CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761165Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

BIOSIMILAR MULTIDISCIPLINARY EVALUATION AND REVIEW

Application Type	351(k) BLA
Application Number	761165
Received Date	August 2, 2021
BsUFA Goal Date	August 2, 2022
Division/Office	Division of Ophthalmology
Review Completion Date	See DARRTS stamped date
Product Code Name	FYB201
Proposed Nonproprietary Name[1]	ranibizumab-eqrn
Proposed Proprietary Name[1]	Cimerli
Pharmacologic Class	vascular endothelial growth factor (VEGF) inhibitor
Applicant	Coherus BioSciences,Inc.
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
Regulatory Action	Approval

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

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OBP = Office of Biotechnology Products
OPMA = Office of Pharmaceutical Manufacturing Assessment
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error and Prevention Analysis
DRISK = Division of Risk Management
DPMH = Division of Pediatric and Maternal Health

Glossary

AC	Advisory Committee
ADA	Anti-drug Antibodies
AE	Adverse Event
BLA	Biologics License Application
BMER	Biosimilar Multidisciplinary Evaluation and Review
BMI	Body Mass Index
BPD	Biosimilar Biological Product Development
BsUFA	Biosimilar User Fee Agreements
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	Confidence Interval
CMC	Chemistry, Manufacturing, and Controls
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CSC	Computational Science Center
CTD	Common Technical Document
CV	Coefficient of Variation
DEPI	Division of Epidemiology
DIA	Division of Inspectional Assessment
DMC	Data Monitoring Committee
DMA	Division of Microbiology Assessment
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
DRISK	Division of Risk Management
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio

ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product
ITT	Intention to Treat
LLOQ	Lower Limit of Quantitation
MAPP	Manual of Policy and Procedure
mITT	Modified Intention to Treat
MOA	Mechanism of Action
Nab	Neutralizing Antibody
OBP	Office of Biotechnology Products
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
OSIS	Office of Study Integrity and Surveillance
PD	Pharmacodynamics
PeRC	Pediatric Review Committee
PK	Pharmacokinetics
PMC	Postmarketing Commitments
PMR	Postmarketing Requirements
PREA	Pediatric Research Equity Act
PHS	Public Health Service
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
REMS	Risk Evaluation and Mitigation Strategies
ROA	Route of Administration
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
US-Lucentis	US-licensed Lucentis

Executive Summary

1.1 Product Introduction

FYB201 is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment for intraocular use that has been developed as a proposed interchangable biosimilar to US-licensed Lucentis (ranibizumab injection). Ranibizumab binds to the receptor binding sites of Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

The Applicant is seeking licensure for the 0.5 mg (10 mg/mL) and 0.3 mg (6 mg/mL) strengths each in a single-dose vial. The 0.5 mg (10 mg/mL) dose is for the following indications which are the same as those previously approved for US-licensed Lucentis[2]:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV).

The 0.3 mg (6 mg/mL) strength is for the following indications which are the same as those previously approved for US-licensed Lucentis[3]:

- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR).

For neovascular (wet) age-related macular degeneration (AMD), FYB201 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For macular edema following retinal vein occlusion (RVO), FYB201 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For myopic choroidal neovascularization (mCNV), FYB201 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days) for up to three months. For diabetic macular edema (DME) and diabetic retinopathy (DR), FYB201 0.3 mg (0.05 mL of 6 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

[2] U.S. Prescribing Information, US-licensed Lucentis, Accessed July 13, 2022 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf
[3] U.S. Prescribing Information, US-licensed Lucentis, Accessed July 13, 2022 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf

The proposed dosing regimens are the same as approved for US-licensed Lucentis.

1.2 Determination Under Section 351(k)(2)(A)(ii) of the Public Health Service (PHS) Act

The Applicant submitted animal studies in its 351(k) application. However, as described in this review, the applicant's analytical and clinical data supports a demonstration that FYB201 is highly similar to U.S.-licensed Lucentis notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between FYB201 and U.S.-licensed Lucentis in terms of safety, purity and potency. Moreover, the product quality review team did not identify any impurity issues that warranted animal studies. Accordingly, FDA has determined that the animal studies are unnecessary in this 351(k) application.

1.3 Mechanism of Action, Route of Administration, Dosage Form, Strength, and Conditions of Use Assessment

This BLA contains sufficient data and information to demonstrate that FYB201 and US-licensed Lucentis utilize the same mechanism of action (MOA) to the extent known for the proposed neovascular (wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), diabetic retinopathy (DR), diabetic macular edema (DME) and myopic choroidal neovascularization (mCNV) indications. FYB201 binds to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to contribute to retinal neovascularization and retinal leakage. The binding of FYB201 to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

To support the demonstration that FYB201 is highly similar to US-licensed Lucentis, Coherus performed a comparative analytical assessment of FYB201 and US-licensed Lucentis. The comparative analytical assessment data provided support the conclusion that FYB201is highly similar to US-licensed Lucentis. FYB201 has the same mechanism(s) of action as that of U.S.-licensed Lucentis.

US-licensed Lucentis is licensed in 0.3mg (6mg/mL) and 0.5mg (10mg/mL) strengths, in single-dose vials and in single-dose pre-filled syringes. Coherus is seeking licensure for both the 0.5mg (10mg/mL) strength and 0.5 (6mg/mL) strength in single-dose vials. The route of administration (ROA), dosage form, and the strength of the proposed product are the same as those of the US-licensed reference product.

The condition(s) of use for which the applicant is seeking licensure have been previously approved for US-licensed Lucentis.

1.4 Inspection of Manufacturing Facilities

The following facilities were inspected and found to be in compliance with cGMPs:

Facility Name and Location	Activity
(b) (4)	Manufacture of the DS, release, stability, and in-process control testing. Storage of the WCB, release and stability testing of the DP.
	Release and in-process control testing of the DS. Release testing of the DP
	Release and stability testing of the DS, and stability testing of the DP.
	Release and stability testing of the DS, and stability testing of the DP.
	Manufacture and visual inspection of the DP. Release, stability, and in-process control testing of the DP.
	Release and stability testing of the DP.
	Release and stability testing of the DP.
	Secondary packaging of the DP.

1.5 Scientific Justification for Use of a Non-US-licensed Comparator Product

Not applicable.

1.6 Biosimilarity and Interchangeability Assessment

Table 1: Summary and Assessment of Biosimilarity and Interchangeability

Comparative Analytical Studies[4]	
Summary of Evidence	• FYB201 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components • FYB201 0.5 mg (10 mg/mL) and FYB201 0.3 mg (6 mg/mL) in single dose vials are the same strengths as those of US-licensed Lucentis • The dosage form and route of administration is the same as that of US-licensed Lucentis
Assessment of Residual Uncertainties	• There are no residual uncertainties from a product quality perspective.
Animal/Nonclinical Studies	
Summary of Evidence	• A 2-week pharmacokinetic, ocular and systemic tolerance/ toxicity study following a single intravitreal administration in albino rabbits was submitted. • FDA has determined that the animal studies are unnecessary in this 351(k) application.
Assessment of Residual Uncertainties	• There are no residual uncertainties.
Clinical	
Clinical Pharmacology Studies	

[4]Refer to the Product Quality Review, including the Comparative Analytical Assessment (CAA) Chapter of therein for additional information regarding comparative analytical data.

Summary of Evidence	• Systemic exposure of FYB201 and US-licensed Lucentis evaluated in a subset of subjects with neovascular AMD in Study FYB201-C2015-01-P3 were comparable based on descriptive analysis, supporting a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis. • Comparable incidence of ADA/NAb formation between FYB201 and US-licensed Lucentis in patients with neovascular AMD supports a demonstration of no clinically meaningful differences.
Assessment of Residual Uncertainties	• There are no residual uncertainties from a clinical pharmacology perspective.
Clinical Studies	
Summary of Evidence	• In Study FYB201-C2015-01-P3, there were no meaningful differences in terms of efficacy or safety between FYB201 and US-licensed Lucentis. The data from this study support a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis. • In Study FYB201-C2015-01-P3, the contralateral eye was concurrently treated with US-licensed Lucentis in individuals with bilateral disease requiring therapy. This contralateral administration exposed individuals to both FYB201 and US-licensed Lucentis concurrently. There were no meaningful differences in terms of efficacy or safety in either eye. The data from this study support a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical or clinical statistical perspectives.
Switching Study	

Summary of Evidence	• FDA determined that a switching study is unnecessary to support a demonstration of interchangeablility for FYB201.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Any Given Patient Evaluation	
Summary of Evidence	• The analytical data and clinical data support a demonstration that FYB201 can be expected to produce the same clinical result as that of US-licensed Lucentis in any given patient. The Applicant has provided adequate data and information to support a demonstration that FYB201 can be expected to produce the same clinical result as that US-licensed Lucentis.
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.
Extrapolation	

Summary of Evidence	• The information submitted in the original BLA supports a demonstration that FYB201 and US-licensed Lucentis are highly similar notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences in terms of safety, purity, and potency. • The data and information provided by the Applicant are sufficient to demonstrate that FYB201 can be expected to produce the same clinical result as US-licensed Lucentis in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis is not greater than the risk of using US-licensed Lucentis without alternation or switch. • DO has determined that the Applicant has provided adequate scientific justification and agrees with the applicant's justification for extrapolation to the other indications listed in the US-licensed Lucentis package insert being sought for licensure based on: 1) the mechanism of action of ranibizumab, including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, diabetic macular edema, diabetic retinopathy and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication.

	• The data and information submitted by the Applicant, including the justification for extrapolation, supports licensure of FYB201 as an interchangeable biosimilar to US-licensed Lucentis for the following indications for which US-licensed Lucentis has been previously approved: o Neovascular (Wet) Age-Related Macular Degeneration (AMD) o Macular Edema Following Retinal Vein Occlusion (RVO) o Diabetic Macular Edema (DME) o Diabetic Retinopathy (DR) o Myopic Choroidal Neovascularization (mCNV)
Assessment of Residual Uncertainties	• There are no residual uncertainties from the clinical perspective.

1.7 Conclusions on Approvability

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB201 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB201 and US-licensed Lucentis in terms of the safety, purity, and potency of the product. The data and information provided by the Applicant are sufficient to demonstrate that FYB201 can be expected to produce the same clinical result as US-licensed Lucentis in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis is not greater than the risk of using US-licensed Lucentis without alternation or switch.

Therefore, the data and information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB201 is biosimilar to and interchangable with US-licensed Lucentis for each of the following indications for which US-licensed Lucentis has been previously approved and for which the Applicant is seeking licensure of FYB201: [5]

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)

[5]The proposed FYB201 labeling states: Cimerli (ranibizumab- eqrn) is interchangeable with Lucentis (ranibizumab injection).

- Diabetic macula edema (DME)
- Diabetic retinopathy (DR).

There are no biological products relying on the reference product for FYB201 0.5 mg (10 mg/mL) and FYB201 0.3 mg (6 mg/mL) in single-dose vials that have received a determination of interchangeability for any condition of use. FYB201 0.5 mg (10 mg/mL) and FYB201 0.3 mg (6 mg/mL) in single-dose vials are the first biological products relying on their respective reference products to receive a determination of interchangeability for any condition of use.

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Deputy Division Director

2. Introduction and Regulatory Background

2.1 Summary of Presubmission Regulatory History Related to Submission

The sponsor at the time (bioeq GmbH) sought guidance concerning the overall development program in one BPD Type 1 Meeting (May 6, 2020), three BPD Type 2 Meetings (May 12, 2015, November 29, 2016, and January 22, 2021, (no meeting held upon request of the sponsor)), one BPD Type 3 Meeting (November 15, 2017), and one Type 4 meeting (December 14, 2018).

The sponsor originally submitted a BLA on December 3, 2019, for FYB201 0.5 mg (10 mg/mL) and FYB201 0.3 mg (6 mg/mL) in single dose vials with FYB201 drug substance supplied from (b) (4) During the first 60 days of the fileability assessment, FDA became aware that the upstream processing (USP) part of the FYB201 manufacturing process was relocated (b) (4) after execution of process performance qualification (PPQ) batches. Based on FDA expectation to have manufacturing data from the new USP suite and a corresponding comparability study at the time of BLA filing, bioeq GmbH decided on February 4, 2020, to withdraw the BLA.

On July 9, 2021, the Agency was notified that the ownership of PIND 125841 / BLA 761165 for FYB201 biosimilar ranibizumab was transferred from bioeq GmbH to Bioeq AG. On April 1, 2022, the Agency was notified that ownership of BLA 761165 for FYB201 biosimilar ranibizumab was transferred from Bioeq AG to Coherus BioSciences, Inc. (Coherus).

2.2 Studies Submitted by the Applicant

Refer to the Product Quality review, including the Comparative Analytical Assessment (CAA) Chapter for information regarding comparative analytical studies provided to support a demonstration of biosimilarity.

Table 2: Animal Studies Submitted

Study Title	Study Number	Species	Number Per Treatment Arm	Study Duration	Route of administration/Dose
Animal Studies					
2-week pharmaco-kinetic and ocular and systemic tolerance/ toxicity study following a single intravitreal administration in albino rabbits	FYB201 PK2015 01 E	Albino rabbits	Arm A: ocular tolerance and systemic toxicity assessment N=3 animals per group, 12 total Arm B pharmacokinetics N=3 animals per group, 54 total	2 weeks	Intravitreal; 0.5 mg/eye, single dose

Table 3: Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study					
FYB201-C2015-01-P3	NCT02611778	Comparative safety, efficacy, PK, and immunogenicity	Randomized, double-masked, parallel-group, multicenter (International study sites only. No US sites.)	Subjects with nAMD	FYB201 or US-licensed Lucentis administered at a dose of 0.5 mg to the study eye every 4 weeks up to Week 44

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3. Summary of Conclusions of Other Review Disciplines

3.1 Office of Pharmaceutical Quality (OPQ)

FYB201 binds to the receptor binding site of human alternatively spliced Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells resulting in the reduction of endothelial cell proliferation, vascular leakage and new blood vessel formation. FYB201 drug product is manufactured to have the same strength, dosage form, and route of administration as the 0.5 mg (10 mg/mL) strength and 0.3 mg (6 mg/mL) strength of US-licensed Lucentis in single-dose vials. It also has the same formulation and presentation as US-licensed Lucentis. FYB201 is a sterile, preservative-free, colorless to pale yellow solution in a single-dose glass vial.

Manufacture of the proposed product is well-controlled and leads to a product that is safe, pure, and potent. To support the demonstration that FYB201 is highly similar to US-licensed Lucentis, the applicant performed a comparative analytical assessment of FYB201 and US-licensed Lucentis. As part of the comparative analytical assessment, the quality attributes of ranibizumab were collectively assigned to appropriate assessment categories and a sufficient number of lots of each product were evaluated. A comprehensive array of analytical methods was used to support a demonstration that the products are highly similar. Each method was demonstrated to be suitable to detect and/or quantitate potential differences in critical quality attributes between FYB201 and US-licensed Lucentis. FYB201 is highly similar to US-licensed Lucentis notwithstanding minor differences in clinically inactive components.

Based on the comparative analytical assessment and manufacturing data, the proposed presentation of FYB201 has the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as US-licensed Lucentis 0.5 mg (10 mg/mL) and 0.3 mg (6 mg/mL). Each FYB201 0.5 mg carton will contain a single-dose, 2-mL glass vial with a blue cap designed to deliver 0.05 mL of 10 mg/mL drug product solution. Each FYB201 0.3 mg carton will contain a single-dose, 2-mL glass vial with a white cap designed to deliver 0.05 mL of 6 mg/mL drug product solution.

3.2 Division of Medication Error Prevention and Analysis (DMEPA)

The Applicant's proposed nonproprietary name for FYB201, ranibizumab-eqrn, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated 6/9/22. The proposed proprietary name for FYB201 is conditionally approved as Cimerli. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable in a letter to the applicant dated 11/2/21. DMEPA completed a labeling review of the original applicant-submitted prescribing information, container labels, and carton labeling on 1/10/22.

3.3 Office of Study Integrity and Surveillance (OSIS)

Not applicable.

3.4 Office of Scientific Investigations (OSI)

Study FYB201-C2015-01-P3 was conducted in its entirety at non-US investigational sites. International inspections were not requested because there were no serious issues to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations. No single investigational site included enough subjects to significantly alter the final result of the clinical trial. There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices.

Study FYB201-C2015-01-P3 is considered to have been conducted adequately, and the data generated by the applicant appeared acceptable in support of the application.

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4. Nonclinical Pharmacology and Toxicology Evaluation and Recommendations

4.1 Nonclinical Executive Summary and Recommendation

A 2-week pharmacokinetic, ocular and systemic tolerance/ toxicity study following a single intravitreal administration in albino rabbits was submitted. However, as described in this review, the applicant's analytical and clinical data supports a demonstration that FYB201 is highly similar to U.S.-licensed Lucentis notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between FYB201 and U.S.-licensed Lucentis in terms of safety, purity and potency. Moreover, the product quality review team did not identify any impurity issues that warranted animal studies. Accordingly, FDA determined that the animal studies are unnecessary in this 351(k) application.

4.1.1 Nonclinical Residual Uncertainties Assessment

There were no nonclinical residual uncertainties.

4.2 Product Information

Product Formulation

FYB201 is a sterile, colorless to pale yellow solution. FYB201 is supplied as a preservative-free, sterile aqueous solution in a single-dose vial designed to deliver by intravitreal injection 0.05 mL of either 10 mg/mL (0.5 mg dose vial) or 6 mg/mL (0.3 mg dose vial) solution. Each solution includes 10 mM histidine HCl, 10% α,α trehalose dihydrate, 0.01% polysorbate 20, at pH 5.5. The composition of FYB201 DP is shown in the following table.

Table 4: Composition of FYB201 Drug Product Vial Formulation per Strength

Component	Function	Reference to Standard[1]	Quantity per mL	
			6 mg/mL	10 mg/mL
FYB201	(b) (4)	n-house specification	6 mg	10 mg
(b) (4		EP, USP		(b) (4)
Histidine hydrochloride				
(b) (4		EP		
α, α-Trehalose dihydrate		EP, USP		
Polysorbate 20		EP, USP		
Water for Injection		EP, USP		

1 For compendial monographs the current version is applied as appropriate

FYB201 and US-licensed Lucentis have the same formulation. The excipients in FYB201 are the same and present in the same levels as the excipients in US-licensed Lucentis.

No impurities of concern were identified.

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5. Clinical Pharmacology Evaluation and Recommendations

5.1 Clinical Pharmacology Executive Summary and Recommendation

Table 5: Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of FYB201 and US-licensed Lucentis evaluated in the a subset of subjects with neovascular AMD in Study FYB201-C2015-01-P3 were comparable based on descriptive analysis which supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB201 and US-licensed Lucentis in subjects with neovascular AMD supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.

5.1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding the PK and immunogenicity assessment for FYB201 and US-licensed Lucentis.

5.2 Clinical Pharmacology Studies to Support the Use of a Non-US-licensed Comparator Product

Not applicable.

5.3 Human Pharmacokinetic and Pharmacodynamic Studies

A PK similarity study using traditional PK endpoints, such as AUC and C_{max}, in healthy subjects is not considered to be feasible for the following reasons: 1) ranibizumab is administered by intravitreal (IVT) injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following IVT injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of IVT injections. Therefore, a PK

sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

Clinical Pharmacology Study Design Features and Endpoints

Study FYB201-C2015-01-P3 was a 48-week, randomized, active-controlled, evaluation-masked, parallel-group, multicenter study to evaluate the comparative efficacy, safety, and immunogenicity of FYB201 compared with US-licensed Lucentis in the treatment of patients with neovascular AMD (n=477). Eligible patients were randomized to receive FYB201 or US-licensed Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) through IVT injection every 4 weeks for 44 weeks. The PK profiles of FYB201 and US-licensed Lucentis were descriptively evaluated within a subgroup of neovascular AMD patients as part of the comparative clinical study. The PK data were pre-specified to be analyzed qualitatively. Analyses included:

a. Systemic exposure measured at 24±3 hours post-dose (close to maximum serum concentration (Cmax)) after the first and the sixth IVT injections in a subgroup of patients from both treatment groups
b. Incidence of anti-drug antibodies (ADAs) to FYB201 and US-licensed Lucentis
c. Incidence of neutralizing antibodies (NAbs) to FYB201 and US-licensed Lucentis

Of the 477 subjects enrolled, 29 [6.1%] and 30 [6.3%] subjects in the FYB201 and US-licensed Lucentis treatment groups, respectively, were included in PK subgroup analysis set.

Bioanalytical PK method and performance

FYB201 or ranibizumab concentrations in human plasma were measured using a validated electrochemiluminescent immunoassay (ECLIA) of Meso Scale Discovery platform. The lower and upper quantification limits for plasma study drug concentrations were 500 pg/mL and 20000 pg/mL, respectively. All PK samples from Study FYB201-C2015-01-P3 were analyzed (between February 05, 2018, and February 13, 2018) within the demonstrated stability period.

PK of FYB201 and US-licensed Lucentis in patients with neovascular AMD (Study FYB201-C2015-01-P3)

In Study FYB201-C2015-01-P3, 60 patients at selected sites were enrolled in PK subgroup analysis set and randomly (1:1) assigned to recive either FYB201 or US-licensed Lucentis. One patient was excluded from the PK subgroup analysis set bcause of major protocol deviations (measurable ranibizumab concentration at baseline). Blood samples for PK assessments were collected prior to the first IVT injection and at 24 hours (±3 hours) following the first (Day 1) and sixth (Week 20) IVT injections.

The summary statistics of the systemic study drug concentrations for each of the treatment subgroups are presented in Table 7. The descriptive PK comparison showed that the systemic study drug concentrations close to Cmax after the first and the sixth IVT injections were comparable between FYB201 and US-licensed Lucentis treatment groups.

Table 6: Pharmacokinetic Results (Pharmacokinetic Analysis Set)

Systemic study drug concentrations close to Cmax (pg/mL) after 1st and 6th IVT injections (Study FYB201-C2015-01-P3 PK subgroup analysis set)

	FYB201 (N = 29)		US-licensed Lucentis (N = 30)	
Analysis Visit	**V1a[1]**	**V6a[2]**	**V1a[1]**	**V6a[2]**
N*	29	27	30	30
N	29	26	30	30
Missing	0	1	0	0
Geometric mean	2330.91	2333.15	2551.51	2792.75
%Geom. CV	61.36	67.69	61.16	58.38
Arithmetic Mean	2713.6	2742.3	2963.6	3162.7
SD	1543.44	1490.86	1702.35	1493.08
%CV	56.88	54.37	57.44	47.21
Median	2190.0	2425.0	2590.0	2895.0
Range (min–max)	900–6550	614–6130	559–6940	703–6310

N = total number of patients, N* = total number of patients still in the study for the respective analysis visit, n =number of patients with non-missing assessment, Missing = number of patients with missing assessment

Notes: [1]blood sample drawn at 24h±3h after 1st IVT injection, [2]blood sample drawn at Week 20 24h±3h after 6th IVT injection, Values below the limit of quantification were set to 0 and values above the limit of quantification were set to the upper limit of quantification for the purpose of summary statistics. PK measurement of patient (b) (6) (FYB201 treatment group) at visit 6a was set to be missing because drug treatment in the fellow eye was administered too close to visit 6a and the PK measurement may be confounded.

PD similarity assessment

Not applicable.

5.4 Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity (ADA and Nab) was evaluated in Study FYB201-C2015-01-P3 as one of the secondary endpoints.

Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of FYB201 and US-licensed Lucentis.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood samples for immunogenicity assessment were collected in all subjects at Week 0, Week 1 (PK subgroup only), Week 4, Week 12, Week 24, and Week 48 (end-of-study visit).

Comparison of Incidence of ADA and NAb

The incidence of ADA and NAb by treatment group and time points in Study FYB201-C2015- 01-P3 were summarized in the following table. The incidence of an ADA positive response was generally low and comparable between treatment groups throughout the study. Only one patient in FYB201 treatment group was detected positive for NAb at Week 48.

Table 7: Incidence of Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb) by Visit (Safety Set, Study FYB201-C2015-01-P3)

Category	Treatment week				
	Visit 1 /Baseline	4	12	24	48
FYB201 (N=238)					
No. of patients #	234 §	226	226	225	229
No. ADA positive	0	2	1	6	9
% ADA positive	0	0.9	0.4	2.7	3.9
Median titer	n.c.	10.0	10.0	30.0	60.0
Min/Max titer	n.c.	10 / 10	10 / 10	10 / 90	10 / 810
No. NAb positive	0	0	0	0	1
% NAb positive	0	0	0	0	0.4
US-licensed Lucentis (N=239)					
No. of patients #	238 §	228	226	225	225
No. ADA positive	5	2	2	6	12
% ADA positive	2.1	0.9	0.9	2.7	5.3
Median titer	30.0	10.0	10.0	30.0	10.0
Min/Max titer	10 / 90	10 / 10	10 / 10	10 / 90	10 / 90

No. NAb positive	0	0	0	0	0
% NAb positive	0	0	0	0	0

= number of patients with non-missing assessment; n.c. = not calculable; *NR* = No result

§ = includes further pre-dose samples that were taken at Visit 1b

Tables 1.1.1.1, 1.1.3.1 & 1.1.5.1, End of Text Tables for ISI Analysis Final v05, 11-Jan-2021, ISI Appendix 2
(Source: Table 39, BLA761165 Integrated Summary of Immunogenicity)

Comparison of ADA Titers

The distribution of ADA titers is comparable between the FYB201 and US-licensed Lucentis treatment groups as seen in the previous table. There was no specific trend indicating the difference in the distribution of ADA titers between the FYB201 and US-licensed Lucentis treatment groups.

Comparison of Immunogenicity Impact on PK

Among 59 subjects who were included in the PK subgroup analysis set, only 5 subjects had positive ADA results by Week 48 (2 of 29 subjects in FYB201 group and 3 of 30 subjects in US-licensed Lucentis group). Therefore, no conclusion could be made regarding the correlation between blood levels and antibody rates.

Comparison of Immunogenicity Impact on Efficacy

The primary efficacy endpoint of Study FYB201-C2015-01-P3 is the change from baseline in best corrected distance visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) between FYB201 and US-licensed Lucentis treatments. The number of ADA-positive subjects was small (<1%) and equally divided between treatment arms at Week 4 (2 (0.9%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group) and Week 12 (1 (0.4%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group). Comparable low incidence of ADA formation and no NAb formation in each group supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.

Comparison of Immunogenicity Impact on Safety

The comparison of immunogenicity impact on safety was evaluated based on the assessment of selected treatment-emergent adverse events (TEAEs) by overall anti-drug antibody result up to end of study (Week 48), including drug hypersensitivity, anaphylaxis, and intra-ocular inflammation (see following table). Overall, none of these TEAEs was reported in patients with overall ADA positive status up to Week 48 in either treatment group.

Table 8: Summary of selected TEAE's up to Week 48 by ADA status and treatment

	FYB201 (N=238)		Lucentis (N=239)	
	ADA Negative (n=224)	ADA Positive (n=14)	ADA Negative (n=223)	ADA Positive (n=16)
Drug hypersensitivity	1 (0.4%)	0	1 (0.4%)	0
Anaphylaxis	0	0	0	0
Intra-ocular inflammation	0	0	0	0

(Source: Table 52, BLA761165 Integrated Summary of Immunogenicity)

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6. Statistical and Clinical Evaluation and Recommendations

6.1 Statistical and Clinical Executive Summary and Recommendation

The application includes a randomized, double-masked, parallel group, multicenter comparative clinical study of FYB201 to US-licensed Lucentis among subjects with nAMD. The study evaluated efficacy by comparing the primary endpoint of change in best corrected distance visual acuity (BCVA) from baseline to Week 8 between FYB201 and US-licensed Lucentis. The results of the comparative efficacy analysis would support that there are no meaningful differences between FYB201 and US-licensed Lucentis if the two-sided 90% confidence interval (CI) of the difference of least square means of the primary endpoint between arms was within the pre-defined equivalence margin of [−3 letters, 3 letters]. The data from Study FYB201-C2015-01-P3 contained in this submission compared 0.5 mg (10 mg/mL) of each product administered by intravitreal injection once a month (approximately 28 days) in patients with age-related macular degeneration. Study FYB201-C2015-01-P3 demonstrated comparable efficacy between groups with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 8.

6.1.1 Statistical and Clinical Residual Uncertainties Assessment

There are no residual uncertainties based on the clinical analyses.

6.2 Review of Comparative Clinical Studies with Statistical Endpoints

The application includes a single comparative clinical study (Study FYB201-C2015-01-P3) to support a demonstration of no clinically meaningful differences.

6.2.1 Study FYB201-C2015-01-P3

This was a randomized, double-masked, parallel group, multicenter study to evaluate the comparative efficacy, safety, and immunogenicity of FYB201 compared with US-licensed Lucentis in subjects with neovascular age-related macular degeneration (nAMD). A PK sub-study was included to descriptively compare the peak serum study drug concentrations.

Subjects who met all inclusion/exclusion criteria were randomized in a 1:1 ratio to receive 0.5 mg of either FYB201 or US-licensed Lucentis via intravitreal injection every 4 weeks (approximately every 28 days) up to Week 44. The last assessment was done at Week 48. The primary comparative efficacy analysis was assessed at Week 8. The safety analyses were assessed through Week 48.

Data and Analysis Quality

Randomization
Randomized treatment assignments of the study were verified based on predefined randomization method.

Masking
Subjects, evaluating investigators, and the other study personnel were masked to the treatment assignments throughout the study period.

Amendments
The study protocol was amended 7 times; the original protocol (Version 1.0 dated: 14-Jul-2015) and Protocol versions 1.0, 2.0 and 3.0 were prepared in response to discussions with health authorities; the first patient was enrolled under protocol version 4.0. The key features of each Amendment are summarized below.

Table 9: Study FYB201-C2015-01-P3 Protocol Amendments

Amendment No.	Version	Date	Topic of Changes
1	2.0	9/9/2015	DSMB members specified to be external. New exclusion criteria added: prisoners and employees
2	3.0	11/19/2015	Added BCVA as stratification factor, specified ETDRS charts to be used
3	4.0	11/30/2015	Additional sampling endpoints in PK subgroup
4	5.0	7/26/2016	Clarification on fellow eye during enrollment, corticosteroid treatment, physical assessment
5	6.0	1/18/2017	Change US primary endpoint, clarify interim analysis
6	7.0	3/8/2017	Replaced Amendment 5. Harmonization of primary EU and US endpoint, removal of interim analysis and trough level sampling
4,5,6	8.0	5/10/2017	Local protocol for France

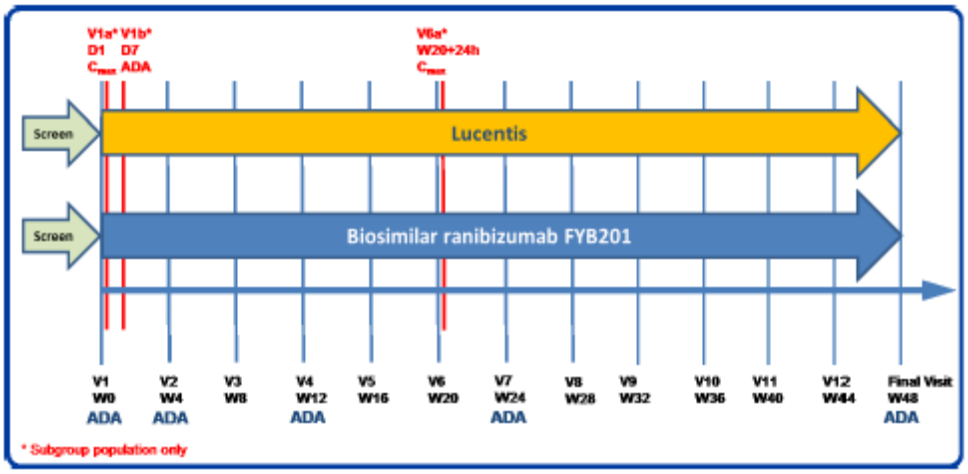
Amendment No.	Version	Date	Topic of Changes
7	9.0	8/29/2017	Inclusion of Metronomia and additional labs PK and nAb assay
7	9.0 FRA	8/29/2017	Country specific protocol version for France

Abbreviations: DSMB = Data Safety and Monitoring Board, BCVA = Best Corrected Visual Acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, EU = European Union, FRA = France

Study Design and Endpoints

This was a 48-week, randomized, active-controlled, evaluation-masked, parallel-group, multicenter study to compare clinical pharmacology, efficacy and safety of FYB201 with US-licensed Lucentis in the treatment of patients with subfoveal nAMD.

Figure 1: Schematic of the study design



For the US, this endpoint was evaluated in all patients with a baseline BCVA between 20/32 and 20/100 Snellen equivalent, while for the EU the endpoint was evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent.

As discussed and agreed with the FDA and EMA, the relevant primary study endpoint was the change in BCVA after 2 months. This time point lies in the steepest part of the BCVA time response curve, allowing detection of potential clinically relevant differences on visual function between the biosimilar candidate and the approved reference product.

Eligibility Criteria

Inclusion Criteria

General

1) Age ≥ 50 years of either gender

2) Signed informed consent form must have been obtained before any study related procedure was performed
3) Willingness and ability to undertake all scheduled visits and assessments
4) Women must have been postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (with documentation in the patient's medical records)

Ocular (Study Eye)

5) Newly diagnosed, angiographically documented, primary active CNV lesion secondary to AMD

a) All subtypes of nAMD CNV lesions were eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Active primary CNV had to be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by Spectral Domain Optical Coherence Tomography (SDOCT) or Retinal Pigment Epithelium (RPE) detachment)
b) Total area of whole lesion had to be equal or less than 12 disc areas
c) Total CNV area encompassed equal or more than 50% of total lesion area based on Fluorescein Angiography, including all subtypes of nAMD

6) Sufficiently clear ocular media and adequate pupillary dilation to permit good quality ocular imaging
7) BCVA in the study eye, determined by standardized ETDRS testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent
8) FCP retinal thickness at Screening ≥ 350 µm. (FCP thickness was defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea)

Ocular (Fellow Eye)

9) BCVA in the fellow eye, determined by standardized ETDRS testing, at least 20/100 (0.2) Snellen equivalent

Exclusion Criteria

General

1) Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who were legally institutionalized

Prior or current ocular therapy

2) Any prior treatment with IVT anti-VEGF agent (e.g., bevacizumab, aflibercept, ranibizumab) in either eye
3) History of vitrectomy, macular surgery, or other surgical intervention for AMD in the study eye
4) History of IVT or periocular injections of corticosteroids or device implantation within six months prior to Screening in the study eye
5) Prior treatment with verteporfin (PDT), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation) in the study eye
6) Topical ocular corticosteroids administered for at least 30 consecutive days within three months prior to Screening

7) Any other intraocular surgery (including cataract surgery) in the study eye within three months prior to Screening

CNV lesion characteristics

8) Sub- or intra-retinal hemorrhage that comprised more than 50% of the entire lesion in study eye
9) Fibrosis or atrophy involving the center of the fovea or influencing central visual function in the study eye
10) CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Current ocular conditions

11) Retinal pigment epithelial tear involving the macula in the study eye
12) History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT imaging of any size) in the study eye
13) History of retinal detachment in the study eye
14) Current vitreous hemorrhage in the study eye
15) Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
16) For patients who had undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye could not exceed 8 diopters of myopia
17) History of corneal transplant in the study eye
18) Aphakia in the study eye. Absence of an intact posterior capsule was allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation
19) Active or recent (within 4 weeks) intraocular inflammation of clinical significance in the study eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis or endophthalmitis
20) Uncontrolled hypertension or glaucoma in the study eye (defined as intraocular pressure (IOP) ≥ 30 mm Hg, despite treatment with anti-glaucomatous medication)
21) Ocular disorders in the study eye (i.e., retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on visual acuity) at the time of enrollment that could have confounded interpretation of study results and compromised visual acuity
22) Any concurrent intraocular condition in the study eye (e.g., glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the Investigator, would either have required surgical intervention during the study to prevent or treat visual loss that might have resulted from that condition or affect interpretation of study results.

Systemic medical history and conditions at Screening

23) Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives from Screening, whichever was longer
24) Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it might have biased the assessment of the clinical status of the patient to a significant degree or put the patient at special risk

25) Stroke or myocardial infarction within three months prior to Screening
26) Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg
27) Known hypersensitivity to the investigational drug (ranibizumab or any component of the ranibizumab formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation
28) Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines and ethambutol
29) History of recurrent significant infections and/or current treatment for active systemic infection
30) Pregnancy or lactation
31) Systemic treatment with high doses of corticosteroids (administration of >10 mg/day of prednisolone equivalent) during the last six months prior to Screening
32) Inability to comply with study or follow-up procedures

Ocular (Fellow Eye)

33) Any diagnosis and/or signs of nAMD requiring treatment with an IVT anti-VEGF agent (e.g., aflibercept, bevacizumab, ranibizumab) within the screening period or at study treatment initiation (Visit 1) in the fellow eye.

The study enrolled subjects who met all the inclusion criteria and none of the exclusion criteria.

Study eye

Only one eye that met the eligibility criteria was considered as the study eye. For subjects who had both eyes eligible, the eye with the worst visual acuity (VA) was selected as the study eye. If both eyes had equal VA, the study eye was selected at the Investigator's discretion.

List of Investigators

The study was conducted at 75 sites in Europe (Austria 1, Czech Republic 6, Germany 8, Spain 7, France 6, United Kingdom (UK) 5, Hungary 7, Italy 9, Poland 8, and Ukraine 3), Russia (4 sites) and Israel (11 sites).

Safety Assessments
Adverse events, clinical laboratory test, physical examination, vital signs, full ophthalmic examinations (slit-lamp biomicroscopy, IOP measurements, and fundus examinations).

Statistical Methodologies

Primary endpoints measurement
The primary endpoint was the change in best corrected distance (4 meters) visual acuity (BCVA) at Week 8 from the Baseline.

Sample size
The required sample size for the primary endpoint was calculated based on a 1:1 randomization ratio and a standard deviation (SD) of 10 ETDRS letters. The calculation was based on a 95% confidence interval (CI; two-sided significance level of 2.5%) to establish equivalence in line with EMA requirements. A total of 412 evaluable patients were required (206 patients each for treatment with FYB201 or Lucentis), when requesting a 90% power of the study, assuming no difference between both treatment groups, and using an equivalence margin of 3.5 ETDRS letters.

A total of 460 patients were needed to be treated as the EU-specific analysis was limited to patients with a screening Snellen equivalent of 20/40 or worse and assuming that approximately 10% of all randomized patients would be in the 20/32 stratum. A sample size of 460 was also sufficient for the US-specific analysis. In particular, 230 patients per treatment group would provide at least 95% power for assessing equivalence in the change in BCVA using a 90% CI, a SD of 10 ETDRS letters, no expected difference between the treatment groups, and an equivalence margin of 3.5 ETDRS letters.

Analysis populations
The (Full Analysis Set United States) FAS_US was based on the intention to treat (ITT) principle (i.e., patients were analyzed according to their randomized treatment irrespective of the treatment they actually received) and included all patients who received at least one injection of investigational medicinal product (IMP), and for whom BCVA results at least after 1 month were available and who had a screening BCVA between 20/32 and 20/100 Snellen equivalent in the study eye. Sensitivity analyses were performed for Foveal Center Point (FCP) retinal thickness based on the (Per-Protocol S United States) PPS_US.

The safety set comprised all patients who had received at least one injection with IMP. The safety set was used as general analysis set for all kinds of safety and tolerability data. Patients were analyzed according to the treatment they actually received irrespective of their randomized treatment. If only single injections from the wrong treatment were administered, it was to be decided on a case-by-case basis how the patient was to be analyzed.

Efficacy Analysis
The primary efficacy variable was the change from baseline in BCVA by ETDRS letters

calculated for the data at Week 8. The change (CHG) from baseline in BCVA at Week 8 was calculated per patient via: CHGBCVA = BCVAWeek 8 – BCVABaseline, where the baseline assessment was obtained at analysis visit V1. The hypothesis that both treatments FYB201 and US-licensed Lucentis are similar with respect to the primary endpoint was tested in terms of a two-sided equivalence test. The equivalence margin in BCVA of 3 ETDRS letters (as rounded to the nearest integer) was tested.

An analysis of covariance (ANCOVA) model was used for the analysis with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects. The 90% (US) and 95% (EU) CIs for the treatment difference between FYB201 (t1) and US-licensed Lucentis (t2) were calculated using Least Square Means. If the respective CI for the treatment difference was completely contained in the interval [-3.5; 3.5] ETDRS letters, equivalence of FYB201 and US-licensed Lucentis could be concluded for the primary endpoint.

The analysis of the primary endpoint was based on all patients in the FAS_US. Sensitivity analyses were based on the PPS_US. The analysis of ophthalmic assessments of secondary efficacy objectives were: BCVA, FCP and FCS retinal thickness, total lesion area, CNV leakage, and the percentage of patients with fluid-free macula.

Missing Data Methods

Discontinued or withdrawn patients were not replaced. Data from patients who prematurely discontinued the trial were used to the maximum extent possible. The applicant did not impute the missing BCVA data for primary efficacy analysis. The evaluation of the primary endpoint took place at Week 8 (Visit 3) which was relatively an early time point in the 48-week study period. Therefore, the impact of missing data in the primary endpoint was expected to be minimal. The table below summarizes the number of subjects who had missing BCVA assessments for the primary efficacy analysis.

Table 10: Summary of Subjects with Missing BCVA Data at Week 8 for Primary Efficacy Analysis (ITT Population)

	FYB201 (N=236)	Lucentis (N=239)	Total (N=475)
Subjects with missing BCVA at Week 8	8 (3.4%)	6 (2.5%)	14 (2.9%)
Subjects who had missing BCVA assessments at Week 8 but completed study	6 (2.5%)	5 (2.1%)	11 (2.3%)
Subjects who discontinued study before Week 8 due to intercurrent events	2 (0.8%)	1 (0.4%)	3 (0.6%)
Withdrawal by subject	1 (0.4%)	0 (0.0%)	1 (0.2%)
Adverse event	0 (0.0%)	1 (0.4%)	1 (0.2%)
Patient's death	1 (0.4%)	0 (0.0%)	1 (0.2%)

Interim analysis and statistical corrections:
No formal interim analysis was planned or performed for this study. Analysis of study data was performed after 24 Weeks (main analysis) and 48 Weeks (final analysis). The submitted CSR presents the study results of the final analysis performed after all randomized patients have either completed the Week 48 assessments or have discontinued the study (database lock 01-Oct-2018). Preceding this final analysis, a main analysis was performed after all patients had either completed the Week 24 assessments or had discontinued the study before the Week 24 assessments (database lock 20-Apr-2018). The Sponsor remained blinded on a by-patient level for the preceding main analysis.

Planned sub-group analyses
The applicant did not perform subgroup analyses. The Statistical reviewer conducted subgroup analyses to evaluate the change from baseline in BCVA at Week 8 in the ITT population for the demographic variables, gender, and age, and for the stratification factor of screening BCVA category. Race was not considered for subgroup analysis by the Statistical reviewer because 98% of the study subjects were Caucasian. The disease condition is not evenly distributed by race. Prevalence is higher in populations with lighter colored fundi.

Efficacy Analyses
The primary comparative efficacy analysis was performed for the FAS with the change from baseline of BCVA at Week 8 using an analysis of covariance model with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects. Equivalence for the United States was defined as a two-sided 90% Confidence Interval (CI) of the difference in mean changes from baseline at Week 8, lying within a 3-letter margin.

There was no formal hypothesis testing planned for the secondary endpoints and the analyses of the secondary endpoints were not required. The secondary endpoints were analyzed similarly to the primary endpoint.

Subject Disposition

A total of 477 subjects were randomized into two groups: 238 in FYB201 and 239 in US-licensed Lucentis. A total of 32 (6.7%) and 25 (5.2%) subjects discontinued from the treatment and from the study before Week 48, respectively. The discontinuation rates from the treatment were comparable between the treatment groups (6.7%) and the discontinuation rates from the study were comparable between the treatment groups (about 5%).

Table 11: Subject Disposition

	FYB201		Lucentis		Total	
	n	%	n	%	n	%
Screenings	-	-	-	-	722	-
Re-screenings					10	
Screened patients					712	
Exclusions	-	-	-	-	245	-
Re-screenings					4	
Excluded patients					241	
Failed inclusion/met exclusion criteria					211	
Randomized and treated	238	100%	239	100%	477	100%
Completed 24 Weeks assessments	230	96.6%	233	97.5%	463	97.1%
Discontinued treatment up to main analysis	7	2.9%	3	1.3%	10	2.1%
Completed 48 Weeks assessments	226	95.0%	226	94.6%	452	94.8%
Discontinued treatment up to final analysis	16	6.7%	16	6.7%	32	6.7%
Discontinued study up to final analysis	12	5.0%	13	5.4%	25	5.2%
Reasons						
Withdrawal by patient	2	16.7%	8	61.5%	10	40.0%
Adverse event(s)	1	8.3%	2	15.4%	3	12.0%
Major protocol deviation	1	8.3%	0	0.0%	1	4.0%
Need for alternative treatment	1	8.3%	0	0.0%	1	4.0%
Loss to follow-up	3	25.0%	1	7.7%	4	16.6%
Other	4	33.3%	2	15.4%	6	24.0%

Abbreviations: n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100
Notes: Percentages are based on the number of patients randomized (within each group).
Percentages are based on the number of patients who discontinued the study for reasons for early discontinuation.

The groups are similar. No concerns are raised from the number of subjects in the dataset.

Protocol Deviations

Patients with major protocol deviations were excluded from the per-protocol sets (PPS), whereas minor protocol deviations did not lead to exclusion from any analysis set. Overall, the number of patients with major protocol deviations was well balanced between both treatment groups (18 patients with major protocol deviations in the FYB201 group and 14 patients in the US-licensed Lucentis group). Main reasons for exclusion from the PPS were the lack of valid BCVA assessment between Day 50 and 64 (18 patients; 3.8%) and violation of in- or exclusion criteria (11 patients; 2.3%).

Table 12: Protocol Deviations - Safety Set

	FYB201 (N = 238)		Lucentis (N = 239)	
	n	**%**	**n**	**%**
Major protocol deviations	18	7.6%	14	5.9%
No BCVA assessment between Day 50–64	10	4.2%	8	3.3%
Injection 2 before Day 22 or after Day 36	0	0.0%	2	0.8%
Missing injections	2	0.8%	3	1.3%
Violation of inclusion/exclusion criteria	8	3.4%	3	1.3%
PK data (interference with interpretation of ranibizumab concentration data)	0	0.0%	1	0.4%
Prohibited concomitant medications	1	0.4%	1	0.4%
Minor protocol deviations	**111**	**46.6%**	**114**	**47.7%**
BCVA assessment between Day 50–53 or Days 61–64	15	6.3%	12	5.0%
Blood sample issue	5	2.1%	8	3.3%
Violation of inclusion/exclusion criteria	5	2.1%	5	2.1%
Missing ADA assessment	2	0.8%	4	1.7%
Prohibited concomitant medications	17	7.1%	18	7.5%
Randomization procedure and possible unblindings	2	0.8%	1	0.4%
Other	0	0.0%	1	0.4%
from injection schedule:	**68**	**28.6%**	**80**	**33.5%**
Injection deviates from schedule more than ±14 days	4	1.7%	4	1.7%
Injection 2 between Day 22–25 or Day 33–36	12	5.0%	12	5.0%
Missing injections	28	11.8%	40	16.7%
Time between 2 injections <22 days	9	3.8%	15	6.3%
Time between 2 injections >34 days	59	24.8%	73	30.5%
from study procedures:	**31**	**13.0%**	**22**	**9.2%**
Missing study procedures	23	9.7%	12	5.0%
Study procedures out of window	8	3.4%	11	4.6%
from visit schedule:	**36**	**15.1%**	**40**	**16.7%**
Missing visits	31	13.0%	36	15.1%
Visits out of window	6	2.5%	5	2.1%
Any minor GCP issue	89	37.4%	92	38.5%
Blood sample issue	15	6.3%	16	6.7%
Failure to report SAE in a timely manner	3	1.3%	7	2.9%
Informed consent procedure	78	32.8%	74	31.0%
Personnel, facilities or equipment	2	0.8%	5	2.1%

Abbreviations: BCVA = best-corrected visual acuity, PK = pharmacokinetic, N = total number of patients. Source: Post-text tables 14.1.1.7.1, 14.1.1.8.1

The groups are similar. No concerns are raised from the protocol deviations.

Table 13: Number (%) of Subjects in the Analysis Sets

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
Analysis Set	n	(%)	n	(%)	n	(%)
Safety Set (SAF)	238	100.0%	239	100.0%	477	100.0%
Full Analysis Set for US (FAS_US)	237	99.6%	238	99.6%	475	99.6%
Full Analysis Set for EU (FAS_EU)	215	90.3%	214	89.5%	429	89.9%
Per Protocol Set for US (PPS_US)	220	92.4%	225	94.1%	445	93.3%
Per Protocol Set for EU (PPS_EU)	200	84.0%	202	84.5%	402	84.3%
Pharmacokinetic Subgroup Analysis Set (PKS)	29	100.0%	30	96.8%	59	98.3%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100, SAF: Safety set, FAS US = Full analysis set for the US, FAS EU = Full analysis set for the EU, PPS US = Per protocol set for the US, PPS EU = Per protocol set for the EU
Notes: Percentages are based on the number of patients randomized within each group, whereby the patients are tabulated according to the planned treatment.

The groups are similar. No concerns are raised from the protocol deviations.

Demographics and Baseline Characteristics

Table 14: Demographics and other baseline characteristics – SAF

	FYB201 (N = 238)	Lucentis (N = 239)
Gender [n (%)]		
Male	103 (43.3%)	105 (43.9%)
Female (no women of childbearing potential)	135 (56.7%)	134 (56.1%)
Age at Screening [years]		
Mean (SD)	74.9 (8.26)	76.1 (7.84)
Median	76.0	77.0
Interquartile range (Q1–Q3)	69.0–81.0	71.0–81.0
Range (min–max)	50–91	50–94
Age Categories at Screening [n (%)]		
50–64 years	25 (10.5%)	19 (7.9%)
65–75 years	91 (38.2%)	86 (36.0%)
>75 years	122 (51.3%)	134 (56.1%)
Race [n (%)]		
Caucasian	236 (99.2%)	233 (97.5%)
Asian	0 (0.0%)	2 (0.8%)
Other	2 (0.8%)	4 (1.7%)
BMI at Screening [kg/m^2]		

Mean (SD)	27.17 (4.084)	27.40 (4.467)
Median	26.28	26.83
Interquartile range (Q1–Q3)	24.46–29.07	24.06–30.11
Range (min–max)	19.9–42.9	17.8–44.0

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100, SD = standard deviation, Q1= first quartile, Q3 = third quartile, min = minimum, max = maximum, SAF = Safety Set, BMI = Body Mass Index

All demographics were similar in both treatment groups and differences in demographics in the different analysis sets were negligible compared to the SAF. Gender, race, and age groups were similarly distributed in both treatment groups.

Table 15: Other baseline ophthalmic characteristics by treatment group -SAF

	FYB201	Lucentis
	(N = 238)	(N = 239)
OD (right eye)	127 (53.4%)	127 (53.1%)
OS (left eye)	111 (46.6%)	112 (46.9%)
Iris color [n (%)]		
Light	89 (37.4%)	89 (37.4%)
Medium	104 (43.7%)	100 (42.0%)
Dark	45 (18.9%)	49 (20.6%)
Missing	0	1
Baseline Snellen equivalent in study eye [n (%)]		
20/32	24 (10.1%)	22 (9.2%)
20/40	43 (18.1%)	38 (15.9%)
20/50	45 (18.9%)	39 (16.3%)
20/63	37 (15.5%)	46 (19.2%)
20/80	37 (15.5%)	37 (15.5%)
20/100	52 (21.8%)	57 (23.8%)
Baseline Snellen equivalent in fellow eye [n (%)]		
20/12.5	2 (0.8%)	3 (1.3%)
20/16	20 (8.4%)	7 (2.9%)
20/20	63 (26.5%)	53 (22.2%)
20/25	42 (17.6%)	59 (24.7%)
20/32	47 (19.7%)	59 (24.7%)
20/40	22 (9.2%)	27 (11.3%)
20/50	21 (8.8%)	12 (5.0%)
20/63	10 (4.2%)	8 (3.3%)
20/80	6 (2.5%)	4 (1.7%)
20/100	5 (2.1%)	7 (2.9%)

Baseline ocular characteristics were comparable across treatment groups.

Analysis of Primary Clinical Endpoint(s)

The equivalence of FYB201 to US-licensed Lucentis to treat subjects with nAMD was evaluated based on the endpoint of the change in BCVA at Week 8 from the Baseline.

Table 16: Absolute change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8 – FAS_US

	FYB201	Lucentis
	(N = 237)	(N = 238)
N*	234	238
N	228	233
Missing	6	5
Mean (SD)	5.1 (7.52)	5.6 (8.63)
Median	5.0	5.0
Interquartile range (Q1–Q3)	0.0–10.0	1.0–11.0
Range (min–max)	-16–30	-39–25

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS US = full analysis set for the US, N = total number of patients, N* = total number of patients still in the study for the respective analysis visit, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, min = minimum, max = maximum SD = standard deviation, Q1 = first quartile, Q3 = third quartile

The LS means difference for the change from baseline in BCVA at Week 8 between FYB201 and US-licensed Lucentis was -0.4 ETDRS letters with a 90% CI for the US-specific analysis of [-1.6; 0.9] ETDRS letters (see table below). The 90% CI was completely within the predefined equivalence margin of {-3.5; 3.5} ETDRS letters meeting the predefined criterion for similarity of FYB201 to US-licensed Lucentis.

Table 17: ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8 – FAS_US

	n	Missing	Arithmetic Mean	LS mean[1]	SE LS mean	90% CI
FYB201	228	6	5.1	5.1	0.58	[4.1; 6.0]
Lucentis	233	5	5.6	5.4	0.58	[4.5; 6.4]
Difference						
FYB201 - Lucentis		-0.5	-0.4	0.76	[-1.6; 0.9]	
CI contained in [-3.5; 3.5][2]					yes	

[1] Estimates are adjusted for pooled country and baseline BCVA [letters].

[2] If confidence interval for difference in LS means is completely contained in the interval [-3.5 letters, 3.5 letters], FYB201 and Lucentis are considered equivalent.

Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS US = full analysis set for the US, LS = Least squares, n = number of patients with non-missing assessment at analysis visit V3/Week 8, Missing = number of patients with missing assessment at analysis visit V3/Week 8, SE = standard error

Notes: Two-sided 90% confidence interval based on normal approximation.

Sensitivity analyses for the primary efficacy endpoint US

The sensitivity analysis for the primary efficacy endpoint for the US-specific analysis was the change from baseline in BCVA at Week 8 in the PPS_US population.

Table 18: Absolute change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8 – PPS_US

	FYB201 (N = 220)	Lucentis (N = 225)	Total (N = 445)
Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8			
Mean (SD)	5.2 (7.59)	5.7 (8.64)	5.5 (8.13)
Median	5.0	6.0	5.0
Interquartile range (Q1–Q3)	0.0–10.0	1.0–11.0	1.0–10.0
Range (min–max)	-16–30	-39–25	-39–30

Table 19: ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8 – PPS_US

	n	Missing	Arithmetic mean	LS mean[1]	SE LS mean	90% CI
FYB201	220	0	5.2	5.2	0.59	[4.2; 6.1]
Lucentis	225	0	5.7	5.6	0.59	[4.6; 6.6]
Difference						
FYB201 - Lucentis		-0.5	-0.4	0.78	[-1.7; 0.9]	
CI contained in [-3.5; 3.5][2]					yes	

[1] Estimates are adjusted for pooled country and baseline BCVA [letters].

[2] If confidence interval for difference in LS means is completely contained in the interval [-3.5 letters, 3.5 letters], FYB201 and Lucentis are considered equivalent.

Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, PPS US = per protocol set for the US, LS = Least squares, n = number of patients with non-missing assessment at analysis visit V3/Week 8, Missing = number of patients with missing assessment at analysis visit V3/Week 8, SE = standard error, Notes: Two-sided 90% confidence interval based on normal approximation.

6.3 Review of Safety Data

6.3.1 Methods

Categorization of Adverse Events

Safety of FYB201 and US-licensed Lucentis in Study FYB201-C2015-01-P3 was comparatively assessed by monitoring treatment-emergent adverse events (TEAEs, ocular/non-ocular), serious adverse events (SAEs, ocular/non-ocular), adverse events of special interest (AESI), clinical laboratory evaluations, ophthalmic assessments, and as well as immunogenicity.

6.3.2 Major Safety Results

Deaths

Three patients died during the study; two patients were exposed to FYB201 and one patient was exposed to US-licensed Lucentis.

Table 20: Deaths

Treatment	Patient Number	Narrative
FYB201	(b) (6)	Worsening bronchiectasis and worsening of severe obstructive pulmonary disease resulting in death
FYB201		Severe cardiopulmonary failure resulting in death
Lucentis		Severe respiratory failure resulting in death

The deaths which occurred during the study are consistent with past medical history of the subjects enrolled.

Treatment Emergent Adverse Events

Table 21: Frequency of TEAEs up to Week 48 by MedDRA SOC and PT in ≥2.0% of patients – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)	
PT	N	%	n	%
Any	154	64.7%	167	69.9%
Eye disorders				
Overall	100	42.0%	100	41.8%
Neovascular age-related macular degeneration	19	8.0%	22	9.2%
Conjunctival haemorrhage	14	5.9%	19	7.9%
Punctate keratitis	8	3.4%	12	5.0%

Visual acuity reduced	6	2.5%	11	4.6%
Eye pain	9	3.8%	6	2.5%
Cataract	1	0.4%	11	4.6%
Lacrimation increased	9	3.8%	2	0.8%
Choroidal neovascularization	6	2.5%	4	1.7%
Conjunctival hyperaemia	4	1.7%	6	2.5%
Retinal haemorrhage	7	2.9%	3	1.3%
Vitreous detachment	6	2.5%	4	1.7%
Infections and infestations				
Overall	55	23.1%	57	23.8%
Nasopharyngitis	12	5.0%	16	6.7%
Bronchitis	9	3.8%	5	2.1%
Upper respiratory tract infection	8	3.4%	6	2.5%
Conjunctivitis	9	3.8%	2	0.8%
Investigations				
Overall	32	13.4%	39	16.3%
Intraocular pressure increased	11	4.6%	12	5.0%
C-reactive protein increased	10	4.2%	5	2.1%
Musculoskeletal and connective tissue disorders				
Overall	17	7.1%	29	12.1%
Back pain	5	2.1%	8	3.3%
Nervous system disorders				
Overall	10	4.2%	26	10.9%
Headache	4	1.7%	9	3.8%
Gastrointestinal disorders				
Overall	13	5.5%	22	9.2%
Vascular disorders				
Overall	10	4.2%	23	9.6%
Hypertension	3	1.3%	14	5.9%
Injury, poisoning and procedural complications	13	5.5%	18	7.5%
General disorders and administration site conditions	17	7.1%	13	5.4%
Respiratory, thoracic, and mediastinal disorders				
Overall	15	6.3%	9	3.8%
Cough	5	2.1%	5	2.1%
Cardiac disorders	8	3.4%	10	4.2%
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6	2.5%	7	2.9%
Blood and lymphatic system disorders	8	3.4%	4	1.7%
Renal and urinary disorders	5	2.1%	6	2.5%
Skin and subcutaneous tissue disorders	6	2.5%	4	1.7%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % = number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event
Notes: MedDRA version 19.0 was used.

The overall ocular adverse event rates were similar between FYB201 and US-licensed Lucentis.

Dropouts and/or Discontinuations

Table 22: Adverse Events Leading to Study Discontinuation (Safety Set) – Week 48

System Organ Class (SOC) Preferred Term (PT)	STUDY FYB201-C2015-01-P3	
	FYB201 (N=238) n (%) Events	Lucentis (N=239) N (%) Events
Any adverse event leading to discontinuation	1 (0.4) 1	2 (0.8) 2
Worsening of nAMD	1 (0.4) 1	0 (0.0) 0
Benign pancreatic neoplasm	0 (0.0) 0	1 (0.4) 1
Malignant tongue neoplasm	0 (0.0) 0	1 (0.4) 1

No clinically relevant differences between the two treatment groups were identified.

6.3.3 Additional Safety Evaluations

Table 23: Number and percentage of patients with Serious Ocular local (study eye) TEAEs (SAEs) up to Week 48 by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Endophthalmitis	1	0.4%	2	0.8%	3	0.6%
Cataract	0	0.0%	1	0.4%	1	0.2%
Iridocyclitis	1	0.4%	0	0.0%	1	0.2%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % = number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event Notes: Local TEAEs were defined as TEAEs occurring in the study eye. MedDRA version 19.0 was used.

Local SAEs, occurring in the study eye were observed in 5 patients; 2 patients in the FYB201group (PTs: Endophthalmitis and Iridocyclitis) and 3 patients in the US-licensed Lucentis group (PTs: Endophthalmitis in 2 patients, and Cataract in 1 patient). There was no significant difference between the two groups.

Table 24: Number and percentage of patients with Serious Non-ocular systemic TEAEs (SAEs) up to Week 48 by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Cardiac disorders						
Overall	7	2.9%	5	2.1%	12	2.5%
Atrial fibrillation	3	1.3%	1	0.4%	4	0.8%
Myocardial infarction	1	0.4%	2	0.8%	3	0.6%
Nervous system disorders						
Overall	2	0.8%	5	2.1%	7	1.5%

Syncope	1	0.4%	1	0.4%	2	0.4%
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)						
Overall	2	0.8%	4	1.7%	6	1.3%
Respiratory, thoracic, and mediastinal disorders						
Overall	3	1.3%	3	1.3%	6	1.3%
Respiratory failure	1	0.4%	2	0.8%	3	0.6%
Musculoskeletal and connective tissue disorders						
Overall	1	0.4%	4	1.7%	5	1.0%
Intervertebral disc protrusion	1	0.4%	2	0.8%	3	0.6%
Osteoarthritis	0	0.0%	2	0.8%	2	0.4%
Infections and infestations	3	1.3%	1	0.4%	4	0.8%
Renal and urinary disorders						
Overall	2	0.8%	2	0.8%	4	0.8%
Acute kidney injury	2	0.8%	0	0.0%	2	0.4%
Vascular disorders	1	0.4%	3	1.3%	4	0.8%
Blood and lymphatic system disorders	1	0.4%	2	0.8%	3	0.6%
Gastrointestinal disorders	0	0.0%	3	1.3%	3	0.6%
Injury, poisoning and procedural complications	1	0.4%	1	0.4%	2	0.4%
Metabolism and nutrition disorders	0	0.0%	2	0.8%	2	0.4%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % = number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event
Notes: Systemic TEAEs were defined as TEAEs not occurring in the study eye. MedDRA version 19.0 was used.

The reported rates in each group were similar. No concerns were raised by the comparison.

6.4 Clinical Conclusions

Study FYB201-C2015-01-P3 demonstrated that FYB201 is comparable to US-licensed Lucentis with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 8. The adverse event profile was not significantly different between subjects treated with FYB201 and US-licensed Lucentis. No concerns are raised from the comparison.

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6.5 Risk in Terms of Safety or Diminished Efficacy of Switching Between Products and the Any Given Patient Evaluation (to Support a Demonstration of Interchangeability)

The Applicant has developed FYB201 as a proposed interchangeable biosimilar to US-licensed Lucentis and is seeking licensure of FYB201 for the same indications, same dosage form, strengths and route of administration as US-licensed Lucentis.

FDA believes that the risk of a clinically impactful immunogenic response from systemic anti-drug antibodies and intraocular inflammation when alternating or switching between FYB201 and US-licensed Lucentis is low. A switching study that compares immunogenicity and PK and/or PD, as generally recommended by FDA, will not be informative to demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis. A switching study would also not be informative to demonstrate that the risk is not greater than using the reference product without such alternation or switch.

The Applicant provided sufficient justification that FYB201 will produce the same clinical result in any given patient for each condition of use for which licensure is sought and for which US-licensed Lucentis has been previously approved. The scientific justification considered the following issues that are described in the FDA guidance for industry, Considerations in Demonstrating Interchangeability with a Reference Product.

Mechanism of Action

The Applicant provided adequate justification to support that FYB201 has the same known and potential mechanisms of action as US-licensed Lucentis for Neovascular (wet) AMD, RVO, DME, DR and mCNV.

Pharmacokinetics (PK)

Overall, the post-dose PK sampling time-points, the arithmetic mean concentrations were below the concentration range of ranibizumab that is necessary to inhibit the biological activity of VEGF-A by 50%, as measured in an *in vitro* cellular proliferation assay. Given the low concentrations observed in both treatment groups, the levels are not considered clinically meaningful and unlikely to have any implications on systemic safety.

Immunogenicity

The incidences of Anti-Drug Antibody (ADA) and Neutralizing Antibodies (Nab) were very low and comparable between FYB201 and US-licensed Lucentis treatment groups across all timepoints up to Week 52 in the comparative clinical study. AMD, RVO, mCNV, DME, and DR do not differ in clinical characteristics that would affect immunogenicity. The low incidences do not pose a safety concern for any of the US-licensed Lucentis indications.

Toxicity

AMD, RVO, mCNV, DME, and DR do not differ in clinical characteristics that would affect toxicity. The safety profile resulting from the intravitreal administration of a comparable anti-VEGF product would not be expected to differ on the basis of the indication.

The data and information provided by the Applicant are sufficient to demonstrate that FYB201 can be expected to produce the same clinical result as US-licensed Lucentis in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis is not greater than the risk of using US-licensed Lucentis without alternation or switch.

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6.6 Extrapolation

The Applicant submitted data and information in support of a demonstration that FYB201 is highly similar to US-licensed Lucentis notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between FYB201 and US-licensed Lucentis in terms of safety, purity, and potency. In addition, the totality of evidence submitted in the application sufficiently demonstrates that FYB201 can be expected to produce the same clinical results as US-licensed Lucentis in any given patient and that, the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis is not greater than the risk of using US-licensed Lucentis without such alteration or switch.

The Applicant is seeking licensure of FYB201 for the following indication(s) for which US-licensed Lucentis has been previously licensed and for which FYB201 has not been directly studied: macular edema following retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), diabetic macular edema (DME) and diabetic retinopathy (DR).

The Applicant provided a justification for extrapolating data and information submitted in the application to support licensure of FYB201 as an interchangeable biosimilar for each such indication for which licensure is sought and for which US-licensed Lucentis has been previously approved.

Therefore, the totality of the evidence provided by the Applicant supports licensure of FYB201 as a biosimilar to and interchangeable with US-licensed Lucentis for each of the following indication(s) for which the Applicant is seeking licensure of FYB201: neovascular (Wet) age-related macular degeneration (AMD), macular edema following

retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), diabetic macular edema (DME), and diabetic retinopathy (DR).

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7. Labeling Recommendations

7.1 Nonproprietary Name

The Applicant's proposed nonproprietary name, ranibizumab-eqrn, was found to be conditionally acceptable by the Office of Medication Error Prevention and Risk Management in a letter to the applicant dated June 9, 2022.

7.2 Proprietary Name

The proposed proprietary name for FYB201 is conditionally approved as Cimerli. This name has been reviewed by the Division of Medication Error Prevention and Analysis (DMEPA), who concluded the name was acceptable in a letter to the applicant dated November 2, 2021.

7.3 Other Labeling Recommendations

The proposed labeling which follows, submitted to the application on July 11, 2022, (prescribing information), and July 22, 2022, (carton and container labeling), is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR), is clinically meaningful and scientifically accurate, and conveys the essential scientific information needed for safe and effective use of the product.

Division of Medication Error Prevention and Analysis 1 (DMEPA 1) completed a review of the July 22, 2022, carton and container labeling and found the revisions to be acceptable.

The Office of Biotechnology Products (OBP) completed a final review of the submitted and on July 29, 2022, and found it to be acceptable.

31 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

8. Human Subjects Protections/Clinical Site and other Good Clinical Practice (GCP) Inspections/Financial Disclosure

The data quality and integrity of the studies were acceptable. The BLA submission was in electronic common technical document (eCTD) format and was adequately organized.

Documented approval was obtained from institutional review boards (IRBs) and independent ethics committees (IECs) prior to study initiation. All protocol modifications were made after IRB/IEC approval. The studies were conducted in accordance with good clinical practice (GCP), code of federal regulations (CFR), and the Declaration of Helsinki.

The Applicant has adequately disclosed financial interests and arrangements with the investigators. Form 3454 is noted in Section 14.2 and verifies that no compensation is linked to study outcome. The Principal Investigators (PIs) did not disclose any proprietary interest to the sponsor.

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9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee was held for this biosimilar application, as it was determined that there were no issues where the Agency needed input from the Committee.

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10. Pediatrics

The Pediatric Review Committee (PeRC) discussed this application on June 7, 2022. The labeling for U.S.-licensed Lucentis does not contain pediatric information for the indications for which the applicant is seeking licensure, and PREA requirements were waived for U.S.-licensed Lucentis for those indications. Therefore, the agency has determined that, no pediatric studies will be required under PREA for this BLA. See QA.I.16, FDA Guidance for Industry: Questions and Answers on Biosimilar Development and the BPCI Act (Rev. 2) (Sept. 2021).

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11. REMS and Postmarketing Requirements and Commitments

11.1 Recommendations for Risk Evaluation and Mitigation Strategies

None.

11.2 Recommendations for Postmarket Requirements and Commitments

The Office of Pharmaceutical Quality has recommended the following post-marketing commitments and the approval letter will include them:

4307-1
Complete drug substance transport validation study and submit the final transportation validation report.

The timetable submitted on July 22, 2022, states that this study will be conducted and the Final Report results submitted by Q3 2023 (i.e., September 30, 2023).

4307-2
Complete drug product bulk and drug product transport validation studies and submit the final transportation validation report.

The timetable submitted on July 22, 2022, states that these studies will be conducted and the Final Report results submitted by Q3 2023 (i.e., September 30, 2023).

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12. Comments to Applicant

There are no additional comments for the applicant.

13. Division Director Comments

13.1 Division Director (OND – Clinical) Comments

The Review Team is in agreement that the application supports FYB201 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components. FYB201 is included in a single-dose vial with sufficient drug product to enable administration of 0.5 mg of the 10 mg/mL, and 0.3 mg of the 6 mg/mL, the same strengths as that of US-licensed Lucentis. The dosage form and route of administration is also the same as that of US-licensed Lucentis. There are no residual uncertainties from a product quality perspective. The Product Quality review team in a review dated June, 3, 2022, concluded that there was sufficient comparative analytical data (i.e., structural and functional characterization) between FYB201 and US-licensed Lucentis to support a demonstration that FYB201 is highly similar to US-licensed Lucentis.

Systemic exposure of FYB201 and US-licensed Lucentis was evaluated in the a subset of patients with neovascular AMD in the comparative clinical study FYB201-C2015-01-P3. There were comparable, low systemic exposures of both FYB201 and US-licensed Lucentis supporting a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis. There were also comparable, low incidences of ADA/NAb formation in both FYB201 and US-licensed Lucentis supporting a demonstration of no clinically meaningful differences.

Study FYB201-C2015-01-P3 supported that there are no clinically meaningful differences in efficacy or safety between FYB201 and US-licensed Lucentis in patients with AMD. In Study FYB201-C2015-01-P3, patients with bilateral disease were concurrently treated with US-licensed Lucentis in the contralateral eye. For those who were randomized to receive FYB201 in the study eye, this contralateral administration exposed individuals to both FYB201 and US-licensed Lucentis concurrently. There are no residual uncertainties from the clinical or clinical statistical perspectives regarding a demonstration that FYB201 is biosimilar to US-licensed Lucentis.

The Applicant provided adequate scientific justification for extrapolation to the other indications listed in the US-licensed Lucentis package insert being sought for licensure (i.e., RVO, DME, DR and mCNV) based on: 1) the mechanism of action of ranibizumab, including the structure and drug-target interactions in each condition being consistent across all approved indications. For each of the indications being sought for licensure, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and 2) the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications being sought is consistent and there are no known differences in expected toxicities for each indication being sought. The applicant submitted data and information demonstrating that FYB201 can be expected to produce the same clinical result as US-licensed Lucentis in any given patient and that the risk in terms of safety or diminished efficacy of alternating or switching between use of FYB201 and US-licensed Lucentis is not greater than the risk of using US-licensed Lucentis without alternation or switch. The data in this BLA and this justification supports licensure of FYB201 as an interchangeable biosimilar for the following indications for which US-licensed Lucentis has been previously approved: neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema, diabetic retinopathy and myopic choroidal neovascularization. There are no residual uncertainties regarding the scientific justification for extrapolation.

Author:
Wiley A. Chambers, M.D.
Division Director

14. Appendices

14.1 Financial Disclosure

Covered Clinical Study FYB201-C2015-01-P3: A Single Randomized, Active-Controlled, Evaluation-masked, Parallel Group, Multicenter Study designed to demonstrate clinical equivalence in terms of clinical pharmacology, efficacy, and safety of FYB201 with Lucentis in the treatment of subjects with nAMD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75 principal, >400 total		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
08/02/2022 10:59:44 AM

WILEY A CHAMBERS
08/02/2022 11:18:31 AM

BIOSIMILAR CLINICAL REVIEW

Application Type	351(k) BLA
Application Number	761165
Received Date	August 2, 2021
BsUFA Goal Date	August 2, 2022
Division/Office	Division of Ophthalmology
Review Completion Date	See DARRTS stamped date
Product Code Name	FYB201
Proposed Nonproprietary Name[1]	ranibizumab-eqrn
Proposed Proprietary Name[1]	Cimerli
Pharmacologic Class	vascular endothelial growth factor (VEGF) inhibitor
Applicant	Coherus BioSciences,Inc.
Applicant Proposed Indication(s)	Indicated for the treatment of patients with: • Neovascular (Wet) Age-Related Macular Degeneration (AMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy (DR) • Myopic Choroidal Neovascularization (mCNV)
Recommendation on Regulatory Action	Recommend Approval

[1]Section 7 of the Biosimilar Multidisciplinary Evaluation and Review discusses the acceptability of the proposed nonproprietary and proprietary names, which are conditionally accepted until such time that the application is approved.

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

FYB201 (ranibizumab-eqrn; Cimerli) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment for intraocular use that has been developed as a proposed biosimilar/interchangable to US-licensed Lucentis. Ranibizumab-eqrn binds to the receptor binding sites of Vascular Endothelial Growth Factor-A (VEGF-A) isoforms, including the proteolytically cleaved VEGF-A 110 isoform. The binding of ranibizumab to VEGF-A reduces the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2).

The Applicant is seeking licensure for the 0.5 mg (10 mg/mL) and 0.3 mg (6 mg/mL) strengths each in a single-dose vial. The 0.5 mg (10 mg/mL) dose for the following indications which are the same as those previously approved for US-licensed Lucentis[2]:

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV).

The 0.3 mg (6 mg/mL) strength for the following indications which are the same as those previously approved for US-licensed Lucentis[3]:

- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR).

For neovascular (wet) age-related macular degeneration (AMD), Cimerli 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For macular edema following retinal vein occlusion (RVO), Cimerli 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days). For myopic choroidal neovascularization (mCNV), Cimerli 0.5 mg (0.05 mL of 10 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days) for up to three months. For diabetic macular edema (DME) and diabetic retinopathy (DR), Cimerli 0.3 mg (0.05 mL of 6 mg/mL solution) is recommended to be administered by intravitreal injection once a month (approximately 28 days).

[2] U.S. Prescribing Information, US-licensed Lucentis, Accessed August 26, 2021 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf
[3] U.S. Prescribing Information, US-licensed Lucentis, Accessed August 26, 2021 from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125156s117lbl.pdf

These dosing regimens are the same as approved for US-licensed Lucentis.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB201 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between FYB201 and US-licensed Lucentis in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB201 is biosimilar/interchangable to US-licensed Lucentis for each of the following indications for which US-licensed Lucentis has been previously approved and for which the Applicant is seeking licensure of FYB201: [4]

- Neovascular (wet) age-related macular degeneration (AMD)
- Macular edema following retinal vein occlusion (RVO)
- Myopic choroidal neovascularization (mCNV)
- Diabetic macula edema (DME)
- Diabetic retinopathy (DR).

1.3. Benefit-Risk Assessment

[4]The proposed FYB201 labeling states: (b) (4)

Benefit-Risk Integrated Assessment

In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB201 is highly similar to US-licensed Lucentis, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between Cimerli (FYB201) and US-licensed Lucentis in terms of the safety, purity, and potency of the product. The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB201 is biosimilar to US-licensed Lucentis for each of the following indications for which US-licensed Lucentis has been previously approved and for which the Applicant is seeking licensure of FYB201.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Neovascular (Wet) Age-Related Macular Degeneration (nAMD) if untreated will lead to visual loss. The Applicant is seeking to treat all the following conditions: • Neovascular (Wet) Age-Related Macular Degeneration (nAMD) • Macular Edema Following Retinal Vein Occlusion (RVO) • Diabetic Macular Edema (DME) • Diabetic Retinopathy • Myopic Choroidal Neovascularization (mCNV)	Treatment is needed to prevent visual loss. To support the demonstration that Cimerli (FYB201) is highly similar to US-licensed Lucentis, bioeq GmbH performed a clinical trial (FYB201-C2015-01-P3) to compare the efficacy, safety, PK and immunogenicity between FYB201 and US-licensed Lucentis. The data provided supported the conclusion that FYB201 is highly similar to US-licensed Lucentis. FYB201 has the same mechanism(s) of action as that of U.S.-licensed Lucentis.
Current Treatment Options	Lucentis (ranibizumab injection), Eylea (aflibercept), Beovu (brolucizumab-dbll) injection, Vabysmo (faricimab-svoa) and MACUGEN (pegaptanib sodium injection) are all approved for the treatment of nAMD. Visudyne (verteporfin for injection) is approved for the treatment of patients with predominantly classic subfoveal	The approved products are all safe and effective treatments for nAMD. Except for Visudyne, all treatment options require intravitreal injections every 1 to 3 months.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. AVASTIN (bevacizumab) injection is used off-label to treat nAMD.	Clinical trial (FYB201-C2015-01-P3) compared the efficacy, safety, PK and immunogenicity between Cimerli (FYB201) and US-licensed Lucentis; this data supported the conclusion that FYB201 is highly similar to US-licensed Lucentis.
Benefit	FYB201is biosimilar to Lucentis in its ability to maintain visual acuity over a 48 week period in nAMD. In considering the totality of the evidence submitted, the data submitted by the Applicant demonstrate that FYB201 is highly similar to US-licensed Lucentis in treating the listed indications.	The approved products reduce the risk of visual loss in patients with nAMD. Clinical trial (FYB201-C2015-01-P3) compared the efficacy, safety, PK and immunogenicity between Cimerli (FYB201) and US-licensed Lucentis; this data supported the conclusion that FYB201 is highly similar to US-licensed Lucentis.
Risk and Risk Management	FYB201 is highly similar to US-licensed Lucentis. Additional risk assessments (PMCs or PMRs, etc.) are not required.	The risks associated with the products are the same between FYB201 and US-licensed Lucentis.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Sec 6.1 Study Endpoints
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant is seeking licensure of FYB201 for the following indication(s) for which US licensed Lucentis has been previously licensed and for which FYB201 has not been directly studied: macular edema following retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), diabetic macular edema (DME) and diabetic retinopathy (DR).

The Applicant provided a justification for extrapolating data and information submitted in the

application to support licensure of FYB201 as a biosimilar for each such indication for which licensure is sought and for which US licensed Lucentis has been previously approved. This Applicant's justification was evaluated and considered adequate, as summarized below.

The mechanism of action of ranibizumab including the structure and drug-target interactions in each condition is consistent across all approved indications. For each of the indications, effective treatment can be expected by binding to the receptor binding site of active forms of VEGF-A. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis and vascular occlusion and is thought to contribute to pathophysiology of neovascular AMD, macular edema following RVO, and myopic choroidal neovascularization by reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation; and the analysis of the known safety and immunogenicity profiles of ranibizumab across each of the indications is consistent and there are no known differences in expected toxicities for each indication.

Therefore, the totality of the evidence provided by the Applicant supports licensure of FYB201 for each of the following indication(s) for which the Applicant is seeking licensure of FYB201: neovascular (Wet) age-related macular degeneration (AMD), macular edema following retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), diabetic macular edema (DME), and diabetic retinopathy (DR).

2.2. Analysis of Current Treatment Options

Lucentis (ranibizumab injection), Eylea (aflibercept), Beovu (brolucizumab-dbll) injection, Vabysmo ™ (faricimab-svoa) and Macugen (pegaptanib sodium injection) are all approved for the treatment of nAMD. Visudyne (verteporfin for injection) is approved for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. Avastin (bevacizumab) injection is used off-label to treat nAMD.

The approved products are all safe and effective treatments for nAMD. Except for Visudyne, all treatment options require intravitreal injections every 1 to 3 months.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

FYB201 (ranibizumab-eqrn; Cimerli) is a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment for intraocular use that has been developed as a proposed biosimilar/interchangeable to US licensed Lucentis. It is not currently licensed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The sponsor at the time (bioeq GmbH) sought for guidance concerning the overall development program in one FDA Type 1 Meeting (May 6, 2020), three FDA Type 2 Meetings (May 12, 2015, November 29, 2016, and January 22, 2021, (no meeting held upon request of the sponsor)), one FDA Type 3 Meeting (November 15, 2017), and one Type 4 meeting (December 14, 2018).

The sponsor originally submitted a BLA on December 3, 2019, for the vial dosage form of FYB201 with FYB201 drug substance supplied from (b) (4). During the first 60 days of the fileability assessment, FDA became aware that the upstream processing (USP) part of the FYB201 manufacturing process was relocated (b) (4) after execution of process performance qualification (PPQ) batches. Based on FDA expectation to have manufacturing data from the new USP suite and a corresponding comparability study at the time of BLA filing, bioeq GmbH decided on February 4, 2020, to withdraw the BLA.

On July 9, 2021, the Agency was notified that the ownership of PIND 125841 / BLA 761165 for FYB201 biosimilar ranibizumab was transferred from bioeq GmbH to Bioeq AG. On April 1, 2022, the Agency was notified that ownership of BLA 761165 for FYB201 biosimilar ranibizumab was transferred from Bioeq AG to Coherus BioSciences, Inc. (Coherus).

3.3. Foreign Regulatory Actions and Marketing History

No foreign approvals or marketing.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Study FYB201-C2015-01-P3 was conducted in its entirety at non-US investigational sites. International inspections were not requested because there were no serious issues to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations. No single investigational site included enough subjects to significantly alter the final result of the clinical trial. There is no evidence to suggest that the clinical trial was not conducted in compliance with good clinical practices.
Study FYB201-C2015-01-P3 is considered to have been conducted adequately, and the data generated by the applicant appeared acceptable in support of the application.

4.2. Product Quality

Product Formulation
FYB201 is a sterile, colorless to pale yellow solution. FYB201 is supplied as a preservative-free, sterile aqueous solution in a single-dose vial designed to deliver by intravitreal injection 0.05 mL of either 10 mg/mL ranibizumab-eqrn (0.5 mg dose vial) or 6 mg/mL ranibizumab-eqrn (0.3 mg dose vial) solution. Each solution includes 10 mM histidine HCl, 10% α, α trehalose dihydrate,

0.01% polysorbate 20, at pH 5.5. The composition of FYB201 DP is shown in the following table.

Table 1: Composition of FYB201 Drug Product Vial Formulation per Strength

Component	Function	Reference to Standard[1]	Quantity per mL	
			6 mg/mL	10 mg/mL
Ranibizumab	Active ingredient	In-house specification	6 mg	10 mg
(b) (4)	(b) (4)	EP, USP	(b) (4)	
Histidine hydrochloride (b) (4)		EP		
α, α-Trehalose dihydrate		EP, USP		
Polysorbate 20		EP, USP		
Water for Injection		EP, USP		

1 For compendial monographs the current version is applied as appropriate

FYB201 and US-licensed Lucentis have the same formulation. The excipients in FYB201 are the same and present in the same levels as the excipients in US-licensed Lucentis.

No impurities of concern were identified.

4.3. Clinical Microbiology

Not applicable. This is not an anti-effective.

4.4. Nonclinical Pharmacology/Toxicology

The Product Quality review team concluded that there was sufficient comparative analytic data (i.e., structural and functional characterization) between FYB201 and US licensed Lucentis to support safety, and did not identify any impurity issues that warranted additional studies. Therefore, the 2-week pharmacokinetic, ocular and systemic tolerance/toxicity study following a single intravitreal administration in albino rabbits was not needed to initiate the proposed comparative clinical study. The study data do not preclude a demonstration of biosimilarity between FYB201 and US licensed Lucentis and did not raise new safety questions.

4.5. Clinical Pharmacology

Systemic exposure of FYB201 and US licensed Lucentis evaluated in a subset of subjects with neovascular AMD in Study FYB201-C2015-01-P3 were comparable based on descriptive analysis which supports a demonstration of no clinically meaningful differences between FYB201 and US licensed Lucentis.

Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB201 and US-licensed Lucentis in subjects with neovascular AMD supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.

4.6. Devices and Companion Diagnostic Issues

Not applicable. This is a drug product without a device component.

4.7. Consumer Study Reviews

There were no consumer study reviews.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) no.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study					
FYB201-C2015-01-P3	NCT02611778	Comparative safety, efficacy, PK, and immunogenicity	Randomized, double-masked, parallel-group, multicenter (International study sites only. No US sites.)	Subjects with nAMD	FYB201or US-licensed Lucentis administered at a dose of 0.5 mg to the study eye every 4 weeks up to Week 44

5.2. Review Strategy

The application includes a randomized, double-masked, parallel group, multicenter comparative clinical study of FYB201 to US licensed Lucentis among subjects with nAMD. The study evaluated efficacy by comparing the primary endpoint of change in best corrected distance visual acuity (BCVA) from baseline to Week 8 between FYB201 and US licensed Lucentis. The results of the comparative efficacy analysis would support that there are no meaningful differences between FYB201 and US licensed Lucentis if the two-sided 90% confidence interval (CI) of the difference of least square means of the primary endpoint between arms was within the pre-defined equivalence margin of [−3 letters, 3 letters]. The data from Study FYB201-C2015-01-P3 contained in this submission compared 0.5 mg (10 mg/mL) of each product administered by intravitreal injection once a month (approximately 28 days) in patients with age-related macular degeneration.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study Title: Study FYB201-C2015-01-P3

Efficacy and Safety of the Biosimilar Ranibizumab FYB201 in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD).

6.1.1. Study Design

This was a randomized, double-masked, parallel group, multicenter study to evaluate the comparative efficacy, safety, and immunogenicity of FYB201 compared with US-licensed Lucentis in subjects with neovascular age-related macular degeneration (nAMD). A PK sub-study was included to descriptively compare the peak serum study drug concentrations. Subjects who met all inclusion/exclusion criteria were randomized in a 1:1 ratio to receive 0.5 mg of either FYB201 or US-licensed Lucentis via intravitreal injection every 4 weeks (approximately every 28 days) up to Week 44. The last assessment was done at Week 48. The primary comparative efficacy analysis was assessed at Week 8. The safety analyses were assessed through Week 48.

Data and Analysis Quality

Randomization
Randomized treatment assignments of the study were verified based on predefined randomization method.

Masking
Subjects, evaluating investigators, and the other study personnel were masked to the treatment assignments throughout the study period.

Amendments
The study protocol was amended 7 times; the original protocol (Version 1.0 dated: 14-Jul-2015) and Protocol versions 1.0, 2.0 and 3.0 were prepared in response to discussions with health authorities; the first patient was enrolled under protocol version 4.0. The key features of each Amendment are summarized below.

Table 3: Study FYB201-C2015-01-P3 Protocol Amendments

Amendment No.	Version	Date	Topic of Changes
1	2.0	9/9/2015	DSMB members specified to be external. New exclusion criteria added: prisoners and employees
2	3.0	11/19/2015	Added BCVA as stratification factor, specified ETDRS charts to be used

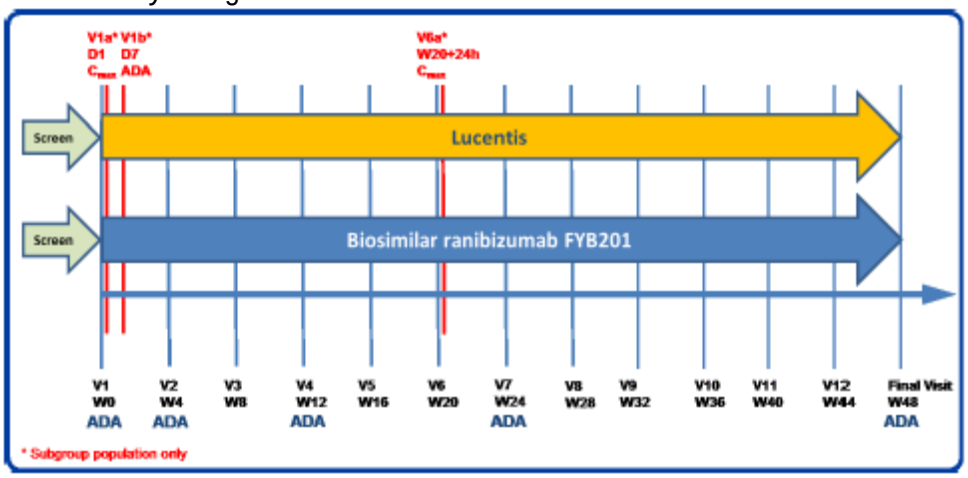
Amendment No.	Version	Date	Topic of Changes
3	4.0	11/30/2015	Additional sampling endpoints in PK subgroup
4	5.0	7/26/2016	Clarification on fellow eye during enrollment, corticosteroid treatment, physical assessment
5	6.0	1/18/2017	Change US primary endpoint, clarify interim analysis
6	7.0	3/8/2017	Replaced Amendment 5. Harmonization of primary EU and US endpoint, removal of interim analysis and trough level sampling
4,5,6	8.0	5/10/2017	Local protocol for France
7	9.0	8/29/2017	Inclusion of Metronomia and additional labs PK and nAb assay
7	9.0 FRA	8/29/2017	Country specific protocol version for France

Abbreviations: DSMB = Data Safety and Monitoring Board, BCVA = Best Corrected Visual Acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, EU = European Union, FRA = France

Study Design and Endpoints

This was a 48-week, phase 3, randomized, active-controlled, evaluation-masked, parallel-group, multicenter study to demonstrate clinical equivalence in terms of clinical pharmacology, efficacy and safety of FYB201 with Lucentis in the treatment of patients with subfoveal nAMD.

Schematic of the study design



For the US, this endpoint was evaluated in all patients with a baseline BCVA between 20/32 and 20/100 Snellen equivalent, while for the EU the endpoint was evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent.

As discussed, and agreed with the FDA and EMA, the relevant primary study endpoint was the change in BCVA after 2 months. This time point lies in the steepest part of the BCVA time

response curve, allowing detection of potential clinically relevant differences on visual function between the biosimilar candidate and the approved reference product.

Eligibility Criteria

Inclusion Criteria

General

1) Age ≥ 50 years of either gender
2) Signed informed consent form must have been obtained before any study related procedure was performed
3) Willingness and ability to undertake all scheduled visits and assessments
4) Women must have been postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (with documentation in the patient's medical records)

Ocular (Study Eye)

5) Newly diagnosed, angiographically documented, primary active CNV lesion secondary to AMD

a) All subtypes of nAMD CNV lesions were eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Active primary CNV had to be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by Spectral Domain Optical Coherence Tomography (SDOCT) or Retinal Pigment Epithelium (RPE) detachment)
b) Total area of whole lesion had to be equal or less than 12 disc areas
c) Total CNV area encompassed equal or more than 50% of total lesion area based on Fluorescein Angiography, including all subtypes of nAMD

6) Sufficiently clear ocular media and adequate pupillary dilation to permit good quality ocular imaging
7) BCVA in the study eye, determined by standardized ETDRS testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent
8) FCP retinal thickness at Screening ≥ 350 μm. (FCP thickness was defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea)

Ocular (Fellow Eye)

9) BCVA in the fellow eye, determined by standardized ETDRS testing, at least 20/100 (0.2) Snellen equivalent

Exclusion Criteria

General

1) Employees of clinical study sites, individuals directly involved with the conduct of the study or immediate family members thereof, prisoners, and persons who were legally institutionalized

Prior or current ocular therapy

2) Any prior treatment with IVT anti-VEGF agent (e.g., bevacizumab, aflibercept, ranibizumab) in either eye
3) History of vitrectomy, macular surgery, or other surgical intervention for AMD in the study eye
4) History of IVT or periocular injections of corticosteroids or device implantation within six months prior to Screening in the study eye
5) Prior treatment with verteporfin (PDT), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g., focal laser photocoagulation) in the study eye
6) Topical ocular corticosteroids administered for at least 30 consecutive days within three months prior to Screening
7) Any other intraocular surgery (including cataract surgery) in the study eye within three months prior to Screening

CNV lesion characteristics

8) Sub- or intra-retinal hemorrhage that comprised more than 50% of the entire lesion in study eye
9) Fibrosis or atrophy involving the center of the fovea or influencing central visual function in the study eye
10) CNV in either eye due to other causes, such as ocular histoplasmosis, trauma, or pathologic myopia

Current ocular conditions

11) Retinal pigment epithelial tear involving the macula in the study eye
12) History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT imaging of any size) in the study eye
13) History of retinal detachment in the study eye
14) Current vitreous hemorrhage in the study eye
15) Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
16) For patients who had undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye could not exceed 8 diopters of myopia
17) History of corneal transplant in the study eye
18) Aphakia in the study eye. Absence of an intact posterior capsule was allowed if it occurred as a result of YAG laser posterior capsulotomy in association with prior posterior chamber intraocular lens (IOL) implantation
19) Active or recent (within 4 weeks) intraocular inflammation of clinical significance in the study eye such as active infections of the anterior segment (excluding mild blepharitis) including conjunctivitis, keratitis, scleritis, uveitis or endophthalmitis
20) Uncontrolled hypertension or glaucoma in the study eye (defined as intraocular pressure (IOP) ≥ 30 mm Hg, despite treatment with anti-glaucomatous medication)
21) Ocular disorders in the study eye (i.e., retinal detachment, pre-retinal membrane of the macula or cataract with significant impact on visual acuity) at the time of enrollment that could have confounded interpretation of study results and compromised visual acuity

22) Any concurrent intraocular condition in the study eye (e.g., glaucoma, cataract, or diabetic retinopathy) that, in the opinion of the Investigator, would either have required surgical intervention during the study to prevent or treat visual loss that might have resulted from that condition or affect interpretation of study results.

Systemic medical history and conditions at Screening

23) Use of other investigational drugs (excluding vitamins, minerals) within 30 days or 5 half-lives from Screening, whichever was longer
24) Any type of advanced, severe, or unstable disease, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it might have biased the assessment of the clinical status of the patient to a significant degree or put the patient at special risk
25) Stroke or myocardial infarction within three months prior to Screening
26) Presence of uncontrolled systolic blood pressure >160 mmHg or uncontrolled diastolic blood pressure >100 mmHg
27) Known hypersensitivity to the investigational drug (ranibizumab or any component of the ranibizumab formulation) or to drugs of similar chemical class or to fluorescein or any other component of fluorescein formulation
28) Current or planned use of systemic medications known to be toxic to the lens, retina, or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines and ethambutol
29) History of recurrent significant infections and/or current treatment for active systemic infection
30) Pregnancy or lactation
31) Systemic treatment with high doses of corticosteroids (administration of >10 mg/day of prednisolone equivalent) during the last six months prior to Screening
32) Inability to comply with study or follow-up procedures

Ocular (Fellow Eye)

33) Any diagnosis and/or signs of nAMD requiring treatment with an IVT anti-VEGF agent (e.g., aflibercept, bevacizumab, ranibizumab) within the screening period or at study treatment initiation (Visit 1) in the fellow eye.

Study eye

Only one eye that met the eligibility criteria was considered as the study eye. For subjects who had both eyes eligible, the eye with the worst visual acuity (VA) was selected as the study eye. If both eyes had equal VA, the study eye was selected at the Investigator's discretion.

List of Investigators

The study was conducted at 75 sites in Europe (Austria 1, Czech Republic 6, Germany 8, Spain 7, France 6, United Kingdom (UK) 5, Hungary 7, Italy 9, Poland 8, and Ukraine 3), Russia (4 sites) and Israel (11 sites).

Safety Assessments
Adverse events, clinical laboratory test, physical examination, vital signs, full ophthalmic examinations (slit-lamp biomicroscopy, IOP measurements, and fundus examinations).

Statistical Methodologies
Primary endpoints measurement
The primary endpoint was the change in best corrected distance (4 meters) visual acuity (BCVA) at Week 8 from the Baseline.

Sample size
The required sample size for the primary endpoint was calculated based on a 1:1 randomization ratio and a standard deviation (SD) of 10 ETDRS letters. The calculation was based on a 95% confidence interval (CI; two-sided significance level of 2.5%) to establish equivalence in line with EMA requirements. A total of 412 evaluable patients were required (206 patients each for treatment with FYB201 or Lucentis), when requesting a 90% power of the study, assuming no difference between both treatment groups, and using an equivalence margin of 3.5 ETDRS letters.

A total of 460 patients were needed to be treated as the EU-specific analysis was limited to patients with a screening Snellen equivalent of 20/40 or worse and assuming that approximately 10% of all randomized patients would be in the 20/32 stratum. A sample size of 460 was also sufficient for the US-specific analysis. In particular, 230 patients per treatment group would provide at least 95% power for assessing equivalence in the change in BCVA using a 90% CI, a SD of 10 ETDRS letters, no expected difference between the treatment groups, and an equivalence margin of 3.5 ETDRS letters.

Analysis populations
The (Full Analysis Set United States) FAS_US was based on the intention to treat (ITT) principle (i.e., patients were analyzed according to their randomized treatment irrespective of the treatment they actually received) and included all patients who received at least one injection of investigational medicinal product (IMP), and for whom BCVA results at least after 1 month were available and who had a screening BCVA between 20/32 and 20/100 Snellen equivalent in the study eye. Sensitivity analyses were performed for Foveal Center Point (FCP) retinal thickness based on the (Per-Protocol S United States) PPS_US.

The safety set comprised all patients who had received at least one injection with IMP. The safety set was used as general analysis set for all kinds of safety and tolerability data. Patients were analyzed according to the treatment they actually received irrespective of their randomized treatment. If only single injections from the wrong treatment were administered, it was to be decided on a case-by-case basis how the patient was to be analyzed.

Efficacy Analysis

The primary efficacy variable was the change from baseline in BCVA by ETDRS letters calculated for the data at Week 8. The change (CHG) from baseline in BCVA at Week 8 was calculated per patient via: CHGBCVA = BCVAWeek 8 – BCVABaseline, where the baseline assessment was obtained at analysis visit V1. The hypothesis that both treatments FYB201 and Lucentis are biosimilar with respect to the primary endpoint was tested in terms of a two-sided equivalence test. The equivalence margin in BCVA of 3 ETDRS letters (as rounded to the nearest integer) was tested.

An analysis of covariance (ANCOVA) model was used for the analysis with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects. The 90% (US) and 95% (EU) CIs for the treatment difference between FYB201 (t1) and Lucentis (t2) were calculated using Least Square Means. If the respective CI for the treatment difference was completely contained in the interval [-3.5; 3.5] ETDRS letters, equivalence of FYB201 and Lucentis could be concluded for the primary endpoint.

The analysis of the primary endpoint was based on all patients in the FAS_US. Sensitivity analyses were based on the PPS_US. The analysis of ophthalmic assessments of secondary efficacy objectives were: BCVA, FCP and FCS retinal thickness, total lesion area, CNV leakage, and the percentage of patients with fluid-free macula. There was no formal hypothesis testing planned for the secondary endpoints and the analyses of the secondary endpoints were not required.

Planned sub-group analyses

The applicant did not perform subgroup analyses. The Statistical reviewer conducted subgroup analyses to evaluate the change from baseline in BCVA at Week 8 in the ITT population for the demographic variables, gender, and age, and for the stratification factor of screening BCVA category. Race was not considered for subgroup analysis by the Statistical reviewer because 98% of the study subjects were Caucasian. The disease condition is not evenly distributed by race. Prevalence is higher in populations with lighter colored fundi.

Missing Data Methods

Discontinued or withdrawn patients were not replaced. Data from patients who prematurely discontinued the trial were used to the maximum extent possible. The applicant did not impute the missing BCVA data for primary efficacy analysis. The evaluation of the primary endpoint took place at Week 8 (Visit 3) which was relatively an early time point in the 48-week study period. Therefore, the impact of missing data in the primary endpoint was expected to be minimal. The table below summarizes the number of subjects who had missing BCVA assessments for the primary efficacy analysis.

Table 4: Summary of Subjects with Missing BCVA Data at Week 8 for Primary Efficacy Analysis (ITT Population)

	FYB201 (N=236)	Lucentis (N=239)	Total (N=475)
Subjects with missing BCVA at Week 8	8 (3.4%)	6 (2.5%)	14 (2.9%)
Subjects who had missing BCVA assessments at Week 8 but completed study	6 (2.5%)	5 (2.1%)	11 (2.3%)
Subjects who discontinued study before Week 8 due to intercurrent events	2 (0.8%)	1 (0.4%)	3 (0.6%)
Withdrawal by subject	1 (0.4%)	0 (0.0%)	1 (0.2%)
Adverse event	0 (0.0%)	1 (0.4%)	1 (0.2%)
Patient's death	1 (0.4%)	0 (0.0%)	1 (0.2%)

Interim analysis and statistical corrections:
No formal interim analysis was planned or performed for this study. Analysis of study data was performed after 24 Weeks (main analysis) and 48 Weeks (final analysis). The submitted CSR presents the study results of the final analysis performed after all randomized patients have either completed the Week 48 assessments or have discontinued the study (database lock 01-Oct-2018). Preceding this final analysis, a main analysis was performed after all patients had either completed the Week 24 assessments or had discontinued the study before the Week 24 assessments (database lock 20-Apr-2018). The Sponsor remained blinded on a by-patient level for the preceding main analysis.

Subject Disposition
A total of 477 subjects were randomized into two groups: 238 in FYB201 and 239 in Lucentis. A total of 32 (6.7%) and 25 (5.2%) subjects discontinued from the treatment and from the study before Week 48, respectively. The discontinuation rates from the treatment were comparable between the treatment groups (6.7%) and the discontinuation rates from the study were comparable between the treatment groups (about 5%).

Table 5: Subject Disposition

	FYB201		Lucentis		Total	
	n	%	n	%	n	%
Screenings	-	-	-	-	722	-
Re-screenings					10	
Screened patients					712	
Exclusions	-	-	-	-	245	-
Re-screenings					4	
Excluded patients					241	
Failed inclusion/met exclusion criteria					211	
Randomized and treated	238	100%	239	100%	477	100%
Completed 24 Weeks assessments	230	96.6%	233	97.5%	463	97.1%

Discontinued treatment up to main analysis	7	2.9%	3	1.3%	10	2.1%
Completed 48 Weeks assessments	226	95.0%	226	94.6%	452	94.8%
Discontinued treatment up to final analysis	16	6.7%	16	6.7%	32	6.7%
Discontinued study up to final analysis	12	5.0%	13	5.4%	25	5.2%
Reasons						
Withdrawal by patient	2	16.7%	8	61.5%	10	40.0%
Adverse event(s)	1	8.3%	2	15.4%	3	12.0%
Major protocol deviation	1	8.3%	0	0.0%	1	4.0%
Need for alternative treatment	1	8.3%	0	0.0%	1	4.0%
Loss to follow-up	3	25.0%	1	7.7%	4	16.6%
Other	4	33.3%	2	15.4%	6	24.0%

Abbreviations: n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100
Notes: Percentages are based on the number of patients randomized (within each group).
Percentages are based on the number of patients who discontinued the study for reasons for early discontinuation.

The groups are similar. No concerns are raised from the number of subjects in the dataset.

Protocol Deviations

Patients with major protocol deviations were excluded from the per-protocol sets (PPS), whereas minor protocol deviations did not lead to exclusion from any analysis set. Overall, the number of patients with major protocol deviations was well balanced between both treatment groups (18 patients with major protocol deviations in the FYB201 group and 14 patients in the Lucentis group). Main reasons for exclusion from the PPS were the lack of valid BCVA assessment between Day 50 and 64 (18 patients; 3.8%) and violation of in- or exclusion criteria (11 patients; 2.3%).

Table 6: Protocol Deviations - Safety Set

	FYB201 (N = 238)		Lucentis (N = 239)	
	n	%	n	%
Major protocol deviations	18	7.6%	14	5.9%
No BCVA assessment between Day 50–64	10	4.2%	8	3.3%
Injection 2 before Day 22 or after Day 36	0	0.0%	2	0.8%
Missing injections	2	0.8%	3	1.3%
Violation of inclusion/exclusion criteria	8	3.4%	3	1.3%
PK data (interference with interpretation of ranibizumab concentration data)	0	0.0%	1	0.4%
Prohibited concomitant medications	1	0.4%	1	0.4%
Minor protocol deviations	111	46.6%	114	47.7%
BCVA assessment between Day 50–53 or Days 61–64	15	6.3%	12	5.0%
Blood sample issue	5	2.1%	8	3.3%
Violation of inclusion/exclusion criteria	5	2.1%	5	2.1%
Missing ADA assessment	2	0.8%	4	1.7%

Prohibited concomitant medications	17	7.1%	18	7.5%
Randomization procedure and possible unblindings	2	0.8%	1	0.4%
Other	0	0.0%	1	0.4%
from injection schedule:	68	28.6%	80	33.5%
Injection deviates from schedule more than ±14 days	4	1.7%	4	1.7%
Injection 2 between Day 22–25 or Day 33–36	12	5.0%	12	5.0%
Missing injections	28	11.8%	40	16.7%
Time between 2 injections <22 days	9	3.8%	15	6.3%
Time between 2 injections >34 days	59	24.8%	73	30.5%
from study procedures:	31	13.0%	22	9.2%
Missing study procedures	23	9.7%	12	5.0%
Study procedures out of window	8	3.4%	11	4.6%
from visit schedule:	36	15.1%	40	16.7%
Missing visits	31	13.0%	36	15.1%
Visits out of window	6	2.5%	5	2.1%
Any minor GCP issue	89	37.4%	92	38.5%
Blood sample issue	15	6.3%	16	6.7%
Failure to report SAE in a timely manner	3	1.3%	7	2.9%
Informed consent procedure	78	32.8%	74	31.0%
Personnel, facilities or equipment	2	0.8%	5	2.1%

Abbreviations: BCVA = best-corrected visual acuity, PK = pharmacokinetic, N = total number of patients.
Source: Post-text tables 14.1.1.7.1, 14.1.1.8.1

The groups are similar. No concerns are raised from the protocol deviations.

Table 7: Number (%) of Subjects in the Analysis Sets

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
Analysis Set	n	(%)	n	(%)	n	(%)
Safety Set (SAF)	238	100.0%	239	100.0%	477	100.0%
Full Analysis Set for US (FAS_US)	237	99.6%	238	99.6%	475	99.6%
Full Analysis Set for EU (FAS_EU)	215	90.3%	214	89.5%	429	89.9%
Per Protocol Set for US (PPS_US)	220	92.4%	225	94.1%	445	93.3%
Per Protocol Set for EU (PPS_EU)	200	84.0%	202	84.5%	402	84.3%
Pharmacokinetic Subgroup Analysis Set (PKS)	29	100.0%	30	96.8%	59	98.3%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100, SAF: Safety set, FAS US = Full analysis set for the US, FAS EU = Full analysis set for the EU, PPS US = Per protocol set for the US, PPS EU = Per protocol set for the EU
Notes: Percentages are based on the number of patients randomized within each group, whereby the patients are tabulated according to the planned treatment.

The groups are similar. No concerns are raised from the protocol deviations.

Demographics and Baseline Characteristics

Table 8: Demographics and other baseline characteristics – SAF

	FYB201 (N = 238)	Lucentis (N = 239)
Gender [n (%)]		
Male	103 (43.3%)	105 (43.9%)
Female (no women of childbearing potential)	135 (56.7%)	134 (56.1%)
Age at Screening [years]		
Mean (SD)	74.9 (8.26)	76.1 (7.84)
Median	76.0	77.0
Interquartile range (Q1–Q3)	69.0–81.0	71.0–81.0
Range (min–max)	50–91	50–94
Age Categories at Screening [n (%)]		
50–64 years	25 (10.5%)	19 (7.9%)
65–75 years	91 (38.2%)	86 (36.0%)
>75 years	122 (51.3%)	134 (56.1%)
Race [n (%)]		
Caucasian	236 (99.2%)	233 (97.5%)
Asian	0 (0.0%)	2 (0.8%)
Other	2 (0.8%)	4 (1.7%)
BMI at Screening [kg/m^2]		
Mean (SD)	27.17 (4.084)	27.40 (4.467)
Median	26.28	26.83
Interquartile range (Q1–Q3)	24.46–29.07	24.06–30.11
Range (min–max)	19.9–42.9	17.8–44.0

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100, SD = standard deviation, Q1= first quartile, Q3 = third quartile, min = minimum, max = maximum, SAF = Safety Set, BMI = Body Mass Index

All demographics were similar in both treatment groups and differences in demographics in the different analysis sets were negligible compared to the SAF. Gender, race, and age groups were similarly distributed in both treatment groups.

Table 9: Other baseline ophthalmic characteristics by treatment group -SAF

	FYB201	Lucentis
	(N = 238)	(N = 239)
OD (right eye)	127 (53.4%)	127 (53.1%)
OS (left eye)	111 (46.6%)	112 (46.9%)
Iris color [n (%)]		
Light	89 (37.4%)	89 (37.4%)
Medium	104 (43.7%)	100 (42.0%)
Dark	45 (18.9%)	49 (20.6%)
Missing	0	1
Baseline Snellen equivalent in study eye [n (%)]		
20/32	24 (10.1%)	22 (9.2%)
20/40	43 (18.1%)	38 (15.9%)
20/50	45 (18.9%)	39 (16.3%)
20/63	37 (15.5%)	46 (19.2%)
20/80	37 (15.5%)	37 (15.5%)
20/100	52 (21.8%)	57 (23.8%)
Baseline Snellen equivalent in fellow eye [n (%)]		
20/12.5	2 (0.8%)	3 (1.3%)
20/16	20 (8.4%)	7 (2.9%)
20/20	63 (26.5%)	53 (22.2%)
20/25	42 (17.6%)	59 (24.7%)
20/32	47 (19.7%)	59 (24.7%)
20/40	22 (9.2%)	27 (11.3%)
20/50	21 (8.8%)	12 (5.0%)
20/63	10 (4.2%)	8 (3.3%)
20/80	6 (2.5%)	4 (1.7%)
20/100	5 (2.1%)	7 (2.9%)

Baseline ocular characteristics were comparable across treatment groups.

6.1.2. Study Results

Compliance with Good Clinical Practices
The study was conducted in accordance with Good Clinical Practice (GCP). The reviewer found the quality of the submitted data and analysis acceptable. There are no concerns regarding the data quality and integrity for this clinical study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
Concomitant medications and treatments were recorded for all patients (477; 100%) of the SAF and were balanced between treatment groups.

Efficacy Results – Primary Endpoint
The equivalence of FYB201 to US-licensed Lucentis to treat subjects with nAMD was evaluated based on the endpoint of the change in BCVA at Week 8 from the Baseline.

Table 10: Absolute change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8: FAS_US

	FYB201	Lucentis
	(N = 237)	(N = 238)
N*	234	238
N	228	233
Missing	6	5
Mean (SD)	5.1 (7.52)	5.6 (8.63)
Median	5.0	5.0
Interquartile range (Q1–Q3)	0.0–10.0	1.0–11.0
Range (min–max)	-16–30	-39–25

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS US = full analysis set for the US, N = total number of patients, N* = total number of patients still in the study for the respective analysis visit, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, min = minimum, max = maximum SD = standard deviation, Q1 = first quartile, Q3 = third quartile

The LS means difference for the change from baseline in BCVA at Week 8 between FYB201 and Lucentis was -0.4 ETDRS letters with a 90% CI for the US-specific analysis of [-1.6; 0.9] ETDRS letters (see table below). The 90% CI was completely within the predefined equivalence margin of {-3.5; 3.5} ETDRS letters meeting the predefined criterion for biosimilarity of FYB201 to Lucentis.

Table 11: ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8: FAS_US

	n	Missing	Arithmetic Mean	LS mean[1]	SE LS mean	90% CI
FYB201	228	6	5.1	5.1	0.58	[4.1; 6.0]
Lucentis	233	5	5.6	5.4	0.58	[4.5; 6.4]
Difference FYB201 - Lucentis		-0.5	-0.4	0.76	[-1.6; 0.9]	
CI contained in [-3.5; 3.5][2]					yes	

[1] Estimates are adjusted for pooled country and baseline BCVA [letters].

[2] If confidence interval for difference in LS means is completely contained in the interval [-3.5 letters, 3.5 letters], FYB201 and Lucentis are considered equivalent.

Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS US = full analysis set for the US, LS = Least squares, n = number of patients with non-missing assessment at analysis visit V3/Week 8, Missing = number of patients with missing assessment at analysis visit V3/Week 8, SE = standard error
Notes: Two-sided 90% confidence interval based on normal approximation.

Sensitivity analyses for the primary efficacy endpoint US
The sensitivity analysis for the primary efficacy endpoint for the US-specific analysis was the change from baseline in BCVA at Week 8 in the PPS_US population.

Table 12: Absolute change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8: PPS_US

	FYB201 (N = 220)	Lucentis (N = 225)	Total (N = 445)
Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8			
Mean (SD)	5.2 (7.59)	5.7 (8.64)	5.5 (8.13)
Median	5.0	6.0	5.0
Interquartile range (Q1–Q3)	0.0–10.0	1.0–11.0	1.0–10.0
Range (min–max)	-16–30	-39–25	-39–30

Table 13: ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis V3/Week 8: PPS_US

	n	Missing	Arithmetic mean	LS mean[1]	SE LS mean	90% CI
FYB201	220	0	5.2	5.2	0.59	[4.2; 6.1]
Lucentis	225	0	5.7	5.6	0.59	[4.6; 6.6]
Difference FYB201 - Lucentis		-0.5	-0.4	0.78	[-1.7; 0.9]	
CI contained in [-3.5; 3.5][2]					yes	

[1] Estimates are adjusted for pooled country and baseline BCVA [letters].

[2] If confidence interval for difference in LS means is completely contained in the interval [-3.5 letters, 3.5 letters], FYB201 and Lucentis are considered equivalent.
Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, PPS US = per protocol set for the US, LS = Least squares, n = number of patients with non-missing assessment at analysis visit V3/Week 8, Missing = number of patients with missing assessment at analysis visit V3/Week 8,
SE = standard error, Notes: Two-sided 90% confidence interval based on normal approximation.

7. Review of Safety

7.1. Safety Review Approach

There is no integrated assessment of safety across trials as the application includes only a single pivotal study (FYB201-C2015-01-P3) to support the safety assessment of FYB201.

The review focuses on the safety database from Study FYB201-C2015-01-P3 which has:

- A study duration of 48 weeks
- A treatment group with FYB201 0.5 mg (0.05 mL of a 10 mg/ml solution) intravitreal injections administered as twelve (12) monthly (every 4 weeks) IVT injections given at Visit 1 to Visit 12 (Week 44) with last follow up at 48 weeks.

7.2. Review of the Safety Database

7.2.1. Overall Exposure

The median cumulative amount of administered study medication was 3.0 mg (mean [SD]: 2.92 [0.317] mg) up to Week 24 and 6.0 mg (mean [SD]: 5.74 [0.829] mg) up to Week 48, corresponding to the planned cumulative amount of study medication.

7.2.2. Relevant characteristics of the safety population:

The study population includes patients ≥ 50 years with newly diagnosed active sub-foveal choroidal neovascularization secondary to AMD in the study eye.

7.2.3. Adequacy of the safety database:

The safety data was adequate to demonstrate risks of FYB201.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

The reviewer found the quality of the submitted data and analysis acceptable.

7.3.2. Categorization of Adverse Events

Safety of FYB201 and US-licensed Lucentis in Study FYB201-C2015-01-P3 was comparatively assessed by monitoring treatment-emergent adverse events (TEAEs, ocular/non-ocular), serious adverse events (SAEs, ocular/non-ocular), adverse events of special interest (AESI), clinical laboratory evaluations, ophthalmic assessments, and as well as immunogenicity.

7.3.3. Routine Clinical Tests

The routine clinical testing required to evaluate the safety concerns of intravitreally administered products (i.e., biomicroscopy, fundoscopy, visual acuity, etc.) were adequately addressed in the design and conduct of the trials for this product. Refer to schedule of events in section for procedures and scheduled assessments for laboratory evaluations.

7.4. Safety Results

7.4.1. Deaths

Three patients died during the study; two patients were exposed to FYB201 and one patient was exposed to Lucentis.

Table 14: Deaths

Treatment	Patient Number	Narrative
FYB201	(b) (6)	Worsening bronchiectasis and worsening of severe obstructive pulmonary disease resulting in death
FYB201		Severe cardiopulmonary failure resulting in death
Lucentis		Severe respiratory failure resulting in death

The deaths which occurred during the study are consistent with past medical history of the subjects enrolled.

7.4.2. Serious Adverse Events

Table 15: Number and percentage of patients with Serious Ocular local (study eye) TEAEs (SAEs) up to Week 48 by MedDRA SOC and PT – SAF

FYB201 MedDRA SOC (N =			Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Endophthalmitis	1	0.4%	2	0.8%	3	0.6%
Cataract	0	0.0%	1	0.4%	1	0.2%
Iridocyclitis	1	0.4%	0	0.0%	1	0.2%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % = number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event Notes: Local TEAEs were defined as TEAEs occurring in the study eye. MedDRA version 19.0 was used.

Local SAEs, occurring in the study eye were observed in 5 patients; 2 patients in the FYB201group (PTs: Endophthalmitis and Iridocyclitis) and 3 patients in the Lucentis group (PTs: Endophthalmitis in 2 patients, and Cataract in 1 patient). There was no significant difference between the two groups.

Table 16: Number and percentage of patients with Serious Non-ocular systemic TEAEs (SAEs) up to Week 48 by MedDRA SOC and PT – SAF

FYB201 MedDRA SOC (N =			Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Cardiac disorders						
Overall	7	2.9%	5	2.1%	12	2.5%
Atrial fibrillation	3	1.3%	1	0.4%	4	0.8%
Myocardial infarction	1	0.4%	2	0.8%	3	0.6%
Nervous system disorders						
Overall	2	0.8%	5	2.1%	7	1.5%
Syncope	1	0.4%	1	0.4%	2	0.4%
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)						
Overall	2	0.8%	4	1.7%	6	1.3%
Respiratory, thoracic, and mediastinal disorders						
Overall	3	1.3%	3	1.3%	6	1.3%
Respiratory failure	1	0.4%	2	0.8%	3	0.6%
Musculoskeletal and connective tissue disorders						
Overall	1	0.4%	4	1.7%	5	1.0%
Intervertebral disc protrusion	1	0.4%	2	0.8%	3	0.6%
Osteoarthritis	0	0.0%	2	0.8%	2	0.4%

Infections and infestations	3	1.3%	1	0.4%	4	0.8%
Renal and urinary disorders						
Overall	2	0.8%	2	0.8%	4	0.8%
Acute kidney injury	2	0.8%	0	0.0%	2	0.4%
Vascular disorders	1	0.4%	3	1.3%	4	0.8%
Blood and lymphatic system disorders	1	0.4%	2	0.8%	3	0.6%
Gastrointestinal disorders	0	0.0%	3	1.3%	3	0.6%
Injury, poisoning and procedural complications	1	0.4%	1	0.4%	2	0.4%
Metabolism and nutrition disorders	0	0.0%	2	0.8%	2	0.4%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % =number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event Notes: Systemic TEAEs were defined as TEAEs not occurring in the study eye. MedDRA version 19.0 was used.

The reported rates in each group were similar. No concerns were raised by the comparison.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 17: Adverse Events Leading to Study Discontinuation (Safety Set) – Week 48

System Organ Class (SOC) Preferred Term (PT)	STUDY FYB201-C2015-01-P3	
	FYB201 (N=238) n (%) Events	Lucentis (N=239) N (%) Events
Any adverse event leading to discontinuation	1 (0.4) 1	2 (0.8) 2
Worsening of nAMD	1 (0.4) 1	0 (0.0) 0
Benign pancreatic neoplasm	0 (0.0) 0	1 (0.4) 1
Malignant tongue neoplasm	0 (0.0) 0	1 (0.4) 1

No clinically relevant differences between the two treatment groups were identified.

7.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 18: Frequency of TEAEs up to Week 48 by MedDRA SOC and PT in **≥2.0%** of patients: SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)	
PT	N	%	n	%
Any	154	64.7%	167	69.9%
Eye disorders				
Overall	100	42.0%	100	41.8%
Neovascular age-related macular degeneration	19	8.0%	22	9.2%
Conjunctival haemorrhage	14	5.9%	19	7.9%
Punctate keratitis	8	3.4%	12	5.0%
Visual acuity reduced	6	2.5%	11	4.6%
Eye pain	9	3.8%	6	2.5%
Cataract	1	0.4%	11	4.6%

Lacrimation increased	9	3.8%	2	0.8%
Choroidal neovascularization	6	2.5%	4	1.7%
Conjunctival hyperaemia	4	1.7%	6	2.5%
Retinal haemorrhage	7	2.9%	3	1.3%
Vitreous detachment	6	2.5%	4	1.7%
Infections and infestations				
Overall	55	23.1%	57	23.8%
Nasopharyngitis	12	5.0%	16	6.7%
Bronchitis	9	3.8%	5	2.1%
Upper respiratory tract infection	8	3.4%	6	2.5%
Conjunctivitis	9	3.8%	2	0.8%
Investigations				
Overall	32	13.4%	39	16.3%
Intraocular pressure increased	11	4.6%	12	5.0%
C-reactive protein increased	10	4.2%	5	2.1%
Musculoskeletal and connective tissue disorders				
Overall	17	7.1%	29	12.1%
Back pain	5	2.1%	8	3.3%
Nervous system disorders				
Overall	10	4.2%	26	10.9%
Headache	4	1.7%	9	3.8%
Gastrointestinal disorders				
Overall	13	5.5%	22	9.2%
Vascular disorders				
Overall	10	4.2%	23	9.6%
Hypertension	3	1.3%	14	5.9%
Injury, poisoning and procedural complications	13	5.5%	18	7.5%
General disorders and administration site conditions	17	7.1%	13	5.4%
Respiratory, thoracic, and mediastinal disorders				
Overall	15	6.3%	9	3.8%
Cough	5	2.1%	5	2.1%
Cardiac disorders	8	3.4%	10	4.2%
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	6	2.5%	7	2.9%
Blood and lymphatic system disorders	8	3.4%	4	1.7%
Renal and urinary disorders	5	2.1%	6	2.5%
Skin and subcutaneous tissue disorders	6	2.5%	4	1.7%

Abbreviations: N = total number of patients, n = number of patients with at least one AE of specified AE type, % = number of patients with at least one AE of specified AE type/total number of patients*100, SAF = safety analysis set, MedDRA = Medical Dictionary for Regulatory Activities, SOC = system organ class, PT = preferred term, TEAE = treatment-emergent adverse event
Notes: MedDRA version 19.0 was used.

The overall ocular adverse event rates were similar between FYB201 and Lucentis.

7.4.5. Laboratory Findings

None of the clinical chemistry parameters Sodium, Chloride, Total protein, Albumin, Total bilirubin and Calcium showed clinically significant changes between screening and Visit 7/Week 24 and between screening and the Final Visit/Week 48.

7.4.6. Vital Signs

For vital signs. radial pulse, systolic blood pressure and diastolic blood pressure, absolute values at screening, at analysis visit V7/Week 24 and Final Visit/Week 48 and the absolute changes from screening were summarized by treatment group. No clinically important findings were revealed up to Week 48 and the vital signs measurements were balanced between both treatment groups.

7.4.7. Electrocardiograms (ECGs)

Not applicable.

7.4.8. QT

Not applicable.

7.4.9. Immunogenicity

Design Features of the Clinical Immunogenicity Assessment
Immunogenicity (ADA and Nab) was evaluated in Study FYB201-C2015-01-P3 as one of the secondary endpoints.

Immunogenicity Endpoints
Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples
The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of FYB201 and US-licensed Lucentis.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation
The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood samples for immunogenicity assessment were collected in all subjects at Week 0, Week 1 (PK subgroup only), Week 4, Week 12, Week 24, and Week 48 (end-of-study visit).

Comparison of Incidence of ADA and NAb
The incidence of ADA and NAb by treatment group and time points in Study FYB201-C2015-01-P3 were summarized in the following table. The incidence of an ADA positive

response was generally low and comparable between treatment groups throughout the study. Only one patient in FYB201 treatment group was detected positive for NAb at Week 48.

Table 19: Incidence of Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb) by Visit (Safety Set, Study FYB201-C2015-01-P3)

Category	Treatment week				
	Visit 1 /Baseline	4	12	24	48
FYB201 (N=238)					
No. of patients #	234 §	226	226	225	229
No. ADA positive	0	2	1	6	9
% ADA positive	0	0.9	0.4	2.7	3.9
Median titer	n.c.	10.0	10.0	30.0	60.0
Min/Max titer	n.c.	10 / 10	10 / 10	10 / 90	10 / 810
No. NAb positive	0	0	0	0	1
% NAb positive	0	0	0	0	0.4
Lucentis (N=239)					
No. of patients #	238 §	228	226	225	225
No. ADA positive	5	2	2	6	12
% ADA positive	2.1	0.9	0.9	2.7	5.3
Median titer	30.0	10.0	10.0	30.0	10.0
Min/Max titer	10 / 90	10 / 10	10 / 10	10 / 90	10 / 90
No. NAb positive	0	0	0	0	0
% NAb positive	0	0	0	0	0

= number of patients with non-missing assessment; n.c. = not calculable; *NR* = No result
§ = includes further pre-dose samples that were taken at Visit 1b
Tables 1.1.1.1, 1.1.3.1 & 1.1.5.1, End of Text Tables for ISI Analysis Final v05, 11-Jan-2021, ISI Appendix 2
(Source: Table 39, BLA761165 Integrated Summary of Immunogenicity)

Comparison of ADA Titers
The distribution of ADA titers is comparable between the FYB201 and US-licensed Lucentis treatment groups as seen in the previous table and following figure. There was no specific trend indicating the difference in the distribution of ADA titers between the FYB201 and US-licensed Lucentis treatment groups.

Comparison of Immunogenicity Impact on PK
Among 59 subjects who were included in the PK subgroup analysis set, only 5 subjects had positive ADA results by Week 48 (2 of 29 subjects in FYB201 group and 3 of 30 subjects in US-licensed Lucentis group). Therefore, no conclusion could be made regarding the correlation between blood levels and antibody rates.

Comparison of Immunogenicity Impact on Efficacy or Safety
The primary efficacy endpoint of Study FYB201-C2015-01-P3 is the change from baseline in best corrected distance visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) between FYB201 and US-licensed Lucentis treatments. The number of ADA-positive subjects was small (<1%) and equally divided between treatment arms at Week 4 (2 (0.9%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group) and Week 12 (1 (0.4%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group). The comparison of immunogenicity impact on safety was evaluated based on the assessment of selected treatment-emergent adverse events (TEAEs) by overall anti-drug antibody result up to end of study (Week 48), including drug hypersensitivity, anaphylaxis, and intra-ocular inflammation. Comparable low incidence of ADA formation and no NAb formation in each group supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.

7.5. Analysis of Submission-Specific Safety Issues
There were no submission-specific safety issues.

7.6. Safety Analyses by Demographic Subgroups
In the clinical studies of patients randomized to treatment with ranibizumab ≥ 65 years of age and ≥ 75 years of age; no notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

7.7. Specific Safety Studies/Clinical Trials
There were no specific safety issues.

7.8. Safety in the Postmarket Setting
7.8.1. Safety Concerns Identified Through Postmarket Experience
Tearing of retinal pigment epithelium among patients with neovascular AMD has been identified during post-approval use of ranibizumab products. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

7.9. Integrated Assessment of Safety
Study FYB201-C2015-01-P3 demonstrated that FYB201 is comparable to US-licensed Lucentis with respect to the change in best-corrected visual acuity (BCVA) from baseline to Week 8. The adverse event profile was not significantly different between subjects treated with FYB201 and US-licensed Lucentis. No concerns are raised from the comparison.

8. Advisory Committee Meeting and Other External Consultations
The information submitted by the Applicant, including adequate justification for extrapolation of data and information, demonstrates that FYB201 is biosimilar/interchangable to US licensed Lucentis for each of the indications for which US licensed Lucentis has been previously licensed.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

Refer to the attached labeling below.

10. Risk Evaluation and Mitigation Strategies (REMS

None.

11. Postmarketing Requirements and Commitments

The Office of Pharmaceutical Quality has recommended the following post-marketing commitments and the approval letter will include them. See the approval letter for exact wording and due dates:

- Complete DS transport validation study and submit the final transportation validation report.

- Complete DP bulk vial and DP final product shipment validation studies and submit the final transportation validation report.

12. Appendices

12.1. References

None.

12.2. Financial Disclosure

Covered Clinical Study FYB201-C2015-01-P3: A Single Phase 3, Randomized, Active-Controlled, Evaluation-masked, Parallel Group, Multicenter Study designed to demonstrate clinical equivalence in terms of clinical pharmacology, efficacy, and safety of FYB201 with Lucentis in the treatment of subjects with nAMD

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 75 principal, >400 total		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

12.3 Labeling

This application is recommended for approval with the attached labeling.

(b) (4)

32 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MARTIN P NEVITT
08/01/2022 09:22:06 AM

JENNIFER D HARRIS
08/02/2022 10:56:23 AM

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	BLA 761165
Supplement #:	Original-1
Drug Name:	Biosimilar Ranibizumab, 0.5 mg, intravitreal injection
Indication(s):	Treatment of neovascular age-related macular degeneration (nAMD)
Applicant:	Bioeq GmbH
Date(s):	Stamp Date: 08/02/2021 PDUFA Date: 08/02/2022 Review Date: 04/02/2022
Review Priority:	Standard
Biometrics Division:	IV
Statistical Reviewer:	Nam Hee Choi, Ph.D.
Concurring Reviewers:	Guoxing Soon, Ph.D., Team Leader
Medical Division:	Division of Ophthalmology
Clinical Team:	Martin Nevitt, M.D. William Boyd, M.D.
Project Manager:	Michael Puglisi

Keywords: Biosimilarity, Neovascular Age-related Macular Degeneration, Best Corrected Visual Acuity

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1 EXECUTIVE SUMMARY

The applicant submitted Biologics License Application (BLA) 761165 to demonstrate biosimilarity of FYB201 (Ranibizumab, 0.5 mg, intravitreal injection) to US-licensed Lucentis, based on the totality of evidence including analytical, nonclinical, and clinical data. The clinical program includes COLUMBUS-AMD (FYB201-C2015-01-P3) clinical comparative efficacy and safety study in patients with neovascular (wet) age-related macular degeneration (nAMD) and pharmacokinetic (PK) subgroup study within COLUMBUS-AMD (FYB201-C2015-01-P3). Study COLUMBUS-AMD was a randomized, parallel-group, active-controlled, evaluation-masked, multicenter study with a duration of 48 weeks (12 months) in patients with nAMD to further evaluate whether there are clinically meaningful differences between the FYB201 and Lucentis.

Subjects who met all eligibility criteria were randomized into one of the two treatment groups in a 1:1 ratio (FYB201:Lucentis). Randomization was stratified by site and screening best corrected visual acuity (BCVA) category (20/32 Snellen equivalent, or 20/40 – 20/100 Snellen equivalent). Subjects received FYB201 or Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as 12 monthly intravitreal (IVT) injections starting at Visit 1 (Week 0) through Visit 12 (Week 44).

The primary efficacy endpoint was the change from baseline in BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) of treatment. The primary efficacy analysis was an evaluation of similarity between FYB201 and Lucentis in the primary efficacy endpoint on the intent-to-treat (ITT) population including all randomized subjects. The similarity margin was set as ± 3.5 letters.

The study demonstrated similarity of FYB201 and Lucentis with respect to the change from baseline in BCVA at Week 8. The adjusted mean changes in BCVA from baseline at Week 8 were comparable for the two treatment groups with 5.1 letters for FYB201 and 5.4 letters for Lucentis. The mean difference (FYB201 minus Lucentis) was -0.4 letters with 90% confidence interval (-1.6, 0.9) letters, which was contained within the similarity margins of (-3.5, 3.5) letters.

2 INTRODUCTION

2.1 Overview

In this BLA submission, the applicant seeks approval of FYB201 (Ranibizumab, 0.5 mg, intravitreal injection) as a biosimilar to US-licensed Lucentis for all indications approved by the Agency for Lucentis. The original application was submitted on 12/03/2019. However, the applicant withdrew the application on 02/07/2020 to avoid a likely Refuse to File decision as FDA became aware of manufacturing issues during the first 60 days of the fileability assessment. The applicant resubmitted the BLA on 08/02/2021 after amending the application based on the BPD Type 1 meeting (05/06/2020) and the BPD Type 2 meeting (01/22/2021).

Lucentis (ranibizumab) was approved in 2006 as an intravitreal (IVT) injection for the treatment of neovascular (wet) age-related macular degeneration (nAMD) and subsequently was approved for the treatment of retinal vein occlusion (RVO), diabetic macular edema (DME), diabetic retinopathy (DR), and myopic choroidal neovascularization (mCNV).

The applicant conducted one Phase 3 study (COLUMBUS-AMD, study code: FYB201-C2015-01-P3) to further evaluate whether there are clinically meaningful differences between FYB201 and Lucentis. Table 1 shows the summary of Study COLUMBUS-AMD.

Table 1 List of All Relevant Submitted Clinical Studies

Study Identity	National Clinical Trial (NCT) No.	Study Objective	Study Design	Study Population	Treatment Groups
Comparative Clinical Study					
COLUMBUS-AMD (FYB201-C2015-01-P3)	NCT02611778	Comparative efficacy, safety, PK, and immunogenicity of FYB201 and Lucentis	Randomized, active-controlled, evaluation-masked, parallel-group, multicenter study (75 sites in 12 countries)	Subjects with nAMD	FYB201 or US-licensed Lucentis administered at a dose of 0.5 mg in study eye every 4 weeks for 12 months

2.2 Data Sources

The data source for this review included the clinical study report, study protocol, statistical analysis plan, and the analysis and tabulation datasets. They are provided in an electronic submission located at \\CDSESUB1\evsprod\BLA761165\0009. The primary analysis datasets are located at \\CDSESUB1\evsprod\BLA761165\0009\m5\datasets.

3 STATISTICAL EVALUATION

This application includes a single comparative clinical study COLUMBUS-AMD to further evaluate whether there are clinically meaningful differences between FYB201 (test product) and Lucentis (reference product) in the treatment of patients with nAMD.

3.1 Data and Analysis Quality

There are no concerns regarding data quality and integrity.

3.2 Evaluation of Efficacy

In this section, the descriptions of study design and the study endpoints are presented in Section 3.2.1, the statistical methodologies used are presented in Section 3.2.2, the summary of patient disposition, demographic and baseline characteristics are presented in Section 3.2.3, and the results and conclusions are discussed in Section 3.2.4.

3.2.1 Study Design and Endpoints

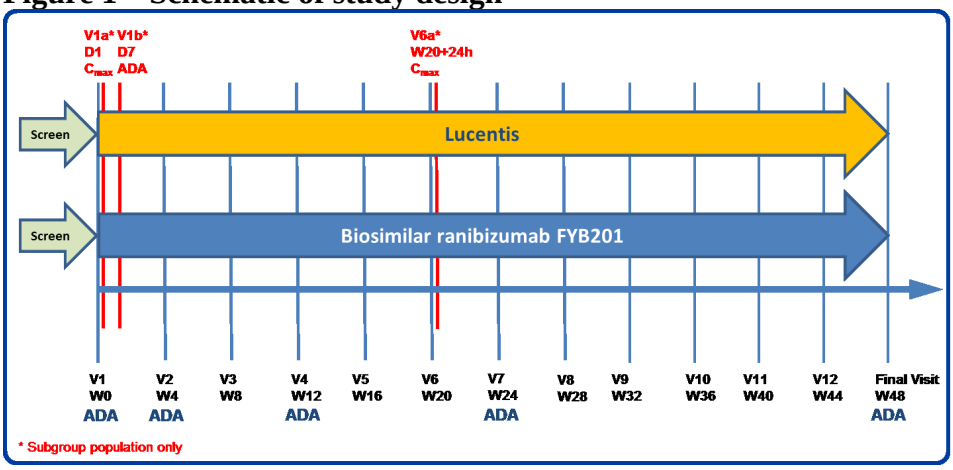
Study Design

Study COLUMBUS-AMD was a randomized, parallel-group, active-controlled, evaluation-masked, multicenter study with a duration of 48 weeks (12 months) comparing FYB201 and Lucentis in patients with nAMD.

The primary objective of Study COLUMBUS-AMD was to evaluate and compare functional changes in best corrected visual acuity (BCVA) after 2 months (8 weeks) of treatment with FYB201 or Lucentis, compared to baseline BCVA. Analysis of study data was performed after 24 weeks (main analysis) and 48 weeks (final analysis).

Subjects who met all eligibility criteria were randomized into one of the two treatment groups in a 1:1 ratio (FYB201:Lucentis). Randomization was stratified by site and screening BCVA category (20/32 Snellen equivalent, or 20/40 – 20/100 Snellen equivalent). Subjects received FYB201 or Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as 12 monthly intravitreal (IVT) injections starting at Visit 1 (Week 0) through Visit 12 (Week 44).

Figure 1 Schematic of study design



Source: Figure 9-1 of Clinical Study Report COLUMBUS-AMD

In addition to inclusion and exclusion criteria, patients had to meet the following eligibility criteria to be randomized at Visit 1 (Day 0):

(a) There was no significant anatomical change in the study eye following ophthalmological and SD-OCT examination between the Screening visit and Visit 1 (i.e., large subretinal hemorrhage, retinal pigment epithelial (RPE) tear, pigment epithelial detachment).

(b) Visual acuity in the study eye was within the defined inclusion criteria range (using ETDRS testing Snellen equivalent 20/32 [0.63] to 20/100 [0.2]) and within 5 letters (better or worse) of the Screening VA. Thus:

- If difference in BCVA was greater than 5 ETDRS letters (better or worse) between Screening and Visit 1, the patient was NOT allowed to be randomized.
- If the Snellen equivalent at Visit 1 was no longer within the inclusion criteria (Snellen equivalent 20/32 to 20/100), the patient was NOT allowed to be randomized.

(c) No diagnosis and/or signs of nAMD requiring immediate treatment with an IVT anti-VEGF agent in the fellow eye (e.g., aflibercept, bevacizumab, ranibizumab).

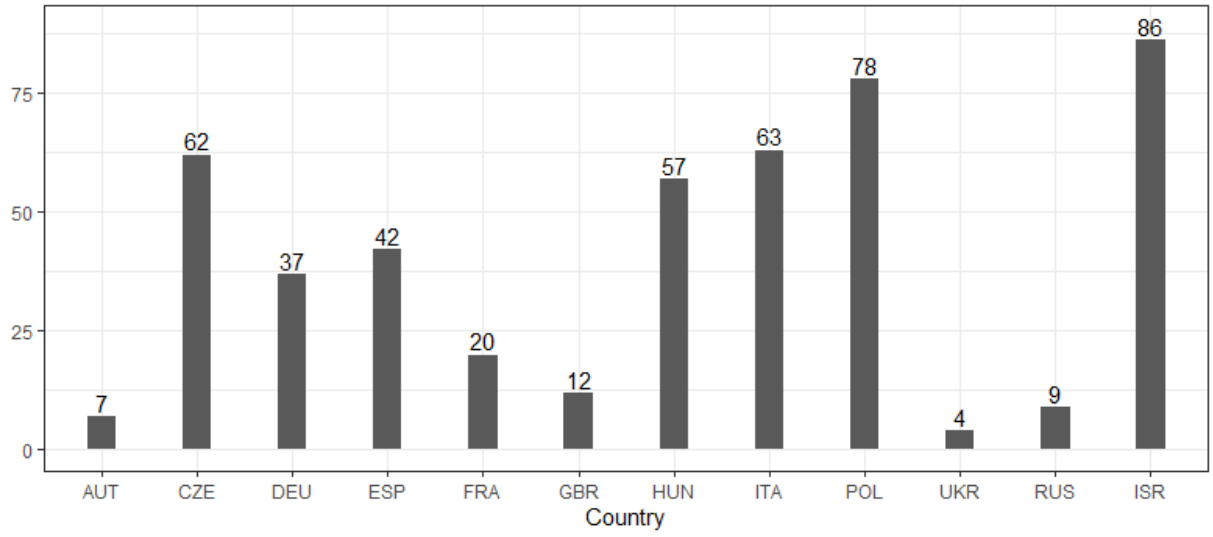
Reviewer's Comments: Two subjects in the applicant's analysis sets did not meet the eligibility criteria for randomization but were randomized in error.

- Subject (b) (6) did not meet two criteria, (a) and (b).
- Subject (b) (6) did not meet one criterion, (b).

Those two subjects were excluded from FDA's Intent-to-Treat and Per Protocol sets.

A total of 477 subjects were randomized at 75 study sites in 12 countries in Europe [Austria (1), Czech Republic (6), France (6), Germany (8), Hungary (7), Italy (9), Poland (8), Spain (7), United Kingdom (5) and Ukraine (3)], Russia (4), and Israel (11). Figure 2 presents the number of randomized subjects by country. The countries with less than fifteen patients were pooled with another country for the statistical analyses following the pooling algorithm in the applicant's statistical analysis plan (SAP): Russia-Ukraine, Austria-Germany, and Great Britain-France.

Figure 2 Number of Randomized Subjects Enrolled by Country



Study Endpoints

The primary study endpoint was the change from baseline in BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) of treatment. The primary endpoint was identical for the main analysis and the final analysis but performed after 24 weeks and after 48 weeks, respectively.

The following were some of the secondary endpoints for the final analysis:

- Change from baseline in BCVA by ETDRS letters over time
- Change from baseline in BCVA by ETDRS letters after 12 Months (averaged over Months 10 [Week 40], 11 [Week 44] and 12 [Week 48])
- Changes from baseline in foveal center point (FCP) retinal thickness and foveal central subfield (FCS) retinal thickness over time

3.2.2 Statistical Methodologies

Analysis Populations

The applicant defined three analysis populations for the analyses of efficacy and safety variables.

(i) Safety Set (SAF) included all patients who had received at least one injection with investigational medicinal product (IMP). SAF was used to evaluate safety.

(ii) Full Analysis Set (FAS) included all patients who received at least one injection of IMP, and for whom BCVA results at least after 1 month were available and who had a screening BCVA between 20/32 and 20/100 Snellen equivalent in the study eye. FAS was used for the applicant's primary efficacy analysis.

(iii) Per Protocol Set (PPS) included all patients who belonged to the FAS who had no major protocol deviations until Visit 3 (after 8 weeks) that would interfere with the interpretation of BCVA efficacy data. PPS was used for sensitivity analyses.

Reviewer's Comments: FDA's primary efficacy analysis was based on intent-to-treat (ITT) population, which included all randomized subjects, while the applicant used FAS for primary efficacy analysis.

Sample Size Determination

The applicant planned to randomize a total of 460 patients (230 patients per arm). The sample size calculation was based on the following assumptions:

- Standard deviation (SD) of 10 ETDRS letters
- No mean difference between two treatment groups
- Similarity margin of 3.5 ETDRS letters
- 90% power
- 95% confidence interval (significance level of 2.5%) (EMA requirements)
- 1:1 randomization ratio

With the above assumptions, a total of 412 patients was needed to achieve 90% power. As the EU-specific analysis was restricted to patients with screening Snellen equivalent of 20/40 or worse, assuming that 10% of randomized patients would have screening Snellen equivalent of 20/32, a sample size of 460 was planned for the study.

Reviewer's Comments: The reviewer confirmed that a sample size of 460 would provide 96.5% power for the US-specific analysis which requires 5% significance level (corresponding to 90% confidence interval) and includes patients with screening Snellen equivalent of 20/32.

Primary Efficacy Analysis

To assess similarity between FYB201 and Lucentis for the primary endpoint, the following hypotheses were tested using two one-sided tests (TOST) procedure.

$$H_0: \mu_{FYB201} - \mu_{Lucentis} \leq -3.5 \text{ or } \mu_{FYB201} - \mu_{Lucentis} \geq 3.5$$
$$H_a: -3.5 < \mu_{FYB201} - \mu_{Lucentis} < 3.5$$

The 90% confidence interval for the mean difference was constructed based on an analysis of covariance (ANCOVA) model with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as factors. If the 90% confidence interval for the mean difference was contained within the interval (-3.5, 3.5), similarity of FYB201 and Lucentis could be concluded for the primary endpoint (α=0.05).

Reviewer's Comments: The applicant used the term "two-sided equivalence test", which seems to mean two one-sided tests (TOST) procedure for equivalence test.

Handling of Missing Values

The applicant did not impute the missing BCVA data for primary efficacy analysis.

Reviewer's Comments: The evaluation of the primary endpoint took place at Week 8 (Visit 3) which was relatively an early time point in the 48-week study period. Therefore, the impact of missing data in the primary endpoint was expected to be minimal. Table 2 summarizes the number of subjects who had missing BCVA assessments for the primary efficacy analysis.

Table 2 Summary of Subjects with Missing BCVA Data at Week 8 for Primary Efficacy Analysis (ITT Population)

	FYB201 (N=236)	**Lucentis (N=239)**	**Total (N=475)**
Subjects with missing BCVA at Week 8	8 (3.4%)	6 (2.5%)	14 (2.9%)
Subjects who had missing BCVA assessments at Week 8 but completed study	6 (2.5%)	5 (2.1%)	11 (2.3%)
Subjects who discontinued study before Week 8 due to intercurrent events	2 (0.8%)	1 (0.4%)	3 (0.6%)
Withdrawal by subject	1 (0.4%)	0 (0.0%)	1 (0.2%)
Adverse event	0 (0.0%)	1 (0.4%)	1 (0.2%)
Patient's death	1 (0.4%)	0 (0.0%)	1 (0.2%)

Sensitivity/Supplementary Analyses

The applicant performed sensitivity analyses (i) based on the PPS and (ii) based on the ITT population with a mixed model repeated measurements (MMRM) using all data from Visit 2 to Visit 7.

The reviewer conducted the following additional sensitivity/supplementary analyses to assess the robustness of the primary efficacy analysis results with respect to the handling of missing data and intercurrent events:

(iii) Analysis based on the ITT population, imputing the 11 subjects, who completed the study but had missing BCVA assessments at Week 8, using Next Observation Carried Backward approach

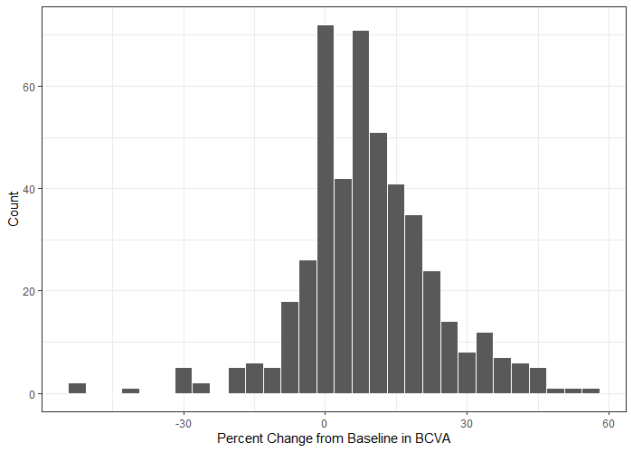
(iv) Analysis based on the ITT population, imputing the 14 subjects with missing BCVA at Week 8, with a conservative approach (54% reduction in BCVA from baseline for FYB201 group and 54% increase in BCVA from baseline for Lucentis group)

Reviewer's Comments: The assumptions for the FDA's conservative approach in (iv) were based on the distribution of the individual subjects' percent change from baseline in BCVA at Week 8,

$$\frac{\text{Week 8} - \text{Baseline}}{\text{Baseline}} \times 100,$$

as the minimum and maximum values of the percent change from baseline were -54% and 54%, respectively (See Table 3).

Table 3 Histogram of Percent Change from Baseline in BCVA at Week 8 and Summary Statistics (ITT Population)



Summary Statistics for the Distribution of Percent Change from Baseline in BCVA at Week 8	
Minimum	-54.1%
First Quartile	1.3%
Median	8.2%
Mean	9.1%
Third Quartile	16.7%
Maximum	54.5%

Secondary Efficacy Analysis

There was no formal hypothesis testing planned for the secondary endpoints and the analyses of the secondary endpoints were intended to be supporting exploratory analyses. The secondary endpoints were analyzed similarly to the primary endpoint.

Planned Subgroup Analyses

The applicant did not perform subgroup analyses. The reviewer conducted subgroup analyses to evaluate the change from baseline in BCVA at Week 8 in the ITT population for the demographic variables, gender and age, and for the stratification factor of screening BCVA category. Race was not considered for subgroup analysis because 98% of the study subjects were Caucasian.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Table 4 shows the summary of subject disposition and the primary reasons for study discontinuation during the 48-week study period.

A total of 477 subjects were randomized into two groups: 238 in FYB201 and 239 in Lucentis. A total of 32 (6.7%) and 25 (5.2%) subjects discontinued from the treatment and from the study before Week 48, respectively. The discontinuation rates from the treatment were comparable between the treatment groups (6.7%) and the discontinuation rates from the study were comparable between the treatment groups (about 5%).

The most common reason for discontinuation from the study among all randomized subjects was withdrawal by subject (2.1%). The discontinuation reasons for the two subjects who were randomized in error were recorded as 'Major protocol deviation' for one subject and 'Other' for the other subject in the applicant's study report. The discontinuation reason for those two subjects is shown as 'Randomized in error' in Table 4.

A total of three subjects died during the 48-week treatment period (2 in FYB201 and 1 in Lucentis).

Table 4 Summary of Subject Disposition and Reasons for Discontinuation (All Randomized Subjects)

	FYB201	Lucentis	Total
Randomized and Treated	238 (100%)	239 (100%)	477 (100%)
Discontinued treatment up to final analysis (Week 48 assessments)	16 (6.7%)	16 (6.7%)	32 (6.7%)
Discontinued study up to final analysis (Week 48 assessments)	12 (5.0%)	13 (5.4%)	25 (5.2%)
Reasons for discontinuation			
Withdrawal by patient	2 (0.8%)	8 (3.3%)	10 (2.1%)
Adverse events	1 (0.4%)	2 (0.8%)	3 (0.6%)
Need for alternative treatment	1 (0.4%)	0 (0.0%)	1 (0.2%)
Loss to follow-up	3 (1.3%)	1 (0.4%)	4 (0.8%)
Randomized in error	2 (0.8%)	0 (0.0%)	2 (0.4%)
Other	3 (1.3%)	2 (0.8%)	5 (1.0%)
• Patient's Death	2 (0.8%)	1 (0.4%)	3 (0.6%)

Source: Table 10-1 of Clinical Study Report COLUMBUS-AMD and Reviewer's Analysis

Analysis Populations

Table 5 shows the summary of the analysis populations. A total of 477 subjects were randomized and treated. Of the randomized subjects, two subjects were randomized in error and were excluded from the Intent-to-Treat (ITT) population. A total of 30 subjects (16 in FYB201 and 14 in Lucentis) were excluded from the Per Protocol Set (PPS) due to major protocol deviations.

Table 5 Summary of Analysis Populations

Analysis Set	FYB201	Lucentis	Total
Safety Set (SAF)	238	239	477
Intent-to-Treat (ITT)	236	239	475
Per Protocol Set (PPS)	220	225	445
Major Protocol Deviation	16	14	30

Source: Table 10-4 of Clinical Study Report COLUMBUS-AMD and Reviewer's Analysis

Demographic and Baseline Characteristics

The summary of the baseline demographic and disease characteristics for subjects in the ITT population is presented in Table 6.

Most subjects in the study were Caucasian (98%), greater than 75 years of age (54%), and female (56%). The average age of subjects in the study was about 76 years (range 50 to 94 years). The average BMI of subjects 27.3 (range from 17.8 to 44.0). The average baseline BCVA in the study eye was 61.2 letters (range from 43 to 78 letters).

The baseline demographic and disease characteristics were comparable between the two treatment groups.

Table 6 Demographics and Baseline Characteristics (ITT Population)

	FYB201 (N=236)	Lucentis (N=239)	Total (N=475)
Gender			
Female	133 (56.4%)	134 (56.1%)	267 (56.2%)
Male	103 (43.6%)	105 (43.9%)	208 (43.8%)
Age			
Mean (SD)	74.9 (8.26)	76.1 (7.84)	75.5 (8.07)
Median	76.0	77.0	76.0
Range	50 – 91	50 – 94	50 – 94
Age Category			
50–64 years	25 (10.6%)	19 (7.9%)	44 (9.3%)
65–75 years	90 (38.1%)	86 (36.0%)	176 (37.1%)
>75 years	121 (51.3%)	134 (56.1%)	255 (53.7%)
Race			
Caucasian	234 (99.2%)	233 (97.5%)	467 (98.3%)
Asian	0 (0.0%)	2 (0.8%)	2 (0.4%)
Other	2 (0.8%)	4 (1.7%)	6 (1.3%)
BMI			
Mean (SD)	27.2 (4.09)	27.4 (4.47)	27.3 (4.28)
Median	26.3	26.8	26.7
Range	19.9 – 42.9	17.8 – 44.0	17.8 – 44.0
Baseline BCVA			
Mean (SD)	61.4 (8.70)	60.9 (8.43)	61.2 (8.56)
Median	61.5	61.0	61.0
Range	43 – 78	44 – 78	43 – 78
Screening BCVA Category			
20/32	22 (9.3%)	24 (10.0%)	46 (9.7%)
20/40	48 (20.3%)	38 (15.9%)	86 (18.1%)
20/50	42 (17.8%)	40 (16.7%)	82 (17.3%)
20/63	37 (15.7%)	42 (17.6%)	79 (16.6%)
20/80	32 (13.6%)	36 (15.1%)	68 (14.3%)
20/100	55 (23.3%)	59 (24.7%)	114 (24.0%)

Source: Reviewer's Analysis

3.2.4 Results and Conclusions

Primary Efficacy Endpoint: Change from Baseline in BCVA at Week 8

The objective of the primary efficacy analysis was an evaluation of similarity of FYB201 to Lucentis in the primary efficacy variable of the change in BCVA from baseline at Week 8 using a similarity margin of ± 3.5 letters.

Table 7 shows the summary of the mean BCVA at baseline and Week 8, the mean change in BCVA from baseline at Week 8, and the adjusted mean change in BCVA from baseline at Week 8 based on the ANCOVA model.

Table 7 Summary of Mean Change in BCVA from Baseline at Week 8 (ITT Population)

		FYB201 (N = 236)	Lucentis (N = 239)	Total (N = 475)
Mean BCVA				
Baseline	Mean (SD)	61.51 (8.66)	60.97 (8.41)	61.24 (8.53)
	Median (Range)	61.5 (43 – 78)	61.0 (46 – 78)	61.0 (43 – 78)
Week 8	Mean (SD)	66.62 (11.22)	66.57 (11.18)	66.60 (11.19)
	Median (Range)	68 (28 – 85)	69 (34 – 89)	68 (28 – 89)
Mean Change from Baseline in BCVA				
Week 8	Mean (SD)	5.11 (7.52)	5.60 (8.63)	5.36 (8.10)
	Median (Range)	5 (-16 – 30)	5 (-39 – 25)	5 (-39 – 30)
Adjusted Mean Change from Baseline in BCVA (ANCOVA)[1]				
Week 8	LS Mean (SE)	5.08 (0.58)	5.44 (0.58)	
	LS Mean Difference (SE)	-0.37 (0.76)		
	90% CI	**(-1.62, 0.88)**		

[1] ANCOVA with treatment and country as factors and baseline BCVA as covariate
Source: Reviewer's Analysis

As shown in Table 7, similarity of FYB201 and Lucentis was demonstrated for the primary endpoint, because the adjusted mean changes in BCVA from baseline at Week 8 were comparable for the two treatment groups with 5.1 letters for FYB201 and 5.4 letters for Lucentis and the mean difference (FYB201 minus Lucentis) was -0.4 letters with 90% confidence interval (-1.6, 0.9) letters, which was contained within the similarity margins of (-3.5, 3.5) letters.

Sensitivity/Supplementary Analyses

To assess robustness of the primary efficacy analysis results with respect to the handling of missing and intercurrent events, sensitivity and supplementary analyses were performed.

Table 8 shows the summary of sensitivity/supplementary analysis results. As shown, the sensitivity and supplementary analysis results were consistent with the primary efficacy analysis results, leading to the same conclusion for a robust interpretation of the similarity finding.

Table 8 Sensitivity/Supplementary Analyses for Primary Efficacy Endpoint

	FYB201 (N=236)		**Lucentis (N=239)**
PP Population			
LS Mean (SE)	5.16 (0.59)		5.59 (0.59)
LS Mean Difference (SE)		-0.43 (0.78)	
90% CI		**(-1.70, 0.85)**	
MMRM using All Data from Visit 2 to Visit 7			
LS Mean (SE)	5.11 (0.56)		5.48 (0.56)
LS Mean Difference (SE)		-0.37 (0.75)	
90% CI		**(-1.60, 0.87)**	
Next Observation Carried Backward Approach[1]			
LS Mean (SE)	5.08 (0.58)		5.33 (0.57)
LS Mean Difference (SE)		-0.25 (0.75)	
90% CI		**(-1.49, 0.98)**	
FDA's Conservative Approach[2]			
LS Mean (SE)	3.85 (0.69)		6.10 (0.69)
LS Mean Difference (SE)		-2.25 (0.90)	
90% CI		**(-3.73, -0.77)**	

[1] Analysis based on the ITT population, imputing the 11 subjects, who completed the study but had missing BCVA assessments at Week 8, using Next Observation Carried Backward approach

[2] Analysis based on the ITT population, imputing the 14 subjects with missing BCVA at Week 8, with a conservative approach (54% reduction in BCVA from baseline for FYB201 group and 54% increase in BCVA from baseline for Lucentis group)

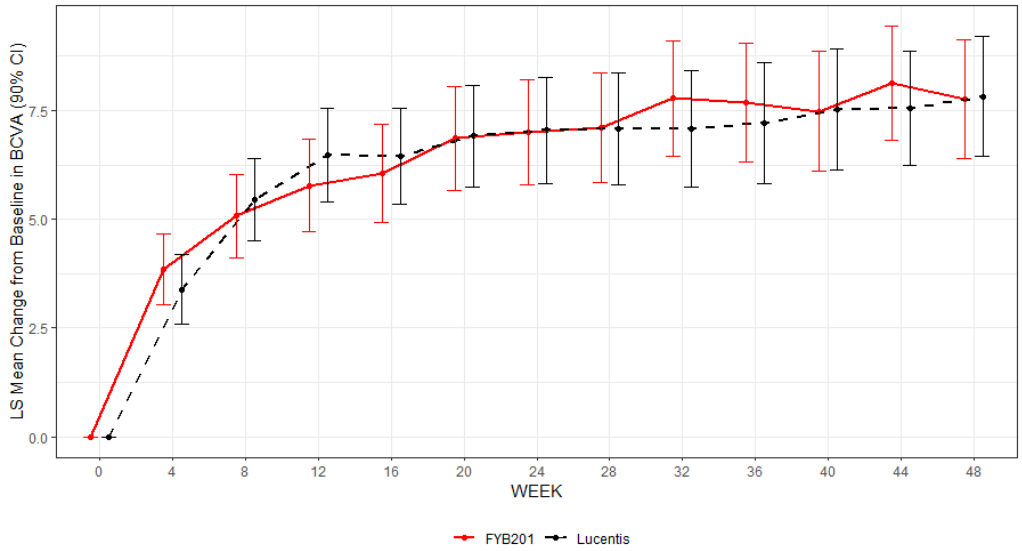
Source: Reviewer's Analysis

Secondary Efficacy Endpoint: Change from Baseline in BCVA over time

One of the secondary objectives of the study was to evaluate and compare functional changes of the retina by BCVA over time. Figure 3 and Figure 4 present the analysis results of the secondary endpoint, change from baseline in BCVA over time, which compare functional changes of BCVA over the 48-week treatment period between the two treatment groups.

Figure 3 displays the adjusted mean change in BCVA from baseline through Week 48 with the 90% confidence intervals (vertical bars at each visit). The results for FYB201 and Lucentis appeared comparable.

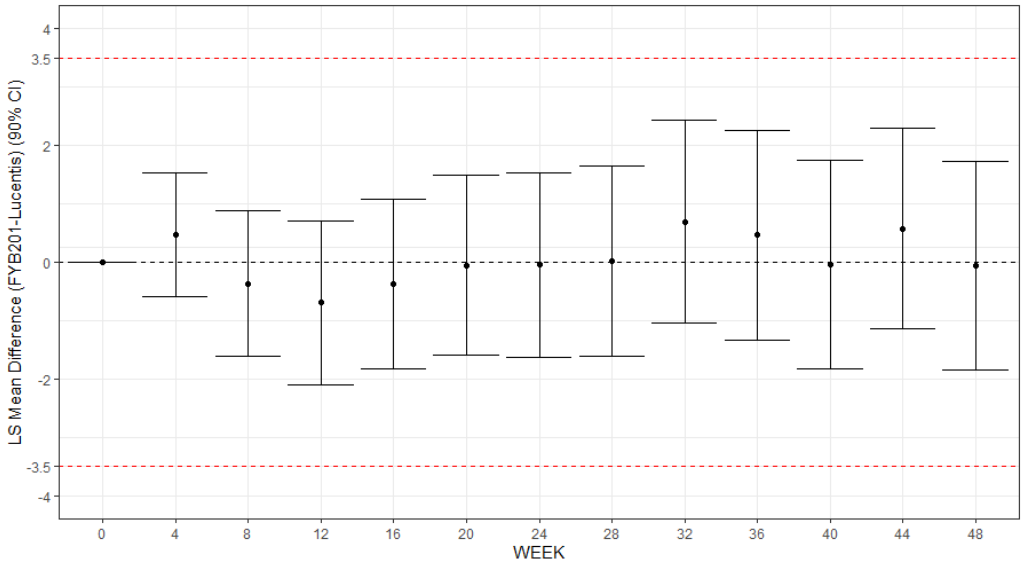
Figure 3 Plot of Adjusted Mean Change from Baseline in BCVA with 90% Confidence Intervals from Baseline Through Week 48 (ITT Population)



Source: Reviewer's Analysis

Figure 4 displays the difference (FYB201 minus Lucentis) in adjusted mean change in BCVA from baseline through Week 48 with the 90% confidence intervals (vertical bars at each visit) based on the ANCOVA models with baseline BCVA as covariate and treatment and country as factors. All of the 90% confidence intervals were contained within the similarity margin of (-3.5, 3.5) letters.

Figure 4 Plot of Difference (FYB201 - Lucentis) in Adjusted Mean Change from Baseline in BCVA Between the Two Treatments with 90% Confidence Intervals from Baseline Through Week 48 (ITT Population)



Source: Reviewer's Analysis

Other Secondary Efficacy Endpoints

The analyses of the other secondary endpoints, change from baseline in BCVA after 12 months (averaged over Week 40, Week 44, and Week 48) and changes from baseline in FCP retinal thickness and FCS retinal thickness over time are summarized in Table 9 and Figure 5.

Table 9 shows the summary of the adjusted mean change in BCVA from baseline after 12 months (averaged over Week 40, Week 44, and Week 48) based on an ANCOVA model with baseline BCVA as covariate and treatment and country as factors. The adjusted mean changes in BCVA from baseline after 12 months were comparable for the two treatment groups with 7.8 letters for FYB201 and 7.7 letters for Lucentis and the mean difference (FYB201 minus Lucentis) was 0.06 letters with 90% confidence interval (-1.7, 1.8) letters.

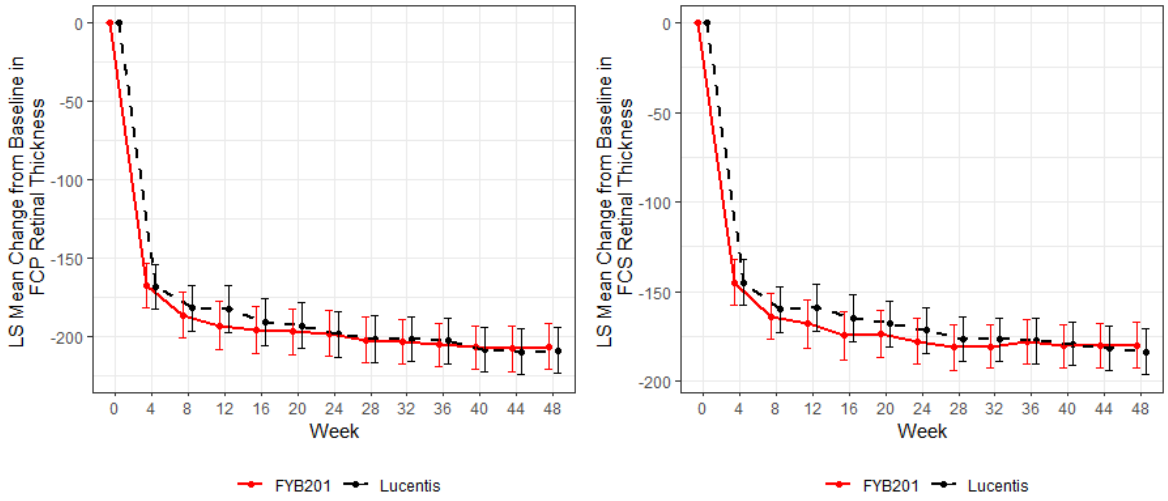
Figure 5 displays the adjusted mean changes in FCP retinal thickness and FCS retinal thickness from baseline through Week 48 with the 90% confidence intervals (vertical bars at each visit) based on ANCOVA models with baseline FCP/FCS retinal thickness as covariate and treatment and country as factors. The two treatment groups appeared comparable in the adjusted mean changes from baseline in FCP retinal thickness and FCS retinal thickness over time.

Table 9 Summary of Secondary Efficacy Analysis for Change from Baseline in BCVA after 12 Months (ITT Population)

	FYB201 (N=236)	**Lucentis (N=239)**
Change from Baseline in BCVA after 12 Months (Averaged over Week 40, Week 44, and Week 48)		
LS Mean (SE)	7.78 (0.80)	7.72 (0.80)
LS Mean Difference (SE)	0.06 (1.04)	
90% CI	(-1.66, 1.77)	

Source: Reviewer's Analysis
Note: ANCOVA with treatment and country as factors and baseline BCVA as covariate was used

Figure 5 Plots of Adjusted Mean Changes from Baseline in FCP Retinal Thickness and FCS Retinal Thickness with 90% Confidence Intervals from Baseline Through Week 48 (ITT Population)



Source: Reviewer's Analysis

Conclusion

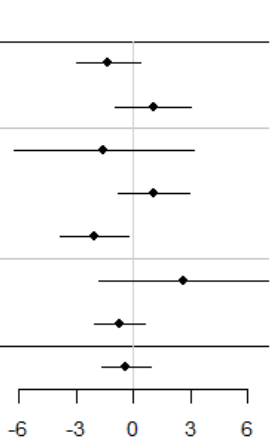
Study COLUMBUS-AMD demonstrated similarity of FYB201 and Lucentis with respect to the change from baseline in BCVA at Week 8. The adjusted mean change in BCVA from baseline at Week 8 was comparable for the two treatment groups with 5.1 letters for FYB201 and 5.4 letters for Lucentis. The mean difference (FYB201 minus Lucentis) was -0.4 letters with 90% confidence interval (-1.6, 0.9) letters, which was contained within the similarity margins of (-3.5, 3.5) letters.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The primary efficacy endpoint of the change from baseline in BCVA at Week 8 was summarized by the subgroups of gender, age and by the stratification factor of screening BCVA category. The subgroup analysis by race was not applicable because 98% of the study subjects were Caucasian. See Table 6 for the sample sizes used within each subgroup.

Figure 6 Adjusted Mean Change in BCVA from Baseline at Week 8 by Subgroup (ITT Population)

Subgroup	Labels	FYB201	Lucentis	Difference (90% CI)
Gender	Female	4.6 (0.8)	5.9 (0.8)	-1.3 (-3.0, 0.3)
	Male	5.7 (0.9)	4.6 (0.9)	1.0 (-0.9, 3.0)
Age	50-64 years	7.7 (1.9)	9.2 (2.1)	-1.5 (-6.2, 3.2)
	65-75 years	5.8 (0.8)	4.8 (0.9)	1.1 (-0.8, 2.9)
	>75 years	3.4 (1.0)	5.5 (1.0)	-2.1 (-3.9, -0.3)
Screening BCVA	20/32	4.7 (2.1)	2.0 (1.8)	2.7 (-1.8, 7.1)
	20/40-20/100	5.1 (0.6)	5.8 (0.6)	-0.7 (-2.0, 0.6)
Overall		5.1 (0.6)	5.4 (0.6)	-0.4 (-1.6, 0.9)



Source: Reviewer's Analysis

Figure 6 shows the summary of the adjusted mean changes in BCVA from baseline at Week 8 by the subgroup variables. The adjusted mean changes were comparable between the two treatment groups within the levels of each of the subgroup variables. The adjusted mean differences in BCVA at Week 8 between the two treatment groups across the subgroup levels were consistent with the overall population.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues in this study.

5.2 Collective Evidence

Support for similarity between FYB201 and Lucentis for the treatment of nAMD was further assessed using one pivotal Phase 3 study (COLUMBUS-AMD). In the study, subjects treated with FYB201 had a comparable adjusted mean change in BCVA from baseline at Week 8 compared to subjects treated with Lucentis (5.1 vs. 5.4 letters). The study demonstrated similarity of FYB201 and Lucentis for the primary endpoint because the 90% confidence interval for the treatment difference of the adjusted means was (-1.62, 0.88) which was contained within the pre-specified similarity margin (-3.5, 3.5).

5.3 Conclusions and Recommendations

Based on the collective evidence from Study COLUMBUS-AMD, the reviewer concludes that the application provided substantial evidence for similarity in the primary clinical endpoint between FYB201 and Lucentis.

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CLINICAL PHARMACOLOGY REVIEW

BLA	761165
Submission Date	08/02/2021
Applicant	Bioq AG
Proposed Brand Name	Cimerli
Nonproprietary Name	FYB201, a proposed biosimilar to ranibizumab
Indication	Proposed all the indications approved for US-licensed Lucentis
Dosage form	0.05 mL of 10 mg/mL or 6 mg/mL solution in single-use glass vial
Route of Administration	Intravitreal injection
Dosage Regimen	Proposed the same dosing regimens as those approved for US-licensed Lucentis
Clinical Pharmacology Reviewer	Lei He, PhD
Clinical Pharmacology Team Leader	Ping Ji, PhD
OCP Division	Division of Inflammation and Immune Pharmacology
OND Division	Division of Ophthalmology Products
Submission Type; Code	351(k), standard review

1. Clinical Pharmacology Executive Summary and Recommendation

Lucentis (ranibizumab), a vascular endothelial growth factor (VEGF) inhibitor, has been approved for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

The Applicant submitted this BLA application under section 351(k) of the Public Health Service Act (PHS Act) for FYB201, a recombinant humanized IgG1 kappa isotype monoclonal antibody fragment designed for intraocular use, as a proposed biosimilar to US-licensed Lucentis (ranibizumab). The proposed dosage form, indications, and dosage regimens for FYB201 are same as those approved for US-licensed Lucentis.

BLA 761165 application consists of one comparative clinical study in patients with newly diagnosed neovascular AMD (Study FYB201-C2015-01-P3, n=477), in which the PK profiles of FYB201 and US-licensed Lucentis were evaluated in a subgroup of neovascular AMD patients.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) has reviewed the clinical pharmacology data submitted under this BLA application and had the following recommendations regarding clinical pharmacology review issues (Table 1).

Table 1. Clinical Pharmacology Major Review Issues and Recommendations

Review Issue	Recommendations and Comments
PK similarity	• Systemic exposure of FYB201 and US-licensed Lucentis evaluated in a subset of subjects with neovascular AMD in Study FYB201-C2015-01-P3 were comparable based on descriptive analysis, supporting a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.
PD similarity, if applicable	• Not applicable.
Immunogenicity assessment	• Comparable incidence of anti-drug antibody (ADA) and neutralizing antibody (NAb) formation between FYB201 and US-licensed Lucentis in subjects with neovascular AMD supports a demonstration of no clinically meaningful differences between FYB201 and US-licensed Lucentis.

1.1 Clinical Pharmacology Residual Uncertainties Assessment

There are no clinical pharmacology residual uncertainties regarding the PK and immunogenicity assessment for FYB201 and US-licensed Lucentis.

2. Clinical Pharmacology Studies to Support the Use of a Non-US-licensed Comparator Product

Not applicable.

3. Human Pharmacokinetic and Pharmacodynamic Studies

A PK similarity study using traditional PK endpoints, such as AUC and C_{max}, in healthy subjects is not considered to be feasible for the following reasons: 1) ranibizumab is administered by intravitreal (IVT) injection directly into the eye to treat diseases that are localized to the eye and the systemic exposures following IVT injection is low (i.e., negligible) and variable, and 2) the conduct of a PK study in healthy subjects is considered unethical due to the invasiveness of IVT injections. Therefore, a PK sub-study within the comparative clinical study was recommended to provide PK data in support of no clinically meaningful differences in systemic safety. The objective of the PK sub-study was to descriptively compare the peak serum study drug concentrations.

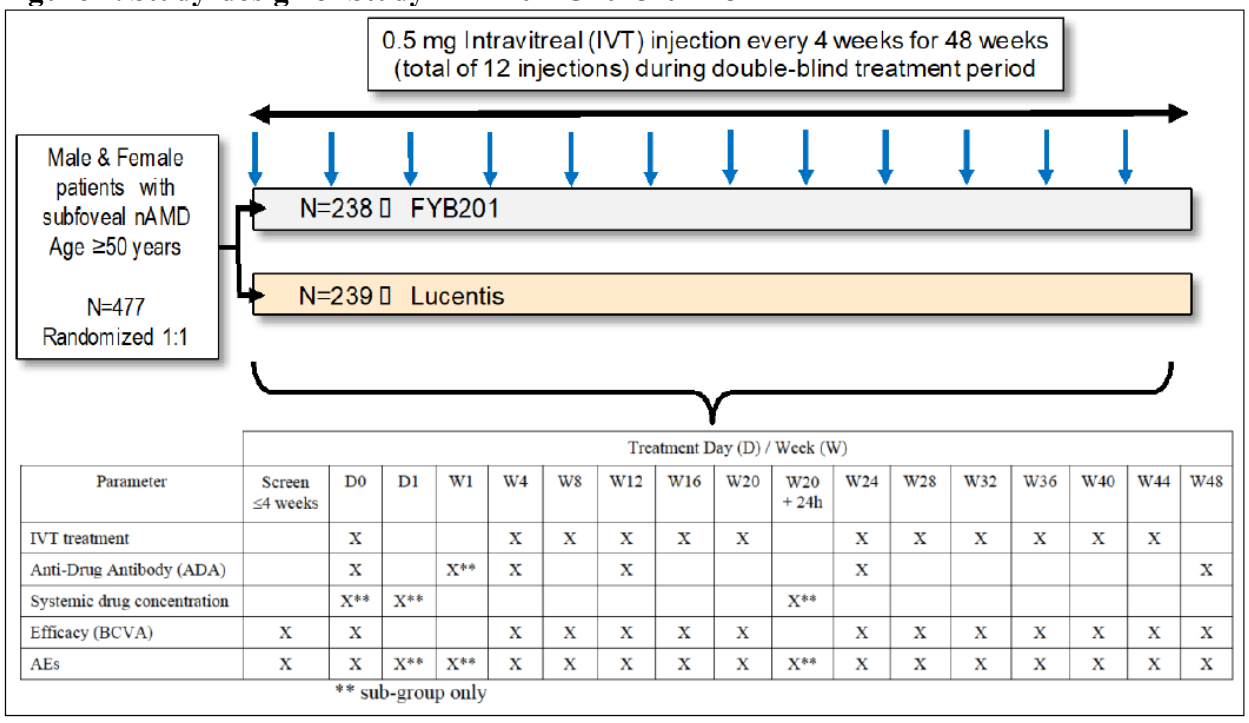
Clinical Pharmacology Study Design Features and Endpoints

Study FYB201-C2015-01-P3 was a 12-month (48-week), randomized, active-controlled, evaluation-masked, parallel-group, multicenter study to evaluate the comparative efficacy, safety, and immunogenicity of FYB201 compared with US-licensed Lucentis in the treatment of patients with neovascular AMD (n=477) (Figure 1). Eligible patients were randomized to receive FYB201 or US-licensed Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) through IVT injection every 4 weeks for 12 months. The PK profiles of FYB201 and US-licensed Lucentis were descriptively evaluated within a subgroup of neovascular AMD patients as part of the comparative clinical study. The PK data were pre-specified to be analyzed qualitatively. Analyses included:

a. Systemic exposure measured at 24±3 hours post-dose (close to maximum serum concentration (Cmax)) after the first and the sixth IVT injections in a subgroup of patients from both treatment groups
b. Incidence of anti-drug antibodies (ADAs) to FYB201 and US-licensed Lucentis
c. Incidence of neutralizing antibodies (NAbs) to FYB201 and US-licensed Lucentis

Of the 477 subjects enrolled, 29 [6.1%] and 30 [6.3%] subjects in the FYB201 and US-licensed Lucentis treatment groups, respectively, were included in PK subgroup analysis set.

Figure 1. Study design of Study FYB201-C2015-01-P3



	Treatment Day (D) / Week (W)															
Parameter	Screen ≤4 weeks	D0	D1	W1	W4	W8	W12	W16	W20	W20 + 24h	W24	W28	W32	W36	W40	W44	W48
IVT treatment		X			X	X	X	X	X		X	X	X	X	X	X	
Anti-Drug Antibody (ADA)		X		X**	X		X				X						X
Systemic drug concentration		X**	X**							X**							
Efficacy (BCVA)	X	X			X	X	X	X	X		X	X	X	X	X	X	X
AEs	X	X	X**	X**	X	X	X	X	X	X**	X	X	X	X	X	X	X

** sub-group only

(Source: Figure 20, BLA761165 Integrated Summary of Immunogenicity)

Bioanalytical PK method and performance

FYB201 or ranibizumab concentrations in human plasma were measured using a validated electrochemiluminescent immunoassay (ECLIA) of Meso Scale Discovery platform. The lower and upper quantification limits for plasma study drug concentrations were 500 pg/mL and 20000 pg/mL, respectively. All PK samples from Study FYB201-C2015-01-P3 were analyzed (between February 05, 2018 and February 13, 2018) within the demonstrated stability period. Refer to Appendix for more detailed information regarding the bioanalytical method validation.

PK of FYB201 and US-licensed Lucentis in patients with neovascular AMD (Study FYB201-C2015-01-P3)

In Study FYB201-C2015-01-P3, 60 patients at selected sites were enrolled in PK subgroup analysis set and randomly (1:1) assigned to recive either FYB201 or US-licensed Lucentis. One patient was excluded from the PK subgroup analysis set bcause of major protocol deviations (measurable ranibizumab concentration at baseline). Blood samples for PK assessments were collected prior to the first IVT injection and at 24 hours (±3 hours) following the first (Day 1) and sixth (Week 20) IVT injections.

The summary statistics of the systemic ranibizumab concentrations for each of the treatment subgroups are presented in Table 2. The descriptive PK comparison showed that the systemic ranibizumab concentrations close to Cmax after the first and the sixth IVT injections were comparable between FYB201 and US-licensed Lucentis treatment groups.

Table 2. Systemic ranibizumab concentrations close to Cmax (pg/mL) after 1st and 6th IVT injections (Study FYB201-C2015-01-P3 PK subgroup analysis set)

	FYB201 (N = 29)		Lucentis (N = 30)	
Analysis Visit	**V1a/ Day 1[1]**	**V6a/ Week 20[2]**	**V1a/ Day 1[1]**	**V6a/ Week 20[2]**
N*				
n	29	26	30	30
Missing		1		
Geometric mean	2330.91	2333.15	2551.51	2792.75
%Geom. CV	61.36	67.69	61.16	58.38
Arithmetic Mean	2713.6	2742.3	2963.6	3162.7
SD	1543.44	1490.86	1702.35	1493.08
%CV	56.88	54.37	57.44	47.21
Median	2190.0	2425.0	2590.0	2895.0
Range (min–max)	900–6550	614–6130	559–6940	703–6310

N = total number of patients, N* = total number of patients still in the study for the respective analysis visit, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment
Notes: [1] blood sample drawn at 24h±3h after 1st IVT injection, [2] blood sample drawn at Week 20 24h±3h after 6th IVT injection, Values below the limit of quantification were set to 0 and values above the limit of quantification were set to the upper limit of quantification for the purpose of summary statistics. PK measurement of patient (b) (6) (FYB201 treatment group) at visit 6a was set to be missing because drug treatment in the fellow eye was administered too close to visit 6a and the PK measurement may be confounded.

(Source: Table 3, Study FYB201-C2015-01-P3 patient PK and initial tolerability study report)

PD similarity assessment
Not applicable.

4. Clinical Immunogenicity Studies

Design Features of the Clinical Immunogenicity Assessment

Immunogenicity (ADA and Nab) was evaluated in Study FYB201-C2015-01-P3 as one of the secondary endpoints.

Immunogenicity Endpoints

Serum samples collected for immunogenicity assessment were first tested for ADA. Samples confirmed as positive for ADA were further tested for NAb.

Immunogenicity Assay's Capability of Detecting the ADA in the Presence of Proposed Product, Reference Product, and Any Other Comparator Product (as applicable) in the Study Samples

The Applicant developed binding and neutralizing antibody assays that are suitable for detecting ADA and NAb in the presence of expected levels of FYB201 and US-licensed Lucentis.

Adequacy of the Sampling Plan to Capture Baseline, Early Onset, and Dynamic Profile (Transient or Persistent) of ADA Formation

The sampling plans were adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of ADA formation. Blood sampling for immunogenicity assessment were collected in all subjects at Week 0, Week 1 (PK subgroup only), Week 4, Week 12, Week 24, and Week 48 (end-of-study visit).

Comparison of Incidence of ADA and NAb
The incidence of ADA and NAb by treatment group and time points in Study FYB201-C2015-01-P3 were summarized in Table 3. The incidence of an ADA positive response was generally low and comparable between treatment groups throughout the study. Only one patient in FYB201 treatment group was detected positive for NAb at Week 48.

Table 3. Incidence of Anti-drug Antibody (ADA) and Neutralizing Antibodies (NAb) by Visit (Safety Set, Study FYB201-C2015-01-P3)

Category	Treatment week				
	Visit 1 / Baseline	4	12	24	48
FYB201 (N=238)					
No. of patients #	234 §	226	226	225	229
No. ADA positive	0	2	1	6	9
% ADA positive	0	0.9	0.4	2.7	3.9
Median titer	n.c.	10.0	10.0	30.0	60.0
Min/Max titer	n.c.	10 / 10	10 / 10	10 / 90	10 / 810
No. NAb positive	0	0	0	0	1
% NAb positive	0	0	0	0	0.4
Lucentis (N=239)					
No. of patients #	238 §	228	226	225	225
No. ADA positive	5	2	2	6	12
% ADA positive	2.1	0.9	0.9	2.7	5.3
Median titer	30.0	10.0	10.0	30.0	10.0
Min/Max titer	10 / 90	10 / 10	10 / 10	10 / 90	10 / 90
No. NAb positive	0	0	0	0	0
% NAb positive	0	0	0	0	0

= number of patients with non-missing assessment; n.c. = not calculable; *NR* = No result

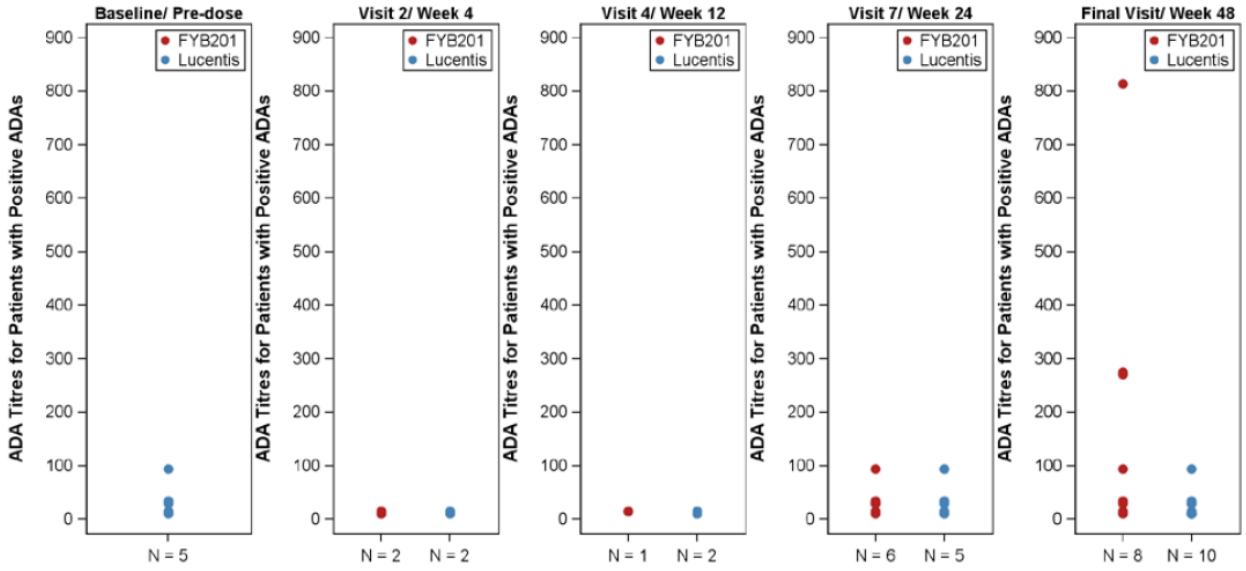
§ = includes further pre-dose samples that were taken at Visit 1b

(Source: Table 39, BLA761165 Integrated Summary of Immunogenicity)

Comparison of ADA Titers

The distribution of ADA titers is comparable between the FYB201 and US-licensed Lucentis treatment groups as seen in Table 3 and Figure 2. There was no specific trend indicating the difference in the distribution of ADA titers between the FYB201 and US-licensed Lucentis treatment groups.

Figure 2. Grouped dotplot of ADA titers for patients with positive ADAs by visit and treatment group (Safety Set, Study FYB201-C2015-01-P3)



(Source: Figure 22, BLA761165 Integrated Summary of Immunogenicity)

Comparison of Immunogenicity Impact on PK

Among 59 subjects who were included in the PK subgroup analysis set, only 5 subjects had positive ADA results by Week 48 (2 of 29 subjects in FYB201 group and 3 of 30 subjects in US-licensed Lucentis group). Therefore, no conclusion could be made regarding the correlation between blood levels and antibody rates.

Comparison of Immunogenicity Impact on Efficacy

The primary efficacy endpoint of Study FYB201-C2015-01-P3 is the change from baseline in best corrected distance visual acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) between FYB201 and US-licensed Lucentis treatments. The number of ADA-positive subjects was small (< 1%) and equally divided between treatment arms at Week 4 (2 (0.9%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group) and Week 12 (1 (0.4%) subjects in FYB201 group and 2 (0.9%) subjects in US-licensed Lucentis group). Comparable low incidence of ADA formation and no NAb formation in each group supports a demonstration of no clinically meaningful differences between SB11 and US-licensed Lucentis.

Comparison of Immunogenicity Impact on Safety

The comparison of immunogenicity impact on safety was evaluated based on the assessment of selected treatment-emergent adverse events (TEAEs) by overall anti-drug antibody result up to end of study (Week 48), including drug hypersensitivity, anaphylaxis, and intra-ocular inflammation (Table 4). Overall, none of these TEAEs was reported in patients with overall ADA positive status up to Week 48 in either treatment group.

Table 4. Summary of selected TEAE's up to Week 48 by ADA status and treatment

	FYB201 (N=238)		Lucentis (N=239)	
	ADA Negative (n=224)	ADA Positive (n=14)	ADA Negative (n=223)	ADA Positive (n=16)
Drug hypersensitivity	1 (0.4%)	0	1 (0.4%)	0
Anaphylaxis	0	0	0	0
Intra-ocular inflammation	0	0	0	0

(Source: Table 52, BLA761165 Integrated Summary of Immunogenicity)

Appendix. Summary of Bioanalytical Method Validation

FYB201 or ranibizumab concentrations in human plasma were measured using a validated electrochemiluminescent immunoassay (ECLIA) of Meso Scale Discovery platform (Table 4). The lower and upper quantification limits for plasma study drug concentrations were 500 pg/mL and 20000 pg/mL, respectively.

Table 5. Summary of the bioanalytical method to measure FYB201 and ranibizumab in human plasma (Method Validation Report (b) (4) 21861-01 and amendments)

Method description	• Assay format: Electrochemiluminescent immunoassay (ECLIA) to detect active drug • Platform: Meso Scale Discovery QuickPlex® SQ 120 imager with MSD GOLD 96-Well Small Spot Streptavidin SECTOR® plate (L45SA) • Test matrix: human plasma (lithium heparin) • Primary incubation: 10 µl sample/control + 40 µl assay buffer + 100 µl Bridging reagent (biotin-VEGF165 + Rabbit anti-FYB201 IgG) incubated O/N at 5°C shaking

	• Detection: Transfer 50 µl of sample/master mix to streptavidin plates, incubate for 1 hr at 25°C on a shaking incubator • Wash and add 50 µl SULFO-TAG Labeled Anti-Rabbit Antibody, incubate for 1 hr at 25°C on a shaking incubator • Wash and add 150 µl per well of MSD Read buffer		
Materials used for calibration curve & concentration	FYB201 Lot No. F16128 250 (anchor point), 500, 1000, 2000, 4000, 7000, 10,000, 16,000, and 20,000 pg/ml (prepared in bulk; aliquots stored at -80°C)		
Validated assay range	500 to 20,000 pg/ml		
Material used for QCs & concentration	FYB201 Lot No. F16128 US-licensed Lucentis (Genentech Lot No. 3006210) LLOQ QC = 500 pg/ml; QC A = 1500 pg/ml; QC B = 6000 pg/ml; QC C = 15000 pg/ml; ULOQ = 20000 pg/ml (prepared in bulk; aliquots stored at -80°C)		
Minimum required dilutions (MRDs)	1:15		
Source & lot of reagents (LBA)	• Reference standard: FYB201 Lot No. F16128 US-licensed Lucentis (Genentech Lot No. 3006210) • Biotinylated Human VEGF165, epitope tag free, ultra-sensitivity (primary amine labeling), Acro Biosystems, Catalog No. VE5-H8210 • Rabbit Anti-FYB201 IgG, 0.959 mg/mL, Formycon AG, Part No. PN-383/16-a • MSD® SULFO-TAG Labeled Anti-Rabbit Antibody (Goat), 500 µg/mL, Meso Scale Discovery, Catalog No. R32AB • Block buffer: 3% Blocker A in PBS-Tween® buffer • Assay buffer: 1% Blocker A in PBS-Tween® buffer • Wash buffer: PBS-Tween® buffer		
Regression model & weighting	4PL, 1/Y		
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Table 5 of [redacted] report no. [redacted]21861-01
	Cumulative accuracy (%bias) from LLOQ to ULOQ FYB201	-1.8 to 1.9%	Table 5 of [redacted] report no. [redacted]21861-01

	Cumulative precision (%CV) from LLOQ to ULOQ FYB201	 ≤ 3.9%	Table 5 of (b) (4) report no. (b) (4) 21861-01
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: FYB201 US Lucentis	 -1.4 to 3.5% -2.7 to 5.5%	Table 2 and Table 3 of (b) (4) report no. (b) (4) 21861-01
	Inter-batch %CV QCs: FYB201 US Lucentis	 ≤ 6.5% ≤ 5.9%	Table 2 and Table 3 of (b) (4) report no. (b) (4) 21861-01
	Total Error (TE) QCs: FYB201 US Lucentis	 ≤ 10.0% ≤ 11.4%	Table 2 and Table 3 of (b) (4) report no. (b) (4) 21861-01
Selectivity & matrix effect	10 plasma (heparin) lots from normal human subjects spiked with FYB201 or US Lucentis: FYB201: LLOQ (500 pg/mL): -14.6 to 13.4 %bias (in 9/10 lots; 1 lot below LLOQ) HQC (15.000 pg/mL): -45.1 to 15.3 %bias (0.0 to 15.3 %bias in 9/10 lots) US Lucentis: LLOQ (500 pg/mL): -1.0 to 11.0 %bias (in 10/10 lots) HQC (15.000 pg/mL): -44.7 to 18.0 %bias (-0.7 to 18.0 %bias in 9/10 lots) 10 plasma (heparin) lots from special population human subjects (healthy donors 50 years or older and not taking any immunosuppressant drugs) spiked with FYB201 or US Lucentis: FYB201: LLOQ (500 pg/mL): -6.2 to 18.6 %bias (in 10/10 lots) HQC (15.000 pg/mL): -3.3 to 18.0 %bias (in 10/10 lots) US Lucentis: LLOQ (500 pg/mL): -3.4 to 32.4 %bias (-3.4 to 15.4 %bias in 9/10 lots) HQC (15.000 pg/mL): 1.3 to 16.7 %bias (in 10/10 lots)		Table 9 to Table 12 of (b) (4) report no. (b) (4) 21861-01
Interference & specificity	• No quantitation greater LLOQ in any of the 10 unspiked plasma (heparin) lots from normal human subjects and 10 unspiekd plasma (heparin) lots from special population human subjects (healthy donors 50 years or older and not taking any immunosuppressant drugs)		Section 5.3.1 and 5.3.2 of (b) (4) report no. (b) (4) 21861-01

	• VEGF165 levels up to 100,000 pg/mL showed no interference in the assay	Table 13 and Table 14 of (b) (4) report no. (b) (4) 21861-01
Hemolysis effect	5 hemolyzed human plasma (heparin) lots (fortified with 5% whole blood) spiked with FYB201 or US Lucentis: FYB201: LQC (1,500 pg/mL): -1.3 to 4.7 %bias (in 5/5 lots) HQC (15.000 pg/mL): -28.7 to 16.0 %bias (7.3 to 16.0 %bias in 4/5 lots) US Lucentis: LQC (1,500 pg/mL): -14.7 to -0.7 %bias (in 5/5 lots) HQC (15.000 pg/mL): -4.7 to 30.7 %bias (-4.7 to 3.3 %bias in 4/5 lots)	Table 15 and Table 16 of (b) (4) report no. (b) (4) 21861-01
Lipemic effect	5 lipemic human plasma (heparin) lots (fortified with 5% whole blood) spiked with FYB201 or US Lucentis: FYB201: LQC (1,500 pg/mL): 9.3 to 18.0 %bias (in 5/5 lots) HQC (15.000 pg/mL): -4.0 to 12.7 %bias (in 5/5 lots) US Lucentis: LQC (1,500 pg/mL): 2.0 to 16.7 %bias (in 5/5 lots) HQC (15.000 pg/mL): -0.7 to 18.7 %bias (in 5/5 lots)	Table 17 and Table 18 of (b) (4) report no. (b) (4) 21861-01
Dilution linearity & hook effect	• Highest concentration tested: 50,000 pg/mL – No hook effect (prozone) observed • 3 Dilutions tested (1:5, 1:10, 1:25) • Range of observed % bias: FYB201: 5.6 - 13.6% Lucentis: -3.0 - 2.0%	Table 33 and Table 34 of (b) (4) report no. (b) (4) 21861-01
Bench-top/process stability	• 24 hours at ambient temperature under white light (FYB201 & Lucentis)	Table 25 and Table 26 of (b) (4) report no. (b) (4) 21861-01
Freeze-Thaw stability	• 6 freeze-thaw cycles from -80 °C to ambient temperature (FYB201 & Lucentis)	Table 23 and Table 24 of (b) (4) report no. (b) (4) 21861-01
Long-term storage	• FYB201: 120 days stored at -20 °C, 504 days stored at -80 °C • Lucentis: 77 days stored at -20 °C, 766 days stored at -80 °C	Table 19 to Table 22 of (b) (4) report no. (b) (4) 21861-01
Parallelism	• Not performed as study sample analysis was performed only with dilution 1.	
Carry over	Not applicable for LBA	

(Source: Adapted from Table 5 of Summary of biopharmaceutics and associated analytical methods)

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