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Immunogenicity With Ranibizumab Biosimilar SB11 (Byooviz) and Reference Product Lucentis and Association With Efficacy, Safety, and Pharmacokinetics

A Post Hoc Analysis of a Phase 3 Randomized Clinical Trial

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IMPORTANCE SB11 and reference ranibizumab (RBZ) are monoclonal anti–vascular endothelial growth factor (VEGF)–A antibodies approved for the treatment of neovascular age-related macular degeneration (nAMD) and other retinal diseases. The association of ranibizumab immunogenicity and treatment outcomes in patients with nAMD is unclear but relevant regarding concerns about immunogenicity of anti-VEGF biological products.

OBJECTIVE To examine the association of immunogenicity to ranibizumab products (SB11 and RBZ) with efficacy, safety, and pharmacokinetics.

DESIGN, SETTING, AND PARTICIPANTS This was a post hoc analysis of a randomized, double-masked, parallel-group phase 3 equivalence study with participants from 75 centers in 9 countries conducted from March 14, 2018, to December 9, 2019. Included were participants 50 years or older with nAMD and active subfoveal choroidal neovascularization lesions.

INTERVENTIONS Intravitreal injection of SB11 or RBZ, 0.5 mg, every 4 weeks through week 48.

MAIN OUTCOMES AND MEASURES Serum antidrug antibodies (ADAs) were analyzed during the study period until week 52 to measure immunogenicity. Analyses were performed on immunogenicity (overall ADA positivity) with best-corrected visual acuity (BCVA) and central subfield thickness (CST). Adverse events associated with intraocular inflammation (IOI) and serum ranibizumab levels were compared between overall ADA-positive and ADA-negative participants.

RESULTS A total of 705 participants (mean [SD] age, 74.1 [8.5] years; 403 female individuals [57.2%]) were included in the study. The overall incidence of ADA-positivity was 32 of 657 (4.9%) at week 52. The least-squares mean (SE) differences between overall ADA-positive and ADA-negative participants up to week 52 for BCVA and CST, respectively, were 1.6 (2.2) letters (95% CI, −2.7 to 5.8; $P = .46$) and 3 (13) µm (95% CI, −23 to 29; $P = .83$). IOI-related events occurred in 1 of 32 overall ADA-positive participants (3.1%) and 4 of 620 overall ADA-negative participants (0.6%). Mean (SD) serum ranibizumab concentrations over time were slightly lower in overall ADA-positive participants compared with those of ADA-negative participants, with a maximum value of 1389.3 (875.4) pg/mL at week 16 vs 1665.4 (1124.0) pg/mL at week 36, respectively.

CONCLUSIONS AND RELEVANCE Results of this post hoc analysis of an equivalence trial suggest that immunogenicity was not associated with efficacy and safety of SB11 and RBZ in participants with nAMD. With a low overall ADA incidence, no clear association was identified between overall ADA positivity and pharmacokinetics. These findings support the biosimilarity of SB11 and RBZ, with no safety concern identified for SB11 vs RBZ associated with immunogenicity.

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Supplemental content

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Therapeutic biologic agents (biologics) targeting vascular endothelial growth factor A (VEGF-A) are currently the main pharmaceutical treatment option for patients with neovascular age-related macular degeneration (nAMD).[1] Despite their treatment success, biologics can incite immune responses (ie, immunogenicity) against themselves, which can lead to the production of antidrug antibodies (ADAs).[2,3] Some ADAs with specificity to the antigen-binding site have a neutralizing effect.[4] Such neutralizing ADAs (NAb) may alter pharmacokinetic (PK) properties and impair drug efficacy.[5] Furthermore, ADAs may increase the likelihood for hypersensitivity or other adverse events and thus potentially affect the safety profile of the biologic.[6]

Ranibizumab-nuna (Byooviz) (SB11; Samsung Bioepis) is a biosimilar of ranibizumab (Lucentis) (RBZ; trademark of Genentech Inc).[7] Biosimilars are biologics that are highly similar and without clinically relevant differences in quality, PK, efficacy, or safety profiles compared with the reference product based on the comprehensive comparability exercise.[8-14] Equivalent efficacy of SB11 in study participants with nAMD was demonstrated in a head-to-head comparison at each visit through 52 weeks of treatment.[15] SB11 was approved by the European Commission on August 18, 2021, and by the US Food and Drug Administration (FDA) on September 17, 2021, for the treatment of nAMD and other retinal diseases.[16,17]

Based on historical RBZ data, ADA were present in approximately 1% to 9% of participants after a treatment period of 6 to 24 months compared with baseline values (preexisting ADA) of approximately 0% to 5%.[18] The observation that some of the participants with the highest ADA levels developed vitritis or iritis led to concerns about a potential association between the immunogenicity of RBZ and a propensity for intraocular inflammation (IOI).[18,19] If such an association indeed exists, it is unclear whether ADA are the consequence of inflammatory changes in the eye or vice versa.

To date, the potential association of immunogenicity of ranibizumab products (SB11 and RBZ) with treatment outcomes is unknown. Thus, potential safety concerns regarding immunogenicity to anti-VEGF biosimilar products intended for common use would seem to warrant further investigation. Therefore, the association between ranibizumab immunogenicity and PK, efficacy, and safety parameters was investigated in a post hoc analysis of a phase 3 clinical trial in participants with nAMD treated with SB11 or RBZ for 52 weeks.[15]

Key Points

Question How is immunogenicity to ranibizumab products associated with efficacy, safety, and pharmacokinetic (PK) profiles in patients with neovascular age-related macular degeneration (nAMD)?

Findings This post hoc analysis of a randomized equivalence trial did not reveal statistical or clinically relevant differences for best-corrected visual acuity or central subfield thickness between participants with and without antidrug antibodies. The observed association with PK and safety did not appear to be clinically relevant.

Meaning Results suggest that the incidence of antidrug antibodies was low for ranibizumab products, and its immunogenicity did not seem to have a clinically relevant association with their efficacy, safety, or PK profiles.

Methods

Study Design

This post hoc analysis of a randomized, double-masked, parallel-group, multicenter, phase 3 equivalence trial examined the association between immunogenicity and PK, efficacy, and safety profiles of 2 ranibizumab products.[20] A description of trial procedures, eligibility criteria, and end points has been published previously (Supplement 1 and Supplement 2).[15,21] Participants from the following races completed the 52-week follow-up: Asian, White, and other, and participants from the following ethnicities completed the 52-week follow-up: Hispanic or Latino, Indian (Indian subcontinent), Japanese, multiethnic, and other. Other race or ethnicity included individuals who identified with a race or ethnicity not previously listed, that could not be reported per local regulations, or was unknown. Race and ethnicity data were collected as a regulatory guidance requirement. After participants signed the written informed consent that was approved by local institutional review boards, they were randomly assigned 1:1 to receive intravitreal injections of either SB11, 0.5 mg, or RBZ, 0.5 mg, every 4 weeks until week 48. Study participants did not receive any compensation or incentives for participation. The primary outcome was change in best-corrected visual acuity (BCVA) from baseline to week 8 for the FDA and change in central subfield thickness (CST) from baseline to week 4 for the European Medicines Agency. Secondary outcomes included adverse events (AEs), serum concentrations of ranibizumab, and immunogenicity at different time points. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Immunogenicity Analysis and Measurement

Immunogenicity analyses were performed on the safety set (SAF), which included all randomly assigned participants who received at least 1 ranibizumab injection during the study period. Blood samples for the assessment of immunogenicity were collected before ranibizumab injection at week 0 (day 1), 4, 8, 16, 24, 36, and at any day during week 1 and 52. ADA and NAb were measured using a validated electrochemiluminescence immunoassay with an assay sensitivity level higher than that required by the most recent FDA guideline on immunogenicity assay development (eMethods in Supplement 3).[22,23] Overall ADA results were categorized into overall ADA negative, preexisting ADA, or overall ADA positive for this study. Participants were determined to be overall ADA negative if they had ADA-negative results at baseline (week 0, predose), as well as after baseline. Participants with a positive baseline ADA result without titer increase during the study period were considered to have preexisting ADA. Study participants were considered overall ADA positive in the following cases: (1) negative

ADA result at baseline and at least 1 positive postbaseline ADA result or (2) positive ADA result at baseline and at least 1 postbaseline ADA result with a higher titer than at baseline (ie, an increase in ADA level). Overall ADA status was defined as the accumulated count of ADA-positive results. NAbs were analyzed in ADA-positive participants. Overall NAb positive was defined as at least 1 positive NAb measurement at any time during the study (including baseline).

Analyses were conducted on the association of immunogenicity with efficacy, safety, and PK parameters (excluding participants with preexisting ADA). In a preplanned analysis, participants from both treatment arms were pooled based on overall ADA and NAb status to increase statistical power to detect potential associations between immunogenicity and other outcome measurements of ranibizumab products.

Association of Immunogenicity With Efficacy Parameters

Analyses on efficacy parameters were performed on the full analysis set. The full analysis set included all randomly assigned participants who received at least 1 ranibizumab injection. Analyzed efficacy parameters included BCVA and CST at each visit. Analyses were based on overall ADA and NAb results up to week 52, respectively.

Immunogenicity and Safety

To assess the association of overall ADA-positivity with safety, IOI-related AEs were investigated using the SAF. Individual IOI-related cases were briefly summarized. AEs were reported by the investigator and coded to preferred term in the Medical Dictionary for Regulatory Activities, version 20.1 (International Council for Harmonisation). The preferred term for IOI was selected under the high-level group term of ocular infections, irritation, and inflammation (eTable 1 in Supplement 3).

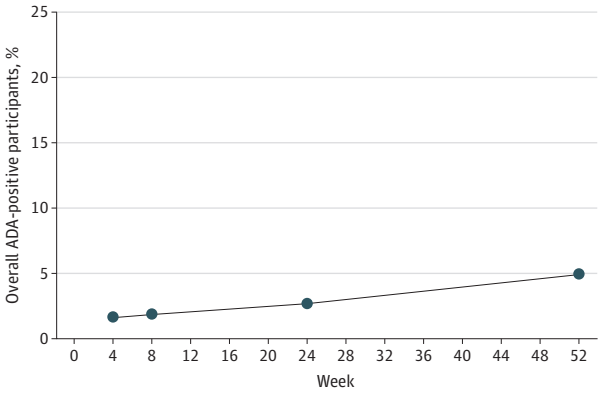
PK Analyses

Analyses were performed on participants in the PK analysis set, with at least 1 serum ranibizumab measurement. Blood samples for the assessment of PK parameters were collected before ranibizumab injection (predose), as well as 24 to 72 hours after ranibizumab injection (postdose) at week 0 (day 1), week 4, 8, 16, 24, and 36, and during the visit at any day of week 1 and 52 (end of study visit). Mean and maximum serum ranibizumab concentrations were analyzed according to overall ADA status up to week 52.

Statistical Analysis

Association between immunogenicity and efficacy of ranibizumab products was determined by analysis of covariance that adjusted for baseline difference between overall ADA-positive and ADA-negative participants resulting in least-square (LS) means with 95% CI. For BCVA outcome, the analysis of covariance model included baseline BCVA as a covariate and region (country) and overall ADA status as fixed factors. The same approach was used for CST using baseline CST as a covariate instead. All *P* values were 2-sided, but no threshold was chosen for statistical significance given the exploratory nature of these post hoc analyses. SAS software, version 9.4 (SAS Institute) was used for this post hoc analysis.

Figure 1. Incidence of Overall Antidrug Antibody (ADA)– and Neutralizing ADA (NAb)–Positive Participants at Week 4, 8, 24, and 52 (Safety Set, Pooled Treatment Groups)



Percentages for overall ADA-positive participants were based on a total number of 657 participants: week 4, 13 of 657 (2%), week 8, 15 of 657 (2.3%), week 24, 20 of 657 (3.0%), and week 52, 32 of 657 (4.9%). In terms of NAb-positive participants, percentages were as follows: week 4, 3 of 19 ADA-positive participants (including both overall ADA positive and preexisting ADA positive); at week 8, 4 of 21; week 24, 5 of 25; and week 52, 7 of 37.

Results

Study Participant Disposition and Baseline Characteristics by Overall ADA Status

Of 1095 screened patients, 705 study participants (mean [SD] age, 74.1 [8.5] years; 403 female individuals [57.2%]; 302 male individuals [42.8%]) were randomly assigned to receive either SB11 (n = 351 [49.8%]) or RBZ (n = 354 [50.2%]) across 75 centers in 9 countries globally from March 14, 2018, to December 9, 2019. A total of 634 participants (89.9%; SB11 group, 307 [48.4%]; RBZ group, 327 [51.6%]) completed the 52-week follow-up visit.[15] Participants from the following races completed the 52-week follow-up: 94 Asian (14.8%), 536 White (84.5%), and 4 other (0.6%), and participants from the following ethnicities completed the 52-week follow-up: 8 Hispanic or Latino (1.3%), 19 Indian (Indian subcontinent) (3.0%), 1 Japanese (0.2%), 32 multiethnic (5.0%), and 574 other (90.5%).

Preexisting ADA were present in 11 of 691 participants (1.6%; SB11 group, 7 of 343 [2.0%]; RBZ group: 4 of 348 [1.1%]). Of these, 1 of 11 participants (9.1%) had NAb (SB11 group, 1 of 7 [14.3%]; RBZ group, 0 of 4 [0%]). The incidence of overall ADA-positive participants up to week 52 was similar, with 14 of 330 participants (4.2%) and 18 of 327 participants (5.5%) for the SB11 and RBZ groups, respectively (32 of 657 for pooled treatment groups [4.9%]) (**Figure 1**; eTable 2 in Supplement 3; ADA-positive rates at each visit are shown in eTable 3 in Supplement 3). The overall incidences of NAb in ADA-positive (overall or preexisting ADA) participants treated with SB11 and RBZ up to week 52 were 4 of 18 (22%) and 3 of 19 (16%), respectively, (7 of 37 [19%] for pooled treatment groups) (Figure 1; eTable 2 in Supplement 3).

Baseline demographics and disease characteristics did not reveal any notable difference between overall ADA-positive and

Table 1. Demographic and Baseline Characteristics Between Overall Antidrug Antibody (ADA) Status (Randomized Set, Pooled Treatment Groups)[a]

Characteristic	Overall ADA, mean (SD)		*P* value[b]
	Positive (n = 32)	Negative (n = 620)	
Age, y	71.3 (9.9)	74.1 (8.4)	.07
Sex, No. (%)			
Male	16 (50.0)	264 (42.6)	.41
Female	16 (50.0)	356 (57.4)	
Race, No. (%)[c]			
American Indian or Alaska Native	0	0	.57
Asian	6 (18.8)	87 (14.0)	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	
White	26 (81.3)	528 (85.2)	
Other[d]	0	4 (0.6)	
Weight, kg	76.9 (15.8)	76.2 (16.3)	.83
Height, cm	169.0 (11.8)	165.1 (9.6)	.03
BMI[e]	26.8 (4.1)	27.9 (4.9)	.22
BCVA, letter score	60.9 (9.2)	58.2 (10.8)	.16
Approximate Snellen equivalent	20/63	20/63	
CST, µm	364 (108)	412 (119)	.03
CRLT, µm	318 (117)	357 (143)	.13
CNV size, mm^2	7.26 (5.56)	8.07 (5.05)	.38
Lesion type, No. (%)			
No CNV	0	1 (0.2)	.16
Classic CNV	2 (6.3)	49 (7.9)	
Classic and occult CNV	6 (18.8)	218 (35.2)	
Occult CNV	24 (75.0)	352 (56.8)	
Disciform scar	0	0	

Abbreviations: BCVA, best-corrected visual acuity; BMI, body mass index; CNV, choroidal neovascularization; CRLT, central retinal lesion thickness; CST, central subfield thickness.

[a] Participants from both treatment groups were pooled to make a subgroup analysis feasible.

[b] Fisher exact test was used for race and lesion type, χ^2 test was used for other categorical measures, and *F* test was used for continuous measures.

[c] Race was classified into American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or other based on self-identification from options predetermined by the clinical study case report form.

[d] Other race included individuals who identified with a race not previously listed, a race that could not be reported per local regulations, or unknown race.

[e] BMI is calculated as weight in kilograms divided by height in meters squared.

ADA-negative participants up to week 52 (pooled treatment arms are listed in **Table 1**). Mean (SD) baseline BCVA letter score did not differ between overall ADA-positive and ADA-negative participants: overall ADA positive, 60.9 (9.2); approximate Snellen equivalent, 20/63 vs overall ADA negative, 58.2 (10.8); approximate Snellen equivalent, 20/63; difference, 2.7 letters; 95% CI, −1.1 to 6.5 letters; *P* = .16. However, baseline CST was smaller in the overall ADA-positive group with a mean (SD) of 364 (108) µm vs 412 (119) µm for the overall ADA-negative group (difference = −48 µm; 95% CI, −90 to −5 µm; *P* = .03).

Efficacy Association

Analysis of BCVA letter score changes from baseline to week 8 showed no differences between overall ADA-positive participants (n = 15) and overall ADA-negative participants (n = 627) up to week 8: LS mean (SE) changes were 3.6 (2.1) letters and 6.8 (0.4) letters, and LS mean (SE) difference was −3.2 (2.1) letters (95% CI, −7.3 to 1.0; *P* = .13). Similarly, the change in CST from baseline to week 4 did not differ between overall ADA-positive participants (n = 13 at week 4) and overall ADA-negative participants (n = 633 at week 4): LS mean (SE) changes were −94 (21) µm and −105 (4) µm, respectively, and LS mean (SE) difference was 11 (21) µm (95% CI, −30 to 53 µm; *P* = .58).

From baseline to week 52, the changes in BCVA and CST were not associated with overall ADA status (**Table 2; Figure 2**A and C). For BCVA letter score, the LS mean (SE) changes for overall ADA-positive participants vs overall ADA-negative participants were 11.7 (2.2) letters vs 10.1 (0.6) letters, and the LS mean (SE) difference was 1.6 (2.2) letters (95% CI, −2.7 to 5.8; *P* = .46) at week 52. The LS mean (SE) changes in CST for overall ADA-positive participants vs overall ADA-negative participants were −130 (13) µm vs −133 (4) µm, and the LS mean (SE) difference was 3 (13) µm (95% CI, −23 to 29; *P* = .83) at week 52.

The association with NAb has also been analyzed (Figures 2B and D). The results are presented as exploratory summary statistics, as adjusting for baseline factors would not have been meaningful due to the small number of participants with NAb (n = 7). Mean (SD) changes from baseline to week 52 in overall NAb-positive and NAb-negative participants were, respectively, 16.2 (6.1) letters vs 10.6 (7.2) letters for BCVA letter score and −108 (107) µm and −82 (81) µm for CST.

Safety Association

Among the 32 participants of the SAF who had an overall ADA-positive result by week 52, drug-related IOI AEs occurred in 1 participant (participant A in the SB11 group) (eTable 5 in Supplement 3), resulting in an incidence rate of IOI among ADA-positive participants of 1 of 32 (3.1%). Participant A had 3 IOI AEs in total (iridocyclitis and vitritis on study day 225 and vitritis on study day 309). All IOI events resolved after treatment

Table 2. Absolute Values and Change From Baseline in Best-Corrected Visual Acuity (BCVA) and Central Subfield Thickness (CST) by Visit and Overall Antidrug Antibody (ADA) and Neutralizing ADA (NAb) Status Over Time up to Week 52 (Full Analysis Set, Pooled Treatment Groups)[a]

	Overall ADA status						Overall NAb status					
	Positive (n = 32)			Negative (n = 620)			Positive (n = 7)			Negative (n = 30)		
		Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]	
Time point, wk	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline
BCVA, letter score												
0 (BL)	32	60.9 (9.2) [57.6 to 64.2]	NA	620	58.2 (10.8) [57.3 to 59.0]	NA	7	59.6 (10.3) [50.1 to 69.1]	NA	30	60.9 (8.6) [57.7 to 64.1]	NA
Approximate Snellen equivalent		20/63			20/63			20/63			20/63	
1	32	64.1 (10.1) [60.4 to 67.7]	3.2 (3.9) [1.8 to 4.6]	618	61.6 (11.8) [60.7 to 62.6]	3.4 (6.1) [3.0 to 3.9]	7	64.6 (13.2) [52.4 to 76.8]	5.0 (4.0) [1.3 to 8.7]	30	63.8 (9.1) [60.4 to 67.2]	3.0 (3.9) [1.5 to 4.4]
Approximate Snellen equivalent		20/50			20/63			20/50			20/50	
4	32	65.5 (11.7) [61.3 to 69.7]	4.6 (5.0) [2.8 to 6.4]	617	64.1 (12.4) [63.1 to 65.0]	5.9 (7.1) [5.3 to 6.4]	7	65.4 (12.3) [54.1 to 76.8]	5.9 (3.5) [2.6 to 9.1]	30	65.5 (11.5) [61.3 to 69.8]	4.7 (5.6) [2.6 to 6.8]
Approximate Snellen equivalent		20/50			20/50			20/50			20/50	
8	32	66.1 (13.1) [61.3 to 70.8]	5.2 (7.7) [2.4 to 7.9]	611	65.3 (13.0) [64.2 to 66.3]	7.1 (8.2) [6.5 to 7.8]	7	67.3 (14.9) [53.5 to 81.1]	7.7 (9.2) [-0.8 to 16.2]	30	66.0 (12.3) [61.4 to 70.6]	5.2 (7.4) [2.4 to 7.9]
Approximate Snellen equivalent		20/50			20/50			20/50			20/50	
12	31	68.4 (10.7) [64.5 to 72.4]	6.7 (6.6) [4.3 to 9.2]	609	66.3 (13.1) [65.3 to 67.4]	8.0 (9.0) [7.3 to 8.8]	7	66.0 (13.0) [54.0 to 78.0]	6.4 (8.6) [-1.6 to 14.4]	29	69.2 (9.7) [65.6 to 72.9]	7.6 (6.2) [5.2 to 9.9]
Approximate Snellen equivalent		20/40			20/50			20/50			20/40	
16	31	70.4 (10.1) [66.7 to 74.1]	8.7 (5.3) [6.8 to 10.7]	604	66.6 (13.4) [65.6 to 67.7]	8.4 (9.4) [7.6 to 9.1]	7	71.1 (10.0) [61.9 to 80.4]	11.6 (4.4) [7.5 to 15.6]	29	69.9 (10.1) [66.0 to 73.7]	8.2 (5.6) [6.0 to 10.3]
Approximate Snellen equivalent		20/40			20/50			20/40			20/40	
20	31	70.1 (10.9) [66.1 to 74.1]	8.5 (6.0) [6.2 to 10.7]	601	66.9 (13.3) [65.8 to 67.9]	8.6 (9.6) [7.8 to 9.4]	7	71.1 (11.9) [60.1 to 82.1]	11.6 (3.9) [8.0 to 15.2]	29	69.9 (10.4) [66.0 to 73.9]	8.2 (6.4) [5.8 to 10.7]
Approximate Snellen equivalent		20/40			20/50			20/40			20/40	
24	30	71.4 (9.4) [67.9 to 74.9]	9.0 (5.8) [6.8 to 11.2]	593	67.2 (13.6) [66.1 to 68.3]	8.9 (10.2) [8.1 to 9.7]	7	72.1 (10.8) [62.1 to 82.1]	12.6 (5.7) [7.3 to 17.8]	28	71.4 (9.6) [67.7 to 75.1]	9.0 (6.7) [6.4 to 11.6]
Approximate Snellen equivalent		20/40			20/50			20/40			20/40	

(continued)

Table 2. Absolute Values and Change From Baseline in Best-Corrected Visual Acuity (BCVA) and Central Subfield Thickness (CST) by Visit and Overall Antidrug Antibody (ADA) and Neutralizing ADA (NAb) Status Over Time up to Week 52 (Full Analysis Set, Pooled Treatment Groups)[a] (continued)

	Overall ADA status						Overall NAb status					
	Positive (n = 32)			Negative (n = 620)			Positive (n = 7)			Negative (n = 30)		
		Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]	
Time point, wk	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline
28	26	72.3 (9.5) [68.5 to 76.1]	9.9 (6.0) [7.5 to 12.4]	582	67.5 (13.7) [66.4 to 68.7]	9.2 (10.6) [8.4 to 10.1]	6	71.5 (12.5) [58.4 to 84.6]	11.8 (6.7) [4.8 to 18.8]	25	72.6 (9.1) [68.8 to 76.3]	10.2 (6.6) [7.5 to 13.0]
Approximate Snellen equivalent		20/40			20/40			20/40			20/32	
32	27	73.4 (8.9) [69.9 to 76.9]	10.1 (6.1) [7.7 to 12.5]	581	67.8 (13.8) [66.6 to 68.9]	9.3 (10.7) [8.5 to 10.2]	6	71.0 (11.3) [59.2 to 82.8]	11.3 (3.8) [7.3 to 15.4]	25	73.3 (8.8) [69.7 to 77.0]	9.9 (6.7) [7.2 to 12.7]
Approximate Snellen equivalent		20/32			20/40			20/40			20/32	
36	29	72.5 (9.3) [69.0 to 76.1]	10.0 (6.9) [7.4 to 12.7]	577	67.9 (14.0) [66.8 to 69.1]	9.6 (11.0) [8.7 to 10.5]	6	71.8 (11.1) [60.2 to 83.4]	12.2 (6.1) [5.8 to 18.5]	28	72.6 (9.2) [69.0 to 76.1]	10.1 (7.4) [7.3 to 13.0]
Approximate Snellen equivalent		20/32			20/40			20/40			20/32	
40	29	73.2 (9.7) [69.6 to 76.9]	10.8 (6.6) [8.2 to 13.3]	569	68.0 (14.5) [66.8 to 69.1]	9.7 (11.5) [8.7 to 10.6]	6	73.5 (12.4) [60.5 to 86.5]	13.8 (4.5) [9.2 to 18.5]	28	72.5 (9.2) [69.0 to 76.1]	10.1 (6.9) [7.4 to 12.8]
Approximate Snellen equivalent		20/32			20/40			20/32			20/32	
44	29	72.3 (8.5) [69.1 to 75.6]	9.9 (5.8) [7.7 to 12.0]	569	67.8 (14.6) [66.6 to 69.0]	9.4 (12.0) [8.4 to 10.4]	6	72.0 (10.6) [60.8 to 83.2]	12.3 (5.5) [6.6 to 18.1]	28	72.6 (8.5) [69.3 to 75.9]	10.1 (6.5) [7.6 to 12.7]
Approximate Snellen equivalent		20/40			20/40			20/40			20/32	
48	28	73.0 (10.0) [69.1 to 76.9]	10.6 (6.9) [7.9 to 13.3]	564	68.3 (14.6) [67.1 to 69.5]	9.9 (11.7) [9.0 to 10.9]	6	74.2 (12.0) [61.6 to 86.7]	14.5 (7.4) [6.7 to 22.3]	27	72.7 (9.4) [69.0 to 76.4]	10.3 (7.0) [7.6 to 13.1]
Approximate Snellen equivalent		20/32			20/40			20/32			20/32	
52	28	73.2 (9.6) [69.5 to 76.9]	10.8 (6.8) [8.2 to 13.4]	563	68.5 (14.3) [67.3 to 69.6]	10.1 (11.5) [9.1 to 11.0]	6	75.8 (10.2) [65.1 to 86.6]	16.2 (6.1) [9.8 to 22.5]	27	73.0 (9.4) [69.3 to 76.7]	10.6 (7.2) [7.7 to 13.4]
Approximate Snellen equivalent		20/32			20/40			20/32			20/32	
CST, μm												
0 (Baseline)	32	364 (108) [325 to 403]	NA	620	412 (119) [402 to 421]	NA	7	387 (133) [264 to 509]	NA	30	355 (102) [317 to 393]	NA
1	32	297 (73) [271 to 324]	−66 (73) [−93 to −40]	617	336 (94) [329 to 343]	−76 (77) [−82 to −69]	7	286 (50) [240 to 332]	−100 (94) [−187 to −13]	30	300 (82) [269 to 331]	−55 (68) [−80 to −29]
4	32	285 (82) [256 to 315]	−79 (69) [−103 to −54]	615	307 (95) [300 to 315]	−105 (98) [−113 to −97]	7	271 (72) [205 to 337]	−116 (79) [−189 to −43]	30	287 (83) [256 to 318]	−68 (64) [−92 to −44]

(continued)

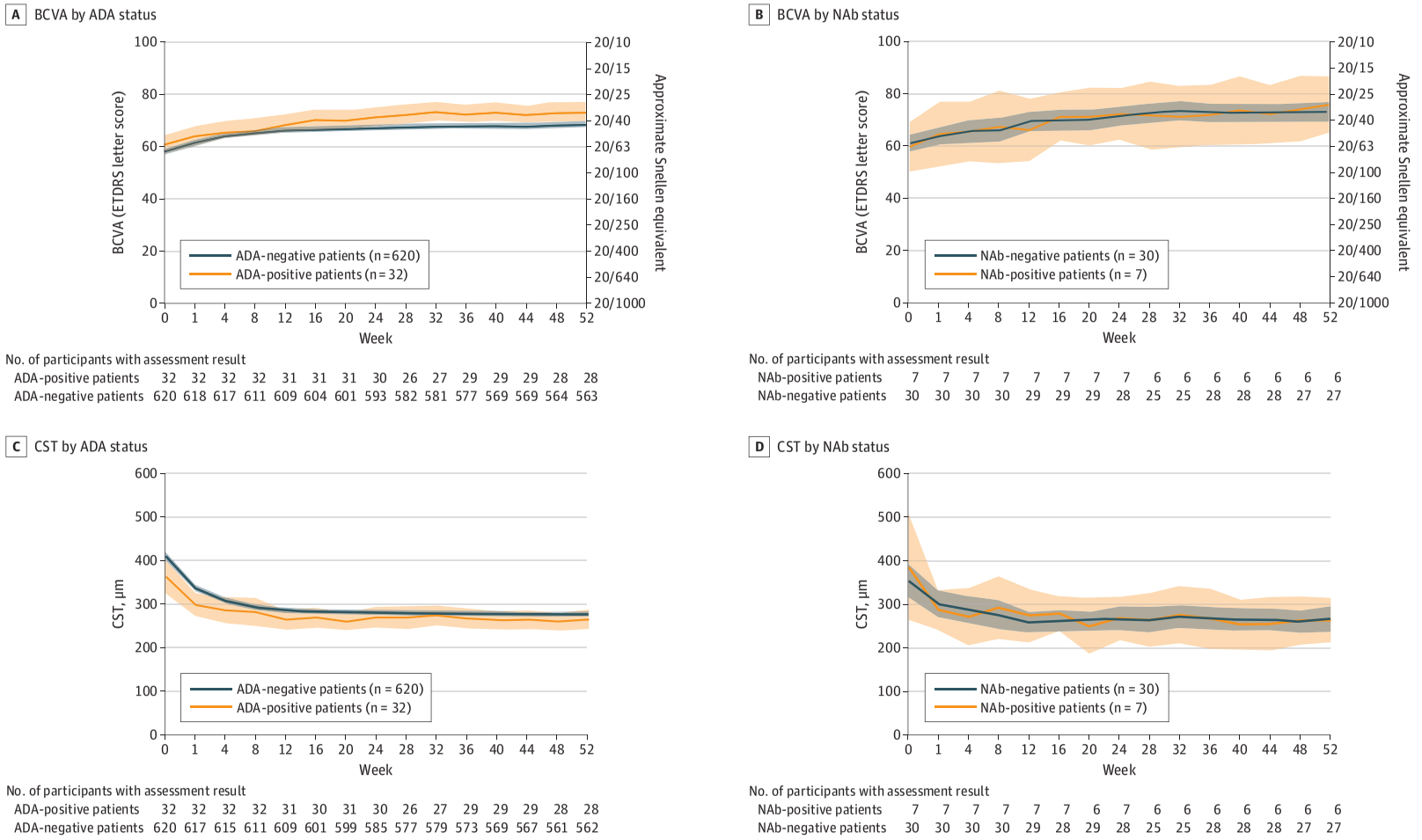
Table 2. Absolute Values and Change From Baseline in Best-Corrected Visual Acuity (BCVA) and Central Subfield Thickness (CST) by Visit and Overall Antidrug Antibody (ADA) and Neutralizing ADA (NAb) Status Over Time up to Week 52 (Full Analysis Set, Pooled Treatment Groups)[a] (continued)

	Overall ADA status						Overall NAb status					
	Positive (n = 32)			Negative (n = 620)			Positive (n = 7)			Negative (n = 30)		
		Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]			Mean (SD) [95% CI]	
Time point, wk	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline	No.	Absolute value	Change from baseline
8	32	281 (88) [249 to 313]	−83 (92) [−116 to −50]	611	292 (90) [285 to 300]	−120 (106) [−128 to −111]	7	292 (78) [220 to 364]	−94 (142) [−225 to 37]	30	275 (89) [242 to 308]	−80 (73) [−107 to −52]
12	31	263 (61) [240 to 285]	−95 (91) [−128 to −61]	609	285 (79) [278 to 291]	−126 (107) [−135 to −118]	7	275 (67) [213 to 337]	−112 (124) [−226 to 3]	29	258 (62) [235 to 282]	−89 (77) [−118 to −60]
16	30	268 (60) [246 to 290]	−94 (85) [−126 to −62]	601	282 (77) [276 to 289]	−129 (103) [−137 to −121]	7	278 (44) [238 to 319]	−108 (95) [−196 to −20]	28	262 (64) [237 to 286]	−90 (79) [−121 to −60]
20	31	259 (55) [239 to 279]	−98 (81) [−128 to −68]	599	281 (74) [275 to 287]	−131 (104) [−139 to −122]	6	250 (62) [185 to 315]	−123 (93) [−221 to −25]	29	261 (57) [239 to 283]	−86 (76) [−115 to −58]
24	30	269 (64) [245 to 293]	−91 (87) [−124 to −59]	585	280 (73) [274 to 286]	−131 (102) [−139 to −122]	7	267 (54) [218 to 317]	−119 (93) [−205 to −33]	28	268 (70) [240 to 295]	−83 (81) [−114 to −51]
28	26	268 (66) [242 to 295]	−77 (65) [−104 to −51]	577	279 (72) [273 to 285]	−132 (106) [−141 to −124]	6	264 (59) [202 to 327]	−107 (96) [−207 to −6]	25	264 (72) [235 to 294]	−74 (55) [−97 to −51]
32	27	273 (57) [251 to 296]	−87 (91) [−123 to −51]	579	279 (70) [273 to 285]	−132 (104) [−141 to −124]	6	276 (63) [210 to 342]	−95 (125) [−226 to 36]	25	271 (62) [246 to 297]	−87 (80) [−120 to −54]
36	29	267 (62) [243 to 290]	−90 (84) [−121 to −58]	573	278 (73) [272 to 284]	−133 (107) [−142 to −124]	6	267 (66) [197 to 336]	−104 (82) [−191 to −18]	28	268 (66) [242 to 293]	−83 (81) [−114 to −51]
40	29	263 (57) [241 to 285]	−93 (81) [−124 to −63]	569	278 (73) [272 to 284]	−134 (108) [−142 to −125]	6	254 (54) [197 to 310]	−117 (95) [−217 to −18]	28	265 (67) [239 to 290]	−86 (77) [−115 to −56]
44	29	264 (57) [242 to 285]	−92 (82) [−123 to −61]	567	275 (71) [270 to 281]	−136 (107) [−145 to −127]	6	255 (59) [193 to 317]	−116 (92) [−213 to −20]	28	265 (65) [240 to 290]	−85 (78) [−115 to −55]
48	28	259 (54) [238 to 280]	−96 (84) [−128 to −63]	561	276 (72) [270 to 282]	−135 (109) [−144 to −126]	6	263 (52) [208 to 318]	−108 (104) [−217 to 1]	27	260 (65) [234 to 286]	−89 (79) [−120 to −57]
52	28	265 (56) [243 to 286]	−90 (85) [−123 to −57]	562	277 (75) [271 to 283]	−134 (111) [−143 to −125]	6	263 (49) [212 to 314]	−108 (107) [−220 to 5]	27	266 (74) [237 to 296]	−82 (81) [−114 to −51]

Abbreviation: NA, not available.

[a] Data presented as mean (SD) of absolute differences, which were not adjusted for baseline differences. Participants from both treatment groups were pooled and stratified according to incidence of overall ADA and NAb positivity up to week 52.

Figure 2. Central Subfield Thickness (CST) and Best-Corrected Visual Acuity (BCVA) According to Overall Antidrug Antibody (ADA) and Neutralizing ADA (NAb) Status at Each Time Point Until Week 52 (Full Analysis Set, Pooled Treatment Groups)



For BCVA by ADA status (A), BCVA by NAb status (B), CST by ADA status (C), and CST by NAb status (D), the lines represent the mean, and the shaded areas represent the 95% CI bands. Any visible differences between the overall ADA-positive group and ADA-negative group at the individual time points were not adjusted for differences in baseline values. BCVA was determined by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score and approximate Snellen equivalent.

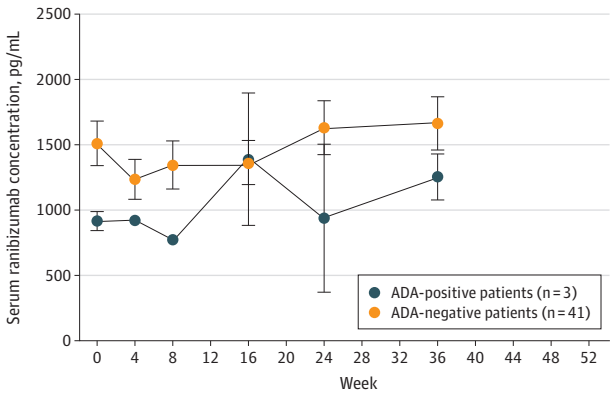
with topical ophthalmic corticosteroids, while study treatment was continued as scheduled. The first positive ADA result in this participant was reported on study day 260, and ADA positivity lasted until the end of the study. However, no immunogenicity assessment was performed between study days 170 and 259 for this participant as planned by the protocol; therefore, the exact timing of ADA occurrence could not be determined. The participant completed the study through the week-52 visit. There were no BCVA changes due to inflammation in this participant.

In the overall ADA-negative group, 4 of 620 participants (0.6%) experienced at least 1 IOI event in the study eye (participants B-E in the SB11 group) (eTable 5 in Supplement 3). Most events were reported not to be associated with the study drug as participants B and C had clinically confirmed infectious endophthalmitis. Participant D had serious (ie, sight-threatening and hospitalization-requiring) iridocyclitis necessitating study drug discontinuation, and the investigator reported that the protocol-related procedure is the cause of the event other than the study drug, and the persistent BCVA decrease was due to cataract progression. Participant E developed uveitis 4 days after cataract surgery, and both participants D and E were noted to have a hypopyon. For participant D, cultures were negative; for participant E, no culture results were available. All 4 participants underwent vitrectomy with antibiotic treatment. No participant had retinal vasculitis-associated adverse events.

PK Association

No formal statistical analysis was warranted due to the low total numbers of ADA-positive participants in the PK analysis set (3 of 54 [5.6%]).[15] Of the 3 overall ADA-positive participants, 2 were treated with SB11. In both participants, ADA were detected at the end of the trial (week 52). At this time point, serum ranibizumab concentrations were below the limit of quantification, similarly to predose concentrations at other visits. The third participant was treated with RBZ and was ADA positive at week 36. Predose and postdose serum ranibizumab concentrations at week 36 were comparable with those of previous visits. Overall, maximum observed mean (SD) postdose concentrations up to week 52 were 1389.3 (875.4) pg/mL at week 16 and 1665.4 (1124.0) pg/mL at week 36 for overall ADA-positive and ADA-negative participants, respectively. Mean serum ranibizumab concentrations over time were lower in overall ADA-positive participants compared with ADA-negative participants (**Figure 3** and eTable 4 in Supplement 3).

Figure 3. Mean Serum Concentration of Ranibizumab According to Overall Antidrug Antibody (ADA) Status up to Week 52 (Pharmacokinetics Analysis Set, Pooled Treatment Groups)



The circles represent the mean, and the error bars represent the SEM at each time point. The graph shows post-dose measurement values only. Because the study drug was not given at week 1 and 52, no postdose values are available.

Discussion

Results of this post hoc analysis of a randomized, controlled, phase 3 equivalence trial in participants with nAMD treated with SB11 or RBZ, suggest that immunogenicity was not associated with efficacy or safety of the ranibizumab products. Both products had similarly low overall ADA-positivity and NAb-positivity rates, with approximately 5% of participants developing ADA, and 19% of the aforementioned 5% developing NAb within 1 year of treatment. Baseline characteristics were well balanced between overall ADA-positive and ADA-negative participants, although overall ADA-positive participants had a slightly smaller CST. As no confounding factor was identified that could explain this finding, the difference might have arisen due to chance. The efficacy analyses indicated no association of overall ADA positivity and/or NAb positivity with changes in the clinical (BCVA) and anatomical (CST) efficacy end points. Overall, NAb-positive participants appeared to have similar efficacy outcomes compared with NAb-negative participants with no detectable association of NAb with ranibizumab efficacy.

To investigate the association of immunogenicity with safety, IOI-related AEs were examined. Of 5 participants (0.7%) who experienced IOI in this trial, 1 (participant A) was ADA positive. The IOI resolved after treatment with topical ophthalmic corticosteroids, without discontinuation of the investigational product. Association of IOI events with ranibizumab vs injection procedure or patient-related confounding factors, including the underlying disease, could not be clearly established. This conclusion was based on the safety profile of ranibizumab, according to which the majority of AEs were associated with the intravitreal injection procedure[24] and on the observation that all IOI events experienced by participant A resolved without treatment discontinuation.

Previous RBZ clinical studies, which investigated RBZ, 0.5 mg, in nAMD, reported IOI-related AE rates of 0.5% to 15% after 1 year of treatment.[25,26] Among AEs after intravitreal injections, subclinical anterior-chamber inflammation has been reported in up to 2% of participants who were treated with RBZ,[27] and sterile uveitis/endophthalmitis was observed in 0.05% to 4.4% of participants, depending on the type of anti-VEGF treatment, which is consistent with the data shown here.[28,29] So far, only brolucizumab was described to induce inflammatory retinal vasculitis (eg, 3.3% of brolucizumab injections in the Efficacy and Safety of RTH258 vs Aflibercept

Study 1 (HAWK) and Efficacy and Safety of RTH258 vs Aflibercept Study 2 (HARRIER) trials.[28,30,31] In the trial reported here, no IOI was associated with retinal vasculitis. Busch and colleagues[32] reported higher ADA-positivity rates in participants treated with brolucizumab than in those treated with RBZ (18.2% vs 2.6%). Nevertheless, high ADA levels did not necessarily result in IOI. However, IOI occurred more often in ADA-positive than ADA-negative brolucizumab-treated participants (6% vs 2%).[33]

In summary, the IOI cases observed in this study appeared consistent with the known safety profile of ranibizumab, where the relatively rare risk of IOIs is described among intravitreal injection-related reactions.[24] Notably, the IOIs with SB11 did not appear to be atypical in their presentation or clinical course, and there was no evidence of occlusive retinal vasculitis.

Although no formal statistical analysis was possible due to the low numbers of ADA-positive cases, the data indicated a possible negative association between ADA occurrence and serum ranibizumab concentrations. However, this finding may have little clinical relevance due to the extremely low serum levels (ie, 0.1% of vitreous fluid concentrations) and large variations in serum ranibizumab concentrations.[34] Very few data are available on the association of serum and vitreous ranibizumab concentrations. Serum half-life was estimated to be approximately 2 hours to 5.8 days, compared with approximately 7 to 9 days in vitreous fluid.[35] Thus, vitreous fluid drug concentration measurements would have been needed to determine whether overall ADA positivity led to lower drug concentrations at the site of action (ie, the retina). However, vitreous fluid sampling was not feasible in this study and may have exposed study participants to unnecessary procedures.

The main factors contributing to immunogenicity can be distinguished in patient- or disease-related factors (eg, genetics, age, underlying disease) and product-related factors (eg, preexisting antibodies, protein structure, aggregation, or impurities).[36-38] Notably, development of biosimilars requires extensive scientific analyses and stringent manufacturing processes as defined by Good Manufacturing Practice conditions.[39] Concordantly, both SB11 and RBZ seem to elicit low immunogenicity responses. To our knowledge, this was the first report examining the association of immunogenicity with the efficacy, safety, and PK profiles of ranibizumab products. These data may be relevant to allay concerns regarding immunogenicity of anti-VEGF biosimilar products, eg, SB11, in daily use.[29]

Limitations

An important limitation of this study was the small number of participants who developed ADA and/or NAb over the course of the study period and the limited number of participants with PK measurements, which reduced the power to avoid false-negative results. Thus, additional studies with larger patient cohorts (eg, studies from clinical practice settings obtained from big data sets) seem warranted.

Conclusions

Results of this post hoc analysis of a randomized, controlled, phase 3 equivalence trial revealed no apparent association of immunogenicity with efficacy or safety of 2 ranibizumab products (SB11 and RBZ) in participants with nAMD. A potential association between immunogenicity and PK profiles of SB11 and RBZ could not be excluded. SB11 and RBZ appeared to have comparable immunogenicity and safety profiles, supporting previously published data regarding the safety and efficacy of SB11 in patients with nAMD.[15,21,29] These findings suggest that particular concerns about immunogenicity and overall safety of this anti-VEGF biosimilar that will be used to treat retinal diseases[29] do not appear warranted at this time, although routine pharmacovigilance monitoring remains warranted.

ARTICLE INFORMATION

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Author Contributions: Dr Woo had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bressler, Oh, Russo, M. Kim, Woo.
Acquisition, analysis, or interpretation of data: Bressler, T. Kim, Russo, M. Kim, Woo.
Drafting of the manuscript: T. Kim, M. Kim.
Critical revision of the manuscript for important intellectual content: Bressler, Oh, Russo, M. Kim, Woo.
Statistical analysis: T. Kim.
Administrative, technical, or material support: M. Kim.
Supervision: Oh, Woo.

Conflict of Interest Disclosures: Dr Bressler reported receiving grants from Samsung Bioepis to Johns Hopkins University and receiving grants from Bayer, Biogen, Boehringer Ingelheim, F. Hoffman-LaRoche, Genentech, and Regeneron and having a patent to System and Method for Automated Detection of Age-Related Macular Degeneration and Other Retinal Abnormalities issued. Drs T. Kim, Oh, Russo, and M. Kim reported being employees of Samsung Bioepis. Dr Woo reported being a consultant for Samsung Bioepis, Janssen, Novartis, Curacle, Novelty Nobility, Sometech, Rznomics; being an equity owner of Retimark and Panolos Bioscience; receiving grants from Samsung Bioepis, Novelty Nobility, Pharmabcine, Novartis, Alteogen, Geneuintech, and Curacle; and receiving lecture fees from Novartis, Bayer, Allergan, Abbvie, Retimark, and Alcon outside the submitted work. No other disclosures were reported.

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Additional Information: This trial was registered in EudraCT (2017-000422-36). Deidentified participant data is available with this publication. To gain access, data requestors must enter into a data access agreement with Samsung Bioepis. Upon request, and subject to certain criteria, conditions and exceptions, Samsung Bioepis will provide access to individual deidentified participant data. 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. Data may be made available with a signed data access agreement.

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