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COMMENT

Approved biosimilar ranibizumab—a global update

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The innovator ranibizumab molecule's (Lucentis, Genentech, USA) patent expired in June 2020 (USA) and July 2022 (EU) [1]. This has led to a flurry of new drug applications and approval of biosimilar ranibizumab across the globe. There are many biosimilar ranibizumab molecules that have already been approved worldwide. Some molecules are being marketed with different brand names in different regions. This manuscript will help update ophthalmologists about the approved biosimilar ranibizumab worldwide with data of the phase 3 results in brief (Table 1).

Food and Drug Administration (FDA) and European Medical Agency (EMA) approved

(UK, US, Europe, Canada)

Ranibizumab-nuna (Byooviz, Samsung Bioepis, South Korea/ Biogen, USA)

This is the first biosimilar ranibizumab molecule to receive approval by both the FDA and EMA [1, 2]. Both 6 and 12 month clinical data of phase 3 trials have been published pertaining to its safety and efficacy [3, 4]. It has been approved for all the indications for which reference ranibizumab (RBZ) is approved in Europe {neovascular-age related macular degeneration (n-AMD), diabetic macular edema (DMO), Diabetic Retinopathy (DR), retinal vein occlusion (RVO), myopic choroidal neovascular membrane (m-CNVM)}. However, it has not yet received approval for diabetic macular edema (DMO) and diabetic retinopathy (DR) in the US.

Phase 3 clinical trial data

In total, 705 participants with treatment naïve n-AMD {biosimilar ranibizumab (SB11), 351; reference ranibizumab (RBZ), 354} were included in this equivalence study. All the subjects were treated at 4 weekly intervals for 48 weeks. Interim analysis was done at 24 weeks with primary efficacy end points of best corrected visual acuity (BCVA) improvement in letters at 8 weeks and central subfield thickness (CST) improvement at 4 weeks. Predefined equivalence margins for adjusted treatment differences of −3 letters to +3 letters for BCVA and −36 to +36 µm for CST were utilized. At 24 and 52 weeks, difference was within the predefined equivalence margin. Safety was also found equivalent in both the arms [3, 4].

UK Medicines & Healthcare Regulatory Agency (MHRA) Approved (United Kingdom)

Ongavia (Bioeq AG Switzerland/Teva Pharmaceuticals, Israel), FDA approved,

Ranibizumab-eqrn (CIMERLI, Coherus Biosciences, USA) EMA Approved,

Ranivisio® (Bioeq AG Switzerland/ Polpharma Biologic, Poland)

Ongavia was developed in collaboration with BioEq. As part of the partnership, Teva will have exclusive commercialization rights in the United Kingdom, the European Union, and Canada. Coherus has exclusive commercialization rights in the US. The biosimilar has received EMA approval recently (29th August, 2022) with the name as Ranivisio [5]. Submission for Canadian approval is expected to be completed in late 2022 [6].

CIMERLI is the brand name of the same molecule (FYB 201) as Ongavia and Ranivisio. CIMERLI has received FDA approval as the first interchangeable biosimilar ranibizumab available globally [7]. It has received exclusivity for this status for 12 months. It has been approved for all the indications for which RBZ is approved. (n-AMD, DMO, DR, RVO, m-CNVM).

Phase 3 clinical trial data

In total, 477 participants with treatment naïve n-AMD {biosimilar ranibizumab (FYB201), 238; reference ranibizumab (RBZ), 239} were included in this equivalence study. All the subjects were treated at 4-week intervals for 48 weeks. The primary end point was change from baseline in BCVA by ETDRS letters at 8 weeks before the third monthly intravitreal injection. Predefined equivalence margins for adjusted treatment differences of −3.5 letters to +3.5 letters for BCVA. The BCVA improved in both groups, with a mean improvement of +5.1 (FYB201) and +5.6 (RBZ) ETDRS letters at week 8. Efficacy equivalence was established along with safety which was monitored throughout the study [8].

Drug Controller General of India approved (DCGI, India)

Razumab (Intas Pharmaceuticals, Ahmedabad, GJ, India)

Razumab was globally the first biosimilar ranibizumab molecule that was approved in India by its regulator DCGI in June 2015 [9]. It is approved for all the indications for which the reference ranibizumab is approved (n-AMD, DMO, RVO, m-CNVM). Razumab has also been approved for retinopathy of prematurity (ROP).

Phase 3 clinical trial data

In total, 104 participants with n-AMD {biosimilar ranibizumab (Razumab),78; reference ranibizumab (RBZ), 26} were included in this study. All the subjects were treated at 4-week intervals up to 12 weeks. Primary efficacy end point was the proportion of patients with of loss of <15 letters on ETDRS at 12 weeks. Secondary endpoint was mean increase in BCVA and CST improvement at 12 weeks. Immunogenicity assessment was done throughout 12 weeks. None of the parameters were different between these two arms throughout the study. (Data from file).

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Table 1. Key characteristics of phase 3 clinical trial design.

Biosimilar name	Approval authority (date)	Sample size	Primary outcome	Equivalence margin	Total study duration	Safety assessment criteria
Byooviz/ Ranibizumab-nuna (SB11)	US-FDA and EMA	705 (SB11-351) (RBZ-354)	BCVA improvement (8 weeks) CST (4 weeks)	BCVA (−3 to +3 ETDRS letters) CST (−36 to +36 μm)	12 months	TEAEs ADA
Ongavia (FYB 201) CIMERLI/ Ranibizumab-eqrn (FYB 201) Ranivisio (FYB 201)	UKMHRA US-FDA EMA	477 (FYB 201-238) (RBZ-239)	BCVA improvement (8 weeks)	BCVA (−3.5 to +3.5 ETDRS letters)	12 months	TEAEs ADA
Ranibizumab Biosimilar 1 (Ranibizumab-BS1)	Japan Ministry of Health, Labour and Welfare (Japan)	351 (Ranibizumab BS 1-176) (RBZ-175)	BCVA improvement (12 weeks)	BCVA (−4 to +4 ETDRS letters)	12 months	TEAEs ADA
Razumab	DCGI India	104 (Razumab-78) (RBZ-26)	Loss of <15 letters on ETDRS at 12 weeks	NA	3 months	TEAEs ADA
Ranizurel	DCGI India	160 (Ranizurel-107) (RBZ-53)	Loss of <15 letters on ETDRS at 16 weeks	NA	6 months	TEAEs ADA
Ranieyes	DCGI India	202 (Ranieyes-101) (RBZ-101)	Loss of <15 letters on ETDRS at 12 weeks	±8.5%	3 months	TEAEs ADA

US-FDA Unites States Food and Drug Administration, *EMA* European Medical Agency, *UKMHRA* United Kingdom The Medicines and Healthcare products Regulatory Agency, *DCGI* Drug Controller General of India, *BCVA* best corrected visual acuity, *ETDRS* Early Treatment Diabetic Retinopathy Study Letters, *TEAEs* treatment emergent adverse events, *ADA* anti drug antibodies, *RBZ* reference ranibizumab, *CST* central subfoveal thickness, *NA* not available.

Ranizurel (Reliance Life Sciences Ltd, Mumbai, India)

Ranizurel was the second biosimilar ranibizumab molecule approved in India by the DCGI in October 2020. It is approved in India for n-AMD.

Phase 3 clinical trial data

In this study, a total of 160 subjects of treatment naïve n-AMD were randomized as 107 subjects in the biosimilar ranibizumab (RanizuRel) group and 53 subjects in the reference ranibizumab (RBZ) group in order to dose 159 subjects with the study medication i.e., 106 subjects in the RanizuRel group and 53 subjects in the RBZ group. Patients received RanizuRel or RBZ 0.5 mg (0.05 ml of 10 mg/ml solution) as an intravitreal injection once every 4 weeks for the treatment period of 24 weeks. Efficacy and safety were found equivalent [10].

Ranieyes (Lupin Limited, Mumbai, India)

Ranieyes was the third biosimilar ranibizumab molecule approved in India by the DCGI in Nov 2021 for n-AMD and in June 2022 for DMO, RVO and CNV due to pathological myopia.

Phase 3 clinical trial data

In total, 170 evaluable participants (randomized 202) with treatment naïve n-AMD {biosimilar ranibizumab (Ranieyes), 101; reference ranibizumab (RBZ), 101} were included in this equivalence study. All the subjects were treated at 4-week intervals for 12 weeks. Primary efficacy endpoint was the proportion of patients losing fewer than 15 letters (~3 lines) from baseline BCVA in the study eye at the end of 3 months, assessed with the ETDRS chart. Predefined equivalence margin for the same was of ±8.5%. Efficacy and safety were found equivalent [11].

Pharmaceuticals and Medical Devices Agency (PMDA) Japan

Ranibizumab BS 1 (Senju Pharmaceutical Co., Ltd, in collaboration with Kids well Bio Corporation, Japan)—It received approval in Japan on September 27, 2021 for nAMD.

Phase 3 clinical trial data

In total, 351 participants with treatment naïve n-AMD {biosimilar ranibizumab (BS), 176; reference ranibizumab (RBZ), 175} were included in this equivalence study. BS or RBZ was administered once every 4 weeks for a total of 3 doses from baseline to 8 weeks. BS was administered using a flexible regimen according to the participants' symptoms in both groups from 12 weeks to 48 weeks. And then, safety and efficacy were evaluated at 52 weeks.

The primary end point was change from baseline in (BCVA) by ETDRS letters at 12 weeks from the first treatment day (baseline). Predefined equivalence margins for adjusted treatment differences of −4 letters to +4 letters for BCVA. The difference between the groups (the BS group the RBZ group) was −1.5 letters (95% CI: −3.2 to 0.3), and the result also showed equivalence in terms of safety between the BS group and the RBZ group. (Data on file of the company).

To summarize, biosimilars are becoming an important part of the retinal pharmacotherapy globally. For the next few years, retinal specialists might witness many biosimilar anti-VEGF molecules receiving approval. It is important for retina specialists to be well aware and updated about this new wave of molecules. This will not only help biosimilars utilize their real potential but also would help patients and health systems to reduce their financial burden.

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AUTHOR CONTRIBUTIONS

AS: conception, analysis, drafting, integrity check, final approval. MK, CI, NP, NK, FB, AL, and BDK: drafting, revision, analysis, integrity check.

COMPETING INTERESTS

AS: Consultant: for Novartis, Allergan, Bayer and Intas. MK: Clinical Research: Alcon, Bayer, Hoya, Kowa, Novartis, Otsuka, Santen, Senju; Consultant: Chugai, Daicel, Novartis, Ono, Sanofi, Asahi-Kasei, Senju. CI: none. FB: Consultant: Allergan, Bayer, Boehringer Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. AL reports other from Allergan, other from Novartis, other from Roche, other from Notal Vision, other from Forsightslabs, other from Beyeonics, other from Bayer Health Care. BDK: Clinical Research: Alimera, Allegro, Allergan, Apellis, Boehringer Ingelheim, Clearside, Genentech, GSK, Ionis, IvericBio, jCyte, Novartis, Regeneron; Consultant: Alimera, Allegro, Allergan, Eyebio, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics/Ripple Therapeutics, IvericBio, jCyte, Novartis, Regeneron, Revana, Theravance Biopharma. NK: none. NP: none.

ADDITIONAL INFORMATION

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