Biosimilars for Retinal Diseases- Understanding the Phase 3 Clinical Trial Design

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There has been a growing interest in the biosimilars of anti-vascular endothelial growth factors (anti-VEGF).\(^{(1)}\) There are various biosimilar molecules of ranibizumab and aflibercept at various stages of clinical trials.\(^{(1)}\) Results of the Phase 3 trials of two molecules FYB 201 and SB11 (biosimilars of ranibizumab) have been published recently. The study design and regulatory pathway for biosimilars have unique features compared to originator molecules. Of particular note, reliance for approval on only a single clinical trial and the use of a short primary endpoint are common differences seen with biosimilar approvals.\(^{(2,3)}\) Most of the biosimilars of ranibizumab that have completed or are undergoing phase 3 clinical trials have primary endpoint analysis (visual acuity and macular thickness) at 4 or 8 weeks, though a variety of secondary efficacy end point data (including BCVA) is collected through the length of the trials, which are typically up to 12 months long.\(^{(4)}\) In contrast, reference originator molecules usually have primary efficacy endpoints at 12 months. This early primary efficacy endpoint in biosimilar trials is a new concept for the retina specialists who are used to extensive long term data end points since the introduction of anti-VEGFs in this field. Such a phase 3 clinical trial design with a single trial and short primary end points might generate distrust towards the biosimilar molecules even before receiving approval. As such, it is important to develop an understanding about the phase 3 clinical trial design for biosimilars related to retinal diseases at this time.

**Study design**

As the goal in the biosimilar trials is to test equivalence to the reference product, equivalence study designs are preferred in retinal biosimilar trials. These equivalence trials generally use equivalence margins based on the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score and change in central foveal thickness (CFT) on optical coherence tomography (OCT) to
detect clinically meaningful differences between biosimilars and the reference products with a 90-95% confidence interval.

**Sample size**

Sample size should be adequate enough to provide sufficient exposure to the biosimilar and the reference product. Furthermore, it should be able to detect the safety signals. Equivalence margin plays an important role in the determination of the sample size. The narrower the equivalence margin, the larger the sample size needs to be. The US-FDA requires only one phase 3 clinical trial for biosimilars compared to two for the originator molecules. This is predominantly due to the established pharmacoequivalence of the biosimilar molecule to the originator molecule in the early testing phases.

**Selection of endpoints and duration**

The endpoints used in biosimilar trials are similar to the endpoints used in the trials for the approval of the reference product (BCVA and CFT), except that the assessment of the primary efficacy endpoint is at a much earlier timepoint. The assessment at week 8 in the phase 3 results by Holz et al was endorsed by the regulatory authorities because it is in the linear, steep part of the dose response curve. Therefore, it is within the most sensitive timepoint to detect any potential efficacy differences between the reference product and the biosimilar.

**Safety**

Safety assessments are done throughout the study period similar to the trials for the reference molecule and post marketing surveillance is similar to the originator molecules. For
immunogenicity testing, the FDA had released final guidance for developing and validating assays for Anti-Drug Antibody detection for biologics and biosimilars in 2019.\textsuperscript{4}

The Phase 3 trial of FYB 201 tested the clinical equivalence of FYB 201 to reference ranibizumab (Lucentis, Roche/Genentech). The primary end point was change from baseline BCVA by ETDRS letters at 8 weeks before the third monthly intravitreal injection. The biosimilarity of FYB201 to its originator was assessed via a 2-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters. The BCVA improved in both groups, with a mean improvement of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at week 8. Primary end point was met as the 90% CI was within the predefined equivalence margin. The recently published Phase 3 trial of SB11 had similar equivalence margin of 3 ETDRS letters. However, the primary endpoint was change from baseline in BCVA at week 8 for the US-FDA and change from baseline in central subfield thickness at week 4 for EMA and other regulatory agencies. Similar to the FYB201 ranibizumab biosimilar trial, safety and secondary efficacy endpoint data was collected throughout the entire 48 week trial evaluating SB11.

To summarize, biosimilars may be new to ophthalmology, but, overall they are an emerging well-established field with well-defined regulatory guidelines.\textsuperscript{5} Physicians should keep faith in the regulatory agencies such as the US-FDA and EMA because these agencies make sure that even after keeping the clinical trial data minimal for biosimilar molecules, efficacy and safety is not compromised. If we understand this, biosimilar molecules could be of potential help for patients suffering from retinal diseases while providing a significant cost benefit globally though the cost would presumably still be high compared to off label bevacizumab.
References


