Biosimilar SB11 versus reference ranibizumab in neovascular age-related macular degeneration: 1-year phase III randomised clinical trial outcomes

Neil M Bressler,1 Miroslav Veith,2,3 Jan Hamouz,3,4 Jan Ernest,5 Dominik Zalewski,6 Jan Studnička,7,8 Attila Vajas,9 András Papp,10 Gabor Vogt,11 James Luu,12 Veronika Matuskova,13,14 Young Hee Yoon,15,16 Tamás Pregun,17 Taehyung Kim,18 Donghoon Shin,18 Inkyung Oh,18 Hansol Jeong,18 Mercy Yeeun Kim,18 Se Joon Woo*19,20

ABSTRACT

Background/Aims To provide longer-term data on efficacy, safety, immunogenicity and pharmacokinetics (PK) of ranibizumab biosimilar SB11 compared with the reference ranibizumab (RBZ) in patients with neovascular age-related macular degeneration (nAMD).

Methods Setting: Multicentre. Design: Randomised, double-masked, parallel-group, phase III equivalence study. Patient population: ≥50 years old participants with nAMD (n=705), one ‘study eye’. Intervention: 1:1 randomisation to monthly intravitreal injection of 0.5 mg SB11 or RBZ. Main outcome measures: Visual efficacy endpoints, safety, immunogenicity and PK up to 52 weeks.

Results Baseline and disease characteristics were comparable between treatment groups. Of 705 randomised participants (SB11: n=351; RBZ: n=354), 634 participants (89.9%; SB11: n=307; RBZ: n=327) completed the study until week 52. Previously reported equivalence in primary efficacy remained stable up to week 52 and were comparable between SB11 and RBZ. The adjusted treatment difference between SB11 and RBZ in full analysis set at week 52 of change from baseline in best-corrected visual acuity was −0.6 letters (90% CI −2.1 to 0.9) and of change from baseline in central subfield thickness was −14.9 μm (95% CI −25.3 to −4.5). The incidence of ocular treatment-emergent adverse events (TEAEs) (SB11: 32.0% vs RBZ: 29.7%) and serious ocular TEAE (SB11: 2.9% vs RBZ: 2.3%) appeared comparable between treatment groups, and no new safety concerns were observed. The PK and immunogenicity profiles were comparable, with a 4.2% and 5.5% cumulative incidence of antidrug antibodies up to week 52 for SB11 and RBZ, respectively.

Conclusions Longer-term results of this study further support the biosimilarity established between SB11 and RBZ.

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a leading cause of visual impairment and blindness for people over 50 years of age in many parts of the world. Loss of vision can result in reduced participation in daily activities and increased need to rehabilitative facilities, which can lead to loss in vision-related quality of life or depression, and is associated with a total annual direct cost of more than $75.5 million dollars.1-3 Repeated intravitreal injections (IVI) of vascular endothelial growth factor-A (VEGF-A) inhibitors such as aflibercept, brolucizumab or ranibizumab (RBZ) are current standard treatments for nAMD.2-4,9 Given the substantial economic burden of these therapies, the introduction of biosimilars could reduce the cost of nAMD treatment and expand patient’s access to anti-VEGF treatments, similarly to the situation following the introduction of antitumour necrosis factor alpha10-12 or other biosimilars13 for various indications. Therefore, the availability of biosimilars could reduce the socioeconomic burden of blindness caused by nAMD.

Biosimilars are inherently different from chemically synthesised generic drugs as biosimilars are derived from living cells and, therefore, typically have bigger molecular size and more complex structures than generic drugs.20 Nevertheless, biosimilars also should be high-quality products that are manufactured through strictly controlled biotechnology processes in facilities that follow Good Manufacturing Practices guidelines. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approve biosimilars based on the totality of evidence of a comprehensive comparability exercise that demonstrates that there are no clinically meaningful differences between the biosimilar and the reference product in terms of quality characteristics, biological activity, clinical safety and efficacy.15-19 Therefore, biosimilars may have substantially higher research and development risks and cost and be more complex to manufacture than small molecule generic drugs.20 The development of biosimilars costs over 100 times more expensive and it usually takes 3–4 times longer than generic drugs.20

SB11 is a FDA and EMA approved RBZ biosimilar which demonstrated similarity to the reference product in analytical and non-clinical studies. In a phase III randomised clinical trial in patients with nAMD, equivalence in terms of efficacy has been demonstrated for the primary efficacy endpoints of change from baseline of optical coherence tomography (OCT) central subfield thickness (CST) at
week 4 and best-corrected visual acuity (BCVA) at week 8, with additional safety data provided through the 6-month visit.²¹ This report describes the results through the preplanned 52-week final visit including efficacy, safety, immunogenicity and pharmacokinetics (PK).

METHODS
Study design
This randomised, double-masked, parallel-group, multicentre, 52-week phase III clinical trial, registered in clinicaltrials.gov (NCT03150589) and EudraCT (2017-000422-36), evaluated the efficacy and safety of SB11 in comparison with monthly RBZ for treatment of nAMD. The trial was conducted in 75 centres in 9 countries and the trial protocol (SB11-G31-AMD) was reviewed and approved by an Independent Ethics Committee or Institutional Review Board.²¹ The study adhered to the tenets of Declaration of Helsinki, Good Clinical Practice guidelines and International Council for Harmonization. All patients provided written informed consent prior to entering the study.

The full list of inclusion and exclusion criteria for study participants was previously reported.²¹ In brief, participants were included if they were ≥ 50 years of age; had a previously untreated subfoveal choroidal neovascularisation (CNV) lesion secondary to nAMD in the study eye with evidence of activity by FA, following previously published definitions,²¹ ²² just as obscure the boundaries of classic or occult CNV was measured by FA, following previously published definitions,²¹ ²² as it was done in the reference product’s pivotal studies such as MARINA²³ ²⁴ and ANCHOR.²⁵ ²⁶

Prespecified exploratory endpoints included the proportion of participants without intraretinal or subretinal fluid and the change from baseline in subscale scores and composite score of the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) at weeks 24 and 52.

Safety
Safety evaluation at each visit included collection of ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs) through physical and full ophthalmic examinations (including but not limited to external examination of the eye, slit lamp examination, intraocular pressure (IOP) measurements, routine screening for eyelid/pupil and so on). All AEs were recorded from the time the participant signed the written informed consent until week 52 or an earlier termination visit. The AEs that emerged during the treatment with an investigational product (treatment-emergent adverse events (TEAEs)) were analysed for the purpose of safety analyses, accounting for its severity and causality. Adverse events of special interest (AESIs) also were collected up to week 52 using classification criteria previously reported.²¹

Immunogenicity
Immunogenicity analyses were performed in all participants on blood samples collected prior to IVI injection of the study drug at weeks 0, 4, 8, 16, 24, 36 and at any time during the visit at weeks 1 and 52 or early termination visit, using same immunoaasays as previously reported.²¹ If a participant had an unresolved AE that was possibly related to antidrug antibodies (ADAs), the participant was asked to return for blood sampling until antibody titre returned to baseline or stabilised to an acceptable level. Overall ADA results were determined as positive for a participant with treatment-induced or treatment-boosted ADAs, where treatment-induced ADAs indicates at least one positive result after predose of week 0 for participants with negative ADAs at predose of week 0, and treatment-boosted ADAs indicates at least one positive result with higher titre level compared with titre at week 0 for participants with positive ADAs at predose of week 0.

Pharmacokinetics
Serum samples for the measurements of drug concentration were taken predose (trough serum concentration (C_{trough}) and 24–72 hours postdose (close to maximum serum concentration (C_{max})) at weeks 0, 4, 8, 16, 24, 36 and at any time during the visit at weeks 1 and 52. If the fellow eye received RBZ due to nAMD during the study period, all concentrations measured after fellow eye treatment were excluded from summary statistics.

Statistical analysis
Sample size
For the primary endpoint of change from baseline in BCVA, a sample size of 352 participants per treatment group was required to achieve an overall 10% significance level and 80% power to establish equivalence. The calculation was based on the predefined equivalence margin of −3 and 3 letters,²¹ and an assumed 5% loss of randomised participants.

For the primary endpoint of change from baseline in CST, a sample size of 323 participants per treatment group was required to achieve an overall 5% significance level and 80% power to establish equivalence. The calculation was based on historical
data from the MARINA\textsuperscript{21} and PIER\textsuperscript{27} studies, the predefined equivalence margin of $-36$ and $36 \mu m$,\textsuperscript{23} and an assumed 10% loss from the full analysis set (FAS). Therefore, an overall sample size of 704 was chosen to allow for enough power to detect equivalence with both primary endpoints.

**Analysis sets**

The FAS included all randomised participants, excluding one inadvertently randomised participant who did not receive the study drug. The safety set (SAF) consisted of all participants who received at least one study drug administration during the study period after randomisation. The PK analysis set (PKS) included participants who had at least one PK sample analysed.

**Efficacy endpoints analysis**

Details on primary endpoint analysis have been reported previously.\textsuperscript{21}

Secondary endpoint analysis of changes from baseline in BCVA and in CST in the FAS at week 52 was performed using analysis of covariance (ANCOVA) model with the baseline BCVA or CST as a covariate and region (country) and treatment group as factors. For the analysis of proportion of participants who lost fewer than 15 letters or gained 15 letters or more compared with baseline in BCVA, and for the proportion of participants with active CNV leakage in the FAS, the adjusted risk difference between the two treatment groups was calculated using a Cochran-Mantel-Haenszel test with 95% CIs with stratification by region (country). For the analysis of change from baseline in CRLT and CNV size in the FAS, inferential statistics were based on ANCOVA model with the baseline CRLT or CNV size as a covariate and region (country) and treatment as fixed factors, respectively. All secondary endpoint analyses were performed based on available data; no missing data were imputed.

**Exploratory efficacy and other endpoints analysis**

For the exploratory endpoints, the proportion of participants without the presence of intraretinal or subretinal fluid in the FAS was evaluated using OCT and was summarised by treatment group and visit. The change from baseline in subscale and composite scores of NEI VFQ-25 were calculated in the FAS and was summarised by treatment groups and visits, excluding those participants who received RBZ in the fellow eye due to nAMD during the study period after randomisation. Safety, immunogenicity and PK outcomes were summarised descriptively by treatment groups and time points.

**RESULTS**

**Participant disposition, demographics and baseline characteristics**

Among 1095 participants screened from March 2018 to November 2018, 705 participants were randomised to receive either SB11 (N=351) or RBZ (N=354). One ineligible participant was randomised to SB11 group by error of the study coordinator inadvertently clicking the IWRS randomisation button and was subsequently discontinued before administering the study drug. Accordingly, 704 participants received at least one IVI of SB11 (N=350) or RBZ (N=354). A total of 634 (89.9%) received intervention as assigned. 1095 Assessed for eligibility

390 Screen failed
  - 353 Did not meet eligibility criteria
  - 25 Consent withdrawal
  - 2 Lost to follow-up
  - 10 Other reasons

705 Randomized

351 Randomized to receive SB11

350 Received intervention as assigned

44 Discontinued
  - 16 Consent withdrawal
  - 7 Adverse event
  - 4 Protocol deviation
  - 3 Lost to follow-up
  - 2 IP non-compliance
  - 2 Death
  - 3 Other reasons

307 Completed 52 weeks of study

354 Randomized to receive RBZ\textsuperscript{25}

354 Received intervention as assigned

27 Discontinued
  - 9 Consent withdrawal
  - 6 Adverse event
  - 3 Protocol deviation
  - 3 Lost to follow-up
  - 1 IP non-compliance
  - 3 Death
  - 2 Other reasons

327 Completed 52 weeks of study

Figure 1 CONSORT diagram of participants’ flow through the trial. (A) One participant was excluded from both full analysis set and safety set, because this participant was misrandomised and discontinued from the study before first dosing. (B) One participant was initially randomised to receive SB11 but incorrectly received the injection to the fellow eye, while RBZ was injected to the study eye until week 20 (Study day 141) of the study. This participant was discontinued from the study (Study day 164) primarily due to protocol deviation but later included in the RBZ treatment group in the safety set. IP, investigational product; RBZ, reference ranibizumab.
and appeared comparable between treatment groups at all time points up to week 52. Specifically, change from baseline in BCVA was 9.8 letters for SB11 and 10.4 letters for RBZ at week 52 (adjusted treatment difference (SE): −0.6 (0.9); 90% CI −2.1 to −0.9) (figure 2A, table 1). Change from baseline in CST was −140.0 μm for SB11 and −125.1 μm for RBZ at week 52 (adjusted treatment difference (SE): −14.9 (5.3); 95% CI −23.3 to −6.5) (figure 2B, table 1, online supplemental table 2).

The proportions of participants who lost fewer than 15 letters in BCVA (table 1, online supplemental figure 1A) and gained 15 or more letters in BCVA (table 1, online supplemental figure 1B) as well as the change from baseline in CRLT, CNV size and the proportion of participants with active CNV leakage in the FAS (table 1, online supplemental figure 1C) were maintained through week 52, with further improvements from the week 24 results, and were comparable between treatment groups at all timepoints. The analysis of exploratory endpoints showed that the proportion of participants without intraretinal or subretinal fluid in the FAS increased over time (online supplemental figure 2, online supplemental table 3) and were comparable between the treatment groups at week 52 (SB11: 84.4%; RBZ: 81.0%). Quality of life as assessed by NEI VFQ-25 score also improved over time, with mean change from baseline to week 52 (SB11: 4.54; RBZ: 6.47) appearing comparable between treatment groups (online supplemental table 4).

Safety
Exposure was similar between the SB11 (N=350) and RBZ (N=354) groups, with a mean number of study drug administrations (SD) of 12.2 (2.2) vs 12.4 (2.1) and a median duration of study drug exposure (min, max) of 337 days (1, 358) vs 337 days (1, 361), respectively. The incidence of AESIs, including TEAEs, SAEs and TEAEs leading to study drug discontinuation and death was comparable between treatment groups, with most TEAEs of mild or moderate intensity and not related to the study drug (table 2). The incidence of ocular TEAEs in the study eye that led to study drug discontinuation was similar between two groups (SB11: n=7; 2.0% vs RBZ: n=4; 1.1%). Although there was a small numerical difference, there was no statistical or clinically relevant difference between the two groups identified (Difference (SE): −0.009 (0.009); 90% CI −0.027 to 0.009; p=0.328).

There were no myocardial infarction or stroke events. There was one study participant with death of unknown cause in the SB11 treatment group and two participants with death of unknown cause in the RBZ treatment group. Ocular TEAEs in the study eye which occurred in ≥5% of participants were ‘Intraocular pressure increased’ (SB11: n=23; 6.6% vs RBZ: n=26; 7.3%) and ‘Conjunctival haemorrhage’ (SB11: n=16; 4.6% vs RBZ: n=18; 5.1%). No definitive differences in the overall incidence of AESIs between treatment groups were identified. ‘Intraocular pressure increase’ occurred in 3 (0.9%) and 6 (1.7%) participants, while death was reported for 1 (0.3%) and 2 (0.6%) participants within the SB11 and RBZ groups, respectively. Furthermore, 2 (0.6%) and 4 (1.1%) participants in the SB11 group and none in the RBZ group experienced ‘Endophthalmitis’ or ‘Eye disorders’ which included iridocyclitis (n=3; 0.9%), uveitis (n=1; 0.3%) or vitritis (n=1; 0.3%). The number of participants with cells and flare in the anterior chamber and vitreous cells were low with no notable difference between treatment groups.

Immunogenicity and pharmacokinetics
Immunogenicity analyses were performed in the SAF, including total of 330 participants treated with SB11 and 327 participants...
ADAs negative subgroup: SB11: 72.1%, RBZ: 72.4%.

Treatment groups (ADAs positive subgroup: SB11: 78.6%, RBZ: 80.1%).

ADAs result up to week 52 appeared comparable between two treatment groups (SB11: n=25; RBZ: n=29). The mean serum concentrations appeared comparable between SB11 and RBZ up to week 52 (SB11: n=303; RBZ: n=327).

The overall cumulative incidence of ADAs up to week 52 was low (SB11: 14/330; 4.2% vs RBZ: 18/327; 5.5%), and most antibodies were non-neutralising (table 3). No statistical or clinically relevant differences in the incidence of ADAs and neutralising antibodies (NAbs) were observed between treatment groups at any of the timepoints (table 3). The incidence of TEAEs by overall observation duration, although there was a small numerical, but not statistically or clinically relevant difference. A much larger study would be needed to determine if these small numerical differences between SB11 and RBZ. The similarity of all primary and secondary efficacy endpoints was maintained at all timepoints up to week 52, confirming the comparable longer-term efficacy of SB11 and RBZ. Moreover, final 52-week results remained in line with results from previously reported studies with RBZ for nAMD, including MARINA,23 ANCHOR,25 CATT28 and HARBOR.29

The safety profile of SB11 appears to be consistent with the known RBZ profile; no new safety concerns were identified during the study period. TEAEs were mostly mild or moderate in intensity, and the majority of events was not related to the study treatment. There was no difference in incidence of ocular TEAEs in the study eye identified that led to study drug discontinuation, although there was a small numerical, but not statistically or clinically relevant difference. A much larger number of study participants from a much larger case series would be needed to determine if these small numerical differences were due to chance or truly represented a small difference in ocular TEAEs. The incidence of intraocular inflammation (iritis, uveitis and vitritis) observed with SB11 was low compared with that reported for RBZ,29–31 although it was treated with RBZ with available overall ADAs results. The overall cumulative incidence of ADAs up to week 52 was low (SB11: 14/330; 4.2% vs RBZ: 18/327; 5.5%), and most antibodies were non-neutralising (table 3). No statistical or clinically relevant differences in the incidence of ADAs and neutralising antibodies (NAbs) were observed between treatment groups at any of the timepoints (table 3). The incidence of TEAEs by overall observation duration, although there was a small numerical, but not statistically or clinically relevant difference. A much larger study would be needed to determine if these small numerical differences between SB11 and RBZ. The similarity of all primary and secondary efficacy endpoints was maintained at all timepoints up to week 52, confirming the comparable longer-term efficacy of SB11 and RBZ. Moreover, final 52-week results remained in line with results from previously reported studies with RBZ for nAMD, including MARINA,23 ANCHOR,25 CATT28 and HARBOR.29

The safety profile of SB11 appears to be consistent with the known RBZ profile; no new safety concerns were identified during the study period. TEAEs were mostly mild or moderate in intensity, and the majority of events was not related to the study treatment. There was no difference in incidence of ocular TEAEs in the study eye identified that led to study drug discontinuation, although there was a small numerical, but not statistically or clinically relevant difference. A much larger number of study participants from a much larger case series would be needed to determine if these small numerical differences were due to chance or truly represented a small difference in ocular TEAEs. The incidence of intraocular inflammation (iritis, uveitis and vitritis) observed with SB11 was low compared with that reported for RBZ,29–31 although it was

### Table 1 Secondary efficacy endpoints measurements at week 52

| Endpoint at week 52 (analysis set) | Treatment | n' | Responders, n (%) | Adjusted difference (SB11-RBZ) | Adjusted difference (%) | 95% CI |
|-----------------------------------|-----------|---|-------------------|---------------------|--------------------------|----------|
| Participants who lost <15 letters in BCVA compared with baseline (FAS) | SB11 (N=351) | 309 | 299 (96.8) | -1.2 | -3.8 to 1.3 |
|                                  | RBZ (N=353) | 327 | 320 (97.9) |               |                         |          |
| Participants who gained ≥15 letters in BCVA compared with baseline (FAS) | SB11 (N=351) | 309 | 107 (34.6) | -3.2 | -10.5 to 4.2 |
|                                  | RBZ (N=353) | 327 | 123 (37.6) |               |                         |          |
| Participants with active CNV leakage (FAS) | SB11 (N=351) | 303 | 158 (52.1) | -7.4 | -15.0 to 0.2 |
|                                  | RBZ (N=353) | 313 | 185 (59.1) |               |                         |          |

*Inferential statistics were based on an analysis of covariance model with the baseline BCVA as a covariate and region (country) as treatment as fixed factors.
†Inferential statistics were based on analysis of covariance model with the baseline CST as a covariate and region (country) and treatment as fixed factors.
‡Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and region (country) and treatment as fixed factors.
¶The adjusted difference and its 95% CI were calculated using a stratified Cochran-Mantel-Haenszel test with region (country) as a factor.
\$The adjusted difference and its 95% CI were calculated using a stratified Cochran-Mantel-Haenszel test with region (country) as a factor.

BCVA, best-corrected visual acuity (letter score); CNV, choroidal neovascularisation; CRLT, central retinal lesion thickness; CST, central subfield thickness; FAS, full analysis set; n, number of participants with available data at week 52; N, total number of participants; n', number of participants with available assessment results at week 52 (percentages are based on n'); RBZ, reference ranibizumab.

### DISCUSSION

To our knowledge, this is the first manuscript that has reported Phase III, week 52 follow-up data of ranibizumab biosimilar for the treatment of nAMD. This week 52 analysis of the phase III study shows that SB11 and its reference RBZ have comparable efficacy, safety, immunogenicity and PK profiles up to week 52. These data demonstrate no clinically meaningful differences between SB11 and RBZ. The similarity of all primary and secondary efficacy endpoints was maintained at all timepoints up to week 52, confirming the comparable longer-term efficacy of SB11 and RBZ. Moreover, final 52-week results remained in line with results from previously reported studies with RBZ for nAMD, including MARINA,23 ANCHOR,25 CATT28 and HARBOR.29

The safety profile of SB11 appears to be consistent with the known RBZ profile; no new safety concerns were identified during the study period. TEAEs were mostly mild or moderate in intensity, and the majority of events was not related to the study treatment. There was no difference in incidence of ocular TEAEs in the study eye identified that led to study drug discontinuation, although there was a small numerical, but not statistically or clinically relevant difference. A much larger number of study participants from a much larger case series would be needed to determine if these small numerical differences were due to chance or truly represented a small difference in ocular TEAEs. The incidence of intraocular inflammation (iritis, uveitis and vitritis) observed with SB11 was low compared with that reported for RBZ,29–31 although it was
### Table 2

|                     | SB11 (N=350) n (%) | RBZ (N=354) n (%) |
|---------------------|--------------------|-------------------|
| **TEAEs**           |                    |                   |
| Any TEAE            | 255 (72.9)         | 256 (72.3)        |
| Ocular TEAEs in the study eye | 112 (32.0)      | 105 (29.7)        |
| Ocular TEAEs in the fellow eye | 92 (26.3)       | 77 (21.8)         |
| Non-ocular TEAEs    | 194 (55.4)         | 205 (57.9)        |
| Serious TEAE        | 50 (14.3)          | 51 (14.4)         |
| **TEAEs by severity** |                  |                   |
| Mild TEAEs          | 117 (33.4)         | 122 (34.5)        |
| Moderate TEAEs      | 106 (30.3)         | 107 (30.2)        |
| Severe TEAEs        | 32 (9.1)           | 27 (7.6)          |
| **SAEs (by relatedness)** |               |                   |
| Related TEAEs       | 21 (6.0)           | 10 (2.8)          |
| Not related TEAEs   | 234 (66.9)         | 246 (69.5)        |
| **TEAEs leading to IP discontinuation** |            |                   |
| AESI* 8 (2.3)       | 8 (2.3)            |                   |
| **Any TEAE**        | 255 (72.9)         | 256 (72.3)        |
| **Serious ocular SAEs** |                |                   |
| Atrial fibrillation | 3 (0.9)            | 2 (0.6)           |
| Cardiac failure congestive | 2 (0.6)      | 2 (0.6)           |
| Pancreatitis acute  | 0 (0.0)            | 2 (0.6)           |
| Cystitis            | 0 (0.0)            | 2 (0.6)           |
| Femoral neck fracture| 1 (0.3)           | 2 (0.6)           |
| Acute kidney injury | 3 (0.9)            | 1 (0.3)           |
| Chronic obstructive pulmonary disease | 2 (0.6)    | 0 (0.0)           |
| Hypertension        | 3 (0.9)            | 0 (0.0)           |
| AESI* 8 (2.3)       | 8 (2.3)            |                   |
| **TEAEs leading to IP discontinuation** |            |                   |
| Any TEAEs leading to IP discontinuation | 9 (2.6) | 5 (1.4) |

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

Adverse events were coded to System Organ Class and preferred term using 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, i.e., related) for the number of participants (N).

* Adverse events of special interest were collected using six different categories: category 1, any case of new onset intraocular pressure of >21 mm Hg that does not respond to treatment, except the transient pressure rise observed within an hour after intravitreal injection of IP; category 2, any case of intraocular pressure ≥35 mm Hg, at any time, that required treatment; category 3, any case of intraocular infection such as endophthalmitis; category 4, any case of intraocular inflammation such as iritis, vitritis and iridocyclitis; category 5, iatrogenic traumatic cataract; category 6, arterial thromboembolic events defined as non-fatal stroke, non-fatal myocardial infarction or vascular death (including deaths of unknown cause), AE, adverse event; AESI, adverse event of special interest; IP, investigational product; n, number of participants with event; N, total number of participants; RBZ, reference ranibizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

higher numerically in the SB11 group compared with the RBZ group.

The incidence of ADAs and NABs with SB11 is comparable with RBZ, and the cumulative incidence of ADAs at week 52 is within the known 1%–9% range for RBZ.36 Much larger studies would be needed to determine if these small numerical differences truly represented small differences in immunogenicity.

### Table 3

| Timepoint | Parameter Result | SB11 (n=350) n/n’ (%) | RBZ (n=354) n/n’ (%) | P value* |
|-----------|-----------------|------------------------|----------------------|---------|
| Overall cumulative incidence of ADA |                      |                        |                      |         |
| Up to week 52 | ADA Positive | 14/330 (4.2) | 18/327 (5.5) | –       |
|              | Negative | 312/330 (94.5) | 308/327 (94.2) | –       |
|              | Inconclusive | 4/330 (1.2) | 1/327 (0.3) | –       |
| Incidence of ADA and NAb at each visit |                      |                        |                      |         |
| Week 24 | ADA Positive | 7/294 (2.4) | 2/290 (0.7) | 0.18†    |
|          | NAb Positive | 0/7 (0.0) | 1/2 (50.0) | –       |
| Week 36 | ADA Positive | 8/270 (3.0) | 5/274 (1.8) | 0.38§    |
|          | NAb Positive | 2/8 (25.0) | 0/5 (0.0) | –       |
| Week 52 | ADA Positive | 9/257 (3.5) | 12/267 (4.5) | 0.56§   |
|          | NAb Positive | 1/9 (11.1) | 0/12 (0.0) | –       |

*P values calculated by using χ² or Fisher’s exact test to compare the distribution of positivity between treatment groups.

†The result was considered inconclusive in cases of positive ADA result at baseline and either negative ADA result or positive ADA result with equal or lower titre at the subsequent timepoint.

§Two-sided p value was estimated based on Fisher’s exact test, if expected frequency in one cell was less than 5.

36 Much larger studies would be needed to determine if these small numerical differences truly represented small differences in immunogenicity.
results. PK analyses showed comparable PK profiles and furthermore, systemic concentrations of both investigational drugs up to 52 weeks are below the 11–27 ng/mL. RBZ concentration range necessary to inhibit the biological activity of VEGF-A by 50%, thus limiting the potential for unintended effects due to systemic VEGF-A inhibition.\(^{31}\) Additionally, absorption of IVI anti-VEGF product into systemic circulation is very limited and sampling of vitreous fluid was not planned for this study, indicating that systemic PK data have limitations in their interpretation and were evaluated in this study primarily to support the overall assessment of the safety profiles of two products.\(^{32}\)

Experience has shown that biosimilars in other fields of medicine can contribute to reducing healthcare costs and improve patient’s access to therapies with approved labels.\(^{10–13}\) Future research is warranted to investigate the contribution of RBZ biosimilars to reducing undertreatment in nAMD\(^{33–39}\) and improving the visual outcomes in the clinical practice setting.

SB11 is a ranibizumab biosimilar approved by FDA and EMA for nAMD, retinal vein occlusion and myopic choroidal neovascularization.\(^{17}\) An economical component may be associated not only with the selection of a drug, but also the initiation and duration of an effective treatment. With SB11 and a number of other biosimilars under development, the availability of biosimilars may have a major role in ophthalmology,\(^ {40}\) like the introduction of biosimilars (eg, SB2 as a biosimilar of infliximab) in other therapeutic areas.\(^ {10–11}\) In summary, the longer-term results of SB11 support the previously reported efficacy, safety, immunogenicity and PK compared with RBZ in participants with nAMD, supporting its use as a safe and effective RBZ biosimilar.

**Author affiliations**

1Johns Hopkins Medicine Wilmer Eye Institute, Baltimore, Maryland, USA

2Department of Ophthalmology, University Hospital Kralovske Vinohrady, Prague, Czech Republic

3Department of Ophthalmology, Third Faculty of Medicine, Charles University, Prague, Czech Republic

4University Hospital Kralovske Vinohrady, Praha, Czech Republic

5Department of Ophthalmology, Central Military Hospital, Praha, Czech Republic

6Diagnostic and Microsurgery Center of the Eye LENS, Osłocin, Poland

7Department of Ophthalmology, Faculty of Medicine in Hradec Kralove, Charles University, Hradec Kralove, Czech Republic

8University Hospital Hradec Kralove, Hradec Kralove, Královéhradecký, Czech Republic

9Department of Ophthalmology, University of Debrecen, Debrecen, Hajdu-Bihar, Hungary

10Department of Ophthalmology, Semmelweis University, Budapest, Hungary

11Department of Ophthalmology, Hungarian Defence Forces Medical Centre, Budapest, Hungary

12Retina Consultants of Southern Colorado PC, Colorado Springs, Colorado, USA

13Department of Ophthalmology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

14University Hospital Brno, Brno, Czech Republic

15Department of Ophthalmology, Asan Medical Center, Songpa-gu, Seoul, South Korea

16Samsung Bioepis Co Ltd, Incheon, South Korea

17Department of Ophthalmology, Seoul National University College of Medicine, Seoul, South Korea

18Department of Ophthalmology, Seoul National University Bundang Hospital, Seongnam, South Korea

**Acknowledgements** Medical writing support was provided by Daniela Kenzelmann Broz and Suzanne Einmahl (SRL Regulatory Affairs & Scientific Communications, Basel, Switzerland) and funded by Samsung Bioepis Co., Ltd., Incheon, Republic of Korea.

**Contributors** NMB: conceptualisation, methodology, writing—original draft, writing—review and editing, project administration, supervision. MV: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. JH: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. DZ: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. JS: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. AV: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. AP: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. GY: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. JL: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. THY: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. TP: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. Formal analysis, validation, resources, validation, funding acquisition. TM: conceptualisation, investigation, writing—review and editing, resources, validation, funding acquisition. DV: conceptualisation, methodology, writing—review and editing, project administration, supervision. IO: conceptualisation, methodology, writing—original draft, writing—review and editing, project administration. HJ: methodology, writing—review and editing, resources, validation. MYK: conceptualisation, investigation, writing—original draft, writing—review and editing, validation, visualisation, project administration. SJW: conceptualisation, methodology, investigation, writing—original draft, writing—review and editing, funding acquisition, project administration, supervision.

**Funding** Planning, conduct and analysis of the study was funded by Samsung Bioepis Co., Ltd., Incheon, Republic of Korea.

**Competing interests** NB reported receiving grants from Samsung Bioepis to Johns Hopkins University during the conduct of the study and remaining grants from Bayer, Biogen, F. Hoffman-LaRoche, Novartis, Regeneron outside the submitted work. JS is a consultant for Bayer and Zeiss and received lecture fee from Bayer. AV received grants from Novartis, Bayer, Ophthotec/VericBio, Samsung Bioepis, Amgen, Qili, Chengdu Kanghong, Roche, Mylan, Receptos, Shire, Panoptica, Xbrain, Formycon, Genentech, Bioeq, Allergan, Thrombogenics, Regeneron, Alcon and Cleaside Biomedical and is a consultant for and an advisory board member of Novartis, Bayer, Allergan, Bausch & Lomb, Medicontrout and Zeiss. AP is a consultant for Roche, Bayer and Novartis received travel grants from Novartis and his company has received investigator fees from Samsung Bioepis, Roche, IovicBio, Allergan and Chengdu Kanghong. GV is a consultant for Alcon and Novartis, and received travel grants from Novartis and Medicontrout and his department has been involved in the conduct of several studies sponsored by Samsung Bioepis, Allergan, Chengdu Kanghong, Xbrane Biopharma, Thrombogenics, Amgen, Qili, F. Hoffmann-La Roche, Bayer, Ophthotec, Novartis and Regeneron. THY is a consultant for Alcon, Allergan and Bayer and Roche, is Board Member of Allergan, Bayer and Roche, received grants from Allergan, Samsung Bioepis, Bayer, Novartis and Roche and received lecture fee from Allergan, Bayer and Roche. TP received travel grants from Alcon, Novartis and Bausch & Lomb and his department has been involved in the conduct of several studies sponsored by Mylan, Samsung Bioepis, Xbrane Biopharma, Kanghong Pharmaceuticals, F. Hoffmann-La Roche, Allergan and Ophthotec. SJW is a consultant for Samsung Bioepis, Ianssen, Allergan, Novartis, Curacle, Novely Novitx, Alteogen, Alteogen, Panolos Bioscience, is equity owner of BP Mailing and Panolos Bioscience, is Board Member of Novartis and Novely Nobility, received grants from Samsung Bioepis, Novely Nobility, Novitx, Abruvie, Alteogen and Curacel and received lecture fee from Novartis, Bayer, Allergan, Abbiev, Alcon and Taejoon. Inkyung Oh, Hansol Jeong and Merry Yeeun Kim are employees of Samsung Bioepis.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; internally peer reviewed.

**Data availability statement** Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is

Bressler NM, et al. Br J Ophthalmol 2021;1–8. doi:10.1136/bjophthalmol-2021-319637
REFERENCES

1. Friedman DS, O’Colmain BJ, Muñoz B, et al. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 2004;122:564–72.
2. Mitchell P, Liew G, Gopinath B, et al. Age-Related macular degeneration. Lancet 2018;392:1147–59.
3. Lim LS, Mitchell P, Seddon JM, et al. Age-Related macular degeneration. The Lancet 2012;379:1728–38.
4. Agarwal A, Aggarwal K, Gupta V. Management of neovascular age-related macular degeneration: a review on landmark randomized controlled trials. Middle East Afr J Ophtalmol 2016;23:27–37.
5. Bakri SJ, Thorne JE, Ho AC, et al. Safety and efficacy of anti-vascular endothelial growth factor therapies for neovascular age-related macular degeneration: a report by the American Academy of opthalmology. Ophthalmology 2019;126:55–63.
6. Grisant S, Tata O. The role of vascular endothelial growth factor and other endogenous interplayers in age-related macular degeneration. Prog Retin Eye Res 2008;27:372–90.
7. Hussain RM, Ciulla TA. Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration. Expert Opin Emerg Drugs 2017;22:235–46.
8. Saccucci MR, Giuffrè C, Corbelli E, et al. Emerging therapies in the management of macular edema: a review. F1000Res 2019;8. doi:10.12688/f1000research.19198.1. [Epub ahead of print: 12 08 2019].
9. Shao J, Choudhary MM, Schachat AP. Neovascular age-related macular degeneration. Dev Ophthalmol 2016;53:125–36.
10. Jensen TB, Kim SC, Jimenez-Solem E, et al. Shift from adalimumab Originator to biosimilars in Denmark. JAMA Intern Med 2020;180:902–3.
11. Peyrin-Biroulet L, Danese S, Cummings F, et al. Anti-TNF biosimilars in Crohn’s disease: a patient-centric interdisciplinary approach. Expert Rev Gastroenterol Hepatol 2019;13:731–8.
12. Dörmer T, Strand V, Comes P, et al. The changing landscape of biosimilars in rheumatology. Ann Rheum Dis 2016;75:974–82.
13. European Federation of Pharmaceutical Industries and Associations (EFPIA). Promoting safe and effective biosimilars can lead to more affordable biologic medicines. Available: https://www.efpia.eu/publications/data-center/medicines-costs-in-context/biosimilars/ [Accessed 24 Mar 2020].
14. Tripkitt C, Hinnen D, Valentine V. How similar are biosimilars? what do clinicians need to know about Biosimilar and follow-on insulins? Clin Diabetes 2017;35:209–16.
15. Bui LA, Hurst S, Finch GL, et al. Key considerations in the preclinical development of biosimilars. Drug Discov Today 2015;20 Suppl 1:3–15.
16. European Medicines Agency (EMA). Guideline on similar biological medicinal product - Rev 1. Available: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf [Accessed 24 Mar 2020].
17. United States Federal Drug Administration (US FDA). Scientific considerations in demonstrating Biosimilarity to a reference product. Available: https://www.fda.gov/media/82647/download [Accessed 24 Mar 2020].
18. European Medicines Agency (EMA). Biosimilars in the EU - Information guide for healthcare professionals. Available: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf [Accessed 24 Mar 2020].
19. United States Federal Drug Administration (US FDA). Biosimilar development, review, and approval. Available: https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval [Accessed 24 Mar 2020].
20. Blackstone EA, Joseph PF. The economics of biosimilars. Am Health Drug Benefits 2013;6:469–78.
21. Woo SJ, Veith M, Hamouz J, et al. 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. JAMA Ophthalmol 2021;139:68–76.
22. Barbazzo I, Burdan A, Bressler NM, et al. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment—TAP and VIP report No. 2. Arch Ophthalmol 2003;121:1253–68.
23. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
24. Kaiser PK, Bliôdi BA, Shapiro H, et al. Angiographic and optical coherence tomographic results of the marina study of ranibizumab in neovascular age-related macular degeneration. Ophthalmology 2007;114:1868–75.
25. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the anchor study. Ophthalmology 2009;116:57–65.
26. Sadda SR, Stoller G, Boyer DS, et al. Anatomical benefit from ranibizumab treatment of predominantly classic neovascular age-related macular degeneration in the 2-year anchor study. Retina 2010;30:1390–9.
27. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 1. Am J Ophthalmol 2008;145:239–48.
28. CATR Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.
29. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 Mg or 2.0 Mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–56.
30. Lucentis prescribing information. Available: https://www.gene.com/download/pdf/lucents_prescribing.pdf [Accessed 2 Apr 2020].
31. Lucentis - Summary of Product Characteristics. Available: https://www.ema.europa.eu/en/documents/product-information/lucents-eapar-product-information_en.pdf [Accessed 8 Dec 2020].
32. Bressler NM, Ranibizum B. Biosimilar ranibizumab (SB11) vs reference Ranibizumab-Diving deeper for safety and Efficacy-Reply. JAMA Ophthalmol 2021;139:678–9.
33. Dutta B, Hays J, Vulto AG, et al. Identifying key benefits in European Off-Patent biologics and Biosimilar markets: it is not only about price! BioDrugs 2020;34:159–70.
34. Jensen TB, Bartels D, Sædder EA, et al. The Danish model for the quick and safe implementation of infliximab and etanercept biosimilars. Eur J Clin Pharmacol 2020;76:35–40.
35. Chen H, Ranibizumab for the treatment of wet AMD: a summary of real-world studies. Eye 2016;30:270–86.
36. Holz FG, Bandello F, Gillies M, et al. Safety of ranibizumab in routine clinical practice: 1-year retrospective pooled analysis of four European neovascular AMD registries within the luminous programme. Br J Ophthalmol 2013;97:1161–7.
37. Holz FG, Figueroa MS, Bandello F. Ranibizumab treatment in treatment-naive neovascular age-related macular degeneration: results from luminous, a global real-world study. Retina 2019.
38. Holz FG, Tadayoni R, Beatty S, et al. Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration. Br J Ophthalmol 2015;99:220–6.
39. Kiss S, Campbell J, Almony A, et al. Management and outcomes for neovascular age-related macular degeneration: analysis of United States electronic health records. Ophthalmology 2020;127:1179–88.
40. Sharma A, Reddy P, Kuppermann BD, et al. Biosimilars in ophthalmology: “Is there a big change on the horizon?” Clinical Ophthalmology 2018;12:2137–43.