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EFFICACY AND SAFETY OF BIOSIMILAR FYB201 COMPARED WITH RANIBIZUMAB IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

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ABSTRACT

The authors are commenting on the study entitled**:** "Efficacy and safety of biosimilar FYB201 compared with ranibizumab in neovascular age-related macular degeneration" published by Holz *et al* in Ophthalmology 2021 (doi.org./10.1016/j.ophtha.2021.04.031. Published on May 2, 2021), which prospectively investigated the clinical equivalence of the biosimilar FYB201 (n = 238) and reference ranibizumab (n = 239) in 477 patients with treatment-naïve active subfoveal choroidal neovascularization caused by neovascular age-related macular degeneration. The best-corrected visual acuity improved in both groups with a mean improvement of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at week 8 before the third monathly intravitreal injection. Biosimilarity of FYB201 to its original biolog ranibizumab was assessed via a 2-sided equivalence test with an equivalence margin in best-corrected visual acuity of 3 ETDRS letters. The authors concluded that FYB201 is similar to reference ranibizumab in terms of clinical efficacy and ocular and systemic safety in the treatment of patients with neovascular age-related macular degeneration. However, the validation, extrapolation, and generalizabilty of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the equivalence of biosimilar FYB201 and its bio-originator ranibizumab.

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INTRODUCTION

We read with interest the study by Holz *et al.* (2021) which prospectively investigated the clinical equivalence of the biosimilar FYB201 (n = 238) and reference ranibizumab (n = 239) (Lucentis; Genentech, Inc., South San Francisco, CA, USA) in 477 patients with treatment-naïve active subfoveal choroidal neovascularization (CNV) caused by neovascular age-related macular degeneration (nAMD). The best-corrected visual acuity (BCVA) improved in both groups with a mean improvement of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at week 8 before the third monathly intravitreal (IVT) injection. Biosimilarity of FYB201 to its bio-originator was assessed via a 2-sided equivalence test with an equivalence margin in BCVA of 3 ETDRS letters. The authors concluded that FYB201 is similar to its original biolog ranibizumab in terms of clinical efficacy and ocular and systemic safety in the treatment of patients with nAMD. We would like to address several challenges that have arisen from this study which can be specifically summarized below.

First, there was a selection bias, caused by randomization that was stratified by site and screening BCVA category (20/32 or 20/40 to 20/100) based on a dynamic allocation method. Once a maximum of 48 patients with a screening BCVA of 20/32 were enrolled, randomization to this stratum was stopped.

Although the study was evaluation-masked, with both patient and other study staff (including the investigator who performed evaluations) being masked to treatment assignment, the IVT injections were performed by an unmasked ophthalmologist. On the other part, a total of 25 patients (10.5%) in the FYB201 group and 38 patients (15.9%) in the reference ranibizumab group had ≥1 treatment interruption. Taken together, these findings may have confounded the results.

Second, the statistical comparative analysis of the patient baseline characteristics (Table 1) of the 2 study groups was not carried out to see whether they could be compared. Overall, BCVAs of the patients in the FYB201 group obviously seem better than those in the reference ranibizumab group. Specifically, the proportions of the 20/32, 20/40, and 20/50 BCVA categories are larger and those of the 20/63 and 20/100 BCVA strata are smaller in the biosimilar FYB201 group compared to the ones in the bio-originator ranibizumab group.

Third, there were no data in the Table 1 on the proportions of all types of the active nAMD macular neovascularization (MNV) lesions (i.e., occult type 1, predominantly classic type 2, minimally classic mixed type 1 and mixed type 2, and retinal angiomatous proliferation type 3 MNVs) (Spaide *et al.* 2020) which should have been balanced between the 2 study groups at baseline to allow their comparison. The spectral domain optical coherence tomography (SD-OCT) patterns of the 3 phenotypes of the lesions representing 3 main pathways of

progression from original MNV lesions to fibrotic scar during the study period (the type A located underneath the retinal pigment epithelium [RPE]; the type B located above the RPE with intact RPE; and the type C located subretinal with the RPE indistinguishable) were not presented.

Fourth, in the assessment of the 48-week efficacy of treatment we considered the current assertion that evaluation of the outcomes has to be guided by anatomical measure data with visual changes as a secondary guide (Freund *et al.*2015). Accordingly, the effectiveness of the treatment was unsatisfactory in both treatment groups. Although the BCVA improved by +7.8 and +8 ETDRS letters, respectively, in patients of the FYB201 group and reference ranibizumab group, 56.4% and 58.7% of patients, respectively, had fovea-involving fluid leakage related to CNV activity (i.e., sub or intraretinal fluid on SD-OCT or retinal pigment epithelial detachment) and 53.3% and 51.1% of patients, respectively, presented wet macula. These findings highlight unresolved macular edema owing to undertreatment administered (overall average the full 12 injections) with insufficient macular deturgescence and indicate that the disease process is still active and progressive, requiring further treatment with antiangiogenic agents.

Fifth, the following pertinent data that should have been included in the statistical analyses, are missing from the study: the mean time duration of symptoms of the nAMD from diagnosis to the initiation of treatment; the SD-OCT patterns of the vitreoretinal interface abnormalities at baseline and at the end of the study (e.g., epiretinal membranes, vitreomacular adhesion/traction, and combined epiretinal membranes and vitreomacular traction); the existence or otherwise of the disorganization of retinal inner layers and its severity at enrollment and at completion of the study (mild, severe, and severe with damaged ellipsoid zone [EZ]); the proportions of patients with intraretinal and subretinal fluid and the location of the intraretinal fluid (e.g., inner/outer nuclear layers or ganglion cell layer) at presentation and at the end of the study; the SD-OCT patterns of the pigment epithelial detachment (drusenoid/fibrovascular/serous/mixed) at presentation and at the end of the follow-up period; the alterations of the photoreceptor cell layer (disorganization/thinning of the outer nuclear layer, external limiting membrane defects, disruption of the EZ, and interdigitation zone) at enrollment and at the end of the study; the proportion of eyes with subretinal fibrosis at week 48; the existence or otherwise of the 2 distinct phenotypic subgroups of advanced fibrotic lesions at the completion of the study (the fibroatrophic lesions [absence of proliferation under the subretinal space] and the fibroglial lesions [fibroglial proliferation in the subretinal space after RPE erosio]); the existence or not of the 4 phenotypes of de novo atrophies at the end of the study (the complete and incomplete retinal pigment epithelial and outer retinal atrophies and the complete and incomplete outer retinal atrophies) (Sadda *et al*. 2018); the prevalence, number, size, and shape of the tubular structures affecting the outer retina and RPE termed outer retinal tubulation at presentation and at the completion of the study; the quantification of the subretinal hyperreflective material and its composition at baseline and at the end of the study (for example, fibrosis, blood, fibrin, exudation, lipid, vitelliform material, or neovascular tissue); the proportion of eyes with reticular pseudodrusen at baseline and at week 48; and the subfoveal choroidal thickness at enrollment and at the completion of the study (Călugăru *et al.* 2020).

Altogether, the authors documented the equivalence of FYB201 and reference ranibizumab in terms of clinical efficacy, safety, and immunogenicity in patients with nAMD. Still, the validation, extrapolation, and generalizability of these findings can be made only by regression analyses including all the missing data referred to above by us in addition to the baseline characteristics already assessed in this study, serving to identify the potential prognosticators influencing the equivalence of biosimilar FYB201 and its original biolog ranibizumab.

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