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Efficacy and Safety of the Aflibercept Biosimilar SB15 in Neovascular Age-Related Macular Degeneration
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Aflibercept biosimilars can expand available treatment options in retinal diseases and have the potential to improve patient access to safe and effective therapy.

OBJECTIVE To establish equivalence in efficacy and similarity in safety, pharmacokinetics, and immunogenicity of SB15 and reference aflibercept (AFL) in neovascular age-related macular degeneration (nAMD).

DESIGN, SETTING, AND PARTICIPANTS This was a randomized double-masked parallel group phase 3 trial conducted at 56 centers in 10 countries from June 2020 to March 2022, including follow-up through 56 weeks. Of 549 screened participants, 449 participants 50 years and older with treatment-naive nAMD were included and randomly assigned to SB15 (n = 224) or AFL (n = 225). Key exclusion criteria included considerable scarring, fibrosis, atrophy, and hemorrhage. This report includes results up to the end of the parallel group period at week 32. Of the 449 randomized participants, 438 (97.6%) completed week 32 follow-up.

INTERVENTION Participants were randomized 1:1 to receive 2 mg of SB15 or AFL every 4 weeks for the first 12 weeks (3 injections), followed by dosing every 8 weeks up to week 48, with final assessments at week 56.

MAIN OUTCOMES AND MEASURES The primary end point was the change in best-corrected visual acuity (BCVA) from baseline to week 8 with predefined equivalence margins of −3 letters to 3 letters. Other key end points were changes in BCVA and central subfield thickness up to week 32, safety, pharmacokinetics, and immunogenicity.

RESULTS The mean (SD) age among the 449 included participants was 74.0 (8.1) years, and 250 participants (55.7%) were female. Baseline demographic characteristics and most disease characteristics were comparable between treatment groups. The least squares mean change in BCVA from baseline to week 8 in the SB15 group was equivalent to that in the AFL group (6.7 letters vs 6.6 letters, respectively; difference, 0.1 letters; 95% CI, −1.3 to 1.4). Comparable efficacy between treatment groups was maintained up to week 32 (least squares mean change from baseline in BCVA: SB15, 7.6 letters vs AFL, 6.5 letters; least squares mean change from baseline in central subfield thickness: SB15, −110.4 µm vs AFL, −115.7 µm). No clinically relevant differences were observed in the incidence of treatment-emergent adverse events (TEAEs) (SB15, 107/224 [47.8%] vs AFL, 98/224 [43.8%]) and ocular TEAEs in the study eye (SB15, 41/224 [18.3%] vs AFL, 28/224 [12.5%]). The serum concentration profiles and cumulative incidences of overall antidrug antibody positive participants were comparable.

CONCLUSIONS AND RELEVANCE In this phase 3 randomized clinical trial, SB15 and AFL showed equivalent efficacy and comparable safety, pharmacokinetics, and immunogenicity in participants with nAMD.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04450329

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Visual Abstract

Supplemental content

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Neovascular age-related macular degeneration (nAMD) causes visual disability and is the leading cause of blindness in older persons. Approximately 90% of all cases of severe vision loss in patients with nAMD are ascribed to choroidal neovascularization (CNV).[1] Dissection of underlying molecular pathogenic pathways revealed that nAMD is causally associated with elevated expression of vascular endothelial growth factor (VEGF). Unraveling the relationship between loss of vision and VEGF led to the development of VEGF inhibition therapies.[2] Nowadays, anti-VEGF agents are considered the gold standard for the treatment of a plethora of VEGF-mediated diseases, including nAMD.[3-6]

Aflibercept is an anti-VEGF agent harboring the binding domains of VEGF receptors 1 and 2 and blocking all VEGF-A isoforms, VEGF-B, and placental growth factor.[7] SB15 has been developed as a biosimilar to reference aflibercept (AFL) and is produced by recombinant DNA technology in Chinese hamster ovary cells. For regulatory approval, the similarity of the biosimilar to a reference product must be demonstrated based on structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, immunogenicity, safety, and effectiveness.[8-10]

The structural, physicochemical, and biological similarity between SB15 and AFL has been demonstrated.[11] The aim of this study was to evaluate equivalent efficacy and comparable safety, pharmacokinetics, and immunogenicity between the 2 drugs. The preplanned interim results up to the end of the parallel group period at week 32 are presented here. Since the primary end point analysis of the study was conducted at an early time point (ie, week 8) and was hence captured by the interim analysis, the results presented herein provide important clinical data about SB15 in demonstrating biosimilarity.

Key Points

Question Does SB15, a proposed aflibercept biosimilar, have equivalent best-corrected visual acuity (BCVA) outcomes and a similar safety profile to reference aflibercept (AFL) in patients with neovascular age-related macular degeneration?

Findings In this phase 3 randomized clinical trial, changes in BCVA from baseline to week 8 were equivalent for SB15 and AFL.

Meaning These results provide evidence that there are no clinically meaningful differences in efficacy between SB15 and AFL.

Methods

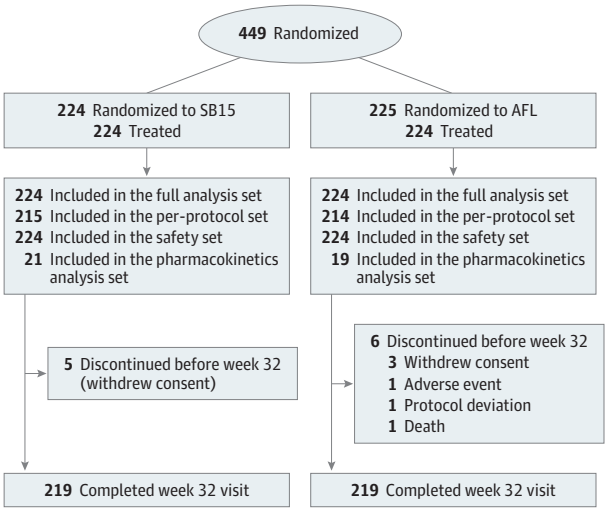
Study Design

This was a phase 3, randomized, double-masked, parallel group, multicenter study (ClinicalTrials.gov: NCT04450329; EudraCT: 2019-003883-28) conducted at 56 sites in 10 countries throughout Asia, Europe, and the US from June 2020 to March 2022, including follow-up through 56 weeks. The clinical study protocol and amendment (Supplement 1) were reviewed and approved by independent ethics committees or institutional review boards at each site. The study followed the International Council for Harmonisation and Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from each participant before entering the study. Participants did not receive any compensation or incentives to participate. An independent data and safety monitoring board reviewed the safety and tolerability data. This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Participants were eligible if they were 50 years or older, had treatment-naive subfoveal CNV lesion secondary to AMD that occupied 50% or more of the total lesion in the study eye, had a total lesion area 9.0 disc areas or less, and had best-corrected visual acuity (BCVA) of 20/40 to 20/200 (letter score of 73 to 34, inclusive) in the study eye at screening and at week 0 (day 1) prior to randomization. Key exclusion criteria were scar, fibrosis, or atrophy involving the center of the fovea in the study eye and hemorrhage comprising 50% or more of the entire lesion or with the size of 1 disc area or larger involving the center of the fovea. A full list of inclusion and exclusion criteria is provided in eAppendix 1 in Supplement 2. Eligibility criteria based on retinal images were confirmed by 2 independent readers in the central reading center (Fundus Photograph Reading Center, Madison, Wisconsin). The data cutoff date for the interim analysis was October 4, 2021 (the date of the last participant's week 32 visit). Of 549 screened participants, 449 randomly received either SB15 (n = 224) or AFL (n = 225), and 438 (97.6%) completed week 32 follow-up (**Figure 1**). The main reason for discontinuation before week 32 was withdrawal of consent (1.8% of all randomized participants). Demographic information, including age, sex, and race, were based on self-report captured information. Race data were collected and categorized as per guidance from the US Food and Drug Administration.

Figure 1. Participant Disposition up to Week 32



AFL indicates reference aflibercept; SB15, aflibercept biosimilar candidate.

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Randomization, Intervention, and Masking

Participants were randomized in a 1:1 ratio to receive either SB15 or AFL. Three consecutive monthly intravitreal injections of 2 mg (0.05 mL) of SB15 or AFL (ie, at weeks 0, 4, and 8) were followed by treatment once every 8 weeks. At week 32, participants were rerandomized to either continue receiving SB15 or AFL or be transitioned from AFL to SB15 to evaluate the impact of switching from AFL to SB15. The week 32 time point was chosen for switching as it is the first dosing time point after week 24, which, according to regulatory authorities, is when the near-maximum serum concentrations under steady state should be measured. In total, SB15 and AFL were administered up to week 48, and the last assessments were performed at week 56 (eFigure 1 in Supplement 2). Participants, investigators, and site personnel remained masked throughout the study period.

Assessments and Study End Points

Ophthalmic examination (BCVA, slitlamp examination, intraocular pressure, and indirect ophthalmoscopy) and optical coherence tomography (OCT) were performed at each visit. BCVA was tested using Early Treatment Diabetic Retinopathy Study charts. Fundus photography and fluorescein angiography were performed at screening, week 32, and week 56. Ocular images (fundus photography, fluorescein angiography, and OCT) were independently assessed in the central reading center.

The primary efficacy end point of the study was the change in BCVA from baseline to week 8. Week 8 was chosen as primary end point because aflibercept treatment typically leads to a substantial initial improvement in visual acuity, during which period the probability of detecting potential clinically meaningful differences is the highest.[12] Secondary efficacy end points included change from baseline at week 32 in BCVA, central subfield thickness (from internal limiting membrane to retinal pigment epithelium in 1-mm central subfield), total retinal thickness (from internal limiting membrane to the Bruch membrane in 1-mm central subfield), and CNV area, as well as the proportion of participants who lost fewer than 15 letters or gained 15 letters or more in BCVA from baseline to week 32, proportion with intraretinal or subretinal fluid and subretinal pigment epithelium fluid at week 32, and proportion with active CNV leakage at week 32. In a post hoc analysis, the proportions of participants with 20/40 or higher (70 letter score) or 20/200 or lower (35 letter score) in the study eye, and with 20/40 or higher (70 letter score) or 20/200 or lower (35 letter score) in the better-seeing eye, as well as the numbers of participants who lost 10 letters or more (2 lines) or 15 letters or more (3 lines) compared to baseline were computed.

Adverse events were assessed at each visit. Reported terms for adverse events (ocular and nonocular) were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) and summarized descriptively. MedDRA preferred terms for intraocular inflammation and the definition of arterial thromboembolic events used for safety analysis are listed in eAppendices 2 and 3 in Supplement 2.

Pharmacokinetics end points were serum trough concentrations measured at predose of weeks 0 (day 1), 4, 8, 24, and 32, as well as the near-maximum serum concentrations measured once between 24 and 72 hours after dosing at week 0 (day 1) and once per day for 3 consecutive days after dosing at week 24.

Immunogenicity end points were the incidences of antidrug antibodies and neutralizing antibodies to aflibercept. Blood samples for immunogenicity assessment were collected prior to intravitreal injection at weeks 0 (day 1), 4, 8, 24, and 32 or at the early termination visit. In terms of cumulative incidence of antidrug antibodies, a participant was considered overall antidrug antibody positive if either treatment-induced (de novo antidrug antibodies in participants who tested negative for antidrug antibodies at predose at week 0) or treatment-boosted antidrug antibodies (at least 1 positive result of a higher antidrug antibody titer level compared to predose at week 0) for participants were detected. Quality of life was assessed by the change from baseline in composite scores of the National Eye Institute 25-Item Visual Function Questionnaire at week 32.

Statistical Analysis

A preplanned interim analysis was performed when the last participant completed week 32. With the equivalence margins set to −3 and 3 letters (in conformity with requirements of regulatory authorities) and an assumed mean difference of 0.5 letters and SD of 9.0, 216 participants per group were calculated to provide 80% power (with a significance level of 5%) to reject the null hypothesis. Based on this, 446 participants (223 per group) were planned to be randomized, allowing for a 3% loss of randomized participants.

Primary end point analysis was performed using the analysis of covariance model with baseline BCVA as covariate and country and treatment groups as factors. Equivalence between groups was declared if the 2-sided 95% or 90% CI (depending on the regulatory authority's requirements) of the difference in least squares mean change from baseline in BCVA at week 8 was contained within the predefined equivalence margins (−3 letters to 3 letters).

Analysis methods used for secondary end points measuring a change from baseline were similar to the ones used for the primary end point. For end points measuring proportions of participants, the adjusted risk difference between groups was calculated using a stratified Cochran-Mantel-Haenszel test with a 95% Mantel-Haenszel CI and country as a factor.

All analyses of efficacy end points were performed on the full analysis set. For primary end point analysis, missing data were imputed using multiple imputation under the missing-at-random assumption. Other analyses were performed based on available data. Definitions of analysis sets are presented in eAppendix 4 in Supplement 2.

Results

Baseline Demographics and Disease Characteristics

The mean (SD) age among the 449 included participants was 74.0 (8.1) years, and 250 participants (55.7%) were female. Baseline demographic characteristics and most disease characteristics were comparable between groups (**Table 1**). For SB15 and

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Table 1. Baseline Demographic and Disease Characteristics (Randomized Set)

Characteristic	No. (%) SB15 (n = 224)	AFL (n = 225)	Total (N = 449)
Age, mean (SD), y	73.7 (8.1)	74.3 (8.1)	74.0 (8.1)
Female	118 (52.7)	132 (58.7)	250 (55.7)
Male	106 (47.3)	93 (41.3)	199 (44.3)
Race[a]			
Asian	52 (23.2)	51 (22.7)	103 (22.9)
White	170 (75.9)	172 (76.4)	342 (76.2)
Other[b]	2 (0.9)	2 (0.9)	4 (0.9)
Region			
Europe	138 (61.6)	139 (61.8)	277 (61.7)
US	14 (6.3)	14 (6.2)	28 (6.2)
Other (Korea, Japan, Russia)	72 (32.1)	72 (32.0)	144 (32.1)
BCVA, mean (SD), total letter score	59.5 (10.6)	58.9 (11.2)	59.2 (10.9)
Approximate Snellen equivalent	20/63	20/63	20/63
BCVA group by letter score (Snellen equivalent)			
<50 (20/100)	36 (16.1)	44 (19.6)	80 (17.8)
≥50 (20/100)	188 (83.9)	181 (80.4)	369 (82.2)
Central subfield thickness, mean (SD), μm[c,d]	353.3 (95.61)	382.3 (121.96)	367.8 (110.44)
Total retinal thickness, mean (SD), μm[e]	445.2 (140.1)	461.7 (145.4)	453.4 (142.9)
Presence of intraretinal fluid[f]	107 (47.8)	136 (60.4)	243 (54.1)
Presence of subretinal fluid	204 (91.1)	210 (93.3)	414 (92.2)
Presence of subretinal pigment epithelium fluid	106 (47.3)	106 (47.1)	212 (47.2)
Lesion type			
Predominantly classic	41 (18.3)	47 (20.9)	88 (19.6)
Minimally classic	40 (17.9)	56 (24.9)	96 (21.4)
Occult	138 (61.6)	117 (52.0)	255 (56.8)
Not available	5 (2.2)	5 (2.2)	10 (2.2)
Area of CNV, mean (SD), mm^2	6.1 (4.3)	6.3 (4.8)	6.2 (4.6)
Lens status in study eye			
Pseudophakia	73 (32.6)	64 (28.4)	137 (30.5)

Abbreviations: AFL, reference aflibercept; CNV, choroidal neovascularization; SB15, aflibercept biosimilar candidate.

[a] Race data were collected and categorized as per guidance from the US Food and Drug Administration.

[b] Including American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, unknown, or cannot be reported per local regulation, consolidated because of small numbers.

[c] Number of participants included in summary statistics: SB15 = 223; AFL = 224.

[d] *P* value = .005.

[e] Number of participants included in summary statistics: SB15 = 223; AFL = 223.

[f] *P* value = .007.

AFL, respectively, the mean (SD) age of participants was 73.7 (8.05) years and 74.3 (8.09) years; 118 of 224 (52.7%) and 132 of 225 (58.7%) were female; 52 of 224 (23.2%) and 51 of 225 (22.7%) were Asian; 170 of 224 (75.9%) and 172 of 225 (76.4%) were White; and 2 of 224 (0.9%) and 2 of 225 (0.9%) were of another race (including American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, unknown, or cannot be reported per local regulation, consolidated because of small numbers). The mean (SD; approximate Snellen equivalent) baseline BCVA was 59.5 (10.6; 20/63) letters for SB15 and 58.9 (11.2; 20/63) for AFL. The mean (SD) baseline central subfield thickness was 353.3 (95.61) μm for SB15 and 382.3 (121.96) μm for AFL. The mean (SD) area of CNV was 6.1 (4.34) mm^2 for the SB15 group and 6.3 (4.76) mm^2 for the AFL group. Lesion types measured at baseline by fluorescein angiography were comparable between groups.

Efficacy

Primary End Point

The primary end point was met. The least squares mean (SE) change in BCVA from baseline to week 8 in the full analysis set was 6.7 (0.56) letters for SB15 and 6.6 (0.57) letters for AFL. The least squares mean difference between groups was 0.1 letters and the 95% CI (−1.3 to 1.4) was within the predefined equivalence margins (**Figure 2**). Sensitivity analysis resulted in a least squares mean difference of 0.1 (95% CI, −1.3, 1.5) letters based on the full analysis set without imputation and −0.2 (95% CI, −1.6, 1.2) letters based on the per-protocol set (eTable 1 in Supplement 2).

Secondary End Points

The least squares mean change in BCVA from baseline through week 32 was comparable between groups (**Table 2**; eFigure 2 in Supplement 2). At week 32, the least squares mean (SE) changes from baseline for SB15 and AFL were 7.6 (0.8) and 6.5 letters (0.8), respectively. Comparable proportions of participants lost fewer than 15 letters (214/219 in SB15 [97.7%] vs 208/215 in AFL [96.7%]) or gained 15 or more letters (48/219 in SB15 [21.9%] vs 40/215 in AFL [18.6%]) in BCVA compared to baseline. Results of the post hoc analysis for BCVA are presented in eTable 2 in Supplement 2.

At week 4, the least squares mean changes from baseline in central subfield thickness (SB15, −101.8 μm vs AFL, −112.9 μm) and total retinal thickness (SB15, −128.2 μm vs AFL, −132.9 μm) were comparable between groups. This comparability was maintained up to week 32 (central subfield thickness:

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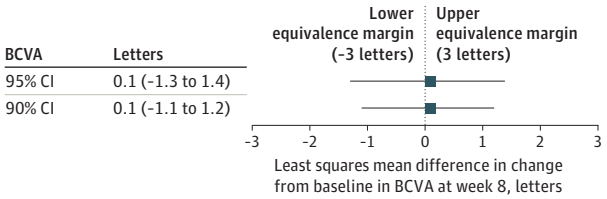
Figure 2. Least Squares Mean Difference in Change in Best-Corrected Visual Acuity (BCVA) from Baseline to Week 8 (Full Analysis Set)



	SB15 (n = 224)	AFL (n = 224)
Least squares mean change from baseline, BCVA letter score	6.7	6.6
Least squares mean difference, BCVA letter score	0.1	

Predefined equivalence margins were set from −3 letters to 3 letters. Equivalence between the 2 treatment groups was to be declared if the 2-sided 90% CI or 95% CI (depending on the regulatory authority's requirements) of the difference in least squares mean change from baseline in BCVA at week 8 was entirely contained within the predefined equivalence margins. AFL indicates reference aflibercept; SB15, aflibercept biosimilar candidate.

SB15, −110.4 µm vs AFL, −115.7 µm; total retinal thickness: SB15, −127.7 µm vs AFL, −131.9 µm) (Table 2; eFigure 2 in Supplement 2).

Proportions of participants with intraretinal or subretinal fluid were 58.4% (128/219) for SB15 and 55.1% (118/214) for AFL at week 32. A total of 31.1% (68/219) and 29.9% (64/214) of participants in the SB15 and AFL groups had subretinal pigment epithelium fluid at week 32, respectively (eFigure 3 in Supplement 2). The least squares mean (SE) change in CNV size from baseline (−1.0 [0.2] mm^2 in SB15 vs −0.4 [0.2] mm^2 in AFL) and the proportions of participants with active CNV leakage at week 32 (187/212 in SB15 [88.2%] vs 192/210 in AFL [91.4%]) were comparable between groups. The mean (SD) change from baseline in composite score of National Eye Institute 25-Item Visual Function Questionnaire was similar (3.1 [10.4] in SB15 vs 2.8 [11.2] in AFL) (Table 2).

Safety

The mean (SD) number of study treatment administrations per participant was comparable between groups (5.0 [0.3] in SB15 vs 4.9 [0.3] in AFL). A total of 205 participants (45.8%; 107/224 [47.8%] in SB15 vs 98/224 [43.8%] in AFL) had a total of 364 treatment-emergent adverse events (TEAEs).

Ocular TEAEs in the study eye were comparable between groups (41/224 [18.3%] in SB15 vs 28/224 [12.5%] in AFL) (**Table 3**). The most common ocular TEAEs were visual acuity reduced (8/224 [3.6%] in SB15 vs 5/224 [2.2%] in AFL) and conjunctival hemorrhage (9/224 [4.0%] in SB15 vs 3/224 [1.3%] in AFL). Three of 224 participants (1.3%) in the SB15 group and 1 of 224 (0.4%) in the AFL group had drug-related ocular TEAEs. One of 224 participants (0.4%) in the AFL group reported a TEAE of intraocular inflammation (iridocyclitis). The incidence of serious ocular TEAEs in the study eye was low (3/224 [1.3%] in SB15 vs 1/224 [0.4%] in AFL), and no participants discontinued the treatment due to ocular TEAEs.

Nonocular TEAEs were comparable between groups (73/224 [32.6%] in SB15 vs 67/224 [29.9%] in AFL) (Table 3). The most common nonocular TEAEs were hypertension (6/224 [2.7%] in SB15 vs 1/224 [0.4%] in AFL) and nasopharyngitis (5/224 [2.2%] in SB15 vs 2/224 [0.9%] in AFL) (eTable 3 in Supplement 2). One of 224 participants (0.4%) in the AFL group reported a TEAE related to study treatment (ischemic stroke). Twenty-two of 448 (4.9%) had nonocular serious TEAEs (8/224 [3.6%] in SB15 vs 14/224 [6.3%] in AFL), including 1 of 224 participants (0.4%) in the AFL group with a TEAE (circulatory collapse) leading to death. None of the TEAEs in the SB15 group led to treatment discontinuation, whereas 1 of 224 participants (0.4%) in the AFL group discontinued the treatment due to a TEAE (chronic myelomonocytic leukemia). Six participants reported arterial thromboembolic events (4/224 [1.8%] in SB15 and 2/224 [0.9%] in AFL).

Pharmacokinetics

Most measurements of serum trough concentrations were below the limit of quantification (5.00 ng/mL). Mean (SD) near-maximum serum concentrations ranged from 28.1 (15.33) to 48.3 (42.13) ng/mL for SB15 and from 47.3 (39.47) to 57.4 (46.38) ng/mL for AFL. The coefficient of variation of all postdose measurements ranged from 54.6% to 89.3% for SB15 and from 77.0% to 100.2% for AFL. Overall, the pharmacokinetic profiles were comparable between groups (eFigure 4, eTable 4 in Supplement 2).

Immunogenicity

Few participants had pretreatment antidrug antibodies at baseline (3/224 [1.3%] in SB15 and 1/224 [0.4%] in AFL). The incidence of antidrug antibodies and neutralizing antibodies by visit was comparable between groups and the cumulative incidence of overall antidrug antibody positivity up to week 32 was low (2/210 [1.0%] in SB15 and 0 in AFL) (eTable 5 in Supplement 2).

Discussion

The results show equivalent efficacy and comparable safety, pharmacokinetics, and immunogenicity between SB15 and AFL in nAMD. A comparative clinical study for a biosimilar development program aims to investigate the clinically meaningful differences between the proposed product and the reference product.[10] Hence, choosing an adequately sensitive study population and end point to detect such differences is of central importance. The present study enrolled participants with nAMD, which is considered a sensitive study population based on the large treatment effect of anti-VEGF therapies.[13-16] Regarding the choice of primary end point, the change in BCVA from baseline to week 8 has been endorsed by regulatory authorities and used as primary end point in other anti-VEGF biosimilar trials before.[17-21]

The BCVA results reported in this study are comparable to previous studies with aflibercept as active control (2 mg dosing every 8 weeks). At week 8, the adjusted mean or mean changes in BCVA ranging from 5.9 to 6.3 letters were observed in the HAWK and HARRIER,[19] TENAYA and LUCERNE,[20] and VIEW 1 and VIEW 2[22] (integrated analysis) studies. At week

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Table 2. Secondary Efficacy and Exploratory End Points (Full Analysis Set)[c]

Parameter	SB15 (n = 224)	AFL (n = 224)
No. of participants with available assessment results at time point	219	215
Change in BCVA from baseline to week 32, least squares mean (SE), letters	7.6 (0.8)	6.5 (0.8)
Least squares mean difference (95% CI)[a]	1.1 (−0.9 to 3.1)	
No. of participants with available assessment results at time point	219	215
Participants with <15 letter loss from baseline at week 32, No. (%)	214 (97.7)	208 (96.7)
Adjusted risk difference (95% CI)[b]	1.0 (−2.0 to 4.1)	
No. of participants with available assessment results at time point	219	215
Participants with ≥15 letter gain from baseline at week 32, No. (%)	48 (21.9)	40 (18.6)
Adjusted risk difference (95% CI)[b]	3.3 (−4.23 to 10.8)	
No. of participants with available assessment results at time point	220	220
Change in CST from baseline to week 4, least squares mean (SE), μm	−101.8 (4.3)	−112.9 (4.3)
Least squares mean difference (95% CI)[a]	11.1 (0.4 to 21.9)	
No. of participants with available assessment results at time point	216	212
Change in CST from baseline to week 32, least squares mean (SE), μm	−110.4 (4.7)	−115.7 (4.9)
Least squares mean difference (95% CI)[a]	5.4 (−6.7 to 17.4)	
No. of participants with available assessment results at time point	219	219
Change in TRT from baseline to week 4, least squares mean (SE), μm	−128.2 (5.4)	−132.9 (5.5)
Least squares mean difference (95% CI)[a]	4.6 (−9.0 to 18.3)	
No. of participants with available assessment results at time point	216	211
Change in TRT from baseline to week 32, least squares mean (SE), μm	−127.7 (7.4)	−131.9 (7.6)
Least squares mean difference (95% CI)[a]	4.3 (−14.4 to 22.9)	
No. of participants with available assessment results at time point	219	214
Participants with intraretinal or subretinal fluid at week 32, No. (%)	128 (58.4)	118 (55.1)
Adjusted risk difference (95% CI)[b]	3.2 (−6.0 to 12.5)	
No. of participants with available assessment results at time point	219	214
Participants with subretinal pigment epithelium fluid at week 32, No. (%)	68 (31.1)	64 (29.9)
No. of participants with available assessment results at time point	212	210
Participants with active CNV leakage at week 32, No. (%)	187 (88.2)	192 (91.4)
Adjusted risk difference (95% CI)[b]	−3.5 (−9.0 to 2.1)	
No. of participants with available assessment results at time point	208	208
Change in CNV size from baseline to week 32, least squares mean (SE), mm^2	−1.0 (0.2)	−0.4 (0.2)
Least squares mean difference (95% CI)[a]	−0.6 (−1.2 to −0.04)	
No. of participants with available assessment results at time point	179	190
Change in NEI VFQ-25 composite score from baseline at week 32, mean (SD)	3.1 (10.4)	2.8 (11.2)

Abbreviations: AFL, reference aflibercept; CNV, choroidal neovascularization; NEI VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire; SB15, aflibercept biosimilar candidate; TRT, total retinal thickness.

[a] Least squares mean difference was calculated with the analysis of covariance model with each baseline value as covariate and country and treatment groups as factors.

[b] The adjusted risk difference between groups was calculated using a stratified Cochran-Mantel-Haenszel test with a 95% Mantel-Haenszel CI with country as a factor.

[c] Data were not imputed for analysis.

32, the adjusted mean or mean changes in BCVA in these studies ranged from 5.0 to 8.0 letters. The similarity of our findings to these previous results further substantiates the herein reported data and supports generalization of the demonstrated equivalent efficacy between SB15 and AFL. Importantly, the equivalence of SB15 and AFL is supported by all other secondary efficacy end points. In addition, the safety profiles of SB15 and AFL were comparable and consistent with the already known safety profile of aflibercept, and no new safety concerns were identified.

The predose and postdose serum concentrations of SB15 and AFL were comparable, as demonstrated by the large coefficient of variation and overlapping error bars at postdose time points and the predominant below the limit of quantification results for serum trough concentrations. The below the limit of quantification results for serum trough concentrations agree with previous reports showing that aflibercept did not accumulate in plasma when administered as repeated doses.[23]

Near-maximum serum concentrations of free aflibercept in the plasma is expected to be attained within 1 to 3 days after intravitreal injection.[23] Hence, to securely detect near-maximum serum concentrations, blood sampling was conducted once per day for 3 consecutive days after intravitreal injection at week 24. Of note, mean near-maximum serum concentration measurements of SB15 were within the specified range for aflibercept[23] and much lower than the concentra-

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Table 3. Summary of Key Treatment-Emergent Adverse Events[k] (TEAEs) up to Week 32 (Safety Set)

Event	Participants, No. (%)		
	SB15 (n = 224)	AFL (n = 224)	Total (N = 448)
Any TEAEs	107 (47.8)	98 (43.8)	205 (45.8)
Ocular TEAEs in the study eye	41 (18.3)	28 (12.5)	69 (15.4)
Ocular TEAEs by preferred term in the study eye (>1% in any treatment group)			
Visual acuity reduced[a]	8 (3.6)	5 (2.2)	13 (2.9)
Conjunctival hemorrhage	9 (4.0)	3 (1.3)	12 (2.7)
Conjunctivitis	2 (0.9)	3 (1.3)	5 (1.1)
Disease progression[b]	2 (0.9)	3 (1.3)	5 (1.1)
Neovascular age-related macular degeneration[c]	2 (0.9)	3 (1.3)	5 (1.1)
Retinal hemorrhage[d]	3 (1.3)	1 (0.4)	4 (0.9)
Cataract[e]	0	4 (1.8)	4 (0.9)
Eye pain	3 (1.3)	0	3 (0.7)
Posterior capsule opacification	3 (1.3)	0	3 (0.7)
Drug-related ocular TEAEs in the study eye	3 (1.3)	1 (0.4)	4 (0.9)
Conjunctival hemorrhage	1 (0.4)	0	1 (0.2)
Macular hole	1 (0.4)	0	1 (0.2)
Retinal pigment epithelial tear	1 (0.4)	0	1 (0.2)
Iridocyclitis	0	1 (0.4)	1 (0.2)
Serious ocular TEAEs in the study eye	3 (1.3)	1 (0.4)	4 (0.9)
Device placement issue[f]	0	1 (0.4)	1 (0.2)
Disease progression[g]	1 (0.4)	0	1 (0.2)
Retinal hemorrhage[h]	1 (0.4)	0	1 (0.2)
Retinal vascular disorder[i]	1 (0.4)	0	1 (0.2)
Ocular TEAEs of special interest in the study eye	3 (1.3)	1 (0.4)	4 (0.9)
Intraocular inflammation	0	1 (0.4)	1 (0.2)
Iridocyclitis	0	1 (0.4)	1 (0.2)
Retinal pigment epithelial tear	1 (0.4)	0	1 (0.2)
Subretinal hemorrhage	2 (0.9)	0	2 (0.4)
Nonocular TEAEs	73 (32.6)	67 (29.9)	140 (31.3)
Drug-related nonocular TEAEs	0	1 (0.4)	1 (0.2)
Ischemic stroke	0	1 (0.4)	1 (0.2)
Serious nonocular TEAEs	8 (3.6)	14 (6.3)	22 (4.9)
Nonocular TEAEs of special interest	7 (3.1)	3 (1.3)	10 (2.2)
Arterial thromboembolic events[j]	4 (1.8)	2 (0.9)	6 (1.3)
Nonocular hemorrhage[j]	3 (1.3)	1 (0.4)	4 (0.9)
TEAEs leading to study treatment discontinuation	0	1 (0.4)	1 (0.2)
Chronic myelomonocytic leukemia	0	1 (0.4)	1 (0.2)
TEAEs leading to death	0	1 (0.4)	1 (0.2)
Circulatory collapse	0	1 (0.4)	1 (0.2)

Abbreviations: AFL, reference aflibercept; SB15, aflibercept biosimilar candidate.

[a] Visual acuity decrease due to unknown causes or visual acuity decrease reported separately from the cause of visual acuity decrease.

[b] Visual acuity decrease due to neovascular age-related macular degeneration progression.

[c] Worsening of neovascular age-related macular degeneration or visual acuity decrease due to neovascular age-related macular degeneration.

[d] Subretinal hemorrhage or visual acuity decrease due to subretinal hemorrhage.

[e] Includes the 2 preferred terms *cataract* and *cataract cortical*.

[f] Malposition of lacrimal cannula.

[g] Decrease in visual acuity of 30 letters from the last assessment due to disease progression.

[h] Subretinal hemorrhage.

[i] Decreased retinal blood flow.

[j] Preferred terms for arterial thromboembolic events and nonocular hemorrhage are available in eTable 3 in Supplement 2.

[k] Adverse events were assigned to system organ class and preferred term using Medical Dictionary for Regulatory Activities version 23.0 coding dictionary.

tion of aflibercept required to half-maximally bind systemic VEGF (2910 ng/mL).[24]

The incidence of antidrug antibody positivity was similarly low for both SB15 and AFL at baseline and increased only slightly after treatment administration. Accordingly, also the cumulative incidence of participants who were antidrug antibody positive was low and comparable between groups. This finding is in agreement with the aflibercept US prescribing information.[23] Of note, in the presented study, no intraocular inflammation was reported for participants who were antidrug antibody positive, and no participant in the pharmacokinetic analysis set had a positive antidrug antibody result up to week 32. Hence, the impact of immunogenicity on pharmacokinetics could not be assessed.

Limitations

A potential limitation of this study is the lack of racial diversity, with most enrolled participants being either Asian or White. Furthermore, this report presents the results of the 32-week parallel-group period of the phase 3 study. To provide long-term evidence and allow the assessment of switching from AFL to SB15, 56-week results, including 24 weeks after switching, are being collected and will be presented when available.

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Conclusions

This 32-week interim analysis of a phase 3 randomized clinical demonstrated equivalent efficacy and comparable safety, pharmacokinetics, and immunogenicity between SB15 and AFL in participants with treatment-naive nAMD. The presented results form part of scientific evidence to support the establishment of biosimilarity between SB15 and AFL.

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