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Association between screening duration and treatment outcomes in the biosimilar clinical trials

Short Title: Association of Screening Duration with Treatment Outcomes

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Abstract

The clinical implications of screening duration prior to treatment initiation in neovascular age-related macular degeneration (nAMD) are not well understood. This post hoc analysis investigated whether screening duration influences treatment outcomes in two multinational phase 3 randomized clinical trials, SB11 and SB15, comprising a total of 1,152 participants (704 from the SB11 trial and 448 from the SB15 trial) with nAMD. Screening duration was assessed in relation to changes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) at weeks 8 and 48. Multiple linear and logistic regression analyses, adjusted for age and baseline BCVA/CST, showed no significant associations between screening duration and either visual or anatomical outcomes at both time points. Linear regression coefficients for screening duration were not statistically significant for BCVA or CST at week 8 (BCVA: $B = -0.058$, $P = 0.242$; CST: $B = -0.050$, $P = 0.908$) or at week 48 (BCVA: $B = -0.015$, $P = 0.843$; CST: $B = 0.036$, $P = 0.930$). These findings suggest that a screening period of up to 21 days does not adversely affect treatment efficacy in clinical trial settings and support the clinical feasibility of short pre-treatment delays.

Keywords: screening duration ; best corrected visual acuity ; central subfield thickness ; anti-VEGF therapy ; neovascular AMD

Introduction

Neovascular age-related macular degeneration (nAMD) is a leading cause of visual disability and blindness in older adults, with approximately 90% of severe vision loss cases linked to choroidal neovascularization (CNV).[1-3] The discovery of vascular endothelial growth factor (VEGF)'s role in vision loss has revolutionized treatment approaches, making anti-VEGF therapies the gold standard for managing VEGF-driven diseases, particularly nAMD and other blinding eye conditions.[4,5] Following the introduction of ranibizumab (Lucentis, Genentech),[6,7] additional therapies such as aflibercept (Eylea, Regeneron), brolucizumab (Beovu, Novartis), and faricimab (Vabysmo, Roche) have received regulatory approval.[8-10] Furthermore, biosimilar anti-VEGF agents have been developed based on comprehensive comparability assessments.

SB11 (AMELIVU®(an KR registered trademark)/BYOOVIZ™, Samsung Bioepis) and SB15 (AFILIVU®(an KR registered trademark)/OPUVIZ™, Samsung Bioepis) represent significant advancements in the development of biosimilars for anti-VEGF therapy. SB11 demonstrated no meaningful differences between ranibizumab (rRBZ) in terms of structure, function, physicochemical properties, efficacy, safety, pharmacokinetics (PK), and immunogenicity over one year of follow-up.[11-13] Similarly, SB15, a biosimilar referencing aflibercept (AFL) with double-masked, randomized phase 3 clinical trial further confirmed analytical similarity[14], clinical equivalence and comparability in efficacy, safety, immunogenicity, and PK up to 56 weeks.[15,16] Based on findings from these two clinical trials and a previous post hoc study[17], factors such as age, baseline best-corrected visual acuity (BCVA), and central subfield thickness (CST) have been shown to influence treatment outcomes.

Following the publication of the previous post hoc study[17], the authors

suggested that the treatment delay due to screening duration might also influence visual and anatomical outcomes in nAMD. In phase 3 anti-VEGF clinical trials, the screening duration—defined as the interval between date of signed informed consent after initial diagnosis in the outpatient clinic and the initiation of intravitreal treatment after meeting the inclusion criteria determined by central reading center reviewers—is an essential process. Screening duration varies across clinical trials depending on protocol specifics, central reading center review times, or logistical constraints, potentially leading to treatment delays. Such variability may introduce bias into outcome measures and confound comparability across studies, thus warranting focused investigation. Many studies have explored treatment delays caused by medical concerns and their impact on visual outcomes[18-20], but only a few research has examined the effect of screening duration on treatment outcomes in anti-VEGF clinical trials, for example Goldberg et al. from the HARBOR post hoc analysis.[21]

Therefore, this post hoc analysis aimed to evaluate whether screening duration influences either the short- or long-term treatment outcomes, focusing on changes in BCVA and CST during the early treatment phase (week 8) and at the final endpoint (week 48).

Results

Baseline demographics and clinical characteristics are summarized in Table 1. The mean age of participants was 73.7 ± 8.2 years, with 56.6% being female. The racial distribution was 17.8% Asian and 81.4% White, while regional representation included 63.0% from the EU, 12.2% from the USA, and 24.8% from Asia and Russia. The mean baseline BCVA was 59.1 ± 11.1 letters (range: 33–77 letters), and the mean CST was 392.3 ± 117.4 μm (range: 143–889 μm).

Trend analyses in Figure 1 illustrate baseline BCVA and CST values, as well as changes in BCVA and CST at weeks 8 and 48, based on screening

duration. Screening duration ranged from day 1 to day 21, with 855 participants (74.2%) screened between days 6 and 15. At week 8, BCVA changes were 6.3±8.6 letters (range: -34-37 letters) and CST changes were -128.7 ± 85.5 μm (range: -498–486 μm). At week 48, BCVA changes were 10.4±7.9 letters (range: -52-47 letters). CST changes at week 48 were -132.8 ± 98.6 μm (range: -600–187 μm). No significant trend between the duration of screening and the treatment outcomes was visualized.

Table 2 presents the results of the multiple regression analysis examining the relationship between screening duration and treatment outcomes. The analysis showed no significant association between screening duration and treatment outcomes, including: Week 8 BCVA changes (B = -0.058, 95% CI: -0.154 to 0.039, P = 0.242) ; Week 8 CST changes (B = -0.050, 95% CI: -0.906 to 0.805, P = 0.908) ; Week 48 BCVA changes (B = -0.015, 95% CI: -0.159 to 0.130, P = 0.843) ; Week 48 CST changes (B = 0.036, 95% CI: -0.770 to 0.842, P = 0.930). This analysis suggests that screening duration does not have a significant impact on BCVA or CST changes at either week 8 or week 48.

Logistic regression analysis was performed to assess treatment success, defined as an improvement of ≥5 ETDRS letter scores in BCVA and a reduction of ≥100 μm in CST thickness, based on daily screening duration from day 1 to day 21. As shown in Figure 2, no significant association was observed between screening duration and treatment outcomes: Week 8 BCVA changes (P = 0.388) ; Week 8 CST changes (P = 0.142) ; Week 48 BCVA changes (P = 0.663) ; Week 48 CST changes (P = 0.293).

A subgroup analysis, divided into four screening duration—days 1–5, 6–10, 11–15, and 16–21—was performed and is presented in Figure 3. No statistically significant differences were observed between the groups across these duration in terms of BCVA and CST changes at weeks 8 and 48, even when comparing the earliest period (days 1–5) to the latest period (days 16–21) (BCVA: P = 0.523, CST: P = 0.126). However, a trend was noted, with the earliest period (days 1–5) showing greater CST improvements compared to the later screening duration. In addition, there were also no differences between SB11 and SB15 participants in terms of

BCVA and CST changes at weeks 8 and 48. Additionally, no significant interaction was observed between the lesion types and screening duration with respect to treatment outcomes.

Discussion

Our findings indicate that screening duration up to 21 days did not significantly impact changes in BCVA or CST during the early treatment phase (week 8) or at the final endpoint (week 48). Additionally, when treatment success was defined as an improvement of ≥5 ETDRS letter scores in BCVA and a reduction of ≥100 μm in CST, logistic regression analysis revealed no statistically significant association with screening duration. These findings provide valuable insight into the relationship between clinical trial screening protocols and treatment efficacy in nAMD. These results may provide reassurance to clinicians and researchers that slight delays in treatment initiation, within the studied time frame, do not significantly impact treatment outcomes.

The association between delays in anti-VEGF treatment and treatment outcomes has been a critical focus in managing retinal diseases such as neovascular age-related macular degeneration (nAMD). Evidence consistently indicates that timely initiation and adherence to anti-VEGF therapy are essential for optimal visual and anatomical outcomes. Delays in treatment, whether due to systemic barriers, patient-related factors, or scheduling challenges, can lead to disease progression, irreversible retinal damage, and poorer visual acuity outcomes. Muether et al. studied 69 patients receiving ranibizumab for the first time and 21 patients undergoing necessary re-treatment. In this study, factors such as approval procedures, limited short-term surgical capacity, and other medical concerns were identified as causes of delayed treatment in real-world clinical settings. They found that while the average visual decline was gradual, approximately one logMAR line over 110 days, some patients experienced a rapid loss of one or more lines within just 21 days. Based on these findings,

the authors recommended that treatment delays should not exceed two weeks to protect vision in individual patients.[19] Recently, the investigations related to the anti-VEGF treatment delay have sprung recently due to COVID-19 lockdown. Hanhart et al. examined the effects of COVID-19-related delays in intravitreal injections for nAMD and found that an average delay of 7.9 ± 5.2 weeks aggravated both BCVA and CST.[18] Specifically, delayed group showed less incidence of BCVA improvement (40% in regular treatment vs. 15% in delayed treatment, P=0.005) and a higher likelihood of BCVA deterioration (12% in regular vs. 34% in delayed, P=0.010). OCT imaging revealed thicker central subfields in delayed (372 ± 103 μm) compared to regular group (294 ± 54 μm), with a 26% difference (P<0.001) at the last pre-COVID-19 lockdown checkup. A retrospective multicenter study by Zarranz-Ventura et al., which included 302 eyes from 245 patients, indicated that treatment delays in nAMD (missed ≥ 1 intravitreal injection during lockdown) led to an average visual acuity loss of -2.0 letters in the delayed treatment group, compared to a loss of -0.6 letters in the group treated on time.[20] These studies primarily compared the outcomes between groups receiving timely regular injections and those with delayed injections. Few studies have specifically examined the relationship between screening delays and treatment outcomes in prospective randomized controlled trials (RCTs). In a post hoc analysis of the HARBOR study, Goldberg et al. reported that the interval from screening to first ranibizumab injection did not significantly affect BCVA change or injection number, with 24-month gains of 9.1 and 8.8 letters and corresponding use of 12.4 and 11.4 injections in the prompt and delayed groups, consistent with our findings.[21]

Although this study offers valuable insights, several limitations must be acknowledged. First, the analysis utilized data from two distinct clinical trials, potentially introducing variability in participant demographics and study methodologies. However, given the similar inclusion and exclusion criteria, the comparable baseline characteristics, and the fact that both studies were conducted in the same region, it can be concluded that the two studies share a high level of homogeneity. Second, while trends in CST reductions hinted at a possible advantage of earlier screening, this study

might have lacked the statistical power to produce significant results of small amount of difference in BCVA and CST changes. In studies with a larger patient population, meaningful results might have been observed. Third, exploring the impact of screening duration in newer anti-VEGF treatments, such as brolucizumab or faricimab, could provide different results from that of our current study using ranibizumab and aflibercept. Additional studies are required to assess whether delays in treatment beyond 21 days impact visual prognosis and to what degree such delays are acceptable.

In conclusion, screening duration up to 3 weeks does not significantly impact BCVA or CST changes in either the short- or long-term in anti-VEGF clinical trials for nAMD. While earlier treatment after signing informed consent form may be associated with better anatomical outcomes, the differences are not statistically significant. These findings highlight the importance of continued investigation into factors influencing treatment outcomes and may guide future clinical trial designs and treatment protocols.

Materials and Methods

The Institutional Review Board of Seoul National University Bundang Hospital (SNUBH) approved this post hoc analysis of previous prospective, phase 3, randomized clinical trials (RCTs), which adhered to the tenets of the Declaration of Helsinki (IRB No. B-2402-881-105). Informed consent was obtained from all subjects.

Brief description of the phase 3 trial study design

The SB11 equivalence study was a phase 3, randomized, double-blinded, parallel-group trial conducted over 52 weeks at 75 centers across 9 countries (ClinicalTrials.gov: NCT03150589) (first trial registration date : 23/3/2018).[11-13] Eligible participants had active subfoveal choroid neovascularization (CNV) secondary to neovascular age-related macular

degeneration (nAMD), ETDRS letter scores of 73 to 34 (approx. 20/40 to 20/200 Snellen equivalent), and lesion areas ≤9.0 disc areas. Participants were randomized 1:1 to receive intravitreal injections of SB11 (0.5 mg) or rRBZ (0.5 mg) every 4 weeks for 48 weeks, with follow-up to week 52. Change from baseline in BCVA and CST were evaluated as primary endpoints at weeks 8 and 4, respectively, due to their sensitivity during the loading phase. Secondary outcomes included safety, immunogenicity, and pharmacokinetics over 52 weeks. The one-year results complemented the primary analyses to confirm biosimilarity.

The SB15 equivalence study was a 56-week, randomized, double-masked, multicenter, phase 3 trial (ClinicalTrials.gov: NCT04450329) (first trial registration date : 02/7/2021) conducted across Europe, the USA, Russia, South Korea, and Japan.[15,16] Participants had treatment-naïve subfoveal CNV lesions secondary to AMD, with at least 50% of the lesion being neovascular, a total lesion area ≤9.0 disc areas, and BCVA of 20/40–20/200 (ETDRS letter score 73–34). Eligibility was confirmed through independent central reading of retinal images. The study included a screening period, a 32-week main period, and a 24-week switching period. At week 0, participants were randomized 1:1 to receive intravitreal injections of SB15 or aflibercept (AFL) every 4 weeks for three doses, followed by dosing every 8 weeks up to week 48. At week 32, AFL participants were re-randomized to continue AFL (AFL/AFL) or switch to SB15 (AFL/SB15), while SB15 participants continued SB15 (SB15/SB15). Assessments included BCVA, OCT, fluorescein angiography, and fundus photography, with central reading of retinal images. Secondary endpoints included changes in BCVA, CST, and CNV area, and fluid presence up to week 56. Safety outcomes covered treatment-emergent adverse events, immunogenicity, and pharmacokinetics.

Post hoc analysis : Participants

Participants were drawn from two prior randomized, double-masked, parallel-group, multicenter phase 3 clinical trials conducted over one year. These trials assessed the efficacy and safety of two anti-VEGF biosimilars:

SB11 (ranibizumab, BYOOVIZ™, Samsung Bioepis)[11-13] and SB15 (aflibercept, OPUVIZ™, Samsung Bioepis).[15,16] A total of 1,152 participants were included in this analysis, comprising 704 participants from the SB11 trial and 448 from the SB15 trial.

Post hoc analysis : Statistical analyses

The study aimed to explore the relationship between screening duration and treatment outcomes, evaluated by changes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) at week 8 (early treatment phase) and week 48 (final treatment phase). Since the final endpoints of the two clinical studies differ—52 weeks for SB11 and 56 weeks for SB15—we chose week 48 as the reference point for comparison, as it represents the overlapping phase of both trials.

Trend analyses were conducted to evaluate baseline BCVA/CST values and changes in BCVA and CST at weeks 8 and 48 for participants in the SB11 and SB15 clinical trials based on their screening duration. Multiple linear regression analyses, including univariable and multivariable models, were performed to assess the relationship between screening duration and treatment outcomes. The multivariable model was adjusted for baseline factors such as age and BCVA/CST, which are known to influence treatment outcomes.[17] Logistic regression analyses were used to explore the association between screening duration and significant treatment outcomes at weeks 8 and 48. Treatment success was defined as an improvement of ≥5 ETDRS letter scores in BCVA and a reduction of ≥100 μm in CST thickness. Additionally, a subgroup analysis was conducted by dividing screening duration into four periods—day 1–5, day 6–10, day 11–15, and day 16–21—to examine the relationship between each screening duration group and changes in BCVA or CST. All participants in this analysis had screening durations of ≤21 days, consistent with the screening periods of up to 28 days used in the original aflibercept and recent faricimab clinical trials.[22,23] Based on our sample size (N = 1,152), standard deviations observed for BCVA and CST changes, and a two-sided alpha of 0.05, our study was powered at >80% to detect a BCVA difference of 2 letters and

CST difference of 40 μm.

Although SB11 and SB15 trials were not identical, they shared similar key design elements, including study population, primary efficacy endpoints, and outcome assessment schedules. Prior to pooling, we systematically compared protocol features and harmonized definitions for all variables. We then performed subgroup and interaction analyses, which revealed no significant differences in treatment effects between trials. Sensitivity analyses confirmed that the pooled results were robust. These steps supported the appropriateness of combining the data, with all protocol differences transparently reported.

Acknowledgements

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Author Contributions: Drs. Hyeong Min Kim and Se Joon Woo had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: H.M. Kim and S.J. Woo
Acquisition, analysis, or interpretation of data: H.M. Kim and S.J. Woo
Drafting of the manuscript: H.M. Kim and S.J. Woo
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Statistical analysis: H.M. Kim
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Administrative, technical, or material support: H.M. Kim and S.J. Woo
Supervision: S.J. Woo

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Data availability :
The datasets generated and/or analysed during the current study are not publicly available due to the ownership of the original data by the Samsung Bioepis but are available from the corresponding author on reasonable request.

Figure Legends

Figure 1. Trend analyses of best corrected visual acuity (BCVA) and central subfield thickness (CST) were conducted according to screening duration from day 1 to day 21. (A, D) Baseline BCVA/CST, (B, E) Week 8 BCVA/CST changes, and (C, F) Week 48 BCVA/CST changes were plotted. Each participant is represented as a dot, with red dots for SB11 participants and blue dots for SB15 participants.

Figure 2. Logistic regression analyses were conducted for (A, C) Week 8 BCVA/CST changes and (B, D) Week 48 BCVA/CST changes. The gray zone and line indicate the odds ratios and probability according to screening time duration day 1 to day 21.

Figure 3. Subgroup analyses were conducted for (A) BCVA and (B) CST changes according to screening duration: day 1-5 (red line), day 6-10 (green line), day 11-15 (blue line), and day 16-21 (purple line).

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Table 1. Baseline demographics and clinical characteristics of the participants

	All (N = 1152)	SB11 (N = 704)	SB15 (N=448)
Age, years (range)	73.7±8.2 (50-96)	73.8±8.1 (51-96)	74.1±7.8 (51-96)
Female, N (%)	652 (56.6%)	403 (57.2%)	249 (55.6%)
Race, N (%)			
Asian	205 (17.8%)	102 (14.5%)	103 (23.0%)
Black or African American	2 (0.2%)	1 (0.1%)	1 (0.2%)
White	938 (81.4%)	597 (84.8%)	341 (76.1%)
Other	7 (0.6%)	4 (0.6%)	3 (0.7%)
Region, N (%)			
EU	725 (63.0%)	449 (63.8%)	276 (61.7%)
USA	141 (12.2%)	113 (16.0%)	28 (6.2%)
Asia & Russia	286 (24.8%)	142 (20.2%)	144 (32.1%)
BCVA, total letter score (range)	59.1±11.1 (33-77)	58.8±11.2 (33-73)	59.4±11.1 (34-77)
CST, µm (range)	392.3±117.4 (143-889)	408.1±118.2 (143-843)	368.8±110.4 (171-889)

BCVA, Best corrected visual acuity ; CST, Central subfield thickness

Table 2. The association between screening time and treatment outcomes*

	Univariable			Multivariable		
	Beta	95% CI	*P* value	Beta	95% CI	*P* value
Week 8 BCVA changes						
Screening time	-0.064	-0.162, 0.034	0.201	-0.058	-0.154, 0.039	0.242
Age				-0.142	-0.198, -0.086	< 0.001
Baseline BCVA				-0.079	-0.122, -0.036	< 0.001
Week 8 CST changes						
Screening time	0.715	-0.521, 1.952	0.257	-0.050	-0.906, 0.805	0.908
Age				-1.207	-1.697, -0.716	< 0.001
Baseline CST				-0.622	-0.657, -0.587	< 0.001
Week 48 BCVA changes						
Screening time	-0.038	-0.186, 0.109	0.611	-0.015	-0.159, 0.130	0.843
Age				-0.218	-0.300, -0.136	< 0.001
Baseline BCVA				-0.176	-0.240, -0.112	< 0.001
Week 48 CST changes						

Screening time	1.096	-0.309, 2.502	0.126	0.036	-0.770, 0.842	0.930
Age				-1.027	-1.485, -0.570	< 0.001
Baseline CST				-0.769	-0.802, -0.736	< 0.001

CI, Confidence Interval ; BCVA, Best corrected visual acuity ; CST, Central subfield thickness
* Multiple linear regression analysis