source data verification to be performed will be outlined in the monitoring plan.

10.3. Data Handling and Record Keeping

The Investigator must maintain essential study documents including protocol and protocol amendments, completed eCRFs, signed written ICFs and its revisions/updates, completed eCRFs, other relevant correspondence according to ICH E6 (R2) GCP, and other relevant study requirements (if applicable) until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years after the formal termination of clinical development of the IP or 15 years from completion of the study, or whichever longer according to the relevant local laws and/or regulations. These documents should be retained for a longer period if required by the applicable regulatory requirements or the investigational site, institution or private practice in which the study is being conducted. Subject identification codes (subject names and corresponding study numbers) will be retained for the same period of time. These documents may be transferred to another responsible party, deemed acceptable by the Sponsor, and who agrees to abide by the retention policies. Written notification of transfer must be submitted to the Sponsor. The Investigator must contact the Sponsor prior to disposing of any study records and obtain written permission to do so.

10.4. Future Use of Stored Specimens and Data

The Sponsor or designated representative can store PK and/or immunogenicity samples for maximum 7 years after the end of the clinical study. The Sponsor or designated representative should operate under the same regulations related to and take the same responsibility to save personal data. The sample may be used for additional assay to be performed if considered scientific relevant or requested by regulatory authorities in order to have the possibility to perform the assay.

10.5. Database Management and Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data

management of the Sponsor (or an appropriate company designated by the Sponsor to perform these activities). The study eCRF is the primary data collection instrument for the study. Subject data will be captured in an eCRF and reviewed by the monitor in order to check adherence to the protocol and to detect any data inconsistency or discrepancy from source document.

The Investigator must ensure that the clinical data required by the study protocol are carefully reported in the eCRF. He/she must also check that the data reported in the eCRF correspond to those in the medical records. The investigator will sign all collected data in eCRF.

Data must be entered into eCRFs in English by the designated investigational site staffs in a timely manner. Source documents should be available during periodic visits by study monitors to enable review for completeness and acceptability. Any correction to the data entered into the eCRF must be carried out by the Investigator or a designated member of staff. These changes may be made either on the initiative of the investigational site staff or in response to monitoring or data queries. Any changes to written data must be made using ICH E6 (R2) GCP corrections and any change to electronic data should be made in a system which can provide an audit trail. Monitors and clinical data managers will review the eCRF for accuracy and can generate queries to the investigational staff for resolution. Corrections will be recorded in an audit trail that records the old information, the new information, and identification of the person making the changes, date of correction made and reason for change. The Investigator must sign and date the eCRF pages as indicated.

Medical/surgical history and underlying diseases and AEs will be coded using MedDRA®. Concomitant medications will be coded using the World Health Organisation-Drug Dictionary Enhanced (WHO-DDE). The versions of coding dictionaries used will be stated in the clinical study report.

10.6. Quality Control and Quality Assurance

During the conduct of the study, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH E6 (R2) GCP are being followed. The monitors may review source documents to confirm that the data recorded on the eCRFs are accurate. The Investigator and institution will allow the domestic and foreign regulatory authorities, sponsor's monitors and auditors' direct access to source documents to perform this verification. The investigational site may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by the Sponsor, and/or to inspection by appropriate regulatory authorities. It is important that Investigators and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

10.7. Protocol Deviation (PD)

PDs will be pre-defined prior to subject enrolment and documented separately named as 'protocol deviation definition list' which includes category (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with treatment), deviation description, severity (major or minor), time point for protocol deviations. Major PDs are defined as those deviations from the protocol likely to have an impact on the perceived efficacy and/or safety of study treatments.

PDs will be reviewed and confirmed prior to database lock to decide which subjects and/or subject data will be excluded from certain analyses. Decisions regarding the exclusion of subjects and/or subject data from analyses will be documented and approved prior to database lock.

11. Ethics Considerations and Administrative procedures

11.1. Institutional Review Boards (IRB) and Independent Ethics Committees (IEC)

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from IRB/IEC.

The Investigator must provide the Sponsor with documentation of IRB/IEC approval of the protocol and written informed consent before the study may begin at the investigational site. The Investigator will supply documentation to the Sponsor relating to the annual renewal of the protocol from the IRB/IEC and any approvals of revisions to the ICF or amendments to the protocol.

The Investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/IEC on a regular basis and in accordance with the timelines required locally. Upon completion of the study, the Investigator will provide the ethics committee with a report on the outcome of the study if required by local regulations.

11.2. Ethical Conduct of the Study

This study will be conducted and informed consent will be obtained from each subject according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for ICH E6 (R2) GCP, and the applicable drug and data protection laws and regulations of the countries where the study will be conducted.

11.3. Written Informed Consent

The written informed consent will be used to explain the risks and benefits of study participation to the subject in simple terms prior to any study related procedures. The written informed consent contains a statement that the consent is freely given, that the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. Written consent must be given by the subject after the receipt of detailed information on the study.

The Investigator is responsible for ensuring that informed consent is obtained from each subject and for obtaining the appropriate signatures and dates on the written informed consent prior to the performance of any protocol procedures and prior to the first IVT injection of IP. The Investigator will provide each subject with a copy of the signed and dated written informed consent and this will be documented in the subject's source notes. Depending on local regulation, authorized site staff can obtain the ICF subjects as well. Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the study. Prior to a subject's participation in the study, the written ICF should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

If the subject is legal blindness or illiterate, an impartial witness should be present during the entire informed consent discussion. After the written informed consent and any other written information to be provided to subjects is read and explained to the subject/impartial witness, and after the subject/impartial witness has orally consented to the subject's participation in the study. The subject (if capable of doing so) and/or the impartial witness will personally sign and date the written informed consent. In case both subject and impartial witness will sign the ICF, the subject will sign first. In particular, by signing the written informed consent, the impartial witness attests that the information in

the written informed consent and any other written information was accurately explained to the subject and apparently understood by the subject, and that written informed consent was freely given by the subject.

11.4. Investigator Information

11.4.1. Investigator Obligations

This study will be conducted in accordance with the ICH E6 (R2) GCP, the ethical principles that have their origin in the Declaration of Helsinki (2013), and other local laws and/or regulations.

The Investigator is the qualified physician who is responsible for ensuring that the study is conducted according to the signed the Investigator statement, the study protocol and applicable regulations; for protecting the rights, safety and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. The Investigator must obtain the written informed consent of each subject to whom IP will be administered. The Investigator is also responsible for supervising any individual or party who conducts study-related duties at investigational site to ensure the integrity.

11.4.2. Training of Investigator Site Personnel

Before the first subject is enrolled into the study, a Sponsor representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and will also train them in any study-specific procedures.

The Investigator will ensure that appropriate training relevant to the study is given to all investigational site staff and that any new information relevant to the performance of this study is forwarded to the investigational site staff involved.

The Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other investigational site staff).

11.4.3. Protocol Signatures

The Investigator must sign the Investigator Signature Page of this protocol prior to enrolling subjects in the study. By signing the protocol signature page, the Investigator attests in writing that he or she has read, understood, and will conduct the study in accordance with the study protocol, ICH E6 (R2) GCP, and other relevant local laws and/or regulations.

11.4.4. Financing and Insurance

Samsung Bioepis Co., Ltd. is the Sponsor of this study and will support the financial aspects for the study conduct at the investigational site.

Details of financial agreements are provided in the Clinical Study Agreements with the investigational sites. The Sponsor has obtained suitable insurance for this study. The insurance details may be provided to the investigational sites and/or Investigators who are responsible for providing the IRB/IEC with these details according to local requirements if any.

12. Publication Policy

The Sponsor supports the efforts of health authorities to increase the transparency of medical research conducted in human subjects. The Sponsor will register and maintain the information of clinical studies on a public registry program. The Sponsor is committed to the public disclosure of the results from clinical studies through posting on public clinical study data banks. The Sponsor will comply with the

guidelines of regulatory authorities with regards to public registration and disclosure of clinical study data.

The clinical study data collected during the study are confidential and proprietary to the Sponsor. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed abstract or presentation.

Any publications from this study should be approved by the Sponsor prior to publication or presentation. The rights of the Investigator with regard to publication of this study are described in the Clinical Study Agreement.

13. References

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[11] Hayreh SS, Podhajsky PA, Zimmerman MB. Natural history of visual outcome in central retinal vein. *Ophthalmology*. 2011; 118(1): 119- 33.

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APPENDIX A: Grading Scale for Anterior Chamber Flare

Grading Scale for Anterior Chamber Flare	
Grade	**Description**
0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

Reference: The Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data: Results of the first international workshop. *Am J Ophthalmol*. 2005; 140 (3): 509-16.

APPENDIX B: Grading Scale for Anterior Chamber Cells

Grading Scale for Anterior Chamber Cells Field size is 1 × 1 mm slit beam	
Grade	**Cells in Field**
0	< 1 cell
0.5+	1-5 cells
1+	6-15 cells
2+	16-25 cells
3+	26-50 cells
4+	> 50 cells

Reference: The Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. *Am J Ophthalmol.* 2005; 140 (3): 509-16.

APPENDIX C: Grading Scale for Vitreous Haze

Grading Scale for Vitreous Haze	
Grade	**Description**
0	No evident vitreous haze at all
0.5+	Trace inflammation, normal striations and reflex of nerve fiber layer not visible
1+	Mild blurring of optic nerve head and retinal vessels
2+	Moderate blurring of optic nerve head and retinal vessels
3+	Optic nerve head visible, but the borders are quite blurry.
4+	Optic nerve head obscured

Reference: Nussenblatt RB, Palestine AG, Chan CC, et al. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology.* 1985 Apr; 92 (4): 467-71.

APPENDIX D: National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25 questionnaire)

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

Version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

RAND hereby grants permission to use the "National Eye Institute Visual Functioning Questionnaire 25 (VFQ-25) July 1996, in accordance with the following conditions which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

1. Changes to the NEI VFQ-25 - July 1996 may be made without the written permission of RAND. However, all such changes shall be clearly identified as having been made by the recipient.

2. The user of this NEI VFQ-25 - July 1996 accepts full responsibility, and agrees to hold RAND harmless, for the accuracy of any translations of the NEI VFQ-25 Test Version - July 1996 into another language and for any errors, omissions, misinterpretations, or consequences thereof.

3. The user of this NEI VFQ-25 - July 1996 accepts full responsibility, and agrees to hold RAND harmless, for any consequences resulting from the use of the NEI VFQ-25.

4. The user of the NEI VFQ-25 - July 1996 will provide a credit line when printing and distributing this document or in publications of results or analyses based on this instrument acknowledging that it was developed at RAND under the sponsorship of the National Eye Institute.

5. No further written permission is needed for use of this NEI VFQ-25 - July 1996.

7/29/96

Instructions:

I’m going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

		(Circle One)
READ CATEGORIES:	Excellent	1
	Very Good	2
	Good	3
	Fair	4
	Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

		(Circle One)
READ CATEGORIES:	Excellent	1
	Good	2
	Fair	3
	Poor	4
	Very Poor	5
	Completely Blind	6

---

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:	None of the time	1
	A little of the time	2
	Some of the time	3
	Most of the time	4
	All of the time?	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:	None	1
	Mild	2
	Moderate	3
	Severe, or	4
	Very severe?	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 ***Skip To Q 15c***

No..... 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove…… 1 ***Skip To Part 3, Q 17***

Gave up……2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ……..1 ***Skip To Part 3, Q 17***

Mainly other reasons……...2 ***Skip To Part 3, Q 17***

Both eyesight and other reasons……..3 ***Skip To Part 3, Q 17***

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1

A little difficulty 2

Moderate difficulty 3

Extreme difficulty..... 4

16. How much difficulty do you have driving at night? Would you say you have:

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. Do you accomplish less than you would like because of your vision?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?.....	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

		Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20.	I stay home most of the time because of my eyesight.....	1	2	3	4	5
21.	I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22.	I have much less control over what I do, because of my eyesight.....	1	2	3	4	5
23.	Because of my eyesight, I have to rely too much on what other people tell me.	1	2	3	4	5
24.	I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25.	I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Protocol Signature Pages

SIGNATURE PAGE

Declaration of Sponsor Representative

Protocol Title: A Phase III randomised, double-masked, parallel group, multicentre study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB15 (proposed aflibercept biosimilar) and Eylea® in subjects with neovascular age-related macular degeneration

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Sponsor Representative

Name: PPD

Institution: Samsung Bioepis Co., Ltd.

Signature: PPD

SIGNATURE PAGE

Declaration of the Principal/Coordinating Investigator

Protocol Title: A Phase III randomised, double-masked, parallel group, multicentre study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB15 (proposed aflibercept biosimilar) and Eylea® in subjects with neovascular age-related macular degeneration

This clinical study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational medicinal product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 2013 and the guidelines on Good Clinical Practice applicable to this clinical study.

Principal/Coordinating Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____
(MMM DD, YYYY)