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Efficacy and Safety of a Proposed Ranibizumab Biosimilar Product vs a Reference Ranibizumab Product for Patients With Neovascular Age-Related Macular Degeneration
A Randomized Clinical Trial

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IMPORTANCE Neovascular age-related macular degeneration is the leading cause of blindness in individuals 50 years or older. The availability of a ranibizumab biosimilar product (SB11) may facilitate access to an effective alternative to this treatment.

OBJECTIVE To demonstrate equivalence of efficacy, similar safety, and similar immunogenicity of SB11 compared with the reference ranibizumab.

DESIGN, SETTING, AND PARTICIPANTS This randomized, double-masked, parallel-group phase 3 equivalence study was conducted in 75 centers in 9 countries from March 14, 2018, to December 9, 2019, among 705 participants 50 years or older with neovascular age-related macular degeneration with active subfoveal choroidal neovascularization lesions. Analysis was performed on an intent-to-treat basis.

INTERVENTIONS Intravitreous injection of SB11 or ranibizumab, 0.5 mg, every 4 weeks through week 48.

MAIN OUTCOMES AND MEASURES Preplanned interim analysis after all participants completed the week 24 assessment of primary efficacy end points at week 8 for change from baseline in best-corrected visual acuity (BCVA) and week 4 for central subfield thickness (CST), with predefined equivalence margins for adjusted treatment differences of −3 letters to 3 letters for BCVA and −36 µm to 36 µm for CST.

RESULTS Baseline and disease characteristics among 705 randomized participants (403 women [57.2%]; mean [SD] age, 74.1 [8.5] years) were comparable between treatment groups (SB11, 351; ranibizumab, 354). Least-squares mean (SE) changes in BCVA from baseline at week 8 were 6.2 (0.5) letters in the SB11 group vs 7.0 (0.5) letters in the ranibizumab group, with an adjusted treatment difference of −0.8 letter (90% CI, −1.8 to 0.2 letters). Least-squares mean (SE) changes in CST from baseline at week 4 were −108 (5) µm in the SB11 group vs −100 (5) µm in the ranibizumab group, with an adjusted treatment difference of −8 µm (95% CI, −19 to 3 µm). Incidences of treatment-emergent adverse events (231 of 350 [66.0%] vs 237 of 354 [66.9%]), including serious treatment-emergent adverse events (44 of 350 [12.6%] vs 44 of 354 [12.4%]) and treatment-emergent adverse events leading to study drug discontinuation (8 of 350 [2.3%] vs 5 of 354 [1.4%]), were similar in the SB11 and ranibizumab groups. Immunogenicity was low, with a cumulative incidence of antidrug antibodies up to week 24 of 3.0% (10 of 330) in the SB11 group and 3.1% (10 of 327) in the ranibizumab group.

CONCLUSIONS AND RELEVANCE These findings of equivalent efficacy and similar safety and immunogenicity profiles compared with ranibizumab support the use of SB11 for patients with neovascular age-related macular degeneration.

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Supplemental content

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Vascular endothelial growth factor-A (VEGF-A) is the principal target for treatment of neovascular age-related macular degeneration (nAMD), and VEGF-A inhibitors are currently the standard of care for most cases of newly occurring, symptomatic nAMD.[1-7] Ranibizumab, a recombinant, humanized, monoclonal antibody fragment that binds to and neutralizes active isoforms of VEGF-A,[1,3] has been approved for the treatment of nAMD by the US Food and Drug Administration (FDA) since 2006[8] and the European Medicines Agency (EMA) since 2007.[9] However, the relatively high cost of ranibizumab and other approved agents likely limits some patient access to these treatments.[1,10] Biosimilar products are highly similar to an approved reference biological product; that is, there are no clinically meaningful differences in terms of efficacy, safety, and immunogenicity.[11-16] The FDA has provided explanations on biosimilar products, including differences between biosimilar and interchangeable products and between biosimilar products and generic drugs.[17] Even though biosimilar products and generic drugs are approved through different abbreviated pathways to prove equivalence in efficacy with an acceptable safety profile as judged by regulatory agency personnel, biosimilar products are different from generic drugs in that active ingredients of generic drugs are the same as those of their respective brand-name drugs, whereas approved biosimilar products are highly similar or equivalent to their reference product except for minor differences in clinically inactive components.[17]

SB11 is a proposed ranibizumab biosimilar product demonstrating similarity to the reference product in extensive analytical and nonclinical analyses. Phase 1 studies have not been conducted because of limited relevance of pharmacokinetics (PK) and intravitreous administration with limited absorption into systemic circulation. This phase 3 randomized clinical study compared SB11 with its reference ranibizumab product for efficacy, safety, and immunogenicity.

Key Points

Question Does SB11, a proposed ranibizumab biosimilar product, have equivalent best-corrected visual acuity (BCVA) and optical coherence tomography central subfield thickness (CST) outcomes and a similar safety profile to the reference ranibizumab product in patients with neovascular age-related macular degeneration?

Findings This randomized clinical equivalence trial found that SB11 demonstrated equivalence in efficacy for both primary end points: adjusted treatment differences between groups were within predefined equivalence margins for mean changes from baseline in both BCVA at week 8 and CST at week 4. Safety and immunogenicity profiles were similar between SB11 and ranibizumab.

Meaning These results indicate that SB11 is similar to its reference product, ranibizumab.

Methods

Study Design

This randomized, double-masked, parallel-group, multicenter phase 3 equivalence study was conducted in 75 centers in 9 countries from March 14, 2018, to December 9, 2019, with an interim analysis performed in May 2019. The clinical study protocol and protocol amendment were reviewed and approved by an independent ethics committee or institutional review board at each clinical site (eAppendix 2 in Supplement 1). This study was conducted in compliance with the International Council for Harmonization and Good Clinical Practice guidelines and the Declaration of Helsinki.[18] A written informed consent form was signed by each patient before entering the study to document the consent process. The trial protocol, including the statistical analysis plan, is available in Supplement 2; no protocol amendments occurred after study initiation. Study participants did not receive any compensation or incentives to participate.

This article reports the results of a preplanned analysis of primary efficacy outcomes, secondary efficacy outcomes, PK data, and immunogenicity data through week 24. Safety analyses include data to week 52, as available.

Participants

Participants were 50 years or older and had untreated subfoveal, choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye, with evidence of activity as documented on optical coherence tomography by the presence of subretinal fluid, intraretinal fluid, retinal pigmented epithelium detachment, or, alternatively, leakage from CNV detected by fluorescein angiography. Best-corrected visual acuity (BCVA) (approximate Snellen equivalent) letter score was 73 (20/40) to 34 (20/200) using original series Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Total lesion area was 9.0 disc areas or less (approximate equivalent, 22.9 mm^2 or less) including areas of blood, scar, and neovascularization. Individuals were excluded if they had subretinal or intraretinal hemorrhage comprising more than 50% of the entire lesion or presence of subfoveal blood of 1 disc area or more in size; had scar, fibrosis, or atrophy that involved the center of the fovea in the study eye; had CNV in either eye due to causes other than AMD; had any concurrent macular abnormality in the study eye other than AMD; had previously received any intravitreous injection of anti-VEGF-A treatment for nAMD in either eye; or had previous treatment with photodynamic therapy or other therapies not allowed during the study period. If both eyes were eligible, 1 eye was designated the study eye as chosen by the investigator with consent of the study participant. The full list of eligibility criteria is in eAppendix 1 in Supplement 1.

Intervention

Participants received an intravitreous injection in the study eye of either 0.5 mg of SB11 (Samsung Bioepis; provided as a ready-to-use formulation) or 0.5 mg of ranibizumab (Lucentis; Genentech) in 0.05 mL every 4 weeks through week 48 (total of 13 doses for those who completed the study). If

warranted, fellow eyes could receive anti-VEGF-A treatment as part of standard care. If the fellow eye received ranibizumab for nAMD during the study period after randomization, the antidrug antibody (ADA) and neutralizing antibody results obtained after treatment for the fellow eye were listed but excluded from the summary statistics.

Randomization and Masking

Participants were randomized 1:1 to receive SB11 or ranibizumab by means of a randomization list produced by a validated, interactive web recognition system. Randomization blocks (fixed size = 4) were allocated to each study site, no stratification was used, and participants were enrolled by the site investigator and assigned to interventions through the interactive web recognition system. Participants, investigators, and site personnel remained masked throughout the study except for staff designated to be unmasked for reporting of the interim analysis.

Outcomes

Primary End Points

For the FDA, the Korea Ministry of Food and Drug Safety, and other regulatory agencies in favor of visual acuity (VA) as the primary end point measure, the primary end point was change from baseline in BCVA at week 8. Visual acuity was assessed by a certified examiner at the investigational site using either the original series ETDRS charts or 2702 series number charts for a participant throughout the study at a starting distance of 4 m, with a repetition at 1 m if necessary. Visual acuity testing was performed before dilation of pupils, fundus photography or fluorescein angiography, and optical coherence tomography assessment. For the EMA and other regulatory agencies in favor of anatomical parameters, the primary end point was change from baseline in central subfield thickness (CST) at week 4. Central subfield thickness measurements were taken with optical coherence tomography devices registered by the central reading center and analyzed centrally.

Secondary End Points

Secondary efficacy end points included change from baseline in BCVA through week 24 and proportions of participants who lost less than 15 letters and gained 15 letters or more in BCVA from baseline at week 24. Secondary efficacy end points included change from baseline in CST and central retinal lesion thickness at week 24, as well as change from baseline in CNV size and proportion of participants with active CNV leakage at week 24. Best-corrected visual acuity was assessed at the investigational site; CST, central retinal lesion thickness, CNV size, and leakage were assessed centrally.

Safety

Reported adverse events (AEs) included ocular AEs in the study and fellow eyes as well as nonocular AEs, coded based on the Medical Dictionary for Regulatory Activities, version 20.1,[19] and were recorded from signature of informed consent until week 52 (end of study visit) or early termination visit. Adverse events of special interest were any case of new-onset intraocular pressure of more than 21 mm Hg unresponsive to treatment except the transient pressure increase observed within 1 hour after intravitreous injection of study drug; any case of intraocular pressure of 35 mm Hg or more at any time; any case of intraocular infection, such as endophthalmitis; any case of intraocular inflammation such as iritis, vitritis, and iridocyclitis; arterial thromboembolic events, defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause); and iatrogenic traumatic cataract.

Immunogenicity

Immunogenicity analyses were performed on blood samples collected prior to intravitreous injection of the investigational product at weeks 0, 1, 4, 8, 16, 24, 36, and 52. A single-assay approach with an SB11 tag was used to assess immunogenicity. Antidrug antibodies were measured using validated bridging electrochemiluminescence immunoassays, and neutralizing antibodies were measured using a competitive ligand-binding assay.[20]

Statistical Analysis

Equivalence Margins

Equivalence margins were determined using historical data by calculating a fixed-effect meta-analysis of the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD)[21] and FOCUS (RhuFab V2 Ocular Treatment Combining the Use of Visudayne to Evaluate Safety)[22] studies for BCVA and MARINA[21] and PIER (Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection–Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects With Subfoveal CNV With or Without Classic CNV Secondary to AMD)[23] studies for CST. For BCVA, calculated weighted mean change at week 24 was 12.4 letters (95% CI, 10.3-14.5 letters), corresponding to 4.9 letters at week 24 when adjusted to predefined equivalence limits of −3 to 3 letters for the 90% CI of the difference between groups for least-squares mean change from baseline at week 8. For CST, calculated weighted mean change in CST was −110 µm (95% CI, −146 to −73 µm), with an estimated equivalence limit of −36 µm to 36 µm at week 4.

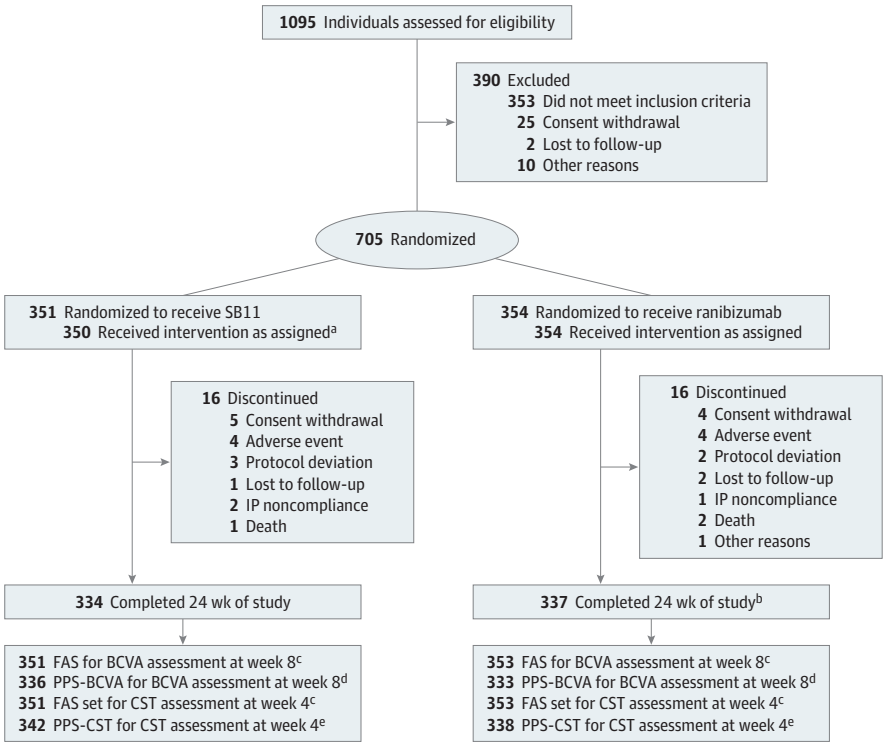
Sample Size

Based on historical data, selected equivalence margins, and an assumed 5% loss of randomized participants, 352 participants were calculated per treatment group for each primary end point to achieve a 5% significance level and 80% power to establish equivalence.

Analysis Sets

The full analysis set (FAS) included all randomized participants, excluding 1 inadvertently randomized participant who did not receive the study drug. The per-protocol set (PPS) for BCVA (PPS-BCVA) included participants who had received the first 2 study drug injections and completed the procedures at week 8 without any major protocol deviation

Figure 1. CONSORT Diagram of Participant Flow Through the Trial



Primary end point analysis groups are indicated in the bottom 2 boxes. BCVA indicates best-corrected visual acuity; CST, central subfield thickness; FAS, full analysis set; IP, investigational product; PPS, per-protocol set; and SB11, ranibizumab biosimilar product.

[a] One participant was incorrectly randomized and did not receive any IP. This participant was excluded from the FAS.

[b] Available data as of the cutoff date in May 2019. Missing participants are classified as neither discontinued nor completed the study.

[c] Including all randomized participants except the participant who was inadvertently randomized and did not receive IP injection.

[d] Including participants in the FAS who had received the first 2 study drug injections and completed the procedures at week 8 without any major protocol deviation that affected BCVA assessment.

[e] Including participants in the FAS who had received the first study drug injection and completed the procedures at week 4 without any major protocol deviation that affected CST measurement.

affecting BCVA assessment. The PPS for CST (PPS-CST) included participants who had received the first study injection and completed procedures at week 4 without any major protocol deviation of CST measurement. The secondary outcomes in BCVA and CST through week 24 were analyzed in the FAS and PPS-BCVA and in the FAS and PPS-CST, respectively. Central retinal lesion thickness, CNV size, and CNV leakage, as well as the proportions of participants who lost less than 15 letters in BCVA and gained 15 or more letters in BCVA compared with baseline, were analyzed in the FAS. The safety set consisted of all participants who received at least 1 administration of study drug during the period after randomization. The PK analysis set included participants who had at least 1 PK sample analyzed.

Primary Efficacy Analysis

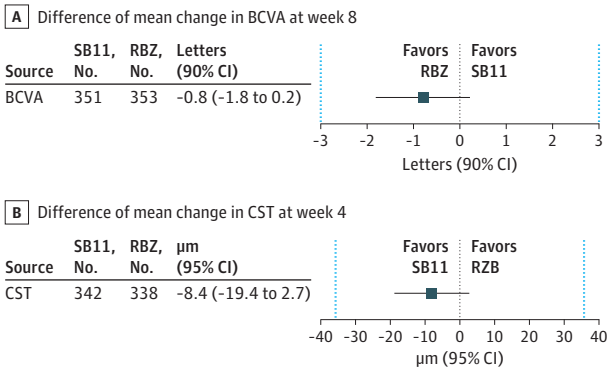
Statistical evaluation of both primary end points was based on analysis of covariance, with baseline BCVA or CST as a covariate and region (country) and treatment group as factors. Equivalence was declared if the 2-sided 90% or 95% CIs for the adjusted treatment difference for BCVA or CST, respectively, were within the predefined equivalence margins. All *P* values were from 2-sided tests, and results were deemed statistically significant at $P < .05$, with no adjustments for multiple analyses. Analyses were performed using SAS software, version 9.3 (SAS Institute Inc) between July 19 and September 2, 2019.

Results

Disposition of Participants

From March 14 to November 29, 2018, 1095 participants were screened; 705 were randomized to receive SB11 (n = 351) or ranibizumab (n = 354). An intent-to-treat analysis for primary outcomes included all but 1 participant inadvertently randomized to the SB11 group but subsequently deemed ineligible and not receiving injections. Thus, 704 participants received at least 1 intravitreous injection and 671 (95.2%) participants completed week 24 (SB11, 334; ranibizumab, 337). Reasons for study drug discontinuations are shown in **Figure 1.** At the data cutoff (May 24, 2019), 112 (15.9%) participants completed week 52 (SB11, 53 of 351 [15.1%]; ranibizumab, 59 of 354 [16.7%]).

Figure 2. Primary Efficacy End Points: Difference of Mean Change in Best-Corrected Visual Acuity (BCVA) and Central Subfield Thickness (CST) Between SB11 and Reference Ranibizumab (RBZ)



A, Difference of mean change from baseline in BCVA at week 8 (SB11 − RBZ); whiskers represent the 90% CI that is contained within the predefined equivalence margins of −3 to 3 letters, represented by the dashed lines. There was a total of 10 people missing BCVA data (5 from SB11 and 5 from RBZ); the missing data were imputed. B, Difference of mean change from baseline in CST at week 4 (SB11 − RBZ); whiskers represent the 95% CI that is contained within the predefined equivalence margin of −36 to 36 μm, represented by the dashed lines. Inferential statistics were based on an analysis of covariance model with the baseline BCVA or CST as a covariate and region (country) and treatment as fixed factors.

Participant Demographics and Baseline Characteristics

Baseline demographic and disease characteristics were similar between treatment groups (eTable 5 in Supplement 1). The mean (SD) age was 74.1 (8.5) years, most participants (597 [84.7%]) were White, and 403 (57.2%) were female. The mean (SD) BCVA letter score was 58.3 (10.6) letters (approximate Snellen equivalent = 20/80) and the mean (SD) CST was 408 (118) μm. Overall, 55 participants (7.8%) had classic CNV without occult CNV, 239 (33.9%) had features of both classic and occult CNV, and 410 (58.2%) had occult CNV with no classic CNV on fluorescein angiography. The mean (SD) CNV area at baseline was 8.1 (5.1) mm^2.

Primary Efficacy End Points

The least-squares mean (SE) changes in BCVA (**Figure 2**) from baseline at week 8 were 6.2 (0.5) letters in the SB11 group (n = 351) and 7.0 (0.5) letters in the ranibizumab group (n = 353); the adjusted treatment difference between groups was −0.8 letters (90% CI, −1.8 to 0.2 letters). The least-squares mean (SE) changes in CST (Figure 2) from baseline at week 4 were −108 (5) μm in the SB11 group (n = 342) and −100 (5) μm in the ranibizumab group (n = 338); the adjusted treatment difference was −8 μm (95% CI, −19 to 3 μm). Consistent results for change from baseline in BCVA at week 8 in the PPS-BCVA population (eTable 1 in Supplement 1) as well as change from baseline in CST at week 4 in the FAS (eTable 2 in Supplement 1) were achieved.

Secondary Efficacy End Points

Secondary efficacy end points at week 24 showed similar results between treatment groups for change from baseline in BCVA (FAS), change in CST from baseline (PPS-CST), change in central retinal lesion thickness (FAS), and change from baseline in total CNV (FAS) (**Table 1** and **Table 2**). Changes in BCVA in the FAS and CST in the PPS-CST at all times to week 24 were comparable between treatment groups (eFigure 1 and eFigure 2 in Supplement 1). Furthermore, similar proportions of participants lost less than 15 letters, gained 15 or more letters, or had active CNV leakage at week 24 (Table 1 and Table 2).

Safety

Exposure was similar between the SB11 (n = 350) and ranibizumab (n = 354) groups, including the mean (SD) number of study drug administrations (10.0 [2.6] vs 10.3 [2.5]) and median duration of study drug exposure (254.0 days [minimum, 1 day; maximum, 351 days] vs 278.5 days [minimum, 1 day; maximum, 361 days]). Incidence of AEs, including treatment-emergent AEs (TEAEs) and serious TEAEs leading to study drug discontinuation and death, was similar between the SB11 and ranibizumab groups (TEAEs, 231 of 350 [66.0%] vs 237 of 354 [66.9%]; serious TEAEs, 44 of 350 [12.6%] vs 44 of 354 [12.4%]; and TEAEs leading to study drug discontinuation and death, 8 of 350 [2.3%] vs 5 of 354 [1.4%]) (**Table 3**). Most TEAEs were mild and considered not related to the study drug. The only ocular TEAE in the study eye occurring in ≥5% of participants was "intraocular pressure increased" (SB11, 22 of 350 [6.3%] vs ranibizumab, 21 of 354 [5.9%]); no study participants in the SB11 group had new-onset intraocular pressure of more than 21 mm Hg compared with 3 (0.8%) in the reference product ranibizumab group. The most common nonocular TEAEs were nasopharyngitis (SB11, 33 of 350 [9.4%] vs ranibizumab, 34 of 354 [9.6%]) and hypertension (SB11, 16 of 350 [4.6%] vs ranibizumab, 23 of 354 [6.5%]). Incidence of AEs of special interest was comparable between treatment groups; most frequently reported AEs of special interest were increased intraocular pressure (SB11, 1 [0.3%]; ranibizumab, 6 [1.7%]) and iridocyclitis (SB11, 3 [0.9%]).

Immunogenicity and Pharmacokinetics

The cumulative incidence of ADAs up to week 24 was low and similar between treatment groups (SB11, 10 of 330 [3.0%]; ranibizumab, 10 of 327 [3.1%]). A minority of ADA-positive participants had neutralizing antibodies (eTable 4 in Supplement 1). The incidence of ADAs and neutralizing antibodies by visit to week 24 was similar between treatment groups (eTable 4 in Supplement 1). The PK analysis (SB11, 25 participants; ranibizumab, 29 participants) is summarized in eFigure 3 and eTable 3 in Supplement 1). Only 3 participants in the PK analysis set were ADA positive, preventing an assessment of the effect of immunogenicity on PK.

Discussion

This study met its primary end points, demonstrating equivalence in efficacy between the proposed biosimilar product intravitreous SB11 and ranibizumab when administered every 4 weeks for the treatment of nAMD. Both the adjusted treatment differences between the treatment groups for change

Table 1. Secondary Efficacy End Point Measurements at Week 24

End point at week 24 (analysis set)	Treatment	No.	Change from baseline, least-squares mean (SE)	Difference (SB11 − RBZ)	
				Mean (SE)	95% CI (90% CI for BCVA)
BCVA (letters)[a]	SB11 (N = 351)	334	8.6 (0.7)	−0.8 (0.8)	−2.0 to 0.5
FAS	RBZ (N = 353)	338	9.3 (0.6)		
CST (μm)	SB11 (N = 342)	324	−136 (4)	−10 (5)	−19 to −0
PPS-CST	RBZ (N = 338)	324	−126 (4)		
CRLT (μm)[b]	SB11 (N = 351)	329	−148 (5)	−10 (6)	−21 to 2
FAS	RBZ (N = 353)	335	−139 (5)		
CNV size (mm^2)[c]	SB11 (N = 351)	326	−4 (0)	0	−1 to 1
FAS	RBZ (N = 353)	329	−4 (0)		

Abbreviations: BCVA, best-corrected visual acuity (letter score); CNV, choroidal neovascularization; CRLT, central retinal lesion thickness; CST, central subfield thickness; FAS, full analysis set; PPS-CST, per-protocol set for central subfield thickness; RBZ, reference ranibizumab.

[a] Inferential statistics were based on an analysis of covariance model, with the baseline BCVA as a covariate and region (country) and treatment as fixed factors.

[b] Inferential statistics were based on an analysis of covariance model, with the baseline CRLT as a covariate and region (country) and treatment as fixed factors.

[c] Inferential statistics were based on an analysis of covariance model, with the baseline total CNV size as a covariate and region (country) and treatment group as fixed factors.

Table 2. Dichotomous Secondary Efficacy End Point Measurements at Week 24

End point at week 24 (analysis set)	Treatment	No.	Responders, No. (%)	Adjusted difference (SB11 − RBZ) (%) (95% CI)
Participants who lost <15 letters in BCVA compared with baseline[a]	SB11 (N = 351)	334	327 (97.9)	−1.5 (−3.3 to 0.2)
FAS	RBZ (N = 353)	338	336 (99.4)	
Participants who gained ≥15 letters in BCVA compared with baseline[a]	SB11 (N = 351)	334	86 (25.7)	−1.7 (−8.3 to 5.0)
FAS	RBZ (N = 353)	338	92 (27.2)	
Participants with active CNV leakage[a]	SB11 (N = 351)	326	211 (64.7)	−1.7 (−8.9 to 5.5)
FAS	RBZ (N = 353)	329	218 (66.3)	

Abbreviations: BCVA, best-corrected visual acuity (letter score); CNV, choroidal neovascularization; FAS, full analysis set; RBZ, reference ranibizumab.

[a] The adjusted difference and its 95% CI were analyzed by a stratified Cochran-Mantel-Haenszel test with region (country) as a factor.

from baseline in BCVA at week 8 and change from baseline in CST at week 4 were within the predefined equivalence margins. Secondary end points assessed at week 24 consistently supported equivalent efficacy between SB11 and ranibizumab. Furthermore, sensitivity analyses of the primary end points showed similar robust equivalency results for the change from baseline in BCVA at week 8 and for the change from baseline in CST at week 4.

In addition, safety, PK, and immunogenicity profiles appeared comparable between treatment groups. Observed TEAEs were consistent with ranibizumab's safety profile, including ocular TEAEs related to monthly intravitreous administration as well as some nonocular AEs associated with systemic VEGF-A inhibition including hypertension, arterial thromboembolic events, nonocular hemorrhage, and proteinuria. The cumulative incidence of ADAs was consistent with the experience with ranibizumab.[21,24,25] The maximum serum concentrations of ranibizumab in both treatment groups through week 52 in individual participants (SB11, 6.67 ng/mL at week 24 after dose; ranibizumab, 2.78 ng/mL at week 8 after dose) were below the concentration range of ranibizumab necessary to inhibit the biological activity of VEGF-A by 50% (11-27 ng/mL).[25] Given the low systemic exposure to SB11 and in line with the reference product, only limited unintended effects due to systemic VEGF-A inhibition are expected.

The functional end point VA is commonly used in clinical studies in individuals with nAMD, although it is associated with some variability in individual disease progression. Mean change from baseline in VA at week 8 detects both improvement and deterioration of disease status and enables analysis before the efficacy plateau is reached and therefore represents a sensitive primary end point for detecting a potential difference between 2 treatments. The anatomical end point change from baseline in CST is associated with endothelial proliferation, vascular leakage, and new blood vessel formation and thus reflects the pharmacodynamic activity of VEGF-A inhibition. Furthermore, it was shown that a mean decrease of CST correlates with a subsequent improvement in mean VA, although visual recovery in an individual after resolution of macular fluid likely depends on many variables.[26,27]

With both primary end points met, equivalent efficacy between SB11 and ranibizumab was demonstrated, contributing to the totality of evidence for biosimilarity. Pharmacokinetic analysis in the vitreous has not been performed because sampling of vitreous fluid was judged as not feasible.

The generalizability of the results from this study is supported by its consistency with those of previous studies of ranibizumab. Specifically, mean changes from baseline in BCVA at week 24 were 9.3 letters compared with 6.5 letters in the MARINA study,[21] 10.6 letters in the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) study,[24] 6.6 letters in the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) study,[28] and approximately 9 letters

Table 3. Summary of All Adverse Events in the Safety-Set Population

Adverse event[a]	Participants, No. (%)[b]		
	SB11 (n = 350)	RBZ (n = 354)	Total (N = 704)
TEAEs			
Any TEAE	231 (66.0)	237 (66.9)	468 (66.5)
Ocular TEAEs in the study eye	97 (27.7)	91 (25.7)	188 (26.7)
Ocular TEAEs in the fellow eye	69 (19.7)	61 (17.2)	130 (18.5)
Nonocular TEAEs	178 (50.9)	191 (54.0)	369 (52.4)
Serious TEAEs	44 (12.6)	44 (12.4)	88 (12.5)
TEAEs by severity			
Mild TEAEs	109 (31.1)	119 (33.6)	228 (32.4)
Moderate TEAEs	95 (27.1)	97 (27.4)	192 (27.3)
Severe TEAEs	27 (7.7)	21 (5.9)	48 (6.8)
TEAEs by relatedness			
Related TEAEs	21 (6.0)	10 (2.8)	31 (4.4)
Not related TEAEs	210 (60.0)	227 (64.1)	437 (62.1)
SAEs			
Any SAE	45 (12.9)	45 (12.7)	90 (12.8)
Related SAEs	6 (1.7)	3 (0.8)	9 (1.3)
Not related SAEs	39 (11.1)	42 (11.9)	81 (11.5)
Serious ocular AE in the study eye by PT			
Any ocular SAE in the study eye	9 (2.6)	7 (2.0)	16 (2.3)
Visual acuity reduced	2 (0.6)	1 (0.3)	3 (0.4)
Endophthalmitis	2 (0.6)	0	2 (0.3)
Cataract	1 (0.3)	0	1 (0.1)
Iridocyclitis	1 (0.3)	0	1 (0.1)
Macular edema	1 (0.3)	1 (0.3)	2 (0.3)
Retinal hemorrhage	1 (0.3)	1 (0.3)	2 (0.3)
Retinal pigment epithelial tear	1 (0.3)	0	1 (0.1)
Subretinal fluid	1 (0.3)	0	1 (0.1)
Vitritis	1 (0.3)	0	1 (0.1)
Cataract subcapsular	0	1 (0.3)	1 (0.1)
Macular degeneration	0	2 (0.6)	2 (0.3)
Serious ocular AE in the fellow eye by PT			
Any ocular SAE in the fellow eye	3 (0.9)	1 (0.3)	4 (0.6)
Retinal hemorrhage	2 (0.6)	0	2 (0.3)
Visual acuity reduced	1 (0.3)	0	1 (0.1)
Vitreous hemorrhage	1 (0.3)	0	1 (0.1)
Retinal artery occlusion	0	1 (0.3)	1 (0.1)
Serious nonocular AE (≥0.5%) by PT			
Any nonocular SAE	35 (10.0)	37 (10.5)	72 (10.2)
Atrial fibrillation	3 (0.9)	3 (0.8)	6 (0.9)
Cardiac failure, congestive	2 (0.6)	2 (0.6)	4 (0.6)
Acute kidney injury	2 (0.6)	1 (0.3)	3 (0.4)
Chronic obstructive pulmonary disease	2 (0.6)	0	2 (0.3)
AESI	5 (1.4)	8 (2.3)	13 (1.8)
TEAEs leading to IP discontinuation			
Any TEAEs leading to IP discontinuation	8 (2.3)	5 (1.4)	13 (1.8)
Ocular TEAEs leading to IP discontinuation in the study eye	6 (1.7)	4 (1.1)	10 (1.4)
Ocular TEAEs leading to IP discontinuation in the fellow eye	0	0	0
Nonocular TEAEs leading to IP discontinuation	2 (0.6)	1 (0.3)	3 (0.4)
Deaths	1 (0.3)	4 (1.1)	5 (0.7)

Abbreviations: AE, adverse event; AESI, adverse event of special interest; IP, investigational product; PT, photodynamic therapy; RBZ, reference ranibizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] Adverse events were coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, version 20.1. If a participant had multiple events with different severity (or causality), then the participant was counted only once at the worst severity (or worst causality [ie, related]) for the number of participants.

[b] Percentages are based on the number of participants in the safety set.

in the HARBOR (The Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis [PRN] in Patients

With Subfoveal Neovascular Age-Related Macular Degeneration) study.[29] In addition, mean changes from baseline in CST at week 24 were −100 µm compared with approximately −160 µm in the HARBOR study.[29]

In nAMD, evidence from clinical practice settings shows that patients may be undertreated and receive fewer injections of anti-VEGF-A therapy than recommended whether following a fixed-dose, as-needed, or treat-and-extend regimen, resulting in lower efficacy than observed in the clinical trial setting.[30-33] Biosimilar products can contribute to cost savings in health care systems and facilitate patients' access to therapy.[34-37] Therefore, a safe and effective biosimilar product of ranibizumab may reduce some restrictions that are currently imposed by health care providers or payors and allow patients to have a greater chance of receiving an effective treatment regimen.

Limitations

This study has some limitations, including that the primary outcome and safety results are from a relatively short period through 24 weeks. Longer-term data are needed. We intend to report a final analysis that includes secondary efficacy and safety results through week 52. Currently, data analysis is ongoing, and these results will be reported separately.

Conclusions

The proposed ranibizumab biosimilar product SB11 demonstrated equivalent efficacy compared with ranibizumab in participants with nAMD. Furthermore, SB11 demonstrated similar safety and immunogenicity profiles, supporting its use as a proposed ranibizumab biosimilar product.

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