Clinical Study Protocol

A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB11 (proposed ranibizumab biosimilar) and Lucentis® in Subjects with Neovascular Age-related Macular Degeneration

Product	SB11 (proposed ranibizumab biosimilar)
EudraCT Number	2017-000422-36
US pre-IND Number	130331
Protocol Number	SB11-G31-AMD
Study Phase	Phase III
Version and Effective Date	Amendment 1 Sep 01, 2017
Sponsor	Samsung Bioepis Co., Ltd. 107, Cheomdan-daero, Yeonsu-gu, Incheon, 21987 Republic of Korea

SYNOPSIS

Name of Sponsor/Company:	Samsung Bioepis Co., Ltd.
Name of Finished Product:	SB11 (proposed ranibizumab biosimilar)
Name of Active Ingredient:	Ranibizumab

Title of Study:
A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB11 (proposed ranibizumab biosimilar) and Lucentis® in Subjects with Neovascular Age-related Macular Degeneration

Protocol No: SB11-G31-AMD	**Phase:** III

Indication: Neovascular Age-related Macular Degeneration (AMD)

Objectives:
Primary Objective:

- To demonstrate the equivalence of efficacy of SB11 to Lucentis® in subjects with neovascular age-related macular degeneration

Secondary Objectives:

- To evaluate the safety of SB11 and Lucentis®
- To evaluate the immunogenicity of SB11 and Lucentis®
- To evaluate the systemic exposure of SB11 and Lucentis® in subjects participating in pharmacokinetics (PK) evaluation

Study Design:
This is a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB11 compared to Lucentis® in subjects with neovascular AMD. Subjects will be randomised in a 1:1 ratio to receive either SB11 or Lucentis® (administered via intravitreal (ITV) 0.5 mg every 4 weeks). Investigational Products (IP) (SB11 or Lucentis®) will be administered up to Week 48, and the last assessment will be done at Week 52.

Number of Subjects:
Approximately a total of 704 subjects are planned to be randomised into 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 (VA) will be selected as the study eye. If both eyes have equal VA, the eye with better visual prognosis (e.g., clearer lens and ocular media and less amount of subfoveal scar or geographic atrophy) 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.

Inclusion criteria

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

1. Age ≥ 50 years at Screening

2. Newly diagnosed, *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 central reading centre during Screening

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

5. Best Corrected Visual Acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34) 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 sterilised, 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 ITV injection of IP

7. Written informed consent form 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. Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye, or presence of subfoveal blood equal to or more than one DA in size (confirmed by central reading centre during Screening)

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

3. Presence of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture or Pathologic Myopia (PM) (confirmed by central reading centre during Screening)

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

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

6. Any concurrent macular abnormality other than AMD in the study eye which could affect the efficacy of IP including but not limited to epiretinal membrane, macular telangiectasia, retinal vascular abnormality, etc. (confirmed by central reading centre during Screening)

7. History of vitrectomy surgery in the study eye

8. History of trabeculectomy or other filtration surgery in the study eye

9. History of submacular surgery or other surgical intervention for AMD in the study eye

10. Any other intraocular surgery (including cataract surgery) or periocular surgery in the study eye within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation

11. Any previous ITV anti-Vascular Endothelial Growth Factor (anti-VEGF) treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD in either eye

12. Any previous systemic anti-VEGF treatment, within 90 days prior to randomisation, and such treatment will not be allowed during the study period

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 mineral will be allowed

14. Any intravitreal injection of corticosteroid (e.g., triamcinolone acetonide) or intravitreal corticosteroid implant in the study eye within 180 days prior to randomisation, and such treatment will not be allowed during the study period

15. Topical ocular corticosteroids administered for ≥ 30 consecutive days in the study eye within

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90 days prior to randomisation

16. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 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 must not exceed 8 diopters of myopia

17. Aphakia or absence of the posterior capsule in the study eye (unless it occurred as a result of a Yttrium Aluminium Garnet [YAG] posterior capsulotomy in association with prior posterior chamber Intraocular Lens [IOL] implantation)

18. Presence of scleromalacia in either eye

19. Current vitreous haemorrhage in the study eye

20. Active or recent (within 28 days prior to randomisation) intraocular, extraocular and periocular inflammation or infection in either eye

21. History of idiopathic or autoimmune uveitis in either eye

22. History of retinal detachment in the study eye

23. History of full-thickness macular hole in the study eye

24. History of corneal transplantation surgery in the study eye

25. Presence of advanced glaucoma or optic neuropathy that affect or threaten the central visual field in the study eye

26. Uncontrolled ocular hypertension (defined as intraocular pressure ≥ 25 mmHg despite treatment with anti-glaucoma medication) in the study eye

27. History of allergy to the fluorescein sodium for injection in angiography

28. Previous participation in clinical studies of ocular investigational products to treat neovascular AMD in either eye or systemic investigational products to treat neovascular AMD, and such participation will not be allowed during the study period

29. Previous participation in any studies of ocular or systemic investigational products (excluding dietary supplements, vitamins and minerals) to treat ocular or systemic disease other than neovascular AMD within 90 days prior to randomisation, and such participation will not be allowed during the study period even if the investigational product is dietary supplements, vitamins or minerals

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30. History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy) or diabetic macular oedema in either eye

31. Any concurrent ocular condition in the study eye which, in the opinion of the Investigator, could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety including, but not limited to ocular media opacities such as corneal opacity or cataract that do not allow proper fundus visualisation and fundus imaging, and ocular surface abnormalities which prevent applanation tonometry during the study period after randomisation

32. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an IP in the opinion of the Investigator

33. Pregnant or lactating women. A serum pregnancy test must be required for women of childbearing potential at Screening

34. Employees of Investigational sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who are legally institutionalised

35. Stroke, transient ischemic attacks, or myocardial infarction within 90 days prior to randomisation

36. History of recurrent significant infections and/or current treatment for active systemic infection

37. Known allergic reactions and/or hypersensitivity to ranibizumab or to any ingredients of the investigational product

38. Prior treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e,g., focal laser photocoagulation) in the study eye, and such treatment will not be allowed during the study period

39. Prior treatment with pan-retinal photocoagulation in the study eye, and such treatment will not be allowed during the study period

40. Current use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin and ethambutol, and such medications will not be allowed during the study period

Planned Study Period:
Screening period will be 21 days.
IPs (SB11 or Lucentis®) will be given up to Week 48, and the last assessment will be done at Week 52.

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Investigational Products:

- Test IP: SB11 (proposed ranibizumab biosimilar)
- Reference IP: Lucentis® (ranibizumab)
- Route of administration: ITV injection
- Dose: 0.5 mg every 4 weeks

Main Criteria for Evaluation

Primary endpoint

For US Food and Drug Administration (FDA), Korea Ministry of Food and Drug Safety (MFDS) or other regulatory agency submissions for those who are in favour of the VA, the primary endpoint is:

- Change from baseline in BCVA at Week 8

For European Medicines Agency (EMA) or other regulatory agency submissions for those who are in favour of the anatomical parameter, the primary endpoint is:

- Change from baseline in Central Subfield Thickness (CST) at Week 4 (based on assessment by central reading centre)

Secondary endpoints

The secondary efficacy endpoints are:

- Change from baseline in BCVA over time up to Week 24 and Week 52
- Proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 24 and Week 52
- Proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 24 and Week 52
- Change from baseline in CST and Central Retinal Lesion Thickness (CRLT) at Week 24 and Week 52 (based on assessment by central reading centre)
- Change from baseline in total CNV size at Week 24 and Week 52 (based on assessment by central reading centre)
- Proportion of subjects with active CNV leakage at Week 24 and Week 52 (based on assessment by central reading centre)

The safety endpoints are:

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- Incidence of ocular Adverse Events (AEs) or serious ocular adverse events
- Incidence of systemic AEs and serious systemic adverse events

The pharmacokinetic endpoints are:

Blood sampling for PK will be collected in approximately **40 subjects participating in PK evaluation** (20 subjects per treatment group).

- Systemic exposure measured pre-dose (C_{trough}) and 24 to 72 hours post-dose (close to C_{max})

The immunogenicity endpoints are:

- Incidence of Anti-Drug Antibodies (ADAs) to ranibizumab
- Incidence of Neutralising Antibodies (NAbs) to ranibizumab

The exploratory endpoints are:

- Proportion of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 (based on assessment by 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 24 and Week 52

Statistical Methods

<u>Efficacy analysis</u>

For US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of the VA, the primary efficacy analysis will be performed for the Full Analysis Set (FAS) with the change from baseline of 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 FAS will consist of all randomised subjects. The subjects will be analysed based on the treatment they were randomised to by intention-to-treat principle. However, subjects who do not qualify for randomisation and are inadvertently randomised into the study will be excluded from the FAS, provided these subjects do not receive any IP during the study period. The equivalence in BCVA will be declared if the two-sided 90% Confidence Interval (CI) of the difference of BCVA Least Squares mean (LS mean) changes from baseline at Week 8 between SB11 and Lucentis® lies within the pre-defined equivalence margin of [−3 letters, 3 letters].

For EMA or other regulatory agency submissions for those who are in favour of the anatomical

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parameter, the primary efficacy analysis will be performed for the per-protocol set (PPS-CST) with the change from baseline of CST at Week 4 using an analysis of covariance model with baseline CST as a covariate and region (or pooled centres) and treatment group as factors. The PPS-CST consists of all FAS subjects who have the first IP injection at Week 0 (Day 1) and complete procedures at Week 4 without any major protocol deviations that have impact on the CST assessment. The equivalence in CST will be declared if the two-sided 95% CI of the difference of CST LS mean changes from baseline at Week 4 between SB11 and Lucentis® lies within the pre-defined equivalence margin of [−36 μm, 36 μm].

There is no formal adjustment of type I error rates.

For the primary analysis with the FAS for BCVA, missing data will be imputed for subjects who drop out for the study prior to the primary analysis time-point. A missing-at-random approach will assume that subjects who withdraw from a study had missing values similar to similar subjects who completed the study in that treatment group. This approach ensures that evidence of lack of equivalence is not diluted when there are missing data. For the components of BCVA, the missing letter will be imputed by multiple imputation method with the assumption of monotone missing pattern and regression method. For the sensitivity analyses, available case analysis and last observation carried forward analysis will be performed. All other efficacy measurements will be summarised descriptively by treatment group and visit.

Safety analyses

All reported terms for AEs (ocular or systemic) 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 systemic 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, and all safety variables will be listed.

Pharmacokinetic analyses

Blood sampling for PK will be collected in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group). Formal PK analysis will not be performed. 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 by treatment group and visit.

NEI VFQ-25 analyses

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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.

Sample size calculation

For the calculation of the equivalence margin for BCVA, the mean changes in VA were referred from two studies of Lucentis® in subjects with neovascular AMD. In MARINA study, the mean change of VA at Week 24 (Standard Deviation [SD]) were −6.6 (13.31) letters and 6.5 (12.00) letters for placebo and 0.5 mg Lucentis® treatment groups, respectively. In FOCUS study, the mean change (SD) of VA at Week 24 were −5.0 (16.14) letters and 4.0 (14.41) letters for placebo and 0.5 mg Lucentis® treatment groups, respectively.

A fixed-effect meta-analysis of the above two studies estimates a weighted mean change in VA of 12.41 letters with a 95% CI [10.34 letters, 14.48 letters]. The derived equivalence limit from meta-analysis is 4.9 letters at Week 24, but by the agency recommendation the equivalence limit at Week 8 will be 3 letters for the comparison with the 90% CI of mean difference between treatment groups.

With the given equivalence margin of [−3 letters, 3 letters], 334 subjects per treatment group was calculated with the assumptions of the mean difference of 0.5 letters and pooled SD of 12.5 letters at the overall 5% significance level. Assuming a 5% loss from randomised subjects after 8 weeks, a sample size of 352 subjects per treatment group (overall sample size of 704) will give 334 completers per treatment group after 8 weeks, which is estimated to give 80% power to detect the equivalence of change from baseline in BCVA within the margin of 3 letters.

For the calculation of the equivalence margin for CST, the mean changes in CST were referred from two studies of Lucentis® in subjects with neovascular AMD. In MARINA study, the mean change of CST at Week 4 (SD) was 8.1 (58.1) μm and −106 (122.5) μm for placebo and 0.5 mg Lucentis® treatment groups, respectively. In PIER study, the mean change (SD) of CST at Week 4 were 15 (94.9) μm and −90 (140.9) μm for placebo and 0.5 mg Lucentis® treatment groups, respectively.

A fixed-effect meta-analysis of the above two studies estimates a weighted mean change in CST of 109.6 μm with a 95% CI [−146.45 μm; −72.65 μm]. The derived equivalence limit from meta-analysis is 36 μm at Week 4.

With the given equivalence margin of [−36 μm, 36 μm], 290 subjects per treatment group was calculated with the assumptions of the mean difference of 0 between treatment groups, common SD of 133.3 μm at the overall 5% significance level. Assuming a 10% loss from FAS, a sample size of 323 per arm (overall sample size of 646) will give 80% power to detect the equivalence within the pre-defined margin.

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Therefore, the sample size of 704 allows enough power to detect the equivalence between treatment groups in both situations.	

FLOW CHARTS

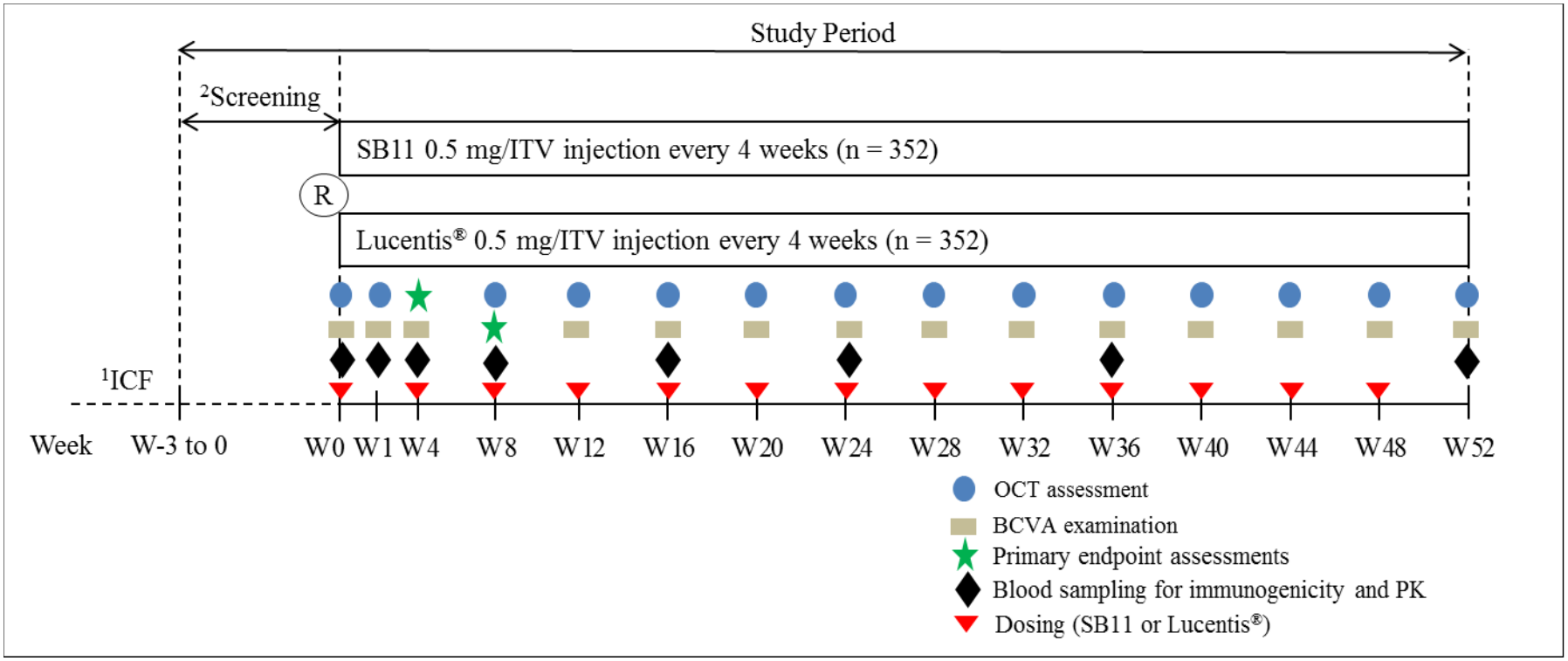

Figure 1. Graphical Study Design

ICF, Informed Consent Form; ®, Randomisation; ITV, Intravitreal; OCT, Optical Coherence Tomography; BCVA, Best Corrected Visual Acuity; PK, Pharmacokinetics

1. Written informed consent must be obtained from the subject prior to any study related procedures.
2. Screening must be done within 21 days prior to randomisation.

Table 1. Schedule of Activities

Procedures	Study Period															
W: Week	**Screening**	**W0**	**W1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48 EOT[24]**	**W52 EOS/ ET[25]**
D: Day (± visit window)	**D-21 to D-1**	**D1**	**D8 (±3)**	**D29 (±7)**	**D57 (±7)**	**D85 (±7)**	**D113 (±7)**	**D141 (±7)**	**D169 (±7)**	**D197 (±7)**	**D225 (±7)**	**D253 (±7)**	**D281 (±7)**	**D309 (±7)**	**D337 (±7)**	**D365 (±7)**
V: Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**
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														
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA examination[6]	X	X[7]	X	X	X[8]	X	X	X	X	X	X	X	X	X	X	X
OCT[9]	X	X	X	X[10]	X	X	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	X	X	X	X	X	X
Slit lamp examination[13]	X	X	X	X	X	X	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	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				X
Blood sampling for PK[18]		X	X	X	X		X		X			X				X
Pregnancy test[19]	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
IP injection[20]		X[21]		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring[22]	Continuously															
Prior or concomitant medication or therapy[23]	Continuously															

EOS, End of Study; EOT, End of Treatment; ET, Early Termination; ETDRS, Early Treatment Diabetic Retinopathy Study; 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 (or year of birth), gender, race and ethnicity.
3. Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit. The physical examination will 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. Body weight will be measured and recorded at Screening and Week 52 (EOS visit) or ET visit, but height will be measured and recorded only at Screening.
4. All subjects' eligibility should be confirmed by the central reading centre and Investigator.
5. Vital signs include blood pressure, pulse rate and body temperature. Vital signs will be assessed at Screening and prior to ITV injection of IP at each visit until Week 48. Vital signs will also be assessed at any time during the visit at Week 52 (EOS visit) or ET visit.
6. Visual acuity will be assessed in both the study eye and fellow (non-study) eye at Screening and prior to ITV injection of IP at each visit until Week 48. Visual acuity will also be assessed at any time during the visit at Week 52 (EOS visit) or ET visit. Subject must use either original series ETDRS charts or 2702 series Number charts (at a starting distance of 4 meters) consistently from Screening to Week 52 (EOS visit) or ET visit. Visual acuity testing must be performed before dilation of pupils and FP/FA and OCT assessment. A decrease in visual acuity of ≥ 15 letters from the last assessment of VA should be reported as AEs/Serious Adverse Events (SAEs) as appropriate. If there is a decrease in VA of ≥ 30 letters from the last assessment of VA or if there is a decrease in VA to the level of Light Perception or worse, it should be reported as SAE.
7. Investigator must confirm that the subject can read between 34 letters to 73 letters using original series ETDRS charts or 2702 series Number charts **at Week 0 (Day1) prior to randomisation**
8. Visit at Week 8 is the most critical as the visit is for the primary endpoint assessment for US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of the VA. Thus, every effort should be made to adhere to the visit schedule for the subjects.
9. OCT will be performed on the study eye at Screening and prior to ITV injection of IP at each visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. Site staffs who will perform OCT scans in this study must be certified by the central reading centre before study starts. OCT devices registered in an Investigational site should be all from the same manufacture and meet the minimum software requirement, The subject should use the OCT device registered by the central reading centre from Screening to Week 52 (EOS visit) or ET visit. OCT images will be sent to the central reading centre.
10. Visit at Week 4 is the most critical as the visit is for the primary endpoint assessment for EMA or other regulatory agency submissions for those who are in favour of the anatomical parameter. Thus, every effort should be made to adhere to the visit schedule for the subjects.
11. FP/FA will be performed on the both eyes at Screening and those images taken from the both eyes will be sent to the central reading centre. FP/FA will also be performed on the study eye prior to ITV injection of IP at Week 24 and at any time during the visit at Week 52 (EOS visit) or ET visit. Those images taken from the study eye will be sent to the central reading centre. Site staffs who will perform FA/FP in this study must be certified by the central reading centre before study starts. Only FP/FA device certified by 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 device consistently from Screening to Week 52 (EOS visit) or ET visit. If any significant change in the posterior pole (i.e., 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.

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 ITV injection of IP and within 15 minutes after ITV injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.
13. Slit lamp examination will be performed in both the study eye and fellow eye (non-study eye) at Screening and prior to ITV injection of IP at each visit until Week 48. Slit lamp examination will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.
14. Intraocular Pressure (IOP) will be measured using Goldmann applanation tonometry. The same method of IOP measurement must be used in each subject from Screening to Week 52 (EOS visit) or ET visit. IOP will be measured on the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48. When IOP is measured prior to ITV injection of IP, IOP should be measured after OCT and FP/FA are completed to avoid corneal erosion. IOP will also be measured at any time during the visit at Week 52 (EOS visit) or ET visit.
15. NEI VFQ-25 should be performed at Week 0 (Day1) after randomisation. Then, NEI VFQ-25 should be performed before dilation of pupil at Week 0 (Day 1), Week 24 and Week 52 (EOS visit) or ET visit.
16. Blood and urine sampling for clinical laboratory test will be collected at Screening and prior to ITV injection of IP at Week 12, Week 24, and Week 36. Blood and urine sampling for clinical laboratory test will also be collected at any time during the visit at Week 52 (EOS visit) or ET visit. Urine samples must be collected before performing FA to avoid false elevations in urine protein values.
    • Haematology: haemoglobin, haematocrit, platelet count, white blood cell count (total and differential)
    • Chemistry: sodium, potassium, creatinine, glucose, calcium, phosphorus, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase
    • Urinalysis (dipstick): protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen
    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 Sponsor.
17. Blood sampling for immunogenicity will be collected prior to ITV injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood sampling for immunogenicity will also be collected at any time during the visit at Week 1 and Week 52 (EOS visit) or ET visit.
18. Blood sampling for PK will be collected **in approximately 40 subjects participating in PK evaluation** (20 subjects per treatment group). Blood sampling for PK will be collected prior to ITV injection of IP (C_{trough}) and 24-72 hours after ITV injection of IP (close to C_{max}) on Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood samples for PK will also be collected at any time during the visit at Week 1 and Week 52 (EOS visit).
19. **For women of childbearing potential**, serum pregnancy test must be performed at Screening. The serum samples taken at Screening will be analysed in central laboratory. Additional serum or urine pregnancy test can be performed in each Investigational site during the study period, if necessary.
20. Subjects will be administered SB11 or Lucentis® 0.5 mg via ITV into the study eye every 4 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). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within 20 days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within 20 days after scheduled dosing visit date. Next scheduled dosing visit date and visit window should not be altered even though previous dosing is not performed on the exact scheduled dosing visit date (but, the interval between two doses injected into the study eye should be at least 14 days) or previous dosing is skipped.

21. The first ITV injection of IP and all other study procedures must be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason.
22. Ocular AEs in the study eye and/or fellow eye as well as systemic AEs will be recorded after the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit.
23. Any medications including prescription drug, non-prescription drugs or any therapy (except dietary supplements vitamins, minerals) received locally (in the study eye and/or fellow eye) or systemically within 180 days prior to Screening until Week 52 (EOS visit) or ET visit will be recorded.
24. End of Treatment (EOT) visit is defined as the visit for the last ITV injection of SB11 or Lucentis® during the study period after randomisation. The Sponsor will not provide IP (SB11 or Lucentis®) to subjects after they complete the EOT visit.
25. End of Study (EOS) visit or Early Termination (ET) visit is defined as 4 weeks (± 7 days) after the last ITV injection of SB11 or Lucentis®.

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 ITV injection	O	O	-
		24-72 hr after ITV injection	O	-	-
V3	Week 1 **(± 3 days)**	Samples to be collected at any time during the visit	O	O	-
V4	Week 4 **(± 7 days)**	Prior to ITV injection	O	O	-
		24-72 hr after ITV injection	O	-	-
V5	Week 8 **(± 7 days)**	Prior to ITV injection	O	O	-
		24-72 hr after ITV injection	O	-	-
V6	Week 12 **(± 7 days)**	Prior to ITV injection	-	-	O
V7	Week 16 **(± 7 days)**	Prior to ITV injection	O	O	-
		24-72 hr after ITV injection	O	-	-
V9	Week 24 **(± 7 days)**	Prior to ITV injection	O	O	O
		24-72 hr after ITV injection	O	-	-
V12	Week 36 **(± 7 days)**	Prior to ITV injection	O	O	O
		24-72 hr after ITV injection	O	-	-
V16	Week 52 (EOS visit) **(± 7 days)**	Samples to be collected at any time during the visit	O	O	O
-	ET visit **(± 7 days)**	Samples to be collected at any time during the visit	-	O	O

* in all subjects who signed written informed consent

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Events of Special Interest
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CFT	Central Foveal Thickness
CI	Confidence Interval
CNV	Choroidal Neovascularisation
CPT	Centre Point Thickness
CRLT	Central Retinal Lesion Thickness
CRO	Contract Research Organisation
CSR	Clinical Study Report
CST	Central Subfield Thickness
DA	Disc Area
DME	Diabetic Macular Oedema
DR	Diabetic Retinopathy
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ET	Early Termination

ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Fundus Photography
GCP	Good Clinical Practice
HUVEC	Human Umbilical Vein Endothelial Cells
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
ITV	Intravitreal
IWRS	Interactive Web Recognition System
LS mean	Least Squares mean
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
MoA	Mechanism of Action
NAb	Neutralising Antibody

NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	Optical Coherence Tomography
PDT	Photodynamic Therapy
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PM	Pathologic Myopia
PPS	Per-protocol Set
QOL	Quality of Life
RAN	Randomised Set
RPE	Retinal Pigment Epithelium
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operation Procedure
TEAE	Treatment-Emergent Adverse Event
US	United States
VA	Visual Acuity
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), left untreated, is a leading cause of adult blindness in the developed world. Most of severe visual loss of AMD occurs from Choroidal Neovascularisation (CNV) or the neovascular form of AMD. Choroidal neovascularisation can be associated with fibrous replacement of the retinal photoreceptors and Retinal Pigment Epithelium (RPE), as well as atrophy of these portions of the retina in the macula, leading to severe visual decline with loss of reading vision, driving vision, and the ability to recognise faces. Vascular Endothelial Growth Factor (VEGF), a protein growth factor that both stimulates angiogenesis and increases vascular permeability, is a major pathogenic factor in CNV due to AMD. Counteracting these effects of VEGF can provide significant therapeutic benefit to subjects suffering from this disorder.

In developed countries, AMD is a leading cause of severe visual loss in people 65 years of age and older in the US, an estimated 6% of individuals aged 65 to 74, and 20% of those older than 75 are affected with some stage of AMD. Also, among white people aged 40 years and older, AMD is the number one cause of visual impairment and blindness in the US. The pathogenesis of AMD is poorly understood. It is characterised by development of focal deposits of long –spacing collagen and phospholipid vesicles within and beneath the basement membrane of the RPE, called “drusen” which can be accompanied by gradual degeneration of photoreceptors and RPE (atrophy), which often results in slow deterioration of central Visual Acuity (VA). This thickening and degeneration of Bruch’s membrane can predispose to abnormal growth of blood vessels from the choriocapillaris, termed choroidal neovascularization. The occurrence of CNV heralds the onset of neovascular AMD. Leakage from the CNV can cause macular oedema with collection of fluid and blood beneath and within the macula, resulting in loss of vision. Growth of the lesions with accompanying fibrovascular or fibroglial tissue further destroys retinal tissue. Overtime, the CNV promotes scarring that damages photoreceptors and the RPE, resulting in permanent vision loss. Neovascular or “wet” AMD accounts for only 10% of cases of AMD yet results in 90% of the severe vision loss. Epidemiological studies suggest that “wet” AMD will develop in almost 1 million persons in the US within the next 5 years [Wu EW et al., 2014, Macular Photocoagulation Study Group. 1991].

1.2. Lucentis®: Ranibizumab Reference Product

Lucentis® is approved for indications including neovascular (wet) AMD, visual impairment due to Diabetic Macular Oedema (DME) and visual impairment due to macular oedema secondary to Retinal Vein Occlusion (branch RVO or central RVO) by both the US FDA and EMA. In addition, the FDA approved Lucentis® for the treatment of Diabetic Retinopathy (DR) in subjects with DME and the EMA approved Lucentis® for the treatment of visual

impairment due to CNV secondary to Pathologic Myopia (PM) [Lucentis® Prescribing Information. 2016, Lucentis® Summary of Product Characteristics. 2016]

Mechanism of Action

Ranibizumab binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110.}$ VEGF-A has been shown to cause neovascularisation and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular oedema following RVO, DR and DME. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation [Lucentis® Summary of Product Characteristics. 2016].

Pharmacodynamics

Increased retinal thickness (i.e., Centre Point Thickness [CPT] or Central Foveal Thickness [CFT]), as assessed by OCT is associated with the activity of neovascular AMD, macular oedema following RVO, and DME. Leakage from CNV as assessed by FA is also associated with the activity of neovascular AMD. Microvascular retinal changes and neovascularisation, as assessed by colour FP, are associated with diabetic retinopathy [Lucentis® Prescribing Information. 2016].

Pharmacokinetics

Following monthly ITV administration of Lucentis® to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/ml, as assessed in an *in vitro* cellular proliferation assay). C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Serum concentrations in a limited number of DME patients indicate that a slightly higher systemic exposure cannot be excluded compared to those observed in neovascular AMD patients. Serum ranibizumab concentrations in RVO patients were similar or slightly higher compared to those observed in neovascular AMD patients.

Based on analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients with neovascular AMD treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately 9 days. Upon monthly ITV administration of Lucentis® 0.5 mg/eye, serum ranibizumab C_{max}, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/ml. Serum ranibizumab concentrations are predicted to be approximately 90,000-fold lower than vitreal ranibizumab concentrations [Lucentis® Summary of Product Characteristics. 2016].

Efficacy

Neovascular (Wet) Age-Related Macular Degeneration

The safety and efficacy of Lucentis® were assessed in three randomised, double or single-masked, sham-or active-controlled studies in subjects with neovascular AMD.

Table 3. Visual Acuity Outcomes at Month 12 and Month 24 in Studies

Study: MARINA			
Outcome	**Month**	**Sham (n = 229)**	**Lucentis® 0.5 mg (n = 230)**
Loss of <15 letters in VA	12	60%	91%
	24	56%	89%
Gain of ≥15 letters in VA	12	6%	31%
	24	4%	30%
Mean change in VA (letters)	12	−11.0 (17.9)	+6.3 (14.1)
	24	−15.0 (19.7)	+5.5 (15.9)
Study: ANCHOR			
Outcome	**Month**	**Verteporfin PDT (n = 141)**	**Lucentis® 0.5 mg (n = 139)**
Loss of <15 letters in VA	12	66%	98%
	24	65%	93%
Gain of ≥15 letters in VA	12	11%	37%
	24	9%	37%
Mean change in VA (letters)	12	−8.5 (17.8)	+11.0 (15.8)
	24	−9.1 (18.7)	+10.9 (17.3)
Study: FOCUS			
Outcome	**Month**	**Verteporfin PDT (n = 56)**	**Lucentis® 0.5 mg+ Verteporfin PDT (n = 105)**
Loss of <15 letters in VA	12	68%	91%
	24	75%	88%
Gain of ≥15 letters in VA	12	5%	24%
	24	7%	25%
Mean change in VA (letters)	12	−8.2 (16.3)	+4.9 (14.7)
	24	−7.8 (18.0)	+4.6 (16.7)
Study: PIER			
Outcome	**Month**	**Sham (n = 63)**	**Lucentis® 0.5 mg** (Quarterly dosing) **(n = 61)**
Loss of <15 letters in VA	12	49%	90%
Mean change in VA (letters)	12	−16.3	−0.2

PDT, Photodynamic Therapy

Source: Lucentis® Prescribing Information. *U. S. Food and Drug Administration*. Nov 2016.
Am J Ophthalmol. 2006;124:1532-1542.
Am J Ophthalmol. 2008;145:862-874.

Macular Oedema Following Retinal Vein Occlusion

The safety and efficacy of Lucentis® were assessed in two randomised, double-masked, 1-year studies in subjects with macular oedema following RVO.

Table 4. Visual Acuity Outcomes at Month 6 in Studies

Study: BRAVO			
Outcome	**Month**	**Sham (n = 131)**	**Lucentis® 0.5 mg (n = 132)**
Gain of ≥15 letters in VA	6	29%	61%
Mean change in VA (letters)	6	+7.3	+18.3
Study: CRUISE			
Outcome	**Month**	**Sham (n = 130)**	**Lucentis® 0.5 mg (n = 130)**
Gain of ≥15 letters in VA	6	17%	48%
Mean change in VA (letters)	6	+0.8	+14.9

Source: Lucentis® Prescribing Information. *U. S. Food and Drug Administration*. Nov 2016.

Diabetic Macular Oedema

The safety and efficacy of Lucentis® were assessed in two randomised, double-masked, 3-year studies. All enrolled subjects had DR and DME at baseline

Table 5. Visual Acuity Outcomes at Month 24 in Studies

Study: RIDE			
Outcome	**Month**	**Sham (n = 130)**	**Lucentis® 0.3 mg (n = 125)**
Loss of <15 letters in VA	24	92%	98%
Gain of ≥15 letters in VA	24	12%	34%
Mean change in VA (letters)	24	+2.3	+10.9
Study: RISE			
Outcome	**Month**	**Sham (n = 127)**	**Lucentis® 0.3 mg (n = 125)**
Loss of <15 letters in VA	24	90%	98%
Gain of ≥15 letters in VA	24	18%	45%
Mean change in VA (letters)	24	+2.6	+12.5

Source: Lucentis® Prescribing Information. *U. S. Food and Drug Administration*. Nov 2016.

Diabetic Retinopathy in subjects with Diabetic Macular Oedema

Efficacy and safety data of Lucentis® are derived from studies RIDE and RISE.

Table 6. ≥3-step and ≥2-step Improvement at Month 24 in Study D-1 and Study D-2

Study: RIDE			
Outcome	**Month**	**Sham (n = 130)**	**Lucentis® 0.3 mg (n = 125)**
≥3-step improvement from baseline in ETDRS-DRSS	24	2%	17%

Study: RIDE			
Outcome	**Month**	**Sham (n = 130)**	**Lucentis® 0.3 mg (n = 125)**
≥2-step improvement from baseline in ETDRS-DRSS	24	4%	39%
Study: RISE			
Outcome	**Month**	**Sham (n = 127)**	**Lucentis® 0.3 mg (n = 125)**
≥3-step improvement from baseline in ETDRS-DRSS	24	0%	9%
≥2-step improvement from baseline in ETDRS-DRSS	24	7%	37%

ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study -Diabetic Retinopathy Severity Scale
Source: Lucentis® Prescribing Information. *U. S. Food and Drug Administration*. Nov 2016.

1.3. SB11: Proposed Ranibizumab Biosimilar

Samsung Bioepis Co., Ltd. (Incheon, Republic of Korea) has developed SB11, a proposed biosimilar of the ranibizumab reference product. SB11 is produced by recombinant DNA technology in *Escherichia coli* cells. Extensive characterisation studies including intact mass, N- and C-terminal sequencing, peptide mapping, icIEF, CE-SDS (reduced, non-reduced), SE-HPLC, amino acid composition, disulfide bond, VEGF binding, VEGF neutralisation, and Human Umbilical Vein Endothelial Cells (HUVEC) anti-proliferation were performed using state-of-the-art techniques. Assays such as CEX-HPLC, UV absorption spectra, free thiol group quantification, SEC-MALS, SV-AUC, CD, DSC and FT-IR were performed for both non-clinical and clinical materials.

After extensive quality similarity studies, a series of *in vitro* non-clinical studies including VEGF binding assay and cell-based assays (HUVEC anti-proliferation assay and VEGF neutralizing assay) were performed to demonstrate similarity in *in vivo* behaviour between SB11 and Lucentis®.

1.4. Rationale for the Study

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 [EMA/CHMP/BMWP/403543/2010, EMEA/CHMP/437/04, U. S. Food and Drug Administration. 2015]. The EMA and the US FDA have developed specific guidelines for a biologic drug to be approved as a biosimilar [EMA/CHMP/BMWP/403543/2010, U. S. Food and Drug Administration. 2015, EMA/CHMP/BWP/247713/2012]. 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, pharmacokinetic properties, and immunogenicity of the biosimilar. The purpose of this study is to demonstrate the equivalence of efficacy of SB11

to Lucentis® and to evaluate the safety and immunogenicity in subjects with neovascular AMD. In addition, systemic exposure of SB11 to Lucentis® will also be evaluated in subjects participating in PK evaluation.

2. STUDY OBJECTIVES

2.1. Primary Objective

- To demonstrate the equivalence of efficacy of SB11 to Lucentis® in subjects with neovascular AMD

2.2. Secondary Objective

- To evaluate the safety of SB11 and Lucentis®
- To evaluate the immunogenicity of SB11 and Lucentis®
- To evaluate the systemic exposure of SB11 and Lucentis® in subjects participating in PK evaluation

3. STUDY DESIGN

3.1. Overview of Study Design

This is a randomised, double-masked, parallel group, multicentre study to evaluate the efficacy, safety, pharmacokinetics and immunogenicity of SB11 compared to Lucentis® in subjects with neovascular AMD. Subjects will be randomised in a 1:1 ratio to receive either SB11 or Lucentis® 0.5 mg via ITV into the study eye every 4 weeks.

The screening period is 21 days. IP (SB11 or Lucentis®) will be given until 48 weeks and the last assessment will be done at Week 52.

3.2. Rationale for the Study Design

The purpose of this study is to demonstrate the equivalence of clinical efficacy of Lucentis® and SB11 in subjects with neovascular AMD.

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 [U. S. Food and Drug Administration. 2015], a Phase I comparative PK study has not been necessary to support a demonstration of biosimilarity due to negligible systemic exposure following ITV injection of ranibizumab. However, for supporting the assessment of overall systemic safety of SB11 relative to Lucentis®, systemic exposures will be collected and compared in the subgroup population (approximately 40 subjects, 20 subjects per treatment group) in Phase III comparative efficacy study.

Lucentis® is approved for indications including neovascular AMD, visual impairment due to DME and visual impairment due to macular oedema secondary to RVO by both the US FDA and EMA. In addition, the US FDA approved Lucentis® for the treatment of DR in subjects with DME and the EMA approved Lucentis® for the treatment of visual impairment due to CNV secondary to PM, respectively.

Improvements of VA have been reported in the pivotal studies of the various indications. For example, at Month 12, the average benefit associated with Lucentis® over that of sham injection or PDT was approximately 13.1 to 20.8 letters, 5.9 or 11.7 letters and 6.2 or 6.6 letters in subjects with AMD, DME and RVO, respectively. The overall difference in Best Corrected Visual Acuity (BCVA) between Lucentis® treated and control group was the largest in subjects with AMD, which indicates that neovascular AMD is the most sensitive indication compared to DME or RVO to show a difference between the treatments [Lee H, 2014]. In addition, neovascular AMD has homogeneous disease progress with fewer compounding factors than DME or RVO. For instance, it results in severe visual impairment with an average loss of around 4 lines of VA within 2 years of disease onset [Chakravarthy U et al. 2010]. 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 [Ferris FL 3rd et al. 1984]. Therefore, Subjects with neovascular AMD are the most appropriate target population to evaluate the product-related difference between Lucentis® and SB11 in this study.

This study has two different endpoints, depending on regulatory agency's requirements for assessing equivalence in efficacy between SB11 and Lucentis®.

For US FDA, Korea Ministry of Food and Drug Safety (MFDS) or other regulatory agency submissions for those who are in favour of the VA, the primary endpoint is the mean change from baseline in BCVA at Week 8. In the pivotal studies for Lucentis®, the proportion of subjects losing < 15 letters was used as primary endpoint to compare the efficacy between Lucentis® treatment group and control group. The endpoint indicates the preventive effect of the loss of VA, but it includes variability in individual disease progression as well as drug-induced effect. For example, approximately 90% of the subjects who received Lucentis® lost VA less than 15 letters but 60% of the subjects who received sham injection (or PDT/verteporfin) also lost VA less than 15 letters. Thus, the proportion of subjects losing < 15 letters could not be a sensitive primary endpoint to detect product-related effect between a proposed biosimilar product and reference product. On the other hand, change from baseline in VA, gain of letters, can reflect any change (improvement or deterioration) in the disease status, thus is more sensitive in detecting a difference between the two treatments. To increase sensitivity, evaluation of equivalence will be conducted at Week 8 before the efficacy plateau is reached, as requested by US FDA.

For EMA or other regulatory agency submission for those who are in favour of the anatomical parameter, the primary objective is to demonstrate the equivalence of SB11 to Lucentis®, in terms of the mean change from baseline in CST at Week 4. The evaluation of CST is important as it addresses the pharmacodynamics aspects of ranibizumab. Ranibizumab binds

with high affinity to all active VEGF-A isoforms (e.g., VEGF110, VEGF121 and VEGF165) on the surface of endothelial cells, thereby preventing binding of VEGF-A to its receptors and reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation which result in reduction of CST [Lucentis® Prescribing Information 2016, Lucentis® Summary of Product Characteristics. 2016]. It indicates that the reduction of CST represents a direct effect of ranibizumab based on the Mechanism of Action (MoA). Furthermore, it has been reported that CST measurements and clinical outcome has a correlation. In OCT-guided, variable-dosing study conducted in neovascular AMD subjects, a statistically significant correlation between the decrease in CST at one month and the subsequent improvement in VA seen at two months and three months [Fung A et al. 2007]. Similarly in PrONTO study, the results indicated that the initial OCT response is predictor of future VA improvements although the strength of the correlation is affected by the fluctuations in macular fluid and the fact that OCT changes are detected before VA is affected. In addition, visual recovery after resolution of macular fluid in neovascular AMD likely depends on many variables including chronicity of disease, viability of photoreceptors and the RPE, progression of the underlying dry AMD (geographic atrophy), as well as the presence of epiretinal membranes, RPE tears, and fibrosis. Despite all these variables, the initial response to ranibizumab characterised by resolution of fluid in the macula as assessed by OCT seems to correlate with future VA improvement and may serve as a useful predictor of treatment efficacy [Lalwani G et al. 2009].

The study design was consulted and agreed with both EMA and FDA prior to start of this study.

4. STUDY POPULATION

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 VA will be selected as the study eye. If both eyes have equal VA, the eye with better visual prognosis (e.g., clearer lens and ocular media and less amount of subfoveal scar or geographic atrophy) 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.

4.1. Inclusion Criteria

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

1. Age ≥ 50 years at Screening

2. Newly diagnosed, *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 central reading centre during Screening

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

5. Best Corrected Visual Acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34) 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 sterilised, 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 ITV injection of IP

7. Written informed consent form 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

4.2. Exclusion Criteria

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

1. Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye, or presence of subfoveal blood equal to or more than one DA in size (confirmed by central reading centre during Screening)

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

3. Presence of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture or Pathologic Myopia (PM) (confirmed by central reading centre during Screening)

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

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

6. Any concurrent macular abnormality other than AMD in the study eye which could affect the efficacy of IP including but not limited to epiretinal membrane, macular telangiectasia, retinal vascular abnormality, etc. (confirmed by central reading centre during Screening)

7. History of vitrectomy surgery in the study eye

8. History of trabeculectomy or other filtration surgery in the study eye

9. History of submacular surgery or other surgical intervention for AMD in the study eye

10. Any other intraocular surgery (including cataract surgery) or periocular surgery in the study eye within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation

11. Any previous ITV anti-Vascular Endothelial Growth Factor (anti-VEGF) treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD in either eye

12. Any previous systemic anti-VEGF treatment, within 90 days prior to randomisation, and such treatment will not be allowed during the study period

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 mineral will be allowed

14. Any intravitreal injection of corticosteroid (e.g., triamcinolone acetonide) or intravitreal corticosteroid implant in the study eye within 180 days prior to randomisation, and such treatment will not be allowed during the study period

15. Topical ocular corticosteroids administered for ≥ 30 consecutive days in the study eye within 90 days prior to randomisation

16. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 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 must not exceed 8 diopters of myopia

17. Aphakia or absence of the posterior capsule in the study eye (unless it occurred as a result of a Yttrium Aluminium Garnet [YAG] posterior capsulotomy in association with prior posterior chamber Intraocular Lens [IOL] implantation)

18. Presence of scleromalacia in either eye

19. Current vitreous haemorrhage in the study eye

20. Active or recent (within 28 days prior to randomisation) intraocular, extraocular and periocular inflammation or infection in either eye

21. History of idiopathic or autoimmune uveitis in either eye

22. History of retinal detachment in the study eye

23. History of full-thickness macular hole in the study eye

24. History of corneal transplantation surgery in the study eye

25. Presence of advanced glaucoma or optic neuropathy that affect or threaten the central visual field in the study eye

26. Uncontrolled ocular hypertension (defined as Intraocular Pressure [IOP] ≥ 25 mmHg despite treatment with anti-glaucoma medication) in the study eye

27. History of allergy to the fluorescein sodium for injection in angiography

28. Previous participation in clinical studies of ocular investigational products to treat neovascular AMD in either eye or systemic investigational products to treat neovascular AMD, and such participation will not be allowed during the study period

29. Previous participation in any studies of ocular or systemic investigational products (excluding dietary supplements, vitamins and minerals) to treat ocular or systemic disease other than neovascular AMD within 90 days prior to randomisation, and such participation will not be allowed during the study period even if the investigational product is dietary supplements, vitamins or minerals

30. History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy) or diabetic macular oedema in either eye

31. Any concurrent ocular condition in the study eye which, in the opinion of the Investigator, could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety including, but not limited to ocular media opacities such as corneal opacity or cataract that do not allow proper

fundus visualisation and fundus imaging, and ocular surface abnormalities which prevent applanation tonometry during the study period after randomisation

32. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an IP in the opinion of the Investigator

33. Pregnant or lactating women. A serum pregnancy test must be required for women of childbearing potential at Screening

34. Employees of Investigational sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who are legally institutionalised

35. Stroke, transient ischemic attacks, or myocardial infarction within 90 days prior to randomisation

36. History of recurrent significant infections and/or current treatment for active systemic infection

37. Known allergic reactions and/or hypersensitivity to ranibizumab or to any ingredients of the investigational product

38. Prior treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e,g., focal laser photocoagulation) in the study eye, and such treatment will not be allowed during the study period

39. Prior treatment with pan-retinal photocoagulation in the study eye, and such treatment will not be allowed during the study period

40. Current use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin and ethambutol, and such medications will not be allowed during the study period

4.3. Subject Discontinuation from Investigational Product

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

- Consent withdrawal by subject

    - If subjects withdraw his/her consent, 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 appropriate reason among the reasons listed below other than consent withdrawal

- Rhegmatogenous retinal detachment or full-thickness macular hole in the study eye

- 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 including but not limited to retinal vascular abnormality

- Any AEs in the study eye (e.g., intraocular inflammation, VA loss, increased IOP, subretinal haemorrhage, vitreous haemorrhage, local or systemic infection etc.) which in the opinion of the Investigator and/or subject would require IP discontinuation

- Intraocular surgery in the study eye (e.g., cataract operation, vitrectomy, glaucoma surgery, etc.) which in the opinion of the Investigator would require IP discontinuation

- 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 (ITV 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

- Decision by the Investigator that the subject requires alternate treatment (e.g., other anti-VEGF agents such as bevacizumab or aflibercept, PDT, PPV etc.) to treat neovascular AMD in the study eye

- Decision by the Sponsor that IP discontinuation is in the subject's best medical interest or administrative decision for a reason (e.g., a suspicion of fraud, the subject enrolling in multiple clinical studies, lack of compliance, etc.) other than that of an AE

- Lost to follow-up

- Unmasking (except unmasking for the purpose of regulatory reporting)

- Pregnancy
- Death of any cause

Any significant change in the posterior pole (e.g., subretinal haemorrhage, macular hole, vitreous haemorrhage or opacity, retinal detachment, etc.) that is detected with fundus examination should be confirmed and documented with FP and/or FA. Investigator should decide IP discontinuation based on the FP and/or FA. The images taken at unscheduled visits will not be sent to the central reading centre.

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 (except for PK sampling) after 4 weeks from the last ITV injection of IP and will be asked to provide continued follow-up and further data collection subsequent to his or her ET visit.

If a subject agrees to continue follow-up for associated clinical outcome information until Week 52 irrespective of IP injection status (as long as an additional ICF e.g., withdrawal form is signed by the subject for this limited participation in the study), the subject's clinical outcome information such as BCVA, CST, AE and concomitant medication will be collected through non-invasive chart review, if available.

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 electronic Case Report Form (eCRF) and in the subject's medical record.

4.4. 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 SB11 or Lucentis® 0.5 mg via ITV into the study eye every 4 weeks up to Week 48 (a total of 13 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 visit date (except Week 0 (Day 1), visit window not allowed). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within 20 days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within 20 days after scheduled dosing visit date.

Next scheduled dosing visit date and visit window should not be altered even though previous dosing is not performed on the exact scheduled dosing visit date (but, the interval between two doses injected into the study eye should be at least 14 days) or previous dosing is skipped.

5.1.2. Withholding Investigational Products

If a subject experiences an AE in the study eye and the subject's safety or well-being could be compromised by ITV injection of IP at the Investigator's discretion, IPs should be withheld until the event has resolved. Such events in the study eye include, but are not limited to:

- A decrease in BCVA of ≥30 letters compared with the last assessment of VA;
- An IOP of ≥30 mmHg;
- A retinal break;

Any significant change in the posterior pole (e.g., subretinal haemorrhage, macular hole, vitreous haemorrhage or opacity, retinal detachment, etc.) that is detected with fundus examination should be confirmed and documented with FP and/or FA. Investigator should decide IP withholding based on the FP and/or FA. The images taken at unscheduled visits will not be sent to the central reading centre.

NOTE: If a subject misses any of first two doses or two consecutive doses during the study period after randomisation, the subject must be discontinued from IPs according to Section 4.3.

5.2. Investigational Product

5.2.1. Identity of Investigational Product

Details of the IPs are provided in Table 7.

Table 7. Investigational Products

Active pharmaceutical ingredient: ranibizumab	
SB11	
Formulation	Solution for ITV injection
Contents	One ml contains 10 mg ranibizumab
Storage conditions	Stored in refrigerator (2-8°C), Do not freeze
US sourced Lucentis®	
Formulation	Solution for ITV injection
Contents	One ml contains 10 mg ranibizumab
Storage conditions	Stored in refrigerator (2-8°C), Do not freeze

The IPs will be supplied to Investigational site in one carton containing a single vial. 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 IPs should be protected from light. 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.

5.2.2. Assignment of Subject Number

A unique subject number will be assigned to the subject by the Interactive Web Response System (IWRS) at Screening.

A unique randomisation number will be assigned to the subject number by the IWRS at randomisation to ensure that treatment group assignment is unbiased and masked to subjects, Investigators, and other study personnel. The randomisation number is linked to the treatment group assignment, which in turn is linked to IP kit number.

The assigned subject number(s) and randomisation number(s) will not be re-used.

5.2.3. 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 (SB11 or Lucentis®). The carton and IP vial will be packed and labelled in identical appearance.

5.2.4. 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, pharmacokinetics, 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 study period

After the last subject completes the procedures at Week 52 (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 unmasking is referred to Section 8.1.6.

5.2.5. Investigational Product Treatment Compliance and Accountability

5.2.5.1. Investigational Product Treatment Compliance

All IP injections will be given by the Investigator to ensure compliance. The exact date and time of IP injection must be recorded in the source documentation and the eCRF.

5.2.5.2. Investigational Product Accountability

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. All unused IPs should be returned to the Sponsor or designated vendor unless local destruction 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.

5.2.6. Investigational Product Administration

Using aseptic technique, all of the SB11 and Lucentis® vial contents are withdrawn through a blunt filter needle attached to a 1-cc syringe. The filter needle should be discarded after withdrawal of the vial contents and should not be used for ITV injection. The filter needle should be replaced with a sterile 30-gauge x 1/2-inch needle for the ITV 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 ITV injection procedure should be carried out under controlled aseptic conditions in accordance with local practice.

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

5.3. Prohibited Medication or Therapy

Prohibited medication and therapy during the study period are presented in Table 8.

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 both prescription, 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 52 (EOS visit) or ET visit. 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 8. Prohibited Medication and Therapy

Medication or Therapy	Time to be prohibited	Eye to be prohibited
ITV anti-VEGF treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD	• Prior to Randomisation	• Study eye • Fellow eye
ITV anti-VEGF treatment except IP (SB11 or Lucentis®)	• From Randomisation to EOS/ET visit	• Study eye
ITV anti-VEGF treatment (e.g., bevacizumab, aflibercept) except ranibizumab	• 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 Lucentis® (ranibizumab) will be allowed to treat AMD.
Systemic Anti-VEGF agents (e.g., bevacizumab)	• Within 90 days prior randomisation • From Screening to EOS/ET visit	N/A

Medication or Therapy	Time to be prohibited	Eye to be prohibited
Systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD. However, dietary supplements, vitamins and minerals are allowed.	• Within 30 days prior randomisation • From Screening to EOS/ET visit	N/A
Systemic 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	N/A
Intravitreal injection of corticosteroid (e.g., triamcinolone acetonide) or intravitreal corticosteroid implant	• Within 180 days prior to randomisation • From Screening to EOS/ET visit	• Study eye
Topical ocular corticosteroids	• ≥ 30 consecutive days within 90 days prior to randomisation	• Study eye
Treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation)	• Prior to Screening • From Screening to EOS/ET visit	• Study eye
Treatment with pan-retinal photocoagulation	• Prior to Screening • From Screening to EOS/ET visit	• Study eye
Ocular investigational products to treat neovascular AMD	• Prior to Screening • From Screening to EOS/ET visit	• Study eye • Fellow eye
Systemic investigational products to treat neovascular AMD	• Prior to Screening • From Screening to EOS/ET visit	N/A
Ocular investigational products to treat ocular diseases other than neovascular AMD	• Within 90 days prior randomisation • From Screening to EOS/ET visit	• Study eye • Fellow eye
Systemic investigational products (excluding dietary supplements, vitamins and minerals) to treat systemic diseases other than neovascular AMD	• Within 90 days prior randomisation • From Screening to EOS/ET visit **NOTE:** During the study period, investigational products such as dietary supplements, vitamins and minerals will be prohibited.	N/A

N/A, Not applicable

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 Lucentis® and should remain in

the study. Lucentis® for treatment in the fellow eye will be reimbursed or provided by Sponsor during the study period after randomisation.

Fellow eye injection will be performed by the Investigator for this study. However, fellow eye visit is 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 ITV injection of IP on the study eye. Ocular adverse events for the fellow eye and systemic adverse events will be monitored and recorded after the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit.

6. STUDY VARIABLES

6.1. Study Endpoints

6.1.1. Primary Endpoint

For US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of the VA, the primary endpoint is:

- Change from baseline in BCVA at Week 8

For EMA or other regulatory agency submission for those who are in favour of the anatomical parameter, the primary endpoint is:

- Change from baseline in CST at Week 4 (based on assessment by central reading centre)

6.1.2. Secondary Endpoints

The secondary efficacy endpoints are:

- Change from baseline in BCVA over time up to Week 24 and Week 52
- Proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 24 and Week 52
- Proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 24 and Week 52
- Change from baseline in CST and Central Retinal Lesion Thickness (CRLT) at Week 24 and Week 52 (based on assessment by central reading centre)
- Change from baseline in total CNV size at Week 24 and Week 52 (based on assessment by central reading centre)
- Proportion of subjects with active CNV leakage at Week 24 and Week 52 (based on

assessment by central reading centre)

The safety endpoints are:

- Incidence of ocular AEs or serious ocular adverse events
- Incidence of systemic AEs or serious systemic adverse events

The pharmacokinetic endpoints are:

Blood sampling for PK will be collected in approximately **40 subjects participating in PK evaluation** (20 subjects per treatment group).

- Systemic exposure measured pre-dose (C_{trough}) and 24 to 72 hours post-dose (close to C_{max})

The immunogenicity endpoints are:

- Incidence of Anti-Drug Antibodies (ADAs) to ranibizumab
- Incidence of Neutralising Antibodies (NAbs) to ranibizumab

6.1.3. Exploratory Endpoint

- Proportion of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 (based on assessment by 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 24 and Week 52

6.2. Efficacy Assessments

6.2.1. Best Corrected Visual Acuity

VA will be assessed in both the study eye and fellow eye (non-study eye) at Screening and prior to ITV injection of IP at each visit until Week 48. VA will also be assessed in both the study eye and fellow eye (non-study eye) at any time during the visit at Week 52 (EOS visit) or ET visit.

VA will be assessed using original series ETDRS charts or 2702 series Number charts at a starting distance of 4 meters, and then repeated at a distance of 1 meter, if necessary. Subject

must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit. VA testing must be performed before dilation of pupils and FP/FA and OCT assessment.

VA examiners and VA lanes at Investigational sites must be certified to ensure consistent measurement of BCVA prior to start of study.

A detailed protocol for conducting VA testing and refraction will be provided in the VA Testing Manual.

A decrease in VA of ≥ 15 letters from the last assessment of VA should be reported as AEs/ Serious Adverse Events (SAEs) as appropriate.

If the event meets one or more of the following criteria, it should be reported as SAE.

- A decrease in VA of ≥ 30 letters from the last assessment of VA
- A decrease in VA to the level of Light Perception or worse

6.2.2. Anatomical Parameters

The average retinal thickness in the central 1-mm area in the ETDRS grid (CST; central subfield thickness), retinal thickness between Internal Limiting Membrane (ILM) and the base of RPE (CRLT; central retinal lesion thickness) and other lesion characteristics will be evaluated using OCT on the study eye at Screening and prior to ITV injection of IP until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.

Lesion characteristics such as CNV size and presence of leakage or haemorrhage will also be evaluated using FP/FA on the study eye at Screening and prior to ITV injection of IP Week 24. FP/FA will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs including ocular AEs in the study eye and/or fellow eye as well as systemic AEs will be recorded from the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit. 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.

6.3.2. Clinical Laboratory Test

Blood and urine sampling for clinical laboratory test will be collected at Screening and prior to ITV injection of IP at Week 12, Week 24, and Week 36. Blood and urine sampling for

clinical laboratory test will also collected at any time during the visit at Week 52 (EOS visit) or ET visit (Table 2). Urine samples must be collected before performing FA to avoid false elevations in urine protein values.

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 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 9.

Table 9. Parameters for Clinical Laboratory Tests

Haematology	Chemistry	Urinalysis[1]
· Haemoglobin · Haematocrit · Platelet count · White blood cell count (total and differential)	· 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 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 Investigator. All laboratory abnormalities that require intervention (e.g., IP withholding, IP discontinuation, concomitant medication) should be assessed as clinically significant and the clinically significant abnormalities should be recorded as AEs.

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

Deleted laboratory test results with technical problems, such as handling error, sampling error, or tube breakage, should be followed by re-test. Result of re-test will be considered as that of an initial.

6.3.3. Pregnancy Test

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

Additional serum or urine pregnancy test can be performed in each Investigational site during the study period, if necessary (at the Investigator's discretion).

Deleted pregnancy test result at Screening with technical problems, such as handling error, sampling error or tube breakage, should be followed by re-test. Result of re-test will be considered as that of an initial.

6.3.4. Physical Examination

Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit. The physical examination will 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 recorded at Screening and Week 52 (EOS visit) or ET visit, but height will be measured only at Screening.

6.3.5. Vital Signs

Vital signs include blood pressure, heart rate and body temperature. Vital signs will be assessed at Screening and prior to ITV injection of IP at each visit until Week 48. Vital signs will also be assessed at any time during the visit at Week 52 (EOS visit) or ET visit (Table 1).

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

6.4. Ophthalmic Assessments

6.4.1. Full Ophthalmic Examinations

The full ophthalmic examination will consist of an external examination of the eye and adnexa routine screening for eyelid/pupil responsiveness (including but not limited to blepharoptosis, abnormal pupil shape, unequal pupils, abnormal reaction to light, and afferent pupillary defect), slit lamp biomicroscopy, IOP measurements and indirect ophthalmoscopy.

The posterior segment should be examined with the slit lamp and indirect ophthalmoscopy. Careful evaluation of the macula, optic nerve, retinal vessels, peripheral retina and vitreous should be included.

Grading scales for slit lamp biomicroscopy and indirect ophthalmoscopy are provided in Appendix A, B and C.

Slit lamp biomicroscopy

The slit lamp examination (cornea, lens, iris, aqueous reaction [cells and flare]) will be performed in both the study eye and fellow eye at Screening and prior to ITV injection of IP at each visit until Week 48, irrespective of whether or not the fellow eye has AMD**.** Slit lamp examination will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. If the fellow eye is not diagnosed with AMD, it will be followed to determine whether or not AMD develops.

Both the anterior segment and posterior segment will be assessed with the slit lamp.

The posterior segment will be examined after dilation of pupil with 2-3 drops of phenylephrine-tropicamid (or any other mydriatic drug) applied topically to the eye.

Intraocular pressure (IOP) measurement

IOP will be measured on the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48. When IOP is measured before ITV injection of IP, IOP should be measured after OCT and FP/FA are completed to avoid corneal erosion. IOP will also be measured at any time during the visit at Week 52 (EOS visit) or ET visit.

IOP should be measured using Goldmann applanation tonometry. The same method of IOP measurement must be used in each subject from Screening to Week 52 (EOS visit) or ET visit.

Indirect ophthalmoscopy

Indirect ophthalmoscopy using in a standard way (i.e., usually using a head-mounted light source and a 20-30 dpt lens)will be performed on the study eye (including evaluation of posterior segment abnormalities of the vitreous, optic nerve, peripheral retina and retinal vasculature, as well as retinal pigment epithelium detachment, ischemic events including cotton wool spots and microaneurysms) at Screening and prior to ITV injection of IP and 0-15 min after ITV injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.

6.4.2. Optical Coherence Tomography (OCT)

OCT will be performed on the study eye at Screening and prior to ITV injection of IP at each study visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.

Site staffs who will perform OCT scans in this study must be certified by the central reading centre before study starts.

OCT devices registered in an Investigational site should be all from the same manufacture and meet the minimum software requirement. The subject should use the OCT devices registered by central reading centre during the study period.

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

FP/FA will also be performed on the study eye prior to ITV injection of IP at Week 24 and at any time during the visit at Week 52 (EOS visit) or ET visit. Those images taken from the study eye will be sent to the central reading centre.

Site staffs who will perform FA/FP in this study must be certified by the central reading centre before study starts.

Only FP/FA device certified by 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 device consistently from Screening to Week 52 (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. A detailed protocol for FP/FA image acquisition and transmission will be provided in the Image Handbook.

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.

6.5. Pharmacokinetic Assessment

Blood sampling for PK will be collected **in approximately 40 subjects** (20 subjects per treatment group) 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 (e.g., -70 °C deep freezer for PK sample storage and temperature controlled centrifuge) 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 PK sub-study. If subject consents to the PK blood sampling, the subject will be enrolled in this study. Subjects enrolled at PK Investigational sites will be "PK subjects" participating in PK evaluation until the expected number of PK subjects is reached. Once the expected number of PK subjects is reached, the following subjects enrolled at PK Investigational sites will be "non-PK subjects" for whom blood sampling for PK will not be performed.

Blood sampling for PK will be collected prior to ITV injection of IP (C_{trough}) and 24-72 hours after ITV injection of IP (close to C_{max}) at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood sampling for PK will also be collected at any time during the visit at Week 1 and Week 52 (EOS visit) (Table 2).

The exact date and time of sample collection must be recorded in the source documentation and the eCRF. A detailed process for PK sampling, handling, storage and shipping will be provided in the Central Laboratory Manual for PK and Immunogenicity.

6.6. Immunogenicity Assessment

Blood sampling for immunogenicity will be collected in all randomised subjects.

Blood sampling for immunogenicity will be collected prior to ITV injection of IP at Week 0 (Day 1), Week 4, Week 8, Week 16, Week 24, and Week 36. Blood sampling for immunogenicity will also be collected at any time during the visit at Week 1 and Week 52 (EOS visit) or ET visit (Table 2).

The exact date and time of sample collection must be recorded in the source documentation and the eCRF. A detailed process for immunogenicity sampling, handling, storage and shipping will be provided in the Central Laboratory Manual for PK and Immunogenicity.

If a subject has an unresolved adverse event that is possibly related to ADA formation, he or she could be asked to return for immunogenicity blood sampling after Week 52 (EOS visit) or ET visit until the antibody titres return to baseline or stabilise at a level acceptable to the Investigator and Sponsor.

6.7. NEI VFQ-25

Vision-related QOL will be assessed using NEI VFQ-25. NEI VFQ-25 should be performed at Week 0 (Day 1) after randomisation. Then, NEI VFQ-25 should be performed before dilation of pupil at Week 0 (Day1), Week 24 and Week 52 (EOS visit) or ET visit.

All questionnaires will be administered in the local language. Investigator or delegated site staff will conduct a questionnaire survey with the subject in a quiet room. The results of the questionnaire will be recorded in a paper questionnaire and then entered into the eCRF.

7. STUDY PROCEDURES

During this study, efficacy, safety, pharmacokinetic and immunogenicity assessments will be performed. All results should 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. Visit 1 (Screening, D-21 to D-1)

Screening should be performed within 21 days before randomisation excluding the day of randomisation.

- Written informed consent

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 Screening, the subject should be screen failed. Once the subject is screen failed, he or she should not be re-screened.

The following procedures should be performed:

- 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 false elevation in urine protein values
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA and OCT assessment)
    - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy

  - OCT (images should be sent to central reading centre)
  - FP & FA (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Concomitant and previous medication or therapy
- Evaluate subject compliance with all inclusion and exclusion criteria

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

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 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) have to be repeated within screening period of 21 days and the subject will retain the subject number initially assigned.

Once the subject is confirmed eligible for the study, the subject will be advised on study restrictions such as contraception, prohibited medications and other study requirements if any.

NOTE

- **The most critical assessment will be at Week 4 and Week 8 as these are the visits for primary endpoint assessment. Thus, every effort should be made to adhere to the visit schedule for the subjects.**
- **A decrease in VA of ≥ 15 letters (compared with the last assessment of VA) should be reported as AEs/SAEs as appropriate.**
- **Intraocular inflammation should be recorded based on the location of inflammation (e.g., "iritis", "vitritis" or "iridocyclitis" rather than "uveitis")**
- **Grading scales for slit lamp biomicroscopy and indirect ophthalmoscopy are provided in Appendix A, B and C.**

7.2. Visit 2 (Week 0/Day 1)

Before randomisation

- Evaluate subject compliance with all inclusion and exclusion criteria
- Investigator must confirm that the subject can read between 34 letters and 73 letters using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment) prior to randomisation (Please see inclusion criteria #5). Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit

Randomisation

- After a subject's eligibility is confirmed by the central reading centre and Investigator, subject should be randomised to either SB11 or Lucentis® treatment group
- The first ITV injection of IP and all other study procedures must be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason

After randomisation

✓ **Before ITV 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 pharmacokinetics for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
    - Slit lamp biomicroscopy
    - Indirect ophthalmoscopy
    - OCT (images should be sent to central reading centre)
    - IOP using Goldmann applanation tonometry

- Adverse event monitoring
- Review of concomitant and previous medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)
- Adverse event monitoring

7.3. Visit 3 (Week 1 ± 3 days)

- Vital signs (temperature, blood pressure and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for pharmacokinetics for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry

- Adverse event monitoring
- Review of concomitant medication or therapy

7.4. Visit 4 (Week 4 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for pharmacokinetics for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)

- Adverse event monitoring

7.5. Visit 5 (Week 8 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)

- Blood sampling for immunogenicity

- Blood sampling for pharmacokinetics for subjects participating in PK evaluation

- Pregnancy test (serum or urine) at the Investigator's discretion

- Ocular assessments:

  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit

  - Slit lamp biomicroscopy

  - Indirect ophthalmoscopy

  - OCT (images should be sent to central reading centre)

  - IOP using Goldmann applanation tonometry

- Adverse event monitoring

- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)

- Adverse event monitoring

7.6. Visit 6 (Week 12 ± 7 days)

✓ **Before ITV injection of IP**

- 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 false elevation in urine protein values

- Pregnancy test (serum or urine) at the Investigator's discretion

- Ocular assessments:

  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit

  - Slit lamp biomicroscopy

  - Indirect ophthalmoscopy

  - OCT (images should be sent to central reading centre)

  - IOP using Goldmann applanation tonometry

- Adverse event monitoring

- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV injection of IP**

- Ocular assessments:

- Indirect ophthalmoscopy (0-15 min post-dose)
- IOP using Goldmann applanation tonometry (30-60 min post-dose)

- Adverse event monitoring

7.7. Visit 7 (Week 16 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Blood sampling for immunogenicity
- Blood sampling for pharmacokinetics for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)

- Adverse event monitoring

7.8. Visit 8 (Week 20 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)

- Pregnancy test (serum or urine) at the Investigator's discretion

- Ocular assessments:

  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit

  - Slit lamp biomicroscopy

  - Indirect ophthalmoscopy

  - OCT (images should be sent to central reading centre)

  - IOP using Goldmann applanation tonometry

- Adverse event monitoring

- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV injection of IP**

- Ocular assessments:

  - Indirect ophthalmoscopy (0-15 min post-dose)

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

- Adverse event monitoring

7.9. Visit 9 (Week 24 ± 7 days)

✓ **Before ITV injection of IP**

- NEI VFQ-25 (before 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 false elevation in urine protein values
- Blood sampling for immunogenicity
- Blood sampling for pharmacokinetics for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - FP & FA (images should be sent to central reading centre)
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)
- Adverse event monitoring

7.10. Visit 10 (Week 28 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV injection of IP**

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

7.11. Visit 11 (Week 32 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
    - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
    - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
    - Slit lamp biomicroscopy
    - Indirect ophthalmoscopy
    - OCT (images should be sent to central reading centre)
    - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV injection of IP**

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

- Adverse event monitoring

7.12. Visit 12 (Week 36 ± 7 days)

✓ **Before ITV injection of IP**

- 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 false elevation in urine protein values

- Blood sampling for immunogenicity

- Blood sampling for pharmacokinetics for subjects participating in PK evaluation

- Pregnancy test (serum or urine) at the Investigator's discretion

- Ocular assessments:

  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit

  - Slit lamp biomicroscopy

  - Indirect ophthalmoscopy

  - OCT (images should be sent to central reading centre)

  - IOP using Goldmann applanation tonometry

- Adverse event monitoring

- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV 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 pharmacokinetics for subjects participating in PK evaluation (24 - 72 hours post-dose)
- Adverse event monitoring

7.13. Visit 13 (Week 40 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV injection of IP**

- Ocular assessments:
  - Indirect ophthalmoscopy (0-15 min post-dose)

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

- Adverse event monitoring

7.14. Visit 14 (Week 44 ± 7 days)

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye.

✓ **After ITV injection of IP**

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

7.15. End of Treatment Visit (Visit 15, Week 48 ± 7 days)

End of Treatment Visit (EOT) is defined as the visit for the last ITV injection of SB11 or Lucentis®. The Sponsor will not provide IP (SB11 or Lucentis®) to subjects after they complete the EOT visit.

✓ **Before ITV injection of IP**

- Vital signs (temperature, blood pressure and pulse rate)
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts (before dilation of the pupils and FP/FA or OCT assessment)
  - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

✓ **ITV injection of IP**

- IP (SB11 or Lucentis®) will be given in the study eye

✓ **After ITV injection of IP**

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

7.16. End of Study (Visit 16, Week 52 ± 7 days) or Early Termination Visit

End of study (EOS) or Early Termination (ET) visit is defined as 4 weeks (± 7 days) after the last ITV injection of SB11 or Lucentis®. For ET visit, PK sampling will be excluded from the following procedures.

- NEI VFQ-25 (before dilation of pupil)
- Vital signs (temperature, blood pressure and pulse rate)
- Physical examination (only body weight)
- Blood and urine sampling for clinical laboratory tests
  - Urine samples must be collected before performing FA to avoid false elevation in urine protein values
- Blood sampling for immunogenicity
- Blood sampling for systemic exposure for subjects participating in PK evaluation
- Pregnancy test (serum or urine) at the Investigator's discretion
- Ocular assessments:
  - BCVA examination using original series ETDRS charts or 2702 series Number charts(before dilation of the pupils and FP/FA or OCT assessment)
    - Subject must use the same chart consistently from Screening to Week 52 (EOS visit) or ET visit
  - Slit lamp biomicroscopy
  - Indirect ophthalmoscopy
  - FP & FA (images should be sent to central reading centre)
  - OCT (images should be sent to central reading centre)
  - IOP using Goldmann applanation tonometry
- Adverse event monitoring
- Review of concomitant medication or therapy

7.17. Early Termination of the Study

The study can be terminated at any time for any reason by the Sponsor. 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 interests. Investigator will be responsible for informing Independent Ethics Committees (IECs) of the early termination of the study.

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events

8.1.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a 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 systemic AEs will be collected from the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit. If the AMD is diagnosed in the fellow eye during the study period, the 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 should not be reported as AEs, however pre-existing conditions which worsen (i.e., change in severity) that meets 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. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. 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.

The AE that emerge during the treatment with an IP (i.e., Treatment-Emergent Adverse Event [TEAE]) will be analysed for the purposes of safety analyses.

8.1.2. Period of Observation for Adverse Events

All AEs (ocular or systemic) will be recorded from the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit.

SAEs that occurred at or before Week 52 (EOS visit) or ET visit must be reported to Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event.

SAEs that are considered to be related to the IP can be collected regardless of the study period. SAEs that occurred after Week 52 (EOS visit) or ET visit and that are considered to be related to the IP must be reported to Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event (see Section 8.2.2.).

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

Unresolved AEs should be followed up until the Week 52 (EOS visit) or ET visit and follow-up information will be recorded in the eCRF. The Investigator should provide proper monitoring of subject's status and related AEs for appropriate medical care of the subject until AE resolution or stabilisation.

Unresolved SAE at Week 52 (EOS visit) or ET visit will be followed until event resolution or stabilisation (see Section 8.2.2.).

8.1.3. Reporting Adverse Events

AEs are to be reported and reviewed by Investigator. When reporting an AE, a diagnosis (when possible and appropriate) rather than each individual signs and symptoms should be reported.

Each AE is to be assessed to determine if it meets the criteria of an SAE (see Section 8.2. for SAE definition). If an AE is classed as an SAE, it must be reported to Sponsor, or its designated representative, promptly according to the timeline specified in Section 8.2.2.

For an SAE, a diagnosis with a description of signs and symptoms as well as other supporting information 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.

8.1.4. Severity Assessment

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

8.1.5. Causality Assessment

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.

8.1.6. Emergency Unmasking for Safety Reasons

Unmasking should be considered only when knowledge of the treatment group assigned to subject is deemed essential for the subject's safety by Investigator. Emergency unmasking may be performed by Investigator through IWRS system if deemed necessary during the study period after randomisation.

If the treatment group assigned to subject is unmasked, Investigator should promptly document and explain to the Sponsor about any premature unmasking (e.g., accidental unmasking, unmasking due to a serious adverse event) of the investigational product(s) which is treated to the subject.

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.

After unmasking (except unmasking for the purpose of pre-planned regulatory reporting in Section 5.2.4.), subjects will be discontinued from the IP (Refer to Section 4.3.).

8.1.7. Expectedness Assessment

Expectedness of AEs will be assessed by referring to the safety information in the Investigator's Brochure (IB) of the relevant safety section. More detailed information on expectedness assessment will be explained in the IB. The latest SmPC of Lucentis®, Annex I of EPAR Product Information posted on EMA website, will be used to assess the expectedness for the AEs.

8.1.8. Withdrawal due to Adverse Events

Subject withdrawal from the IP due to an AE should be distinguished from withdrawal due to personal reasons. Subjects withdrawn due to an AE will be followed up until the time point specified in the protocol (refer to Section 4.3.). If subjects cannot be followed, the reasons will be documented by the Investigator (e.g., lost to follow-up, refusal to be followed up). When a subject withdraws from the IP due to an SAE, the SAE must be reported and followed in accordance with the requirements outlined in Section 8.2.2.

Subjects who are discontinued from IPs because of serious or significant safety issues should be followed closely until the events are fully and permanently resolved or stabilised.

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

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.

Hospitalisation

AEs reported from clinical studies associated with hospitalisation or prolongation of existing 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 existing hospitalisation in the absence of an 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.

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 VA of ≥ 30 letters from the last assessment of VA
- A decrease in VA to the level of Light Perception or worse
- Requirement of surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with ITV injection of anti-biotics, laser treatment, ITV gas injection, or retinal cryopexy) to prevent permanent loss of vision
- Severe intraocular inflammation (e.g., 4+ anterior chamber cell/flare or 4+ vitritis).
- In the investigator's opinion, medical intervention may be required to prevent permanent loss of vision.

8.2.2. Reporting Serious Adverse Events

SAEs that occurred at or before Week 52 (EOS visit) or ET visit must be reported to Sponsor or its designated representative via eCRF SAE report form at least within 24 hours of the Investigator becoming aware of the event.

SAEs that occurred after Week 52 (EOS visit) or ET visit and that are considered to be related to the IP must be reported to Sponsor or its designated representative using the paper SAE report form at least within 24 hours of the Investigator becoming aware of the event.

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

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

The Investigator is obligated to pursue and provide information to Sponsor on all SAEs in accordance with the timeframes for reporting specified above. In addition, Investigator may be requested by 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, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

All SAEs will be followed until event resolution or stabilisation (for chronic events), if possible, even when a subject is discontinued from IP. For chronic events that does not fully resolve until years later, the outcome should be reported as "resolved with sequelae" as soon

as the event has stabilised or returned to baseline. Follow-up information for the SAE should be actively sought and submitted as the information becomes available.

8.3. Adverse Events of Special Interest

The following AEs in the study eye will be classified as Adverse Events of Special Interests (AESIs) in this study:

- Any case of new onset IOP of > 21 mm Hg that does not respond to treatment, except the transient pressure rise observed within an hour after ITV injection of IP
- Any case of IOP ≥ 35 mmHg, at any time, that required treatment
- Any case of intraocular infection such as endophthalmitis
- Any case of intraocular inflammation such as iritis, vitritis and iridocyclitis
- Iatrogenic traumatic cataract
- Arterial thromboembolic events defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown as cause)

8.4. 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 informed consent must be obtained from the female partner before collecting any pregnancy-related data. All pregnancies associated with the subject, from the time the subject receives the first ITV injection of IP until either Week 52 (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 the SAE criteria then the Investigator should report this case according to the SAE reporting process (Section 8.2.2.).

8.5. Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (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 and included in the DSMB Charter. 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, pharmacokinetics, 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 52 or the corresponding visit. All study data will be analysed and reported for final CSR.

9.1. 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.

- Full Analysis Set (FAS) consists of all subjects who are randomised at the randomisation visit. 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 qualify for randomisation and are inadvertently randomised into the study will be excluded from the FAS, provided these subjects do not receive IP during the study period. The FAS will be the primary analysis set for BCVA

- Per-Protocol Set for BCVA (PPS-BCVA) consists of all FAS subjects who have first two IP injections and complete the procedures at Week 8 without any major protocol deviations that have impact on the BCVA assessment. Major protocol deviations that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment group assignment for analyses.

- Per-Protocol Set for CST (PPS-CST) consists of all FAS subjects who have the first IP injection at Week 0 (Day 1) and complete the procedures at Week 4 without any major protocol deviations that have impact on the CST assessment. This PPS-CST will be the primary analysis set for CST. Major protocol deviations that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment codes for analyses.

- Safety Set (SAF) consists of all subjects who receive at least one IP during the study period after randomisation. Subjects will be analysed according to the IP received.

- Pharmacokinetic Analysis Set (PKS) consists of all subjects in the SAF who participate in PK evaluation at PK Investigational sites (PK subjects) and have at least one PK sample analysed.

9.2. Statistical Methods and Analytical Plan

9.2.1. Demographics 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, 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 history will be summarised by treatment group for the RAN.

Duration of exposure to IP and number of injections will be summarised by treatment group with descriptive statistics for the SAF. Prior and concomitant medications and significant non-drug therapies will be summarised by treatment group with frequency and percentage.

9.2.2. Efficacy

For US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of the VA, the primary efficacy analysis will be performed for the FAS with the change from baseline of 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 in BCVA will be declared if the two-sided 90% Confidence Interval (CI) of the difference in terms of BCVA Least Squares mean (LS mean) changes from baseline at Week 8 between SB11 and Lucentis® lies within the pre-defined equivalence margin of [−3 letters, 3 letters].

For EMA or other regulatory agency submissions for those who are in favour of the anatomical parameter, the primary efficacy analysis will be performed for the per-protocol set (PPS-CST) with the change from baseline of CST at Week 4 using an analysis of covariance model with baseline CST as a covariate and region (or pooled centres) and treatment group as factors. The equivalence in CST will be declared if the two-sided 95% CI of the difference of the CST LS mean changes from baseline in Week 4 between SB11 and Lucentis® lies within the pre-defined equivalence margin of [−36 μm, 36 μm].

No formal adjustment of Type I error rates will be performed.

For the primary analysis with the FAS for BCVA, missing data will be imputed for subjects who drop out for the study prior to the primary analysis time-point. A missing-at-random approach will assume that subjects who withdraw from a study had missing values similar to similar subjects who completed the study in that treatment group. This approach ensures that evidence of lack of equivalence is not diluted when there are missing data. For the components of BCVA, the missing letter will be imputed by multiple imputation method with the assumption of monotone missing pattern and regression method. For the sensitivity analyses, available case analysis and last observation carried forward analysis will be performed.

All other secondary efficacy measurements will be summarised descriptively by treatment group and visit, and analysed using analysis of covariance model for continuous outcomes or Cochran-Mentel-Haenszel method for categorical outcomes unless otherwise specified.

9.2.3. Safety

All reported terms for AEs (ocular and systemic) will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). For all AE and SAE tables, subjects will be counted once for each preferred term and each system organ class.

A TEAE will be defined as any AE with an onset date on or after the date of the first ITV injection of IP. AEs which are already present before the first ITV injection of IP and increase in severity after the first ITV injection of IP will be considered as TEAEs. Pre-existing AEs before the first ITV injection of IP with no increase in severity after the first ITV injection of IP will not be considered as TEAEs.

All TEAEs and SAEs will be summarised respectively for study eye (ocular TEAE), fellow eye (ocular TEAE) and others (systemic TEAE) by the frequency and percentage of subjects experiencing events by system organ class, preferred term and treatment group. SAEs leading to IP discontinuation and TEAEs by causality and severity will be summarised similarly. All AEs including those pre-existing before the first ITV injection of IP will be listed by subject.

In addition, systemic TEAEs will also be summarised without subjects who received Lucentis® in the fellow eye due to AMD during the study period after randomisation.

Changes in vital signs and clinical laboratory parameters will be summarised descriptively by treatment group and visit. Other safety variables will be summarised unless otherwise specified, and all safety variables will be listed.

All safety analyses will be performed using the SAF.

9.2.4. Pharmacokinetics

Blood sampling for PK will be collected in approximately 40 subjects participating in PK evaluation (20 subjects per treatment group). The systemic exposure will be summarised descriptively by treatment group and visit.

If fellow eye received Lucentis® due to AMD during the study period after randomisation, the concentration measured after treatment for the fellow eye will be listed, but excluded from the summary statistics.

9.2.5. Immunogenicity

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 Lucentis® due to AMD 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.

9.2.6. NEI VFQ-25

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.

In addition, the subscale scores and composite score of NEI VFQ-25 will be also summarised without subjects who received Lucentis® in the fellow eye due to AMD during the study period after randomisation.

9.3. Determination of Sample Size

For the calculation of the equivalence margin for BCVA, the mean changes in VA were referred from two studies of Lucentis® in subjects with neovascular AMD. In MARINA study, the mean change of VA at Week 24 (SD) were −6.6 (13.31) letters and 6.5 (12.00) letters for placebo and 0.5 mg Lucentis® treatment groups, respectively. In FOCUS study, the mean change (SD) of VA at Week 24 were −5.0 (16.14) letters and 4.0 (14.41) letters for placebo and 0.5 mg Lucentis® treatment groups, respectively.

A fixed-effect meta-analysis of the above two studies estimates a weighted mean change in VA of 12.41 letters with a 95% CI [10.34 letters; 14.48 letters]. The derived equivalence limit from meta-analysis is 4.9 letters at Week 24, but by the agency recommendation the equivalence limit at Week 8 will be 3 letters for the comparison with the 90% CI of mean difference between treatment groups.

With the given equivalence margin of [−3 letters, 3 letters], 334 subjects per treatment groups was calculated with the assumptions of the mean difference of 0.5 letters and pooled standard deviation (SD) of 12.5 letters at the overall 5% significance level. Assuming a 5% loss from randomised subjects after 8 weeks, a sample size of 352 subjects per treatment groups (overall sample size of 704) will give 334 completers per treatment group after 8 weeks, which is estimated to give 80% power to detect the equivalence within the margin of 3 letters.

For the calculation of the equivalence margin for CST, the mean changes in CST were referred from two studies of Lucentis® in subjects with neovascular AMD. In MARINA study, the mean change of CST at Week 4 (SD) was 8.1 (58.1) μm and −106 (122.5) μm for placebo and 0.5 mg Lucentis® treatment groups, respectively. In PIER study, the mean change (SD) of CST at Week 4 were 15 (94.9) μm and −90 (140.9) μm for placebo and 0.5 mg Lucentis® treatment groups, respectively.

A fixed-effect meta-analysis of the above two studies estimates a weighted mean change in CST of −109.6 μm with a 95% CI [−146.45 μm; −72.65 μm]. The derived equivalence limit from meta-analysis is 36 μm at Week 4.

With the given equivalence margin of [−36 μm, 36 μm], 290 subjects per treatment group was calculated with the assumptions of the mean difference of 0 between treatment groups, common SD of 133.3 μm at the overall 5% significance level. Assuming a 10% loss from

FAS, a sample size of 323 per arm (overall sample size of 646) will give 80% power to detect the equivalence within the pre-defined margin.

Therefore, the sample size of 704 allows enough power to detect the equivalence between treatment groups 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) Guideline for 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 GCP. The monitor will provide written reports to the Sponsor on each occasion they make contact 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 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. 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.

Forms 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 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.

10.5. Quality Control and Quality Assurance

During the conduct of the study, Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and ICH 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 IEC, and/or to quality assurance audits performed by 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.

11. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1. Institutional Review Boards and Independent Ethics Committees

The Investigator and the Sponsor will follow all local laws and regulations relating to contact with and approvals from the Institutional Review Board (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 in compliance with the protocol, the ICH GCP, the Declaration of Helsinki (2013) and other relevant laws and/or regulations.

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 ITV 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.

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, and after the subject has orally consented to the subject's participation in the study, and, if capable of doing so, has signed and personally dated the written informed consent, the witness should sign and personally date the written informed consent. By signing the written informed consent, the 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 GCP (1997), ICH GCP E6 R2 (2016), 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 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. Coordinating Investigator

Sponsor will designate a Coordinating Investigator among the Investigators who participate in the study. The roles of the Coordinating Investigator are defined as following:

- Provide scientific and medical advice and/or inputs on current medical practice, protocol development and Investigational site selection
- Review ongoing study activities with Interpretation and presentation of final analyses
- Review clinical study reports
- Involved in development of publication strategy
- The designated Coordinating Investigator will sign the signature page of CSR as a representative of other Investigators.

11.4.3. Training of Investigational 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 staff involved.

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

11.4.4. 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 GCP and other relevant local laws and/or regulations.

11.5. 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 the 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 such as www.ClinicalTrials.gov. 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.

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APPENDIX A: Grading Scale for Anterior Chamber Flare

Grading Scale for Anterior Chamber Flare	
Flare	
0	No protein is visible in the anterior chamber when viewed by an experienced observer using slit lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
Trace	Trace amount of protein detectable in the anterior chamber. This protein is visible only with careful scrutiny by an experienced observer using slit lamp biomicroscopy; a small, bright, focal slit-beam of white light; and high magnification.
1+	Mild amount of protein detectable in the anterior chamber. The presence of protein in the anterior chamber is immediately apparent to an experienced observer using slit lamp biomicroscopy and high magnification, but such protein is detected only with careful observation with the naked eye and a small, bright, focal slit-beam of white light.
2-3+	Moderate amount of protein detectable in the anterior chamber. These grades are similar to 1+ but the opacity would be readily visible to the naked eye of an observer using any source of a focused beam of white light, This is a continuum of moderate opacification, with 2+ being less apparent than 3+.
4+	A large (severe) amount of protein is detectable in the anterior chamber. Similar to 3+, but the density of the protein approaches that of the lens. Additionally, frank fibrin deposition is frequently seen in acute circumstances. It needs to be noted that because fibrin may persist for a period of time after partial or complete restoration of the blood-aqueous barrier, it is possible to have resorbing fibrin present with lower numeric assignations for flare (e.g., 1+ flare with fibrin).

Reference: The Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of Uveitis Nomenclature for Reporting Clinical Data: Results of the First International Workshop. *American journal of ophthalmology*. 2005;140(3): 509-516.

APPENDIX B: Grading Scale for Anterior Chamber Cells

Grading scale for anterior chamber cells The intensity of the cellular reaction in the anterior chamber is graded according to the number of inflammatory cells seen in a 1 x 3 mm high-powered beam at full intensity at a 45°-60° angle.	
Cells	
0	No inflammatory cells.
Trace	< 5 cells.
1+	5 – 9 cells.
2+	10 – 19 cells.
3+	20 – 29 cells.
4+	≥ 30 cells, cells too numerous to count.

Reference: Bloch-Michel E., Nussenblatt RB. International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol*. 1987;103(2):234-5.

APPENDIX C: Grading Scale for Anterior Chamber and Vitreal Inflammatory Response

Grading scale for anterior chamber and vitreal inflammatory response		
Cells in Retro-illuminated Field	**Description**	**Grade**
0-1	Clear	0+
2-20	Few opacities	Trace
21-50	Scattered opacities	1+
51-100	Moderate opacities	2+
101-250	Many opacities	3+
> 250	Dense opacities	4+

Reference: Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology*. 1985;92:467-71.

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

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 <u>driving at night</u>? 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 <u>driving in difficult conditions, such as in bad weather,</u> 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 or Responsible Medical Expert

Protocol Title: A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB11 (proposed ranibizumab biosimilar) and Lucentis® in Subject 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 Signatory/Responsible Medical Expert

Name: [redacted]

Institution: Samsung Bioepis Co., Ltd.

Signature: [redacted] Date: Sep 01, 2017

(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Global Principal/Coordinating Investigator

Protocol Title: A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB11 (proposed ranibizumab biosimilar) and Lucentis® in Subject with Neovascular Age-related Macular Degeneration

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Global Principal/Coordinating Investigator

Name: [redacted]

Institution: [redacted]

Signature: [redacted] Date: Sep 01, 2017

(MMM DD, YYYY)

SIGNATURE PAGE

Declaration of the Principal Investigator

Protocol Title: A Phase III Randomised, Double-masked, Parallel Group, Multicentre Study to Compare the Efficacy, Safety, Pharmacokinetics and Immunogenicity between SB11 (proposed ranibizumab biosimilar) and Lucentis® in Subject with Neovascular Age-related Macular Degeneration

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Principal Investigator

Name: _____

Institution: _____

Signature: _____ Date: _____

(MMM DD, YYYY)

AMENDMENT 1: Sep 01, 2017

Section Affected	Original Content	Amended/New Content	Rationale
Synopsis-Inclusion criteria 4.1. Inclusion Criteria	2. * Active CNV indicates presence of leakage as evidenced by Fluorescein Angiography (FA) and intra- or sub-retinal fluid as evidenced by Optical Coherence Tomography (OCT) which should be confirmed by central reading centre during Screening	2. * Active CNV indicates presence of leakage ~~**as evidenced by Fluorescein Angiography (FA)**~~ and intra- or sub-retinal fluid ~~**as evidenced by Optical Coherence Tomography (OCT)**~~ which should be confirmed by central reading centre during Screening	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	4. Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars and neovascularisation) as assessed by FA in the study eye (confirmed by central reading centre during Screening)	4. Total lesion area ≤ 9.0 Disc Areas (DA) in size (including blood, scars and neovascularisation) ~~**as assessed by FA**~~ in the study eye (confirmed by central reading centre during Screening)	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	5. Best Corrected Visual Acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34) using Early Treatment Diabetic Retinopathy Study (ETDRS) chart or 2702 Number chart in the study eye at Screening and at Week 0 (Day 1) prior to randomisation	5. Best Corrected Visual Acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34) using **original series** Early Treatment Diabetic Retinopathy Study (ETDRS) chart**s** or 2702 **series** Number chart**s** in the study eye at Screening and at Week 0 (Day 1) prior to randomisation	Clarification for charts used in this study
	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	6. Non-childbearing potential female (e.g., permanently ~~**sterilized**~~ **sterilised**, 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	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	system, bilateral tubal occlusion, vasectomised partner, physical barrier, sexual abstinence) from Screening until 3 months after the last ITV injection of IP	device or intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner, physical barrier, sexual abstinence) from Screening until 3 months after the last ITV injection of IP	
Synopsis-Exclusion criteria 4.2. Exclusion Criteria	1. Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye, or presence of subfoveal blood equal to or more than one DA in size as assessed by FA (confirmed by central reading centre during Screening)	1. Sub- or intra-retinal haemorrhage that comprises more than 50% of the entire lesion in the study eye, or presence of subfoveal blood equal to or more than one DA in size **~~as assessed by FA~~** (confirmed by central reading centre during Screening)	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	2. Scar, fibrosis or atrophy involving the centre of the fovea in the study eye as assessed by FA (confirmed by central reading centre during Screening)	2. Scar, fibrosis or atrophy involving the centre of the fovea in the study eye **~~as assessed by FA~~** (confirmed by central reading centre during Screening)	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	3. Presence of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture or Pathologic Myopia (PM) as assessed by FA (confirmed by central reading centre during Screening)	3. Presence of CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, multifocal choroiditis, angioid streaks, history of choroidal rupture or Pathologic Myopia (PM) **~~as assessed by FA~~** (confirmed by central reading centre during Screening)	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	4. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye as assessed by FA (confirmed by central reading centre during Screening)	4. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye **~~as assessed by FA~~** (confirmed by central reading centre during Screening)	Per central reading centre's practice, images used for assessment will be selected at the reader's best knowledge.
	6. Any concurrent macular abnormality other than AMD in the study eye which, in the opinion of Investigator, could affect the efficacy of IP including but not limited to epiretinal membrane, macular telangiectasia, retinal vascular abnormality, etc	6. Any concurrent macular abnormality other than AMD in the study eye which**~~, in the opinion of Investigator,~~** could affect the efficacy of IP including but not limited to epiretinal membrane, macular telangiectasia, retinal vascular abnormality, etc	This criterion will be assessed by central reading centre.

Section Affected	Original Content	Amended/New Content	Rationale
		(confirmed by central reading centre)	
	10. Any other intraocular surgery (including cataract surgery and laser photocoagulation) or periocular surgery in the study eye within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation	10. Any other intraocular surgery (including cataract surgery ~~**and laser photocoagulation**~~) or periocular surgery in the study eye within 90 days prior to randomisation, except for lid surgery, which may not have taken place within 30 days prior to randomisation	Error correction. Laser photocoagulation is not included in the category of surgery.
	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 supplementary, vitamins or mineral will be allowed.	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 ~~**supplementary**~~ **supplements**, vitamins or mineral will be allowed.	Editorial change
	14. Any ITV sustained drug delivery implant in the study eye (e.g., intravitreal corticosteroid implant) within 180 days prior to randomisation, and such treatment will not be allowed during the study period	14. Any ~~**ITV**~~ **intravitreal injection of corticosteroid (e.g., triamcinolone acetonide) or** ~~**sustained drug delivery implant in the study eye (e.g.,**~~ intravitreal corticosteroid implant~~**)**~~ **in the study eye** within 180 days prior to randomisation, and such treatment will not be allowed during the study period	Prohibited medication is added.
	16. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia	16. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 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 must not exceed 8 diopters of myopia**	Clarification for subjects who have undergone refractive or cataract surgery in the study eye
	21. History of idiopathic or autoimmune-associated uveitis in either eye	21. History of idiopathic or autoimmune~~**-associated**~~ uveitis in either eye	Editorial change
	24. History of corneal transplant in the study eye	24. History of corneal transplant**ation surgery** in the study eye	Editorial change
	25. Presence of advanced glaucoma or optic neuropathy that involve or threaten the central visual	25. Presence of advanced glaucoma or optic neuropathy that ~~**involve**~~ **affect** or threaten the central	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	field	visual field **in the study eye**	Target eye is specified.
	29. Previous participation in any studies of ocular or systemic investigational products (excluding dietary supplementary, vitamins and minerals) to treat ocular or systemic disease other than neovascular AMD within 90 days prior to randomisation, and such participation will not be allowed during the study period even if the investigational product is dietary supplementary, vitamins and minerals	29. Previous participation in any studies of ocular or systemic investigational products (excluding dietary ~~**supplementary**~~ **supplements**, vitamins and minerals) to treat ocular or systemic disease other than neovascular AMD within 90 days prior to randomisation, and such participation will not be allowed during the study period even if the investigational product is dietary ~~**supplementary**~~ **supplements**, vitamins and minerals	Editorial change
	30. History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy), diabetic macular oedema or any retinal vascular disease other than AMD in either eye	30. History or clinical evidence of diabetic retinopathy (except for mild non-proliferative diabetic retinopathy)~~**,**~~ **or** diabetic macular oedema ~~**or any retinal vascular disease other than AMD**~~ in either eye	Retinal vascular disease that affects macula will be excluded from exclusion criterion #6.
	31. Any concurrent ocular condition in the study eye which, in the opinion of Investigator, could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety including, but not limited to corneal opacities, cataract, ocular media that do not allow proper fundus visualisation and fundus imaging, and ocular surface abnormalities which prevent applanation tonometry during the study period after randomisation	31. Any concurrent ocular condition in the study eye which, in the opinion of **the** Investigator, could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety including, but not limited to **ocular media opacities such as** corneal ~~**opacities,**~~ **opacity or** cataract~~**, ocular media**~~ that do not allow proper fundus visualisation and fundus imaging, and ocular surface abnormalities which prevent applanation tonometry during the study period after randomisation	Editorial change
	33. Pregnant or lactating women. A serum pregnancy test must be required for all women at Screening	33. Pregnant or lactating women. A serum pregnancy test must be required for ~~**all**~~ women **of childbearing potential** at Screening	Pregnancy test will be performed only for childbearing potential female subjects.
	Not applicable	**35. Stroke, transient ischemic attacks, or myocardial infarction within 90 days prior to**	Exclusion criterion is added as per Korea

Section Affected	Original Content	Amended/New Content	Rationale
		randomisation	MFDS's request.
	Not applicable	**36. History of recurrent significant infections and/or current treatment for active systemic infection**	Exclusion criterion is added as per Korea MFDS's request.
	Not applicable	**37. Known allergic reactions and/or hypersensitivity to ranibizumab or to any ingredients of the investigational product**	Exclusion criterion is added as per Korea MFDS's request.
	Not applicable	**38. Prior treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e,g., focal laser photocoagulation) in the study eye, and such treatment will not be allowed during the study period**	Exclusion criterion is added as per Korea MFDS's request.
	Not applicable	**39. Prior treatment with pan-retinal photocoagulation in the study eye, and such treatment will not be allowed during the study period**	Exclusion criterion is added as per Korea MFDS's request.
	Not applicable	**40. Current use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin and ethambutol, and such medications will not be allowed during the study period**	Exclusion criterion is added as per Korea MFDS's request.
Synopsis- Primary endpoints 6.1.1. Primary Endpoint	For US Food and Drug Administration (FDA), Korea Ministry of Food and Drug Safety (MFDS) or other regulatory agency submissions for those who are in favour of VA, the primary endpoint is: Change from baseline in BCVA at Week 8 For European Medicines Agency (EMA) or other regulatory agency submissions for those who are in	For US Food and Drug Administration (FDA), Korea Ministry of Food and Drug Safety (MFDS) or other regulatory agency submissions for those who are in favour of **the** VA, the primary endpoint is: Change from baseline in BCVA at Week 8 For European Medicines Agency (EMA) or other regulatory agency submissions for those who are in	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	favour of anatomical parameter, the primary endpoint is: Change from baseline in Central Subfield Thickness (CST) at Week 4 (based on assessment by central reading centre)	favour of **the** anatomical parameter, the primary endpoint is: Change from baseline in Central Subfield Thickness (CST) at Week 4 (based on assessment by central reading centre)	
Synopsis-Secondary endpoints 6.1.2. Secondary Endpoints	The secondary efficacy endpoints are: Proportion of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 (based on assessment by central reading centre)	The secondary efficacy endpoints are: ~~**Proportion of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 (based on assessment by central reading centre)**~~	To move exploratory endpoint section. The endpoint has few clinical meaning with high variability.
	The pharmacokinetic endpoints are: PK sampling will be collected in approximately 120 subjects participating in PK evaluation (60 subjects per treatment group).	The pharmacokinetic endpoints are: ~~**PK sampling**~~ **Blood sampling for PK** will be collected in approximately ~~**120**~~**40** subjects participating in PK evaluation (~~**60**~~**20** subjects per treatment group).	Number of subjects participating in PK evaluation is changed as per US FDA's request.
Synopsis-Exploratory endpoint 6.1.3. Exploratory Endpoint	The exploratory endpoint is: 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 24 and Week 52	The exploratory endpoint**s** ~~**is**~~ **are** : **Proportion of subjects without intra- or sub-retinal fluid at Week 24 and Week 52 (based on assessment by 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 24 and Week 52	To move exploratory endpoint section. The endpoint has few clinical meaning with high variability.
Synopsis-Statistical Methods: Efficacy analysis 9.2.2. Efficacy	The primary efficacy analysis will be performed for the FAS with the change from baseline of 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.	**For US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of the VA,** ~~**The**~~ **the** primary efficacy analysis will be performed for the FAS with the change from baseline of 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	Clarification for primary efficacy endpoint analysis for BCVA

Section Affected	Original Content	Amended/New Content	Rationale
		factors.	
	The other primary efficacy analysis will be performed for the FAS and Per-Protocol Set (PPS-CST) with the change from baseline of CST at Week 4 using an analysis of covariance model with baseline CST as a covariate and region (or pooled centres) and treatment group as factors.	~~**The other primary efficacy analysis will be performed for the FAS and Per-Protocol Set (PPS-CST)**~~ **For EMA or other regulatory agency submissions for those who are in favour of the anatomical parameter, the primary efficacy analysis will be performed for the per-protocol set (PPS-CST)** with the change from baseline of CST at Week 4 using an analysis of covariance model with baseline CST as a covariate and region (or pooled centres) and treatment group as factors.	Clarification for primary efficacy endpoint analysis for CST
	For the sensitivity analysis, missing data will be imputed using the Last Observation Carried Forward (LOCF) or other multiple imputation methods for the FAS.	~~**For the sensitivity analysis, missing data will be imputed using the Last Observation Carried Forward (LOCF) or other multiple imputation methods for the FAS.**~~ **For the primary analysis with the FAS for BCVA, missing data will be imputed for subjects who drop out for the study prior to the primary analysis time-point. A missing-at-random approach will assume that subjects who withdraw from a study had missing values similar to similar subjects who completed the study in that treatment group. This approach ensures that evidence of lack of equivalence is not diluted when there are missing data. For the components of BCVA, the missing letter will be imputed by multiple imputation method with the assumption of monotone missing pattern and regression method. For the sensitivity analyses, available case analysis and last observation carried forward analysis will be performed.**	Clarification for missing imputation method
Synopsis-Statistical Methods:	Blood sampling for PK will be collected in approximately 120 subjects participating in PK	Blood sampling for PK will be collected in approximately ~~**120**~~**40** subjects participating in PK	Number of subjects participating in PK

Section Affected	Original Content	Amended/New Content	Rationale
Pharmacokinetic analysis	evaluation (60 subjects per treatment group).	evaluation (~~60~~**20** subjects per treatment group).	evaluation is changed as per US FDA's request.
Synopsis-Statistical Methods: NEI VFQ-25 analyses	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 summarized by treatment group and visit.	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 ~~**summarized**~~ **summarised** by treatment group and visit.	Editorial change
Table 1. Schedule of Activities	NEI VFQ-25: Week 0, Week 12, Week 24, Week 36, Week 52 (EOS/ET)	NEI VFQ-25: Week 0, ~~**Week 12,**~~ Week 24, ~~**Week 36,**~~ Week 52 (EOS/ET)	Frequency of NEI VFQ-25 is changed as per US FDA's request.
Table 1 Footnote	3. Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit. Body weight will be measured and recorded at Screening and Week 52 (EOS visit) or ET visit, but height will be measured and recorded only at Screening.	3. Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit. **The physical examination will 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.** Body weight will be measured and recorded at Screening and Week 52 (EOS visit) or ET visit, but height will be measured and recorded only at Screening.	Clarification for physical examination (systems and organs)
	6. Visual acuity will be assessed in both the study eye and fellow (non-study) eye at Screening and prior to ITV injection of IP at each visit until Week 48. Visual acuity will also be assessed at any time during the visit at Week 52 (EOS visit) or ET visit. Subject must use either ETDRS chart or 2702 Number chart (at a starting distance of 4 meters) consistently from Screening to	6. Visual acuity will be assessed in both the study eye and fellow (non-study) eye at Screening and prior to ITV injection of IP at each visit until Week 48. Visual acuity will also be assessed at any time during the visit at Week 52 (EOS visit) or ET visit. Subject must use either **original series** ETDRS chart**s** or 2702 **series** Number chart**s** (at a starting distance of 4 meters)	Clarification for charts used in this study

Section Affected	Original Content	Amended/New Content	Rationale
	Week 52 (EOS visit) or ET visit. Visual acuity testing must be performed before dilation of pupils and FP/FA and OCT assessment. A decrease in visual acuity of > 15 letters (compared with the last assessment of VA) should be reported as AEs/Serious Adverse Events (SAEs) as appropriate. If there is a decrease in VA of > 30 letters (compared with the last assessment of VA) lasting > 1 hour or if there is a decrease in VA to the level of Light Perception or worse lasting > 1 hour, it should be reported as SAE.	consistently from Screening to Week 52 (EOS visit) or ET visit. Visual acuity testing must be performed before dilation of pupils and FP/FA and OCT assessment. A decrease in visual acuity of **≥** ~~>~~ 15 letters ~~**(compared with**~~ **from** the last assessment of VA~~)~~ should be reported as AEs/Serious Adverse Events (SAEs) as appropriate. If there is a decrease in VA of **≥** ~~>~~ 30 letters ~~**(compared with**~~ **from** the last assessment of VA~~)~~ ~~**lasting > 1 hour**~~ or if there is a decrease in VA to the level of Light Perception or worse ~~**lasting > 1 hour**~~, it should be reported as SAE.	Error correction SAE criteria are changed.
	7. Investigator must confirm that the subject can read between 34 letters to 73 letters using ETDRS chart or 2702 Number chart at Week 0 (Day1) prior to randomisation	7. Investigator must confirm that the subject can read between 34 letters to 73 letters using **original series** ETDRS chart**s** or 2702 **series** Number chart**s** at Week 0 (Day1) prior to randomisation	Clarification for charts used in this study
	8. Visit at Week 8 is the most critical as the visit is for the primary endpoint assessment for US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of VA. Thus, every effort should be made to adhere to the visit schedule for the subjects.	8. Visit at Week 8 is the most critical as the visit is for the primary endpoint assessment for US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of **the** VA. Thus, every effort should be made to adhere to the visit schedule for the subjects.	Editorial change
	9. OCT will be performed only in the study eye at Screening and prior to ITV injection of IP at each visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. Only OCT devices registered and certified by central reading centre are allowed to be used in this study. If one or more OCT devices are registered and certified in an Investigational site, a subject should use the same OCT device consistently from Screening to Week 52 (EOS visit) or ET visit. OCT images will be sent to the central reading centre.	9. OCT will be performed ~~**only in**~~ **on** the study eye at Screening and prior to ITV injection of IP at each visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. **Site staffs who will perform OCT scans in this study must be certified by the central reading centre before study starts. OCT devices registered in an Investigational site should be all from the same manufacture and meet the minimum software requirement.** ~~**Only OCT devices registered and certified by central reading centre are allowed to be**~~	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
		~~**used in this study. If one or more OCT devices are registered and certified in an Investigational site, a subject should use the same OCT device consistently**~~ **The subject should use the OCT device registered by the central reading centre** from Screening to Week 52 (EOS visit) or ET visit.	
	10. Visit at Week 4 is the most critical as the visit is for the primary endpoint assessment for EMA or other regulatory agency submissions for those who are in favour of anatomical parameter. Thus, every effort should be made to adhere to the visit schedule for the subjects.	10. Visit at Week 4 is the most critical as the visit is for the primary endpoint assessment for EMA or other regulatory agency submissions for those who are in favour of **the** anatomical parameter. Thus, every effort should be made to adhere to the visit schedule for the subjects.	Editorial change
	11. FP/FA will be performed only in the study eye at Screening and prior to ITV injection of IP at Week 24. FP/FA will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. Only FP/FA device certified by 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 device consistently from Screening to Week 52 (EOS visit) or ET visit. FP/FA images will be sent to the central reading centre. If any significant change in the posterior pole (i.e. 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 Investigator's discretion, but the images will not be sent to the central reading centre.	11. FP/FA will be performed ~~**only in**~~ **on** the ~~**study**~~ **both** eye**s** at Screening and **those images taken from the both eyes will be sent to the central reading centre. FP/FA will also be performed on the study eye** prior to ITV injection of IP at Week 24 **and**~~**.**~~ ~~**FP/FA will also be performed**~~ at any time during the visit at Week 52 (EOS visit) or ET visit. **Those images taken from the study eye will be sent to the central reading centre. Site staffs who will perform FA/FP in this study must be certified by the central reading centre before study starts.** Only FP/FA device certified by 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 device consistently from Screening to Week 52 (EOS visit) or ET visit. ~~**FP/FA images will be sent to the central reading centre.**~~ If any significant change in the posterior pole (i.e. subretinal haemorrhage, macular hole, vitreous haemorrhage or opacity, retinal detachment, etc.) is detected with fundus examination,	According to exclusion criteria #3, FP/FA images taken from the both eyes should be sent to the central reading centre at Screening. Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
		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.	
	12. Indirect ophthalmoscopy using a standard way (i.e., usually using a head-mounted light source and a 20-30 lens) will be performed only in the study eye at Screening and prior to ITV injection of IP and within 15 minutes after ITV injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at any time during the visit at Week 52 (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 ~~**only in**~~ **on** the study eye at Screening and prior to ITV injection of IP and within 15 minutes after ITV injection of IP at each visit until Week 48. Indirect ophthalmoscopy will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	Editorial change
	14. Intraocular Pressure (IOP) will be measured using Goldmann applanation tonometry only. The same method of IOP measurement must be used in each subject from Screening to Week 52 (EOS visit) or ET visit. IOP will be measured only in the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48.	14. Intraocular Pressure (IOP) will be measured using Goldmann applanation tonometry ~~**only**~~. The same method of IOP measurement must be used in each subject from Screening to Week 52 (EOS visit) or ET visit. IOP will be measured ~~**only in**~~ **on** the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48.	Editorial change
	15. NEI VFQ-25 should be performed at Week 0 (Day1) after randomisation, but prior to starting any other study procedures. Then, NEI VFQ-25 should be performed before starting any other study procedures at Week 12, Week 24, Week 36 and Week 52 (EOS visit) or ET visit.	15. NEI VFQ-25 should be performed at Week 0 (Day1) after randomisation~~**, but prior to starting any other study procedures**~~. Then, NEI VFQ-25 should be performed before ~~**starting any other study procedures**~~ **dilation of pupil** at **Week 0 (Day 1),** ~~**Week 12,**~~ Week 24~~**, Week 36**~~ and Week 52 (EOS visit) or ET visit.	Frequency of NEI VFQ-25 is changed as per US FDA's request.

Section Affected	Original Content	Amended/New Content	Rationale
	16. Blood and urine sampling for clinical laboratory test will be collected at Screening and prior to ITV injection of IP at Week 12, Week 24, and Week 36. Blood and urine sampling for clinical laboratory test will also be collected at any time during the visit at Week 52 (EOS visit) or ET visit. Urine samples must be collected before performing FA to avoid false elevations in urine protein values. • Haematology: haemoglobin, haematocrit, platelet count, white blood cell count (total and differential) • Chemistry: sodium, potassium, creatinine, glucose, calcium, phosphorus, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase • Urinalysis (dipstick): protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen	16. Blood and urine sampling for clinical laboratory test will be collected at Screening and prior to ITV injection of IP at Week 12, Week 24, and Week 36. Blood and urine sampling for clinical laboratory test will also be collected at any time during the visit at Week 52 (EOS visit) or ET visit. Urine samples must be collected before performing FA to avoid false elevations in urine protein values. • Haematology: haemoglobin, haematocrit, platelet count, white blood cell count (total and differential) • Chemistry: sodium, potassium, creatinine, glucose, calcium, phosphorus, total bilirubin, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase • Urinalysis (dipstick): protein, blood, leucocytes, nitrite, glucose, ketone, pH, specific gravity, bilirubin, urobilinogen **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 Sponsor.**	Clarification for central laboratory test
	18. Blood sampling for PK will be collected only in approximately 120 subjects participating in PK evaluation (60 subjects per treatment group).	18. Blood sampling for PK will be collected ~~only~~ in approximately ~~120~~**40** subjects participating in PK evaluation (~~60~~**20** subjects per treatment group).	Number of subjects participating in PK evaluation is changed as per US FDA's request.
	19. For all women, serum pregnancy test must be performed at Screening. Serum or urine pregnancy test may be performed after randomisation at Investigator's discretion.	19. For ~~all~~ women **of childbearing potential**, serum pregnancy test must be performed at Screening. **The serum samples taken at Screening will be analysed in central laboratory. Additional ~~S~~s**erum or urine pregnancy test ~~may~~ **can** be performed ~~after randomisation at Investigator's discretion~~ **in each Investigational site during the study period, if**	Pregnancy test will be performed only for childbearing potential female subjects. Clarification for pregnancy test

Section Affected	Original Content	Amended/New Content	Rationale
		necessary.	
	20. Subjects will be administered SB11 or Lucentis® 0.5 mg via ITV into the study eye every 4 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). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within 21 days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within 21 days (3 weeks) after scheduled dosing visit date. Next scheduled dosing visit date and visit window should not be altered even though previous dosing is not performed on the exact scheduled dosing visit date (but, the interval between two doses injected into the study eye should be at least 14 days) or previous dosing is skipped.	20. Subjects will be administered SB11 or Lucentis® 0.5 mg via ITV into the study eye every 4 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). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within **~~21~~ 20** days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within **~~21~~ 20** days **~~(3 weeks)~~** after scheduled dosing visit date. Next scheduled dosing visit date and visit window should not be altered even though previous dosing is not performed on the exact scheduled dosing visit date (but, the interval between two doses injected into the study eye should be at least 14 days) or previous dosing is skipped.	Error correction
	21. The first ITV injection of IP should be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason.	21. The first ITV injection of IP **and all other study procedures ~~should~~ must** be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason.	Editorial change
Background	Age-related Macular Degeneration, left untreated, is a leading cause of adult blindness in the developed world. Most of severe visual loss of AMD occurs from CNV or the neovascular form of AMD …as well as atrophy of these portions of the retina in	Age-related Macular Degeneration **(AMD)**, left untreated, is a leading cause of adult blindness in the developed world. Most of severe visual loss of AMD occurs from **Choroidal Neovascularisation (**CNV**)** or the neovascular form of AMD … as well as atrophy of these portions of the retina in	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	the macula, leading to severe visual decline with loss of reading vision, driving vision, and the ability to recognize faces. Vascular endothelial growth factor, a protein growth factor that both stimulates angiogenesis and increases vascular permeability,… The pathogenesis of AMD is poorly understood. It is characterized by development of focal deposits of long –spacing collagen and phospholipid vesicles within and beneath the basement membrane of the RPE, called "drusen" which can be accompanied by gradual degeneration of photoreceptors and RPE (atrophy), which often results in slow deterioration of central visual acuity (VA).	the macula, leading to severe visual decline with loss of reading vision, driving vision, and the ability to ~~recognize~~ **recognise** faces. Vascular **Ee**ndothelial **Gg**rowth **Ff**actor **(VEGF)**, a protein growth factor that both stimulates angiogenesis and increases vascular permeability,… The pathogenesis of AMD is poorly understood. It is ~~characterized~~ **characterised** by development of focal deposits of long –spacing collagen and phospholipid vesicles within and beneath the basement membrane of the RPE, called "drusen" which can be accompanied by gradual degeneration of photoreceptors and RPE (atrophy), which often results in slow deterioration of central **V**isual **A**cuity (VA).	
1.2. Lucentis®: Ranibizumab Reference Product	*Neovascular (Wet) Age-Related Macular Degeneration* The safety and efficacy of Lucentis® were assessed in three randomized, double or single-masked, sham-or active-controlled studies in subjects with neovascular AMD. *Macular Oedema Following Retinal Vein Occlusion* The safety and efficacy of Lucentis® were assessed in two randomized, double-masked, 1-year studies in subjects with macular oedema following RVO.	*Neovascular (Wet) Age-Related Macular Degeneration* The safety and efficacy of Lucentis® were assessed in three ~~randomized~~ **randomised**, double or single-masked, sham-or active-controlled studies in subjects with neovascular AMD. *Macular Oedema Following Retinal Vein Occlusion* The safety and efficacy of Lucentis® were assessed in two ~~randomized~~ **randomised**, double-masked, 1-year studies in subjects with macular oedema following RVO.	Editorial change
1.3. SB11: Proposed Ranibizumab Biosimilar	Extensive characterization studies including intact mass, N- and C-terminal sequencing, peptide mapping, icIEF, CE-SDS (reduced, non-reduced), SE-HPLC, amino acid composition, disulfide bond, VEGF binding, VEGF neutralization,	Extensive ~~characterization~~ **characterisation** studies including intact mass, N- and C-terminal sequencing, peptide mapping, icIEF, CE-SDS (reduced, non-reduced), SE-HPLC, amino acid composition, disulfide bond, VEGF binding, VEGF ~~neutralization~~ **neutralisation**,	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
1.4. Rationale for the Study	A biosimilar is a biological medicinal product that is highly similar to an already authorized original biological medicinal product … These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological characterization before initiating clinical studies for the comparison of the efficacy,…	A biosimilar is a biological medicinal product that is highly similar to an already ~~**authorized**~~ **authorised** original biological medicinal product … These guidelines recommend a stepwise approach in developing a biosimilar starting with extensive physicochemical and biological ~~**characterization**~~ **characterisation** before initiating clinical studies for the comparison of the efficacy,…	Editorial change
3.2 Rationale for the Study Design	However, for supporting the assessment of overall systemic safety of SB11 relative to Lucentis®, systemic exposures will be collected and compared in the subgroup population (approximately 120 subjects, 60 subjects per treatment group) in Phase III comparative efficacy study.	However, for supporting the assessment of overall systemic safety of SB11 relative to Lucentis®, systemic exposures will be collected and compared in the subgroup population (approximately ~~**120**~~**40** subjects, ~~**60**~~**20** subjects per treatment group) in Phase III comparative efficacy study.	Number of subjects participating in PK evaluation is changed as per US FDA's request.
	For US FDA, Korea MFDS or other regulatory agency submissions for those who are in favour of VA,… For EMA or other regulatory agency submission for those who are in favour of anatomical parameter,… Ranibizumab binds with high affinity to all active VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165) on the surface of endothelial cells, thereby preventing binding of VEGF-A to its receptors and reducing endothelial cell proliferation,…	For US FDA, Korea **Ministry of Food and Drug Safety (**MFDS**)** or other regulatory agency submissions for those who are in favour of **the** VA,… For EMA or other regulatory agency submission for those who are in favour of **the** anatomical parameter,… Ranibizumab binds with high affinity to all active VEGF-A isoforms (e.g.**,** VEGF110, VEGF121 and VEGF165) on the surface of endothelial cells, thereby preventing binding of VEGF-A to its receptors and reducing endothelial cell proliferation,…	Editorial change
4.3. Subject Discontinuation from Investigational	*Not applicable*	**• 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 including but not limited to retinal vascular**	Subject discontinuation from IP criterion was added as per India regulatory agency's

Section Affected	Original Content	Amended/New Content	Rationale
Product		**abnormality**	request
5.1.1. Dosing and Treatment Schedule	Dosing visits will be allowed within ± 7 days of the scheduled dosing visit date (except Week 0 (Day 1), visit window not allowed). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within 21 days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within 21 days (3 weeks) after scheduled dosing visit date.	Dosing visits will be allowed within ± 7 days of the scheduled dosing visit date (except Week 0 (Day 1), visit window not allowed). If a dose of IP is not given within 7 days of the scheduled dosing visit date, the IP should be given within **~~21~~ 20** days of the scheduled dosing visit date, but the case will be captured as protocol deviation. Dosing skip is defined when a subject does not receive the IP within **~~21~~ 20** days **~~(3 weeks)~~** after scheduled dosing visit date.	Error correction
5.1.2. Withholding Investigational Products	If a subject experiences an AE in the study eye and the subject's safety or well-being could be compromised by ITV injection of IP at Investigator's discretion, IPs could be withhold until the event has resolved. Such events in the study eye include, but are not limited to: • A decrease in BCVA of ≥30 letters compared with the last assessment of VA; • An IOP of ≥30 mmHg; • A retinal break; • A subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area;	If a subject experiences an AE in the study eye and the subject's safety or well-being could be compromised by ITV injection of IP at **the** Investigator's discretion, IPs **should ~~could~~** be **~~withhold~~ withheld** until the event has resolved. Such events in the study eye include, but are not limited to: • A decrease in BCVA of ≥30 letters compared with the last assessment of VA; • An IOP of ≥30 mmHg; • A retinal break; **~~• A subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area;~~**	Editorial change As per SmPC and usual practice from sites
5.2.1. Identity of Investigational Product	The IPs will be supplied to Investigational site in one carton containing a single vial of 3.0 mg of ranibizumab in 0.3 mL solution.	The IPs will be supplied to Investigational site in one carton containing a single vial**~~. of 3.0 mg of ranibizumab in 0.3 mL solution.~~**	Editorial change
Table 7. Investigational Products	[Contents] 3.0 mg of ranibizumab in 0.3 mL solution	[Contents] **~~3.0 mg of ranibizumab in 0.3 mL solution~~** **One ml contains 10 mg ranibizumab**	Editorial change
5.2.6. Investigational	Using aseptic technique, all of the SB11 and Lucentis® vial contents are withdrawn through a 19-gauge filter	Using aseptic technique, all of the SB11 and Lucentis® vial contents are withdrawn through a **~~19-gauge~~ blunt**	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
Product Administration	needle attached to a 1-cc syringe.	filter needle attached to a 1-cc syringe.	
Table 8. Prohibited Medication and Therapy	[Medication or Therapy] ITV anti-VEGF treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD [Time to be prohibited] • Prior to Screening Randomisation • From Screening to EOS/ET visit [Eye to be prohibited] • Study eye • Fellow eye NOTE: If a subject has AMD in the fellow eye during the study period after randomisation, ONLY Lucentis® (ranibizumab) will be allowed to treat AMD.	[Medication or Therapy] ITV anti-VEGF treatment (e.g., bevacizumab, aflibercept, ranibizumab) to treat neovascular AMD [Time to be prohibited] • Prior to ~~**Screening**~~ **Randomisation** ~~**• From Screening to EOS/ET visit**~~ [Eye to be prohibited] • Study eye • Fellow eye ~~**NOTE: If a subject has AMD in the fellow eye during the study period after randomisation, ONLY Lucentis® (ranibizumab) will be allowed to treat AMD.**~~	Editorial change
	Not applicable	[Medication or Therapy] **ITV anti-VEGF treatment except IP (SB11 or Lucentis®)** [Time to be prohibited] **• From Randomisation to EOS/ET visit** [Eye to be prohibited] **• Study eye**	Prohibited ITV anti-VEGF treatment is specified for the study eye.
	Not applicable	[Medication or Therapy] **ITV anti-VEGF treatment (e.g., bevacizumab, aflibercept) except ranibizumab** [Time to be prohibited] **• From Randomisation to EOS/ET visit** [Eye to be prohibited] **• Fellow eye** **NOTE: If a subject has AMD in the fellow eye during the study period after randomisation, ONLY**	Prohibited ITV anti-VEGF treatment is specified for the fellow eye.

Section Affected	Original Content	Amended/New Content	Rationale
		Lucentis® (ranibizumab) will be allowed to treat AMD.	
	[Medication or Therapy] Systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD. However, dietary supplementary, vitamins and minerals are allowed [Time to be prohibited] • Within 30days prior to randomisation • From Screening to EOS/ET visit [Eye to be prohibited] • N/A	[Medication or Therapy] Systemic treatment or therapy (including prescribed herbal medication) to treat neovascular AMD. However, dietary ~~**supplementary**~~ **supplements**, vitamins and minerals are allowed [Time to be prohibited] • Within 30days prior to randomisation • From Screening to EOS/ET visit [Eye to be prohibited] • N/A	Editorial change
	Not applicable	[Medication or Therapy] **Systemic medications known to be toxic to the lens, retina or optic nerve including deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, vigabatrin and ethambutol** [Time to be prohibited] **• From Screening to EOS/ET visit** [Eye to be prohibited] **N/A**	Prohibited medication or therapy is added as per Korea MFDS's request.
	[Medication or Therapy] ITV sustained drug delivery implant (e.g., ITV corticosteroid implant) [Time to be prohibited] • Within 180 days prior to randomisation • From Screening to EOS/ET visit [Eye to be prohibited] • Study eye	[Medication or Therapy] ~~**ITV**~~ **Intravitreal injection of corticosteroid (e.g., triamcinolone acetonide) or** ~~**sustained drug delivery implant (e.g., ITV**~~ **intravitreal** corticosteroid implant~~)~~ [Time to be prohibited] • Within 180 days prior to randomisation • From Screening to EOS/ET visit [Eye to be prohibited] • Study eye	Prohibited medication or therapy is revised according to updated exclusion criteria #15.

Section Affected	Original Content	Amended/New Content	Rationale
	Not applicable	[Medication or Therapy] **Treatment involving macula with photodynamic therapy with verteporfin, transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation)** [Time to be prohibited] **• Prior to Screening** **• From Screening to EOS/ET visit** [Eye to be prohibited] **• Study eye**	Prohibited medication or therapy is added as per Korea MFDS's request.
	Not applicable	[Medication or Therapy] **Treatment with pan-retinal photocoagulation** [Time to be prohibited] **• Prior to Screening** **• From Screening to EOS/ET visit** [Eye to be prohibited] **• Study eye**	Prohibited medication or therapy is added as per Korea MFDS's request.
	[Medication or Therapy] Systemic investigational products (excluding dietary supplementary, vitamins and minerals) to treat systemic diseases other than neovascular AMD [Time to be prohibited] • Within 90 days prior to randomisation • From Screening to EOS/ET visit NOTE: During the study period, investigational products such as dietary supplementary, vitamins and minerals will be prohibited. [Eye to be prohibited] • N/A	[Medication or Therapy] Systemic investigational products (excluding dietary ~~**supplementary**~~ **supplements**, vitamins and minerals) to treat systemic diseases other than neovascular AMD [Time to be prohibited] • Within 90 days prior to randomisation • From Screening to EOS/ET visit NOTE: During the study period, investigational products such as dietary ~~**supplementary**~~ **supplements**, vitamins and minerals will be prohibited. [Eye to be prohibited] • N/A	Editorial change
5.4. Fellow Eye Treatment	Lucentis® for treatment in the fellow eye will be reimbursed or provided by Sponsor.	Lucentis® for treatment in the fellow eye will be reimbursed or provided by Sponsor **during the study**	Period of providing Lucentis for fellow eye

Section Affected	Original Content	Amended/New Content	Rationale
		period after randomisation.	treatment is specified.
	Fellow eye injection will be performed by the Investigator for this study. However, fellow eye visit is not part of study, thus it will be scheduled in accordance with local practice.	Fellow eye injection will be performed by the Investigator for this study. However, fellow eye visit is 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 ITV injection of IP on the study eye.**	To provide guideline for fellow eye injection
6.2.1. Best Corrected Visual Acuity	VA will be assessed using ETDRS chart or 2702 Number charts (only for subjects who are not familiar with alphabet or subjects with illiteracy) at a starting distance of 4 meters, and then repeated at a distance of 1 meter, if necessary.	VA will be assessed using **original series** ETDRS chart**s** or 2702 **series** Number charts ~~**(only for subjects who are not familiar with alphabet or subjects with illiteracy)**~~ at a starting distance of 4 meters, and then repeated at a distance of 1 meter, if necessary.	Clarification for charts used in this study
	VA examiners and VA lanes at Investigational sites must be certified to ensure consistent measurement of BCVA prior to start of study. VA examiners should be masked to the subject's treatment group and should not perform any other study procedures.	VA examiners and VA lanes at Investigational sites must be certified to ensure consistent measurement of BCVA prior to start of study. ~~**VA examiners should be masked to the subject's treatment group and should not perform any other study procedures.**~~	Requirement is changed.

Section Affected	Original Content	Amended/New Content	Rationale
	A decrease in VA of > 15 letters (compared with the last assessment of VA) should be reported as AEs/ SAEs as appropriate. If there is a decrease in VA of > 30 letters (compared with the last assessment of VA) or there is a decrease in VA to the level of Light Perception or worse, VA should be re-assessed after at least 1 hour. If the event meets one or more of the following criteria, it should be reported as SAE. • A decrease in VA of > 30 letters (compared with the last assessment of VA) lasting > 1 hour • A decrease in VA to the level of Light Perception or worse lasting > 1 hour	A decrease in VA of ~~>~~ ≥15 letters ~~**(compared with**~~ **from** the last assessment of VA~~)~~ should be reported as AEs/ **Serious Adverse Events (**SAEs**)** as appropriate. ~~**If there is a decrease in VA of > 30 letters (compared with the last assessment of VA) or there is a decrease in VA to the level of Light Perception or worse, VA should be re-assessed after at least 1 hour.**~~ If the event meets one or more of the following criteria, it should be reported as SAE. • A decrease in VA of ~~>~~ ≥ 30 letters ~~**(compared with**~~ **from** the last assessment of VA~~)~~ ~~**lasting > 1 hour**~~ • A decrease in VA to the level of Light Perception or worse ~~**lasting > 1 hour**~~	Error correction SAE criteria are changed.
6.2.2. Anatomical Parameters	The average retinal thickness in the central 1-mm area in the ETDRS grid (CST; central subfield thickness), retinal thickness between Internal Limiting Membrane (ILM) and the base of RPE (CRLT; central retinal lesion thickness) and other lesion characteristics will be evaluated using OCT only in the study eye at Screening and prior to ITV injection of IP until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. Lesion characteristics such as CNV size and presence of leakage or haemorrhage will also be evaluated using FP/FA only in the study eye at Screening and prior to ITV injection of IP Week 24. FP/FA will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	The average retinal thickness in the central 1-mm area in the ETDRS grid (CST; central subfield thickness), retinal thickness between Internal Limiting Membrane (ILM) and the base of RPE (CRLT; central retinal lesion thickness) and other lesion characteristics will be evaluated using OCT ~~**only**~~ ~~**in**~~ **on** the study eye at Screening and prior to ITV injection of IP until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit. Lesion characteristics such as CNV size and presence of leakage or haemorrhage will also be evaluated using FP/FA ~~**only**~~ ~~**in**~~ **on** the study eye at Screening and prior to ITV injection of IP Week 24. FP/FA will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
6.3.2. Clinical Laboratory Test	Clinical laboratory test including haematology, clinical chemistry, urinalysis and pregnancy test can be repeated ….	Clinical laboratory test including haematology, clinical chemistry, **and** urinalysis ~~**and pregnancy test**~~ can be repeated ….	Pregnancy test will be provided in the separate section.
Table 9. Parameters for Clinical Laboratory Tests	[Others] Pregnancy test[2] at Screening (serum)[2] [2] Serum or urine pregnancy tests may be performed after randomisation at Investigator's discretion.	~~**[Others] Pregnancy test[2] at Screening (serum)[2]**~~ ~~**[2] Serum or urine pregnancy tests may be performed after randomisation at Investigator's discretion.**~~	Pregnancy test will be provided in the separate section.
6.3.3. Pregnancy Test	*Not applicable*	**For women of childbearing potential, serum pregnancy test must be performed at Screening. The serum samples taken at Screening will be analysed in central laboratory.** **Additional serum or urine pregnancy test can be performed in each Investigational site during the study period, if necessary (at the Investigator's discretion).** **Deleted pregnancy test result at Screening with technical problems, such as handling error, sampling error or tube breakage, should be followed by re-test. Result of re-test will be considered as that of an initial.**	Clarification for pregnancy test
6.3.4. Physical Examination	Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit. 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.	Physical examination will be performed at Screening and Week 52 (EOS visit) or ET visit**. The physical examination will 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.	Clarification for physical examination (systems and organs)
6.4.1. Full	The examination of the anterior segment is performed	~~**The examination of the anterior segment is**~~	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
Ophthalmic Examinations - Slit lamp biomicroscopy	only with the slit lamp without any additive drugs or lenses. The posterior segment should be examined with the slit lamp and the appropriate lens. For this examination the pupil of the eye must be dilated with 2-3 drops of phenylephrine-tropicamid (or any other mydriatic) applied topically to the eye.	~~performed only with the slit lamp without any additive drugs or lenses.~~ **Both the anterior segment and posterior segment will be assessed with the slit lamp.** The posterior segment ~~should~~ **will** be examined after dilation of pupil ~~with the slit lamp and the appropriate lens. For this examination the pupil of the eye must be dilated~~ with 2-3 drops of phenylephrine-tropicamid (or any other mydriatic **drug**) applied topically to the eye.	
6.4.1. Full Ophthalmic Examinations - Intraocular pressure (IOP) measurement	IOP will be measured only in the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48.	IOP will be measured ~~only~~ ~~in~~ **on** the study eye at Screening and prior to ITV injection of IP and 30-60 minutes after ITV injection of IP at each visit until Week 48.	Editorial change
	IOP should be measured using Goldmann applanation tonometry only.	IOP should be measured using Goldmann applanation tonometry ~~only~~.	Editorial change
6.4.1. Full Ophthalmic Examinations - Indirect ophthalmoscopy	Indirect ophthalmoscopy using in a standard way (i.e., usually using a head-mounted light source and a 20-30 dpt lens)will be performed only in the study eye (including evaluation of posterior segment abnormalities of the vitreous, optic nerve, peripheral retina and retinal vasculature, as well as retinal pigment epithelium detachment, ischemic events including cotton wool spots and microaneurysms) at Screening and prior to ITV injection of IP and 0-15 min after ITV injection of IP at each visit until Week 48.	Indirect ophthalmoscopy using in a standard way (i.e., usually using a head-mounted light source and a 20-30 dpt lens)will be performed ~~only in~~ **on** the study eye (including evaluation of posterior segment abnormalities of the vitreous, optic nerve, peripheral retina and retinal vasculature, as well as retinal pigment epithelium detachment, ischemic events including cotton wool spots and microaneurysms) at Screening and prior to ITV injection of IP and 0-15 min after ITV injection of IP at each visit until Week 48.	Editorial change
6.4.2. Optical Coherence Tomography (OCT)	OCT will be performed only in the study eye at Screening and prior to ITV injection of IP at each study visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	OCT will be performed ~~only~~ ~~in~~ **on** the study eye at Screening and prior to ITV injection of IP at each study visit until Week 48. OCT will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	Editorial change

Section Affected	Original Content	Amended/New Content	Rationale
	Only OCT devices registered and certified by central reading centre are allowed to be used in this study. If one or more OCT devices are registered and certified in an Investigational site, a subject should use the same OCT device consistently during the study period. If OCT devices registered and certified in an Investigational site are all from the same manufacturer and they use the same imaging system and the same version of software, the subject could use either of them during the study period.	**Site staffs who will perform OCT scans in this study must be certified by the central reading centre before study starts.** ~~**Only OCT devices registered and certified by central reading centre are allowed to be used in this study. If one or more OCT devices are registered and certified in an Investigational site, a subject should use the same OCT device consistently**~~ **OCT devices registered in an Investigational site should be all from the same manufacture and meet the minimum software requirement. The subject should use the OCT devices registered by central reading centre** during the study period. ~~**If OCT devices registered and certified in an Investigational site are all from the same manufacturer and they use the same imaging system and the same version of software, the subject could use either of them during the study period.**~~	Editorial change
6.4.3. Fundus Photography (FP) and Fluorescein Angiography (FA)	FP/FA will be performed only in the study eye at Screening and prior to ITV injection of IP at Week 24. FP/FA will also be performed at any time during the visit at Week 52 (EOS visit) or ET visit.	FP/FA will be performed ~~**only in**~~ **on** the ~~**study**~~ **both** eye**s** at Screening and **those images taken from the both eyes will be sent to the central reading centre**. **FP/FA will also be performed on the study eye** prior to ITV injection of IP at Week 24 **and**~~**. FP/FA will also be performed**~~ at any time during the visit at Week 52 (EOS visit) or ET visit. **Those images taken from the study eye will be sent to the central reading centre.** **Site staffs who will perform FA/FP in this study must be certified by the central reading centre before study starts.**	According to exclusion criteria #3, FP/FA images taken from the both eyes should be sent to the central reading centre at Screening. Editorial change
6.5. Pharmacokinetic	Blood samples for PK will be collected in approximately 120 subjects (60 subjects per treatment	Blood ~~**samples**~~**sampling** for PK will be collected in approximately ~~**120**~~**40** subjects (~~**60**~~**20** subjects per	Number of subjects participating in PK

Section Affected	Original Content	Amended/New Content	Rationale
Assessment	group) participating in PK evaluation.	treatment group) participating in PK evaluation.	evaluation is changed as per US FDA's request.
6.6. Immunogenicity Assessment	…he or she could be asked to return for immunogenicity blood sampling after Week 52 (EOS visit) or ET visit until the antibody titres return to baseline or stabilize at a level acceptable to the Investigator and Sponsor.	…he or she could be asked to return for immunogenicity blood sampling after Week 52 (EOS visit) or ET visit until the antibody titres return to baseline or ~~**stabilize**~~ **stabilise** at a level acceptable to the Investigator and Sponsor.	Editorial change
6.7. NEI VFQ-25	Vision-related QOL will be assessed using NEI VFQ-25. NEI VFQ-25 should be performed at Week 0 (Day 1) after randomisation, but prior to starting any other study procedures. Then, NEI VFQ-25 should be performed before starting any other study procedures at Week 12, Week 24, Week 36 and Week 52 (EOS visit) or ET visit. All questionnaires will be administered in the local language. A certified person will conduct a questionnaire survey with the subject in a quiet room.	Vision-related QOL will be assessed using NEI VFQ-25. NEI VFQ-25 should be performed at Week 0 (Day 1) after randomisation~~**, but prior to starting any other study procedures**~~. Then, NEI VFQ-25 should be performed before ~~**starting any other study procedures**~~ **dilation of pupil** at **Week 0 (Day 1),** ~~**Week 12,**~~ Week 24~~**, Week 36**~~ and Week 52 (EOS visit) or ET visit. All questionnaires will be administered in the local language. ~~**A certified person**~~ **Investigator or delegated site staff** will conduct a questionnaire survey with the subject in a quiet room.	Frequency of NEI VFQ-25 is changed as per US FDA's request. Certification for the interviewer is not required for this study.
7. Study Procedures-all pages	• Ocular assessments: • BCVA examination using ETDRS chart or 2702 Number chart (before dilation of the pupils and FP/FA and OCT assessment) • IOP using Goldmann applanation tonometry only	• Ocular assessments: • BCVA examination using **original series** ETDRS chart**s** or 2702 **series** Number chart**s** (before dilation of the pupils and FP/FA and OCT assessment) • IOP using Goldmann applanation tonometry~~ **only**~~	Clarification for charts used in this study Editorial change
7.1. Visit 1 (Screening , D-21 to D-1)	If the subject is not randomized within 21 days after Screening,	If the subject is not ~~**randomized**~~ **randomised** within 21 days after Screening,	Editorial change
	• Pregnancy test (serum, all female)	• Pregnancy test **for women of childbearing potential** (serum~~**, all female**~~)	Pregnancy test will be performed only for childbearing potential female subjects.

Section Affected	Original Content	Amended/New Content	Rationale
	If the subject is screen failed due to any reasons other than central review results, OCT and FP/FA images may not be transferred to central reading centre.	If the subject is screen failed due to any reasons **before the Investigator send OCT and/or FP/FA images to central reading centre, the Investigator does not have to send the subject's OCT and/or FP/FA images to central reading centre.** ~~**other than central review results, OCT and FP/FA images may not be transferred to central reading centre.**~~	Editorial change
	NOTE A decrease in VA of > 15 letters (compared with the last assessment of VA) should be reported as AEs/SAEs as appropriate.	NOTE A decrease in VA of ~~>~~ ≥15 letters (compared with the last assessment of VA) should be reported as AEs/SAEs as appropriate.	Error correction
7.2. Visit 2 (Week 0/Day 1)	Before randomisation • Investigator must confirm that the subject can read between 34 letters and 73 letters using ETDRS chart or 2702 Number chart (before dilation of the pupils and FP/FA or OCT assessment) prior to randomisation (Please see inclusion criteria #5).	Before randomisation • Investigator must confirm that the subject can read between 34 letters and 73 letters using **original series** ETDRS chart**s** or 2702 **series** Number chart**s** (before dilation of the pupils and FP/FA or OCT assessment) prior to randomisation (Please see inclusion criteria #5).	Clarification for charts used in this study
	Randomisation • After a subject's eligibility is confirmed by the central reading centre and Investigator, subject should be randomized to either SB11 or Lucentis® treatment group. • IP injection and study procedures which should be performed before ITV injection of IP must be performed must be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason.	Randomisation • After a subject's eligibility is confirmed by the central reading centre and Investigator, subject should be ~~**randomized**~~ **randomised** to either SB11 or Lucentis® treatment group. • **The first ITV injection of** IP ~~**injection**~~ and **all other** study procedures ~~**which should be performed before ITV injection of IP must be performed**~~ must be performed at the same day of randomisation or the following day after randomisation at the latest with a proper reason.	Editorial change
	After randomisation Before ITV injection of IP	After randomisation Before ITV injection of IP	Requirement is changed.

Section Affected	Original Content	Amended/New Content	Rationale
	• NEI VFQ-25 (prior to starting any other study procedures after randomisation)	• NEI VFQ-25 (prior to ~~**starting any other study procedures**~~ **dilation of pupil** after randomisation)	
7.6. Visit 6 (Week 12 ± 7 days) 7.12. Visit 12 (Week 36 ± 7 days)	Before ITV injection of IP • NEI VFQ-25 (before starting any other study procedures)	Before ITV injection of IP ~~**• NEI VFQ-25 (before starting any other study procedures)**~~	Frequency of NEI VFQ-25 is changed as per US FDA's request.
7.9. Visit 9 (Week 24 ± 7 days) 7.16. End of Study (Visit 16, Week 52 ± 7 days) or Early Termination Visit	Before ITV injection of IP • NEI VFQ-25 (before starting any other study procedures)	Before ITV injection of IP • NEI VFQ-25 (before ~~**starting any other study procedures**~~ **dilation of pupil**)	Requirement is changed.
8.1.1. Definition of Adverse Event	All AEs including ocular AEs in the study eye and/or fellow eye as well as systemic AEs will be collected from the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit.	All AEs including ocular AEs in the study eye and/or fellow eye as well as systemic AEs will be collected from the written informed consent is obtained from the subject until Week 52 (EOS visit) or ET visit. **If the AMD is diagnosed in the fellow eye during the study period, the event should be also reported as AE.**	To provide guideline for AE reporting for AMD in the fellow eye
8.2.1. Definition of Serious Adverse Event	*Not applicable*	**<u>Life-threatening</u>** **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.** **<u>Hospitalisation</u>** **AEs reported from clinical studies associated with hospitalisation or prolongation of existing 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**	Clarification for "Life-threatening" and "Hospitalisation"

Section Affected	Original Content	Amended/New Content	Rationale
		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 Investigator based on medical judgement.** **Hospitalisation or prolongation of existing hospitalisation in the absence of an 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.**	

Section Affected	Original Content	Amended/New Content	Rationale
	• A decrease in VA of > 30 letters (compared with the last assessment of VA) lasting > 1 hour (confirmed by re-assessment) • A decrease in VA to the level of Light Perception or worse lasting > 1 hour (confirmed by re-assessment)	• A decrease in VA of ~~>~~ ≥ 30 letters **~~(compared with~~ from** the last assessment of VA**~~)~~** **~~lasting > 1 hour (confirmed by re-assessment)~~** • A decrease in VA to the level of Light Perception or worse **~~lasting > 1 hour (confirmed by re-assessment)~~**	Error correction SAE criteria are changed.
8.2.2. Reporting Serious Adverse Events	In addition, an Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion.	In addition, **~~an~~** Investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion.	Editorial change
8.3. Adverse Events of Special Interest	• Any case of ocular infection such as endophthalmitis	• Any case of **intra**ocular infection such as endophthalmitis	Editorial change
	Not applicable	**• Iatrogenic traumatic cataract** **• Arterial thromboembolic events defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknowns cause)**	Events are added as AESI as per EMA SmPC and FDA Prescribing Information.
9.1. Analysis Sets	• Per-Protocol Set for CST (PPS-CST) consists of all FAS subjects who have the first IP injection at Week 0 (Day 1) and complete the procedures at Week 4 without any major protocol deviations that have impact on the CST assessment. This PPS-CST will be the primary analysis set for CST in addition to FAS. Major protocol deviations that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment codes for analyses.	• Per-Protocol Set for CST (PPS-CST) consists of all FAS subjects who have the first IP injection at Week 0 (Day 1) and complete the procedures at Week 4 without any major protocol deviations that have impact on the CST assessment. This PPS-CST will be the primary analysis set for CST **~~in addition to FAS~~**. Major protocol deviations that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment codes for analyses.	Clarification analysis set for CST
9.2.4. Pharmacokinetics	Blood sampling for PK will be collected in 120 subjects participating in PK evaluation (60 per treatment group).	Blood sampling for PK will be collected in **approximately ~~12~~40** subjects participating in PK evaluation (**~~6~~020 subjects** per treatment group).	Number of subjects participating in PK evaluation is changed as per US FDA's request.
10.1. Data Confidentiality	A list linking the code and the subject's name will be kept in the Investigational site files as required by International Conference on Harmonisation's (ICH)	A list linking the code and the subject's name will be kept in the Investigational site files as required by International **~~Conference on~~ Council for**	Error correction

Section Affected	Original Content	Amended/New Content	Rationale
	Guideline for Good Clinical Practice (GCP) to protect the subject's confidentiality.	Harmonisation~~'s~~ (ICH) Guideline for Good Clinical Practice (GCP) to protect the subject's confidentiality.	
LIST OF ABBREVIATIONS	ICH: International Council on Harmonisation	ICH: International Council ~~on~~**for** Harmonisation	Error correction
	LOCF: Last Observation Carried Forward	~~**LOCF: Last Observation Carried Forward**~~	
	RPE: Retinal Pigment Epithelial	RPE: Retinal Pigment ~~**Epithelial**~~ **Epithelium**	
LIST OF STUDY STAFF	Clinical Project Manager [redacted]	Clinical Project Manager [redacted]	Responsible person is changed.
	Clinical Research Physician [redacted]	Clinical Research Physician [redacted]	Responsible person is changed.
	Statistician [redacted]	Statistician [redacted]	Responsible person is changed
	Project Safety Lead [redacted]	Project Safety Lead [redacted]	Responsible person is changed
Appendix D: National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25	*Not applicable*	*National Eye Institute 25-Item Visual Function Questionnaire is added.*	NEI VFQ-25 questionnaire is added.

Section Affected	Original Content	Amended/New Content	Rationale
questionnaire)			
All pages	at Investigator's discretion	at **the** Investigator's discretion	Editorial change
	in the opinion of Investigator	in the opinion of **the** Investigator	Editorial change