BMJ Open Ophthalmology

Biosimilar SB15 versus reference aflibercept in neovascular age-related macular degeneration: 1-year and switching results of a phase 3 clinical trial

Se Joon Woo ,[1] SriniVas R Sadda ,[2,3] Mario Bradvica,[4] Attila Vajas,[5] Min Sagong,[6] Jan Ernest,[7] Jan Studnička,[8] Miroslav Veith,[9,10] Edward Wylegala,[11] Sunil Patel,[12] Cheolmin Yun,[13] Michal Orski ,[14] Sergei Astakhov,[15] Edit Tóth-Molnár,[16] Adrienne Csutak,[17] Lajos Enyedi,[18] Wooree Choi,[19] Inkyung Oh,[19] Hyerin Jang[19]

To cite: Woo SJ, Sadda SR, Bradvica M, *et al*. Biosimilar SB15 versus reference aflibercept in neovascular age-related macular degeneration: 1-year and switching results of a phase 3 clinical trial. *BMJ Open Ophthalmology* 2023;**8**:e001561. doi:10.1136/bmjophth-2023-001561

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjophth-2023-001561).

Sadda SR, Woo SJ, et al. Phase III Randomized Clinical Trial Comparing SB15 with Reference Aflibercept in Neovascular Age-Related Macular Degeneration. Presented at: ARVO 2023; April 23-27, 2023; New Orleans. Paper 464.

Received 6 November 2023
Accepted 22 November 2023

For numbered affiliations see end of article.

Correspondence to
Dr Se Joon Woo; sejoon1@snu.ac.kr

ABSTRACT

Background/aims To evaluate efficacy, safety, pharmacokinetics (PK) and immunogenicity of SB15 versus reference aflibercept (AFL), and switching from AFL to SB15 in neovascular age-related macular degeneration (nAMD).

Design Prospective, double-masked, randomised, phase 3 trial.

Methods Participants with nAMD were randomised 1:1 to receive SB15 (N=224 participants) or AFL (N=225). At week 32, participants either continued on SB15 (SB15/SB15, N=219) or AFL (AFL/AFL, N=108), or switched from AFL to SB15 (AFL/SB15, N=111). This manuscript reports 1-year and switching results of secondary efficacy endpoints such as changes from baseline to week 56 in best-corrected visual acuity (BCVA), central subfield thickness (CST, from internal limiting membrane (ILM) to retinal pigment epithelium), and total retinal thickness (TRT, from ILM to Bruch's membrane). Additional endpoints included safety, PK and immunogenicity.

Results Efficacy results were comparable between groups. The least squares mean (LSmean) change in BCVA from baseline to week 56 was 7.4 letters for SB15/SB15 and 7.0 letters for AFL/AFL (difference (95% CI)=0.4 (−2.5 to 3.2)). The LSmean changes from baseline to week 56 in CST and TRT were −119.2 µm and −132.4 µm for SB15/SB15 and −126.6 µm and −136.3 µm for AFL/AFL, respectively (CST: difference (95% CI)=7.4 µm (−6.11 to 20.96); TRT: difference (95% CI)=3.9 µm (−18.35 to 26.10)). Switched and non-switched participants showed similar LSmean changes in BCVA from baseline to week 56 (AFL/SB15, 7.9 letters vs AFL/AFL, 7.8 letters; difference (95% CI)=0.0 (−2.8 to 2.8)). Safety, PK and immunogenicity were comparable between groups.

Conclusions Efficacy, safety, PK and immunogenicity were comparable between SB15 and AFL and between switched and non-switched participants.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Biosimilars, the biological products that show no clinically meaningful difference compared with the approved reference products in terms of safety, purity and potency, can improve accessibility to the treatment. SB15 has recently been developed as a biosimilar to reference aflibercept (AFL) and, in the phase 3 clinical trial on neovascular age-related macular degeneration (nAMD), the equivalence in terms of efficacy has been demonstrated for the primary endpoint of change from baseline of best-corrected visual acuity at week 8.

WHAT THIS STUDY ADDS

⇒ This study demonstrated the comparable efficacy, safety, pharmacokinetics and immunogenicity up to week 56 between SB15 and AFL in patients with nAMD, and switching from AFL to SB15 maintained comparable clinical efficacy and safety.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results presented in this report support biosimilarity between SB15 and AFL in terms of totality-of-evidence.

INTRODUCTION

Biosimilars are biological products that are highly similar and show no clinically meaningful difference compared with approved reference products in terms of safety, purity and potency.[1] They expand available therapeutic options, improve accessibility to effective treatment and may optimise clinical outcomes.[2]

SB15 (Samsung Bioepis, Incheon, South Korea) has recently been developed as a biosimilar to reference aflibercept (AFL;

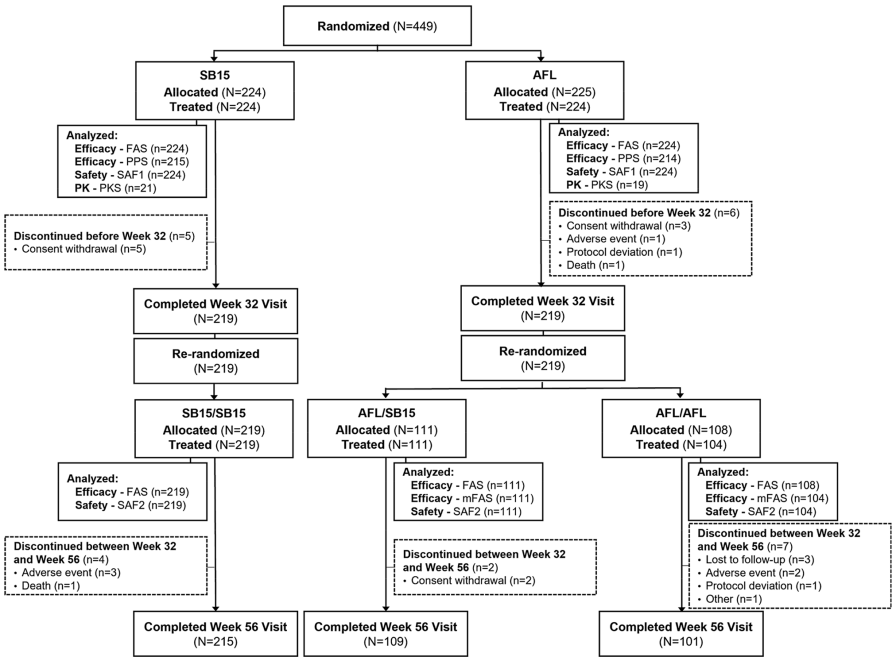

Figure 1 Study participant disposition (randomised set). In total, 449 participants were randomised (SB15: 224; AFL: 225). In both treatment groups, 219 participants completed the first 32 weeks of the study. At week 32, participants were rerandomised to either continue on SB15 (SB15/SB15, N=219) or AFL (AFL/AFL, N=108) or switch to SB15 (AFL/SB15, N=111). In the SB15/SB15 treatment group, 215 participants completed the study (week 56). In the AFL/SB15 and AFL/AFL treatment groups, 109 and 101 participants completed the study (week 56), respectively. AFL, reference aflibercept; FAS, full analysis set; mFAS, modified FAS; PKS, pharmacokinetics analysis set; PPS, per-protocol set; SAF1, safety set 1; SAF2, safety set 2; SB15, aflibercept biosimilar candidate.

Eylea, Regeneron, Rensselaer, New York, USA) for the treatment of neovascular age-related macular degeneration (nAMD). After providing evidence on the structural, physicochemical and biological similarity between SB15 and AFL using state-of-the art analytical methods,[3] a double-masked, randomised, phase 3 clinical study was conducted to evaluate the comparability of efficacy, safety, immunogenicity and pharmacokinetics (PK). Results up to week 32 of the study successfully demonstrating the clinical equivalence between SB15 and AFL have been published previously.[4]

Although evidence suggests that switching from reference product to its biosimilar is as effective and safe as continuing treatment with the reference product, the currently available data on switching to ophthalmic anti-vascular endothelial growth factor (VEGF) biosimilars is not sufficient yet to draw definitive conclusions.[5 6] Here, we report 56-week results of the phase 3 study evaluating efficacy, safety, PK and immunogenicity of SB15 in comparison with AFL, including the clinical outcomes following switching from AFL to SB15 at week 32.

MATERIALS AND METHODS

Study design and participants

The study was a randomised, double-masked, parallel group, multicentre, 56-week phase 3 study (figure 1) registered on ClinicalTrials.gov (SB15-3001; ClinicalTrials.gov: NCT04450329). It was conducted in Europe, the USA, Russia, South Korea and Japan and complied with the tenets of the Declaration of Helsinki, Good Clinical Practice guidelines, and the Health Insurance Portability and Accountability Act regulations. The clinical study protocol was reviewed and approved by Independent Ethics Committee or Institutional Review Board (online supplemental table 1). The study design and results up to week 32 have been published previously[4] and eligibility criteria have not been changed after trial commencement. Key inclusion criteria were the presence of a treatment-naïve subfoveal choroidal neovascularisation (CNV) lesion secondary to AMD occupying at least 50% of the total lesion, a total lesion area of ≤9.0 disc areas (DA; including blood, scars and neovascularisation) and a best-corrected visual acuity (BCVA) score of 20/40–20/200 (letter score of 73–34, inclusive) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The eligibility criteria based on retinal images were assessed by two independent reviewers in a central reading centre (Fundus Photo Reading Center (now 'Wisconsin Reading Center'), Madison, Wisconsin, USA).

The overall study period consisted of a screening period (from the date of informed consent to before randomisation at week 0 (day 1)), a main period (from randomisation at week 0 (day 1) to before rerandomisation at week 32) and a switching period (from rerandomisation at weeks 32–56).

At week 0, participants were randomly allocated in a 1:1 ratio to either receive intravitreal injection of 2 mg

(0.05 mL) SB15 or AFL every 4 weeks for the first three injections (ie, at weeks 0, 4 and 8), followed by dosing once every 8 weeks up to week 48. At week 32, participants who received AFL (AFL group) were randomised again to continue on AFL treatment (AFL/AFL group), or to be switched to SB15 treatment (AFL/SB15 group). To maintain the masking, participants who received SB15 treatment (SB15 group) were also rerandomised to continue on SB15 treatment (SB15/SB15 group). The last assessments were performed at week 56.

Participants, investigators and other study personnel remained masked throughout the study period except for selected staff from the sponsor and the clinical research organisation who were designated per protocol for unmasking after the 32-week interim analysis.

Assessment and outcomes

Full ophthalmic examination including visual acuity testing using ETDRS charts and optical coherence tomography (OCT) were performed at each study visit. Fluorescein angiography and fundus photography were carried out at screening, week 32 and week 56. Efficacy outcomes based on retinal images were assessed by a central reading centre.

Secondary efficacy endpoints included in this manuscript are the change from baseline in BCVA over time up to week 56 and the proportions of participants losing less than 15 letters or gaining 15 or more letters in BCVA from baseline to week 56. In addition, changes from baseline in central subfield thickness (CST), total retinal thickness (TRT) and CNV area over time up to week 56 were included. The proportion of participants with intraretinal or subretinal fluid or with active CNV leakage at week 56 were also included. For exploratory efficacy endpoints, the proportion of participants with subretinal pigment epithelial (RPE) fluid at week 56 and the change from baseline in quality of life as assessed by the National Eye Institute 25 Item Visual Function Questionnaire (NEI VFQ-25) at week 56 were measured.

The characteristics and incidence of treatment-emergent adverse events (TEAEs) up to week 56 were reported as part of the safety results, and the immunogenicity and PK were assessed by measuring the incidence of antidrug antibodies (ADAs) and neutralising antibodies to AFL and the serum trough concentrations (C_{trough}), respectively.

Statistical analysis

The sample size calculation and definitions of the full analysis set (FAS), per-protocol set, safety set 1 (SAF1) and PK analysis set (PKS) were described previously.[4] Briefly, with the equivalence limit of (−3 letters, 3 letters) designated by regulatory agencies including Food and Drug Administration (FDA), EMA and MFDS, a sample size of 216 subjects per treatment group was calculated with the assumption of a 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) were planned to be randomised into the study, allowing a 3% loss from the randomised subjects. Safety set 2 (SAF2) included all participants of the SAF1 who received study treatment at least once after rerandomisation at Week 32.

In addition to preplanned analyses, a post hoc analysis was conducted to add further evidence of the biosimilarity after switching from AFL to SB15. The modified FAS (mFAS), which was used for post hoc analyses of switching data, consisted of all subjects of the FAS who did not miss the baseline visit for rerandomisation at week 32.

Analyses of changes from baseline (week 0) to week 56 in BCVA, CST, TRT and CNV size were performed using the analysis of covariance (ANCOVA) model with the respective baseline values as covariates and country and treatment group as factors. For comparisons of proportions of participants, the adjusted risk difference between treatment groups and its 95% CI were computed using a stratified Cochran-Mantel-Haenszel test with country as a factor.

A post hoc analysis comparing the AFL/SB15 and AFL/AFL treatment groups in terms of efficacy was performed using the ANCOVA model with the respective values at week 32 as covariates and country and treatment group as factors.

All analyses of efficacy endpoints were performed on the FAS or mFAS and based on available data.

For safety analysis, all reported terms for adverse events (AEs; ocular and non-ocular) were coded using the Medical Dictionary for Regulatory Activities, V.23.0. During the switching period, comparisons of safety data between SB15/SB15, AFL/SB15 and AFL/AFL treatment groups were performed on the SAF2. In addition, as part of the post hoc analysis, the profiles of TEAEs after week 32 (switching period) of the AFL/SB15 and AFL/AFL groups were compared with the TEAE profile of the AFL group before week 32 (main period).

For the analysis of immunogenicity, the cumulative incidences of overall ADA-positivity (defined as at least one positive measurement of treatment-induced or treatment-boosted ADAs during the respective study period) were computed from week 32 to week 56 (switching period, SAF2).

PK analysis was performed on the PKS.

Patient and public involvement

For this study, patients or the public were not involved in the design, conduct, reporting or dissemination plans of the research. Patients were only involved as the participants of the research.

RESULTS

Study participant disposition

Participants were recruited across 56 study centres in 10 countries from June 2020 to February 2021. In total, 549 participants were screened, of whom 449 were randomly assigned to receive either SB15 (n=224) or AFL (n=225).

Table 1 Baseline demographics and disease characteristics (randomised set)

Characteristics	SB15 N=224	AFL N=225	AFL/SB15 N=111	AFL/AFL N=108
Age, years				
Mean (SD)	73.7 (8.05)	74.3 (8.09)	74.7 (7.96)	73.8 (8.25)
Gender, n (%)				
Female	118 (52.7)	132 (58.7)	59 (53.2)	69 (63.9)
Race, n (%)				
Asian	52 (23.2)	51 (22.7)	26 (23.4)	24 (22.2)
Black or African American	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.9)
White	170 (75.9)	172 (76.4)	84 (75.7)	83 (76.9)
Other	2 (0.9)	1 (0.4)	1 (0.9)	0 (0.0)
Region, n (%)				
EU	138 (61.6)	139 (61.8)	70 (63.1)	65 (60.2)
USA	14 (6.3)	14 (6.2)	6 (5.4)	8 (7.4)
Others (Korea, Japan, Russia)	72 (32.1)	72 (32.0)	35 (31.5)	35 (32.4)
BCVA, total letter score				
Mean (SD)	59.5 (10.60)	58.9 (11.19)	59.0 (11.37)	59.1 (11.12)
Approximate Snellen equivalent	20/63	20/63	20/63	20/63
BCVA group, n (%)				
<50 letter score	36 (16.1)	44 (19.6)	23 (20.7)	20 (18.5)
≥50 letter score	188 (83.9)	181 (80.4)	88 (79.3)	88 (81.5)
Central subfield thickness, µm*†				
Mean (SD)	353.3 (95.61)	382.3 (121.96)	382.4 (126.24)	381.6 (119.81)
Total retinal thickness, µm‡				
Mean (SD)	445.2 (140.06)	461.7 (145.44)	475.4 (166.17)	448.2 (121.81)
Presence of intraretinal fluid, n (%)§	107 (47.8)	136 (60.4)	63 (56.8)	68 (63.0)
Presence of subretinal fluid, n (%)	204 (91.1)	210 (93.3)	105 (94.6)	99 (91.7)
Presence of sub-RPE fluid, n (%)	106 (47.3)	106 (47.1)	49 (44.1)	54 (50.0)
Lesion type, n (%)				
Predominantly classic	41 (18.3)	47 (20.9)	24 (21.6)	21 (19.4)
Minimally classic	40 (17.9)	56 (24.9)	25 (22.5)	30 (27.8)
Occult	138 (61.6)	117 (52.0)	58 (52.3)	56 (51.9)
Not available	5 (2.2)	5 (2.2)	4 (3.6)	1 (0.9)
Area of CNV, mm^2				
Mean (SD)	6.1 (4.34)	6.3 (4.76)	6.0 (4.59)	6.5 (4.86)
Lens status in study eye, n (%)				
Pseudophakia	73 (32.6)	64 (28.4)	36 (32.4)	26 (24.1)

*Number of study participants included in summary statistics: SB15: 223; AFL: 224.
†P value (SB15 vs AFL)=0.0053.
‡Number of study participants included in summary statistics: SB15: 223; AFL: 223.
§p value (SB15 vs AFL)=0.0070.
AFL, aflibercept; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; RPE, retinal pigment epithelium; SB15, aflibercept biosimilar candidate.

At week 32, 438 (97.6%) participants were rerandomised and either continued on SB15 (n=219), continued on AFL (n=108), or switched from AFL to SB15 (n=111; figure 1). A total of 425 (94.7%) participants completed the study. Reasons for withdrawal from the study during the switching period were AEs (5 of 438 (1.1%)), lost to follow-up (3 of 438 (0.7%)), withdrawal of consent (2 of 438 (0.5%)), death (1 of 438 (0.2%)), protocol deviation

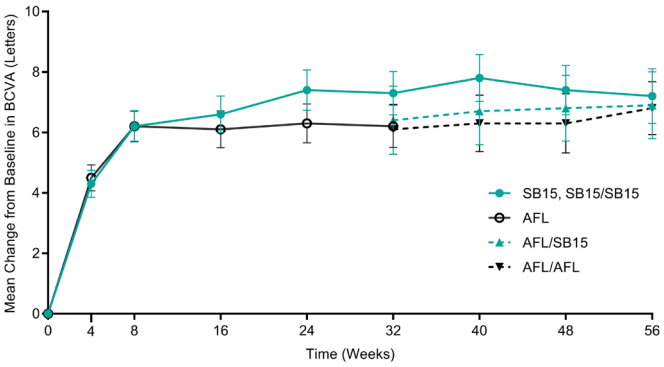

Figure 2 Mean change from baseline in BCVA over time up to week 56 (full analysis set). Solid green line: SB15 (N=224 up to week 32), SB15/SB15 (N=219 after week 32); solid grey line: AFL (N=224); green dotted line: AFL/SB15 (N=111); grey dotted line: AFL/AFL (N=108). Error bars represent the SE of the mean. AFL, reference aflibercept; AFL/AFL, participants starting treatment on AFL and staying on AFL after rerandomisation at week 32; AFL/SB15, participants starting treatment on AFL and switching to SB15 after rerandomisation at week 32; BCVA, best-corrected visual acuity; SB15, aflibercept biosimilar candidate; SB15/SB15, participants starting treatment on SB15 and staying on SB15 after rerandomisation at week 32.

(1 of 438 (0.2%)) and other (ambulatory difficulty following a ischaemic stroke (1 of 438 (0.2%))).

Baseline demographics and disease characteristics

Baseline demographics and baseline disease characteristics were comparable between the SB15 and AFL treatment groups (except for CST (SB15, 353.3 µm vs AFL, 382.3 µm; p=0.0053) and the presence of intraretinal fluid (SB15, 47.8% vs AFL, 60.4%; p=0.0070)) and between the AFL/SB15 and AFL/AFL treatment groups (table 1). Disease characteristics of the AFL/SB15 and AFL/AFL treatment groups were still comparable after rerandomisation at week 32 (online supplemental table 2).

Efficacy

The mean change in BCVA from baseline was comparable between participants treated with SB15 and AFL throughout the overall study period (figure 2). At week 56, the LSmean (SE) changes in BCVA from baseline were similar between the SB15/SB15 and AFL/AFL treatment groups (SB15/SB15, 7.4 (0.93) letters vs AFL/AFL, 7.0 (1.29) letters; LSmean difference (95% CI)=0.4 letters (-2.5 to 3.2)), and the proportions of participants who lost less than 15 letters or who gained 15 or more letters in BCVA compared with the baseline also showed similarity between SB15/SB15 and AFL/AFL treatment groups (table 2).

The results of anatomical endpoints measured by OCT were also comparable between treatment groups. The LSmean changes in CST from baseline were comparable for the SB15 and AFL treatment groups throughout the overall study (online supplemental figure 1A). At week 56, the LSmean (SE) changes in CST from baseline (SB15/SB15, −119.2 (4.36) µm vs AFL/AFL, −126.6 (6.15) µm; LSmean difference (95% CI)=7.4 (−6.11 to 20.96)), the LSmean (SE) changes in TRT from baseline (SB15/SB15, −132.4 (7.19) µm vs AFL/AFL, −136.3 (10.10) µm; LSmean difference (95% CI)=3.9 (−18.35 to 26.10)) were similar between SB15/SB15 and AFL/AFL treatment groups. In addition, the proportion of participants with intraretinal or subretinal fluid, the proportion of participants with sub-RPE fluid, the LSmean changes from baseline in CNV, and the proportion of participants who had CNV leakage were comparable (table 2).

Importantly, the similarity in efficacy between SB15 and AFL was also observed when comparing participants switched from AFL to SB15 with those who stayed on AFL (figure 2 and online supplemental figure 1B). At week 56, LSmean (SE) changes from baseline in BCVA (AFL/SB15, 7.9 (1.13) letters vs AFL/AFL, 7.8 (1.15) letters; LSmean difference (95% CI)=0.0 (−2.8 to 2.8)), the proportions of participants who lost less than 15 letters or who gained 15 or more letters compared with baseline all showed comparable results between those two treatment groups.

The anatomical results measured by OCT including LSmean (SE) changes from baseline in CST (AFL/SB15, −136.4 (6.15) µm vs AFL/AFL, −143.7 (6.38) µm; LSmean difference (95% CI)=7.3 (−8.16 to 22.68)), LSmean (SE) changes from baseline in TRT (AFL/SB15, −151.1 (9.68) µm vs AFL/AFL, −149.4 (10.10) µm; LSmean difference (95% CI)=−1.7 (−26.15 to 22.75)), the proportion of participants with intraretinal or subretinal fluid and the proportion of participants with sub-RPE fluid were also comparable (table 2). In addition, LSmean change in CNV size and the proportion of participants who had CNV leakage at week 56 were similar between groups (table 2).

A post hoc analysis conducted to specifically assess efficacy from week 32 to week 56 between participants switching from AFL to SB15 and staying on AFL revealed comparability. The analysis included the LSmean (SE) changes from week 32 to week 56 in BCVA and CST, and the proportions of participants who lost less than 15 letters or gained 5, 10, 15 or more letters from week 32 to week 56 (online supplemental table 3).

Safety

The mean numbers of study drug administrations per study participant were comparable between treatment groups (SB15/SB15: 8.0; AFL/SB15: 8.0; AFL/AFL: 8.0).

The comparability of the safety profiles of SB15 and AFL during the main study period (up to week 32) has been presented previously.[5] The following results focus specifically on the switching period (week 32 to week 56; table 3).

During the switching period, incidence and characteristics of TEAEs were comparable with each of 80 of 219 (36.5%), 39 of 111 (35.1%), 31 of 104 (29.8%) participants having at least one TEAE in the SB15/SB15, AFL/SB15, AFL/AFL treatment groups, respectively (table 3).

Table 2 Analysis of efficacy and exploratory endpoints at week 56 (full analysis set)

Parameter	SB15/SB15 N=219	AFL/AFL N=108	AFL/SB15 N=111	AFL/AFL N=108
n'	216	101	109	101
Change in BCVA from baseline to Week 56; LSmean, letters (SE)	7.4 (0.93)	7.0 (1.29)	7.9 (1.13)	7.8 (1.15)
LSmean difference (95% CI)	0.4(–2.5 to 3.2)		0.0(–2.8 to 2.8)	
n'	216	101	109	101
Study participants with <15 letters loss from baseline at week 56, n (%)	207 (95.8)	99 (98.0)	105 (96.3)	99 (98.0)
Adjusted risk difference (95% CI)	–2.4(–6.18 to 1.40)		–1.8(–6.32 to 2.63)	
n'	216	101	109	101
Study participants with ≥15 letters gain from baseline at Week 56, n (%)	57 (26.4)	18 (17.8)	25 (22.9)	18 (17.8)
Adjusted risk difference (95% CI)	8.2(–1.38 to 17.86)		4.8(–6.07 to 15.73)	
n'	215	99	109	99
Change in CST from baseline to Week 56; LSmean, µm (SE)	–119.2 (4.36)	–126.6 (6.15)	–136.4 (6.15)	–143.7 (6.38)
LSmean difference (95% CI)	7.4 (–6.11 to 20.96)		7.3 (–8.16 to 22.68)	
n'	215	98	109	98
Change in TRT from baseline to week 56; LSmean, µm (SE)	–132.4 (7.19)	–136.3 (10.10)	–151.1 (9.68)	–149.4 (10.10)
LSmean difference (95% CI)	3.9(–18.35 to 26.10)		–1.7(–26.15 to 22.75)	
n'	216	101	109	101
Study participants with intraretinal or subretinal fluid at week 56, n (%)	102 (47.2)	49 (48.5)	48 (44.0)	49 (48.5)
Adjusted risk difference (95% CI)	–1.5 (–13.25 to 10.19)		–3.8 (–17.20 to 9.68)	
n'	216	101	109	101
Study participants with sub-RPE fluid at week 56, n (%)	52 (24.1)	25 (24.8)	30 (27.5)	25 (24.8)
n'	212	98	106	98
Study participants with active CNV leakage at week 56, n (%)	165 (77.8)	78 (79.6)	89 (84.0)	78 (79.6)
Adjusted risk difference (95% CI)	–2.1 (–11.51 to 7.27)		4.6 (–5.67 to 14.81)	
n'	208	98	104	98
Change in CNV size from baseline to week 56; LSmean, mm^2 (SE)	–1.26 (0.281)	–1.09 (0.392)	–0.68 (0.415)	–1.25 (0.423)
LSmean difference (95% CI)	–0.17 (–1.036 to 0.705)		0.58 (–0.461 to 1.616)	
n'	175	92	90	92
Change in NEI VFQ-25 composite score from baseline at week 56, mean (SD)	4.1 (12.27)	4.1 (12.57)	4.9 (13.37)	4.1 (12.57)

Missing data were not imputed. LSmean was adjusted mean of each treatment after adjusting covariate from each model based on (1) data of SB15/SB15 and AFL/AFL and (2) data of AFL/AFL and AFL/SB15, respectively.
AFL, aflibercept; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; CST, central subfield thickness; LSmean, least squares mean; n, number of study participants with event of interest; n', number of study participants with available assessment results at the respective time point; RPE, retinal pigment epithelium; SB15, aflibercept biosimilar candidate; TRT, total retinal thickness; NEI VFQ-25, National Eye Institute Visual Function Questionnaire.

Most TEAEs were mild or moderate and not related to the study drug or intravitreal injection procedure.

Among the ocular TEAEs in the study eye (SB15/SB15, 20 of 219 (9.1%) vs AFL/SB15, 12 of 111 (10.8%) vs AFL/AFL, 3 of 104 (2.9%) participants) that occurred during the switching period, the most common events were cataract and visual acuity reduced. Ocular TEAEs in the study eye were mostly not related to the study drug, except abnormal sensation in eye, glaucoma and vitreous floater. Two ocular serious TEAEs of retinal haemorrhage and

Table 3 Summary of key TEAEs during the switching period (safety set 2)

	SB15/SB15	AFL/SB15	AFL/AFL
	N=219, n (%)	N=111, n (%)	N=104, n (%)
Any TEAEs	80 (36.5)	39 (35.1)	31 (29.8)
Ocular TEAEs in the study eye	20 (9.1)	12 (10.8)	3 (2.9)
Drug-related ocular TEAEs in the study eye	2 (0.9)	1 (0.9)	0 (0.0)
Non-ocular TEAEs*	55 (25.1)	25 (22.5)	24 (23.1)
Drug-related non-ocular TEAEs	0 (0.0)	0 (0.0)	0 (0.0)
Ocular AESI†	3 (1.4)	0 (0.0)	1 (1.0)
Non-ocular AESI†	2 (0.9)	0 (0.0)	2 (1.9)
Serious ocular TEAEs in the study eye	1 (0.5)	0 (0.0)	1 (1.0)
Serious non-ocular TEAEs	9 (4.1)	6 (5.4)	5 (4.8)
Ocular TEAEs by preferred term in the study eye			
Cataract	4 (1.8)	1 (0.9)	1 (1.0)
Visual acuity reduced	4 (1.8)	1 (0.9)	1 (1.0)
Dry eye	2 (0.9)	0 (0.0)	0 (0.0)
Posterior capsule opacification	0 (0.0)	2 (1.8)	0 (0.0)
Retinal tear	1 (0.5)	1 (0.9)	0 (0.0)
Xerophthalmia	0 (0.0)	2 (1.8)	0 (0.0)
Abnormal sensation in eye	1 (0.5)	0 (0.0)	0 (0.0)
Cataract nuclear	1 (0.5)	0 (0.0)	0 (0.0)
Corneal dystrophy	0 (0.0)	1 (0.9)	0 (0.0)
Corneal oedema	0 (0.0)	1 (0.9)	0 (0.0)
Diplopia	1 (0.5)	0 (0.0)	0 (0.0)
Disease progression	0 (0.0)	1 (0.9)	0 (0.0)
Eye pain	0 (0.0)	0 (0.0)	1 (1.0)
Glaucoma	1 (0.5)	0 (0.0)	0 (0.0)
Hordeolum	0 0.0)	1 (0.9)	0 (0.0)
Intraocular pressure increased	1 (0.5)	0 (0.0)	0 (0.0)
Macular degeneration	1 (0.5)	0 (0.0)	0 (0.0)
Macular fibrosis	1 (0.5)	0 (0.0)	0 (0.0)
Macular hole	1 (0.5)	0 (0.0)	0 (0.0)
Macular oedema	0 (0.0)	1 (0.9)	0 (0.0)
Neovascular age-related macular degeneration	0 (0.0)	1 (0.9)	0 (0.0)
Retinal haemorrhage	0 (0.0)	0 (0.0)	1 (1.0)
Retinal pigment epithelial tear	1 (0.5)	0 (0.0)	0 (0.0)
Subretinal fluid	1 (0.5)	0 (0.0)	0 (0.0)
Vitreous detachment	0 (0.0)	0 (0.0)	1 (1.0)
Vitreous floaters	0 (0.0)	1 (0.9)	0 (0.0)
Vitreous haemorrhage	1 (0.5)	0 (0.0)	0 (0.0)

Adverse events were coded according to System Organ Class and PT using MedDRA version 23.0 coding dictionary.
*PTs available in online supplemental table 6.
†PTs available in online supplemental table 4.
AESI, adverse event of special interest; AFL, reference aflibercept; AMD, age-related macular degeneration; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SB15, aflibercept biosimilar candidate; TEAE, treatment-emergent adverse event.

vitreous haemorrhage were reported in 2 of 434 (0.5%) participants, with none of them assessed to be related to the study drug. No participants experienced intraocular inflammation during the switching period (online supplemental table 4).

A post hoc analysis revealed that the ocular safety profiles of participants were comparable before and after switching from AFL to SB15 (online supplemental table 5)

Non-ocular safety profiles were also comparable among treatment groups during the switching period (participants with at least one TEAE: SB15/SB15, 55 of 219 (25.1%); AFL/SB15, 25 of 111 (22.5%); AFL/AFL, 24 of 104 (23.1%)), with hypertension as the most common non-ocular TEAE (online supplemental table 6). None of the non-ocular TEAEs was related to the study drug or the intravitreal injection procedure. Non-ocular serious TEAEs were reported in comparable proportions of participants (SB15/SB15, 9 of 219 (4.1%); AFL/SB15, 6 of 111 (5.4%); AFL/AFL, 5 of 104 (4.8%); table 3) during the switching period and the numbers of patients with arterial thromboembolic events were low and comparable between treatment groups (online supplemental table 4).

During the switching period, 3 of 434 (0.7%) participants (SB15/SB15, 3 of 219 (1.4%)) had TEAEs that led to discontinuation of the study drug. One study participant had diplopia and gait disturbance, one study participant had macular hole and one study participant had retinal tear and vitreous haemorrhage.

2 of 434 (0.5%) participants died during the switching period (SB15/SB15, 1 of 219 (0.5%) due to unknown cause; AFL/AFL, 1 of 104 (1.0%) due to cerebrovascular accident). None of these events were considered to be related to the study drug.

Immunogenicity

Incidence of treatment-induced or treatment-boosted ADAs up to week 32 were low (SB15, 2 of 210 (1.0%); AFL, 0 of 209 (0.0%)) and comparable between treatment groups.[5] After week 32, treatment-induced ADAs developed in 1 of 96 (1.0%) participants in the AFL/AFL treatment group but in none of the participants in the SB15/SB15 and AFL/SB15 treatment groups (online supplemental table 7).

Pharmacokinetics

Serum concentrations (C_{trough} and C_{max}) were comparable between SB15 and AFL treatment groups before switching.[4] After rerandomisation at week 32, C_{trough} measured predose at week 40 and week 56 were below the limit of quantification (BLQ; 5.00 ng/mL) for all treatment groups.

DISCUSSION

The results of this phase 3 study demonstrate comparable efficacy, safety, PK and immunogenicity between SB15 and AFL up to week 56, and provide evidence of biosimilarity between the two drugs.

In terms of efficacy, SB15/SB15 and AFL/AFL treatment groups showed comparable results for all endpoints at week 56. The gain in BCVA from baseline to week 56 in the SB15 group was comparable to that observed in previous anti-VEGF clinical trials with AFL as test drug or active control (adjusted or unadjusted mean change from baseline at around 1 year ranging from 5.1 to 8.9 letters).[7–9] The observed safety profiles were consistent with previously reported safety profiles of AFL, with no retinal vasculitis or retinal vascular occlusion reported, supporting the generalisability of the here presented results.[10]

Up to week 56, comparability was also observed between participants who stayed on AFL and those who switched from AFL to SB15 in terms of efficacy, safety, PK and immunogenicity.

Overall, these findings support the safe and effective use of SB15 for the treatment of retinal diseases not only in AFL-naïve participants, but also in participants previously treated with reference AFL. To our knowledge, this is the first study showing the clinical data on switching from reference AFL to a proposed biosimilar. The presented data on switching from AFL to SB15 agree with the reports stating that switching from reference biologics to biosimilars is usually not associated with efficacy, safety or immunogenicity issues.[11] Recent approaches by the FDA and European Medicines Agency (EMA) corroborate the generally expected low risk of clinically significant immunogenic responses after switching from intravitreally administered reference products to biosimilars or vice versa. EMA published a joint statement with the Heads of Medicines Agencies proclaiming the interchangeability of biosimilars and FDA granted interchangeable approval to ranibizumab biosimilars without dedicated switching studies being available.[12 13]

Taken together, the results presented in this report together with available non-clinical data[3] suggest biosimilarity between SB15 and AFL and represent a further step towards providing the totality-of-evidence, which is required for the regulatory approval of a biosimilar.[1 14 15]

A potential limitation of this study is the relatively small sample size of the AFL/SB15 and AFL/AFL treatment groups compared with the SB15/SB15 treatment group, and that the results of the secondary endpoints' analysis at week 56 have to be interpreted cautiously as the study was not powered to assess equivalence between treatment groups based on these endpoints at Week 56. Nonetheless, the presented results provide valuable evidence on the safety and efficacy of switching from AFL to SB15.

In conclusion, this report demonstrates comparable efficacy, safety, PK and immunogenicity up to week 56 between SB15 and AFL in patients with nAMD, and supports the biosimilarity of SB15 with the maintained clinical efficacy when switching from AFL to SB15.

Author affiliations
[1]Ophthalmology, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Ophthalmology, Doheny Eye Institute, Pasedena, California, USA
[3]Ophthalmology, University of California, Los Angeles, California, USA
[4]Medical Faculty, Univesity Josip Juraj Strossmayer, Osijek, Croatia
[5]Department of Ophthalmology, University of Debrecen, Debrecen, Hungary
[6]Department of Ophthalmology, Yeungnam University School of Medicine and College of Medicine, Daegu, Korea

[7]Department of Ophthalmology, Axon Clinical, Praha, Czech Republic
[8]Ophthalmology, University Hospital, Hradec Králové, Czech Republic
[9]Department of Ophthalmology, University Hospital Kralovske Vinohrady, Prague, Czech Republic
[10]Department of Ophthalmology, Charles University Third Faculty of Medicine, Prague, Czech Republic
[11]Ophthalmology Department, Medical University of Silesia, Katowice, Poland
[12]Retina Research Institute, Abilene, Texas, USA
[13]Ophthalmology, Korea University Ansan Hospital, Ansan, Gyeonggi-do, Korea
[14]Ophthalmology, Rydygier Memorial Hospital, Krakow, Poland
[15]First Pavlov State Medical University, St.Petersburg, Russian Federation
[16]Department of Ophthalmology, University of Szeged, Szeged, Hungary
[17]Department of Ophthalmology, Pécs University Medical School, Pécs, Hungary
[18]Bajcsy-Zsilinszky Korhaz es Rendelointezet, Budapest, Hungary
[19]Samsung Bioepis Co Ltd, Incheon, Korea

Acknowledgements Medical writing support was provided by Christoph Schürch (SFL Regulatory Affairs & Scientific Communication) and funded by Samsung Bioepis.

Contributors SJW had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SJW, SRS, IO and HJ. Acquisition, analysis or interpretation of data: SRS, AV, MS, JE, JS, MV, EW, SP, CY, MO, SA, ET-M and LE. Drafting of the manuscript: WC, IO and HJ. Critical revision of the manuscript for important intellectual content: SJW, SRS, AV, MS, JE, JS, MV, EW, SP, CY, MO, SA, ET-M, LE, WC, IO and HJ. Statistical analysis: WC. Administrative, technical or material support: IO and HJ. Supervision: SJW, SRS, IO and HJ. SJW is the guarantor.

Funding Planning, conduct, and analysis of the study was funded by Samsung Bioepis, Songdogyoyuk-ro, Yeonsu-gu, Incheon, Republic of Korea.

Competing interests WC, IO and HJ are employed by Samsung Bioepis. Samsung Bioepis funded medical writing support and article processing charges. Additional potential conflicts of interest are listed below. SJW obtained consulting fees from Samsung Bioepis, Janssen, Novartis, Curacle, Novelty Nobility, Sometech, Rznomics and Pharmabcine, grants from Samsung Bioepis, Novelty Nobility, Novartis, Alteogen, Roche, Geneunitech, Bayer, Bio Bank Healing, and Curacle, and payments for lectures from Novartis, Bayer, and Allergan-Abbvie. He serves as equity owner of Retimark and Panolos Bioscience. SRS obtained consulting fees from Apellis, Amgen, Abbvie/Allergan, Samsung Bioepis, Biogen, Boerhinger Ingelheim, Iveric, Novartis, Roche, Bayer, Regeneron, Pfizer, Astellas, Nanoscope, Jannsen, Centervue, Optos and Heidelberg, and honoraria for lectures from Novartis, Roche, Optos, and Heidelberg. He is part of the Data Safety Monitoring/Advisory Board of Regeneron and holds leadership/fiduciary functions in ARVO and Macula Society. MB obtained honoraria for presentations by Novartis and Abbvie. He is part of the advisory board of Novartis and obtained grants for clinical trials from Iveric Bio (former Optotech), Novartis, Roche, Ophthea and Samsung Bioepis. AV obtained consulting fees and honoraria for lectures from Novartis, Roche, Pfizer, Bausch & Lomb, Zeiss, and Alcon. He also obtained support for meeting attendances by Novartis, Pfizer, Bausch & Lomb, Roche, Zeiss, Alcon, Iveric Bio, Amgen, Chengdu, Mylan, Panoptica, Formycon, Thrombogenics, Regeneron and Clearside. He is part of the Data Safety Monitoring/Advisory Board of Zeiss, Bayer, Novartis, Pfizer, and Roche. MS obtained grants from Allergan/Abbvie, Bayer and Novartis, consulting fees from Samsung Bioepis, Bayer, Novartis, Allergan/Abbvie, Roche, Alcon and Curacle, honoraria for lectures from Samsung Bioepis, Bayer, Novartis, Allergan/Abbvie, Roche, Alcon and Johnson & Johnson, and support for meeting attendances from Bayer, Allergan/Abbvie and Novartis. Min Sagong is part of the Data Safety Monitoring/Advisory board of Bayer, Novartis, and Allergan/Abbvie. JS obtained consulting fees from Abbvie and support for meeting attendances from Bayer. MV obtained consulting fees from Abbvie and Roche and support for meeting attendances from Bayer. EW obtained honoraria for lectures from Bayer, Roche, Alfa Sigma, Allergan, Zeiss and Thea, and is part of the advisory board of Allergan. SP obtained grants from Aerie, Aerpio, Allergan, Allgenesis, Apellis, Boehringer Ingelheim, Chengdu Kanghong, Clearside, EyePoint, Genentech-Roche, Ionis Pharmaceuticals, IVERIC Bio, KalVista, Kodiak Sciences, Mylan, Novartis, Oculis, Opthea, Ora, Oxurion, Regeneron, Samsung, SmileBiotek, Stealth Biotherapeutics, ThromboGenics, Xbrane Biopharma, consulting fees from AiViva, Allergan, Allgenesis, Genentech-Roche, Kala, Kodiak Sciences, Oxugenix, and RegenxBio, and support for travel expenses from EyePoint. He is part of the Data Safety Monitoring/Advisory Board of Allergan, Allgenesis Biotherapeutics, Genentech-Roche, Kodiak Sciences, and Iveric Bio and serves as equity owner and chief medical officer for Allgenesis Biotherapeutics. WC received consulting fees from Samsung Bioepis and payments for lectures from Bayer, Novartis and Chong Kun Dang.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the SB15-3001 study adhered to the tenets of the Declaration of Helsinki and was approved by central and local institutional review boards. All central and local ethics committees approved the study and received all related approval letter. They are all archived by the Sponsor. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data available: Yes, on reasonable request. Data types: Deidentified participant data. How to access data: To gain access, data requestors must enter into a data access agreement with Samsung Bioepis. Email address for data requests: med.info@samsung.com. When available: With publication. Who can access the data: On request, and subject to certain criteria, conditions and exceptions, Samsung Bioepis will provide access to individual deidentified participant data. Types of analyses: The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply. Mechanisms of data availability: Data may be made available with a signed data access agreement.

ORCID iDs
Se Joon Woo http://orcid.org/0000-0003-3692-7169
SriniVas R Sadda http://orcid.org/0000-0001-8504-8051
Michal Orski http://orcid.org/0000-0002-9306-1405

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