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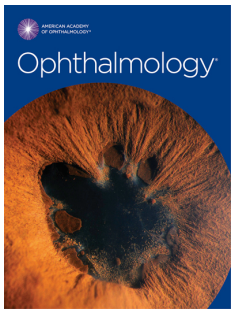


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# Efficacy and Safety of Biosimilar FYB201 Compared With Ranibizumab in Neovascular Age-Related Macular Degeneration

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**Abbreviations:**

ADA, antidrug antibody

AE, adverse event

AMD, age-related macular degeneration

ANCOVA, analysis of covariance

BCVA, best corrected visual acuity

CI, confidence interval

CNV, choroidal neovascularization

$C_{max}$, maximum concentration

ETDRS, Early Treatment Diabetic Retinopathy Study

EU, European Union

FCP, foveal center point

FCS, foveal central subfield

IMP, investigational medicinal product

IVT, intravitreal

nAb, neutralizing antidrug antibody

nAMD, neovascular age-related macular degeneration

SAE, serious adverse event

SD-OCT, spectral domain optical coherence tomography

TEAE, treatment-emergent adverse event

US, United States

VEGF, vascular endothelial growth factor

**Online-only material statement:** This article contains additional online-only material. The following should appear online-only: Supplementary Table 1, Supplementary Table 2, Supplementary Figure 1, and Supplementary Figure 2.

**Abstract (234/350)**

**Purpose:** This trial was conducted to investigate the clinical equivalence of the proposed biosimilar FYB201 and reference ranibizumab in patients with treatment-naive, subfoveal choroidal neovascularization caused by neovascular age-related macular degeneration (nAMD).

**Design:** This was a prospective, multicenter, evaluation-masked, parallel-group, 48-week, phase III randomized study.

**Participants:** A total of 477 patients were randomly assigned to receive FYB201 (n = 238) or reference ranibizumab (n = 239).

**Methods:** Patients received FYB201 or ranibizumab 0.5 mg by intravitreal injection in the study eye every four weeks.

**Main Outcome Measures:** The primary end point was change from baseline in best corrected visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at 8 weeks prior to the third monthly intravitreal injection. Biosimilarity of FYB201 to its originator was assessed via a two-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters.

**Results:** BCVA improved in both groups, with a mean improvement of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at week 8. The analysis of covariance (ANCOVA) least squares mean difference for the change from baseline between FYB201 and reference ranibizumab was –0.4 ETDRS letters with a 90% confidence interval (CI) of –1.6 to 0.9. Primary end point was met as the 90% CI was within the predefined equivalence margin. Adverse events were comparable between treatment groups.

**Conclusions:** FYB201 is biosimilar to reference ranibizumab in terms of clinical efficacy and ocular and systemic safety in the treatment of patients with nAMD.

## Introduction

Age-related macular degeneration (AMD) is the cause of 8.7% of blindness worldwide and the most common cause of blindness in older people in developed countries,[1] with its prevalence increasing with each decade after 50 years.[2] Advanced AMD can be atrophic nonneovascular AMD or neovascular AMD (nAMD). The latter comprises 10%–15% of all AMD but is responsible for more than 90% of AMD-related severe visual loss,[3] with a considerable impact on quality of life and impairment of activity for patients.[4] Choroidal neovascularization (CNV) is the hallmark of nAMD; if left untreated, CNV may result in loss of central vision.[5]

The current standard of care of nAMD is intravitreal (IVT) injections of anti-vascular endothelial growth factor (VEGF), which include ranibizumab, aflibercept, pegaptanib, and brolucizumab, and the off-label use of bevacizumab.[2, 6] Ranibizumab is a humanized murine anti–VEGF-A monoclonal antibody fragment[7] with a high affinity for the binding site of all VEGF-A isoforms, preventing VEGF receptor complex binding and subsequent increased vessel permeability, endothelial cell proliferation, new vessel growth, and nAMD progression.[8] IVT ranibizumab is a well-established treatment for nAMD, with high and rapid retinal penetration and a short half-life, which minimizes systemic effects.[9]

Anti-VEGF treatment for nAMD management carries a substantial burden for patients and health care systems, especially the cost of the medication.[10] Treatment burden because of frequent and expensive injections may limit real-world outcomes,[11] which also affects and causes additional burden on insurance companies and their reimbursement policies.[12-15]

Biosimilars are biologics that are highly similar in their physical, chemical, and biological properties to an already marketed reference drug.[16] Demonstration of biosimilarity relies on comprehensive comparability studies with the reference medicine. Biosimilars have been available for over 10 years and have helped reduce costs and improve patient access to safe and effective biological medicines.[17-19] Biosimilar monoclonal antibodies that have been approved by both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) include rituximab, trastuzumab, and bevacizumab for oncological indications, and infliximab and adalimumab for autoimmune disease. Biosimilars of adalimumab are also indicated for the treatment of noninfectious uveitis.

FYB201 is a candidate biosimilar for ranibizumab that is produced in *E. coli* by periplasmic expression, like the reference product, and has comparable properties, strength, route of administration, posology, and storage conditions to the reference product. The COLUMBUS-AMD trial was conducted to investigate the clinical equivalence of FYB201 and reference ranibizumab in

patients with nAMD. Plasma concentrations of FYB201 and reference ranibizumab were also measured to compare systemic exposure between treatments.

**Methods**

COLUMBUS-AMD was an evaluation-masked, parallel-group, multicenter, 48-week, randomized phase 3 study to assess the clinical equivalence of FYB201 (bioeq GmbH, Holzkirchen, Germany) with reference ranibizumab (Lucentis®, Roche/Genentech, Basel, Switzerland) in terms of clinical pharmacology, efficacy, and safety for the treatment of patients with treatment-naive, subfoveal CNV caused by nAMD (ClinicalTrials.gov, NCT02611778). Details of study investigators are provided in Appendix 1 (available at www.aaojournal.org). All patients provided written informed consent. The study was conducted in compliance with the protocol, regulatory requirements, Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. Institutional review board approval was received for this study.

Eligible patients were male or postmenopausal or sterile female patients aged over 50 years with a newly diagnosed, treatment-naive active CNV secondary to AMD. The complete inclusion and exclusion criteria are provided in Appendix 2 (available at www.aaojournal.org). Key ocular inclusion criteria included either subfoveal or juxtafoveal CNV with fovea-involving leakage related to CNV activity (i.e., sub- or intraretinal fluid on spectral domain optical coherence tomography [SD-OCT] or retinal pigment epithelium detachment); foveal center point (FCP) retinal thickness ≥350 µm on SD-OCT; total lesion area of ≤12 MPS disc areas; and total CNV area ≥50% of total lesion area based on fluorescein angiography and confirmed by a central reading center. All CNV subtypes of nAMD were included. In addition, the Snellen (decimal) equivalent best corrected visual acuity (BCVA) was required to be between 20/32 (0.63) and 20/100 (0.20) in the study eye (Early Treatment Diabetic Retinopathy Study [ETDRS] letters 75-50) and ≥20/100 (0.20) Snellen (decimal) equivalent (ETDRS letters ≥50) in the fellow eye. Key exclusion criteria included prior IVT anti-VEGF treatment in either eye, history of pars plana vitrectomy, macular surgery, or other surgical intervention for AMD in the study eye, and history of IVT corticosteroid therapy or IVT device implantation within 6 months before screening in the study eye.

As part of the screening process, all images were evaluated by a central reading center (GRADE Reading Center, Bonn, Germany) to provide an independent assessment of patient eligibility. Imaging data were transmitted to the central reading center through a secure, web-based portal. Images were then assigned to trained readers who independently assessed qualitative and quantitative grading parameters.

After confirmation of eligibility, patients were randomly assigned 1:1 to receive FYB201 or reference ranibizumab 0.5 mg (0.05 ml of a 10 mg/ml solution) by IVT injection to the study eye every 4 weeks for 48 weeks. Randomization was performed using an interactive voice or web response system and was stratified by site and screening BCVA category (20/32 [0.63] Snellen equivalent, or 20/40 [0.50] to 20/100 [0.20] Snellen equivalent) based on a dynamic allocation method. Once a maximum of 48 patients with a screening BCVA of 20/32 (0.63) were enrolled, randomization to this stratum was stopped.

IVT injections were performed by an unmasked ophthalmologist. However, the study was evaluation-masked, with both patient and other study staff, including the investigator who performed evaluations, being masked to treatment assignment.

BCVA was assessed before any other visual examination that required eye drops (i.e., pupillary dilation for funduscopic examination, fluorescein angiography, color fundus photography, or SD-OCT). BCVA measurements were performed by certified visual acuity examiners masked to treatment and previous BCVA results. FCP and foveal central subfield (FCS) retinal thickness and fluid-free macula were evaluated by monthly SD-OCT. Only 1 SD-OCT device (SPECTRALIS, Heidelberg Engineering GmbH, Heidelberg, Germany) was used at all clinical trial sites. Color fundus photographs and fluorescein angiography images were collected at baseline and the final study visit with a standard fundus camera (minimum resolution, 2000 × 2000 pixels) or confocal scanning laser ophthalmoscopy (Heidelberg Engineering GmbH). All fundus imaging was acquired by study-site technicians and photographers who were certified to perform imaging procedures before any study eye image evaluation. Retinal images of study visits were sent to the central reading center for grading by trained personnel masked to the treatment.

The primary end point for the study was change from baseline in BCVA in ETDRS letters at 8 weeks prior to the third monthly IVT injection. Secondary end points included change from baseline in BCVA at 48 weeks, change from baseline in FCP and FCS retinal thickness at 48 weeks, proportion of patients with active choroidal neovascular leakage, proportion of patients with a fluid-free macula during the study, and change from baseline in total lesion area at 48 weeks.

Mean systemic ranibizumab concentrations close to maximum concentration ($C_{max}$) at 24 ± 3 hours after the first (day 0) and the sixth (week 20) IVT injection were calculated for the pharmacokinetic analysis in a subgroup of 60 patients, at selected sites, randomly assigned in a 1:1 ratio to either FYB201 or reference ranibizumab. These data were summarized using arithmetic and geometric means, ranges, standard deviations, and the coefficient of variation by analysis visit and treatment group.

Safety and the presence of antidrug antibodies (ADAs) were monitored throughout the study. Immunogenicity was summarized by number and percentage of patients with serum ADAs and neutralizing antidrug antibodies (nAbs) by visit.

***Statistical methods***

The safety set comprised all patients who had received at least 1 injection, with patients analyzed according to the treatment received irrespective of their randomized treatment. The full analysis set included all patients who received at least 1 injection and for whom BCVA results after at least 1 month were available, with patients analyzed according to their randomized treatment arms irrespective of the actual treatment received. Since the COLUMBUS-AMD trial was designed to support the registration of FYB201 in the United States (US) and in Europe (EU), 2 full-analysis patient populations were specified in accordance with the requirements of US and EU authorities: the US-relevant patient population (baseline BCVA between 20/32 and 20/100 Snellen equivalent; **Table 1**), and the slightly smaller EU-relevant patient population (baseline BCVA between 20/40 and 20/100 Snellen equivalent; **Table S1**, available at www.aaojournal.org). The sample size, which was calculated based on 1:1 randomization and a standard deviation of 10 ETDRS letters using a 95% confidence interval (CI) for the primary efficacy parameter, was determined to be within the predefined equivalence margin while ensuring an adequate size for the safety population, in accordance with FDA and EMA requirements. Herein, we report the analyses for the US-relevant population since this included all patients enrolled in the trial. Data for the EU-relevant population are reported in the supplemental information (**Table S1** and **S2**; **Figure S1** and **S2**, available at www.aaojournal.org). The pharmacokinetic analysis set included all patients who received at least one injection, who had a valid measurement close to $C_{max}$ (after first dose), and who had no major protocol deviations that would interfere with the interpretation of the ranibizumab concentration data.

The primary end point analysis was performed on both the US- and EU-relevant patient populations, with a sensitivity analysis on the corresponding per-protocol sets (i.e., patients with no major protocol deviations before week 8 that would interfere with interpretation of the BCVA data). For the primary end point, the biosimilarity of FYB201 and reference ranibizumab was assessed via a 2-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters (rounded to the nearest integer), using an analysis of covariance (ANCOVA) model, with change in BCVA between baseline and week 8 as dependent variable, baseline BCVA as covariate, and country/geographic region and treatment group as fixed effects. If the least squares mean CIs for treatment difference

between FYB201 and reference ranibizumab were completely contained in the interval ]-3.5; 3.5[ ETDRS letters, equivalence of FYB201 and reference ranibizumab would be concluded. The original statistical plan specified 90% CIs for the US-relevant population and 95% CIs for the EU-relevant population, in line with regulatory requirements. To enable comparison between baseline populations, and for comparability with other data reported in the field, a post hoc analysis of the US-relevant population data was performed using 95% CIs. Secondary end points for both populations were summarized by analysis visit and treatment group, including the change from baseline by analysis visit. Binary data on CNV leakage and fluid-free macula were summarized by analysis visit and treatment group for the main and final analysis.

## Results

### *Patients*

A total of 477 patients from sites in Austria, Czech Republic, France, Germany, Hungary, Israel, Italy, Poland, Russia, Spain, Ukraine, and the United Kingdom were randomly assigned to receive FYB201 (n = 238) or reference ranibizumab (n = 239). Patient disposition is shown in **Figure 1.** One patient in each group was excluded from the full analysis set (both the US and EU-relevant populations) because of missing BCVA results. One patient in the pharmacokinetic analysis set (n = 60) was excluded because of major protocol deviations interfering with interpretation of ranibizumab concentration data. Baseline characteristics are shown in **Table 1**. Patient characteristics were well balanced between study arms. Week 24 assessments were completed by all but 14 patients (FYB201, 8 patients; reference ranibizumab, 6 patients), who prematurely discontinued the study up to the main analysis (**Figure 1**). At week 48 assessments, 12 patients in the FYB201 group (5.0%) and 13 patients (5.4%) in the reference ranibizumab group prematurely discontinued the study due to withdrawal by patient, loss to follow-up, major protocol deviation, need for alternative treatment, and other reasons (**Figure 1**). Overall, 16 patients (6.7%) in each group discontinued treatment.

Over the course of the study, 199 (83.6%) patients in the FYB201 group and 189 (79.1%) patients in the reference ranibizumab group received the full 12 injections. The number of missed injections was well balanced across treatment groups. A total of 25 (10.5%) patients in the FYB201 group and 38 (15.9%) in the reference ranibizumab group had ≥1 treatment interruption.

### *Primary end point: change in BCVA from baseline at week 8*

In the US-relevant population (i.e., baseline BCVA 20/32 to 20/100 Snellen equivalent), absolute changes in BCVA from baseline to week 8 for both treatment groups are summarized in **Table 2**. The

mean BCVA improved in both groups, with a mean change of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at week 8. The ANCOVA least squares mean difference for the change from baseline in BCVA at week 8 between FYB201 and reference ranibizumab was –0.4 ETDRS letters, with a 90% CI of –1.6 to 0.9. The primary end point was met as the 90% CI was within the predefined equivalence margin of ]-3.5; 3.5[.

In the post hoc analysis, the ANCOVA least squares mean difference for the change from baseline in BCVA at week 8 between FYB201 and reference ranibizumab was –0.4 ETDRS letters, with a 95% CI of –1.9 to 1.1, again meeting the criteria for equivalence between drugs.

In the per-protocol sensitivity analysis, the ANCOVA least squares mean difference for change in BCVA between FYB201 and reference ranibizumab at week 8 was –0.4 ETDRS letters, with a 90% CI of –1.7 to 0.9, also contained within the predefined equivalence margin.

***Change in BCVA during the study***

Study eye BCVA at each visit is shown in **Figure 2.** In both groups, an improvement in BCVA could be seen from the first dose of study medication throughout the study length, with a mean change from baseline of +6.9 ± 10.1 (median 7.0) versus +7.1 ± 10.42 (median 7.0) ETDRS letters at week 24 and +7.8 ± 11.7 (median 8.0) versus +8.0 ± 11.3 (median 8.0) ETDRS letters at week 48 for FYB201 and reference ranibizumab, respectively. At week 24, the ANCOVA least squares mean difference for the change from baseline in BCVA between FYB201 and reference ranibizumab was –0.0 ETDRS letters, with a 90% CI of –1.6 to 1.5; at week 48, the ANCOVA least squares mean difference was –0.1 ETDRS letters, with a 90% CI of –1.8 to 1.7.

***FCP and FCS thickness during the study***

In both treatment groups of the US-relevant population, FCP and FCS retinal thickness showed a sustained decrease after the first dose of study medication (**Figure 3**). For FCP thickness, there was a mean reduction from baseline of 203.9 µm (FYB201) and 205.5 µm (reference ranibizumab) at week 24, and 213.3 µm (FYB201) and 211.0 µm (reference ranibizumab) at week 48. The ANCOVA least squares mean difference for the change from baseline in FCP retinal thickness at week 24 between FYB201 and reference ranibizumab was 0.69 µm, with a 90% CI of –18.22 to 19.60 µm; at week 48, the ANCOVA least squares mean difference was 2.68 µm, with a 90% CI of –16.49 to 21.85 µm. For FCS thickness, there was a mean reduction from baseline of 180.4 µm (FYB201) and 181.6 µm (reference ranibizumab) at week 24, and 182.9 µm (FYB201) and 190.8 µm (reference ranibizumab) at week 48. The ANCOVA least squares mean difference for the change from baseline in FCS retinal thickness at week 24 between FYB201 and reference ranibizumab was –5.91 µm, with a 90% CI of –22.62 to 10.80 µm; at week 48, the ANCOVA least squares mean difference was 3.68 µm, with a 90%

CI of –13.28 to 20.63 µm. There were no obvious differences in either measure of retinal thickness decrease between treatment groups.

***Active CNV leakage, fluid-free macula, and change in total lesion area***

Reduction in proportion of patients with CNV leakage was comparable between groups. At week 24, CNV fluid leakage was present in 52.0% of patients in the FYB201 group and 50.7% of patient in the reference ranibizumab group. At week 48, 56.4% of patients in the FYB201 group and 58.7% of patients in the reference ranibizumab group had CNV fluid leakage. Similarly, increases in the proportion of patients with a fluid-free macula were similar in both treatment groups. Fluid-free macula was seen in 37.9% and 43.3% of patients at week 24, and in 46.7% and 48.9% of patients at week 48 in the FYB201 and reference ranibizumab groups, respectively.

Mean total lesion area decreased from baseline in both treatment groups, with a mean (SD) change in lesion area of –0.57 $mm^2$ (4.79) and –0.7113 $mm^2$ (5.36) at week 24, and –0.64 $mm^2$ (4.8) and –1.18 $mm^2$ (5.43) at week 48, for the FYB201 and reference ranibizumab groups, respectively.

***Pharmacokinetics***

Systemic ranibizumab concentrations close to $C_{max}$ were available for 29 (FYB201) and 30 (reference ranibizumab) patients after the first injection, and 26 (FYB201) and 30 (reference ranibizumab) patients after the sixth injection. Geometric mean concentration (geometric coefficient of variation) concentrations after the first injection were 2330.91 pg/ml (61.36%) and 2551.51 pg/ml (61.16 %) in the FYB201 and reference ranibizumab groups, respectively, and after the sixth injection were 2333.15 pg/ml (67.69%) and 2792.75 pg/ml (58.38 %), respectively.

***Safety***

Adverse events (AEs) during the study are shown in **Table 3**. Overall, the frequency and type of ocular AEs were comparable between the treatment groups. Most AEs were of mild or moderate intensity, and no clinically relevant differences were identified. The most frequent study drug-related AEs in the FYB201 and reference ranibizumab groups, respectively, were cataract (0.0% and 2.1%), retinal pigment epithelium tear (0.4% and 1.3%), reduced visual acuity (0.0% and 1.3%), punctate keratitis (0.0% and 0.8%), vitreous hemorrhage (0.4% and 0.4%), eye pain (0.8% and 0.0%), raised gamma-glutamyl transferase level (0.4% and 0.4%), and raised intraocular pressure (1.3% and 0.8%). 21.4% (FYB201) and 27.6% (reference ranibizumab) of patients experienced AEs related to the IVT injection procedure.

The prevalence of treatment emergent AEs associated with MedDRA preferred terms for intraocular inflammation was similar between FYB201 and reference ranibizumab groups. Of the patients

treated with FYB201, 8.4% (20/238) experienced treatment emergent AEs associated with intraocular inflammation terms, compared to 8.4% (20/239) of patients treated with reference ranibizumab. In both treatment groups, 0.8% of patients experienced treatment emergent AEs possibly related to the investigational medicinal product (IMP), specifically iridocyclitis (n = 1) and conjunctivitis (n = 1) in the FYB201 group, and punctate keratitis (n = 2) in the reference ranibizumab group.

Frequency and type of systemic AEs was also similar between FYB201 and reference ranibizumab groups, with the most frequent, respectively, being nAMD in the fellow eye (7.6% and 8.8%), nasopharyngitis (5.0% and 6.7%), hypertension (1.3% and 5.9%), and increased C-reactive protein level (4.2% and 2.1%). A slightly higher incidence of systemic serious AEs was observed in the reference ranibizumab arm (12.1%) compared with the FYB201 arm (7.1%).

Three patients discontinued the study because of AEs, one in the FYB201 group (worsening of nAMD) and two in the reference ranibizumab group (unrelated benign pancreatic neoplasm and malignant tongue neoplasm of unspecified stage). In addition, AEs led to permanent or temporary withdrawal of study drug in an additional nine patients, five in the FYB201 group and four in the reference ranibizumab group. In the FYB201 group, three patients had interruption of treatment due to mild non-serious AEs (one with upper respiratory tract infection and two with conjunctivitis) and two patients had moderate AEs; one had a chalazion for which treatment was resumed at the subsequent visit without omitting an injection, and one had conjunctivitis for which the patient did not receive the last planned injection). In the reference ranibizumab group, mild non-serious AEs resulted in interruption of treatment in three patients (one each of blepharospasm and visual acuity reduced, vascular anastomosis, and complications associated with device and viral infection) while one patient had severe endophthalmitis. Three patients died during the study (n = 2 in FYB201 group and n = 1 in the reference ranibizumab group), but none of the deaths were considered related to study drug.

***Immunogenicity***

FYB201 and reference ranibizumab had comparable immunogenicity profiles, with few patients developing ADAs during the study. Following the first injection, 14 patients (5.9%) in each group tested positive for ADAs up to week 48, with similar titers in each group. No nAbs were detected up to week 24, and one patient tested positive for nAbs up to week 48 (FYB201 group).

The relationship of ADA status to immune-mediated AEs was analyzed using a subset of terms: drug hypersensitivity, anaphylaxis, and intraocular administration. During the 48-week treatment period, there was only one event of drug hypersensitivity reported in each treatment group; in both cases,

this event concerned ADA negative patients. Therefore, there was no evidence for a negative impact of ADA positive status on drug hypersensitivity, anaphylaxis, or intraocular administration.

***EU-relevant population***

The same trends and similarity in effect between FYB201 and reference ranibizumab were observed in the EU-relevant patient population, i.e., baseline BCVA 20/40 to 20/100 Snellen equivalent (n = 215, FYB201; n = 214, reference ranibizumab; **Table S2** and **Figure S2**, available at www.aaojournal.org). Study eye BCVA at each visit in the EU-relevant patient population is shown in **Figure S1** (available at www.aaojournal.org). For the primary end point, mean change from baseline to week 8 in BCVA was +5.2 ETDRS letters (FYB201) and +6.0 ETDRS letters (reference ranibizumab), with an ANCOVA least squares mean difference for FYB201–reference ranibizumab of –0.7 ETDRS letters (95% CI, –2.3 to 0.9; **Table S2**, available at www.aaojournal.org). As with the overall data set, the 95% CI for the difference was contained within the prespecified equivalence margin, and the primary end point was met.

## Discussion

The present study demonstrates the equivalence of FYB201 and reference ranibizumab in terms of efficacy, safety, and immunogenicity in patients with nAMD. Improvement in BCVA occurred in both treatment groups from the first administration of drug (i.e., observed from week 4 onward), with equivalent improvement in BCVA shown for FYB201 versus reference ranibizumab at week 8, the primary study end point. The assessment at week 8 was endorsed by 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 FYB201. Patients in both treatment groups experienced similar reductions in FCP and FCS retinal thickness, as well as total lesion area. Reduction in the proportion of patients with active CNV leakage and increase in the proportion of patients with a fluid-free macula were similar in both treatment groups. Both drugs were well tolerated, with no differences in immunogenicity and safety profile. There were no obvious safety concerns, with the safety profile of FYB201 consistent with the established safety of the reference product.

Trends and conclusions from the overall population (or US-relevant population) were mirrored in the EU-relevant population, which excluded a small number of patients with slightly better BCVA at enrollment. In both populations, the primary end point was met and there were no clinically meaningful differences between FYB201 and reference ranibizumab.

The first biosimilar that was approved was somatropin, a human growth hormone, in the EU in 2006. Since then, the use of biosimilars has increased across several therapeutic areas and there are now over 50 biosimilars approved in Europe, including growth factors (e.g., epoetin, filgrastim), hormones (e.g., follitropin alfa, insulin glargine), and monoclonal antibodies (e.g., adalimumab, infliximab, rituximab, bevacizumab, and trastuzumab). In the US, the FDA did not release its first biosimilars draft guidance until 2012; the first biosimilar approved in the US was filgrastim, in 2015. Since then, 25 additional biosimilars have been approved by the FDA.

Biosimilar development is based on establishing biosimilarity to the reference drug and involves comprehensive comparability studies with the originator in a step-wise process. The first stage involves *in vitro* studies to compare protein structure and biological function using sensitive analytical techniques that can detect minor differences between the biosimilar and reference medicine. This may be followed by nonclinical studies, including pharmacodynamic studies *in vitro*, and clinical studies designed to confirm biosimilarity and to address any residual uncertainty that may remain from previous analytical or functional studies. The aim of comparability that underlies this process is a well-established scientific principle, previously used to ensure the efficacy and safety of approved products remain similar after manufacturing changes.

Evidence acquired over several years of clinical experience has indicated that biosimilars are as safe and effective in their approved indications as other biological drugs. Over the past 10 years, no safety concerns have been identified with regard to differences in the nature, severity or frequency of adverse effects between biosimilar medicines and their reference medicines.[20] Biosimilars have also been shown to increase price competition between pharmaceutical products.[21] For example, analysis of tumor necrosis factor inhibitors for immune-mediated inflammatory diseases showed that biosimilars were available at a lower cost and also facilitated access to these therapies for more patients.[19]

To date, the use of biosimilars in ophthalmology has been limited. Although a version of ranibizumab is marketed in India, biologic copies marketed in some countries may not have gone through the rigorous biosimilar approval process required in the US, Europe, and elsewhere. However, another consideration in nAMD is the off-label use of bevacizumab; though is not approved for ophthalmological use, it is still widely used. Although safety concerns have been raised over the use of off-label bevacizumab, in particular the potential for compounding-related endophthalmitis, clinical trials and systematic reviews have indicated no significant differences in safety or efficacy between bevacizumab and ranibizumab.[22-26] As such, it will be of interest to see how potential uptake of biosimilar ranibizumab may be influenced by the availability of a low-cost widely used but

unlicensed alternative. However, it is expected that the availability of biosimilars for ranibizumab may increase access to treatment.

In conclusion, FYB201 can be considered biosimilar to reference ranibizumab in terms of clinical efficacy and local and systemic safety in the treatment of patients with newly diagnosed subfoveal nAMD. Biosimilar ranibizumab may offer a new treatment option for patients.

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**Figure Legends**

**Figure 1.** Patient disposition. AE, adverse event; BCVA, best corrected visual acuity; FAS, full analysis set; PPS, per-protocol set; SAF, safety analysis set.

**Figure 2.** Mean ± SD study eye BCVA during the study (US-relevant population, full analysis set). BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.

**Figure 3.** Mean ± SD change in (A) foveal central point, and (B) foveal central subfield, retinal thickness during the study (US-relevant population, full analysis set). SD, standard deviation.

**Table 1. Patient Baseline Characteristics—Safety Analysis Set**

| | **FYB201 (n = 238)** | **Reference ranibizumab (n = 239)** | **Total (N = 477)** |
|---|---|---|---|
| Sex, female/male, no. (%) | 135 (56.7) / 103 (43.3) | 134 (56.1) / 105 (43.9) | 269 (56.4) / 208 (43.6) |
| Age (yrs), median (range) | 76.0 (50–91) | 77.0 (50–94) | 76.0 (50–94) |
| Age group (yrs), no. (%) | | | |
| 50–64 | 25 (10.5) | 19 (7.9) | 44 (9.2) |
| 65–75 | 91 (38.2) | 86 (36.0) | 177 (37.1) |
| >75 | 122 (51.3) | 134 (56.1) | 256 (53.7) |
| Study eye, right eye, no. (%) | 127 (53.4) | 127 (53.1) | 254 (53.2) |
| Study eye Snellen equivalent, no. (%) | | | |
| 20/32 | 24 (10.1) | 22 (9.2) | 46 (9.6) |
| 20/40 | 43 (18.1) | 38 (15.9) | 81 (17.0) |
| 20/50 | 45 (18.9) | 39 (16.3) | 84 (17.6) |
| 20/63 | 37 (15.5) | 46 (19.2) | 83 (17.4) |
| 20/80 | 37 (15.5) | 37 (15.5) | 74 (15.5) |
| 20/100 | 52 (21.8) | 57 (23.8) | 109 (22.9) |

**Table 2. Change in BCVA at Week 8—US-Relevant Population, Full Analysis Set**

| | **FYB201 (n = 237)** | **Reference Ranibizumab (n = 238)** | **Total (N = 475)** |
|---|---|---|---|
| Patients in study at week 8, no. | 234 | 238 | 472 |
| Patients with assessment, no. | 228 | 233 | 461 |
| Patients missing assessment, no. | 6 | 5 | 11 |
| Mean change from baseline, ETDRS letters (SD) | 5.1 (7.52) | 5.6 (8.63) | 5.4 (8.10) |
| Median change from baseline, ETDRS letters | 5.0 | 5.0 | 5.0 |
| Interquartile range (Q1–Q3), ETDRS letters | 0.0–10.0 | 1.0–11.0 | 1.0–10.0 |
| Range, ETDRS letters (min to max) | –16 to 30 | –39 to 25 | –39 to 30 |
| **ANCOVA analysis** | **FYB201 (n = 228)** | **Reference Ranibizumab (n = 233)** | **FYB201 – Reference Ranibizumab** |
| Least squares mean change,[a] ETDRS letters (SE) [90% CI] | 5.1 (0.58) | 5.4 (0.58) | –0.4 (0.76) [-1.6–0.9] |

[a]Adjusted for pooled country and baseline BCVA.

ANCOVA, analysis of covariance; BCVA, best corrected visual acuity; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; SE, standard error.

**Table 3. Adverse Events up to Week 48—Safety Analysis Set**

| No (%) | FYB201 (n = 238) | Reference Ranibizumab (n = 239) | Total (N =477) |
|---|---|---|---|
| TEAEs | 154 (64.7) | 167 (69.9) | 321 (67.3) |
| Local (study eye) | 86 (36.1) | 97 (40.6) | 183 (38.4) |
| Systemic | 123 (51.7) | 147 (61.5) | 270 (56.6) |
| Serious TEAEs (SAEs) | 19 (8.0) | 32 (13.4) | 51 (10.7) |
| Local (study eye) | 2 (0.8) | 3 (1.3) | 5 (1.0) |
| Systemic | 17 (7.1) | 29 (12.1) | 46 (9.6) |
| Severe TEAEs | 11 (4.6) | 22 (9.2) | 33 (6.9) |
| Local (study eye) | 2 (0.8) | 4 (1.7) | 6 (1.3) |
| Systemic | 9 (3.8) | 18 (7.5) | 27 (5.7) |
| Fatal TEAEs | 2 (0.8) | 1 (0.4) | 3 (0.6) |
| Nonfatal serious SAEs | 18 (7.6) | 31 (13.0) | 49 (10.3) |
| TEAEs related to study drug | 20 (8.4) | 25 (10.5) | 45 (9.4) |
| Serious TEAEs | 3 (1.3) | 3 (1.3) | 6 (1.3) |

| | | | |
|---|---|---|---|
| Severe TEAEs | 1 (0.4) | 5 (2.1) | 6 (1.3) |
| TEAEs related to IVT injection procedure | 51 (21.4) | 66 (27.6) | 117 (24.5) |
| TEAEs leading to withdrawal of study drug | 6 (2.5) | 6 (2.5) | 12 (2.5) |
| Eye disorders in ≥2% patients | | | |
| Neovascular age-related macular degeneration | 19 (8.0) | 22 (9.2) | 41 (8.6) |
| In fellow eye | 18 (7.6) | 21 (8.8) | 39 (8.2) |
| Worsening in study eye | 1 (0.4) | 1 (0.4) | 2 (0.4) |
| Conjunctival hemorrhage | 14 (5.9) | 19 (7.9) | 33 (6.9) |
| Punctate keratitis | 8 (3.4) | 12 (5.0) | 20 (4.2) |
| Visual acuity reduced | 6 (2.5) | 11 (4.6) | 17 (3.6) |
| Eye pain | 9 (3.8) | 6 (2.5) | 15 (3.1) |
| Cataract | 1 (0.4) | 11 (4.6) | 12 (2.5) |
| Lacrimation increased | 9 (3.8) | 2 (0.8) | 11 (2.3) |
| Choroidal neovascularization | 6 (2.5) | 4 (1.7) | 10 (2.1) |
| Conjunctival hyperemia | 4 (1.7) | 6 (2.5) | 10 (2.1) |
| Retinal hemorrhage | 7 (2.9) | 3 (1.3) | 10 (2.1) |
| Vitreous detachment | 6 (2.5) | 4 (1.7) | 10 (2.1) |

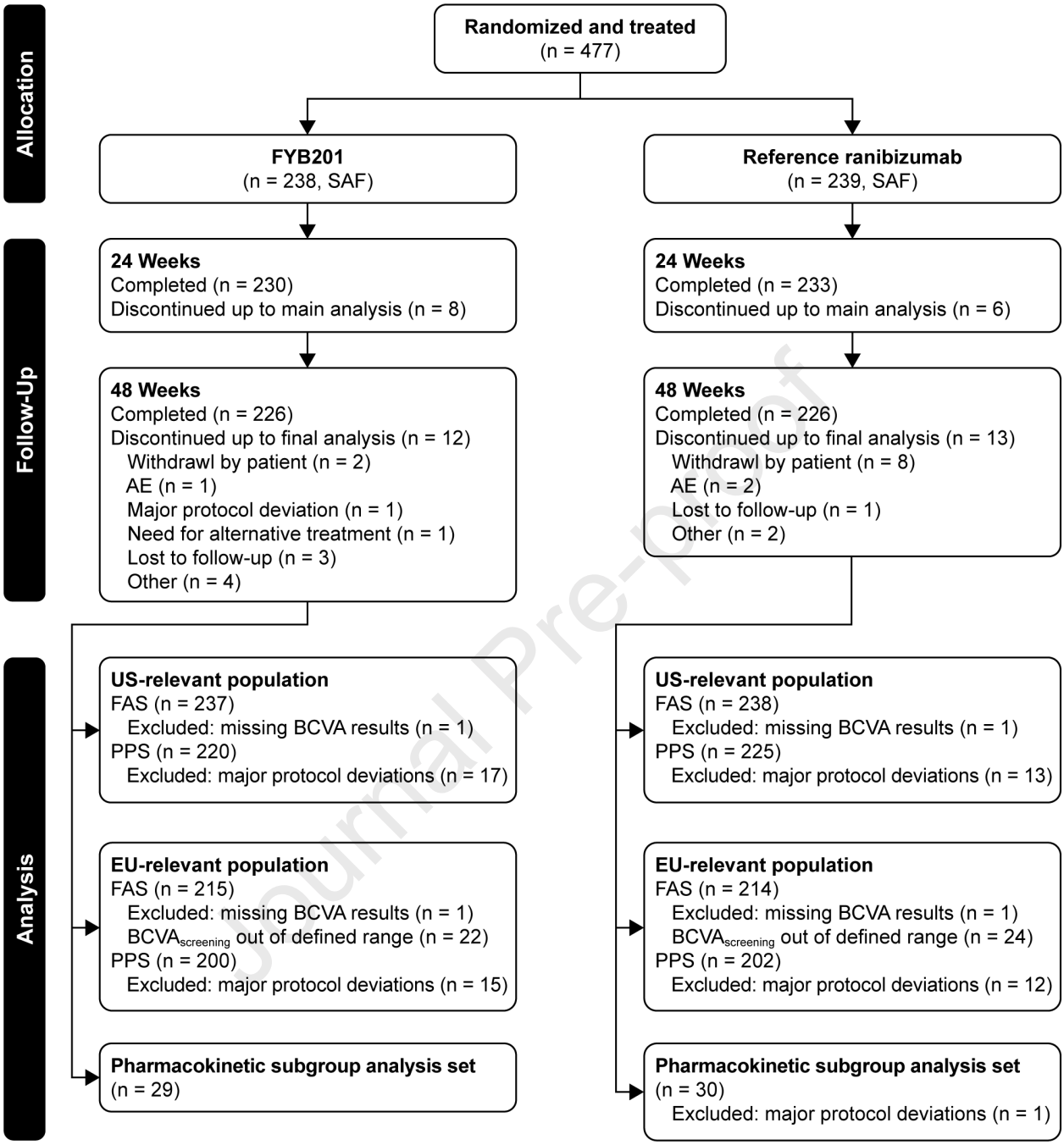
| Prevalence of TEAEs associated with MedDRA preferred terms for 'intraocular inflammation' | | | |
|---|---|---|---|
| TEAEs, n (%) | 20 (8.4) | 20 (8.4) | 40 (8.4) |
| At least possibly IMP-related | 2 (0.8)[a] | 2 (0.8)[b] | 4 (0.8) |
| Severity | | | |
| Mild | 1 (0.4) | 2 (0.8) | 3 (0.6) |
| Moderate | 1 (0.4) | 0 | 1 (0.2) |
| Seriousness | | | |
| Non-serious | 1 (0.4) | 2 (0.8) | 3 (0.6) |
| Serious | 1 (0.4) | 0 | 1 (0.2) |
| Outcome | | | |
| Recovered/resolved | 2 (0.8) | 2 (0.8) | 4 (0.8) |
| Unresolved | 0 | 0 | 0 |
| Systemic adverse events in ≥2% patients | | | |
| Nasopharyngitis | 12 (5.0%) | 16 (6.7%) | 28 (5.9%) |
| Bronchitis | 9 (3.8%) | 5 (2.1%) | 14 (2.9%) |
| Upper respiratory tract infection | 8 (3.4) | 6 (2.5) | 14 (2.9) |
| Conjunctivitis | 9 (3.8) | 2 (0.8) | 11 (2.3) |
| Intraocular pressure increased | 11 (4.6) | 12 (5.0) | 23 (4.8) |

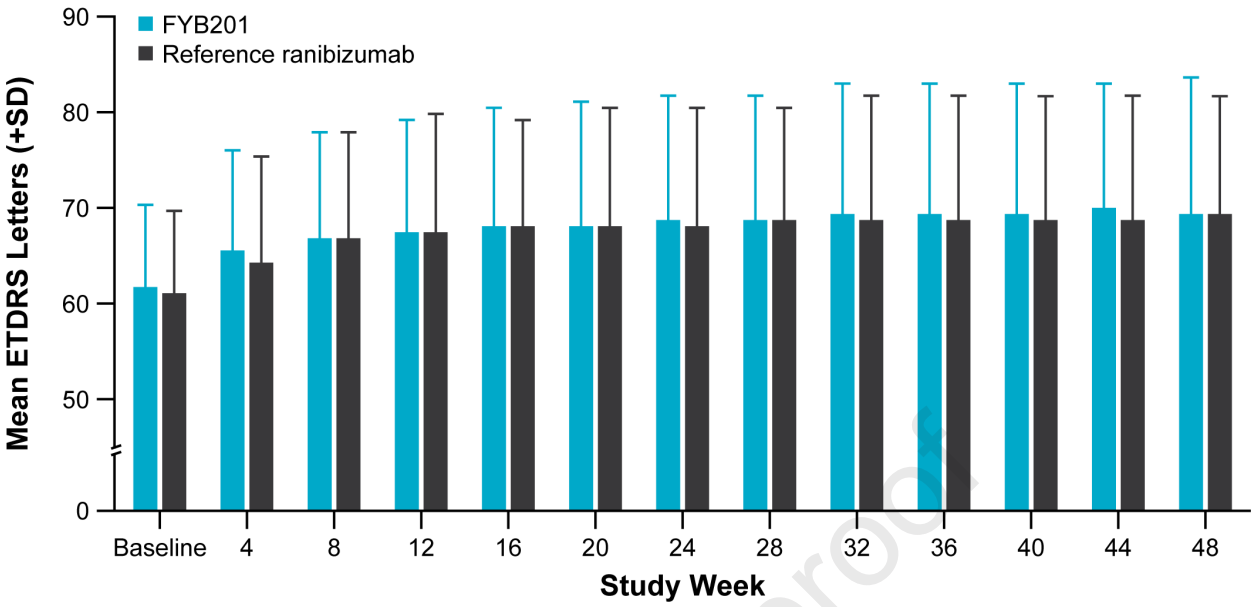
| | | | |
|---|---|---|---|
| C-reactive protein increased | 10 (4.2) | 5 (2.1) | 15 (3.1) |
| Back pain | 5 (2.1) | 8 (3.3) | 13 (2.7) |
| Headache | 4 (1.7) | 9 (3.8) | 13 (2.7) |
| Hypertension | 3 (1.3) | 14 (5.9) | 17 (3.6) |
| Cough | 5 (2.1) | 5 (2.1) | 10 (2.1) |

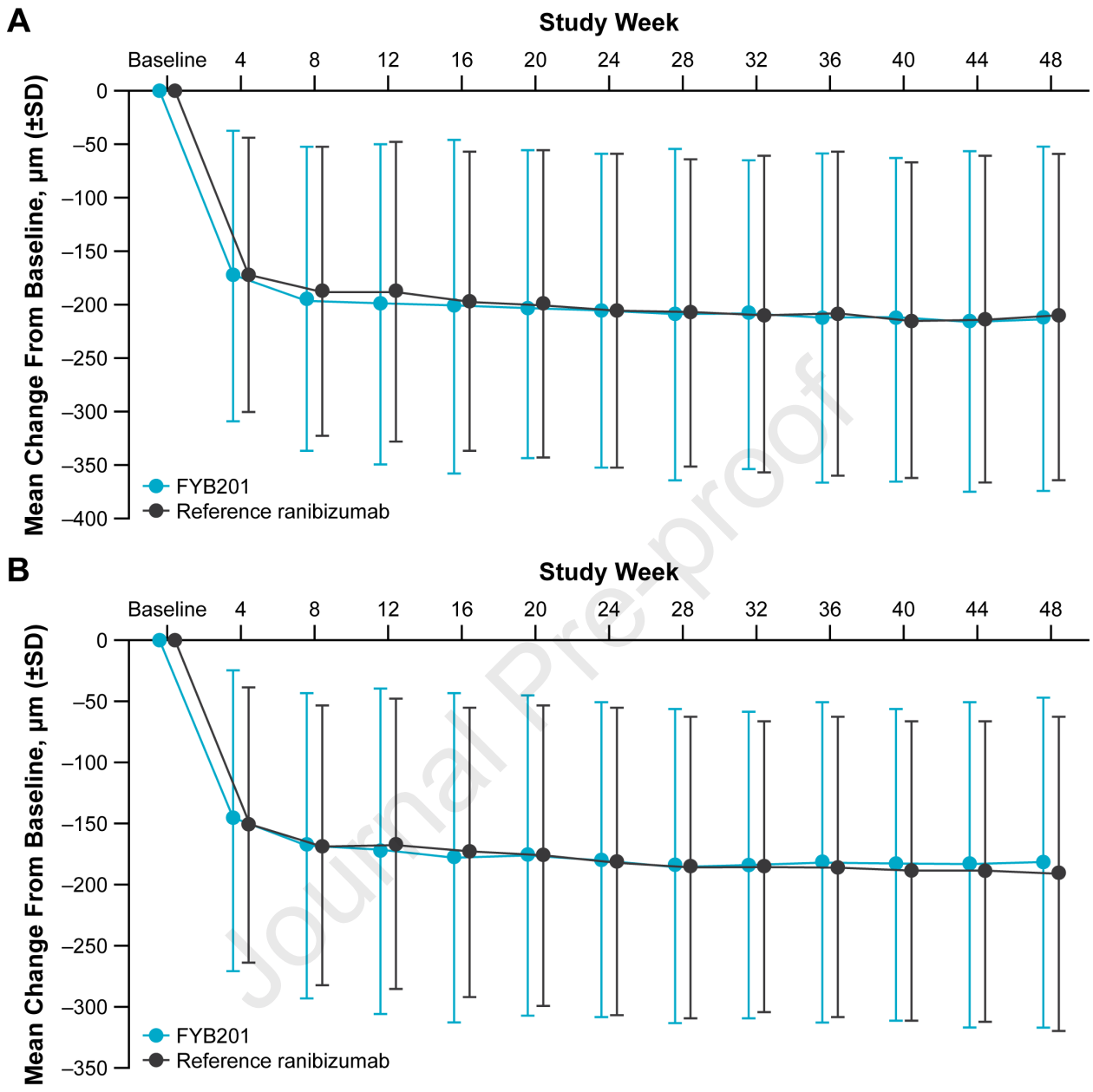
[a]Iridocyclitis (n = 1), conjunctivitis (n = 1).

[b]Punctate keratitis (n = 2).

AE, adverse event; IMP, investigational medicinal product; IVT, intravitreal; SAE, serious AE; TEAE, treatment-emergent AE.


Allocation
Follow-Up
Analysis
Randomized and treated
(n = 477)
FYB201
(n = 238, SAF)
Reference ranibizumab
(n = 239, SAF)
24 Weeks
Completed (n = 230)
Discontinued up to main analysis (n = 8)
24 Weeks
Completed (n = 233)
Discontinued up to main analysis (n = 6)
48 Weeks
Completed (n = 226)
Discontinued up to final analysis (n = 12)
Withdrawl by patient (n = 2)
AE (n = 1)
Major protocol deviation (n = 1)
Need for alternative treatment (n = 1)
Lost to follow-up (n = 3)
Other (n = 4)
48 Weeks
Completed (n = 226)
Discontinued up to final analysis (n = 13)
Withdrawl by patient (n = 8)
AE (n = 2)
Lost to follow-up (n = 1)
Other (n = 2)
US-relevant population
FAS (n = 237)
Excluded: missing BCVA results (n = 1)
PPS (n = 220)
Excluded: major protocol deviations (n = 17)
US-relevant population
FAS (n = 238)
Excluded: missing BCVA results (n = 1)
PPS (n = 225)
Excluded: major protocol deviations (n = 13)
EU-relevant population
FAS (n = 215)
Excluded: missing BCVA results (n = 1)
BCVAscreening out of defined range (n = 22)
PPS (n = 200)
Excluded: major protocol deviations (n = 15)
EU-relevant population
FAS (n = 214)
Excluded: missing BCVA results (n = 1)
BCVAscreening out of defined range (n = 24)
PPS (n = 202)
Excluded: major protocol deviations (n = 12)
Pharmacokinetic subgroup analysis set
(n = 29)
Pharmacokinetic subgroup analysis set
(n = 30)
Excluded: major protocol deviations (n = 1)





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