SAMSUNG BIOEPIS

Statistical Analysis Plan

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

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Study Phase	Phase III
Type of analyses	Clinical Study Report (CSR)
Authors	PPD
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorised Version
Draft 0.1	Aug 05, 2020	PPD	Not applicable – First version
Pre-final	Jan 27, 2021	PPD	
Pre-final 0.2	Mar 31, 2021	PPD	1. “Region (Centre)” is replaced by “Centre”, “Region (Country)” is replaced by “Country” 2. “Summary of TEAE for COVID-19” is added to section 9
Pre-final 0.3	May 20, 2021	PPD	Add “Iris color in study eye” in section 5 and subgroup analysis in section 4.5
Pre-final 0.4	Aug 27, 2021	PPD	Update time point for IA in section 1
Pre-final 0.5	Sep 23, 2021	PPD	Update section 6, PT is sorted by descending order of subject frequency based on total treatment group in shell and dry run, but SAP is inconsistently mentioned SB15 treatment group, so SAP is updated to use total treatment group instead.
Pre-final 0.6	Oct 28, 2021	PPD	Update section 5 to add fisher’s exact test
			Update appendix 1 to use date of last participation instead of date of last visit for CM
			Update section 9 to add AE definition for transition period analysis
Pre-final 0.7	Nov 15, 2021	PPD	Update section 7.1.3 to impute components of BCVA instead of BCVA total score
			Update section 7.2.2 to remove tipping point
			Update section 9 to excluding 'Related to COVID-19' VACCINE or VACCINATION from TEAE for COVID-19
			“South Korea” is replaced by “Korea” everywhere
Pre-final 0.8	Nov 22, 2021	PPD	Replace “date of last visit” by “date of

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			last participation" in appendix 1 algorithm for concomitant
1.0	Dec 14, 2021	PPD	Finalization
Amendment 1	May 10, 2022	PPD	1. The treatment groups for the summary and analysis were elaborated for the clarification in the section 3 2. Tipping point analysis was removed and more details about the missing data imputation methods of handling missing secondary efficacy variables were added for the clarification in section 7.2.3

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMD	Age-related Macular Degeneration
ANCOVA	Analyses of Covariance
ATC	Anatomical Therapeutic Chemistry
BCVA	Best Corrected Visual Acuity
BLQ	Below Limit of Quantitation
BM	Bruch's Membrane
BMI	Body Mass Index
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal Neovascularisation
COVID-19	Coronavirus Disease 2019
CRO	Clinical Research Organisation
CSR	Clinical Study Report
CST	Central Subfield Thickness
CV	Coefficient Variation
DA	Disc Area
DBP	Diastolic Blood Pressure
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENR	Enrolled Set
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analyses Set
FDA	Food and Drug Administration
ILM	Internal Limiting Membrane
IOP	Intraocular Pressure
IP	Investigational Product
IVT	Intravitreal
LSMean	Least Squares Mean
MAR	Missing-at-Random
MCMC	Markov-Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities

MI	Multiple Imputation
MNAR	Missing-not-at-Random
NAb	Neutralizing Antibody
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
OCT	Optical Coherence Tomography
RPE	Retinal Pigment Epithelium
PD	Protocol Deviation
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PPS	Per-Protocol Set
Pre-AEs	Pre-treatment Adverse Events
PT	Preferred Term
QOL	Quality of Life
RAN	Randomised Set
SAE	Serious Adverse Events
SAF	Safety Set
SAP	Statistical Analyses Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDRG	Study Data Reviewer's Guide
SDTM	Study Data Tabulation Model
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TOST	Two One-sided Equivalence Tests
TRT	Total Retinal Thickness
US	United States of America
VEGF	Vascular Endothelial Growth Factor

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetics (PK), and immunogenicity data for SB15-3001. It describes the data to be summarised and analysed, including specifics of the statistical analyses to be performed. This Statistical Analyses Plan (SAP) is based on the Protocol version 1.0, dated Oct 30, 2019. The following analyses will be performed for this study.

For main Clinical Study Report (CSR) the safety, efficacy, PK, and immunogenicity analyses will be performed on available data when all subjects complete the procedures at Week 32, or its corresponding visit. The detail data cut-off rule used for main CSR reporting will be implemented for Study Data Tabulation Model (SDTM) datasets and described in SDTM specification and Study Data Reviewer's Guide (SDRG).

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

For final CSR the safety, efficacy, PK and immunogenicity analyses will be performed after the last subject completes the procedures at Week 56 or the corresponding visit. All study data will be analysed and reported for the final CSR.

All study data collected until End of Study (EOS) or Early Termination (ET) of the study including Safety follow-up (If done) will be used for reporting of the summary and analysis results. Data collected in Follow-up period upon data collection agreement will just be provided in study listings in the CSR.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to demonstrate the equivalence in efficacy of SB15 compared to Eylea® in subjects with neovascular age-related macular degeneration (AMD).

2.2. Secondary Objectives

The secondary objectives are:

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

- To evaluate the immunogenicity of SB15 compared to Eylea®.

2.3. Sample Size Calculation

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

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

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

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

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

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

With the equivalence limit of [−3 letters, 3 letters] for the US FDA submission, 173 subjects per treatment group (overall sample size of 346) was calculated with the assumptions of the mean

difference of 0.5 letters and SD of 9.0 at the overall 10% significance level, providing 80% power to reject the null hypothesis.

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

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

3. GENERAL CONSIDERATIONS

GRAPHICAL STUDY DESIGN AND SCHEDULE OF ACTIVITIES

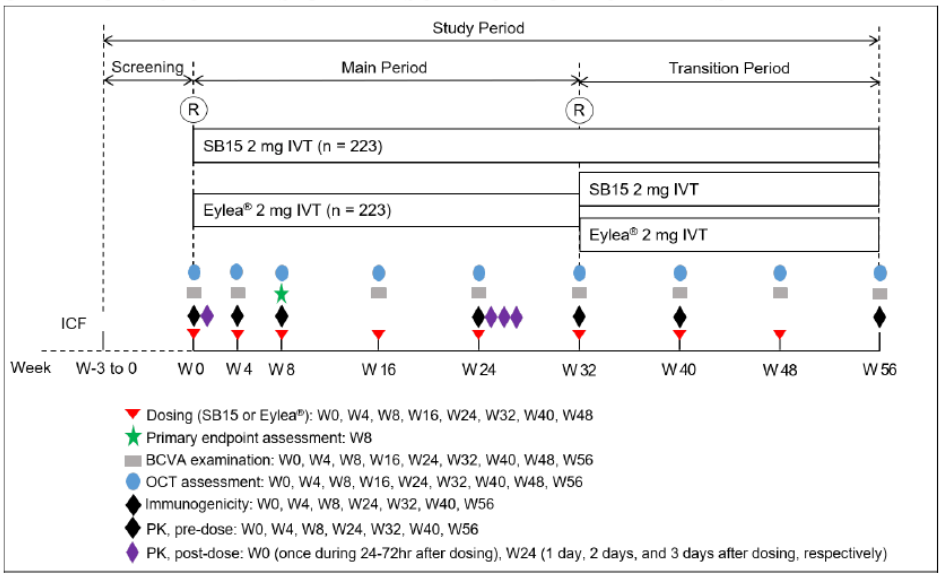

Figure 1. Graphical Study Design
ICF = informed consent form; ® = randomisation; IVT = intravitreal; OCT = optical coherence tomography; BCVA = best corrected visual acuity; PK = pharmacokinetics; W = week

The analysis study period consists of screening, main period and transition period (Figure 1), each period is defined as below:

Screening period is defined as study period from informed consent date prior to randomisation at Week 0 (Day 1).

Main period is defined as study period on or after randomisation at Week 0 (Day 1) and before re-randomisation at Week 32, or until last study participation date if patients withdrew/discontinued before Week 32.

Transition period is defined as study period from the re-randomisation at Week 32 until end of study (Week 56) or until last study participation date if patients withdrew/discontinued after Week 32.

Overall period is defined as study period consisting of screening period, main period and transition period.

According to study design, descriptive statistics and results of efficacy analysis of **main period** will be provided by following main treatment groups in general:

- SB15
- Eylea®

Treatment effect comparison will be performed between SB15 and Eylea®.

For the summary of **transition period**, the results will be provided by following transition treatment groups in general:

- SB15+SB15
- Eylea® Overall (Eylea®+SB15 / Eylea®+Eylea®)
- Eylea®+SB15
- Eylea®+Eylea®

Treatment effect comparison in efficacy analysis will be performed between following treatment groups:

- SB15 (SB15* / SB15+SB15) vs. Eylea® (Eylea®* / Eylea®+Eylea®)
- Eylea®+SB15 vs. Eylea®+Eylea®
- SB15 vs. Eylea® overall

SB15* or Eylea®* refers to subjects who is randomised to SB15 or Eylea® respectively and discontinued from IP before transition at Week 32.

Summary of **overall study period** will be provided by following overall treatment groups in general:

- SB15 (SB15* / SB15+SB15)
- Eylea® Overall (Eylea®* / Eylea®+Eylea® / Eylea®+SB15)
- Eylea®+SB15
- Eylea®+Eylea®

Treatment groups for the listing will be presented as below:

- SB15
- SB15+SB15
- Eylea®
- Eylea®+Eylea®
- Eylea®+SB15

3.1. Analyses Sets

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

- Enrolled Set (ENR) consists of all subjects who provide informed consent for this study.

- Randomised Set (RAN) consists of all subjects who receive a randomisation number at the randomisation visit.

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

- Per-Protocol Set (PPS) consists of all FAS subjects who have BCVA assessment result at baseline and Week 8 without any major protocol deviations (PDs) that have impact on the primary BCVA assessment. Major PDs that will lead to exclusion from this set will be pre-defined prior to unmasking the treatment group assignment for analyses. Subjects meeting any of following criteria will be excluded from PPS as well even if it's not captured as a PD:

  a. Subjects missed any of IP injection at Week 0 or Week 4

  b. IP injection (+/- 7 days) at Week 4 is out of visit window

- Safety Set 1 (SAF1) consists of all subjects who receive at least one IP during the study period. Subjects will be analysed according to the IP received.

- Safety Set 2 (SAF2) consists of all subjects in the SAF1 who receive at least one IP after re-randomisation at Week 32. Subjects will be analysed according to the IP received.

- Pharmacokinetic Analysis Set (PKS) consists of all subjects in the SAF1 who participate in PK evaluation at PK investigational sites (PK subjects) and have at least one serum concentration data.

The number of subjects in the analysis sets will be summarised by overall treatment group for the RAN. A by-subject listing of analyses population details will be provided for the RAN by treatment group and will include country, centre, subject identifier, inclusion/exclusion flag for each analysis set and reason for exclusion from PPS.

3.2. Protocol Deviations

PDs will be pre-defined prior to subject enrolment and documented separately named as Protocol Deviation Definition List which includes category (e.g., violation of inclusion/exclusion criteria, use of prohibited medication, non-compliance with treatment), deviation description, severity (major or minor), time point for each PD. Major PDs are defined as those deviations from the protocol likely to

have an impact on the perceived efficacy and/or safety of study treatments. PDs that are a result of COVID-19 will be identified in the DV domain through PD categories of COVID-19. This will allow the reporting of the PDs related to COVID-19 in the SDTM datasets.

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

A summary of the number and percentage of subjects with PD by severity (major and minor) and category will be presented for the RAN by main treatment group. Percentages will be based on the number of subjects in RAN by main treatment group. The summary of PD will be also provided by centre and main treatment group.

A by-subject listing of major and minor PDs will be provided including subject identifier, category, PD description, severity, PDs related to COVID-19 and exclusion from analyses set (Yes/No) for the RAN.

3.3. Disposition and Withdrawals

Subject Disposition

A clear accounting of the disposition of all subjects who enter the study will be provided for the ENR, from enrolment to study completion. The subject disposition summaries include the following:

- The number of subjects enrolled, the number and percentage of screen failures and reasons for screen failure will be summarised by treatment group.
- Subjects completed IP at Week 8, subjects discontinued from IP before Week 8, the reasons of discontinuation of treatment, subjects discontinued from IP before Week 8 related to COVID-19 will be summarised by treatment group.
- Subjects completed at Week 32, subjects discontinued from IP of main treatment period before re-randomisation at Week 32, the reasons of discontinuation of treatment, subjects discontinued from IP before Week 32 related to COVID-19 will be summarised by treatment group.
- Subjects completed IP after transition at Week 32 up to Week 48, subjects discontinued from IP of transition treatment period after re-randomisation at Week 32, the reasons of discontinuation of treatment, subjects discontinued from IP after transition at Week 32 related to COVID-19 will be summarised by treatment group.
- Subjects with EOS visit completed, subjects with EOS visit not performed, the reasons for EOS visit not done will be summarised by treatment group.

The summary of subject disposition above will be also provided by centre and treatment group.

- A by-subject listing of subject disposition will be generated using the ENR, including start/end date of treatment period, primary reasons of withdrawal or screening failure, and reasons for EOS visit not done.

Visit not performed/ window deviation (including relatedness to COVID-19)

- Subjects with planned visit not performed, visit window deviation, reason for visit not performed and visit window deviation including relatedness to COVID-19 will be summarised using the RAN by visit and treatment group.

- A by-subject listing of planned visits not performed, visit window deviation will be generated using the RAN, including reasons not performed, reasons for visit window deviation, and relatedness to COVID-19.

3.4. Study Day

Study Day will be calculated from the first IP dosing date and will be used to show start/end day of assessments and events. Study day of the first IP dosing date will be Day 1.

- If the date of the event is on or after the first IP dosing date, then:

  Study Day = (date of event – first IP dosing date) + 1

- If the date of the event is prior to the first IP dosing date, then:

  Study Day = (date of event – first IP dosing date)

When the event date is partial or missing, study day will be calculated after proper imputation as described in APPENDIX 1, and the event date will appear as it is along with the calculated study day in the listing.

3.5. Baseline

The baseline value will be defined as the last available measurement value prior to the first IP administration.

3.6. Retests, Unscheduled Visits and Early Termination Data and Visit Mapping

In general, the data recorded at the scheduled visit will be presented in the by visit summaries.

Early termination data will be mapped to the next scheduled visit for by visit summaries. By-subject listings will display original early termination visit.

Unscheduled/repeated measurements will not be included in the by visit summaries. However, unscheduled/repeated measurements (except for the baseline value) will contribute to the worst-case value for shift tables and incidence of significant abnormality tables.

Listings will include scheduled, unscheduled, repeated, and early termination visit. And visit label of Week X (R) to indicate the measurement if it is retested or unscheduled.

3.7. Common Calculations

For the purpose of converting days to years or months, 1 year will be equal to 365.25 days, 1 month will be equal to 30.44 days and 1 week will be equal to 7 days.

For quantitative measurements, change from baseline at Visit X will be calculated as follows:

Change at Visit X = Test Value at Visit X (Value) – Baseline Value (Base)

3.8. Software Version

All report outputs will be conducted using SAS® version 9.4 or a higher version.

4. STATISTICAL CONSIDERATIONS

4.1. Multicentre Studies

This study will be conducted by multiple investigators at multiple centres internationally. The participating countries in the study are Czech Republic, Hungary, Poland, Estonia, Russia, Latvia, Korea, Japan, United States, and Croatia. Multicentre will be pooled by country, for the primary efficacy variable, the statistical model to be used for the estimation of treatment effects will adjust for country, by including country as a main effects term in the model. Adjustment for country will also be performed, wherever possible, in the analysis of the secondary efficacy variables.

4.2. Missing Data

Missing safety data will not be imputed generally unless otherwise specified. Handling method of partial or missing dates is described in APPENDIX 1; Missing efficacy data will be handled as described in Section 7 of this analysis plan.

4.3. Multiple Comparisons/Multiplicity

No multiple comparison adjustments for type I error will be used.

4.4. Active-Control Studies Intended to Show Equivalence

This is an active-control study to demonstrate the equivalence of efficacy of SB15 to Eylea® in subjects with neovascular AMD. The null hypothesis tested for the primary efficacy analysis is that either (1)

SB15 is inferior to Eylea® or (2) SB15 is superior to Eylea® based on a pre-specified equivalence margin.

For FDA submission, the equivalence between the main treatment groups will be declared if the 90% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

For European Medicines Agency (EMA) submission, equivalence between the main treatment groups will be declared if the 95% CI of the difference is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

4.5. Examination of Subgroups

Best Correct Visual Acuity (BCVA)

The primary efficacy variable BCVA will be summarised and analysed by the following prognostic factors at baseline or immunogenicity (8-week anti-drug antibodies (ADA) result was defined as an overall ADA result up to Week 8, refer to Section 8.6) results for exploratory purpose:

- Summary of change from baseline in BCVA by overall ADA result up to Week 8 for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by overall ADA result up to Week 8 for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by lesion type (Occult, Predominantly Classic, and Minimally Classic) at baseline for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by total lesion area (≤4DA vs. > 4DA) at baseline for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by country for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by BCVA baseline (<50 letter score vs. ≥ 50 letter score) for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by Age group (<75 years vs. ≥ 75 years) for FAS
- Subgroup analysis of change from baseline in BCVA at Week 8 by Iris Color Group in Study Eye (Light Color and Dark Color) for FAS

In addition, forest plot will be used to display the difference of LSMean of change from baseline in BCVA at Week 8 between main treatment groups, with 95% CI and 90% CI respectively by pre-defined subgroups above, for each subgroup level, a covariance model with baseline BCVA as a covariate (except for subgroup factor BCVA baseline analyses), country and treatment as fixed factors will be used to construct the difference of LSMean and CI.

Treatment-Emergent Adverse Event (TEAE)

All TEAEs based on categories of overall ADA result (Positive, Negative, Inconclusive) will be summarised by System Organ Class (SOC), Preferred Term (PT), including the number and percentage of subjects experiencing events.

- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result up to Week 56, overall treatment group, system organ class and preferred term for SAF1 and overall period
- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result up to Week 32, main treatment group, system organ class and preferred term for SAF1 and main period
- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result after transition up to Week 56, transition treatment group, system organ class and preferred term for SAF2 and transition period

5. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Subject demographics and baseline characteristics will be summarised by overall treatment group for the RAN and main treatment group for the PKS. Continuous variables (e.g., age, weight, height, Body mass index (BMI)) will be summarised by treatment group with descriptive statistics (n, mean, SD, median, minimum, and maximum). Qualitative variables (e.g., gender, race, and ethnicity) will be summarised by treatment group with frequency and percentages. The summary of subject demographics and baseline characteristics will be also provided by country and treatment group.

By-subject listings of demographic and other baseline characteristics will be provided.

Demographics Characteristics

- Age (years) – calculated at the time of signing the Informed Consent form as follows.

  Age = Year of Informed Consent - Year of Birth

- Age Group (years) – < 75, ≥ 75
- Gender – Female, Male
- Childbearing potential – Yes, No, Not applicable (Male)
- Race – White, American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, Other
- Ethnicity – Hispanic or Latino, Chinese, Indian (Indian subcontinent), Japanese, Mixed ethnicity, Other
- Weight (kg) and Height (cm) at Screening

- BMI (kg/m^2) – derived as weight (kg)/[height(m)]^2
- Country – Czech Republic, Hungary, Poland, Estonia, Latvia, Croatia, United States, Korea, Japan and Russia.
- Region – EU (Czech Republic, Hungary, Poland, Estonia, Latvia and Croatia), United States, and Others (Korea, Japan and Russia)
- Iris Color in Study Eye – Blue, blue/grey, grey, Green, Hazel, Brown or dark brown, Unknown
- Iris Color Group in Study Eye– Light Color (Blue, blue/grey, grey, Green, Hazel), Dark Color (Brown or dark brown).

Other Baseline Characteristics

- BCVA (Total letter score)
- BCVA Group – < 50 letter score, ≥ 50 letter score
- Central subfield thickness (CST) (µm)
- Total retinal thickness (TRT) (µm)
- Presence of intra- or sub-retinal fluid
- Presence of sub-Retinal pigment epithelium (RPE) fluid
- Total lesion area (mm^2)
- Area of Choroidal Neovascularisation (CNV) (mm^2)
- Lesion type (Predominantly Classic, Minimally Classic, Occult, Not Available)
- Presence of CNV leakage
- Years since first diagnosis of neovascular AMD in study eye (year)
- Years since first diagnosis of neovascular AMD in fellow eye (year)
- Intraocular Pressure (mmHg)
- Lens status in study eye (No cataract, Cataract, Pseudophakia, Pseudophakia with Open Posterior Capsule)
- Composite scores of National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25)

Statistical Tests for Demographic and Other Baseline Characteristics

Comparison between main treatment groups in baseline characteristics will be performed using the chi-square test, F-test, or Fisher's exact 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.

6. OCULAR AND NON-OCULAR SURGICAL AND MEDICAL HISTORY

Medical and surgical histories will be coded using Medical Dictionary for Regulatory Activities central coding dictionary (MedDRA version 23.0).

Ocular medical/surgical histories and Non-ocular medical/ surgical histories will be summarised separately by SOC and PT by main treatment group. Percentages will be based on the number of subjects in the RAN. Primary system organ classes were presented alphabetically; within a SOC, PTs were sorted by descending order of subject frequency based on the total treatment group. If the frequency of the preferred terms were tied, the preferred terms were ordered alphabetically. Also, if a subject had multiple conditions with the same preferred term and primary system organ class, the subject was counted only once.

By-subject listings will be provided separately for ocular and non-ocular medical or surgical history for the RAN.

7. EFFICACY AND PHARMACOKINETIC ANALYSES

Efficacy analyses will be performed for the study eye and will be based on the randomised treatment group or treatment group for the study eye.

The primary efficacy analysis will be performed for the FAS with the change from baseline in BCVA at Week 8 using an analysis of covariance (ANCOVA) model with the baseline BCVA as a covariate and country, specified in section 4.1) and treatment group as factors after the multiple imputation (MI) under the missing at random (MAR) assumption.

7.1. Primary Efficacy Analysis

7.1.1. Analysis of Primary Efficacy Endpoint

The primary efficacy analysis will be performed for the FAS with the change from baseline in BCVA at Week 8 using ANCOVA model with the baseline BCVA as a covariate and country and treatment group as factors. The equivalence between the main treatment groups will be declared if

the two-sided 90% CI of the difference of LSMean of change from baseline in BCVA at Week 8 is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

For the EMA submission, the primary efficacy analysis will be performed for the FAS with the change from baseline in BCVA at Week 8 using ANCOVA model with the baseline BCVA as a covariate and country and treatment group as factors. The equivalence between the main treatment groups will be declared if the two-sided 95% CI of the difference of LSMean of change from baseline in BCVA at Week 8 is entirely contained within the pre-defined equivalence margin of [−3 letters, 3 letters].

- Methodology for the total BCVA letter score:
  There are two test procedures specified for the BCVA scoring. 4-meter test with 14 parameters and 1-meter test with 6 parameters. In both the test procedures, if 3 letters or less are read correctly on any row, testing procedure will be stopped.

  4-meter test parameters: 20/200, 20/160, 20/125, 20/100, 20/80, 20/63, 20/50, 20/40, 20/32, 20/25, 20/20, 20/16, 20/12.5 and 20/10.

  1-meter test parameters: 20/800, 20/640, 20/500, 20/400, 20/320, and 20/250.

  1) From 4-meter test, Total Number Correct at 4 meters will be obtained by adding 'Number Correct at 4 meters' for all the 14 parameters.

  2) If the Total Number Correct at 4 meters is greater than 19 then 1-meter test will not be performed. If the Total Number Correct at 4 meters is less than or equal to 19 then 1-meter test will be performed and obtain the 'Total Number Correct at 1 meter' by adding 'Number Correct at 1 meter 'for all the 6 parameters.

  3) Total BCVA Letter Score will be computed as below,

     If Total Number Correct at 4 meters > 19 then Total Number Correct at 4 meters + 30
     Otherwise, Total Number Correct at 4 meters + Total Number Correct at 1 meter.

7.1.2. Missing Data Methods of Primary Efficacy Endpoint

For the primary analysis with the FAS for BCVA, missing data will be imputed for subjects who have a missing value prior to or on the primary analysis time-point. A MAR approach will assume that subjects who had missing values are similar to similar subjects who completed the study in that main treatment group.

For the components of BCVA, the missing letter will be imputed by MI method with Markov-Chain Monte Carlo (MCMC)/Monotone Regression procedures.

The MI method will be applied as follows based on components of BCVA:

- **For the intermittent missing values**, the missing value will be filled in using the MCMC method with multiple chains, monotone missing data imputing pattern. A total of 100 sets of

imputations will be performed. The seed used for these imputations will be 4238 and all other multiple imputation procedures described in this SAP will use this same seed as well.

The resulting 100 imputed data sets will have a monotone missing pattern and will be imputed using a method for monotone missingness:

- **For monotone missing data,** monotone regression will be used to impute missing data. The procedure will be based on the 100 imputed datasets generated from the MCMC procedure and will be performed by Imputation. This will be based on 100 sets of imputations.

The SAS® PROC MI procedure will be used for the imputation. The sample SAS code for the multiple imputation can be found in APPENDIX 5 specifically.

7.1.3. Sensitive Analysis of Primary Efficacy Endpoint

For the BCVA, available case analysis will be performed for PPS and FAS.

An additional sensitivity analysis using the tipping-point approach which assume Missing-not-at-Random (MNAR) will be conducted to assess the robustness of the primary analysis result. Assumptions (tipping point) under which the 90% CI or 95% CI no longer rules out unacceptable differences in efficacy as determined by BCVA change from baseline at Week 8 between SB15 and Eylea® will be identified.

The analysis will be performed based on components of BCVA using a general three-step approach:

(1) Achieve monotone missing data pattern by MCMC procedure, a total of 100 sets of imputations will be performed. Impute the missing data by monotone regression, and apply delta adjustments for Week 8 total BCVA letter score, subjects with missing data have, on average, worse or better efficacy compared to those who have values. The mean difference between the (unobserved) missing values and observed values can vary independently for the different treatment groups.

(2) Each of these imputed datasets (which contains identical values of non-missing data but different values imputed for missing data) will be analysed using standard SAS procedure, e.g., PROC MIXED etc.

(3) Results from all imputed datasets are then combined together for overall inference using PROC MIANALYZE.

For BCVA change from baseline at Week 8, seven equally spaced shifts (-6 to 6 by 2) for the BCVA change from baseline for subjects with missing data will be explored.

7.1.4. Supportive Analysis of Primary Efficacy Endpoint

Not applicable.

7.2. Secondary Efficacy Analysis

7.2.1. Secondary Efficacy Variables and Derivations

The secondary efficacy endpoints are:

Change from baseline in BCVA over time up to Week 32 and up to Week 56

BCVA will be derived as described in section 7.1.1 of this analysis plan.

Proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32 and Week 56 (proportion of subjects who maintained BCVA)

BCVA will be derived as described in section 7.1.1 of this analysis plan. If change from baseline in BCVA is less than 15 letters loss then 'Yes', otherwise 'No'.

Proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 32 and Week 56

BCVA will be derived as described in section 7.1.1 of this analysis plan. If change from baseline in BCVA is equal to or greater than 15 letters gain then 'Yes', otherwise 'No'.

Change from baseline in CST and TRT at Week 4, and over time up to Week 32 and up to Week 56 (based on assessment by the central reading centre)

CST measured from internal limiting membrane (ILM) to RPE in 1-mm central subfield

TRT measured from ILM to Bruch's membrane (BM) in 1-mm central subfield

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

If the presence of Intra- or sub-retinal fluid then 'Yes', otherwise 'No'

Change from baseline in CNV area at Week 32 and Week 56 (based on assessment by the central reading centre)

Proportion of subjects with active CNV leakage at Week 32 and Week 56 (based on assessment by the central reading centre)

7.2.2. Analysis of Secondary Efficacy Endpoints

In general, treatment comparison of interest for time points prior to re-randomisation (week 32 included) include the comparison between main treatment SB15 and Eylea®; treatment comparison of interest for time points after re-randomisation include the comparison between treatment group SB15 and Eylea®, Eylea®+SB15 and Eylea®+Eylea®, SB15 and Eylea® overall.

The following analyses will be performed for the secondary efficacy endpoints:

Analysis of change from baseline in BCVA over time up to Week 32 and up to Week 56

Change from baseline in BCVA at Week 32 and Week 56 will be analysed using the same model for primary analysis as described in section 7.1.1 for the FAS, based on available case, and multiple imputation assuming MAR. BCVA will be summarised descriptively by treatment group and visit based on available case. The BCVA change from baseline will be plotted by treatment group and visit up to Week 32 and Week 56 for the FAS with mean and standard error based on available case.

Analysis of proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32 and Week 56 (proportion of subjects who maintained BCVA)

The adjusted risk difference between the two treatment groups at Week 32 will be calculated using a stratified Cochran-Mantel-Haenszel (CMH) test and 95% Mantel-Haenszel CIs will be presented for FAS. The stratification factor for CMH test is Country. The adjusted risk difference between treatment group at Week 56 will also be calculated respectively using same method.

The sample SAS codes for implementing the analyses can be found in APPENDIX 6.

Analysis of proportion of subjects who gained 15 letters or more in BCVA compared to baseline at Week 32 and Week 56

This secondary efficacy variable will be analysed similarly to the proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32/56 using FAS.

Analysis of change from baseline in CST and TRT at Week 4, and over time up to Week 32 and up to Week 56 (based on assessment by the central reading centre)

Change from baseline in CST and TRT at Week 4 will be analysed similarly to primary analysis using FAS.

Change from baseline in CST and TRT over time up to Week 32 and up to Week 56 will be analysed similarly to analysis of change from baseline in BCVA over time up to Week 32 and up to Week 56 using FAS.

Analysis of proportion of subjects with intra- or sub-retinal fluid on OCT at Week 32 and Week 56 (based on assessment by the central reading centre)

This secondary efficacy variable will be analysed similarly to the proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32/56 using FAS.

Analysis of change from baseline in CNV area at Week 32 and Week 56 (based on assessment by the central reading centre)

Change from baseline in CNV area at Week 32 and Week 56 will be analysed similarly to primary analysis using FAS.

Analysis of proportion of subjects with active CNV leakage at Week 32 and Week 56 (based on assessment by the central reading centre)

This secondary efficacy variable will be analysed similarly to the proportion of subjects who lost fewer than 15 letters in BCVA compared to baseline at Week 32/56 using FAS.

7.2.3. Missing Data Methods for Secondary Efficacy Variables

Unless otherwise specified, all analyses of secondary efficacy variables will be based on available data. For change from baseline in BCVA at Week 32 and Week 56, missing values will be imputed by multiple imputation assuming MAR as specified at Section 7.1.2.

A MAR approach will assume that subjects who had missing values are similar to similar subjects who completed the study in the treatment group.

- Week 32: Main treatment group (SB15, Eylea®)
- Week 56: SB15 (SB15* / SB15+SB15), Eylea® (Eylea®* / Eylea®+Eylea®) and Eylea®+SB15.

7.3. Exploratory Efficacy Analysis

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

Summary of proportion of subjects with sub-RPE fluid on OCT at Week 32 and Week 56 by overall treatment group will be performed for FAS.

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

The Quality of Life (QOL) is assessed using NEI VFQ-25.

NEI VFQ-25 analyses on FAS: 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, color 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 for FAS.

Subscale scores and Composite score will be calculated according to the Scoring Methodology for VFQ-25 in APPENDIX 8.

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

Listing on Composite and Subscale Score (NEI VFQ-25) will be generated for FAS.

7.4. Pharmacokinetic Analysis

The PK analysis will be performed for the PK population.

Individual PK blood sampling time and serum concentrations (pre-dose, C_{trough} and post-dose, C_{max}) will be listed for the PK population. All raw PK data will be reported and analysed with the same precision as the source regardless of how many significant figures or decimals the data carry.

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

Serum concentrations will be summarised descriptively at each scheduled sampling time for main treatment group (number of subjects (n), arithmetic mean, SD, median, minimum, maximum, coefficient variation (CV%), geometric mean, geometric SD, and geometric CV%). Below the limit of quantitation (BLQ) concentrations will be set to zero for the computation of descriptive statistics, except for geometric mean, geometric SD, and geometric CV%, for which they will be excluded. If

serum concentration is not collected within sampling window, it will be excluded from summary statistics. But it will be listed.

The following figures of the serum concentration will be provided:

- The arithmetic mean (±SD) serum concentration-versus time of SB15 and Eylea® will be presented by main treatment group on a linear scale for Week 0 and Week 24. The treatments will be overlaid on the same plot.

- Individual serum concentration versus time of SB15 and Eylea® will be presented by subject on a linear scale for Week 0 and Week 24.

8. SAFETY ANALYSES

Safety analyses will be performed for main period (or screening + main period to include assessments and events occurred at screening period), transition period, and overall study period unless specified otherwise. Analyses for screening and main period will be performed in the SAF1 by actual treatment group received at main period, and analyses for transition period will be performed in the SAF2 by actual treatment group (SB15+SB15, Eylea®+SB15, Eylea®+Eylea®, and Eylea® overall (Eylea®+SB15 and Eylea®+Eylea®)), and analyses for the overall study period will be performed in the SAF1 by actual treatment group (SB15, Eylea®+SB15, Eylea®+Eylea®, and Eylea® overall (subjects received Eylea® treatment at initial randomisation)).

There will be no statistical comparisons for safety data, unless otherwise specified with the relevant section.

8.1. Study Medication Exposure

The duration of exposure to intravitreal (IVT) injection of IP will be calculated as follows for each study period.

Exposure duration (days) up to Week 32/Week 56:

- If IP is completed or discontinued after week 8, and prior to cut-off date,

  Exposure duration up to Week 32 = Minimum (Last IVT injection date before Week 32 + 56 days, cut-off date + 1 day) - first IVT injection date;

  Exposure duration up to Week 56 = Minimum (Last IVT injection date + 56 days, cut-off date + 1 day) - first IVT injection date.

- If IP is discontinued prior to cut-off date and before week 8,

  Exposure duration up to Week 32/Week 56 = Minimum (Last IVT injection date + 28 days, cut-off date + 1 day) - first IVT injection date.

- If ongoing at cut-off date and before Week 32,

Exposure duration up to Week 32/Week 56 = Cut-off date - first IVT injection date + 1 day.

- If ongoing at cut-off date and on or after Week 32,

  Exposure duration up to Week 32 = Minimum (Last IVT injection date before Week 32 + 56 days, cut-off date + 1 day) - first IVT injection date;

  Exposure duration up to Week 56 = Cut-off date - first IVT injection date + 1 day.

Transition Period:

- If IP is completed or discontinued at transition period prior to cut-off date,

  Exposure duration = Minimum (Last IVT injection date + 56 days, cut-off date + 1 day) - first IVT injection date at transition period.

- If ongoing at cut-off date and on or after Week 32,

  Exposure duration = Cut-off date - first IVT injection date at transition period + 1 day.

There are no ongoing subjects for final CSR, the pre-defined cut-off date and rule for ongoing subjects will not be considered for final CSR.

The analyses of exposure to study drug will be performed for different study period specified in Section 8.

Interruptions, compliance, and dose changes are not considered for duration of exposure.

The duration of exposure to IVT injection of IP (days) will be summarised descriptively including n, mean, median, SD, minimum, and maximum by treatment group.

The exposure duration on IVT injection of IP will be categorized in different time period:

Main period: >=1 day, >=29 days, >=57 days, >=113 days, >=169 days.
Transition period: >=1 day, >=57 days, >=113 days.
Overall study period: >=1 day, >=29 days, >=57 days, >=113 days, >=169 days, >=225 days, >=281 days, >=337 days.

Extent of exposure will be summarised according to the number and percentage of subjects in each category for treatment group.

In addition, the number of IVT injections of IP will be summarised descriptively including n, mean, median, SD, minimum, and maximum by treatment group.

A by-subject listing of IP administration will be provided. And listing of Non-IP administration (Eylea® for fellow eye treatment) will include injection start date/time and injected eye and whether it is injected to the fellow eye.

A by-subject listing of randomised allocation to IP treatment consisting of randomisation number, treatment allocation and randomised date will be provided for the RAN.

A by-subject listing of randomised allocation to IP treatment by centre consisting of randomisation number, treatment allocation and randomised date will be provided for the RAN.

A by-subject listing of allocated Investigational Products Information consisting IWRS dispensed Med ID, treatment and lot no., actual Med ID, treatment and lot no. will be provided for the RAN.

8.2. Prior/Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug dictionary Global Mar 2020 B3. Any medications, including prescription drugs, non-prescription drugs, or any therapy received locally (in the study eye and/or fellow eye) or systemically reported until Week 56 (EOS visit) or ET visit (including a safety follow-up visit or telephone interview) will be included for the analyses.

A summary of prior and concomitant medication giving the number and percentage of subjects and the number of events will be provided by Anatomical Therapeutic Chemistry (ATC) Drug Class and/or preferred term for each treatment group.

- Concomitant medications will contain medications ended on or after the first dose of IVT injection of IP or medications started prior to the first dose of IVT injection of IP and continue (missing end date) on therapy. Summary of concomitant medications will be performed for different study period specified in Section 8. Concomitant medications started at main period and ended after main period will only be included for main period analysis and not included for transition period analysis.

- Prior medications will contain medications ended prior to the first dose of IVT injection of IP. Summary of Prior medications will be analysed in SAF1 and provided for main treatment group and all subjects.

Handling method of partial or missing dates is described in APPENDIX 1. For the medication, which is impossible to define as prior or concomitant, the medication will be considered as concomitant medication (i.e., worst case).

By-subject listings of prior and concomitant medications will be provided.

8.3. Prohibited Medications

Prohibited medications with ATC code/Preferred term will be defined in APPENDIX 2.

Summary of prohibited medication giving the number and percentage of subjects and the number of events will be provided by ATC drug class and/or preferred term for different study period (screening and main period, transition period, and overall study period) specified in Section 8, in the similar manner as concomitant medications analysis.

By-subject listing of prohibited medications will be provided.

8.4. Laboratory Evaluations

The following laboratory test results from the central laboratory will be reported in International System of Units (SI) unit and analyse in SAF1:

- **Haematology**: Haemoglobin (HGB), Haematocrit (HCT), Platelet count (PLT), White Blood Cell (WBC), Neutrophils (NEU), Lymphocytes (LYM), Monocytes (MON), Basophils (BAS), Eosinophils (EOS)

  In case only percent (%) of NEU, LYM, MON, BAS, and EOS are collected from a subject, the following formula will be used to derive absolute count (10^9/L) and vice versa.

  Absolute count (10^9/L) = Percent (%) x 0.01 x White Blood Cells (10^9/L)

  Derived percent (%) and absolute count (10^9/L) will be used for summary of Haematology parameters and included in the listing.

- **Chemistry:** Sodium (SOD), Potassium (POT), Creatinine (CREA), Glucose (GLUC), Calcium (CALC), Phosphorus (PHOS), Total Bilirubin (TBIL), Albumin (ALB), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALK PHS), Lactate dehydrogenase (LDH)

- **Urinalysis:** Protein, Blood, Leucocytes, Nitrite, Glucose, Ketone, pH, Specific Gravity, Bilirubin, Urobilinogen.

The quantitative lab values with <x will be replaced by x and >y will be replaced by y where x and y are lower limit of quantification and upper limit of quantification respectively. The following summaries will be provided for laboratory tests:

- Summary of actual value and change from baseline for Haematology and Chemistry by visit and overall treatment group in SAF1.

- Summary of the overall assessment (Normal, Abnormal NCS, and Abnormal CS) results for Urinalysis by visit and overall treatment group in SAF1.

- Shift from baseline to timepoint Week 8, Week 32, Week 40 and Week 56 (worst case change from baseline) by overall treatment group in SAF1 for haematology and chemistry parameters with respect to normal range where low, normal and high was defined in relation with the normal range. Unscheduled/repeated measurements (except for the baseline value) will contribute to the worst-case value for shift tables. The denominator of percentages at each visit will be based the number of subjects with available assessment results at each visit.

By-subject listings of haematology, chemistry, urinalysis parameters and pregnancy test results will be provided respectively. Significant abnormalities for haematology and chemistry will be listed separately. Laboratory normal range of haematology and chemistry parameters will be listed with corresponding low and high range in SI unit.

8.5. Vital Signs

Vital signs (blood pressure, pulse rate and body temperature) will be reported for this study using SAF1.

- A summary of actual value, and change from baseline by visit and overall treatment group.
- Incidence of clinically significant abnormalities for vital sign parameters. Unscheduled/repeated measurements (except for the baseline value) will contribute to the worst-case value for incidence of significant abnormalities. In addition, subjects with at least one significant abnormal value until Week 32 and Week 56 will be summarised as overall incidence. The denominator of percentages at each visit will be based the number of subjects with available assessment results at each visit.

By-subject listings of vital sign parameters will be provided.

Clinically Significant Abnormal Criteria

Clinically significant abnormal quantitative vital signs measurements will be identified in accordance with the following predefined clinically significant abnormal criteria:

Table 2. Clinically Significant Abnormal Criteria of Vital Signs

Variable	Unit	Low	High
Systolic Blood Pressure (SBP)	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
Diastolic Blood Pressure (DBP)	mmHg	≤ 50 mmHg AND change from baseline ≤ -15 mmHg	≥ 100 mmHg AND change from baseline ≥ 15 mmHg
Pulse rate	bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 110 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	≤ 35˚C AND change from baseline ≤ - 1.1˚C	≥ 38.3˚C AND change from baseline ≥ 1.1˚C

8.6. Immunogenicity Analysis

The number and percentage of subjects with ADA results (i.e., Positive, Negative) and neutralizing antibodies (NAbs) results (i.e., Positive, Negative) will be presented by overall treatment group and visit using SAF1.

In addition, the number and percentages of subject with ADA positive will be summarised by titre and overall treatment group in each visit using SAF1.

The incidence of overall ADA results (i.e., Positive, Negative, Inconclusive) up to Week 8, Week 32, and Week 56 will be presented by overall treatment group using SAF1. Unscheduled measurements will contribute to the incidence of overall assessment results. Overall ADA result is defined as below:

- "Positive" for a subject with treatment-induced or treatment-boosted ADA, where treatment-induced ADA indicates at least one positive result after pre-dose of Week 0 for subjects with negative ADA at pre-dose of Week 0, and treatment-boosted ADA indicates at least one positive result with higher titre level compared to pre-dose of Week 0 after pre-dose of Week 0 for subjects with positive ADA at pre-dose of Week 0.

- "Negative" for a subject with negative ADA at Week 0 and without positive ADA until Week 8, Week 32, and Week 56.

- "Inconclusive" for a subject with positive ADA at Week 0 and without positive result with higher titre level observed after pre-dose of Week 0 up to Week 8, Week 32, and Week 56.

In addition, the incidence of overall ADA results (i.e., Positive, Negative, Inconclusive) for transition period from Baseline (up to Week 32) to Week 56 will be presented by transition treatment group using SAF2. Overall ADA results for transition period at Week 56 will be summarised for subjects with at least one ADA result after transition up to Week 56 respectively. Overall ADA result for transition period is defined as below:

- "Positive" for a subject with transition treatment-induced or transition treatment-boosted ADA, where transition treatment-induced ADA indicates at least one positive result after Week 32 for subjects with overall negative ADA up to Week 32, and transition treatment-boosted ADA indicates at least one positive result with higher titre level after Week 32 compared to maximum positive ADA up to Week 32, for subjects with at least one positive ADA result up to Week 32.

- "Negative" for a subject with overall negative ADA at Baseline (up to Week 32), and without positive ADA after Week 32 until Week 56.

- "Inconclusive" for a subject with at least one positive ADA result up to Week 32 and without positive result with higher titre level observed after Week 32 up to Week 56, compared to the maximum positive ADA up to Week 32.

For exploratory purposes, the summary for immunogenicity results will be provided by visit with the following statistics:

- The association between ADA result and main treatment group will be assessed using Chi-square test or Fisher's exact test for SAF1 in overall period.

- The association between ADA result and transition treatment group (just Eylea®+Eylea® vs. Eylea®+SB15) will be assessed using Chi-square test or Fisher's exact test for SAF2 in transition period.

A by-subject listing of immunogenicity assessment will be provided.

If the fellow eye received Eylea® 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.

8.7. Other observations related to Safety Analyses

Slit Lamp Examination

Incidence of Slit Lamp Examination for study eye by Visit and overall treatment group for each of the parameters (Anterior chamber flare, Anterior chamber cells, Lens status) will be summarised in SAF1.

In addition, the incidence of overall assessment results up to Week 32 and Week 56 by overall treatment group for each of the parameters (Anterior chamber flare, Anterior chamber cells) will be summarised. Unscheduled/repeated measurements (except for the baseline value) will contribute to the severe result for incidence of overall assessment results. Overall assessment result is counted only once for the highest result up to the timepoint except for the baseline value.

By-subject listing for slit Lamp Examination will be provided.

Intraocular pressure (IOP) measurement

Summary Statistics of Intraocular Pressure (Pre-Injection) actual value and change from baseline will be generated by visit and overall treatment group in SAF1.

Summary Statistics of Change in Intraocular Pressure (change will be calculated using subjects with both Pre-Injection and Post-injection at each visit) will be generated by visit and overall treatment group in SAF1.

By-subject listing for Intraocular Pressure will be provided.

Indirect ophthalmoscopy

Incidence of the vitreous inflammation for study eye by Visit (including overall assessment until Week 32 and Week 56) and overall treatment group in SAF1.

By-subject listing for indirect ophthalmoscopy will be provided.

Ocular Surgery and Intervention

Incidence of Ocular Surgery and Intervention in the study eye will be performed for different study period specified in Section 8.

By-subject listing for Ocular Surgery and Intervention will be provided.

9. ADVERSE EVENTS

All reported terms for Adverse Events (AEs) will be coded using MedDRA version 23.0 and the AEs reported until Week 56 (EOS visit) or ET visit (including a safety follow-up visit or telephone interview) will be reported for the study.

- Pre-treatment AE will be defined as any AE with an onset date before the date of first administration of IVT of IP.
- Treatment-emergent AE (TEAE) will be defined as any AE with an onset date on or after the date of first dose of IP. If pre-treatment AEs increase in severity during the treatment period, they will be considered as TEAEs. Pre- treatment AEs with no increase in severity during the treatment period will not be considered as TEAEs.
- AE of Special Interest (AESI) is defined as the following AEs in the study eye:
    a) Intraocular pressure increase
        - New onset pre-injection IOP of ≥ 25 mmHg
        - Post-injection IOP ≥ 35 mmHg
    b) Any case of intraocular infection (suspected infection) such as endophthalmitis
    c) Any case of non-infectious intraocular inflammation such as iritis, vitritis, and iridocyclitis.
    d) Iatrogenic traumatic cataract
    e) Retinal pigment epithelial tear
    f) Subretinal haemorrhage with the size of 1 DA or more involving the centre of the fovea, or if the size of the haemorrhage is ≥ 50% of the total lesion area
- Other, non-ocular, AESIs include the following:

g) Arterial thromboembolic events including non-myocardial infarction ATEs and cardiovascular ischaemic events

h) Non-ocular haemorrhage

In general, AEs will be summarised using the number of subjects reporting at least one AE and the total number of events reported by SOC, PT for different study period and treatment group as specified at Section 8. AE started at main period and ended after main period will only be included for main period analysis, and will not be included for transition period analysis. AE started in transition period will be summarised in transition period analysis.

See APPENDIX 1 for handling of partial dates for AEs. In the case where it is not possible to define as AE as treatment-emergent or not, the AE will be classified by the worst case: i.e., treatment-emergent.

Summary of all adverse events

All AEs will be summarised by number, percentage of subjects and number of events. The following categories will be presented in the summary of adverse events for different study periods as specified at Section 8.

- AEs
- TEAEs by severity and causality
- Ocular TEAEs in the study eye by severity and causality
- Ocular TEAEs in the fellow eye by severity and causality
- Non-ocular TEAEs by severity and causality
- AESIs by category
- Intraocular Inflammation TEAEs
- Intraocular Inflammation TEAEs in the study eye
- Intraocular Inflammation TEAEs in the fellow eye
- Treatment Emergent Adverse Events leading to IP discontinuation
- Ocular TEAEs leading to IP discontinuation in the study eye
- Ocular TEAEs leading to IP discontinuation in the fellow eye
- Non-ocular TEAEs leading to IP discontinuation
- Serious Adverse Events (SAEs) by causality

- Serious TEAEs by causality
- Ocular Serious TEAEs in the study eye
- Ocular Serious TEAEs in the fellow eye
- Non-Ocular Serious TEAEs
- TEAEs leading to death

In addition, the following category will be presented in the summary of adverse events for main period (including screening period) :

- Pre-treatment Adverse Events (Pre-AEs)

Summary of TEAEs for COVID-19

The following categories will be presented in the summary of adverse events for overall study period.

- TEAEs of COVID-19: COVID-19 were defined using specific PTs which are 'v23.0' in 'Version added' of the MedDRA version 23.0 for COVID-19, which include 'Suspected COVID-19' (Defined in APPENDIX 7)
- TEAEs related to COVID-19 (TEAE other than COVID-19): TEAEs other than COVID-19 which have a relationship with COVID-19 infection/disease (excluding COVID-19 vaccination itself)
- TEAEs among COVID-19 positive subjects (TEAE other than COVID-19)

Summary of SAEs for COVID-19

The following categories will be presented in the summary of adverse events for overall study period.

- Serious adverse events of COVID-19: COVID-19 were defined using specific PTs which are 'v23.0' in 'Version added' of the MedDRA version 23.0 for COVID-19, which include 'Suspected COVID-19' (Defined in APPENDIX 7)
- Serious adverse events related to COVID-19 (SAE other than COVID-19): SAEs other than COVID-19 which have a relationship with COVID-19 infection/disease (excluding COVID-19 vaccination itself)
- Serious adverse events among COVID-19 positive subjects (SAE other than COVID-19)

TEAEs

The following TEAEs will be summarised by treatment group for different study periods as specified at Section 8 (TEAEs for fellow eye will only be summarised for overall study period).

Incidence of all TEAEs by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

Incidence of ocular TEAEs in the study eye and fellow eye, and non-ocular TEAEs by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

Incidence of TEAEs with incidence > 5% of Patients in either treatment group by System Organ Class and Preferred Term will be presented.

Incidence of other Adverse Events (TEAE excluding serious adverse events) with incidence > 5% of Patients in either treatment group by System Organ Class and Preferred Term will be presented for overall study period.

By-subject listing for TEAEs will be provided.

TEAEs by Severity

The following TEAEs by severity will be summarised by treatment group for different study periods as specified at Section 8 (TEAEs for fellow eye will only be summarised for overall study period).

Incidence of ocular TEAEs in study eye and fellow eye, and non-ocular TEAEs by treatment group will be presented by SOC, PT, and severity using number and percentage of subjects and number of events.

Severity will be reported as mild, moderate, or severe. TEAEs with a missing severity will be considered as severe TEAE (i.e., worst case). If a subject reported TEAEs in the same SOC (or PT) more than once with different severity, the subject will be counted once in the worst-case severity.

TEAEs by Causality (Relationship to drug or IVT injection)

The following TEAEs by causality will be summarised by treatment group for different study periods as specified at Section 8 (TEAEs for fellow eye will only be summarised for overall study period).

Incidence of ocular TEAEs in study eye and fellow eye, and non-ocular TEAEs by treatment group will be presented by SOC, PT, and causality (Drug) using number and percentage of subjects and number of events.

Incidence of ocular TEAEs in study eye by treatment group will be presented by SOC, PT, and causality (IVT injection) using number and percentage of subjects and number of events.

Causality will be reported as Related (Drug) or not related (Drug), Related (IVT injection) or not related (IVT injection), causality with both Drug & IVT injection will be reported as Related (Drug) and Related (IVT injection) respectively. If a subject report the same AE more than once within that SOC/PT, the AE with the worst-case relationship to IP will be used in the corresponding relationship summaries.

TEAEs by overall ADA result

As specified in Section 8.6, all TEAEs based on categories of overall ADA result (Positive, Negative, Inconclusive) will be summarised by treatment group, SOC and PT, including the number and percentage of subjects experiencing events.

- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result up to Week 56, overall treatment group, system organ class and preferred term for SAF1 and overall period
- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result up to Week 32, main treatment group, system organ class and preferred term for SAF1 and main period
- Ocular TEAEs in the study eye, fellow eye, and non-ocular TEAEs by overall ADA result after transition up to Week 56, transition treatment group, system organ class and preferred term for SAF2 and transition period

SAEs

The following SAEs will be summarised by treatment group for different study periods as specified at Section 8.

Incidence of all SAEs by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

By-subject listing for SAEs will be provided.

Serious TEAEs

The following serious TEAEs will be summarised by treatment group for different study periods as specified at Section 8.

Incidence of serious TEAEs by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

Incidence of ocular serious TEAEs in the study eye and fellow eye, and non-ocular serious TEAEs by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

Incidence of ocular serious TEAEs in the study eye and fellow eye, and non-ocular serious TEAEs by treatment group will be presented by SOC, PT, and severity using number and percentage of subjects and number of events.

Incidence of ocular serious TEAEs in the study eye and fellow eye, and non-ocular serious TEAEs by treatment group will be presented by SOC, PT, and causality (Drug) using number and percentage of subjects and number of events.

Incidence of ocular serious TEAEs in the study eye by treatment group will be presented by SOC, PT, and causality (IVT injection) using number and percentage of subjects and number of events.

AESIs

The following AESIs will be summarised by treatment group for different study periods as specified at Section 8.

Incidence of ocular AESIs in the study eye, and non-ocular AESIs by treatment group will be presented by SOC and PT using number and percentage of subjects with number of events.

By-subject listing for AESIs will be provided.

Intraocular Inflammation

The following TEAEs for intraocular inflammation will be summarised by treatment group for different study period as specified at Section 8 (TEAEs for intraocular inflammation for fellow eye will only be summarised for overall study period).

Incidence of TEAEs for intraocular inflammation by treatment group in study eye and fellow eye will be presented by SOC and PT using number and percentage of subjects with number of events.

TEAEs leading to discontinuation of study medication

The following TEAEs leading to discontinuation of study medication will be summarised by treatment group for different study periods as specified at Section 8.

Incidence of TEAEs leading to discontinuation of study medications by treatment group will be presented by SOC and PT using number and percentage of subjects and number of events.

By-subject listing for TEAEs leading to discontinuation of study medication will be provided.

TEAEs leading to death

The following TEAEs leading to death will be summarised by treatment group for different study periods as specified at Section 8.

Incidence of TEAEs leading to death by treatment group be presented by SOC and PT using number and percentage of subjects and number of events.

By-subject listing for TEAEs leading to death will be provided.

10.REFERENCES

Chakravarthy U, Wong T, Fletcher A, et al. Clinical risk factors for age-related macular degeneration: a systematic review and meta-analyses. BMC Ophthalmology. 2010,10(31)

APPENDIX 1. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. However, in general, when calculating relative days, partial dates with missing day only will be assumed to be 15th of the month, and partial dates with both missing day and month will be assumed to be June 30. Otherwise, the following rules in the given table will be applied for each case.

Algorithm for Adverse Events and Medications

When the start date is missing,

	Case	Imputed Value
Missing Day	year and month = year and month of first IP taken date	first IP taken date
	year and month <> year and month of first IP taken date	the 1st of the month
Missing Day and Month	year = year of first IP taken date	first IP taken date
	year <> year of first IP taken date	1st of January
Completely Missing	N/A	

When the end date is missing,

	Case	Imputed Value
Missing Day	year and month < year and month of last visit date	last day of the month
	year and month = year and month of last visit date	last visit date
Missing Day and Month	year < year of last visit date	31st of December
	year = year of last visit date	last visit date
Completely Missing	N/A	

Algorithm for Treatment-Emergent

After imputation for partial dates is implemented, whether AE is TEAE will be decided.

When start date is present,

- If known/imputed start date ≥ the date of first dose of IP, then AE is considered as TEAE

When start date is completely missing but end date is present

- If known/imputed end date ≥ the date of first dose of IP, then AE is considered as TEAE

When both start date and end date are completely missing
- AE is considered as TEAE

Algorithm for Concomitant

After imputation for partial dates is implemented, whether medication is concomitant will be decided.

When both start date and end date are present
- If known/imputed end date ≥ the date of first dose of IP and known/imputed start date≤the date of last participation, then medication is considered as concomitant

When start date is present and end date is completely missing
- If known/imputed start date ≤ the date of last participation, then medication is considered as concomitant

When start date is completely missing but end date is present
- If known/imputed end date ≥ the date of first dose of IP, then medication is considered as concomitant

When both start date and end date are completely missing
- Medication is considered as concomitant

APPENDIX 2. CODE FOR PROHIBITIVE MEDICATION

SB15 Prohibitive Medication List for

APPENDIX 3. LABORATORY TEST PARAMETERS

SB15 Lab Normal Range.xlsx

APPENDIX 4. VISIT LABEL FOR STDUY PERIOD

Time Point	Visit Name	Source Visit Name
Screening Period	VISIT 1	VISIT 1 (Screening)
Main Period	VISIT 2	VISIT 2 (W0)
	VISIT 3	VISIT 3 (W4)
	VISIT 4	VISIT 4 (W8)
	VISIT 5	VISIT 5 (W16)
	VISIT 6	VISIT 6 (W24)
Transition Period	VISIT 7	VISIT 7 (W32)
	VISIT 8	VISIT 8 (W40)
	VISIT 9	VISIT 9 (W48, EOT)
	VISIT 10	VISIT 10 (W56, EOS) or ET
	SAFETY FOLLOW-UP VISIT	VISIT 10 (W56, EOS) or ET
	FOLLOW UP <X>	FU
	<VISIT> UNSCHEDULED <Y> For example: VISIT 1 UNSCHEDULED 01	UNS

APPENDIX 5. SAMPLE CODES FOR PRIMARY ANALYSIS

SB15 Missing Imputation.docx

APPENDIX 6. SAS CODE OF ADJUSTED RISK DIFFERENCE

```
PROC FREQ DATA = <input_dataset>;
      TABLES <strata_var>*<treat_var>*<response_var>/commonriskdiff
      (CL=MH) ALPHA=0.05;
RUN;
```

APPENDIX 7. CODE FOR COVID-19 RELATED TERMS

SB15 COVID-19
Related Terms in M

APPENDIX 8. SCORING METHODOLOGY FOR VFQ-25:

The VFQ- 25 generates the following vision-targeted subscales:
global vision rating (1), difficulty with near vision activities (3), difficulty with distance vision activities (3), limitations in social functioning due to vision (2), role limitations due to vision (2), dependency on others due to vision (3), mental health symptoms due to vision (4), driving difficulties (3), limitations with peripheral (1) and color vision (1), and ocular pain (2).

First, original numeric values are re-coded following the scoring rules. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

Scoring Key: Recoding of Items

Item Numbers	Change original response category	To recoded value of:
1,3,4,15c@	1	100
	2	75
	3	50
	4	25
	5	0
2	1	100
	2	80
	3	60
	4	40
	5	20
	6	0
5,6,7,8,9,10,11,12,13,14,16,16a	1	100

	2	75
	3	50
	4	25
	5	0
	6	*
17,18,19,20,21,22,23,24,25	1	0
	2	25
	3	50
	4	75
	5	100

@Item 15c has four-response levels but is expanded to a five-levels using item 15b.
Note: If 15b=1, then 15c should be recoded to "0"
If 15b=2, then 15c should be recoded to missing.
If 15b=3, then 15c should be recoded to missing.

Next, items within each sub-scale are averaged together to create the 12 sub-scale scores. Below table indicates which items contribute to each specific sub-scale. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

Sub scale score calculation:

Items within each sub-scale are averaged together to create the 12 sub-scale scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

Mean= (Score for each item with a non-missing answer) / Total number of items with non-missing answers

Composite Score Calculation

To calculate an overall composite score for the VFQ-25, simply average the vision-targeted subscale scores, excluding the general health rating question. By averaging the sub-scale scores rather than the individual items we have given equal weight to each sub-scale, whereas averaging the items would give more weight to scales with more items.

STATISTICAL ANALYSES PLAN SIGNATURE PAGES

SIGNATURE PAGE

Declaration of the authors

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

Protocol Number: SB15-3001

Protocol Version and Effective Date: Version 1.0 Oct 30, 2019

Authors

Name: PPD

Institution: PPD

Signature: _____ Date: _____
(Mmm dd, yyyy)

Name: PPD

Institution: Samsung Bioepis Co., Ltd.

Signature: _____ Date: _____
(Mmm dd, yyyy)