23 June 2022
EMA/640346/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ranivisio

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/005019/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ranivisio
Applicant:	Midas Pharma GmbH Rheinstr. 49 55218 Ingelheim GERMANY
Active substance:	Ranibizumab
International Non-proprietary Name/Common Name:	Ranibizumab
Pharmaco-therapeutic group (ATC Code):	ocular vascular disorder agents, antineovascularisation agents (S01LA04)
Therapeutic indication(s):	*Ranivisio is indicated in adults for:* • *The treatment of neovascular (wet) age-related macular degeneration (AMD)* • *The treatment of visual impairment due to diabetic macular oedema (DME)* • *The treatment of proliferative diabetic retinopathy (PDR)* • *The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)* • *The treatment of visual impairment due to choroidal neovascularisation (CNV)*
Pharmaceutical form(s):	Solution for injection
Strength(s):	10 mg/ml

Route(s) of administration:	Intravitreal use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell mediated cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AKT	Protein kinase B
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
ATE	Arterial thromboembolic events
BCVA	Best corrected visual acuity
BMI	Body mass index
CD	Circular dichroism
CDC	Complement dependent cytotoxicity
CE-SDS	Sodium dodecyl sulfate capillary gel electrophoresis
CEX-HPLC	Cation exchange chromatography
CFT	Central foveal thickness
CI	Confidence interval
CNV	Choroidal neovascularisation
CPT	Centre point thickness
CRT	Central retinal thickness
CSR	Clinical Study Report
CTD	Common technical document
CZE	Capillary zone electrophoresis
DME	Diabetic macular oedema
DR	Diabetic retinopathy
DRSS	DR severity score
EEA	European Economic Area
EMA	European Medicines Agency
ERK	Extracellular signal-regulated kinase
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography

Fab	Fragment antigen binding
FAS	Full analysis set
FCP	Foveal centre point
FCS	Foveal central subfield
FDA	Food and Drug Administration
FTIR	Fourier-transform infrared spectroscopy
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HMW	High molecular weight
HUVEC	Human umbilical vein endothelial cell
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEF	Isoelectric focusing
Ig	Immunoglobulin
IgG	Immunoglobulin G
IOP	Intraocular pressure
ISI	Integrated Summary of Immunogenicity
IVT	Intravitreal
L	Liter
LC-MS	Liquid chromatography–mass spectrometry
LloQ	Lower limit of quantification
LMW	Low molecular weight
LOQ	Limit of quantitation
LS	Least squares
MAA	Marketing authorisation application
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed model repeated measurements
n	Number
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
ns	Not statistically significantly different

OCT	Optical coherence tomography
PD	Pharmacodynamics
PDR	Proliferative diabetic retinopathy
PDT	Photodynamic therapy
PK	Pharmacokinetics
PlGF	Placental growth factor
PM	Pathologic myopia
PPS	Per-protocol set
PRP	Panretinal photocoagulation
PT	Preferred term
Ref.	Reference
RP-HPLC	Reverse phase high-performance liquid chromatography
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SD-OCT	Spectral-domain optical coherence tomography
SDS-PAGE	sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SE-HPLC	Size exclusion-high performance liquid chromatography
SmPC	Summary of product characteristics
SOC	System organ class
SV-AUC	Sedimentation velocity analytical ultracentrifugation
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	Unites States
UV	Ultraviolet
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
vs.	Versus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Midas Pharma GmbH submitted on 25 June 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ranivisio, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Ranivisio is indicated in adults for:

- *The treatment of neovascular (wet) age-related macular degeneration (AMD)*
- *The treatment of visual impairment due to diabetic macular oedema (DME)*
- *The treatment of proliferative diabetic retinopathy (PDR)*
- *The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)*
- *The treatment of visual impairment due to choroidal neovascularisation (CNV)*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 10(4) of Directive 2001/83/EC – relating to applications for a biosimilar medicinal products.

The application submitted is composed of administrative information, complete quality data, appropriate non-clinical and clinical data for a similar biological medicinal product.

The chosen reference product is a Medicinal product which is authorised in accordance with Union provisions in force and to which biosimilarity has been demonstrated by appropriate studies:

- Product name, strength, pharmaceutical form: Lucentis 10 mg/ml solution for injection
- Marketing authorisation holder: Novartis Europharm Limited
- Date of authorisation: 22-01-2007
- Marketing authorisation granted by: Union

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
18 December 2014	EMA/CHMP/SAWP/772413/2014 Procedure No. EMEA/H/SA/2899/1/2014/SME/III	Dr Jens Reinhardt and Dr David Silverman
24 September 2015	EMA/CHMP/SAWP/593880/2015 Procedure No. EMEA/H/SA/2899/1/FU/1/2015/SME/II	Dr Ferran Torres and Dr Walter Janssens
15 December 2016	EMA/CHMP/SAWP/807108/2016 Procedure No. EMEA/H/SA/2899/1/FU/2/2016/III	Dr Jens Reinhardt and Prof Andrea Laslop

The Scientific advice pertained to the following aspects:

EMEA/H/SA/2899/1/2014/SME/III; The Scientific advice pertained to the following aspects - quality development, pre-clinical development and clinical development

Quality. The applicant request feedback on the sufficiency of: the proposed panel of physico-chemical methods and in-vitro assays, the number of Lucentis (EU and US) and FYB201 batches, the proposed statistical approach intended for the demonstration of similarity, the proposed panel of comparative *in vitro* studies investigating binding and biological activity, the approach to the evaluation of non-binding to other members of the VEGF family, tissue cross reactivity and epitope mapping.

Non-clinical. The applicant requested feedback on proposed comparative investigations in rabbits to evaluate pharmacokinetic properties of Lucentis® and FYB201, and approach to Anti-drug antibodies.

Clinical. The applicant requested feedback on the proposed approach to assessment of PK of Lucentis® and FYB201, use and definition of central retinal thickness as a primary endpoint in the pivotal study, definition of the most sensitive patient population, inclusion, exclusion criteria and design of the confirmatory comparative efficacy trial, the extrapolation to all other approved indications of Lucentis®, the use of Lucentis® sourced from US instead of EU reference product, he approach to assessment of safety and immunogenicity, and the choice of bioanalytical methods.

EMA/CHMP/SAWP/593880/2015; The Scientific advice pertained to the following aspects - clinical

Clinical
The applicant requested feedback on the acceptability of the proposed changes in the study design of the pivotal COLUMBUS-AMD STUDY (primary endpoint for the EU, duration of treatment and dosing, randomisation scheme, adjusted secondary study endpoints, revised inclusion / exclusion criteria, use of the modified ETDRS visual acuity charts), the measurement of systemic serum ranibizumab levels, the timing of Antidrug-antibody (ADA) testing.

EMA/CHMP/SAWP/807108/2016; The Scientific advice pertained to the following aspects - quality development, and clinical development

Quality
The applicant requested feedback on the proposed panel of methods for the side-by-side analysis, the proposed number and rationale for selection of FYB201 and Lucentis batches to be included into the side-by-side analysis.
Clinical
The applicant requested feedback on the PK assay validation, the timing of sampling for PK trough levels, the adequacy of ADA assay set-up, the proposed handling of emerging diseases in the non-study eye, and the proposed submission planning for EMA based on efficacy, safety, and immunogenicity data up to week 24 and timing of submission of one-year safety and immunogenicity data.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Ondřej Slanař

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Ulla Wändel Liminga

The application was received by the EMA on	25 June 2021
The procedure started on	15 July 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 November 2021
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	22 April 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ranivisio on	23 June 2022

2. Scientific discussion

2.1. About the product

Ranivisio was developed as a proposed similar biological medicinal product to Lucentis (International Non-proprietary Name [INN]: Ranibizumab; ATC code S01LA04) having ranibizumab as an active substance. Lucentis was initially registered via the Centralised Procedure in the European Union (EU) in 2007.

Ranibizumab, the active substance of Ranivisio, is a recombinant humanised monoclonal antibody fragment composed of a light chain linked by a disulfide bond at its C-terminus to the N-terminal segment of the heavy chain that binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, VEGF-A165. VEGF-A has been shown to cause neovascularisation and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to pathophysiology of neovascular (wet) age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DME), proliferative diabetic retinopathy (PDR), visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO), visual impairment due to choroidal neovascularisation (CNV), and retinopathy of prematurity (ROP). The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR-1 and VEGFR-2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation.

The claimed therapeutic indications for Ranivisio are:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

The recommended posology and method of administration correspond to those of Lucentis.

2.2. Quality aspects

2.2.1. Introduction

Ranivisio (company code FYB201) has been developed as a similar biological medicinal product (biosimilar) to the reference medicinal product Lucentis.

The finished product is presented as single-use type I glass vial as a solution for injection containing 10 mg/mL of ranibizumab as active substance. Other ingredients are: histidine, histidine hydrochloride monohydrate, α,α-trehalose dihydrate, polysorbate 20 and water for injections (WfI).

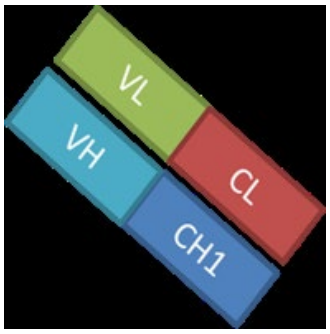
Each vial contains 2.3 mg of ranibizumab in 0.23 ml solution. This provides a usable amount to deliver a single dose of 0.05 ml containing 0.5 mg ranibizumab to adult patients.

2.2.2. Active Substance

2.2.2.1. General information

Ranibizumab (FYB201) is an immunoglobulin antigen binding fragment (Fab) binding to vascular endothelial growth factor (VEGF)–A, thereby inhibiting the binding of VEGF to its receptors on the surface of endothelial cells. FYB201 belongs to the group of anti-neovascularisation agents specifically developed for intraocular use and is administered via intravitreal injection. The Fab fragment is composed of one constant and one variable domain of each of the heavy and the light chain (see Figure 1).

Figure 1 Schematic structure of ranibizumab



Green VL: presents the variable region of the light chain; Light blue VH: presents the variable region of the heavy chain; Red (CL): presents the constant

The molecule is connected via one intermolecular disulphide bond, two intramolecular disulphide bonds in the light chain and two intramolecular disulphide bonds in the heavy chain. The 214-residue light-chain is linked at its C-terminus (C214) extremity to the 231-residue N-terminal segment of the heavy chain (C226). FYB201 has an approximate weight of 48 kDa and does not possess post-translational modifications. As a Fab fragment, FYB201 does not contain the Fc-region that is involved in antibody-mediated effector functions.

2.2.2.2. Manufacture, characterisation and process controls

Manufacturers

Manufacture is conducted at Polpharma Biologics S. A., Poland. A valid GMP compliance certificate has been submitted.

Description of manufacturing process and process controls

The FYB201 active substance manufacturing process has been adequately described. The number of WCB vials used to produce one discrete batch of active substance is presented in the dossier. A typical batch size of FYB201 active substance is adequately defined. One batch of active substance is filled into multiple bottles. The manufacturing process involves a cell culture process and a purification process. The active substance manufacturing process starts with thawing of a vial of the working cell bank which is an E. coli strain transfected with FYB201 expression vector. After thawing of the working cell bank (WCB) vial, the culture is serially expanded in cell mass and volume for inoculation into the production fermenter. The cell culture fluid

is subsequently purified through a series of chromatographic and filtration steps. The description of the manufacturing process steps includes flow charts, which comprised the manufacturing phase, critical parameters for the manufacturing process of FYB201 and the validated maximum hold times. The ranges of critical process parameters and the routine in-process controls along with acceptance criteria, including controls for microbial purity and endotoxin, are described for specified steps. There are no reprocessing steps during the manufacture of FYB201 active substance. The container closure system for FYB201 active substance consists of plastic bottles. Adequate specifications have been proposed for the container closure system. The active substance manufacturing process is considered acceptable.

Control of materials

The raw materials are listed for each step. For compendial materials, reference to the applicable pharmacopeia is made. For non-compendial materials, testing procedures are indicated. No materials of human/animal origin are used. All materials of biological origin are certified as BSE/TSE free. Material, pore size and release criteria are stated for filters and membranes in the dossier.

The composition of the cell culture media, solutions and buffers and solutions used in the upstream and downstream process was described appropriately. The source, history and generation of the cell substrate was described and is in compliance with ICH Q5B and ICH Q5D guidelines. Specifications regarding viability, strain identity, genetic stability and purity were set, and all acceptance criteria were met. The specification for the viability of the master cell bank (MCB) and working cell bank (WCB) is appropriate. The contamination control includes checking for atypical colonies, adventitious spore formers, phage infection and microscopic imaging. The analytical methods applied for cell bank characterisation and testing were described and are adequate.

The concept of the cell banking system is a two-tiered cell bank with a MCB and WCBs. The vials are stored at separate storage sites. Future WCBs will be prepared and released according to the specifications as stated in the dossier.

The stability protocol for the MCB testing is considered appropriate.

Control of critical steps and intermediates

All in-process controls (IPCs) and tests of the active substance manufacturing process are provided. They are listed in a tabulated format including their classification for criticality and the associated action limits or acceptance criteria. Information about intermediate hold times and conditions are provided. Definition of process parameter and their classification into critical and non-critical process parameters is also provided. Similarly, IPCs are categorised into critical and non-critical controls. Either acceptance criteria, action limits or alert limits are proposed for the IPCs. Strategies in case of violation of the criteria are described. In case of violation of an acceptance criterion, an investigation will be performed to evaluate the root cause and the impact on product quality and the batch will be rejected if the violation of the acceptance criterion is confirmed.

Overall, the parameters controlled during manufacture of the FYB201 active substance appear appropriate.

Process validation and/or evaluation

Process validation has been carried out on three commercial scale batches and was supported by studies at a different scale at a different manufacturing site as well as laboratory scale studies using qualified scale down

models, where applicable, and risk assessments. PPQ studies were conducted on consecutive active substance batches for verification of the process controls. Pre-defined acceptance criteria for in-process controls were met with a few exceptions. Those deviations have been adequately justified. All critical and key process parameters were kept within the pre-defined acceptable ranges during production of the PV batches with few exceptions which are considered minor, in particular because the proposed limits are considered sufficiently tight to control the process. The process consistency validation studies demonstrate that the commercial manufacturing process produces an active substance of consistent quality.

A process- and product-related impurity clearance study for the FYB201 active substance downstream manufacturing process was performed at manufacturing scale during process consistency validation by testing the content of process- and product-related impurities on all relevant process steps/intermediates and/or at active substance level for the defined validation batches.

A risk assessment of raw materials, primary packaging materials and the equipment, facilities and utilities used during manufacturing process revealed that the level of all metals listed in ICH Q3D guideline are below required limits in FYB201 active substance. No further studies are warranted.

Furthermore, a risk assessment for potential nitrosamine impurities in FYB201 active substance was performed and no potential entry of nitrosamine impurities was identified. The risk assessment is considered sufficient and there is no concern remaining.

The maximum number of resin cycles defined for each chromatography column were determined. The protocol for column performance and integrity verification at commercial scale was also provided.

Five hold points were identified in the FYB201 active substance manufacturing process. An overview of results of the stability for the defined hold points was provided.

A brief summary of a shipping qualification of the active substance was submitted. Shipping container with the product can maintain product temperature while maintaining product integrity during the transportation.

Manufacturing process development

The manufacturing process of FYB201 active substance was developed and the process controls were established to meet the quality criteria required for a biosimilar product and to define the commercial manufacturing process. Process characterisation studies were performed to systematically assess the impact of the process on critical quality attributes (CQAs), to define parameter criticality and determine acceptable ranges. Quality attributes for FYB201 were identified based on the published information on ranibizumab, well-established knowledge on antibodies and fusion proteins, and in house *in vitro* data evaluating structure-function relationships. Regarding the identification of CQAs each quality attribute of ranibizumab was evaluated for criticality using a predefined risk ranking and filtering approach. Criticality ranking is determined by two factors: impact and uncertainty. The ranking is performed based on the criticality of investigated biological function with respect to the mechanism of action (MoA), pharmacokinetics (PK), and safety. Overall, the identification and classification of QAs is sufficient and adequate.

Process parameter criticality and acceptable ranges were determined based on the process development data generated at the clinical manufacturing site including a comprehensive process characterisation (PC) exercise and successful process validation. Prior to the initial process characterisation, a process risk assessment (RA) based on FMEA methodology was used to assess the process- and product-related risks of the FYB201 active substance manufacturing process. Based on the outcome, selected process parameters were further investigated during experimental process characterisation studies. The selected parameters were designated as potential critical process parameters (pCPPs). Within the PC studies, the identified process parameters

were evaluated as input parameters with respect to their impact on performance and quality attributes (outputs). Based on their impact on the performance and quality attributes within the characterised range the input parameters were classified into critical, key and non-key process parameters (CPPs, KPPs and NKPPs) and their acceptable ranges were defined.

After manufacturing site transfer and scale-up additional PC studies were conducted to broaden the process knowledge. After completion of PC and PV activities, the gained process understanding was re-assessed in post-PC/PV process RAs. All process parameters and their criticality and acceptable ranges were re-assessed as part of this exercise resulting in the overall process control strategy for process parameters. The final classification of process parameters, e.g. CPPs, and the defined acceptable ranges which are often tighter than the characterised ranges, are considered appropriate. Overall, the ranges defined for the commercial manufacturing process seem justified. Processing times and proposed hold times were adequately validated.

Analytical comparability exercise of the commercial and clinical scales has been presented and the processes seem comparable.

Characterisation

Elucidation of structure and other characteristics

For characterisation, mainly selected finished product batches as well as the primary reference standard were analysed with regard to primary and higher order structure, post-translational modifications, variants and biological function. The selection of finished product batches instead of active substance batches is acceptable, as there are only minor modifications and active substance and finished product are considered comparable. The comparison to the originator Lucentis is described in the section "biosimilarity". The same panel of methods was also used for the biosimilarity exercise.

A range of state-of-the-art orthogonal methods were used including physicochemical and biological testing in accordance with ICH Q6B guideline. Except liquid chromatography with tandem mass spectrometry (LC-MS/MS) & Edman degradation, the methods were qualified or validated. The included finished product batches were either used in the confirmatory clinical study or are representative for the commercial process.

The combination of LC-MS/MS peptide mapping and Edman sequencing revealed 100 % identity of the amino acid sequence compared to the Lucentis amino acid sequence. The molecular masses of the analysed samples correspond to the expected theoretical value. The secondary structure was determined with Fourier-transform infrared (FTIR) spectroscopy and far ultraviolet (UV) circular dichroism (CD) spectroscopy and the tertiary structure with near UV CD spectroscopy. The overlay of the spectra shows similarity between the three analysed samples. Disulfide linkage confirmed five bridges peptides as expected.

Size variants were identified using Size Exclusion-High Performance Liquid Chromatography (SE-HPLC), sedimentation velocity analytical ultracentrifugation (SV-AUC), capillary electrophoresis sodium dodecyl sulfate (CE-SDS) (reduced and non-reduced) and sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE). In summary, the amount of size variants was very low, indicating a high purity of the samples.

Charge variants were determined with the methods CEX-HPLC, capillary zone electrophoresis (CZE) and isoelectric focusing (IEF).

Deamidation, oxidation, acetylation, methylation, glycation, pyroglutamate formation and norleucine levels were analysed as post-translational modifications. The deamidation level at one deamidation site was higher in one batch compared to the others, nevertheless, in general, the levels of post-translational modifications were low. Incorporation of norleucine at methionine positions is a translational modification for recombinant

proteins produced in *E. coli*. There are two methionine positions in ranibizumab as possible norleucine incorporation sites: Met 34 and Met 83, the former being located in the complementarity-determining region (CDR). It is noted that norleucine incorporation is relevant (being 0.5% or higher) and that the norleucine content was the highest in the batch representative for commercial production. The applicant has conducted a root cause analysis for parameters that promote this misincorporation. The slightly enhanced norleucine levels are not expected to pose a safety risk. The presence of norvaline as possible mis-incorporation was also analysed and no concerns were identified.

The biological intensity was analysed using Bio-layer interferometry (BLI). The primary mechanism of action of ranibizumab is binding to VEGF-A and subsequently, inhibiting the VEGFR2 pathway. Binding of FYB201 to VEGF-A isoforms VEGF-A165, VEGF-A121, VEGF-A111 and VEGF-A189 were analysed. The main isoform is VEGF-A165 (ca 44 %) and VEGF-A121 (ca 38%) and they are mainly expressed in the eye. The isoforms VEGF-A111 and VEGF-A189 (ca 18%) are less relevant. Ranibizumab binds to the VEGF receptor binding domain which consist of the same amino acid residues in all VEGF-A isoforms. It was demonstrated that FYB201 binds to all isoforms in a comparable manner.

Finally, the effect of FYB201 to downstream signalling was analysed. *In vitro* inhibition of VEGF-A induced cell proliferation of human umbilical vein endothelial cells (HUVECs) was analysed. The potencies are reported relative to the reference standards. Further, downstream signalling in HUVECs was investigated by Western Blot analysis, indicating that FYB201 suppressed the phosphorylation of VEGFR-2, Akt and ERK1/2. FYB201 further inhibited VEGF-A165 induced expression of tissue factor in HUVECs (qRT-PCR), inhibited VEGF-A165 induced HUVEC migration and did not bind to VEGF-B, VEGF-C, VEGF-D and P1GF-2.

In summary, the characterisation of FYB201 is considered sufficient.

Impurities

Product- and process related impurities were investigated and their impact on bioactivity was discussed. Size variants (high molecular weight (HMW); low molecular weight (LMW); LC-LC homodimers), charge variants (basic and acidic species) and post-translational modifications (deamidation, oxidation, glycation, norleucine, pyroglutamate, methylation and acetylation) were identified as possible impurities. Several batches were included in the analyses from the clinical and the commercial manufacturing site.

Levels of HMW and LMW were generally very low, and successful depletion of LC-LC homodimers during the downstream process was demonstrated.

Charge variants are analysed by CEX-HPLC at release and stability. Amounts of basic and acidic variants in general are low but increase at accelerated and stressed conditions. An in-depth analysis of charge variants was provided. Herein, samples of one batch of FYB201 and one batch of Lucentis US were stressed at 40 °C to induce charge variants which were further isolated and characterised by liquid chromatography–mass spectrometry (LC–MS) peptide mapping reduced, SE-HPLC, CE-SDS non-reduced, and HUVEC proliferation assay. Please refer to the biosimilarity section for assessment.

As possible process-related impurities, antifoam, protein L, polysorbate 20, HCP, DNA, bioburden, endotoxin, extractables and leachables, elemental impurities and nitrosamines have been identified and a comprehensive risk assessment of each factor has been provided.

In summary, control and clearance strategy of process related impurities is acceptable.

2.2.2.3. Specification

The active substance release and shelf life specification includes tests for identity, content/activity, purity, impurities and microbial purity and general tests e.g. for pH, osmolality.

The proposed specifications are acceptable and in accordance with ICH Q6B guideline and monograph 2031. Quality attributes with regard to appearance (clarity, colour), general attributes (pH, osmolality, polysorbate 20 content), identity (RP-HPLC peptide map non-reduced, CE-SDS non-reduced), content (UV280 nm), biological activity (iLite assay), purity (CEX-HPLC, SE-HPLC, CE-SDS non-reduced), impurities (residual DNA, HCP) and microbial purity (TAMC, TYMC, endotoxins) will be analysed.

For shelf life, less attributes are monitored but the acceptance criteria remain the same. The SOP numbers are added in the AS specifications table to establish the clear link between specifications, methods and method validations.

Analytical procedures

The descriptions for the in-house analytical methods are sufficiently detailed and acceptable. For the release and stability, there was a change in the analytical method for biological activity: the HUVEC proliferation assay was replaced by the iLite assay. The acceptance criteria remain the same except the unit. The iLite assay was not implemented for the batches analysed in the characterisation or at the biosimilarity exercise and therefore, a bridging study was conducted. This is acceptable. The bridging study between HUVEC proliferation assay and iLite assay was provided in which no significant differences between the results were noted, also including samples that were stressed or analysed with regard to stability. The applicant has provided a side-by-side comparision of Lucentis US and Lucentis EU with FYB201 using the iLite assay to further support bridging between the two assays. The information provided is sufficient. The analytical procedures have been sufficiently validated. The validation is in line with the guideline ICH Q2(R1).

Batch analyses

Batch data for the batches manufactured at the clinical manufacturing scale (21 batches) and the commercial scale (10 batches) are provided. In general, data have low variation, indicating a robust and well-controlled manufacture.

A specification history is presented. All changes are mentioned and justified. The information provided is sufficient.

Reference standards of materials

Different reference standards are established on the basis of the development stage. The results for each reference standards are given. A protocol for qualification of primary and secondary reference standards and their requalification is provided. The requalification of the primary standard is performed yearly for 5 years, afterwards every second year. The requalification of the secondary standard is performed yearly. This is acceptable. Storage conditions have been adequately described.

Container closure system

FYB201 active substance is stored in a sterile polyethylene terephthalate glycol modified copolyester bottle with white high-density polyethylene screw closure and in line with USP and Ph. Eur. Drawings of the bottle are provided in the dossier. The suitability of the material was investigated in the extractables and leachables study. The information about the container closure system is considered sufficient.

2.2.2.4. Stability

So far, 13 batches (1 engineering, 5 GMP and 7 PPQ batches) were set on stability: three batches at clinical scale, for which up to 60 months of data for long-term storage condition are available, supported by 24 months data of storage at 5 °C and 6 months data of storage at 25 °C. For the additional four batches manufactured at clinical scale, real time data of 18 - 24 months storage at -65 °C are available, supported by 6 months data of storage at 5 °C and 3 months data at 25 °C. For batches manufactured at commercial scale, 6 months real time data are available now for storage at -65 °C and 5 °C with additional 3 months data for storage at 25 °C.

In general, stability testing is in accordance with ICH Q5C. Stability data of sufficient batches are presented and are representative of the manufacturing scale of production. The quality of the batches is representative of the quality of the material used for the clinical studies.

Methods of stability analyses are validated, and the same analytical procedures are used for batch release. A stability protocol is provided. The protocol includes specifications and test intervals throughout the proposed period. The stability protocol covers analytical methods with regard to appearance (Clarity of solution, color of solution, pH), identity (CE-SDS non-reduced), Content (UV 280 nm), purity (SE-HPLC, CEX HPLC), biological activity (HUVEC proliferation assay that will be replaced with iLite assay) and in the most recent batches also sterility (bioburden). The tested parameters are considered appropriate to monitor the stability of the samples. The most sensitive parameter in the accelerated and stressed conditions is CEX-HPLC. However, it is noted that the decrease in main peak and increase in charge variants is less distinctive in the initial batches (Batches 6, 8 and 9). A clear correlation to biological activity could not be detected. The requested shelf life of 60 months is acceptable since at the long-term storage temperature of -65 °C no significant changes and trends are observed.

One batch of FYB201 AS will be placed on stability each year. A schedule is provided for the post-approval stability studies. The applicants commit to continue these studies through the proposed shelf life. Any out-of-specification (OOS) results within the claimed shelf-life at the intended storage temperature will be notified to the competent authority and appropriate corrective actions will be proposed.

2.2.3. Finished Medicinal Product

2.2.3.1. Description of the product and pharmaceutical development

The FYB201 finished product has the same dosage form, route of administration, dosing regimen and concentration as the originator Lucentis. FYB201 is a sterile solution for injection with 10 mg/mL ranibizumab for intravitreal injection presented in single-dose glass vials. The excipients and the stopper are the same as used by the reference product Lucentis. The formulation of FYB201 finished product (FP) contains 10 mg/mL ranibizumab as active substance with α,α-trehalose dihydrate, histidine buffer, and polysorbate 20 at a target pH of 5.5. All excipients comply with compendial monographs.

Analysis of Lucentis composition revealed that FYB201 finished product has the same qualitative and quantitative buffer composition. After analysis of the quality characteristics of the originator Lucentis, a formulation robustness study was conducted. Different formulation variants were tested and no substantial differences between the different formulations were noted except a slight effect on stability after pH variations. The required deliverable volume of 0.05 mL per injection has been verified in an overfill study. No overage of active substance is used for production for FYB201.

Manufacturing process development

For FYB201 finished product manufacture, the frozen FYB201 AS is thawed, diluted to the desired concentration, filtered and filled into the vials.

FYB201 has been manufactured at two sites so far. After process development and two engineering batches six GMP batches were produced for use in the clinical confirmatory study. Afterwards, for commercial production the process was transferred to commercial manufacturing site. Changes in the manufacturing processes are adequately described and rationale and risk assessment of the differences is provided. In summary, differences between the manufacturing processes were restricted to larger scale production.

Analytical comparability assessment between clinical and commercial batches included comparison of IPC results, additional characterisation programme, release, stability profiles and forced degradation results. Some differences were identified in the additional characterisation analyses. All differences were adequately justified by the applicant.

The comparative stability study revealed differences between batches manufactured at clinical and commercial manufacturing site, the latter showing a higher degradation at accelerated and stressed conditions at CEX-HPLC and SE-HPLC. The applicant has discussed this finding with reference to method variability and presented potential causes of the proposed higher variability of CEX-HPLC method (e.g., different lots of columns, different instruments, different sets of solutions, different analysts). Further, an investigation is ongoing for the evaluation of potential method improvements. The applicant should provide the investigation report where the potential causes and evaluation of the potential improvements is detailed. (Recommendation).

Overall, the comparability, also with respect to data provided for biosimilarity, is confirmed.

A growth promotion study was performed to establish adequate hold times.

The suitability of the mixing parameters was shown in an experimental setting. The suitability of process materials with finished product contact was demonstrated.

The choice of materials for primary packaging is justified. Since different stoppers were used at the clinical and commercial manufacturing site, a compatibility study was conducted at elevated temperatures (please refer also to section P.7). The applicant claims that available results of extractable studies after 35 days at 42°C simulate a storage of 12 months at 5 ± 3°C. The calculations involved to establish this extrapolation were provided with additional details. The applicant commits to perform an additional leachable screening at the end of the shelf-life (36 months at 5 ± 3°C) which is found acceptable and sufficient to support the final conclusion on leachable characterisation. Results should be provided by November 2023. (Recommendation)

Results of in-use compatibility study performed with devices used in the clinical trial were provided and show no negative impact on quality of finished product after 24 hours at room temperature in the syringe.

2.2.3.2. Manufacture of the product and process controls

Description of manufacturing process and process controls

GMP compliance was confirmed for the finished product manufacturer.
A diagram of the manufacturing process of FYB201 finished product has been provided. The materials entering the process are indicated. In process controls are defined. The FYB201 finished product manufacturing process is a standard manufacturing process (fill and finish) for monoclonal antibodies. The

process consists of 1) Thawing of the active substance, 2) Preparation of polysorbate 20 and excipient solution, 3) Compounding of the FYB201 finished product solution, 4) prefiltration, 5) sterile filtration, 6) aseptic filling and stoppering of the vials and 7) visual inspection.

The preparation of the glass vials and stoppers is described. The glass vials are washed and sterilised/depyrogenated in a dry heat oven. Stoppers and crimp caps are steam sterilised, all procedures are according to written standard procedures. According to the description the filled vials are closed with stoppers and sealed via crimping. The area where each step takes place are described. All vials are 100 % visually inspected by qualified personnel and defect vials are rejected.

Description of secondary packaging and transport is included in the dossier. The transport validation is currently ongoing and should be provided once available. (Recommendation).

Critical process parameters and in process controls have been identified and seem appropriate to control the process.

Suitability of endotoxin testing of the excipients was demonstrated with a spiking study. Also, bioburden testing suitability was analysed. The information provided is sufficient.

Process validation and/or evaluation

Process validation has been performed at the commercial production facility. The manufacturing process has been validated on three consecutive process performance qualification (PPQ) batches with predefined acceptance criteria. All PPQ batches met the acceptance criteria. Holding times are supported by real time data.

Sterile filter validation included a bacterial retention study. Media fill runs were run, to qualify this site for aseptic filling of FYB201 finished product.

2.2.3.3. Product specification

The specification for FYB201 finished product include tests for appearance (Clarity, colour), general attributes (pH, osmolality, filling volumes), identity (RP-HPLC peptide map non-reduced, CE-SDS non-reduced), content (UV 280nm), potency (iLite assay), purity and impurities (particles, CEX-HPLC, SE-HPLC, CE-SDS non-reduced) and microbial purity (sterility, endotoxins, container closure integrity).

For compendial methods, reference is made to the respective PH. Eur. Monographs. For the internal methods, a reference to the respective in-house SOP or an alternative solution for analytical method unique identifier was added into the active substance specification.

As FYB201 finished product formulation is almost identical to FYB201 active substance, most parameters and acceptance criteria are identical between AS and FP. Acceptance criteria for CEX-HPLC and SE-HPLC and CE-SDS non-reduced are wider than for the AS based on batch data. The container closure integrity is not tested at release since the first batches manufactured at the commercial manufacturing site passed CCI testing, indicating that the machine settings at the filling line are properly defined and lead to an integer container closure system. Sterility is confirmed at release. This is acceptable.

Justification of specifications

Justification for the proposed specifications is provided. Shelf-life specifications on finished product level were established by considering the observed change during storage at the intended condition.

For CEX-HPLC the applicant the applicant commits to re-evaluate the acceptance criteria after the production of 30 finished product batches and this will also be included as a part of the comparability study during the planned scale-up of the finished product manufacturing process (Recommendation).

In addition, a summary of control strategy was provided. The endotoxin control strategy is described in detail and considered adequate.

Process related impurities of the active substance which could be carried over into the finished product is monitored on the AS level. It is agreed that these impurities are not expected to increase during storage or manufacture of finished product.

An extractable and leachable evaluation was performed. The maximal identified amount is low with regard to the permitted daily exposure (PDE). Used PDE limits were justified. Product-related substances and impurities are discussed in the active substance section.

A thorough risk assessment with regard to the potential presence of elemental impurities has been provided according to ICH Q3D. All excipients are compliant to EP and/or USP. Based on the supplier information each assessed elemental impurity (As, Co, Ni and Pt) was below 0.2% of the respective PDE. For the process equipment potential sources were identified and tested in the extractable study. Analytical results revealed that the induction of elemental impurities is low and posed no risk to the finished product. This is acceptable.

The assessment for nitrosamine impurities was initially missing and this point was raised as a Major Objection. The applicant provided an assessment for the presence of nitrosamines which was performed on a theoretical basis which is acceptable. No risk was identified. Also, for residual solvents a risk assessment was provided on a mainly theoretical basis.

In summary, the characterisation and evaluation with regard to a potential risk appears sufficient and appropriate.

Analytical procedures

The analytical methods have been sufficiently described. Reference is made to the active substance section for the validation. Compendial methods have been adequately described. The validations for analytical procedures not performed at active substance level (filing, container closure integrity, appearance) are provided and are considered as adequate.

Batch analyses

Batch data are presented including three finished product PPQ batches manufactured according to the intended commercial manufacturing process. Also, data from 8 batches manufactured at the former clinical manufacturing site are presented. All specifications were met and in general, no significant changes between the batches were noted, indicating that the manufacturing process is adequate to produce FYB201 finished product of consistent quality.

Reference Standards or Materials

The same reference standard as for the active substance is used. No other product-specific reference standards are used in the testing of the finished product. Reference is made to the active substance section.

Container Closure System

The container closure system for FYB201 finished product consists of a 2R glas vial and a chlorobutyl serum stopper. Both materials are compliant with Eur. Ph. and USP. An exemplary CoA of glass and stopper have

been provided. The aluminium seal with plastic flip off cap attached has no direct product contact. Drawings of the vial and stopper as well as an exemplary certificate of analysis has been provided. Specifications and routine testing are described. The sterilisation process for vial, stopper and crimp cap is sufficiently described. The chosen container closure system is considered appropriate.

2.2.3.4. Stability of the product

A shelf life of 3 years when stored at 2°C – 8°C is claimed for the finished product.

Stability studies were conducted in accordance with relevant guidelines. To date 36 months stability data at the intended storage temperature (2-8°C) is available from three 10 mg/mL finished product batches manufactured at the clinical manufacturing site. Furthermore, 12 months data is available from the three - process performance qualification finished product batches manufactured at the commercial manufacturing site.

Stability data at 2-8°C is supplemented by accelerated and stress condition stability data (25°C ± 2°C /60% RH ± 5% RH and 3 months at 40°C ± 2°C /75% RH ± 5% RH). Further, impact of shake stress, photo stress and freeze/thaw cycles were evaluated.

Additional studies included analysis of the impact of shaking and photo stress and freeze/thaw cycles. No impact was noted for shaking stress and freeze/thaw cycles, whereas photo stress had an impact on product quality. The vial should be kept in the outer carton in order to protect from light.

Based on the stability results the claimed shelf life of 3 years at the storage condition of 2°C – 8°C for the finished product is acceptable.

The post-approval stability protocol and stability commitment was provided. One batch of FYB201 finished product will be place on stability each year. This is acceptable.

Biosimilarity

For the analytical similarity assessment, the quality attributes of FYB201 and the reference product Lucentis were analysed. The analysis was conducted with Lucentis sourced from EU (Lucentis EU) and compared to Lucentis sourced from US (Lucentis US). Further, FYB201 finished product was first tested in an animal study and compared with EU-approved Lucentis and US-licensed Lucentis. Comparability of FYB201 to Lucentis was finally analysed in the confirmatory clinical study (Columbus-AMD) using Lucentis US. Lucentis US is approved for two presentations: 6 mg/mL and 10 mg/mL, whereas in Europe only the 10 mg/mL presentation is approved. With regard to global development, the applicant also included the 6 mg/mL formulation as supportive information provided that comparability between the two concentrations was demonstrated.

The above-described strategies for biosimilarity assessment were discussed with the EMA prior the submission of the Marketing Authorisation and are considered acceptable. The biosimilarity exercise included extended characterisation, forced degradation studies and stability studies.

For data evaluation, batches of FYB201 were compared to the quality ranges of Lucentis EU batches.

Methods that are/were used for release are fully validated. Most assays were qualified except amino acid sequence analysis and assays for evaluation of non-target related binding.

FYB201 GMP finished product batches as well as one representative finished product engineering batch are included. At least 10 batches were included for attributes that were assigned the criticality "very high", "high" or "moderate" for quantitative methods- For the originator, 18 batches from EU sourced Lucentis were available, supported by thirteen 10 mg/mL batches and six 6 mg/mL batches of Lucentis US.

First, similarity of primary structure (amino acid sequence) was verified with a combination of LC-MS/MS peptide mapping and Edman sequencing in which 100 % amino acid coverage could be assured. Also, very low variation of masses and an accordance in mass spectra was demonstrated, indicating that FYB201 and Lucentis have an identical primary structure.

Overlays of FTIR spectroscopy, far- and near-UV CD spectroscopy, and chromatograms of RP-HPLC peptide mapping as indicator for disulfide linkage did no raise concerns with regard to biosimilarity of FYB201 to Lucentis EU and comparability of Lucentis EU and Lucentis US. Also, the thermodynamic stability was similar between FYB201 and Lucentis, albeit one batch of Lucentis EU was slightly out of range. In summary, similarity of FYB201 to Lucentis EU with regard to primary and higher order structure was sufficiently demonstrated. Also, it can be concluded that Lucentis EU is comparable to Lucentis US.

For assessment of size variants, Lucentis and FYB201 were analysed by SE-HPLC, Sedimentation velocity analytical ultracentrifugation (SV-AUC), CE-SDS reduced and non-reduced and SDS-PAGE non-reduced.

Using SE-HPLC for determination of size variants, it can be generally concluded that the main peak value is high and the HMW is low. One outlier from the EU Lucentis range was noticed for one Lucentis EU batch and one Lucentis US batch. Given the high purity, this is acceptable. Of note, the distribution of the size variants was very narrow in FYB201 batches and in sum, the biosimilar has a slightly higher purity than the originator. SV-AUC was used as orthogonal method to SE-HPLC and confirmed the low amounts of HMW species as well as similarity to Lucentis. Analysis by CE-SDS non-reduced revealed that FYB201 is similar with even slightly less impurities compared to Lucentis EU and Lucentis US with regard to both main peak and LMW species. However, this is most likely due to the fact that the FYB201 batches were mainly fresh batches whereas the sourced Lucentis batches are closer to the expiry date. In accordance, slightly more LMW species in Lucentis batches were also visible in the gel using SDS-PAGE, but in sum the band pattern was comparable. Similarity was also demonstrated for LMW species with CE-SDS reduced.

Analysis for charge variants was performed with the methods CEX-HPLC, Capillary zone electrophoresis and isoelectric focussing. FYB201 batches showed a higher purity than Lucentis batches in CEX-HPLC, and in accordance, three batches were out of range at main peak and one batch at basic peak. This is in general acceptable as it might be an advantage regarding safety, however, most likely the higher purity of the batches is a result of the batch age. FYB201 had in mean an age of 1,7 months, Lucentis EU 19 months and Lucentis US 20 months. At the orthogonal method CZE the age at analysis was in mean 11.5 months for FYB201 batches, 20.2 months for Lucentis EU batches and 25.8 months for Lucentis US batches. All batches were within the predefined range; however, FYB201 batches tend to show higher levels of acidic variants in comparison to Lucentis batches. No difference was noted between FYB201, Lucentis US and Lucentis EU at isoelectric focussing. Conclusively, the outcome from the orthogonal methods was different regarding the distribution of charged variants. A discussion was provided regarding the different results between the two methods.

An in-depth analysis of charge variants was provided in the section S.3.2 Impurities. Herein, samples of FYB201 and Lucentis US were stressed at 40 °C to induce charge variants which were further isolated and characterised by LC-MS peptide mapping reduced, SE-HPLC, CE-SDS non-reduced, and HUVEC proliferation assay. No significant differences with regard to post-translational modifications were identified between

biosimilar and originator. Also, percentages of HMW species and monomer in CEX fractions were comparable. With regard to biological activity, it was clearly demonstrated that both acidic and basic variants significantly decrease the potency.

For amino acid modifications no significant differences to Lucentis were observed except the content of Norleucin, which is discussed in section 3.2.S.3.2. The representative LC-UV-chromatogram profiles for FYB-201 finished product, Lucentis-EU and Lucentis-US were provided and were found be to highly similar. Also, no significant differences were noted with regard to protein content.

Overall, although some differences in profile of charged variants tested by CZE and CEX-HPLC were observed, this has been satisfactorily justified by the applicant and is not considered to have an impact on the conclusion regarding the analytical similarity between FYB201 and EU/US Lucentis.

For functional characterisation, binding of FYB201 to the VEGF-A isoforms VEGF-A165, VEGF-A121, VEGF-A111 and VEGF-A189 was analysed using Bio-Layer Interferometry. For VEGF-A121 and VEGF-A111, one batch of FYB201 was outside the range with KD (VEGF-A121) or KD, Koff and Kon. Also, some batches of Lucentis US were not within the range. Thus, with regard to binding to VEGF-121 and VEGF-A111, differences of FYB201 and Lucentis US compared to Lucentis EU were noted. While similarity with respect to VEGF-A121 of FYB201 and Lucentis US to Lucentis EU could be demonstrated with additional evaluation of two Lucentis EU batches, differences in binding affinity from FYB201 and Lucentis US still remain. The applicant has provided a discussion about the clinical relevance of the isoform VEGF-A111 in particular considering that in clinical trials Lucentis US was used as comparator and it is agreed that the differences observed in Bio-Layer Interferometry are not expected to have an impact in the clinic. Other functional characterisation (inhibition of VEGF-A165-induced cell signalling, inhibition of VEGF-A165 induced expression of tissue factor mRNA, inhibition of VEGF-A165-induced HUVEC migration activity, inhibition of VEGF-A165, VEGF-A121 and VEGF-A111 induced cell proliferation activity, non-binding to VEGF-B, VEGF-C, VEGF-D and P1GF-2) did not raise concern with regard to biosimilarity of FYB201 to Lucentis EU and comparability of Lucentis EU and Lucentis US.

Forced degradation studies were conducted and samples were stressed by high temperature, mechanically, light, oxidation and pH. At high temperature,and at mechanical stress minor differences were observed for some quality attributes. However, since all other parameters did not change significantly, this slight deviation might be acceptable. Light stress, oxidation stress and pH stress (acidic and basic) in general had an effect on the quality in all batches in a comparable way.

A stability study was conducted. In general, stability of the product was comparable between Lucentis and FYB201. Slight differences were noted for the main peak and HMW species detected with SE-HPLC and protein content, however, the changes were within a small range. Potency was determined with the HUVEC proliferation assay. Herein, differences were observed between FYB201 and Lucentis at 25°C, but not at 40°C.

In summary, a large panel of standard and state-of-the-art methods were used to compare FYB201 to its originator Lucentis. It is concluded that some differences with regard to binding to VEGF isoform VEGF-A111 was observed. However, these differences could be sufficiently justified and do not preclude biosimilarity per se.

Overall, the data claim that Ranivisio is similar in structure, physicochemical and most biological attributes as well as for stability to Lucentis. Further, it could be agreed that Lucentis US can be considered representative of Lucentis EU.

The outcome of the physicochemical and biological comparability exercise between Ranivisio and Lucentis is summarised in the tables below:

Table 1. Summary of the characterisation results between Ranivisio and Lucentis

Quality attribute	Methods	Key findings
Structural characterisation		
Amino acid sequence	MS/MS sequencing; Edman degradation	Identical
Molecular mass	LC-MS intact mass	Similar
Secondary structure	FTIR spectrometry	Similar
Secondary structure	Far-UV CD spectroscopy	Similar
Tertiary structure	Near-UV CD spectroscopy	Similar
Disulfide linkage	RP-HPLC peptide mapping non-reduced	Similar
Thermodynamic stability	Far-UV CD spectroscopy	Similar
Product-related substance and impurities		
Main peak purity (size variants)	SE-HPLC	Similar
	SV-AUC	Similar
	CE-SDS non-reduced	Similar
	SDS-PAGE non-reduced	Similar
HMW species	SE-HPLC	Similar
	SV-AUC	Similar
LMW species	CE-SDS non-reduced	Similar
	CE-SDS reduced	Similar
Acidic species	CEX-HPLC	Similar
	CZE	Similar
Basic species	CEX-HPLC	Similar
	CZE	Similar
Main peak purity (charge variants)	CEX-HPLC	8 of 11 FYB201 batches within range (73 %), 3 of 11 FYB201 batches (27 %) showed higher level of main peak purity.
	CZE	Similar
Isoelectric point	IEF	Similar
Deamidation	LC-MS pepmap reduced	Similar
Oxidation		Similar
Pyroglutamate HC Glu1		9 of 11 FYB201 batches within range (82 %), 2 of 11 (18 %) showed lower level of this modification.

Quality attribute	Methods	Key findings
Norleucine H		FYB201 showed consistently higher modification level for all batches, but without impact on biological activity or safety.
Glycation	LC-MS intact mass reduced	Similar
General properties		
Total protein content	UV280	Similar
VEGF-A165 binding K_D	BLI	Similar
VEGF-A165 binding k_{on}		Similar
VEGF-A165 binding k_{off}		Similar
VEGF-A121 binding K_D	BLI	Similar
VEGF-A121 binding k_{on}		Similar
VEGF-A121 binding k_{off}		Similar
VEGF-A111 binding K_D	BLI	7 of 11 FYB201 batches within range (64 %), 4 of 11 FYB201 batches (36 %) slightly outside range.
VEGF-A111 binding k_{on}		Similar
VEGF-A111 binding k_{off}		7 of 11 FYB201 batches within range (64 %), 4 of 11 FYB201 batches (36 %) slightly outside range.
VEGF-A189 binding K_D	BLI	Similar
VEGF-A189 binding k_{on}		Similar
VEGF-A189 binding k_{off}		Similar
Inhibition of cell signaling	Western Blot	Similar
Inhibition of tissue factor expression	qRT-PCR	Similar
Inhibition of HUVEC migration	Modified Boyden Chamber assay	Similar
Bioactivity	HUVEC proliferation assay VEGF-A165	Similar
Bioactivity	HUVEC proliferation assay VEGF-A121	Similar
Bioactivity	HUVEC proliferation assay VEGF-A111	Similar
Non-binding to VEGF-B	ELISA	Similar
Non-binding to VEGF-D		Similar
Non-binding to PIGF-2		Similar
Non-binding to VEGF-C	BLI	Similar

Post approval change management protocol(s)

A scale up of the finished product manufacturing process is planned. The planned batch formula has been provided. No change in material or IPCs will occur. The validated time out of refrigerator will not be changed, however, the compounding hold time and the filling time will be extended . A development mixing study will be performed. Product quality will be tested by analysing additional samples after compounding finished product solution, sterile filtration and filling. Finally, the validation batches will be put on stability. This approach is considered acceptable.

2.2.3.5. Adventitious agents

The active substance and finished product, including the excipients, are manufactured without direct animal- or human-derived materials. Likewise, the raw materials used for cell banking are not of animal origin. Materials of biological origin have been identified as of being of plant or microbial origin. A TSE/BSE statement has been provided by Polpharma biologics, the active substance manufacturer, stating that all materials (biological starting materials, primary container/closure system, and processing aids (including single-use systems)) used during the manufacturing of ranibizumab active substance (at Polpharma Biololgics, Poland) and finished product are in compliance with the requirements set out in guidance EMA/410/01 Rev.3. Future *E. coli* WCBs will be prepared using the same media and supplements as the current WCB ensuring a priori sufficient TSE safety. Furthermore, virus and TSE safety for all materials of biological origin used in the ranibizumab manufacturing process has been adequately assured.

In summary, Ranibizumab seems to be free of TSE risk substances and its manufacture is overall in compliance with EMA/410/01 Rev. 03. Due to the expression in recombinant *E. coli*, no virus safety testing on cell banks (except bacteriophages) and unprocessed bulk harvests has been performed and the purification process was not validated for its virus reducing capacity. This approach is in compliance with current guidelines. Testing of both cell banks, MCB and WCB, for non-endogenous bacteriophages and spores has shown absence of these adventitious agents. In summary, the viral safety of ranibizumab has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Ranivisio is a proposed biosimilar to the reference medicinal product Lucentis. FYB201 is an immunoglobulin antigen binding fragment (Fab) binding to vascular endothelial growth factor (VEGF)–A, thereby inhibiting the binding of VEGF to its receptors on the surface of endothelial cells. A well-designed Module 3 has been provided in support of the marketing authorisation application for Ranivisio as a biosimilar to Lucentis.

The manufacturing process of the active substance and the finished product, together with the control strategy, characterisation, pharmaceutical development, specifications and stability are sufficiently addressed. Quality and control of material was adequately addressed. All excipients used for the finished product formulation comply with the Ph. Eur. Process validation has been provided for active substance and finished product batches and seems appropriate. Consistent quality of the product is assured with adequate specifications and acceptance criteria.

For the biosimilarity assessment, the applicant has conducted a comprehensive and well-established biosimilarity exercise including extended characterisation, forced degradation study and stability data at accelerated and stressed conditions. FYB201 was compared to Lucentis sourced in EU. Since the phase 3 clinical trial was conducted with US-approved Lucentis only as comparator, a three-way comparison was conducted between FYB201, Lucentis EU and Lucentis US. The data demonstrate that Lucentis US is representative of the EU reference product (Lucentis EU).

In summary, a large panel of standard and state-of-the-art methods were used to compare FYB201 to its originator Lucentis. Overall, the data claim that FYB201 is similar in structure, physicochemical and most biological attributes as well as for stability. It is concluded that some difference with regard to binding to VEGF isoform VEGF-A111 was observed. However, this difference was sufficienty justified.

Some recommendations as outlined below concerning the CEX-HPLC method, an additional leachable screening at the end of the shelf-life and the results of the transport validation of the finished product have been agreed with the applicant.

From a quality perspective, Ranivisio is considered as a biosimilar to the reference medicinal product Lucentis.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Ranivisio is considered acceptable when used in accordance with the conditions as defined in the SmPC. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Ranivisio is considered approvable and biosimilarity to Lucentis is considered satisfactorily demonstrated from the quality point of view.

The applicant agreed to the CHMP Recommendations.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some additional points for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Ranivisio has been developed as a similar biological medicinal product to the reference medicinal product Lucentis. The mechanism of action of ranibizumab is binding to VEGF-A, thereby inhibiting signal transduction and subsequent endothelial cell proliferation, revascularisation and vascular leakage.

2.3.2. Pharmacology

A battery of receptor-binding studies and cell-based assays are provided as part of the comparability exercise in order to assess if any differences in reactivity are present. The functionality *in vitro* assays cover all the relevant modes of actions. Binding of Ranivisio to the VEGF-A isoforms VEGF-A189, VEGF-A165, VEGF-A121 and VEGF-A111 was investigated using Bio-layer interferometry (BLI). The range of KD of Ranivisio was comparable to EU-approved Lucentis (Lucentis EU) and US-licensed Lucentis (Lucentis US) for the isoforms VEGF-A189 and VEGF-A165; however, for VEGF-A121 one batch of Ranivisio was outside the range. Similarly, the range of KD for binding of VEGF-A111 was exceeded from 4 batches of Ranivisio and 2 batches of Lucentis US. The range was very narrow due to low deviation of Lucentis EU batches. The deviation of the

ranges is discussed in the quality assessment. Ranivisio dose-dependently inhibited VEGF-A165-, VEGF-A121, and VEGF-A111-induced proliferation of HUVECs. Ranivisio dose-dependently inhibited VEGF-A165-induced migration of HUVECs.

Assessment and discussion of the data are also provided in the quality section.

No *in vivo* PD animal studies have been performed to provide complementary information on biosimilarity in addition to the totality of data obtained including quality, *in vitro* and clinical data and these studies are not required.

The applicant has conducted pharmacological *in vitro* assays to demonstrate biosimilarity between Ranivisio and EU- and US-Lucentis. Assays include binding to VEGF (VEGF-A165, VEGF-A121, VEGF-A189 and VEGF-A111), inhibition of VEGF induced proliferation of endothelial cells (VEGF-A165, VEGF-A121, and VEGF-A111), inhibition of VEGF-A165 induced HUVEC proliferation and inhibition of VEGF-A165 induced expression of tissue factor mRNA. Further, inhibition of downstream signalling was demonstrated by Western blot. Finally, non-binding of Ranivisio to VEGF-B, VEGF-C, VEGF-D and P1GF-2 was shown.

The applicant´s approach is in line with the "Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Non-clinical and Clinical Issues" (EMA/CHMP/BMWP/403543/2010) and also in accordance with EMA scientific advice.

2.3.3. Pharmacokinetics

The applicant has conducted a pharmacokinetic study in New Zealand rabbits. It is acknowledged that extensive evaluation of ocular pharmacokinetics in humans is not feasible, however, *in vivo* nonclinical studies should only be conducted if they are deemed necessary for biosimilarity. In previous EMA scientific advice an *in vivo* PK study was not explicitly requested, nevertheless the design is in accordance with the scientific advice. Of note, PK studies in animals are not expected to be sensitive enough to detect relevant differences between originator and biosimilar. In order to detect ranibizumab in vitreous humour, aqueous humour and serum of NZW rabbits, three ELISAs with VEGF-A165 as capture antibody were developed. ELISAs were sufficiently validated. NZW rabbits were dosed with Ranivisio, Lucentis US or Lucentis EU IVT in both eyes. As expected, ranibizumab distributed from the vitreous humour to the aqueous humour and was later detectable in serum, where Cmax was reached after 24h for Lucentis and 48h for Ranivisio. In general, concentration curves in vitreous humour, aqueous humour and serum were very similar between Ranivisio and Lucentis. No analysis of anti-drug antibodies was performed in accordance with EMA scientific advice as this is not meaningful since immunogenicity in humans cannot be predicted from non-clinical studies and it was analysed in the human studies.

2.3.4. Toxicology

NZW rabbits were dosed with Ranivisio, Lucentis EU, Lucentis US or vehicle in each eye at the intravitreal route. Effects on clinical signs, food consumption, body weight, haematology and clinical chemistry were evaluated. Further, necropsy of eye and other organs was conducted including macroscopic examination and organ weight. In summary, no relevant findings were recorded in any of the parameters that are suspected to be test item-related.

The applicant has conducted a PK/toxicology study on NZW rabbits which is in general not requested in the development of a biosimilar. It is unclear if the rabbit is a relevant species for the assessment of systemic

toxicology, thus the relevance of conclusions with regard to toxicology remains highly questionable. The safety profile is already well-known from the originator, and the biosimilar does not differ from the originator with regard to composition, concentration and route of administration.

The applicant however conducted the study. No test article-related issues were identified and the toxicity profile was comparable to Lucentis EU and Lucentis US.

2.3.5. Ecotoxicity/environmental risk assessment

Given that Ranivisio is developed as biosimilar to Lucentis, and proteins are unlikely to pose a significant risk to the environment, Raniviso is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Ranivisio was developed as biosimilar product to the EU reference product Lucentis. The nonclinical programme is in accordance with the current guideline concerning biosimilars. The *in vitro* assays are provided as part of the comparability exercise. The functionality *in vitro* assays cover all relevant modes of actions. Further, a comparative pharmacokinetic and toxicology study was conducted which is limited due to the insensitivity of the animal models and can only be considered as supportive.

2.3.7. Conclusion on the non-clinical aspects

Overall, the presented data do not raise concerns with regard to biosimilarity (for further details and assessment of the *in vitro* pharmacology data please refer to the quality part). The *in vivo* data from the pharmacokinetic and toxicology study in rabbits are not required for MAA, however, the pharmacokinetic and toxicologic profile was comparable between Ranivisio and Lucentis.

2.4. Clinical aspects

2.4.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status, Type of Report
Efficacy and Safety	FYB201-C2015-01-P3	5.3.5.1	To compare the efficacy, safety, PK and immunogenicity between FYB201 and US-licensed Lucentis	Parallel group, 1:1 randomized, active-controlled, evaluation masked, multicenter study	Patients received either FYB201 or US-licensed Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as monthly (every 4 weeks) intravitreal injections in study eye	477	Newly diagnosed neovascular age-related macular degeneration (nAMD)	Approx. 12 months	Complete; Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

No PK studies were conducted in healthy volunteers for ethical and safety reasons (IVT mode of application). However, the comparative systemic exposure was to be shown as a safety endpoint in a subset of patients with neovascular AMD within the confirmatory comparative clinical safety and efficacy study FYB201-C2015-01-P3. Of 477 randomised patients, 59 patients were included in the Pharmacokinetic Analysis Set (PKS) and received monthly treatment with either Ranivisio (29 patients) or Lucentis (30 patients). A sampling point at 24 hours (approximate Cmax) after the first and the sixth IVT injection was measured for supportive evidence and reassurance of systemic safety. Another sample one week after first IVT injection was used to determine ADAs. Formal statistical testing to demonstrate PK similarity between Ranivisio and US-licensed Lucentis was not performed.

2.4.2.1.1. Bioanalytical methods

Pharmacokinetic assay:

The analytical electrochemiluminescence immunoassay (ECLIA) method was developed and validated for the analysis of Ranivisio and Lucentis in human plasma (heparin) with the aim to determine the concentration of ranibizumab (Ranivisio and Lucentis).

The validation of the bioanalytical method was conducted in accordance with the Guideline on Bioanalytical Method Validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

The limit of Quantification (LLOQ) in the validated assay was 500 pg ranibizumab/mL undiluted human plasma (lithium heparin) to measure systemic drug levels at the pre-defined sampling time-points (i.e. close to Cmax).

The standard concentrations for Ranivisio and Lucentis ranged from 500 pg/mL to 20,000 pg/mL with an anchor point of 250 pg/mL and 5 QC sample concentrations (500 (LLOQ), 1500 (Low), 6000 (Medium), 15,000 (High), and 20,000 (ULOQ) pg/mL) were used to assess accuracy and precision of the method. For precision and accuracy (PA) batches, the inter-batch and intra-batch precision and accuracy results for Ranivisio QC samples as well as for Lucentis QC samples prepared at LLOQ, low, medium, high, and ULOQ concentrations were within the pre-defined acceptance criteria and in accordance with the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Dilutional linearity was evaluated. The precision of the final concentration (50.000 pg/ml) were below 20% and the accuracy (% Theoretical) of the mean back-calculated concentration for each dilution level was within 80-120% and thus in accordance with the acceptance criteria. Results showed that samples diluted up to 25-fold can be quantified for Ranivisio and Lucentis.

The selectivity was analysed using 10 individual human plasma samples and evaluated for interference. In addition, during the assay validation a matrix of healthy donors 50 years or older, were used to mimic the matrix of the study population of age-related macular degeneration (AMD). The inter-batch and intra-batch precision and accuracy results for LLOQ QC and ULOQ QC samples met the acceptance criteria (≤20% [≤25% at the LLOQ and ULOQ]).

The potential interference of VEGF165 was evaluated by fortifying and analysing Ranivisio or Lucentis QC samples at LLOQ and ULOQ concentration with VEGF165 at 100, 300, 1000, 3000, 10,000, 30,000, 100,000, 300,000 and 1,000,000 pg/mL. 100,000 pg/mL was the highest VEGF165 concentration that met the accuracy criteria and thus was reported as the maximum level without interference. No significant matrix effect was observed in any of the tested human plasma (heparin) lots that were fortified with Ranivisio or Lucentis® at the concentration of the LLOQ or in 9 of the 10 human plasma (heparin) lots that were fortified at the concentration of the high QC sample. In addition, no significant matrix effect was observed in any of the 10 special population human plasma (heparin) lots that were fortified with Ranivisio or Lucentis at the concentration of the LLOQ or in any of the 10 special population human plasma (heparin) lots that were fortified at the concentration of the high QC sample.

No effect from lipemia on the quantification of Ranivisio and Lucentis® and no effect from haemolysis on the quantitation of Ranivisio and Lucentis® at haemolysis levels up to 15000 pg/ml was observed.

The ranibizumab concentration in human serum was stable for 6 freeze (-80°C) and thaw (ambient temperature) cycles. Long-term stability has been performed by -20°C and -80°C. The Ranivisio concentration in human serum at -20°C was stable for 120 days and at -80°C for 504 days. The stability of the medical product Lucentis was demonstrated for up to 77 days at -20°C and for up to 766 days at -80°C. The maximum time from sample collection to the end of sample analysis did not exceed 413 days.

The results derived from these validation activities in general demonstrated bioanalytical similarity of Ranivisio and Lucentis and support the conclusion that the assay (ELCIA method) is reliable and suitable for measuring Ranivisio and Lucentis concentration in human plasma samples.

Anti-drug-antibody assay:

A 3-tiered approach for the determination of anti-Ranivisio antibodies in human serum, using a semi-homogenous assay format on the MSD platform, comprising a screening assay followed by a confirmatory assay and the characterisation of ADA titre, was developed and validated. This strategy for immunogenicity assessment is in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

A single-antigen approach using either Ranivisio or Lucentis as labelled antigen, has been applied for the ADA assay.

The introduction of an acid dissociation step did not improve the signal-to-noise ratio and thus sensitivity of the ADA assay.

No Hook Effect evident up to a concentration of 35,000 ng/mL in 10% human serum (350 µg/mL whole serum equivalent) of both Positive Control antibodies was demonstrated in the initial validation).

The screening cut-point factor determined for the initial validation was 73 RLU and defined in the in-study validation/supplementary validation as 1.3 multiplication factor to detect false-positive rate in the screening assay. The screening cut-point (73 RLU) identified 8.8% potentially positive samples over the 12 batches analysed in the initial validation. The confirmatory cut-point factor of this assay showed 38% inhibition (at the 99th confidence level) and were improved in the in-study validation/supplementary validation to 39.9% inhibition to detect 1% false-positive rate in the confirmatory assay.

Drug tolerance was investigated in the initial assay at three different ADA concentrations (100 ng/ml, 500 ng/ml, 7500 ng/ml). The method is tolerant to drugs up to 50 ng/mL at a Positive Control concentration of 500 ng/mL and above. At a positive control concentration of 100 ng/ml the method showed a tolerant to drugs up to ≤5 ng/ml. Thus, the original assay validation demonstrated drug tolerance at 5 and 50 ng/mL for PC concentrations of 500 and 7,500 ng/mL. In the supplementary validation it was further confirmed that the assay tolerates up to including 5 ng/mL drug at a LPC level of 100 ng/mL.

In the initial validation the intra-assay precision resulted ≤ 19.3% and ≤ 21.3 %CV for PCs and NC, respectively. In supplementary validation intra-run precision (HPC = 7500 ng/mL, MPC = 1000 ng/mL, LPC = 100 ng/mL and NC) resulted in screening precision of ≤ 6.8 % and ≤ 1.7 %CV for PCs and NC and confirmatory precision of ≤ 4.8 % and ≤ 5.1 %CV for PCs and NC, respectively.

The inter-run precision of the initial validation (%CV, ranged from 14.9 to 18.1%) and the supplementary validation (%CV ranged from 6.6 to 16.4% for the screening assays and from 5.8 to 8.6% for the confirmatory assay) were ≤20 % and thus met the acceptance criteria.

The Positive Control antibodies (anti-Ranivisio and anti-Lucentis) were found to be stable for up to 24 hours at room temperature, for up to 5 freeze-thaw cycles from nominally -80°C to room temperature (nominally +22°C) and up to 14 weeks when stored at nominally -20°C. With the further validation the sample stability could be improved up to 936 days for the positive Controls stored at nominally -80°C and up to 25 weeks when stored at nominally -20°C.

During the ADA Assay Method evaluation also the target tolerance of VEGF were investigated. Based on these data, a potential influence of serum VEGF on baseline signals in the AMD patient population cannot be excluded.

Neutralizing antibody (nAb) assay:

A competitive ligand binding assay (CLBA) format was selected to detect neutralizing anti-Ranivisio or -Lucentis ADA because it was found to be some 40-fold more sensitive than a cell-based assay. This method was developed and validated for the detection of neutralizing anti-ranibizumab (anti-Lucentis® and anti-ranibizumab biosimilar candidate) antibodies (NAb) in human serum samples. The method is based on a competitive Ligand Binding Assay (cLBA), with elektrochemoluminescence as read-out.

The minimum required dilution was evaluated during assay development and was found to be 1:2, corresponding to 50 % serum in the assay matrix.

The mean assay cut point was identified by 22.66% of inhibition. Based on the assay cut point a multiplicative correction factor of 0.773 (1-22.66/100) was determined.

Sensitivity of the assay was determined by evaluating a 2-fold dilution series of the positive control (anti-ranibizumab biosimilar candidate). The relative sensitivity (mean of 6 runs) was determined to be 47.95 ng/mL.

Drug tolerance for Lucentis® is 150 ng/mL in combination with 500 ng/mL positive control and 37.5 ng/mL in combination with 100 ng/mL positive control. The drug tolerance for Ranivisio is 250 ng/mL in combination with 500 ng/mL positive control and 17.2 ng/mL in combination with 100 ng/mL positive control.

Selectivity was assessed by preparing low- and high-level positive controls (SSC low and SSC high) and comparing the responses in serum to the median response of all individual samples. The %CV for the deviation from the median was < 25.0 % for all individual serum samples at both concentration levels. All spiked serum samples displayed ECL values were below the plate-specific cut point (PSCP). However, the %CV of the dilution buffer for SSC high and two samples as well as the dilution buffer of SSC low were ≥20 % and thus does not correspond with the acceptance criteria of the EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

The lower limit of %inhibition was measured with three system suitability controls (SSC) concentrations: high (4000 ng/mL), mid (700 ng/mL) and low (200 ng/mL). None of the positive control samples tested had to be rejected due to a CV > 20.0 % for the duplicate analysis, one set of NC samples in QR01 showed a CV > 20.0 % and was excluded from the calculation of % inhibition values for high, mid, and low QC. All other SSC samples fulfilled the pre-defined acceptance criteria (≤20 %) and correspond with the EMA guidance acceptance criteria (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Stability at room temperature and refrigerated (5°C) as well as freeze-thaw stability was assessed by preparing low and high level positive controls (SSC low and SSC high) and a negative control. All mean concentrations (CV%) at each level were within 20 % of the nominal concentration and thus met the acceptance criteria of the EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). Thus, all samples demonstrated a stability at room temperature and refrigerated (5°C) for up to 24 hours and a stability for up to 3 freeze/thaw cycles at -20 and -75 °C.

2.4.2.1.2. PK data from COLUMBUS-AMD

Introduction

The COLUMBUS-AMD study (FYB201-C2015-01-P3) is a parallel-group, 1:1 randomised, active-controlled, evaluation-masked, multicentre study to demonstrate clinical equivalence in terms of clinical efficacy, pharmacology, and safety of Ranivisio with Lucentis over 12 months of treatment in patients with subfoveal neovascular age-related macular degeneration (nAMD).

At Screening, the study site registered each patient within the IVRS or IWRS and provided information about his/her eligibility for participation in the study and, if applicable, in the PK Subgroup. Treatment allocation in the PK subgroup may not be fully balanced between Ranivisio and Lucentis, as the inclusion in the PK subgroup was independent of the randomisation.

The systemic ranibizumab concentration close to Cmax after the 1st and the 6th IVT injection was assessed at selected sites in a PK subgroup of up to 60 patients. The mean ranibizumab concentrations at 24 hours after the 1st and the 6th intravitreal injection were calculated for the PKS analysis set, based on data collected up to the main analysis, and summarised using arithmetic and geometric means, ranges, SDs and the coefficient of variation by analysis visit and treatment group.

Study results

Pharmacokinetic results of PK Subgroup Analysis Set (PKS) of the pivotal therapeutic equivalence study FYB201-C2015-01-P3

The PK Subgroup Analysis Set (PKS) comprised 59 patients, 29 of whom had been treated with Ranivisio and 30 with US-licensed Lucentis. Blood samples were collected 24 ± 3 hours after the first and sixth IVT injections to measure systemic ranibizumab concentration corresponding to estimated Cmax.

Table 2: Systemic ranibizumab concentration close to Cmax (pg/mL) after 1st and 6th IVT injection - PKS

	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

Abbreviations: % Geom. CV = geometric coefficient of variation, %CV = coefficient of variation, PKS = PK subgroup analysis set, 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

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 06-010-007 (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: Post-text table 14.4.1 in Clinical Study Report

2.4.2.2. Pharmacodynamics

No dedicated (comparative) pharmacodynamics (PD) investigations have been performed as part of the clinical biosimilarity exercise. Pharmacodynamics (PD) similarity of Ranivisio and Lucentis® with respect to biological activity, has been evaluated in nonclinical *in vitro* studies (e.g. *in vitro* functional characterisation and analytical comparability).

Primary pharmacology

Immunogenicity results of the pivotal therapeutic equivalence study FYB201-C2015-01-P3

The clinical immunogenicity database for Ranivisio comprises results of the single clinical study, FYB201-C2015-01-P3, which was designed to demonstrate therapeutic equivalence between Ranivisio and Lucentis.

Relative immunogenicity of Ranivisio vs. Lucentis was evaluated for the final analysis by determining the number of patients within the SAF who developed binding anti-drug-antibodies (ADAs) and neutralizing anti-drug antibodies (nAbs) in blood serum up to Week 48.

ADA assessments were scheduled at eCRF Visits V1 (baseline; pre-first dosing), V2/Week 4, V4/Week 12, V7/Week 24, and the Final Visit/Week 48.

The incidence of confirmed ADA positive patients through the 48-week treatment period was 5.9% in both the Ranivisio and US-Lucentis treatment groups.

Only one ADA sample in the Ranivisio treatment group at the final visit were detected positive for neutralizing ADA. All other samples were nAbs negative.

Table 3: Frequency of patients with anti-drug antibodies (ADAs) pre- and post-first dosing – SAF

Pre- or post-first dosing	FYB201		Lucentis		Total	
Positive or negative ADAs	n	%	n	%	n	%
SAF	**(N = 238)**		**(N = 239)**		**(N = 477)**	
Pre-first dosing	232		236		468	
Positive	0	0.0%	5	2.1%	5	1.1%
Negative	232	100.0%	231	97.9%	463	98.9%
Missing	6		3		9	
Post-first dosing	237		238		475	
Positive	14	5.9%	14	5.9%	28	5.9%
Negative	223	94.1%	224	94.1%	447	94.1%
Missing	1		1		2	

Table 4: ADA and NAb frequency and titer in study FYB201-C2015-01-P3 (SAF)

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: 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

Table 5: Treatment-induced, treatment-induced persistent and treatment-boosted ADAs

	FYB201 (N = 238)*		Lucentis (N = 239)*		Rate Diff	95% CI
	Patient n	Patient %	Patient n	Patient %		Wald method (normal approximation)
Treatment-induced ADAs**	14	5.9	11	4.6	1.38%	-2.714%, 5.474%
Treatment-induced persistent ADAs***	4	1.7	1	0.4	1.31%	-0.571%, 3.183%
Treatment-boosted ADAs****	0	0	0	0	n.a.	n.a.

*A patient is defined as evaluable, if at least one baseline ADA test and one post-baseline ADA test is available.

**A patient is defined as having treatment-induced ADAs, if the result is negative at baseline and positive post-dose.

*** A patient is defined as having treatment-induced persistent ADAs, if the result is negative at baseline and positive at more than 1 time point post-dose.

**** A patient is defined as having treatment-boosted ADAs, if the result is positive at baseline and the titer increased by at least 2 dilutions after dosing.

Source: Tables 1.1.9.1, and Tables 1.1.11.1, End of Text Tables for ISI Analysis Final v05, 11-Jan-2021, ISI Appendix 2

The incidence of treatment-induced ADAs through the 48-week treatment period was a bit higher in the Ranivisio treatment groups (5.9%) than in the US-Lucentis treatment group (4.6%).

The incidence of treatment-induced persistent ADAs through the 48-week treatment period was low in both treatment groups. However, a slightly higher amount of treatment-induced persistent ADAs was detected in the Ranivisio treatment group (1.7%) vs. in the US-Lucentis treatment group (0.4%).

The 95% confidence interval (CI) of the difference between treatment groups spans zero, indicating that the numerical difference is not statistically significant.

Effect of ADAs on efficacy endpoints

The relationship of ADA status to the different efficacy endpoints (change from baseline in BCVA, FCP and FCS retinal thickness, total lesion area) in the FYB201-C2015-01-P3 clinical study were evaluated. The results compare absolute and change from baseline values at different time-points for ADA positive and ADA negative patients in each treatment group.

Since only one patient gave a positive result in the NAb assay at week 48, the corresponding data outputs for NAb status are not presented.

- *Change from baseline in BCVA over time*

Based on the absolute mean values of BCVA, Ranivisio and Lucentis showed similar results in ADA negative patients, whereas patients, which were treated with Lucentis and were ADA positive, demonstrated a higher mean value of BCVA compared to Ranivisio. In addition, a tendency could be observed that ADA negative patients in the Ranivisio treatment group demonstrated better BCVA results than the ADA positive patients, while the opposite was observed for the Lucentis treatment group. Moreover, the change in arithmetic mean

BCVA (letters) from baseline at Week 8, 24 & Week 48 were lower in patients which were ADA positive in both Lucentis and Ranivisio treatment groups. This might indicate a potential for reducing the efficacy in ADA positive patients. The differences between ADA positive and ADA negative patients in the mean change of BCVA from baseline up to week 48 were higher in the Ranivisio treatment group than in the Lucentis group.

- *Changes from baseline in FCP retinal thickness and FCS retinal thickness over time*

The treatment groups Ranivisio and Lucentis showed similar results in ADA negative patients. In the Ranivisio treatment group, ADA positive patients appeared to respond to a slightly higher extent than ADA negative patients, while the opposite effect was evident for the Lucentis treatment.

To assess whether there could be a trend for reducing efficacy in ADA-positive patients, time course of changes and grouped boxplot of change from baseline in FCP/FCS retinal thickness [µm] by patient and ADA status in both, Lucentis and Ranivisio, treatment groups were performed. It could be observed that more patients with ADA positive values were above the arithmetical mean of the patients with ADA negative, than below. However, all results from ADA positive patients were in the range of the results of patients with negative ADA results.

- *Change from baseline in total lesion area at 24 and 48 weeks*

In the Ranivisio ADA negative sub-population an improvement in the total lesion area has occurred over the course from baseline to week 48, whereas no clear change or improvement in the total lesion area were observed in the Ranivisio ADA positive sub-population. In contrast, such an effect did not occur for the Lucentis ADA positive sub-population. In both, Lucentis ADA positive and Lucentis ADA negative sub-population an improvement in the total lesion area has occurred over the course from baseline to week 48.

Based on the data regarding change in arithmetic mean Total Lesion Area (mm²) from baseline at Week 24 & Week 48, both the ADA positive and ADA negative sub-populations in each treatment group demonstrated a reduction of arithmetic mean Total Lesion Area (mm²) from baseline at Week 24 & Week 48. While in the ADA negative sub-population the change in arithmetic mean total lesion area showed an improvement between weeks 24 and 48, the change in arithmetic mean total lesion area in the ADA positive sub-population decreased in both the Lucentis and Ranivisio treatment groups. Moreover, Lucentis appears to have a slightly better effect on total lesion area from baseline to week 48 than Ranivisio, regardless of the ADA status. Considering the main efficacy results (see below), this is not considered to translate into a clinically meaningful difference.

Impact of ADA on clinical safety

Based on the current limited available data, only one mild severity event of drug hypersensitivity was reported in each of the treatment groups. In both cases the patients were ADA negative throughout the treatment period. No TEAE (drug hypersensitivity, anaphylaxis or intra-ocular inflammation) were reported for ADA positive patients. Overall, no clinically significant safety issues were reported.

Effect of ADAs on pharmacokinetics

The PK Subgroup Analysis Set (PKS) comprised 59 patients, 29 of whom had been treated with Ranivisio and 30 with US-licensed Lucentis. Blood samples were collected 24 ± 3 hours after the first and sixth IVT injections to measure systemic ranibizumab concentration corresponding to estimated Cmax. Another sample

one week after first IVT injection was used to determine ADAs. Samples for ADA testing were collected pre-treatment and at 4, 12, 24 and 48 weeks post-treatment.

In the period from baseline to week 24, no positive ADAs were detected in the PK subgroup, neither in the FYB group (n=29) nor in the Lucentis group (n=30). Only in the final Visit at week 48, five (5) patients (8.5%) were observed with positive ADAs. However, the number and percentage of patients with detected ADAs in blood serum by scheduled eCRF visit up to Week 48 were balanced between both treatment groups (Ranivisio: 2 patients (6.9%) ; Lucentis: 3 patients (10%)).

No ADA sample were detected positive as neutralizing ADA.

Table 6: Frequency of patients with anti-drug antibodies (ADAs) pre- and post-first dosing –PKS

Pre- or post-first dosing	FYB201		Lucentis		Total	
Positive or negative ADAs	n	%	n	%	n	%
PKS	**(N = 29)**		**(N = 30)**		**(N = 59)**	
Pre-first dosing	29		30		59	
Positive	0	0.0%	0	0.0%	0	0.0%
Negative	29	100.0%	30	100.0%	59	100.0%
Missing	0		0		0	
Post-first dosing	29		30		59	
Positive	2	6.9%	3	10.0%	5	8.5%
Negative	27	93.1%	27	90.0%	54	91.5%
Missing	0		0		0	

Abbreviations: N = total number of patients, n = number of patients within specified class, % = number of patients within specified class/total number of patients per visit*100, SAF = safety analysis set, PKS = PK Subgroup analysis set

Notes: Pre-first dosing refers to the ADA assessment performed prior to the first injection, post-first dosing was defined as the combination of all ADA assessments performed after the first injection, Visit 1b was only performed for patients in the PK subgroup.

Source: Post-text tables 14.4.3.1 and 14.4.3.2

To evaluate whether the ADA status has an impact on the pharmacokinetics, the ranibizumab concentration was analysed in the PK Subgroup Analysis Set (PKS) and the PK profile of 54 patient samples was compared between the two products Ranivisio (n=27) and Lucentis (n=27).

- *ADA negative patient samples*

For Visit 1a, the geometric mean and the geometric coefficient of variation (Geom. CV) for the ADA negative samples was 2376.62 pg/mL (Geom.CV: 62.74%) in the Ranivisio group and 2646.11 pg/mL (Geom.CV: 63.64%) in the Lucentis group; for Visit 6a, the geometric mean and Geom. CV was 2379.95 pg/mL (Geom.CV: 68.23%) in the Ranivisio group and 2906.31 pg/mL (Geom.CV: 60.19%) in the Lucentis group. The geometric mean of Ranivisio was lower than the geometric mean of Lucentis, for both visits (V1a and V6a).

- *ADA positive patient samples*

For Visit 1a, the geometric mean and the geometric coefficient of variation (Geom. CV) for the ADA negative samples was 1793.32 pg/mL (Geom.CV: 43.02%) in the Ranivisio group and 1838.68 pg/mL (Geom.CV: 8.66%) in the Lucentis group; for Visit 6a, the geometric mean and Geom. CV was 1420.00 pg/mL (Geom.CV: n.c.) in the Ranivisio group and 1950.95 pg/mL (Geom.CV: 13.82%) in the Lucentis group. The geometric mean of Ranivisio was lower than the geometric mean of Lucentis, for both visits (V1a and V6a).

2.4.3. Discussion on clinical pharmacology

Ranivisio, a recombinant humanised Immunoglobulin G (IgG) 1 kappa isotype monoclonal antibody fragment designed for intraocular use, was established to demonstrate the biosimilarity between Ranivisio and the reference medicinal product Lucentis in the most sensitive indication "neovascular age-related macular degeneration (nAMD)". The PK profile was evaluated within the confirmatory comparative clinical safety and efficacy study FYB201-C2015-01-P3.

Usually, a pivotal PK study is recommended to obtain information on biosimilarity. However, in this case, no PK studies in healthy volunteers were conducted for ethical and safety reasons (IVT mode of application) and no pivotal PK study in the target population was performed. This is considered to be acceptable because the systemic exposure is too low for a formal bioequivalence study and therefore instead assessed as a safety parameter in a subset of patients within the confirmatory study, which allows further investigation of the clinical impact of variable pharmacokinetics and possible changes in the PK over time. Thus, sampling for Cmax following the first and the 6th dose in the pivotal study is intended to confirm that there is no excess systemic exposure of Ranivisio compared to the reference medical product. In addition, in the scientific advice (EMEA/H/SA/2899/1/2014/SME/III) as well as during the follow-up advice received in September 2015 (EMEA/H/SA/2899/1/FU/1/2015/SME/II), it was agreed, that it is not necessary to perform a formal bioequivalence testing due to the low levels of systemic exposure. The CHMP agreed in the scientific advice, that the PK analysis was limited to measurement of systemic ranibizumab concentration at three time-points only (pre-treatment, 24-hour post-first IVT dose and 24-hour post sixth IVT dose), and in a sub-set (N=30 per treatment group) of the patients. Therefore, a comparative pharmacokinetic analysis of the systemic exposure at both start of treatment and steady state between the reference and the biosimilar product was expected for the MAA, which should be correlated with the product safety profile, in consideration that a formal statistical bioequivalence analysis will not be meaningful.

Bioanalytical methods

Pharmacokinetic assay

The bioanalytical method for detection of Ranivisio and Lucentis in human plasma has been appropriately described. The PK assay is based on electrochemiluminescence immunoassay (ECLIA) technology.

The method development and validation of VEGF in human plasma rather than serum is considered acceptable, because it excludes the measurement of the VEGF sequestered in platelets and provides a better approximate of the VEGF concentrations to which the endothelial cells are exposed (Avery et al. 2014).

The validation of the bioanalytical method was conducted in accordance with the Guideline on EMA's 2011 Bioanalytical Method Validation.

The limit of Quantification (LLOQ) in the validated assay was 500 pg ranibizumab/mL undiluted human plasma (lithium heparin), which was adequately low to measure systemic drug levels at the pre-defined sampling time-points (i.e. close to Cmax). However, the sensitivity of the PK assay (LLoQ of 500 pg/ml) is still not as high as for the assays which has already been developed for Lucentis (LLoQ of 0.3 ng/ml for ECLA-based PK assay and later improved to LLoQ of 0.015 ng/ml (Avery et al., 2014)). Although, the assay is not as sensitive as the assays developed by the RMP license holder, the sensitivity of the PK assay was improved from 1.44 ng/ml (follow-up scientific advice (EMEA/H/SA/2899/1/FU/2/2016/III)) to 500 pg/ml and thus should cover the majority of the data points. This limits the likelihood of bias of comparative PK results. Therefore, this PK assay sensitivity is considered to be acceptable to quantify the levels of systemic exposure of Ranibizumab.

The main characteristics of a bioanalytical method that are essential to ensure the acceptability of the performance and the reliability of analytical results (selectivity, lower limit of quantification, the response function and calibration range (calibration curve performance), accuracy, precision, matrix effects, stability of the analyte) were analysed and in accordance with the acceptance criteria of the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

For the ability to exclude an interference with endogenous components, potential interference of VEGF165 was evaluated by fortifying and analysing Ranivisio or Lucentis QC samples at LLOQ and ULOQ concentration with VEGF165 at 100, 300, 1000, 3000, 10,000, 30,000, 100,000, 300,000 and 1,000,000 pg/mL. Since Ranibizumab binds with high affinity to various VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165). The main characteristics as precision and accuracy, selectivity, matrix effect, haemolysis, lipemia, sensitivity, dilution integrity, short-term stability (24h), long-term stability (-20°, -80°C) and freeze-thaw stability were evaluated adequately and the data met predefined acceptance criteria and are in accordance with the current Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Bioanalytical similarity between Ranivisio and Lucentis was evaluated by comparing the % difference of the mean Ranivisio QC values vs. the mean Lucentis QC values and the Ranivisio inter-batch mean bias (% RE) vs. the 90% confidence interval for the Lucentis inter-batch mean bias (% RE).

The acceptance criteria for the 90% confidence interval for the Ranivisio inter-batch mean bias (% RE) vs. the 90% confidence interval for the Lucentis inter-batch mean bias (% RE) correspond to the target acceptance criteria reported in white paper of Marini et al. 2014 and is considered to be acceptable.

The acceptance criteria were met and the use of a single calibrant (Ranivisio) for analysis of clinical samples from subjects treated with either Ranivisio or Lucentis is considered to be acceptable.

Based on the provided data, the bioanalytical similarity for detection of Ranivisio and Lucentis was demonstrated and support the conclusion that the assay (ELCIA method) is reliable and suitable for measuring Ranivisio and Lucentis concentration in human plasma samples.

Anti-drug-Antibody assay

As ranibizumab is a therapeutic protein, there is a possibility that patients receiving ranibizumab (Ranivisio) will form antibodies against this macromolecule. In addition, it is mentioned in the dossier, that in common with other humanised therapeutic antibodies, in silico analyses reveal potential MHC Class II binding motifs located within the non-human-germline sequences. Thus, there is a potential for immunogenicity with Ranibizumab and the development and validation of a bioanalytical method to detect ADAs and NAbs precisely is therefore required for the MAA.

A 3-tiered approach for the determination of anti-Ranivisio antibodies in human serum, using a semi-homogenous assay format on the MSD platform, comprising a screening assay followed by a confirmatory assay and the characterisation of ADA titre, was developed and validated. This strategy for immunogenicity assessment is in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1).

A single-antigen approach using either Ranivisio or Lucentis as labelled antigen, has been applied for the ADA assay. To support the use of a one-assay format, the applicant has investigated the antigenic equivalence of these assays using the same assay and reagents in a competitive mode that can compare inhibition of the positive control signal by a range of concentrations of unlabeled Ranivisio or unlabeled Lucentis added to the solution-phase as a competing antigen. The curves generated with the biosimilar and the originator are visually overlapping. Thus, based on the provided data, the use of a single-assay approach is endorsed.

Furthermore, it is suggested that any ADA against ranibizumab (free and drug-bound) can be detected by the assay method, since the introduction of an acid dissociation step did not improve the signal-to-noise ratio and thus sensitivity.

Relevant assay performance parameters including sensitivity, drug tolerance, selectivity, matrix interference, sample stability and assay precision were investigated and almost all assay parameters validated and provided met the acceptance criteria of the respective EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

However, in the initial validation the intra-assay precision resulted ≤ 19.3 % and ≤ 21.3 %CV for PCs and NC, respectively. Based on the predefined acceptance criteria of ≤30 % for NC, this would be acceptable, but ≤30 % for NC does not meet the acceptance criteria (≤20 %) of the respective EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). In supplementary validation intra-run precision (HPC = 7500 ng/mL, MPC = 1000 ng/mL, LPC = 100 ng/mL and NC) resulted in screening precision of ≤ 6.8 % and ≤ 1.7 %CV for PCs and NC and confirmatory precision of ≤ 4.8 % and ≤ 5.1 %CV for PCs and NC, respectively. The intra-assay precision did not exceed 20 % in the supplementary validations and thus is considered acceptable. In addition, selectivity was validated by spiking the low-level positive control antibody (LPC, 500 ng/mL) into a panel of 12 (initial validation) or 10 (supplementary validation) individual sera from healthy volunteers, including 2 hyperlipaemic samples and 2 haemolysed samples. The signal for the spiked samples were greater than the plate-specific cut point of the individual samples. Only 1 un-spiked selectivity sample was above the cut point before spiking with anti-Ranivisio positive control antibody. This is considered to be acceptable.

Moreover, during the ADA Assay Method evaluation also the target tolerance of VEGF were investigated. Based on these data, a potential influence of serum VEGF on baseline signals in the AMD patient population cannot be excluded. Nevertheless, in the Method evaluation Report following rationale was provided that target interference might be not an anticipated concern for this assay and interpretation of clinical samples: "The observed interfering concentration of VEGF to produce a screening positive result in this assay was determined to be approximately 0.75 ng/mL, while screening positive samples confirmed positive in the presence of at least 1 ng/mL VEGF. As per data obtained from literature sources (Serum and Plasma Vascular Endothelial Growth Factor Concentrations Before and After Intravitreal Injection of Aflibercept or Ranibizumab for Age-Related Macular Degeneration, Wang et al., 2014 and Jin et al. 2017), the expected baseline serum VEGF concentration in AMD patients was recorded in the range of approximately 0.03 to 0.4 ng/mL, whereas high standard deviations are present. Furthermore, it was shown that systemic VEGF levels were not significantly affected under ranibizumab treatment (0.5 mg intravitreal Ranibizumab every 4 weeks) and were comparable to baseline levels 4 weeks after injection when ADA samples are taken. Due to these factors and the observed analytical results, target interference is not an anticipated concern for this assay and interpretation of clinical sample results". The argumentation of the applicant can be followed and is considered acceptable.

Overall, almost all assay parameters validated and provided met the acceptance criteria of the respective EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). In conclusion, the single assay validation approach, using labelled Ranivisio as the antigen, developed and validated for the ADA assay clinical sample analysis, is considered to be acceptable.

Neutralizing antibody assay

This method was developed and validated for the detection of neutralizing anti-ranibizumab (anti-Lucentis® and anti-ranibizumab biosimilar candidate) antibodies (NAb) in human serum samples. The method is based

on a competitive Ligand Binding Assay (cLBA), with elektrochemoluminescence as read-out. This assay format is deemed acceptable because ranibizumab binds to the VEGF-A, thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Due to this mode of action, the inhibition of binding activity which is measurable by the assay in case that nAbs are present reflects the neutralizing capacity.

The method validation report and the bioanalytical sample analysis report of the clinical study FYB201-C2015-P3 has been provided.

Relevant assay performance parameters including sensitivity, drug tolerance, selectivity, sample stability and assay precision were investigated and almost all assay parameters validated met the acceptance criteria of the respective EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

However, selectivity was assessed by preparing low- and high-level positive controls (SSC low and SSC high) and comparing the responses in serum to the median response of all individual samples. The %CV for the deviation from the median was < 25.0 % for all individual serum samples at both concentration levels. All spiked serum samples displayed ECL values were below the plate-specific cut point (PSCP).

In addition, also the acceptance criteria of the %CV of intra- and inter-run precision for the positive controls was pre-defined as ≤ 25.0 %, which does not correspond with the acceptance criteria (≤20 %) of the EMA guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**). However, all samples included in the calculation did not exceed a value of CV>20 % and thus meet the acceptance criterion of the EMA Guideline. Moreover, values with duplicate CV >20% were excluded from the analysis. Therefore, it can be assumed that the pre-defined acceptance criterion for the positive control has no relevance for the bioanalytical results of the study and that the NAb assay demonstrate acceptable intra- and inter-run precision during the clinical sample analysis.

Absorption, distribution, metabolism, elimination (ADME)

No new data were collected on absorption, distribution, metabolism and elimination from the biosimilar study FYB201-C2015-01-P3.

All provided data based on historical data for Lucentis. The provided information by the applicant were essentially based on publicly available regulatory documents on Lucentis (Ref. (CDER, 2006), (FDA, 2018), and (EMA ,2020) and was not part of the development of Ranivisio and thus not part of this assessment.

Special populations

No new data were collected on pharmacokinetics in special populations from the biosimilar study FYB201-C2015-01-P3.

All provided data based on historical data for Lucentis. The provided information is essentially based on publicly available regulatory documents on Lucentis (Ref. (CDER, 2006), (FDA, 2018), and (EMA,2020)).

Thus, no formal studies have been conducted to examine the pharmacokinetics of Ranivisio in patients with renal/hepatic impairment. No specific PK studies were performed to investigating the effect of race, gender and weight on the PK of ranibizumab. However, race, gender and weight are unlikely to have an effect on the systemic exposure of this ophthalmic applied product. Additionally, no investigation has been provided to explore the potential impact of age on the systemic exposure of ranibizumab after IVT injection since this is not required for a biosimilar application.

Clinical bioequivalence study FYB201-C2015-01-P3

Pharmacokinetic profile

The PK profiles between the two products Lucentis and Ranivisio were compared in the clinical Phase III Study FYB201-C2015-01-P3 subgroup of patients (n=59; Ranivisio: 29 patients; Lucentis:30 patients) with neovascular AMD, which is considered the most representative and relevant patient population. The conduct of such a study in healthy volunteers is difficult for obvious ethical and practical reasons (invasiveness of intravitreal injection) and thus it is acceptable that no separate PK study in healthy volunteers was performed.

For the evaluation of the PK profile, both Cmax and Ctrough were recommended in the EMA Scientific Advice (EMEA/H/SA/2899/1/FU/1/2015/SME/II). The inclusion of a PK sampling for assessing approximate Cmax was based on the applicant's rationale that ranibizumab is a locally acting, locally applied drug, which exerts its effect at the site of application, and thus the systemic action, if any, would be considered as an unintended effect. This rational is considered acceptable, as ranibizumab is assumed to be cleared with an elimination half-life of approximately 2h once reaching the systemic circulation. Nevertheless, this systemic exposure might be relevant with regard to the safety. However, Ctrough was not assessed, since Ctrough was not required by the FDA. Therefore, the applicant justified the use of only Cmax to align the FDA and EMA requirement. Additionally, in the follow-up Scientific advice in October 2016 (EMEA/H/SA/2899/1/FU/2/2016/III) the CHMP agreed that, at dose levels prior to the next dose, only few measurable concentrations would be available and that the added information is questionable. As it has been shown by Avery et al (2014) that ranibizumab did not accumulate, the arguments of the applicant that also Cmax values will be sensitive to detect any accumulation could be followed. Therefore, CHMP agreed in the scientific advice that the Ctrough sampling prior to the 7th dose can be removed from the protocol. Thus, the PK parameter chosen (Cmax) are judged acceptable.

Samples obtained pre-first dose, at 24 ± 3 hours after first IVT injection (close to Cmax) and at 24 ± 3 hours after sixth IVT injection (close to Cmax) were used to measure systemic concentration of ranibizumab. The chosen time points for measuring the PK profile was agreed in the EMA Scientific advice and is considered to be acceptable.

All samples analysed at Visit 1/baseline were below limit of quantification (<500 pg/mL) for both Ranivisio and Lucentis. Thus, the drug concentration assay seems to have suitable sensitivity to detect Ranivisio and Lucentis in post-treatment samples. In addition, the systemic ranibizumab concentrations measured close to Cmax after the 1st and 6th IVT injections were broadly similar in both treatment groups for all measurement time points. However, the geometric mean of Ranivisio was lower than the geometric mean of Lucentis, for both visits (V1a and V6a). In addition, a high inter-subject variability [Ranivisio: range 54.37-56.88%; Lucentis: range 47.21%-57.44%] was observed in both treatment groups. However, the standard deviation were quite high, in both the Ranivisio and Lucentis treatment group and only two measurement time point were compared. Nevertheless, based on the provided demographics and other baseline characteristics of the PK-Subpopulation, an imbalance in the baseline characteristics of age, iris colour and Snellen was observed between the Lucentis group and the Ranivisio group. It is possible that this imbalance could have led to the differences in geometric mean between the two treatment arms. Imbalance demographics and baseline characteristics could lead to bias and potential impact on comparability. Therefore, it is still uncertain whether the difference in the PK profile could affect the biosimilarity between the two products. However, considering the high inter-subject variability, the high standard deviation and the small number of analysed patient samples in the PK subpopulation, the data are too limited to make an entire conclusion of the clinical relevance of these differences.

Moreover, the maximum concentrations of both the treatment [Ranivisio: 6550 pg/mL, Lucentis: 6940 pg/mL] were well below the concentration range of ranibizumab that was necessary to inhibit the biological activity of vascular endothelial growth factor-A by 50% [11-27 ng/mL] as measured in an *in vitro* cellular proliferation assay [SmPC Lucentis®] and that may induce adverse events. Therefore, it is considered to be acceptable.

Anti-drug antibodies (ADA)

Compared to small molecules, therapeutic proteins show a high risk of an autoimmune response, resulting in anti-drug antibodies (ADA) development, which is associated with treatment failure. To observe and prevent such a treatment failure, a 3-tiered approach for the determination of anti-Ranivisio antibodies/anti-Lucentis antibodies in human serum, using a semi-homogenous assay format on the MSD platform, were developed, validated and used to evaluate the clinical trial samples.

Anti-drug antibody (ADA) were measured in patients at pre- and post-first dosing. In the Ranivisio treatment group 232 patients provided pre-treatment ADA results and all patients were ADA negative. In contrast, in the Lucentis treatment group, 236 patients provided pre-treatment ADA results of which 5 (2.1 %) patients were positive for ADAs.

In the post-treatment detection of ADAs, the total number of patients treated with Ranivisio and Lucentis with positive ADAs in blood serum were low and similar as reported from earlier studies. 28 patients out of 477 (5.9%) in the SAF (Ranivisio, 14/238 [5.9%] and Lucentis 14/239 patients [5.9%]) had at least one confirmed positive ADA assessment in ≥1 time point after the first administration of study treatment up to 48 weeks. This is considered to be acceptable.

The development of anti-drug antibodies (ADA) in patients treated with therapeutic proteins can result in treatment failure. The clinically most relevant fraction of these antibodies are the neutralizing anti-drug antibodies (nAb) that block the pharmacological function of the drug.

Out of these detected 28 patients with at least one positive ADA from baseline up to week 48, only one ADA sample (one patient) in the Ranivisio treatment group at the final visit were detected positive for neutralizing ADA. All other samples were nAbs negative.

Consequently, as the detection of NAb in plasma is a better predictor of loss of therapeutic response than increased levels of total anti-drug antibodies (ADA) test, no treatment failure due to loss of therapeutical function of Ranivisio is expected, based on the currently provided data, since only one patient gave a positive result in the NAb assay at week 48.

Although, based on the current available data, no numerically significant difference between the treatment groups was observed and the number of patients with positive ADAs is low, there is a tendency for the biosimilar to have a higher number of treatment-induced (Ranivisio: 5.9% vs Lucentis: 4.6%) and persistent (Ranivisio: 1.7% vs. Lucentis: 0.4%) ADAs. These persistent ADAs could lead to a reduction in the efficacy of the biosimilar. Based on the results subsequently submitted by the applicant for the four Ranivisio-treated patients classified as having treatment-induced persistent ADAs, a sustained efficacy response was demonstrated for FCP and FCS retinal thickness in all 4 patients; however uncertainties still remain regarding the impact of persistent ADAs on efficacy with respect to BCVA. However, as the values vary a lot, no further data are available and the occurrence of treatment-induced persistent ADAs was generally very low, no clinically relevant conclusion can be made based on these limited data. Possible discrepancies could also be due to chance.

Impact of ADA/NAb status on efficacy endpoints

To determine any impact of the ADA/NAb status on the efficacy of Ranivisio, the following efficacy endpoint were examined as a function of the ADA status:

- Change from baseline in BCVA over time
- Changes from baseline in FCP retinal thickness and FCS retinal thickness over time
- Change from baseline in total lesion area at 24 and 48 weeks

For all endpoints (BCVA, FCP/FCS retinal thickness and total lesion area) investigated over time, a trend was observed that the ADA status may have an impact on efficacy. Although, based on the boxplot and spaghetti plots, all results of ADA positive patients were within the range of the patients with negative ADA results for all evaluated efficacy endpoints, there was a potentially recognizable deviation of ADA positive results from the arithmetic mean of the ADA negative results.

Moreover, the trend of deterioration in efficacy appears to be greater in the Ranivisio treatment group than in the Lucentis treatment group. However, it is questionable whether these differences observed for all efficacy endpoints analysed are clinical meaningful, considering relatively high inter-patient variability, the small sample size of patients with positive ADA results and the overlapping standard deviations/ 90% confidence interval. Such discrepancies could also be due to chance. Nevertheless, a possible association between ADA status and the efficacy parameters outcome, especially for BCVA, cannot be completely excluded based on the limited data currently available. In conclusion, as no further data are available, the occurrence of ADAs was generally very low and there is no clear clinical evidence that ADAs have a negative impact on the efficacy of Ranivisio, it is currently not considered that the differences alter the benefit-risk ratio to an extent that would suggest major efficacy/safety concerns and thus dissimilarity between both products.

Impact of ADA on clinical safety

Ranibizumab does not contain a Fc region and is therefore not expected to induce Fc-mediated cytotoxicity, to bind complement or to induce antibody-dependent cellular cytotoxicity. However, as a therapeutic protein, there is a possibility that patients receiving ranibizumab (Ranivisio) will form antibodies against this macromolecule and thus develop an immunogenicity reaction.

Based on the current limited available data, only one mild severity event of drug hypersensitivity was reported in each of the treatment groups. In both cases the patients were ADA negative throughout the treatment period. Since no TEAE (drug hypersensitivity, anaphylaxis or intra-ocular inflammation) were reported for ADA positive patients, the safety risk due to clinically relevant treatment-emergent ADAs is assumed to be low.

Please refer to AR Section 3.3.7 "Clinical Safety" for further information and a detailed safety evaluation of Ranivisio.

Results for PK Subgroup Analysis Set (PKS) - Impact of ADA/NAb status on PK

The PK Subgroup Analysis Set (PKS) comprised 59 patients, 29 of whom had been treated with Ranivisio and 30 with US-licensed Lucentis. Blood samples were collected 24 ± 3 hours after the first and sixth IVT injections to measure systemic ranibizumab concentration corresponding to estimated Cmax. Another sample one week after first IVT injection was used to determine ADAs. Samples for ADA testing were collected pre-treatment and at 4, 12, 24 and 48 weeks post-treatment.

In the period from baseline to week 24, no positive ADAs were detected in the PK subgroup, neither in the FYB group (n=29) nor in the Lucentis group (n=30). Only in the final Visit at week 48, five (5) patients (8.5%) were observed with positive ADAs. However, the number and percentage of patients with detected ADAs in blood serum by scheduled eCRF visit up to Week 48 were balanced between both treatment groups [Ranivisio: 2 patients (6.9%) ; Lucentis: 3 patients (10%)]. No ADA sample were detected positive as neutralizing ADA.

Thus, the current available data (Ranivisio: n=2; and Lucentis: n=3) of ADA positive patients in the PKS population are too limited and thus precludes a meaningful analysis of the relationship between ADA positive status and systemic ranibizumab concentration.

2.4.4. Conclusions on clinical pharmacology

From a PK perspective, a possible association between ADA status and efficacy parameter outcome cannot be completely excluded based on the limited data currently available. However, as the occurrence of ADAs was generally low and there is no clear clinical evidence that ADAs have a negative impact on the efficacy of Ranivisio, the observed numerical differences between Lucentis and Ranivisio, are currently not expected to alter the benefit-risk ratio to an extent that would raise major efficacy/safety concerns and thus an apparent dissimilarity between both products.

From a PD perspective, the mechanism of action of ranibizumab is sufficiently described by the applicant and no concerns are raised given the absence of obvious PD biomarkers.

2.4.5. Clinical efficacy

2.4.5.1. Main study

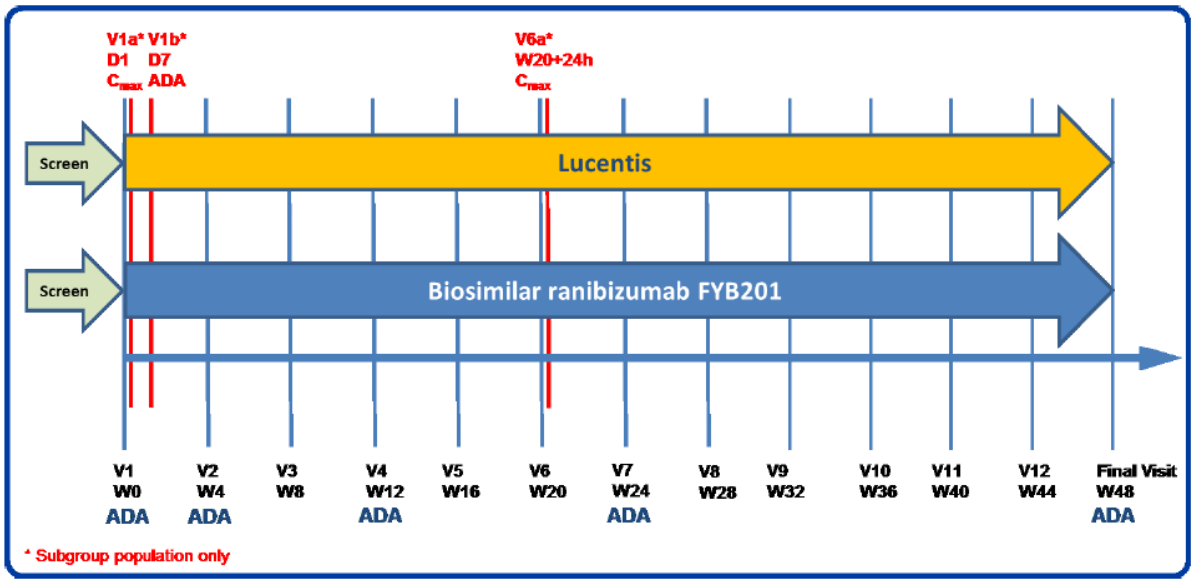
COLUMBUS-AMD (FYB201-C2015-01-P3)

This was a 12-month (48-week), Phase III, randomised, active-controlled, evaluation-masked, parallel-group, multicentre study to demonstrate clinical equivalence in terms of clinical pharmacology, efficacy and safety of Ranivisio with US-Lucentis in the treatment of patients with subfoveal nAMD.

US-Lucentis has been chosen for the clinical biosimilarity exercise. This is in accordance with the EMA GL on Similar Biological Medicinal Products (CHMP/437/04 Rev 1). Hence, it is considered adequate that the Phase III study in AMD patients conducted with US-Lucentis as reference might be sufficient for submission of MAA, provided that an acceptable bridging has been demonstrated on analytical level.

Figure. Schematic of study design for COMLUMBUS-AMD

Figure 9-1 Schematic of study design for protocol FYB201-C2015-01-P3



The study was planned to randomise approximately 460 patients at approximately 80 study sites in the EU, Ukraine, Russia and Israel. Inclusion was stratified according to screening BCVA 20/32 (0.63) Snellen equivalent [maximum 48 patients] vs. equal to or worse than 20/40 (0.50) Snellen equivalent [minimum 412 patients].

An overview of the planned and actual patients randomised is provided in the table below.

Table. Study sites and patients

Table 9-1 Study sites and patients

	Planned	Actual
Study Sites	80	75
Number of randomized patients	460	477
Stratified to screening BCVA 20/40 (0.50) – 20/100 (0.2) Snellen equivalent	412 (minimum)	431
Stratified to screening BCVA 20/32 (0.63) Snellen equivalent	48 (maximum)	46

All patients received monthly IVT injections for a period of approximately 12 months (48 weeks). Patients were studied for approximately 5 months (20 Weeks) and received 6 IVT injections up to the main analysis, and for 12 months (48 Weeks) receiving 12 IVT injections up to the final analysis.

Before participating in the active treatment phase of the study, patients underwent an examination for eligibility during the Screening period, which had a maximum duration of 28 days. As part of the screening process, the Central Reading Center (CRC) received the patient's retinal images to provide an independent, masked assessment of patient eligibility regarding FCP, lesion classification, lesion size and area of CNV. Patients had to meet all eligibility criteria at the screening visit, including positive evaluation of the screening retinal images performed by the CRC. After all eligibility requirements were confirmed, eligible patients were randomised into one of the two treatment groups in a 1:1 ratio (Ranivisio : Lucentis).

Patients received Ranivisio or Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as twelve monthly (every 4 weeks) IVT injections starting at Visit 1 (Week 0) through Visit 12 (Week 44) (total of 12 injections). Up to the main analysis, IVT injections starting at Visit 1 (Week 0) through Visit 6 (Week 20) (total of 6 injections) were administered.

This study was designed to be evaluation-masked, neither the patient nor the Investigator(s) who performed the evaluations knew which treatment the patient received. In each site there were at least 2 Masked Staff members and 1 Unmasked Injector who administered the IMP and performed the ophthalmologic pre- and post-injection assessments and questionnaire administration.

Retinal images of study visits were sent to the CRC for grading by trained personnel (and masked to the patient's treatment).

AEs were recorded from the time that the patient had signed the informed consent form.

An independent Data Safety Monitoring Board (DSMB) reviewed safety data on a regular basis and ad hoc if needed.

All patients had a final follow-up visit at Week 48 (Month 12). In case of premature discontinuation (withdrawal from the study before Week 48), the patient underwent a final follow-up visit at the moment of early termination, if possible.

The end of the study was defined as the date of the last visit of the last patient (last patient last visit [LPLV]).

PK subgroup

Systemic ranibizumab concentration close to Cmax after first and sixth IVT injections, (24 hours post IVT injection), and ADA formation one week after first IVT injection were assessed in a subgroup of up to 60 patients at selected sites randomly assigned in a ratio 1:1 to either Ranivisio or Lucentis.

Samples obtained pre-first dose, at 24 ± 3 hours after first IVT injection (close to Cmax) and at 24 ± 3 hours after sixth IVT injection (close to Cmax) were used to measure systemic concentration of ranibizumab. Another sample one week after first IVT injection was used to determine ADAs.

Overall, the study was adequately designed with Ranivisio versus US-Lucentis administered into the study eye ITV route for 12 doses every 4 weeks (up to Week 48).

Study duration was 48 weeks, which is considered adequately long to investigate long-term efficacy as well as immunogenicity and safety events.

The treatment scheme and posology is identical to that of Lucentis. The dose of Ranivisio was selected to reflect the standard clinical use of Lucentis (0.5 mg via ITV route every 4 weeks) to treat AMD.

A parallel-group design was chosen. This is supported, due to the long average vitreous half-life of ranibizumab of approximately 9 days, and the potential of ADA response.

The selected patient population (neovascular AMD) was considered as the most appropriate population for a clinical Phase III study to demonstrate the similarity in clinical efficacy between Ranivisio and Lucentis. This is endorsed, since in the pivotal studies for the treatment of neovascular AMD with Lucentis, the overall difference in BCVA between Lucentis and control group was largest in subjects with AMD, which supports the choice of neovascular AMD as the most sensitive indication compared to DME, RVO, and CNV to detect possibly existing differences between the treatments. The choice of the patient population was also endorsed by the CHMP during prior EMA SA.

Methods

Study Participants

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 FA, including all subtypes of nAMD

Term	Definition
AMD	Clinical signs (including findings by retinal imaging) attributable to AMD (e. g. pigmentary changes, drusen) and no other likely etiologic explanations for the degenerative changes
Primary	Initial diagnosis within six months of the Screening visit
Subfoveal	Including the center of the fovea
Juxtafoveal	At least some part of CNV lesion must be in an area up to 199 µm from the geometric center of the fovea
Total area of whole lesion	A contiguous area of abnormal tissue that contains a CNV (as documented by FA) with possible additional components of hemorrhages, blocked fluorescence not from hemorrhage, serious detachment of the retinal pigment epithelium, atrophy, and subretinal fibrosis

6) Sufficiently clear ocular media and adequate pupillary dilation to permit good quality ocular imaging

7) BCVA in the study eye, determined by standardised ETDRS testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent

8) FCP retinal thickness at Screening ≥ 350 μ m. (FCP thickness was defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric centre of the fovea)

Ocular (Fellow Eye)

9) BCVA in the fellow eye, determined by standardised 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 institutionalised

Prior or current ocular treatment

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 haemorrhage that comprised more than 50% of the entire lesion in the study eye

9) Fibrosis or atrophy involving the centre 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 haemorrhage 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.

Inclusion and exclusion criteria are considered adequate and suitable for proof of biosimilarity with respect to clinical efficacy between Lucentis and test product. Eligibility criteria are in general in line with previous trials. Patients with newly diagnosed nAMD are appropriate for the biosimilarity study.

Disease severity at inclusion was discussed by CHMP during prior SA. Total area of whole lesion was set among the inclusion criteria. According to the study protocol, it had to be equal or less than 12 disc areas. Reducing the upper limit of lesion size for study inclusion was recommended by the CHMP during the prior SA to improve the homogeneity of the population. This was not followed by the applicant. The applicant decided to stay in line with the MARINA and PIER studies of the originator product in respect of the inclusion criterion "baseline lesion size ≤12 disc areas".

The applicant provided analysis of patients, who had a lesion size between 9 and 12 disc areas: only 8 patients (1.9%) (4 Ranivisio [1.9%] and 4 Lucentis [1.9%]) in the FAS_EU analysis set, and 7 patients (1,7%) (4 Ranivisio [2.0%] and 3 Lucentis [1.5%]) in the PPS_EU analysis set.

As the number of patients who had a lesion size between 9 and 12 disc areas was very low (N=8, 1.9%), no effect on the homogeneity of the study is expected.

An upper BCVA boundary of 20/40 was recommended for study inclusion by the CHMP during prior SA (instead of 20/32, as defined by the applicant in the inclusion criteria), in order to ensure that the study population is sensitive enough to BCVA changes. This was not followed by the applicant.

However, with regard to primary EP analysis, for the EMA the primary endpoint (change from BL in BCVA at Wk 8) was evaluated in the subgroup of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent, in order to fulfill CHMP/ EMA recommendations. This is considered adequate.

The recruitment of patients with FCP retinal thickness at Screening ≥ 350 µm is acceptable.

Uncontrolled hypertension or glaucoma in the study eye defined as intraocular pressure (IOP) ≥ 30 mm Hg was set among the exclusion criteria. Ranibizumab may cause a further increase in intraocular pressure. IOP ≥ 30 mm Hg is at the limit of the value, when the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of an intraocular pressure is ≥30 mmHg, as stated in the SmPC of Lucentis. The applicant was invited to specify how many patients experienced the increase of IOP to ≥ 30 mm Hg during the study and how it was dealt with them during the study. According to the applicant, no patient experienced the increase of pre-injection IOP to ≥30 mmHg during the study. Therefore, no action regarding withholding the dose had to be taken as stated in the SmPC of Lucentis. The increase of post-injection IOP to ≥30 mmHg was observed during the whole study, however, in line with the SmPC of Lucentis the transient increases in IOP have been seen within 60 minutes of injection of ranibizumab.

Systemic comorbidities including uncontrolled systemic hypertension listed among the exclusion criteria are appropriately predetermined. Exclusion criteria regarding prior and concomitant ocular treatment and systemic medical history are acceptable and in line with other trials.

Treatments

The Investigational Medicinal Products (IMPs) were **Ranivisio** and **US-Lucentis**.

After randomisation, patients received Ranivisio (test product) or Lucentis (reference product) at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as twelve (12) monthly (every 4 weeks) IVT injections given at Visit 1 to Visit 12 (Week 44). Up to the main analysis at Visit 7 (Week 24), IVT injections at Visit 1 to Visit 6 (Week 20) (a total of six-monthly injections) were given.

IVT injections were performed by an Unmasked Injector (ophthalmologist) at the clinical study centre. Few days before the injection, the Injector or their staff called the patient to remind him/her the day of the injection visit. The patient's medical history for hypersensitivity reactions was carefully evaluated prior to performing the IVT procedure.

The injection procedure was carried out under aseptic conditions. Adequate anesthesia and a broad-spectrum microbicide to disinfect the periocular skin, eyelid and ocular surface was administered prior the injection, in accordance with local practice, standard practice at the site and at discretion of the Injector. Prior to and 30 minutes following the intravitreal injection, patients were monitored for elevation in intraocular pressure using tonometry. Monitoring could also consist of a check for perfusion of the central retinal artery immediately after the injection. Patients were also monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection. Antibiotic drops (pre-, per-, or postoperative) were not required at the time of or after the procedure, but could be prescribed when considered the standard of care at the site and at the discretion of the Injector.

Selection of doses and timing of dose for each patient

The treatment scheme and posology are identical to that of Lucentis. The dose of Ranivisio was selected to reflect the standard clinical use of Lucentis (0.5 mg via ITV route every 4 weeks) to treat AMD.

Identity of Investigational Products

Both test drug Ranivisio and comparator drug Lucentis were supplied to the Investigators as solution for IVT in single-use glass vials at dose strengths of 10 mg/mL.

The comparator Lucentis was the US-licensed product. Then, it was de-labeled and re-labeled with a label identical to that of the test product (Ranivisio) (booklet label on vial). Primary packaging was similar, only the flip-off caps of Ranivisio and Lucentis primary packaging were colored differently. The secondary packaging of Ranivisio and Lucentis was identical. Packaging and labelling of IMP complied with Annex 13 of the EU Good Manufacturing Practice (GMP) regulations and local regulatory requirements.

Primary packaging: Biosimilar ranibizumab Ranivisio and Lucentis were supplied as solution for IVT injection in single-use glass vials (type I glass).

Withholding study treatment

Study treatment could be withheld, and treatment was not resumed earlier than the next scheduled treatment, in the event of:

- A decrease in BCVA of ≥ 30 letters compared with the last assessment of visual acuity

- An intraocular pressure of ≥ 30 mmHg

- A retinal break

- A subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area

- Performed or planned intraocular surgery within the previous or next 28 days (except in case of cataract surgery, which required withdrawal from the study, see below)

The Masked Investigator finally decided on withholding an IVT injection or withdrawing a patient from the study on a case-by-case basis.

Removal of patients from therapy or assessment

The following criteria were used for withdrawing a patient from the study:

- Patient decided to withdraw from the study (patient withdrew informed consent)

- Administration of concomitant medication prohibited by the protocol

- Cataract surgery in the study-eye

- Concurrent illness

- AEs

- Major protocol deviations

- Need of alternative treatment

- Pregnancy

- Patient was lost to follow-up

The reason and date the patient was withdrawn from the study was documented in the eCRF (e.g. lost to follow-up, consent withdrawn, incorrect enrolment, AEs, lack of efficacy, etc.). If a patient was withdrawn from further treatment with the IMP, the Masked Investigator attempted to complete the final study assessments. Patients who withdrew due to an AE were to be followed up until resolution of the AE, or the Masked Investigator or delegated staff member decided that the AE was stable and needed no further follow-up.

If a patient was withdrawn from the study, all data collected until the time of withdrawal were used in the analyses, unless otherwise required by local regulations.

Objectives

Primary objective

The primary objective of this study was to evaluate and compare functional changes in best corrected visual acuity (BCVA) after 2 months (8 weeks) of treatment with Ranivisio or Lucentis, compared to baseline BCVA.

The primary objective was identical for the main and the final analysis. The primary objective was evaluated based on fully clean data at the main analysis. The primary objective was re-run at the final analysis but no changes of the results were observed.

Secondary objectives for the main analysis

The secondary objectives for the main analysis were to:

- Evaluate and compare functional changes of the retina by BCVA **over time**

- Evaluate and compare changes in foveal centre point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness **over time**

- Evaluate and compare presence of active choroidal neovascularisation (CNV) leakage at **Month 6** compared to baseline

- Evaluate and compare the absence of disease activity (fluid-free macula) **over time**

- Evaluate and compare total lesion size at **Month 6** compared to baseline

- Evaluate and compare systemic ranibizumab concentrations close to Cmax after the first and the sixth doses (24 hours post-dose [± 3 hours]) in a subgroup of up to 60 patients (up to 30 per arm)

- Evaluate and compare change in vision-related functioning and well-being measured by National Eye Institute Visual Function Questionnaire 25 (NEI VFQ-25) at **Month 6** compared to baseline

- Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum

- Evaluate and compare local and systemic adverse events (AEs) and serious adverse events (SAEs)

For all objectives evaluated **over time at the main analysis**, this refers to all assessments performed up to and including Month 6 [Week 24] and final visit assessments for patients who discontinued early prior to Month 6 [Week 24].

Secondary objectives for the final analysis

All secondary objectives evaluated at the main analysis were **re-run** at the final analysis and no changes of the results were observed. Additionally, the following secondary objectives were evaluated or updated at the final analysis:

- Evaluate and compare functional changes of the retina by BCVA **over time**

- Evaluate and compare changes in foveal centre point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness **over time**

- Evaluate and compare presence of active choroidal neovascularisation (CNV) leakage at **Month 12** compared to baseline

- Evaluate and compare the absence of disease activity (fluid-free macula) **over time**

- Evaluate and compare total lesion size at **Month 12** compared to baseline

- Evaluate and compare change in vision-related functioning and well-being measured by NEI VFQ-25 at **Month 12** compared to baseline

- Evaluate and compare the immunogenic profile (anti-drug antibodies [ADAs]) in serum

- Evaluate and compare local and systemic AEs and SAEs

For all objectives evaluated **over time at the final analysis**, this refers to all assessments performed up to and including the final visits of all randomised patients.

Outcomes/endpoints

Primary endpoint

The primary endpoint of the study was the change from baseline in BCVA by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) of treatment.

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.

The primary endpoint was identical for the main and the final analysis. The primary endpoint was evaluated based on fully clean data at the main analysis. The analysis of the primary endpoint was re-run at the final analysis and no changes of the results were observed.

Originally, two independent primary endpoints had been proposed for the COLUMBUS-AMD study: Change from BL in BCVA by ETDRS letters after 12 months for the FDA and change from BL in foveal centre point (FCP) retinal thickness by SD-OCT at Week 4 for the EMA.

The originally designed primary endpoint change from baseline FCP retinal thickness was finally included among secondary endpoints. The change from baseline in BCVA and retinal thickness are both considered as sufficiently sensitive endpoints that allow detection of the product-related differences. The primary endpoint based on BCVA, measured using the ETDRS charts, is validated and continuous metric which captures macular function well and it is a suitable outcome measure for statistical analysis. An early 2-month (8 weeks) time point minimises the potential impact of confounding factors later in the study.

The choice of the originally designed morphological endpoint for the EU was overall endorsed and agreed with CHMP during EMA SA, against the background that visual function endpoints did not detect differences in clinical trials (e.g. the CATT study) when comparing ranibizumab to bevacizumab, in contrast to morphological endpoints for which ranibizumab outperformed bevacizumab, thus being able to sensitively detect product-related differences. During EMA SA, it was also stated by the CHMP that retinal thickness outcomes were expected to correlate with visual acuity in the early treatment phase, to support this morphological endpoint.

Based on this recommendation, the applicant conducted a blinded visual review of the two endpoints in a subset of patients, indicating only limited individual correlation between functional (BCVA) and anatomical (FCP) parameter. With a protocol amendment No. 6 (08 March 2017), the primary EU and US endpoints were "harmonised", i.e. only one primary endpoint for both EU and US, was defined; namely the change in BCVA between baseline and Week 8. This rather late shift of the primary endpoint for the EU was not discussed with the CHMP during any SA procedure; it was communicated to the EMA via notification only. During the EMA pre-submission meeting in June 2020, this change in the primary EP was also discussed. Within this context, the EMA recommended to perform a post-hoc correlation analysis of BCVA-FCP results for all patients.

The applicant was requested to justify this late shift in the primary endpoint, since this was not explicitly addressed in the study protocol and might pose a challenge for the intended robust demonstration of similar efficacy. With their response, the applicant clarified that this change in the primary endpoint was deemed necessary, as the underlying assumption for choosing FCP, i.e. that a correlation between FCP retinal thickness and BCVA could be demonstrated, was proven difficult if not impossible to demonstrate. In addition, it was emphasised that a retrospective analysis showed that also the initially proposed primary EP, the change from BL in FCP retinal thickness up to Wk 4, was met.

Secondary endpoints for the main analysis

Secondary endpoints for the main analysis included:

- Change from baseline in BCVA by ETDRS letters **over time**

- Changes from baseline in FCP retinal thickness and FCS retinal thickness **over time**

- Percentage of patients with active CNV leakage **at Month 6**

- Percentage of patients with fluid-free macula **at each visit**

- Change from baseline in total lesion area **at Month 6**

- Summary of systemic ranibizumab concentrations close to Cmax after the first and the sixth IVT injections (24 hours post-dose [± 3 hours]) in a subgroup of patients (up to 30 per arm, in total up to 60)

- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 **at Month 6**

- Number of patients with anti-drug antibodies **over time**

- Frequency of local and systemic AEs and SAEs (up to the safety cut-off for the main analysis).

For all endpoints evaluated **over time at the main analysis**, this refers to all assessments performed up to and including Month 6 [Week 24] and final visit assessments for patients who discontinued early prior to Month 6 [Week 24]. The local and systemic AEs and SAEs are presented for the entire duration of the study.

Secondary endpoints for the final analysis

All analyses for secondary endpoints evaluated at the main analysis were re-run at the final analysis and no changes of the results were observed.

Additionally, the following secondary endpoints were evaluated or updated at 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 FCP retinal thickness and FCS retinal thickness **over time**

- Percentage of patients with active CNV leakage **at Month 12**

- Percentage of patients with fluid-free macula **at each visit**

- Change from baseline in total lesion area **at Month 12**

- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 **at Month 12**

- Number of patients with anti-drug antibodies **over time**

- Frequency of local and systemic AEs and SAEs

For all objectives evaluated **over time at the final analysis**, this refers to all assessments performed up to and including the final visits of all randomised patients.

Secondary endpoints provide additional supportive and clinical meaningfulness to the primary endpoint. As visual function depends on several components, not only VA, but also contrast sensitivity, near vision, colour vision, and sensitivity to glare, the inclusion of vision-related functioning and well-being measured by NEI VFQ-25 is reasonable. NEI VFQ-25 was reported to be valid and reliable measure of health-related QoL.

In comparison to other trials, responder analyses, such as the proportion of subjects who lost fewer than 15 letters/gained 15 letter or more in BCVA compared with baseline were not included in the initial analyses. On request a responder analysis of patients who lost fewer than 5, 10, 15 letters/gained 5, 10, 15 letter or more in BCVA compared with baseline was provided in test and reference treatment arm to further support the biosimilarity between Ranivisio and the reference medicinal product Lucentis.

Sample size

The sample size was calculated on the basis of the following assumptions and study design features:

- 1:1 randomisation ratio
- 90% power
- 95% confidence interval (alpha 2.5% each side)
- Equivalence margin of 3.5 ETDRS letters
- Standard deviation (SD) of 10 ETDRS letters

A total of 412 patients (206 per group) were planned for the primary analysis. Considering the additional inclusion criteria for the EU population (Snellen equivalent of 20/40 or worse instead of 20/32 for the US population), and assuming that ca. 10% of all the recruited patients would have a Snellen equivalent better than 20/40, 460 patients (230 per group) were planned to be enrolled in the study.

The assumptions for the sample size planning are overall acceptable and the sample size calculation could be replicated. 477 patients were randomised in the study, which is in line with the planned sample size.

Since the primary endpoint was changed over the course of the study, the SD margin was also updated. This is acceptable, however the sponsor was asked to justify the choice of the SD at 10 ETDRS letters, since this was not motivated in the protocol amendments. The applicant motivated the choice of the 10 ETDRS letters for the sample size calculation on the basis of a publicly available report issued by the Center for Drug Evaluation and Research (CDER) for aflibercept (Eylea). Ranibizumab was used as reference product in the pivotal non-inferiority studies.

As the evaluation of the primary endpoint was done in the FAS population (and not, as usually recommended, on the PPS population), it can be post-hoc accepted that no adjustment for the expected rate of protocol deviations or potential drop-outs was included in the sample size calculation. The rate of dropouts in the study were minimal and did not substantially affect the sample size for the primary analysis (475 patients were included in the US analysis, 429 in the EU analysis).

Randomisation and blinding (masking)

Randomisation was performed at a 1:1 ratio stratified by site and screening BCVA category (20/32 (0.63) Snellen equivalent, or 20/40 (0.50) – 20/100 (0.2) Snellen equivalent) based on the dynamic allocation method. Patients were randomised using an interactive voice response system (IVRS) or interactive web response system (IWRS). Once a maximum of 48 patients with a screening BCVA of 20/32 (0.63) were enrolled, randomisation to this stratum was stopped.

Treatment allocation in the PK subgroup was not planned to be fully balanced between the two groups, as the inclusion in the PK subgroup was planned independently from the randomisation.

The randomisation ratio and stratification are acceptable and in line with the objective of the study. Except for France, where twice as many participants were assigned to Ranivisio as to Lucentis (14 to 6, SAF data), other relevant baseline characteristics were well balanced between the two treatment arms.

No further details regarding the randomisation method were presented in the initial submission. The sponsor was asked to provide details on the randomisation procedure to rule out any issues regarding potential determinism or predictability of the treatment group allocation, in particular: 1) how dynamic allocation method works and 2) if randomisation scheme is the same for each centre as randomisation is stratified by site. Randomisation process used in study FYB201-C2015-01-P3 was considered from article Pocock, Simon (1975): Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial, Biometrics 31, 103-115. This process used dynamic allocation to individual treatments as randomisation was stratified by best corrected visual acuity (BCVA) (mild, i.e. 20/32 Snellen equivalent, vs. moderate/severe, i.e. 20/40-20/100 Snellen equivalent) and centre. The applicant provided an example in response to a question from the CHMP. A patient with mild BCVA was considered and was to be randomised either to Ranivisio treatment (Ranivisio) or Lucentis treatment (Lucentis). Value of function G‘(t) was calculated separately for t=1 which represented Ranivisio and for t=2 which represented Lucentis. Value for G‘(t) was obtained as sum of current number of patients with mild BCVA and current number of patients within centre 3 for t=1 (Ranivisio) and t=2 (Lucentis), respectively. If G‘(1)<G‘(2) then there was higher probability to be assigned into Ranivisio (t=1) than into Lucentis (t=2). If G‘(2)<G‘(1) then there was higher probability to be assigned into Lucentis (t=2) than into Ranivisio (t=1). If G‘(1)=G‘(2) then probability of assignment was equal both for Ranivisio and for Lucentis. This can be considered as acceptable randomisation procedure.

This study was designed to be evaluation-masked, i.e. the study staff (except for the Unmasked Injector/s) and the patients were not aware of the treatment assignment.

In each site there were at least 2 Masked Staff members (one of whom was the Principal Investigator and the other was the VA Examiner) and 1 Unmasked Injector (who administered the IMP). There could be also other masked study site staff (e.g. study coordinator, study nurse, OCT technician, photographer, back-up Masked Investigator, back-up VA Examiner). The Unmasked Injector could also have a back-up person and/or designated assistant(s).

The Principal Investigator (or his/her masked study team to whom tasks had been delegated) did all pre- and post-injection assessments (Tonometry and Ophthalmologic Examination, SD-OCT, FA and color fundus photography, blood samples collection [for ADAs, PK and safety laboratory assessments] and NEI VFQ-25 questionnaire administration), except measurements of refraction and VA. The Masked Investigator/s also assessed the relationship of all AEs to IMP, including those noted by the Unmasked Injector.

Only the Masked VA Examiners measured refraction and BCVA. The Masked VA Examiners were not permitted to have any further roles in obtaining data from a patient; however, they were allowed to perform additional study support tasks such as e.g. read-out of the temperature logger.

Only the Unmasked Injector performed IVT injections. They could also perform the safety check or post-dose tonometry, according to the clinical practice of the study site.

Measures were taken to ensure that neither the patient nor the masked study personnel became aware of the treatment administered. Site staff monitored the receipt, storage, dispensing, and accounting of all IMPs. Ranivisio and Lucentis had the same secondary packaging and were indistinguishable. The unmasked clinic staff did not discuss the treatment administered with the masked staff.

The applicant states that a double-blind study was not possible due to the design of the primary packaging of the two products. Therefore, the person administering the injections and conducting the post-injection safety checks was unmasked to the treatment. All other assessments were be performed by masked investigators. This is in contrast to another pivotal study for a ranibizumab biosimilar, where the Sponsor ensured that the primary packaging was identical, and thus also the Injector was masked. Overall, this approach can be accepted, provided stringent steps have been taken to ensure that the patient will remain blind, to avoid any bias on the study outcomes. The approach was also discussed with and agreed by the CHMP during SA procedure (EMA/CHMP/SAWP/772413/2014).

Emergency unmasking of treatment assignment

In the case of a medical emergency or in the event of a serious medical condition, the Masked Investigator or the Unmasked Injector were allowed to decide to unmask a patient's treatment, if it was judged to be essential for the clinical management or welfare of the patient.

No emergency unblinding was required during the study. Five unblindings were performed due to administrative reasons within the pharmacovigilance process in the framework of SUSAR reporting. Patients, Sponsor, Investigators, and all other parties involved in the study remained blinded.

Statistical methods

Analysis sets

Safety Set (SAF):

The safety set comprised all patients who had received at least one injection with investigational medicinal product (IMP). The safety set was used as general analysis set for all kinds of safety and tolerability data. Patients were analysed according to the treatment they actually received irrespective of their randomised 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 analysed.

The following analyses sets were considered for US- and EU-specific populations:

Full Analysis Set for the US (FAS_US):

The FAS_US was based on the intention to treat (ITT) principle (i.e., patients were analysed according to their randomised treatment irrespective of the treatment they actually received) and 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.

Full Analysis Set for the EU (FAS_EU):

The FAS_EU was based on the ITT principle (i.e., patients were analysed according to their randomised treatment irrespective of the treatment they actually received) and 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 20/40 and 20/100 Snellen equivalent in the study eye.

Per-Protocol Set for the US (PPS_US):

The PPS_US included all patients who belonged to the FAS_US who had no major protocol deviations until V3 (Visit 3 after 8 weeks) that would interfere with the interpretation of BCVA efficacy data.

Per-Protocol Set for the EU (PPS_EU):

The PPS_EU included all patients who belonged to the FAS_EU who had no major protocol deviations until V3 (Visit 3 after 8 weeks) that would interfere with the interpretation of BCVA efficacy data.

PK Subgroup Analysis Set (PKS):

The PKS included all patients who received an initial injection of IMP, who had a valid measurement close to Cmax (post-first dose), and who had no major protocol deviations that would interfere with the interpretation of the ranibizumab concentration data (e.g., a high ADA titre may interfere with the PK assay and might lead to a major protocol deviation if the interpretation of the concentration data is disturbed or limited; such cases were discussed on a by-patient basis in the BDRM for the main analysis (see Appendix 16.1.9 for the BDRM minutes for the main analysis)).

Patients in PKS were analysed according to the treatment they actually received irrespective of their randomised treatment.

Handling of Intecurrent events

The applicant evaluated intercurrent events (IEs) retrospectively as guideline ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials was issued on 2020 while study FYB201-C2015-01-P3 was performed between 2015 and 2018.

As shown in the tables below, sixteen (16) IEs occurring in patients in the FAS were mentioned. Strategies for dealing with each mentioned intercurrent event (IE) for full analysis population for the EU (FAS_EU) and per protocol population for the EU (PPS_EU) were treatment policy strategy and principal stratum strategy, respectively. Considering that the trial was run before the fully applicability of the Estimands framework, the description of IEs is sufficient. It is also observed that the incidence of IEs is balanced across treatment groups.

Table. Intercurrent events and strategies for handling them.

Table 25 Intercurrent events and strategies for patients included in the FAS_EU

No.	Protocol deviation criterion text from BDRM or criterion for exclusion from analysis	Intercurrent event	Strategy for FAS_EU / PPS_EU analysis	Occurrence	
				FYB201 (N=215) n (%)	Lucentis (N=214) n (%)
1.	FAS: Definition of visit window for analysis visit V3/Week 8: 43 ≤ study day ≤ 71 PPS: Visit window deviation: No BCVA assessment between scheduled study day 50 and 64	Discontinuation of study when finding out that entry criteria had been violated, with only one post-baseline assessment of BCVA prior to study day 43	Principal stratum (Hypothetical) / Principal stratum	2 (0.9%)	0
2.	FAS: Definition of visit window for analysis visit V3/Week 8: 43 ≤ study day ≤ 71 PPS: Visit window deviation: No BCVA assessment between scheduled study day 50 and 64	Discontinuation of study because of death not related to study medication/procedure, with only one post-baseline assessment of BCVA prior to study day 43	Principal stratum (Hypothetical) / Principal stratum	1 (0.5%)	0
3.	FAS: Definition of visit window for analysis visit V3/Week 8: 43 ≤ study day ≤ 71 PPS: Visit window deviation: No BCVA assessment between scheduled study day 50 and 64	BCVA assessment was not performed between study day 43 and 70 (boundaries included) for unknown reasons and patient completed the study.	Principal stratum (Hypothetical) / Principal stratum	5 (2.3%)	4 (1.9%)
4.	FAS: Definition of visit window for analysis visit V3/Week 8: 43 ≤ study day ≤ 71 PPS: Visit window deviation: No BCVA assessment between scheduled study day 50 and 64	BCVA assessment was not performed between study day 43 and 70 (boundaries included) for unknown reasons and patient discontinued the study later.	Principal stratum (Hypothetical) / Principal stratum	0	1 (0.5%)
5.	PPS: Visit window deviation: No BCVA assessment between scheduled study day 50 and 64	BCVA assessment was performed between study days 43 and 49 or between study days 65 and 70 (boundaries included) and patient completed the study.	Treatment policy/ Principal stratum	0	2 (0.9%)
6.	None	Discontinuation of study for any reason but BCVA assessment between study day 43 and 70 is available	Treatment policy / Treatment policy	7 (3.3%)	11 (5.1%)

No.	Protocol deviation criterion text from BDRM or criterion for exclusion from analysis	Intercurrent event	Strategy for FAS_EU / PPS_EU analysis	Occurrence	
				FYB201 (N=215) n (%)	Lucentis (N=214) n (%)
7.	Concomitant use of any other anti-VEGF agents (except for commercially available Lucentis in the fellow eye after Visit V1) assessed as major PD	Need for concomitant use of any other anti-VEGF agents (except for commercially available Lucentis in the fellow eye after Visit V1) ***prior*** *to the assessment of the primary endpoint.*	Treatment policy / Principal stratum	0	0
8.	Concomitant use of any other anti-VEGF agents (except for commercially available Lucentis in the fellow eye after Visit V1) assessed as minor PD	Need for concomitant use of any other anti-VEGF agents (except for commercially available Lucentis in the fellow eye after Visit V1) ***after*** *the assessment of the primary endpoint.*	Treatment policy / Treatment policy	2 (0.9%)	1 (0.5%)
9.	Intravitreal or periocular injections of corticosteroids or high doses of systemic (oral or intravenous) corticosteroids (administration of >10 mg/day of prednisolone equivalent) assessed as major PD	Need for concomitant use of intravitreal or periocular injections of corticosteroids or high doses of systemic (oral or intravenous) corticosteroids (administration of >10 mg/day of prednisolone equivalent) assessed as *having* ***influence*** *on the primary endpoint assessment*	Treatment policy / Principal stratum	0	1 (0.5%)
10.	Intravitreal or periocular injections of corticosteroids or high doses of systemic (oral or IV) corticosteroids (administration of >10 mg/day of prednisolone equivalent) assessed as minor PD	Need for concomitant use of intravitreal or periocular injections of corticosteroids or high doses of systemic (oral or IV) corticosteroids (administration of >10 mg/day of prednisolone equivalent) assessed as *having* ***no influence*** *on the primary endpoint assessment*	Treatment policy / Treatment policy	8 (3.7%)	8 (3.7%)

No.	Protocol deviation criterion text from BDRM or criterion for exclusion from analysis	Intercurrent event	Strategy for FAS_EU / PPS_EU analysis	Occurrence	
				FYB201 (N=215) n (%)	Lucentis (N=214) n (%)
11.	Current/expected use of systemic medication known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/ hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines and/or ethambutol to be assessed on a case by case basis	Need for concomitant use of systemic medication known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/ hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines and/or ethambutol	Treatment policy / to be assessed	0	0
12.	Injection at Visit 1 at study day 1 has not been administered	Injection at Visit 1 (baseline) was not administered, but subsequent injections were administered	Treatment policy / Principal stratum	0	0
13.	Compliance regarding injections. Injection 2 is prior to study day 22 or later than study day 36	Injection at Visit 2 was administered prior to scheduled study day 22 or later than scheduled study day 36	Treatment policy / Principal stratum	0	2 (0.9%)
14.	Compliance regarding injections. Injection 2 was not administered	Injection at visit 2 was not administered at all.	Treatment policy / Principal stratum	2 (0.9%)	3 (1.4%)
15.	Volumes of injection 1 or 2 were not fully administered (< 0.05mL)	Volumes of injection 1 or 2 not fully administered (i.e. injection volume < 0.05mL)	Treatment policy / Principal stratum	0	0
16.	Discontinuation of treatment prior to assessment of the primary endpoint due to a related AE or treatment failure	Discontinuation of treatment prior to assessment of the primary endpoint due to a related AE or treatment failure	Treatment policy / Treatment policy	0	0

FAS_EU = Full analysis set for the EU, PPS_EU = Per protocol set for the EU, N = number of patients in the FAS_EU and denominator for percentages, n = number of patients within the category, BDRM = Blind data review meeting, BCVA = Best-corrected visual acuity, AE = adverse event

Table 26 Strategies and alignment of estimators for analyses based on the FAS_EU and the PPS_EU

No. (see Table 25)	Strategy for FAS_EU and PPS_EU analysis	Estimator
1. – 4.	Primary FAS analysis: Principal stratum	ANCOVA: Since no relevant post-baseline data was collected for the patient and no change from baseline could be calculated, the patient was excluded from analysis.
1. – 4.	Secondary FAS analysis: Hypothetical	MMRM: Relevant data from other time points and from patients with similar baseline characteristics is used to estimate the missing data at the relevant time point.
5. -15.	FAS Analysis: Treatment policy	ANCOVA and MMRM: Data as assessed was used for analysis without taking into account any intercurrent event.
1. - 5.	PPS Analysis: Principal stratum	ANCOVA
6.	PPS Analysis: Treatment policy	ANCOVA
7.	PPS Analysis: Principal stratum	ANCOVA
8.	PPS Analysis: Treatment policy	ANCOVA
9.	PPS Analysis: Principal stratum	ANCOVA
10.	PPS Analysis: Treatment policy	ANCOVA
11.	PPS Analysis: Treatment policy or principal stratum depending on whether there is an influence on the primary endpoint assessment	ANCOVA
12. - 15.	PPS Analysis: Principal stratum	ANCOVA
16.	PPS Analysis: Treatment policy	ANCOVA or MMRM or other estimation

FAS = Full analysis set for the EU, PPS = Per protocol set for the EU, ANCOVA = analysis of covariance, MMRM = mixed model repeated measures

Primary Endpoint

The primary endpoint was defined as the change in ETDRS letters from baseline to Week 8. The primary hypothesis set to be evaluated was the following:

$H_0 : |\mu_{BCVA,Ranivisio} - \mu_{BCVA,Lucentis}| \geq 3.5$ vs $H_1: |\mu_{BCVA,Ranivisio} - \mu_{BCVA,Lucentis}| < 3.5$

Analysis of covariance (ANCOVA) was planned to be used for the evaluation of the primary endpoint: 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 analysis was planned to be performed on the FAS_EU and the FAS_US.

Handling of missing data: see 'Supplementary Analyses for Primary Endpoint'.

Two analyses were planned to be conducted:

- A main analysis after all randomised patients have either completed the Week 24 assessments or have discontinued the study before 24 Weeks (database lock: 20-Apr-2018)
- A final analysis after all randomised patients have either completed the Week 48 assessments or have discontinued the study (database lock: 01-Oct-2018)

The sponsor disclosed in the study report that the methods for the two analyses overlapped to a broad extent and only presents the results from the final analysis.

Supplementary Analyses for Primary Endpoint

The calculation of the primary endpoint was planned to be repeated on the PPS_EU and PPS_US.

Data from patients who prematurely discontinue the trial were planned to be used to the maximum extent possible. Patterns and reasons for missing data were planned to be examined. A Mixed Model Repeated Measures (MMRM) approach with unstructured covariance matrix was planned as sensitivity analysis to handle missing data.

Secondary Endpoints

As the primary endpoints (US and EU) were changed during the study, the originally planned primary endpoints were evaluated as secondary endpoints. These were:

- Change in BCVA over time (from baseline to Weeks 24, 48, average over Weeks 40, 44 and 48)
- FCP and FCS retinal thickness change over time (from baseline to Weeks 4, 24, 48)

These endpoints were planned to be evaluated via ANCOVA in the respective populations (FAS US and EU, PPS as sensitivity analysis for FCP; PPS_EU for FCS only if at least 10% of the FAS_EU patients had protocol deviation).

Additional secondary endpoints: total lesion area (mm^2, from baseline to Weeks 24 and 48), CNV leakage (% of patients, measured at baseline and at Weeks 24 and 48); fluid-free macula (% of patents, measured at baseline and at Weeks 4 to 48), NEI VFQ-25 Questionnaire (measured at baseline and at Weeks 24 and 48). These endpoints were planned to be evaluated descriptively in the respective populations (FAS US and EU; PPS_EU for total lesion area only if at least 10% of the FAS_EU patients had protocol deviation).

Multiplicity

No multiplicity control was planned or performed in the study.

Interim and Subgroup Analyses

No interim analyses were planned in the final version of the study protocol. No subgroup analyses for efficacy endpoints were planned to be performed, but selected endpoint values were summarised descriptively by country and visit number.

The analysis plan for efficacy data presented in the study protocol version 9.0 and in the SAP was overall acceptable and consistently implemented.

The originally planned primary endpoints for EU and US were homogenised in a later protocol version, which was submitted after approximately one year since the beginning of the study. This is not considered critical, as equivalence was shown also in the originally planned primary endpoints and respective populations (see below).

In general, the primary analysis of an equivalence study should be based on a population that is sensitive to demonstrate equivalence. Protocol violations may tend to bias the results towards a conclusion of equivalence, see ICH E9. Therefore, the PPS is the preferred analysis set for the primary efficacy analysis (CPMP/EWP/482/99). The applicant defined the FAS population to be the primary efficacy population, which is

not endorsed, but provided sensitivity analyses on the PPS, which is accepted since similarity was shown in both analysis sets.

The primary analysis was conducted, as pre-specified, via ANCOVA. However, the boxplots depicting BCVA over time in the two study arms showed a heavy tail in the data, which raised the question whether the ANCOVA assumptions are matched. The applicant addressed this issue by providing additional analyses not relying on the same distributional assumptions as well as appropriate residual plots.

No subgroup analyses had been performed for the primary endpoint. Upon request, the applicant provided additional subgroup analyses by pooled country, total lesion area, and loss in vision acuity at baseline. Overall, biosimilarity was supported in almost all subgroups and no systematic problems were identified.

Overall, the results from the PPS analyses and from the MMRS sensitivity analyses were in line with those from the FAS analyses. The sponsor reported no noticeable patterns in missing data. Nevertheless, the applicant performed required sensitivity analyses to address different patterns of missing data and provided a more detailed description of intercurrent events and their handling.

The sponsor did not perform multiplicity control despite the two different endpoints for two geographical reasons. This is considered acceptable.

The sponsor reported that the methods for the main and final analysis (conducted after having collected the Week 24 and Week 48 data, respectively) were overlapping between the two analyses, and reports no results for the main analysis.

Results

Participant flow

Between 19-Dec-2015 and 14-Jun-2017, 712 patients were enrolled and screened (10 patients were re-screened) in the study in 75 sites in Europe, Russia, Ukraine and Israel (enrollment per country in Table 10-2); 477 patients were randomised into one of the two treatment groups to receive monthly treatment with either Ranivisio or Lucentis, and 241 patients (4 re-screened patients) were not randomised (Figure 10-1).

The most common reasons for not being randomised were failures to meet randomisation criteria (215 patients; 87.8%), withdrawal by subject (19 patients; 7.8%) and AEs (4 patients; 1.6%).

During the first screening, 1 patient did not meet all inclusion and exclusion criteria and was successfully re-screened later

Additionally, 9 further patients were re-screened of whom 5 successfully; these patients were randomised, and 4 still failed to meet randomisation criteria in the second screening; these patients were excluded.

Of the 477 randomised patients, 238 patients were allocated to the Ranivisio treatment group and 239 patients were allocated to the US-Lucentis treatment group.

Up to the final analysis, 12 patients (5.0%) in the Ranivisio group and 13 patients (5.4%) in the Lucentis group discontinued the study prematurely; 16 patients (6.7%) in each group discontinued treatment. Reasons for premature study discontinuation recorded in both treatment groups appeared balanced, with withdrawal by patient (Ranivisio: 2 patients, Lucentis: 8 patients), AE (Ranivisio: 1 patient, Lucentis: 2 patients), lost to follow-up (Ranivisio: 3 patients, Lucentis: 1 patient), and other (Ranivisio: 4 patients, Lucentis: 2 patients). In the Ranivisio group, one additional patient had a major protocol deviation and another patient needed alternative treatment.

Up to the main analysis, 8 patients in the Ranivisio group and 6 patients in the Lucentis group discontinued the study early; a total of 10 patients discontinued treatment up to the main analysis.

Table. Patient disposition

Table 10-1 Patient 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	100.0%	239	100.0%	477	100.0%
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.
Source: Post-text tables 14.1.1.1, 14.1.1.3.1

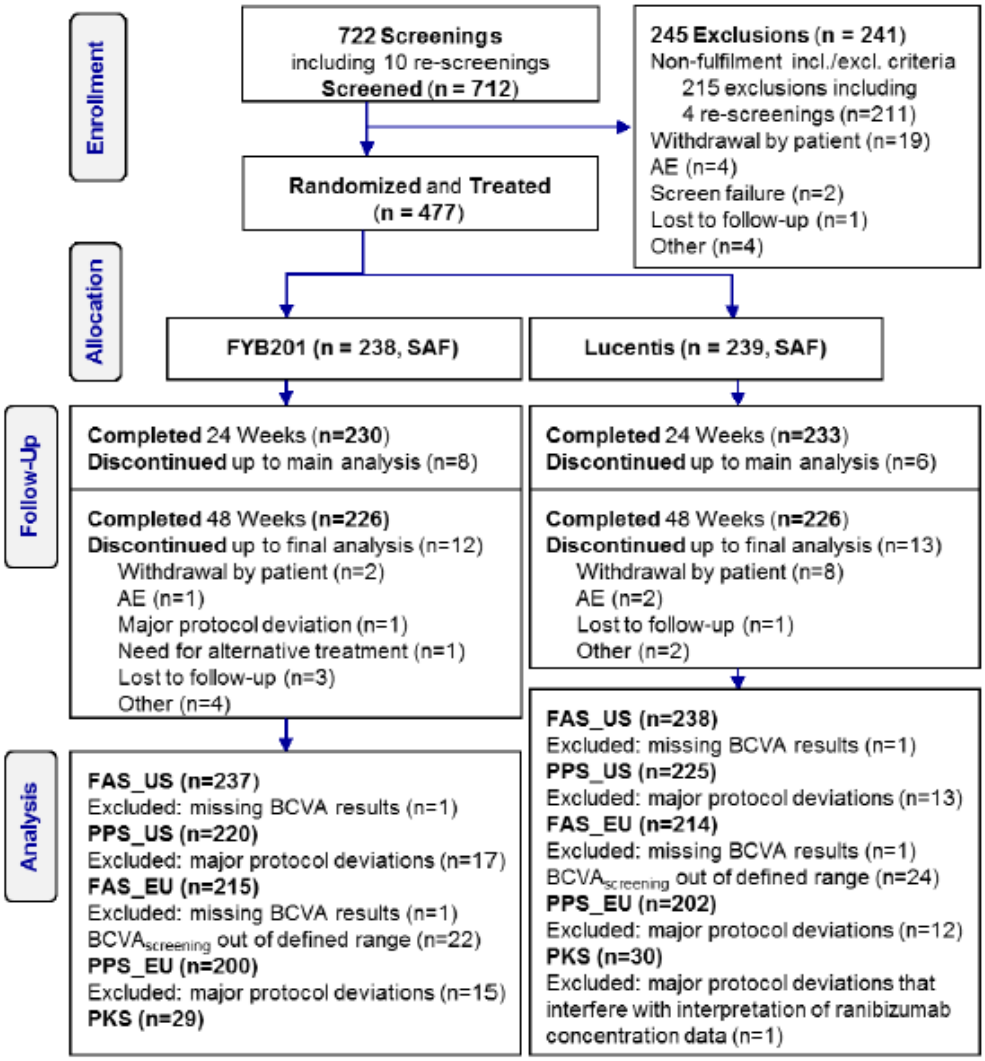


Figure 10-1 Patient disposition diagram

Source: Post-text tables 14.1.1.1, 14.1.1.2, 14.1.1.3., 14.1.1.5 and 14.1.1.6

n = number of patients, AE = adverse event, BCVA = best-corrected visual acuity, SAF= Safety set, FAS_US = Full analysis set for the US (baseline BCVA between 20/32 and 20/100 Snellen equivalent), FAS_EU = Full analysis set for the EU (baseline BCVA between 20/40 and 20/100 Snellen equivalent), PPS_US = Per protocol set for the US, PPS_EU = Per protocol set for the EU, PKS = Pharmacokinetic Subgroup Analysis Set

The number of patients who completed the study were overall comparable between treatment arms. The most common reasons for premature discontinuation (before Week 48) were consent withdrawal and adverse events.

4 patients in the Ranivisio arm and 2 patients in the US-Lucentis arm discontinued the study prematurely due to "other reasons" (see Table 10-1 in CSR). Three patients died (Ranivisio: 2;; Lucentis: 1). One patient (Lucentis) moved. One patient (Ranivisio) was incorrectly enrolled into the study in error and subsequently discontinued the study. One patient (Ranivisio) was withdrawn by the investigator due to multiple adverse events and thus discontinued the study.

Up to week 24, there was an imbalance between treatment arms with regard to study treatment discontinuation (n=7 in the Ranivisio arm vs. n=3 in the Lucentis arm). The applicant provided the reasons for treatment discontinuation prior to Wk 24 and stated that there might be a higher probability of an uneven distribution without reason with such small numbers. This is acknowledged, against the background that, overall up to final analysis, the number of patients who discontinued treatment was similar in both treatment arms (n=16 in each arm).

Recruitment

Study Start: 19 Dec 2015

Study Completion Date: 06 Jun 2018

The study was conducted at a total of 75 sites in 11 EU countries, as well as in Ukraine, Russia and Israel.

Table 7

Table 10-2 provides an overview of the number and percentage of randomized and treated patients within each country.

Table 10-2 Number of patients by country – SAF

Country	FYB201 (N = 238) n (%)	Lucentis (N = 239) n (%)	Total (N = 477) n (%)
Austria	3 (1.3%)	4 (1.7%)	7 (1.5%)
Czech Republic	30 (12.6%)	32 (13.4%)	62 (13.0%)
France	14 (5.9%)	6 (2.5%)	20 (4.2%)
Germany	17 (7.1%)	20 (8.4%)	37 (7.8%)
Hungary	32 (13.4%)	25 (10.5%)	57 (11.9%)
Israel	42 (17.6%)	44 (18.4%)	86 (18.0%)
Italy	33 (13.9%)	30 (12.6%)	63 (13.2%)
Poland	36 (15.1%)	42 (17.6%)	78 (16.4%)
Russia	5 (2.1%)	4 (1.7%)	9 (1.9%)
Spain	20 (8.4%)	22 (9.2%)	42 (8.8%)
Ukraine	1 (0.4%)	3 (1.3%)	4 (0.8%)
United Kingdom	5 (2.1%)	7 (2.9%)	12 (2.5%)

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
Source: Post-text table 14.1.2.2.1.1

Recruitment of subjects by country was overall balanced between treatment arms, except for France, where twofold more subjects were recruited into the Ranivisio treatment arm.

Conduct of the study

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.

The major PDs were slightly higher for Ranivisio than for US-Lucentis with 18 (7.6%) versus 14 (5.9%). Main reasons for exclusion from the PPS were the lack of valid BCVA assessment between Day 50 to 64 and violation of in- or exclusion criteria.

Nearly half of the patients had at least one minor protocol deviation with 225 patients (47.2%), these minor protocol deviations were well balanced between both treatment groups (Ranivisio: 46.6%; Lucentis: 47.7%). Most of patients with minor protocol deviations had deviations from the injection schedule (148 patients), from study procedures (53 patients), from visit schedule (76 patients), and that the BCVA assessment occurred between Day 50–53 or Day 61–64 (27 patients). Also, intake of prohibited concomitant medication was a frequent minor protocol deviation (35 patients).

The number and proportion of minor protocol deviations regarding compliance to visit-, injection-, and assessment-schedule over a study duration of 12 months can be explained by the patient population with an interquartile (IQR) age range between 70.0 and 81.0 years, with concomitant diseases ongoing at screening in 440 patients (92.2%) and concomitant medications recorded in all 477 patients.

Any minor GCP issues were recorded in 181 patients (37.9%), with an issue concerning the informed consent procedure as the most frequent issue (152 patients; 31.9%), these patients signed a new version of the informed consent form delayed or had signed a version of the informed consent form that did not include PK sampling. Also, a number of patients had a blood sample issue (31 patients; 6.5%) in which blood sample collection or handling was not according to protocol. Fewer patients had minor GCP issues with respect to failure to report SAE in a timely manner (10 patients; 2.1%) and to personnel, facilities or equipment (7 patients; 1.5%).

Table 8

Table 10-3 Protocol deviations – SAF

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Major protocol deviations	18	7.6%	14	5.9%	32	6.7%
No BCVA assessment between Day 50–64	10	4.2%	8	3.3%	18	3.8%
Injection 2 before Day 22 or after Day 36	0	0.0%	2	0.8%	2	0.4%
Missing injections	2	0.8%	3	1.3%	5	1.0%
Violation of inclusion/exclusion criteria	8	3.4%	3	1.3%	11	2.3%
PK data (interference with interpretation of ranibizumab concentration data)	0	0.0%	1	0.4%	1	0.2%
Prohibited concomitant medications	1	0.4%	1	0.4%	2	0.4%

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Minor protocol deviations	**111**	**46.6%**	**114**	**47.7%**	**225**	**47.2%**
BCVA assessment between Day 50–53 or Days 61–64	15	6.3%	12	5.0%	27	5.7%
Blood sample issue	5	2.1%	8	3.3%	13	2.7%
Violation of inclusion/exclusion criteria	5	2.1%	5	2.1%	10	2.1%
Missing ADA assessment	2	0.8%	4	1.7%	6	1.3%
Prohibited concomitant medications	17	7.1%	18	7.5%	35	7.3%
Randomization procedure and possible unblindings	2	0.8%	1	0.4%	3	0.6%
Other	0	0.0%	1	0.4%	1	0.2%
from injection schedule:	**68**	**28.6%**	**80**	**33.5%**	**148**	**31.0%**
Injection deviates from schedule more than ±14 days	4	1.7%	4	1.7%	8	1.7%
Injection 2 between Day 22–25 or Day 33–36	12	5.0%	12	5.0%	24	5.0%
Missing injections	28	11.8%	40	16.7%	68	14.3%
Time between 2 injections <22 days	9	3.8%	15	6.3%	24	5.0%
Time between 2 injections >34 days	59	24.8%	73	30.5%	132	27.7%
from study procedures:	**31**	**13.0%**	**22**	**9.2%**	**53**	**11.1%**
Missing study procedures	23	9.7%	12	5.0%	35	7.3%
Study procedures out of window	8	3.4%	11	4.6%	19	4.0%
from visit schedule:	**36**	**15.1%**	**40**	**16.7%**	**76**	**15.9%**
Missing visits	31	13.0%	36	15.1%	67	14.0%
Visits out of window	6	2.5%	5	2.1%	11	2.3%
Any minor GCP issue	89	37.4%	92	38.5%	181	37.9%
Blood sample issue	15	6.3%	16	6.7%	31	6.5%
Failure to report SAE in a timely manner	3	1.3%	7	2.9%	10	2.1%
Informed consent procedure	78	32.8%	74	31.0%	152	31.9%
Personnel, facilities or equipment	2	0.8%	5	2.1%	7	1.5%

Abbreviations: BCVA = best-corrected visual acuity, PK = pharmacokinetic, N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients (within each group) * 100
Source: Post-text tables 14.1.1.7.1, 14.1.1.8.1

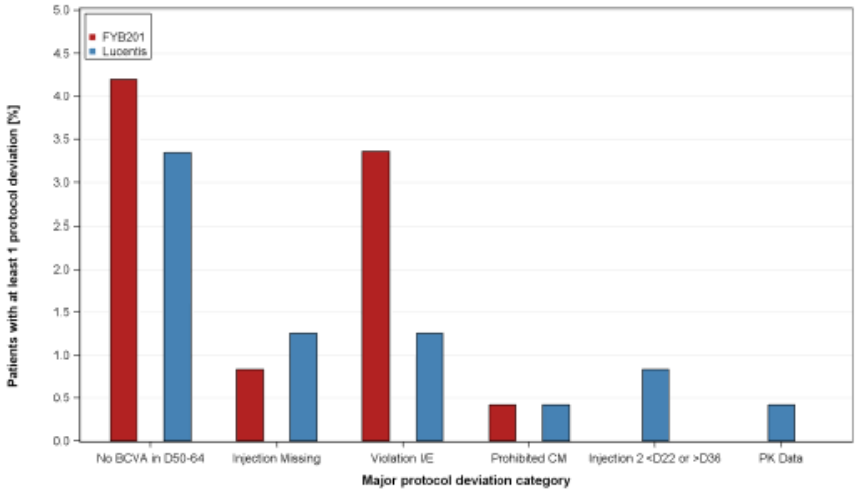


Figure 10-2 Major protocol deviations - SAF

BCVA = best-corrected visual acuity, D = day, CM = concomitant medication, I/E = inclusion/exclusion criteria, PK = pharmacokinetic, SAF: Safety set

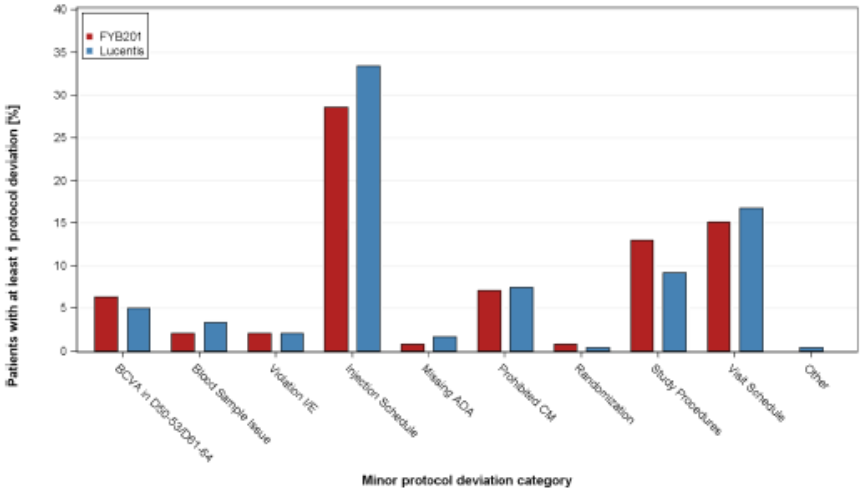


Figure 10-3 Minor protocol deviations - SAF

ADA = anti-drug antibody, BCVA = best-corrected visual acuity, D = day, CM = concomitant medication, I/E = inclusion/exclusion criteria, SAF: Safety set

Note: The following minor protocol deviation categories were summarized: "Injection schedule" includes Injection deviates from schedule more than ±14 days, Injection 2 between Day 22–25 or Day 33–36, Missing injections, Time between 2 injections <22 days, and Time between 2 injections >34 days; "Study procedures" includes Missing study procedures and Study procedures out of window; "Visit schedule" includes Missing visits and Visits out of window.

Changes in the conduct of the study

No changes in the conduct of the study occurred.

However, various amendments to the protocol have been made:

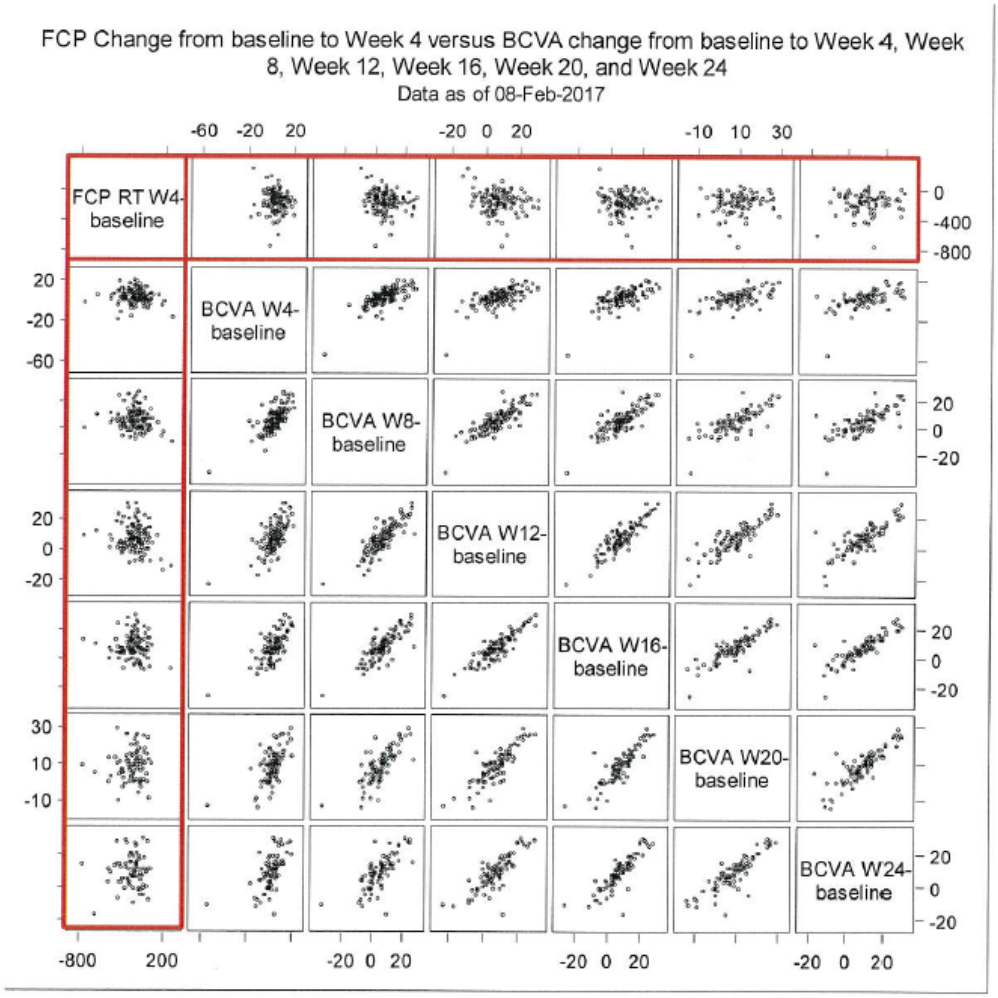
Table 9

16.1.1.1 Overview of protocol amendments

Amendment No.	Leading to protocol		Topic of the changes
	Version	Date	
1 (non-substantial)	2.0	09-Sep-2015	In response to comments received during the VHP, withholding criteria added, DSMB members specified to be external, new exclusion criterion added: prisoners and employees
2 (non-substantial)	3.0	19-Nov-2015	Addition of baseline BCVA as stratification factor, insertion of additional exclusion criteria, specification of ETDRS charts to be used
3 (substantial)	4.0	30-Nov-2015	Additional sampling points in PK Subgroup, exclusion criterion related to acute treatment need of fellow eye at Visit 1 added
4 (non-substantial)	5.0	26-Jul-2016	Clarification on fellow eye during enrollment, corticosteroid application, physical assessment
5 (substantial, withdrawn)	6.0	18-Jan-2017	Change of US primary endpoint, clarification on interim analysis, removal of trough level sampling
6 (substantial)	7.0	08-Mar-2017	Replaced Amendment 5. Harmonization of primary EU and US endpoint, adaption of sample size, removal of interim analysis and trough level sampling
4, 5, 6 (substantial)	8.0	10-May-2017	Local protocol version for France due to comments from the French CA.
7 (non-substantial)	9.0	29-Aug-2017	Inclusion of [redacted] and additional labs for PK and nAb assay, following protocol version 7.0
7 (non-substantial)	9.0 FRA	29-Aug-2017	Country-specific protocol version for France following version 8.0 incorporates all changes added to protocol version 9.0
Local 3 ITA (substantial, withdrawn)	6.0	18-Jan-2017	Equivalent to global amendments 3, 4 and 5
Local 3 ITA (substantial)	7.0	08-Mar-2017	Equivalent to global amendments 3, 4, 5 and 6
Local 1 RUS (substantial, withdrawn)	6.0	18-Jan-2017	Equivalent to global Amendments 4 and 5
Local 1 RUS (substantial)	7.0	08-Mar-2017	Equivalent to global Amendments 4, 5 and 6

Based on scientific advice given by EMA and FDA, two independent primary endpoints had been defined initially: Change in BCVA (FDA) and Change from baseline in foveal centre point (FCP) retinal thickness at Week 4 (EMA). With respect to the morphological endpoint (FCP thickness), scientific advice by EMA requested the correlation of retinal thickness with visual acuity in the early treatment phase.

Figure 1 Visual assessment of correlation between change in FCP retinal thickness (Week 4 – baseline) and changes in visual acuity between baseline and weeks 4, 8, 12, 16, 20, and 24



The presented pooled data regarding the correlation between FCP change at Week 4 and BCVA at Weeks 4 to 24 show that the two variables are not correlated at Week 4, but that the correlation improves over time. This is in line with the improvement over time in FCP and BCVA presented in Figure 1 and Figure 2 of the Clinical Overview.

It should be noted that such a correlation between a highly specific, "isolated" morphological endpoint reflecting retinal thickness and a more "broad" and complex functional endpoint such as BCVA would not have been expected during the early treatment phase.

Subsequently, the study protocol was changed by a substantial amendment (Amendment 6) addressing the following aspects:

• Harmonisation of the primary endpoint(s), i.e. only one primary endpoint for both EMA and FDA, namely the **change in BCVA between baseline and Week 8**

• Adaptation of the sample size

• Amendment of the secondary endpoints to include the assessment of change in BCVA between baseline and scores at Months 10-12 (previously the US primary endpoint)

• Removal of the interim analysis

Changes in the planned analysis

The study protocol was substantially amended in March 2017 (V7.0). In the previous version of the protocol (V4.0), one primary endpoint for EU and one for US were defined. In the amended version, the endpoint was homogenised, and the same endpoint was used in both geographical regions (although the two estimand still differed in the analysis population).

Primary endpoints as defined in protocol V4.0 (30-Nov-2015)	**Primary endpoint as defined in protocol V7.0 (08-Mar-2017)**
For the EU: Change from baseline in FCP retinal thickness by SD-OCT at month 1 (4 weeks). This endpoint will be evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent.	Change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment. For the US, this endpoint will be evaluated in all patients with a baseline BCVA between 20/32 and 20/100 Snellen equivalent, while for the EU the endpoint will be evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent.
For the US: Change from baseline in BCVA by ETDRS letters after 12 months of treatment, averaged over months 10 (40 weeks), 11 (44 weeks) and 12 (48 weeks). This endpoint will be evaluated in all patients with a baseline BCVA between 20/32 and20/100 Snellen equivalent.	

As a consequence, key study assumptions were amended and the sample size updated (null expected difference, randomisation ratio 1:1 and power ≥ 90% unchanged):

Key assumptions and sample size as defined in protocol V4.0 (30-Nov-2015)	**Key assumptions and sample size as defined in protocol V7.0 (08-Mar-2017)**
Total sample size: 650 subjects, of which 400 in the stratum 20/40 Snellen equivalent or worse and 250 in the stratum 20/32 to 20/40 Snellen equivalent.	Total sample size: 460 patients, of which 412 in the stratum 20/40 Snellen equivalent or worse and 48 in the stratum 20/32 to 20/40 Snellen equivalent.
For the EU: - Equivalence margin for primary endpoint: 40 µm - SD: 100 µm	- Equivalence margin for primary endpoint: 3.5 ETDRS letters - SD: 10 ETDS letters - CI: 95% (EMA requirements)

- CI: 95% (EMA requirements) - Drop out: 20% Resulting in a sample size of 328 evaluable patients with a BCVA between 20/40 and 20/100 Snellen equivalent.	- Drop out: 20% - Patients with BVCA better than 20/40: 10% Resulting in a sample size of 412 evaluable patients, thus 460 patients with a BCVA between 20/32 and 20/100 Snellen equivalent.
For the US: - Equivalence margin for primary endpoint: 4.5 ETDRS letters - SD: 15 ETDRS letters - CI: 90% (FDA requirements) - Drop out: 20% - Expected reduction of sample size due to reduction in the within-subject variance: 12.5% Resulting in a sample size of 536 evaluable patients, thus 650 patients with a BCVA between 20/32 and 20/100 Snellen equivalent to be randomised.	

Moreover, a change in the stratification parameter (from "baseline BCVA" to "screening BCVA") triggered a series of amendments in the endpoint and population definitions The change in the patient stratification was documented in a corresponding protocol Amendment 6, reflecting Section 6.3 of the Protocol V9.0:

- Change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment.

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

The definitions of the US- and EU-specific FAS were amended accordingly in the SAP and "baseline BCVA" was replaced by "screening BCVA" throughout. However, in the study report (e.g. sections 8.2 (endpoints), 11.1 (efficacy analysis results)), in the last protocol version and in the clinical overview, the formulation "change from baseline" is still used. The Sponsor was asked to clarify (and correct) the errors in the study report, or to specify when baseline and screening are meant. The applicant has clarified that patient eligibility and allocation were defined by the screening BCVA value (Visit 0, screening), but the change from baseline (Visit 1, prior to first injection of the study treatment) was evaluated as the primary endpoint. Furthermore, the definitions of the US- and EU-specific FAS were revised in the SAP and the criterion "for whom efficacy results at least after 1 month are available" was changed to "for whom BCVA results at least after 1 month are available" to provide a more precise definition.

Baseline data

Patient demographics of the SAF are presented in table 16

Table 10

Table 10-5 Demographics and other baseline characteristics – SAF

	FYB201 (N = 238)	Lucentis (N = 239)	Total (N = 477)
Gender [n (%)]			
Male	103 (43.3%)	105 (43.9%)	208 (43.6%)
Female (no women of childbearing potential)	135 (56.7%)	134 (56.1%)	269 (56.4%)
Age at Screening [years]			
n	238	239	477
Missing	0	0	0
Mean (SD)	74.9 (8.26)	76.1 (7.84)	75.5 (8.07)
Median	76.0	77.0	76.0
Interquartile range (Q1–Q3)	69.0–81.0	71.0–81.0	70.0–81.0
Range (min–max)	50–91	50–94	50–94
Age Categories at Screening [n (%)]			
50–64 years	25 (10.5%)	19 (7.9%)	44 (9.2%)
65–75 years	91 (38.2%)	86 (36.0%)	177 (37.1%)
>75 years	122 (51.3%)	134 (56.1%)	256 (53.7%)
Race [n (%)]			
Caucasian	236 (99.2%)	233 (97.5%)	469 (98.3%)
Asian	0 (0.0%)	2 (0.8%)	2 (0.4%)
Other	2 (0.8%)	4 (1.7%)	6 (1.3%)
BMI at Screening [kg/m^2]			
n	238	239	477
Missing	0	0	0
Mean (SD)	27.17 (4.084)	27.40 (4.467)	27.29 (4.277)
Median	26.28	26.83	26.67
Interquartile range (Q1–Q3)	24.46–29.07	24.06–30.11	24.42–29.72
Range (min–max)	19.9–42.9	17.8–44.0	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
Source: Post-text table 14.1.2.1.1

The mean (SD) age of patients in the SAF was 75.5 (8.07) years, and the mean BMI was 27.29 (4.227) kg/m^2. 56.4% of the patients (269 patients) in the SAF were female; the majority of patients were Caucasian (98.3%) and about half of the patients were older than 75 years.

In general, the demographic characteristics were balanced between treatment arms. There was slight predominance of older patients (age category >75 years) in test arm in comparison with Lucentis arm. Overall females were represented in greater numbers in the study throughout the arms.

Baseline characteristics for patients of the SAF are summarised in Table 17.

Table 11

Table 10-6 Other baseline characteristics – SAF

	FYB201 (N = 238)	Lucentis (N = 239)	Total (N = 477)
Study eye [n (%)]			
OD (right eye)	127 (53.4%)	127 (53.1%)	254 (53.2%)
OS (left eye)	111 (46.6%)	112 (46.9%)	223 (46.8%)
Iris color [n (%)]			
Light	89 (37.4%)	89 (37.4%)	178 (37.4%)
Medium	104 (43.7%)	100 (42.0%)	204 (42.9%)
Dark	45 (18.9%)	49 (20.6%)	94 (19.7%)
Missing	0	1	1
Baseline Snellen equivalent in study eye [n (%)]			
20/32	24 (10.1%)	22 (9.2%)	46 (9.6%)
20/40	43 (18.1%)	38 (15.9%)	81 (17.0%)
20/50	45 (18.9%)	39 (16.3%)	84 (17.6%)
20/63	37 (15.5%)	46 (19.2%)	83 (17.4%)
20/80	37 (15.5%)	37 (15.5%)	74 (15.5%)
20/100	52 (21.8%)	57 (23.8%)	109 (22.9%)
Baseline Snellen equivalent in fellow eye [n (%)]			
20/12.5	2 (0.8%)	3 (1.3%)	5 (1.0%)
20/16	20 (8.4%)	7 (2.9%)	27 (5.7%)
20/20	63 (26.5%)	53 (22.2%)	116 (24.3%)
20/25	42 (17.6%)	59 (24.7%)	101 (21.2%)
20/32	47 (19.7%)	59 (24.7%)	106 (22.2%)
20/40	22 (9.2%)	27 (11.3%)	49 (10.3%)
20/50	21 (8.8%)	12 (5.0%)	33 (6.9%)
20/63	10 (4.2%)	8 (3.3%)	18 (3.8%)
20/80	6 (2.5%)	4 (1.7%)	10 (2.1%)
20/100	5 (2.1%)	7 (2.9%)	12 (2.5%)

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100
Source: Post-text table 14.1.2.1.1

All baseline characteristics were comparable between both treatment groups and differences in baseline characteristics in the different analysis sets were negligible compared to the SAF.

However, the applicant was requested to present a tabulated summary of the study population per treatment arm by region (EU/ non-EU), for the sake of completeness. Tabulated summaries of the analysis sets have been provided for both the EU and non-EU region, as requested. Demographic data and other baseline characteristics were overall comparable between both regions.

The right eye was treated as the study eye for 53.2% of the patients (254 patients) in the SAF; the iris color was light for 37.4% (178 patients), medium for 42.9% (204 patients), and dark for 19.7% (94 patients) of the patients in the SAF. The baseline BCVA ranged from 20/32 to 20/100 Snellen equivalent for the study eye and from 20/12.5 to 20/100 Snellen equivalent for the fellow eye for patients in the SAF.

Other baseline characteristics by visual acuity strata

Following patient eligibility criteria for screening BCVA, all patients in the SAF had the visual acuity stratum screening BCVA 20/32 (0.63) to 20/100 (0.2) Snellen equivalent fulfilled and therefore, other baseline characteristics for the patients within the visual acuity stratum screening BCVA 20/32 (0.63) to 20/100 (0.2) Snellen equivalent are displayed in *Table 13* above.

Differences for other baseline characteristics between patients of the SAF who were stratified to screening BCVA 20/40 (0.50) - 20/100 (0.2) Snellen equivalent compared to patients in the SAF were negligible (*Table 14*). All baseline characteristics were similar in both treatment groups for both visual acuity strata.

Morphological BL characteristics of the study participants, such as CST and CPT, as well as IOP and total lesion area at baseline for both treatment arms have been provided, as requested. CST, CPT, IOP and total lesion area at BL were overall comparable between both treatment arms, in all three analysis sets.

Table 12

Table 10-7 Other baseline characteristics in patients with screening BCVA 20/40 (0.50) – 20/100 (0.2) Snellen equivalent – SAF

	FYB201 (N = 216)	Lucentis (N = 215)	Total (N = 431)
Study eye [n (%)]			
OD (right eye)	116 (53.7%)	115 (53.5%)	231 (53.6%)
OS (left eye)	100 (46.3%)	100 (46.5%)	200 (46.4%)
Iris color [n (%)]			
Light	77 (35.6%)	84 (39.3%)	161 (37.4%)
Medium	97 (44.9%)	88 (41.1%)	185 (43.0%)
Dark	42 (19.4%)	42 (19.6%)	84 (19.5%)
Missing	0	1	1
Baseline Snellen equivalent in study eye [n (%)]			
20/32	9 (4.2%)	2 (0.9%)	11 (2.6%)
20/40	36 (16.7%)	34 (15.8%)	70 (16.2%)
20/50	45 (20.8%)	39 (18.1%)	84 (19.5%)
20/63	37 (17.1%)	46 (21.4%)	83 (19.3%)
20/80	37 (17.1%)	37 (17.2%)	74 (17.2%)
20/100	52 (24.1%)	57 (26.5%)	109 (25.3%)
Baseline Snellen equivalent in fellow eye [n (%)]			
20/12.5	1 (0.5%)	2 (0.9%)	3 (0.7%)
20/16	19 (8.8%)	5 (2.3%)	24 (5.6%)
20/20	55 (25.5%)	47 (21.9%)	102 (23.7%)
20/25	39 (18.1%)	54 (25.1%)	93 (21.6%)
20/32	42 (19.4%)	55 (25.6%)	97 (22.5%)
20/40	20 (9.3%)	25 (11.6%)	45 (10.4%)
20/50	20 (9.3%)	12 (5.6%)	32 (7.4%)
20/63	10 (4.6%)	7 (3.3%)	17 (3.9%)
20/80	6 (2.8%)	3 (1.4%)	9 (2.1%)
20/100	4 (1.9%)	5 (2.3%)	9 (2.1%)

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100

Source: Post-text table 14.1.2.2.2.1

CNV in the fellow eye of the patients was recorded at screening and is presented in *Table 15* for the SAF only. At screening, similar numbers and percentages of patients with and without CNV in the fellow eye were recorded in both treatment groups.

Table 13

Table 10-8 CNV in the fellow eye at screening – SAF

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Patients with CNV assessment in fellow eye	176	100.0%	182	100.0%	358	100.0%
No CNV	164	93.2%	176	96.7%	340	95.0%
CNV	12	6.8%	6	3.3%	18	5.0%
Missing	62		57		119	

Abbreviations: CNV = Choroidal Neovascularization, N = total number of patients, n = number of patients within specified category, % = number of patients within specified category / total number of patients per visit * 100
Source: Post-text table 14.1.2.5

Baseline BCVA in US- and EU-specific range (strata)

The number and percentage of patients who had a screening and baseline BCVA within the US or EU-specific range are presented in *Table 16*.

Table 14

Table 10-9 Patients with EU- or US-specific baseline BCVA – FAS_US and FAS_EU

FAS_US **Baseline BCVA within US-specific range** (20/32 (0.63) – 20/100 (0.2) Snellen equivalent)	**FYB201 (N = 237)**	**Lucentis (N = 238)**	**Total (N = 475)**
Yes [n (%)]	237 (100%)	238 (100%)	475 (100%)
No [n (%)]	0 (0.00%)	0 (0.00%)	0 (0.00%)
FAS_EU **Baseline BCVA within EU-specific range** (20/40 (0.50) – 20/100 (0.2) Snellen equivalent)	**FYB201 (N = 215)**	**Lucentis (N = 214)**	**Total (N = 429)**
Yes [n (%)]	206 (95.8%)	212 (99.1%)	418 (97.4%)
No [n (%)]	9 (4.2%)	2 (0.9%)	11 (2.6%)

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/ total number of patients * 100,
Source: Post-text tables 14.1.2.4.1, 14.1.2.4.2

All patients with a screening BCVA within the US-specific range also had a baseline BCVA within the US-specific range. For the EU-specific range, 11 patients had a screening BCVA but no baseline BCVA within the specific range. The applicant outlines that these patients would have been excluded from the EU-specific analysis if the baseline BCVA would have been considered for stratification.

Medical history

In the SAF, 440 patients (92.2%) had an ongoing medical history at screening (*Table 17*). Similar numbers and percentages of patients who had any medical history at all or who had any specific medical histories ongoing at screening were observed in both treatment groups, and no relevant imbalances were identified.

Most frequently, medical history was recorded in the system organ class (SOC) Vascular disorders with 326 patients (68.3%) and the most common preferred term (PT) was Hypertension with 298 affected patients (62.5%).

Additionally, medical history was frequently reported in the SOCs Metabolism and nutrition disorders (252 patients; 52.8%), Musculoskeletal and connective tissue disorders (151 patients; 31.7%), Cardiac disorders (113 patients; 23.7%), Gastrointestinal disorders (95 patients; 19.9%), Psychiatric disorders (92 patients;

19.3%) and Endocrine disorders (75 patients; 15.7%). Other medical histories were reported in less than 15% of the overall number of patients.

The incidence of patients reporting any ongoing medical history at screening and the type of reported medical history was in accordance with an elderly patient population.

Table 15

Table 10-10 Medical history that was ongoing at screening in ≥15% of patients - SAF

MedDRA SOC PT	FYB201 (N = 238) n	 %	Lucentis (N = 239) n	 %	Total (N = 477) n	 %
Any medical history ongoing at screening	217	91.2%	223	93.3%	440	92.2%
Vascular disorders						
Overall	157	66.0%	169	70.7%	326	68.3%
Hypertension	146	61.3%	152	63.6%	298	62.5%
Metabolism and nutrition disorders						
Overall	115	48.3%	137	57.3%	252	52.8%
Hypercholesterolaemia	65	27.3%	70	29.3%	135	28.3%
Musculoskeletal and connective tissue disorders						
Overall	65	27.3%	86	36.0%	151	31.7%
Cardiac disorders						
Overall	56	23.5%	57	23.8%	113	23.7%
Gastrointestinal disorders						
Overall	42	17.6%	53	22.2%	95	19.9%
Psychiatric disorders						
Overall	37	15.5%	55	23.0%	92	19.3%
Endocrine disorders						
Overall	41	17.2%	34	14.2%	75	15.7%
Reproductive system and breast disorders						
Overall	27	11.3%	39	16.3%	66	13.8%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/total number of patients*100, MedDRA = Medical Dictionary for Regulatory Activities, SAF = Safety Set, SOC = System Organ Class, PT = Preferred Term
Notes: MedDRA version 19.0 was used
Source: Post-text table 14.1.3.1.1

Ophthalmologic history

In the SAF, all patients (477 patients; 100.0%) had an ophthalmologic medical history that was ongoing at screening (*Table 18*). The frequency and the type of all reported ophthalmologic medical history that was ongoing at screening was balanced between both treatment groups and no important differences were identified.

Information with regard to the mean interval since first diagnosis of neovascular AMD at baseline for both treatment arms has been provided as requested: The time since first diagnosis of nAMD was calculated in two analyses. Since the date of the nAMD diagnosis was not fully provided for 66 patients (26 in the Ranivisio and 40 patients in the Lucentis arm, respectively), for one analysis the time since diagnosis was estimated. In the other analysis, patients without complete information were excluded.

When excluding estimated data, the mean time since first nAMD diagnosis was 40.8 days in the Ranivisio arm versus 30.8 days in the Lucentis arm. When estimated data were included, the difference between study arms was smaller: 72.1 days versus 65.9 days.

Table 16

Table 10-11 Ophthalmologic history that was ongoing at screening in ≥2% of patients - SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any ophthalmologic history ongoing at screening	238	100.0%	239	100.0%	477	100.0%
Eye disorders						
Overall	238	100.0%	239	100.0%	477	100.0%
Neovascular age-related macular degeneration	238	100.0%	239	100.0%	477	100.0%
Dry age-related macular degeneration	98	41.2%	85	35.6%	183	38.4%
Cataract	84	35.3%	72	30.1%	156	32.7%
Age-related macular degeneration	18	7.6%	18	7.5%	36	7.5%
Choroidal neovascularisation	11	4.6%	11	4.6%	22	4.6%
Glaucoma	10	4.2%	8	3.3%	18	3.8%
Macular fibrosis	8	3.4%	7	2.9%	15	3.1%
Cataract nuclear	8	3.4%	4	1.7%	12	2.5%
Macular degeneration	6	2.5%	6	2.5%	12	2.5%
Astigmatism	8	3.4%	2	0.8%	10	2.1%
Surgical and medical procedures						
Overall	15	6.3%	18	7.5%	33	6.9%
Intraocular lens implant	13	5.5%	18	7.5%	31	6.5%

Abbreviations: N = total of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/total number of patients*100, MedDRA = Medical Dictionary for Regulatory Activities, SAF = Safety Set, SOC = System Organ Class, PT = Preferred Term
Notes: MedDRA version 19.0 was used
Source: Post-text table 14.1.3.3.1

Ophthalmologic history was reported in the SOC Eye disorders (477 patients; 100.0%) with PT Neovascular age-related macular degeneration for all patients, as this was the primary disease of the clinical study. Additional frequently reported PTs were Dry age-related macular degeneration (183 patients; 38.4%) and Cataract (156 patients; 32.7%). Also frequently reported in SOC Surgical and medical procedures (33 patients; 6.9%) was PT Intraocular lens implant (31 patients; 6.5%).

Overall, all reported ophthalmologic history ongoing at screening was in accordance with an elderly patient population suffering from nAMD.

Any ophthalmologic history that had stopped at screening (*Table 19*) was reported for 179 patients (37.5%) of the SAF, with similar frequency and type of reported ophthalmologic history in both treatment groups and no important differences were identified.

Ophthalmologic history that had stopped at screening was most frequently reported in the SOCs Surgical and medical procedures (122 patients; 25.6%) and Eye disorders (117 patients; 24.5%). The most frequently reported PT was Cataract operation (95 patients; 19.9%), followed by Cataract (86 patients; 18.0%). Ophthalmologic histories in the SOC Eye disorders were reported more frequently in the Lucentis group (70 patients; 29.3%) than in the Ranivisio group (47 patients; 19.7%). This difference was not considered important, given the single reported PTs and that the ophthalmologic history had stopped at screening.

Table 17

Table 10-12 Ophthalmologic history not ongoing at screening in ≥2% of patients - SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any ophthalmologic history not ongoing at screening	73	30.7%	106	44.4%	179	37.5%
Surgical and medical procedures						
Overall	51	21.4%	71	29.7%	122	25.6%
Cataract operation	42	17.6%	53	22.2%	95	19.9%
Lens capsulotomy	6	2.5%	8	3.3%	14	2.9%
Lens extraction	4	1.7%	10	4.2%	14	2.9%
Eye disorders						
Overall	47	19.7%	70	29.3%	117	24.5%
Cataract	34	14.3%	52	21.8%	86	18.0%
Dry age-related macular degeneration	5	2.1%	12	5.0%	17	3.6%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/total number of patients*100, MedDRA = Medical Dictionary for Regulatory Activities, SAF = Safety Set, SOC = System Organ Class, PT = Preferred Term
Notes: MedDRA version 19.0 was used
Source: Post-text table 14.1.3.4.1

Other ophthalmologic history

In the SAF, 369 patients (77.4%), reported other past or concomitant ocular diseases than nAMD; 191 patients (40.0%) had past ocular surgeries and most patients (468 patients; 98.1%) reported no planned ocular surgeries (*Table 20*). No important differences concerning other ophthalmologic history were identified between both treatment groups. A higher number of past ocular surgeries was reported for patients in the Lucentis group (111 patients; 46.4%) compared to the patients in the Ranivisio group (80 patients; 33.6%), but considering the reported ophthalmologic history, this difference was not considered relevant.

Table 18

Table 10-13 Other ophthalmologic history - SAF

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Any past/concomitant ocular diseases other than nAMD [n (%)]						
Yes	181	76.1%	188	78.7%	369	77.4%
No	57	23.9%	51	21.3%	108	22.6%
Any past ocular surgeries [n (%)]						
Yes	80	33.6%	111	46.4%	191	40.0%
No	158	66.4%	128	53.6%	286	60.0%
Any planned ocular surgeries [n (%)]						
Yes	4	1.7%	5	2.1%	9	1.9%
No	234	98.3%	234	97.9%	468	98.1%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/total number of patients*100,
Source: Post-text table 14.1.3.5.1

Prior medications and treatments

Prior medications and treatments, defined as medication which had stopped prior to the first dose of study medication, were recorded for all patients in the SAF (477 patients; 100.0%;*Table 21*). The frequency of all types of reported prior medications and therapies was balanced between both treatment groups and no important differences were identified.

Most frequently, prior medications within the ATC level 3 group Mydratics and cycloplegics (474 patients; 99.4%) were reported, with most frequent PTs tropicamide (411 patients; 86.2%) and phenylephrine (210 patients; 44.0%). Other frequently reported ATC level 3 groups were Diagnostic agents (472 patients; 99.0%), Anti-infectives (470 patients; 98.5%) and Local anesthetics (444 patients; 93.1%). Frequent use of mydratics and cycloplegics reflected the eye assessments during screening and frequent use of anti-infectives and local anesthetics reflected the local or standard practice to prepare the patient to receive an IVT injection. In general, the high number and frequency of reported prior medications can be explained by the elderly patient population. Prior medications in ATC level 3 group Other ophthalmologicals were well balanced between both treatment groups and recorded in 90 patients (18.9%), with Iodine (41 patients; 8.6%) and Sodium chloride (19 patients; 4.0%) as most frequent PTs (*Table 21*).

Table 19

Table 10-14 Prior medications and treatments by ATC level 3 and PT in ≥20% of patients or important prior medications - SAF

WHODD ATC level 3	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any prior medication	238	100.0%	239	100.0%	477	100.0%
MYDRATICS and CYCLOPLEGICS						
Overall	235	98.7%	239	100.0%	474	99.4%
TROPICAMIDE	202	84.9%	209	87.4%	411	86.2%
PHENYLEPHRINE	103	43.3%	107	41.8%	210	44.0%
DIAGNOSTIC AGENTS						
Overall	235	98.7%	237	99.2%	472	99.0%
FLUORESCEIN	235	98.7%	235	98.3%	470	98.5%
ANTIINFECTIVES						
Overall	236	99.2%	234	97.9%	470	98.5%
POVIDONE-IODINE	211	88.7%	213	89.1%	424	88.9%
OFLOXACIN	59	24.8%	61	25.5%	120	25.2%
LOCAL ANESTHETICS						
Overall	221	92.9%	223	93.3%	444	93.1%
OXYBUPROCAINE	126	52.9%	119	49.8%	245	51.4%
PROXYMETACAINE	52	21.8%	62	25.9%	114	23.9%
LIDOCAINE	56	23.5%	55	23.0%	111	23.3%
LIPID MODIFYING AGENTS, PLAIN	87	36.6%	99	41.4%	186	39.0%
ANTITHROMBOTIC AGENTS						
Overall	78	32.8%	88	36.8%	166	34.8%
ACETYLSALICYLIC ACID	58	24.4%	61	25.5%	119	24.9%
BETA BLOCKING AGENTS	77	32.4%	80	33.5%	157	32.9%
ACE INHIBITORS, PLAIN	64	26.9%	61	25.5%	125	26.2%
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	45	18.9%	58	24.3%	103	21.6%
OTHER OPHTHALMOLOGICALS	42	17.6%	48	20.1%	90	18.9%
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	14	5.9%	16	6.7%	30	6.3%

Abbreviations: ATC = Anatomical Therapeutic Chemical, 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, PT = Preferred Term, WHODD = World Health Organization (WHO) Drug Dictionary
Notes: WHODD Enhanced Version March 2015 was used.
Source: Post-text tables 14.1.4.1.1

Concomitant medications and treatments

Concomitant medications and treatments were recorded for all patients (477 patients; 100.0%) of the SAF and were balanced between both treatment groups with respect to the occurrence of ATC level 3 groups and PTs (*Table 22*). Again, the high number and frequency of reported concomitant medications and therapies can be explained by the elderly patient population.

The high frequency of the diagnostic agent fluorescein in both treatment groups reflected its necessity to perform the study procedure fluorescein angiography (FA). Frequent use of mydratics and cycloplegics reflected the eye assessments during the study and frequent use of anti-infectives and local anesthetics reflected the local or standard practice to prepare the patient to receive an IVT injection.

Table 20

Table 10-15 Concomitant medications and treatments by ATC level 3 and PT in ≥20% of patients - SAF

WHODD ATC level 3	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any concomitant medication	238	100.0%	239	100.0%	477	100.0%
MYDRATICS and CYCLOPLEGICS						
Overall	236	99.2%	239	100.0%	475	99.6%
TOPICAMIDE	203	85.3%	209	87.4%	412	86.4%
PHENYLEPHRINE	103	43.3%	107	44.8%	210	44.0%
ANTIINFECTIVES						
Overall	237	99.6%	237	99.2%	474	99.4%
POVIDONE-IODINE	214	89.9%	213	89.1%	427	89.5%
OFLOXACIN	61	25.6%	65	27.2%	126	26.4%
DIAGNOSTIC AGENTS						
Overall	233	97.9%	230	96.2%	463	97.1%
FLUORESCEIN	232	97.5%	228	95.4%	460	96.4%
LOCAL ANESTHETICS						
Overall	222	93.3%	224	93.7%	446	93.5%
OXYBUPROCAINE	127	53.4%	120	50.2%	247	51.8%
LIDOCAINE	56	23.5%	59	24.7%	115	24.1%
PROXYMETACAINE	52	21.8%	62	25.9%	114	23.9%
LIPID MODIFYING AGENTS, PLAIN						
Overall	95	39.9%	102	42.7%	197	41.3%
ANTITHROMBOTIC AGENTS						
Overall	86	36.1%	98	41.0%	184	38.6%
ACETYLSALICYLIC ACID	61	25.6%	65	27.2%	126	26.4%
BETA BLOCKING AGENTS	79	33.2%	83	34.7%	162	34.0%
ACE INHIBITORS, PLAIN	68	28.6%	70	29.3%	138	28.9%
DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	52	21.8%	67	28.0%	119	24.9%
OTHER OPHTHALMOLOGICALS	57	23.9%	55	23.0%	112	23.5%
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	21	8.8%	28	11.7%	49	10.3%

Abbreviations: ATC = Anatomical Therapeutic Chemical, 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, PT = Preferred Term, WHODD = World Health Organization (WHO) Drug Dictionary
Notes: WHODD Enhanced Version March 2015 was used.
Source: Post-text table 14.1.4.2.1

Prior surgeries

Prior surgeries were reported for this clinical study as prior procedures for the patients in the SAF in Table 23, and the surgeries were reported in addition to prior surgeries documented in terms of general or ophthalmologic medical history. The types of reported prior surgeries were balanced between both treatment groups, and no important differences could be identified.

Table 21

Table 10-16 Prior surgeries by MedDRA SOC and PT - SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any prior surgery	3	1.3%	1	0.4%	4	0.8%
Surgical and medical procedures						
Overall	2	0.8%	1	0.4%	3	0.6%
Cataract operation	2	0.8%	1	0.4%	3	0.6%
Lens capsulotomy	1	0.4%	0	0.0%	1	0.2%
Social circumstances						
Overall	1	0.4%	0	0.0%	1	0.2%
Orthosis user	1	0.4%	0	0.0%	1	0.2%

Abbreviations: N = total number of patients, n = number of patients in corresponding class, % = number of patients in corresponding class/total number of patients*100, MedDRA = Medical Dictionary for Regulatory Activities, SAF = Safety Set, SOC = System Organ Class, PT = Preferred Term
Notes: MedDRA version 19.0 was used.
Source: Post-text table 14.1.4.3.1

Concomitant surgeries

The limited number of reported concomitant surgeries was overall balanced between both treatment groups for the patients of the SAF.

Numbers analysed

The number of patients included in each analysis set is presented in *Table 24* below.

Table 22

Table 10-4 Patients in each analysis set – All randomized patients

Analysis Set	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	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.
Source: Post-text tables 14.1.1.5, 14.1.1.6

The SAF consisted of 477 patients. The patient numbers analysed are overall balanced between the treatment arms Ranivisio and US-Lucentis.

In each treatment group, 2 patients were excluded from the FAS_US and FAS_EU each because of missing BCVA results. Further 46 patients were excluded from the FAS_EU (Ranivisio: 22 patients, Lucentis: 24

patients) because their screening BCVA in Snellen equivalent was not within the defined range (i.e. 20/40 to 20/100). Thus, the FAS-EU set, including 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 20/40 and 20/100 Snellen equivalent in the study eye, comprised 429 patients (89.9%).

The FAS for the EU comprised 429 patients, 215 in the Ranivisio arm and 214 in the Lucentis comparator arm.

Major protocol deviations led to exclusion of 30 patients from the PPS_US (Ranivisio: 17 patients, Lucentis: 13 patients) and of 27 patients from the PPS_EU (Ranivisio: 15 patients, Lucentis: 12 patients). A total of 445 patients (93.3%) met the criteria for PPS_US, and a total of 402 patients (84.3%) met the criteria for PPS_EU.

One (1) patient in the PKS analysis subset (n=59) was excluded because of major protocol deviations interfering with interpretation of ranibizumab concentration data.

One patient per treatment arm was excluded from the FAS_EU due to missing BCVA results.

Outcomes and estimation

Primary endpoint analysis

Change from Baseline in BCVA at Week 8

The primary efficacy analysis for the change from BL in BCVA by ETDRS letters at Week 8 was based on the FAS_EU population. For the EU, this endpoint was evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent, in order to fulfill CHMP/ EMA recommendations obtained during EMA SA. For the FDA, the primary analysis was conducted in the entire FAS population with a baseline BCVA between 20/32 and 20/100 Snellen equivalent.

In the FAS_EU population, a mean change from baseline BCVA at Week 8 of 5.2 ETDRS letters (SD 7.75) was reached for Ranivisio and of 6.0 ETDRS letters for Lucentis (SD 8.42).

Table 23

Table 11-6 Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8– FAS_EU

	FYB201 (N = 215)	Lucentis (N = 214)	Total (N = 429)
Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8			
N*	212	214	426
n	207	209	416
Missing	5	5	10
Mean (SD)	5.2 (7.75)	6.0 (8.42)	5.6 (8.09)
Median	5.0	6.0	5.0
Interquartile range (Q1–Q3)	0.0–10.0	1.0–11.0	0.0–11.0
Range (min–max)	-16–30	-33–25	-33–30

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS_EU = full analysis set for the EU, N = number of patients in corresponding class, 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
Source: Post-text table 14.2.1.1.1

Biosimilarity was shown by the LS means difference between both treatments of -0.7 ETDRS letters with a 95% CI of [-2.3; 0.9] ETDRS letters, which was completely contained within the pre-defined equivalence margin of ± 3.5 letters.

Table 24

Table 11-7 ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8 – FAS_EU

	n	Missing	Arithmetic mean	LS Mean[1]	SE LS mean	95% CI
FYB201	207	5	5.2	5.1	0.61	[3.9; 6.3]
Lucentis	209	5	6.0	5.8	0.61	[4.6; 7.0]
Difference						
FYB201 - Lucentis			-0.8	-0.7	0.80	[-2.3; 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_EU = full analysis set for the EU, 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 95% confidence interval based on normal approximation.
Source: Post-text table 14.2.1.3.1

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

In the PPS_EU set, a mean (SD) change from baseline in BCVA at Week 8 of 5.3 (7.82; median: 5.0) ETDRS letters for Ranivisio and of 6.2 (8.39; median 6.0) ETDRS letters for Lucentis was observed.

Table 25

Table 11-8 Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8 – PPS_EU

	FYB201 (N = 200)	Lucentis (N = 202)	Total (N = 402)
Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8			
N*	200	202	402
n	200	202	402
Missing	0	0	0
Mean (SD)	5.3 (7.82)	6.2 (8.39)	5.8 (8.12)
Median	5.0	6.0	5.0
Interquartile range (Q1–Q3)	0.0–10.5	1.0–12.0	1.0–11.0
Range (min–max)	-16–30	-33–25	-33–30

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, PPS_EU = per protocol set for the EU, N = number of patients in corresponding class, 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,
Source: Post-text table 14.2.2.1.1

The LS means difference for the change from baseline in BCVA between Ranivisio and Lucentis at Week 8 for the PPS_EU population was -0.8 ETDRS letters with a 95% CI of [-2.4; 0.8] ETDRS letters (*Table 28*). The 95% CI was completely within the equivalence margin of ±3.5 ETDRS letters meeting the pre-defined criterion for biosimilarity of Ranivisio and Lucentis.

Table 26

Table 11-9 ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8 – PPS_EU

	n	Missing	Arithmetic mean	LS mean[1]	SE LS mean	95% CI
FYB201	200	0	5.3	5.2	0.62	[4.0; 6.4]
Lucentis	202	0	6.2	6.0	0.62	[4.8; 7.2]
Difference						
FYB201 - Lucentis			-0.9	-0.8	0.82	[-2.4; 0.8]
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_EU = per protocol set for the EU, 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 95% confidence interval based on normal approximation.
Source: Post-text table 14.2.2.3.1

To address effects of missing data on the primary efficacy endpoint, an MMRM was estimated using data from all patients in the FAS_EU population. Using MMRM, the LS means difference for the change from baseline in BCVA between Ranivisio and Lucentis at Week 8 was -0.7 ETDRS letters with a 95% CI of [-2.3; 0.8] ETDRS letters (*Table 29*). Also the 95% CI resulting from the MMRM was completely within the pre-defined equivalence margin.

Table 27

Table 11-10 MMRM for change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8 – FAS_EU

	n	Missing	Arithmetic Mean[1]	LS Mean[2]	SE LS mean	95% CI
FYB201	207	5	5.2	5.1	0.59	[3.9; 6.3]
Lucentis	209	5	6.0	5.8	0.59	[4.7; 7.0]
Difference						
FYB201 - Lucentis			-0.8	-0.7	0.79	[-2.3; 0.8]
CI contained in]-3.5; 3.5[[3]						**yes**

[1] Arithmetic mean calculation is based on non-missing assessments at analysis visit 3. For the calculation of LS means based on the MMRM, assessments of all patients with non-missing and missing assessments are considered.

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

[3] 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: BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS_EU = Full analysis set for the EU, 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, MMRM: Mixed Model Repeated Measurements, SE = standard error

Notes: Two-sided 95% confidence interval based on normal approximation.

Source: Post-text table 14.2.2.4.1

FDA-specific analysis of the primary endpoint

The primary efficacy endpoint for the US-specific analysis was the change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment in all patients from the FAS population having a baseline BCVA between 20/32 and 20/100 Snellen equivalent (to note: the FAS_EU consisted of patients with a baseline BCVA between 20/40 and 20/100).

The mean change (SD) from baseline in BCVA was 5.1 (7.52) ETDRS letters for Ranivisio and 5.6 (8.63) ETDRS for Lucentis (*Table 30*). The LS means difference for the change from baseline in BCVA at Week 8 between Ranivisio and Lucentis was -0.4 ETDRS letters with a 90% CI for the US-specific analysis of [-1.6; 0.9] ETDRS letters (*Table 31*). The 90% CI was completely within the pre-defined equivalence margin of ±3.5 ETDRS letters, meeting the pre-defined criterion for biosimilarity of Ranivisio to Lucentis for the FDA.

Table 28

Table 11-1 Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8– FAS_US

	FYB201 (N = 237)	Lucentis (N = 238)	Total (N = 475)
Absolute change from baseline in BCVA [ETDRS letters] at analysis visit V3/Week 8			
N*	234	238	472
n	228	233	461
Missing	6	5	11
Mean (SD)	5.1 (7.52)	5.6 (8.63)	5.4 (8.10)
Median	5.0	5.0	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

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
Source: Post-text table 14.2.1.1.2

Table 29

Table 11-2 ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis visit 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.
Source: Post-text table 14.2.1.3.2

The primary analysis was supported by similar results from the sensitivity analysis conducted in the PPS_US population with mean (SD) change from baseline in BCVA at Week 8 of 5.2 (7.59; median: 5.0) ETDRS letters for Ranivisio and of 5.7 (8.64; median 6.0) ETDRS letters for Lucentis. Also the PPS_US showed an LS means difference between both treatments of -0.4 ETDRS letters with a 90% CI of [-1.7; 0.9] ETDRS letters, which was also completely contained within the equivalence margin of ±3.5 ETDRS letters.

The analysis was not influenced by missing data.

The MMRM using the FAS_US population for change from baseline in BCVA at Week 8 showed an LS means difference between both treatments of -0.4 ETDRS letters with a 90% CI of [-1.7; 0.8] ETDRS letters, which was also completely contained within the pre-defined equivalence margin.

Furthermore, the applicant provided tipping point (TP) analysis where several scenarios were considered for shift parameter θ for missing observations estimated by MI method. TP analysis was performed to investigate whether missing as random (MAR) assumption was reasonable for missing observations in data which were used for primary analysis.

Scenarios were as follows: 1) θ=0 for FYB201 and θ≥0 or θ<0 for Lucentis, 2) θ=0 for Lucentis and θ≥0 or θ<0 for FYB201, 3) θ=K for FYB201 and θ=-K for Lucentis where K≥0, 4) θ=K for Lucentis and θ=-K for FYB201 where K≥0.

In all scenarios, TP was first integer point such that corresponding 95% confidence interval (CI) for difference between FYB201 and Lucentis was not fully within equivalence range (-3.5 letters, 3.5 letters). This was equivalent to first insignificant result (on 5% significance level) for treatment difference.

For all scenarios, when no shift was performed on imputed data, i.e., θ=0 for FYB201 with θ=0 for Lucentis, analysis of covariance (ANCOVA) model led to 95% CI which was (-2.24 letters, 0.89 letter) for change in best corrected visual acuity (BCVA) from baseline to Week 8. This 95% CI was within equivalence range (-3.5 letters, 3.5 letters) and agreed with conclusion from original ANCOVA model using data with missing observations. Scenarios with θ=0 for FYB201 and θ=0 for Lucentis corresponded to MAR assumption for missing observations.

In the following, scenarios for investigation of TP, where maximally one treatment has θ=0, are commented. These scenarios reflected missing not at random (MNAR) assumption for missing observations.

For scenario 1), TP was in case of a) θ=0 for FYB201 with θ=46 for Lucentis and corresponding 95% CI for difference was (-3.53 letters, 0.14 letter) or of b) θ=0 for FYB201 with θ=-84 for Lucentis and corresponding 95% CI for difference was (-1.13 letter, 3.51 letters).

For scenario 2), TP was either in case of a) θ=56 for FYB201 with θ=0 for Lucentis and corresponding 95% CI for difference was (-0.76 letter, 3.51 letters) or of b) θ=-30 for FYB201 with θ=0 for Lucentis and corresponding 95% CI for difference was (-3.51 letters, -0.03 letter).

For scenario 3), TP was θ=38 for FYB201 with θ=-38 for Lucentis and corresponding 95% CI for difference was (-0.45 letter, 3.56 letters).

For scenario 4), TP was θ=-20 for FYB201 with θ=20 for Lucentis and corresponding 95% CI for difference was (-3.55 letters, -0.16 letter).

The results are summarised in the table below.

Table 30

Table 21 **ANCOVA for change from baseline in BCVA [ETDRS letters] to analysis visit V3/Week 8 using multiple imputation under an MNAR assumption – tipping point analyses – FAS_EU**

Shift in MNAR imputation (θ)		N	LS mean[1]	SE LS mean	95% CI	CI contained in]-3.5; 3.5[
-19 letters	FYB201	215	4.4	0.65	[3.14; 5.71]	
+19 letters	Lucentis	214	6.2	0.65	[4.94; 7.50]	
	Difference FYB201 – Lucentis		-1.8	0.86	[-3.48; -0.11]	yes
-20 letters	FYB201	215	4.4	0.66	[3.10; 5.68]	
+20 letters	Lucentis	214	6.2	0.66	[4.95; 7.53]	
	Difference FYB201 – Lucentis		-1.9	0.86	[-3.55; -0.16]	no
+37 letters	FYB201	215	6.6	0.77	[5.08; 8.10]	
-37 letters	Lucentis	214	5.1	0.77	[3.58; 6.61]	
	Difference FYB201 – Lucentis		1.5	1.01	[-0.48; 3.48]	yes
+38 letters	FYB201	215	6.6	0.78	[5.11; 8.16]	
-38 letters	Lucentis	214	5.1	0.78	[3.55; 6.60]	
	Difference FYB201 – Lucentis		1.6	1.02	[-0.45; 3.56]	no
+55 letters	FYB201	215	7.3	0.82	[5.64; 8.87]	
0 letters	Lucentis	214	5.9	0.82	[4.31; 7.54]	
	Difference FYB201 – Lucentis		1.3	1.08	[-0.78; 3.45]	yes
+56 letters	FYB201	215	7.3	0.83	[5.67; 8.92]	
0 letters	Lucentis	214	5.9	0.83	[4.29; 7.55]	
	Difference FYB201 – Lucentis		1.4	1.09	[-0.76; 3.51]	no
-29 letters	FYB201	215	4.1	0.67	[2.74; 5.37]	
0 letters	Lucentis	214	5.8	0.67	[4.48; 7.11]	
	Difference FYB201 – Lucentis		-1.7	0.88	[-3.46; -0.01]	yes
-30 letters	FYB201	215	4.0	0.68	[2.69; 5.34]	
0 letters	Lucentis	214	5.8	0.68	[4.47; 7.12]	
	Difference FYB201 – Lucentis		-1.8	0.89	[-3.51; -0.03]	no
0 letters	FYB201	215	5.1	0.71	[3.75; 6.52]	
45 letters	Lucentis	214	6.8	0.71	[5.42; 8.20]	
	Difference FYB201 – Lucentis		-1.7	0.93	[-3.50; 0.15]	yes
0 letters	FYB201	215	5.1	0.71	[3.74; 6.53]	
46 letters	Lucentis	214	6.8	0.71	[5.43; 8.23]	
	Difference FYB201 – Lucentis		-1.7	0.94	[-3.53; 0.14]	no
0 letters	FYB201	215	5.2	0.90	[3.46; 6.97]	
-83 letters	Lucentis	214	4.0	0.90	[2.28; 5.80]	
	Difference FYB201 – Lucentis		1.2	1.18	[-1.14; 3.47]	yes
0 letters	FYB201	215	5.2	0.90	[3.45; 6.98]	
-84 letters	Lucentis	214	4.0	0.90	[2.25; 5.79]	
	Difference FYB201 – Lucentis		1.2	1.18	[-1.13; 3.51]	no

Source: Attachment to question 107, Tables 1.5, 1.7, 2.7, 2.9, 3.10, 3.12, 4.6, 4.8, 5.8, 5.10, 6.13, 6.15

Taking into account all scenarios, the smallest TP (if value θ=0 is excluded) was 20 letters for Lucentis with -20 letters for FYB201. Descriptive statistics for change in BCVA between baseline and Week 8 were provided by the applicant to discuss these results.

For FYB201, minimal value of change was -16 letters for FYB201. Moreover, 1% of all values was equal or less than -15 letters. Thus, TP -20 letters for FYB201 is rather improbable value. For Lucentis, maximum value of change was 25 letters. Moreover, 5% of all values was equal or higher than 20 letters. Thus, TP 20 letters for Lucentis is probable value but percentage of such values is rather small. This all implies that the main conclusion is robust to all sensible deviations from MAR.

Secondary endpoint analyses

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of biosimilarity between Ranivisio and Lucentis.

Change from baseline in BCVA by ETDRS letters over time

One of the secondary efficacy objectives was to evaluate and compare functional changes of the retina by BCVA over time, using the change from baseline in BCVA by ETDRS letters over time as endpoints for the EU-specific analysis.

The time course of BCVA measurements throughout the study up to Week 48 are visualised in grouped box plots by analysis visit in Figure 11-2. A sustained higher BCVA in ETDRS letters was observed in the FAS_EU population from analysis visit V2/Week 4 onwards.

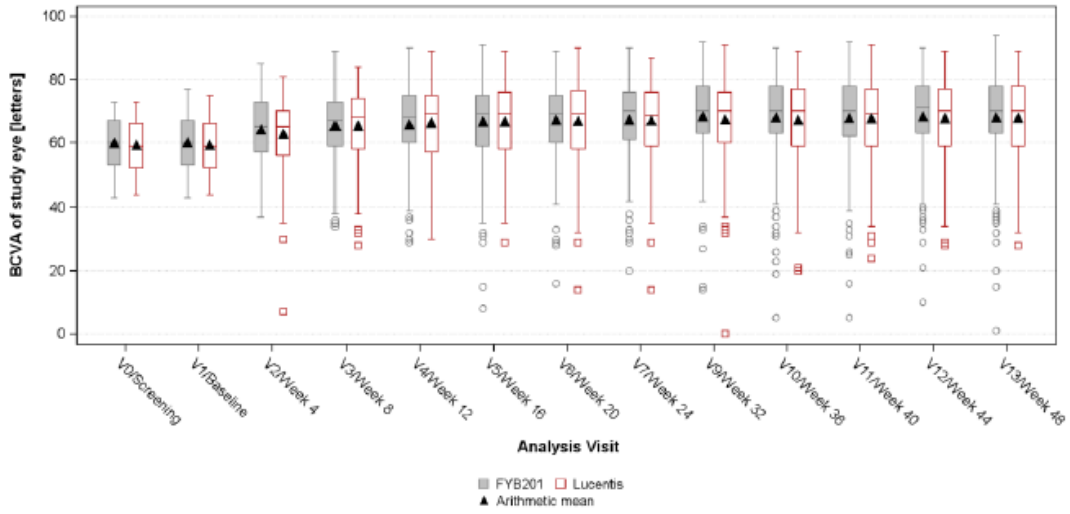


Figure 11-2 Study eye BCVA [ETDRS letters] in patients treated with FYB201 or Lucentis at each analysis visit – FAS_EU

The boxes represent study eye BCVA in [ETDRS letters] of patients treated with FYB201 (shaded boxes) or Lucentis (open boxes) at each study visit. Each box displays data of the 1st to 3rd quartile, the median is represented as a horizontal line inside each box, the arithmetic mean is displayed by a black triangle, and the whiskers extend to the next value above or below 1.5*(3rd–1st quartile) of each box, open dots represent individual data points that fall outside the whiskers.
Source: Post-text figure 14.2.1.2.1

At analysis visit V7/Week 24 the mean (SD) change from baseline in BCVA was 7.1 (10.47; median: 7.0) ETDRS letters for Ranivisio and 7.6 (10.42; median: 8.0) ETDRS letters for Lucentis in the FAS_EU population (*Table 33*).

At the Final Visit/Week 48 the mean (SD) change from baseline in BCVA was 7.9 (12.15; median: 8.0) ETDRS letters for Ranivisio and 8.5 (11.38; median: 9.0) ETDRS letters for Lucentis in the FAS_EU population, similar results were obtained using the average over the last three visits (V11, V12 and Final Visit) reaching a mean (SD) change from baseline in BCVA of 7.9 (11.64; median: 8.0) ETDRS letters for Ranivisio and of 8.4 (11.07; median: 8.7) ETDRS letters for Lucentis (*Table 33*).

Table 31

Table 11-13 Absolute change from baseline in BCVA [ETDRS letters] – FAS_EU

	FYB201 (N = 215)	Lucentis (N = 214)	Total (N = 429)
At analysis visit V7/Week 24			
N*	209	211	420
n	209	208	417
Missing	0	3	3
Mean (SD)	7.1 (10.47)	7.6 (10.42)	7.3 (10.44)
Median	7.0	8.0	7.0
Interquartile range (Q1–Q3)	1.0–14.0	1.0–14.0	1.0–14.0
Range (min–max)	-33–31	-36–34	-36–34
At Final Visit/Week 48			
N*	205	202	407
n	204	201	405
Missing	1	1	2
Mean (SD)	7.9 (12.15)	8.5 (11.38)	8.2 (11.76)
Median	8.0	9.0	9.0
Interquartile range (Q1–Q3)	0.0–16.0	2.0–15.0	1.0–16.0
Range (min–max)	-51–33	-31–37	-51–37
After 12 Months (average over V11/Week 40, V12/Week 44 and Final Visit/Week 48)			
N*	207	203	410
n	207	203	410
Missing	0	0	0
Mean (SD)	7.9 (11.64)	8.4 (11.07)	8.1 (11.35)
Median	8.0	8.7	8.3
Interquartile range (Q1–Q3)	1.0–16.7	2.0–14.7	1.7–15.3
Range (min–max)	-49–32	-37–38	-49–38

Abbreviations: BCVA = best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS_EU = full analysis set for the EU, 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, V= visit
Source: Post-text tables 14.2.1.1.1

The LS means difference for the change from baseline in BCVA between Ranivisio and Lucentis at Week 24 was -0.3 ETDRS letters with a 95% CI of [-2.3; 1.8] ETDRS letters for the FAS_EU population based on the ANCOVA estimates (*Table 34*). At the Final Visit/Week 48 the LS means difference for the change from baseline in BCVA between Ranivisio and Lucentis was also -0.3 ETDRS letters with a 95% CI of [-2.6; 2.0], similar results were obtained using the average over the last three visits (V11, V12 and Final Visit) with an LS means difference of -0.2 ETDRS letters and a 95% CI of [-2.4; 2.0] (*Table 34*).

Table 32

Table 11-14 ANCOVA for change from baseline in BCVA [ETDRS letters] – FAS_EU

	n	Missing	Arithmetic mean	LS Mean[1]	SE LS mean	95% CI
At analysis visit V7/Week 24						
FYB201	209	0	7.1	7.2	0.78	[5.7; 8.7]
Lucentis	208	3	7.6	7.5	0.79	[5.9; 9.0]
Difference						
FYB201 - Lucentis			-0.5	-0.3	1.02	[-2.3; 1.8]
At Final Visit/Week 48						
FYB201	204	1	7.9	7.9	0.89	[6.2; 9.7]
Lucentis	201	1	8.5	8.2	0.90	[6.5; 10.0]
Difference						
FYB201 - Lucentis			-0.5	-0.3	1.17	[-2.6; 2.0]
After 12 Months (average over V11/Week 40, V12/Week 44 and Final Visit/Week 48)						
FYB201	207	0	7.9	8.0	0.85	[6.3; 9.6]
Lucentis	203	0	8.4	8.1	0.87	[6.4; 9.8]
Difference						
FYB201 - Lucentis			-0.4	-0.2	1.13	[-2.4; 2.0]

[1] Estimates are adjusted for pooled country and baseline BCVA [letters].
Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, FAS_EU = full analysis set for the EU, LS = Least squares, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, SE = standard error, V = visit
Notes: Two-sided 95% confidence intervals based on normal approximation.
Source: Post-text tables 14.2.3.1.1, 14.2.3.2.1, 14.2.3.3.1

The ANCOVA for the sensitivity analysis using the PPS_EU population showed an LS means difference of -0.1 ETDRS letters with a 95% CI of [-2.2; 1.9] ETDRS letters for the change from baseline in BCVA between Ranivisio and Lucentis at Week 24 (*Table 35*). At the Final Visit/Week 48 the LS means difference was -0.4 ETDRS letters with a 95% CI of [-2.8; 2.0], similar results were obtained using the average over the last three visits (V11, V12 and Final Visit) with an LS means difference of -0.1 ETDRS letters and a 95% CI of [-2.4; 2.2] (*Table 35*).

Based on the sensitivity analyses using the PPS_EU population, no relevant imbalances between both IVT treatments were observed with respect to changes from baseline in BCVA over time and at Week 24, Week 48 and after 12 months, according to the applicant.

Table 33

Table 11-16 ANCOVA for change from baseline in BCVA [ETDRS letters] at analysis visit V7/Week 24 – PPS_EU

	n	Missing	Arithmetic mean	LS Mean[1]	SE LS mean	95% CI
At analysis visit V7/Week 24						
FYB201	197	0	7.2	7.3	0.81	[5.7; 8.9]
Lucentis	198	1	7.7	7.5	0.82	[5.9; 9.1]
Difference						
FYB201 - Lucentis			-0.4	-0.1	1.06	[-2.2; 1.9]
At Final Visit/Week 48						
FYB201	192	1	7.9	7.9	0.92	[6.1; 9.7]
Lucentis	190	1	8.6	8.3	0.94	[6.4; 10.1]
Difference						
FYB201 - Lucentis			-0.7	-0.4	1.23	[-2.8; 2.0]
After 12 Months (average over V11/Week 40, V12/Week 44 and Final Visit/Week 48)						
FYB201	195	0	8.0	8.0	0.89	[6.4; 9.8]
Lucentis	192	0	8.4	8.2	0.90	[6.4; 9.9]
Difference						
FYB201 - Lucentis			-0.4	-0.1	1.17	[-2.4; 2.2]

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

Abbreviations: ANCOVA = Analysis of Covariance, BCVA = best-corrected visual acuity, CI = confidence interval, ETDRS = Early Treatment Diabetic Retinopathy Study, PPS_EU = per protocol set for the EU, LS = Least squares, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, SE = standard error, V = visit

Notes: Two-sided 95% confidence intervals based on normal approximation.

Source: Post-text tables 14.2.3.1.3, 14.2.3.2.3, 14.2.3.3.3

Change from BL in FCP and FCS retinal thickness over time

For the final analysis, the secondary endpoints "Changes from baseline in FCP and FCS retinal thickness at Week 24 (analysis visit V7) and at Week 48 (Final Visit)" were compared between both treatment groups for all patients in the FAS_EU population.

The same ANCOVA model as specified for the primary endpoint was used to derive the CIs for the LS means difference between both treatment groups, but without formal hypothesis testing. For FCP retinal thickness, also the PPS_EU population was analyzed for sensitivity.

FCP retinal thickness

A sustained lower FCP retinal thickness was observed in the FAS_EU (Figure 11-4) population from analysis V2/Week 4 onwards.

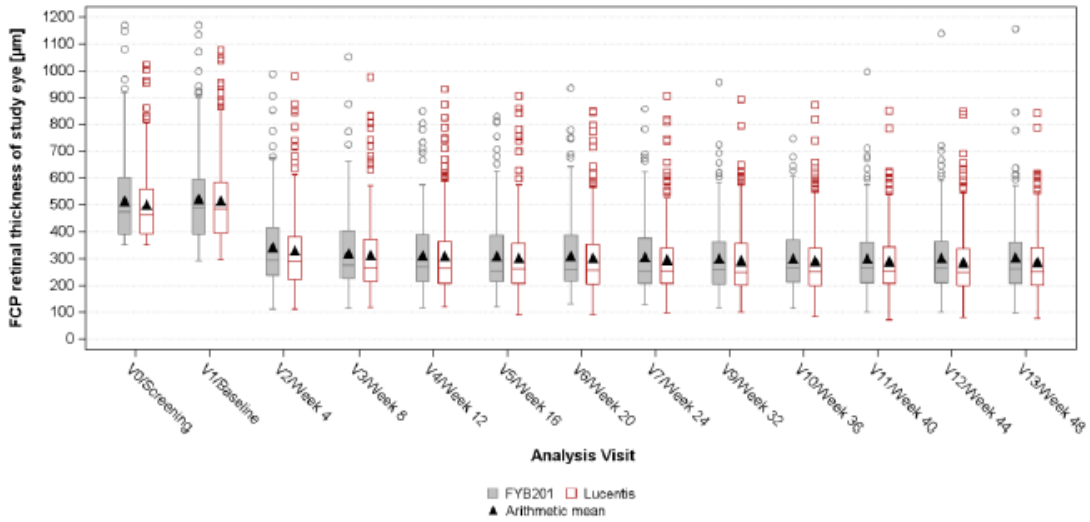


Figure 11-4 FCP retinal thickness [µm] in patients treated with FYB201 or Lucentis at each analysis visit – FAS_EU

The boxes represent study eye FCP retinal thickness in [µm] of patients treated with FYB201 (shaded boxes) or Lucentis (open boxes) at each study visit. Each box displays data of the 1st to 3rd quartile, the median is represented as a horizontal line inside each box, the arithmetic mean is displayed by a black triangle, and the whiskers extend to the next value above or below 1.5*(3rd–1st quartile) of each box, open dots represent individual data points that fall outside the whiskers.
Source: Post-text figure 14.2.3.5.1

At analysis visit V7/Week 24 the mean (SD) change from baseline in FCP retinal thickness reached -207.59 (146.937; median: -184.50) µm for Ranivisio and -212.99 (147.289; median: -201.25) µm for Lucentis in the FAS_EU population (Table 11-17). At the Final Visit/Week 48 a mean (SD) change from baseline in FCP retinal thickness of -218.76 (160.440; median: -194.00) µm for Ranivisio and of -218.49 (150.769; median: -202.50) µm for Lucentis was reached (*Table 36*).

Table 34

Table 2.5.4-7: Absolute change from baseline in FCP retinal thickness [µm] (FAS population)

FAS	FYB201 (N = 215)	Lucentis (N = 214)	Total (N = 429)
At Week 24			
N*	209	211	420
n	199	198	397
Missing	10	13	23
Mean (SD)	-207.59 (146.937)	-212.99 (147.289)	-210.29 (146.951)
Median	-184.50	-201.25	-191.00
Interquartile range (Q1–Q3)	-291.50 – -107.00	-297.00 – -126.50	-291.50 – -118.50
Range (min–max)	-783.0 – 133.0	-769.5 – 394.0	-783.0 – 394.0
At Final Visit/Week 48			
N*	205	202	407
n	201	196	397
Missing	4	6	10
Mean (SD)	-218.76 (160.440)	-218.49 (150.769)	-218.63 (155.545)
Median	-194.00	-202.50	-197.50
Interquartile range (Q1–Q3)	-295.00 – -110.00	-312.00 – -121.50	-299.50 – -118.00
Range (min–max)	-777.0 – 408.0	-768.0 – 150.5	-777.0 – 408.0

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

Based on the ANCOVA estimates, the LS means difference for the change from baseline in FCP retinal thickness between Ranivisio and Lucentis at Week 24 was 9.02 µm with a 95% CI of [-14.93; 32.98] μm and at Week 48 it was 10.66 µm with a 95% CI of [-13.47; 34.79] for the FAS_EU population (*Table 37*).

Table 35

Table 2.5.4-8: ANCOVA for change from baseline in FCP retinal thickness [µm] (FAS population)

	n	Missing	Arithmetic mean	LS Mean[1]	SE LS mean	95% CI
At Week 24						
FYB201	199	10	-207.59	-199.67	9.274	[-217.91; -181.44]
Lucentis	198	13	-212.99	-208.69	9.435	[-227.24; -190.14]
Difference						
FYB201 - Lucentis			5.40	9.02	12.183	[-14.93; 32.98]
At Final Visit/Week 48						
FYB201	201	4	-218.76	-209.88	9.265	[-228.09; -191.66]
Lucentis	196	6	-218.49	-220.53	9.473	[-239.16; -201.91]
Difference						
FYB201 - Lucentis			-0.26	10.66	12.274	[-13.47; 34.79]

[1] Estimates are adjusted for pooled country and baseline FCP retinal thickness [µm].

The ANCOVA for the sensitivity analysis using the PPS population showed an LS means difference for the change from baseline in FCP retinal thickness between Ranivisio and Lucentis of 6.07 µm with a 95% CI of [-18.72; 30.86] µm at Week 24 and of 12.35 µm with a 95% CI of [-12.77; 37.48] µm at Week 48 (see *Table 38* below).

Table 36

Table 11-19 ANCOVA for change from baseline in FCP retinal thickness [µm] – PPS_US and PPS_EU

	n	Missing	Arithmetic mean	LS mean[1]	SE LS mean	CI
PPS_EU						**95% CI**
At analysis visit V7/Week 24						
FYB201	189	8	-211.28	-201.80	9.555	[-220.58; -183.01]
Lucentis	190	9	-210.52	-207.87	9.691	[-226.92; -188.81]
Difference						
FYB201 - Lucentis			-0.76	6.07	12.605	[-18.72; 30.86]
At Final Visit/Week 48						
FYB201	189	4	-220.75	-210.48	9.598	[-229.35; -191.61]
Lucentis	185	6	-220.34	-222.83	9.809	[-242.12; -203.54]
Difference						
FYB201 - Lucentis			-0.41	12.35	12.777	[-12.77; 37.48]

[1] Estimates are adjusted for pooled country and baseline FCP retinal thickness [µm].

Abbreviations: ANCOVA = Analysis of Covariance, CI = confidence interval, FCP = Foveal Center Point, PPS_US = per protocol set for the US, PPS_EU = per protocol set for the EU, LS = Least squares, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, SE = standard error, V = visit

Notes: Two-sided 90% and 95% confidence intervals based on normal approximation.

Source: Post-text table 14.2.3.6.3, 14.2.3.6.4, 14.2.3.7.3, 14.2.3.7.4

FCS retinal thickness

The change from baseline in FCS retinal thickness showed a sustained decrease from analysis Week 4 onwards (Figure 11-6).

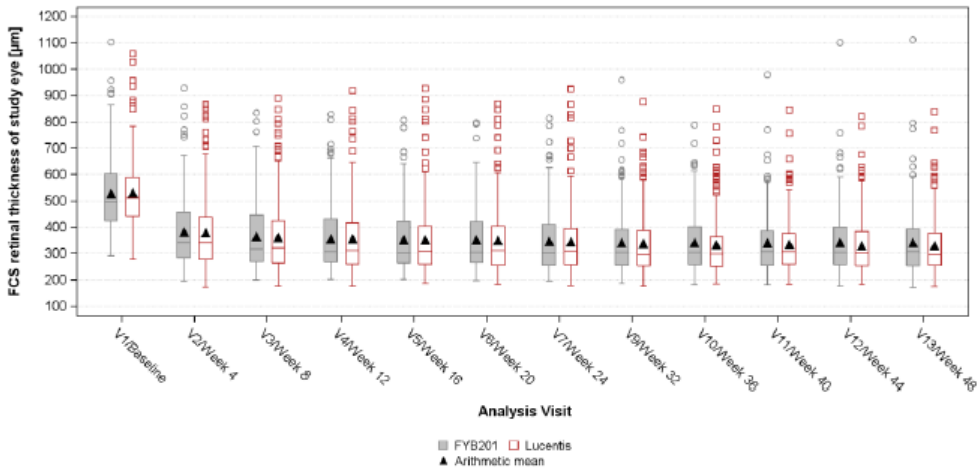


Figure 11-6 FCS retinal thickness [µm] in patients treated with FYB201 or Lucentis at each analysis visit – FAS_EU

The boxes represent study eye FCS retinal thickness in [µm] of patients treated with FYB201 (shaded boxes) or Lucentis (open boxes) at each study visit. Each box displays data of the 1st to 3rd quartile, the median is represented as a horizontal line inside each box, the arithmetic mean is displayed by a black triangle, and the whiskers extend to the next value above or below 1.5*(3rd–1st quartile) of each box, open dots represent individual data points that fall outside the whiskers.

Source: Post-text figure 14.2.3.9.1

At analysis visit Week 24 the mean (SD) change from baseline in FCS retinal thickness reached -184.19 (126.249; median: -161.50) µm for Ranivisio and -186.85 (127.118; median: -174.25) µm for Lucentis.

At analysis visit Week 48 a mean (SD) change from baseline in FCS retinal thickness of -188.15 (131.353; median: -172.75) µm for Ranivisio and of -196.55 (127.650; median: -190.50) µm for Lucentis was reached.

Based on the ANCOVA estimates, the LS means difference for the change from baseline in FCS retinal thickness between Ranivisio and Lucentis at Week 24 was -0.34 µm with a 95% CI of [-21.45; 20.76] µm and at Week 48 it was -8.97 µm with a 95% CI of [-12.24; 30.18] µm.

No sensitivity analyses were performed on the PPS-EU population for this secondary EP.

Total lesion area

Changes from baseline in total lesion area to Week 24 and to Week 48 were compared between both treatment groups in the FAS_EU population. The same ANCOVA model as specified for the primary endpoint was used to derive the CIs for the LS means difference between both treatment groups, but without formal hypothesis testing.

At Week 24 the mean (SD) change from baseline in total lesion area reached -0.5224 (4.80070; median: -0.2775) mm^2 for Ranivisio and -0.7252 (5.14846; median: -0.4600) mm^2 for Lucentis. At Week 48 a mean (SD) change from baseline in total lesion area of -0.6603 (4.84466; median: -0.6950) mm^2 for Ranivisio and of -1.10827 (5.26262; median: -0.7075) mm^2 for Lucentis was reached (*Table 39*).

Table 37

Table 11-22 Absolute change from baseline in total lesion area [mm^2] – FAS_US and FAS_EU

FAS_EU	FYB201 (N = 215)	Lucentis (N = 214)	Total (N = 429)
At analysis visit V7/Week 24			
N*	209	211	420
n	192	185	377
Missing	17	26	43
Mean (SD)	-0.5224 (4.80070)	-0.7252 (5.14846)	-0.6220 (4.96879
Median	-0.2775	-0.4600	-0.4450
Interquartile range (Q1–Q3)	-2.3450 – 1.8550	-2.9200 – 1.6750	-2.7250 – 1.7850
Range (min–max)	-21.860 – 12.575	-17.825 – 15.190	-21.860 – 15.190
At Final Visit/Week 48			
N*	205	202	407
n	147	146	293
Missing	58	56	114
Mean (SD)	-0.6603 (4.84466)	-1.0827 (5.26262)	-0.8708 (5.05300)
Median	-0.6950	-0.7075	-0.6950
Interquartile range (Q1–Q3)	-3.0150 – 2.2000	-3.4450 – 1.3250	-3.2600 – 1.6000
Range (min–max)	-18.120 – 10.635	-21.405 – 16.615	-21.405 – 16.615

Abbreviations: FAS_US = **full analysis set for the US**, FAS_EU = **full analysis set for the EU**, 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, V = visit
Source: Post-text tables 14.2.3.12.1, 14.2.3.12.2

Based on the ANCOVA estimates, the LS means difference for the change from baseline in total lesion area between Ranivisio and Lucentis at Week 24 was 0.221 mm^2 with a 95% CI of [-0.728; 1.171] mm^2 and at Week 48 it was 0.328 mm^2 with a 95% CI of [-0.754; 1.410] mm^2 for the FAS-EU population (*Table 40*).

Table 38

Table 11-23 ANCOVA for change from baseline in total lesion area [mm²] – FAS_US and FAS_EU

	n	Missing	Arithmetic mean	LS Mean[1]	SE LS mean	CI
FAS_EU						**95% CI**
At analysis visit V7/Week 24						
FYB201	192	17	-0.522	-0.543	0.3651	[-1.261; 0.175]
Lucentis	185	26	-0.725	-0.764	0.3836	[-1.518; -0.010]
Difference						
FYB201 - Lucentis			0.203	0.221	0.4829	[-0.728; 1.171]
At Final Visit/Week 48						
FYB201	147	58	-0.660	-0.669	0.4712	[-1.597; 0.258]
Lucentis	146	56	-1.083	-0.997	0.4856	[-1.953; -0.041]
Difference						
FYB201 - Lucentis			0.422	0.328	0.5499	[-0.754; 1.410]

[1] Estimates are adjusted for pooled country and baseline total lesion area [mm²].

Abbreviations: ANCOVA = Analysis of Covariance, CI = confidence interval, FAS_US = full analysis set for the US, FAS_EU = full analysis set for the EU, LS = Least squares, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, SE = standard error, V = visit

Notes: Two-sided 90% and 95% confidence intervals based on normal approximation.

Source: Post-text tables 14.2.3.14.1, 14.2.3.14.2, 14.2.3.15.1, 14.2.3.15.2

CNV leakage and fluid-free macula

Binary secondary efficacy variables evaluated and compared the presence of CNV leakage at Week 24 and Week 48 compared to baseline and the absence of disease activity (fluid-free macula) over time.

CNV leakage

At screening nearly all patients had CNV leakage. This clinical finding improved remarkably upon treatment. As shown above, at Week 48, 44.5% of patients treated with Ranivisio were free of CNV leakage compared with 42.9% of patients treated with Lucentis.

Table 39

Table 2.5.4-9: Number and percentage of patients assessed for CNV leakage by analysis visit (FAS population)

Analysis Visit	FYB201		Lucentis		Total	
CNV leakage?	n	%	n	%	n	%
	(N = 215)		(N = 214)		(N = 429)	
Screening						
Yes	212	99.5%	201	97.6%	413	98.6%
No	1	0.5%	5	2.4%	6	1.4%
Missing	2		8		10	
Week 24						
Yes	104	51.7%	96	49.0%	200	50.4%
No	97	48.3%	100	51.0%	197	49.6%
Missing	8		15		23	
Week 48						
Yes	106	55.5%	101	57.1%	207	56.3%
No	85	44.5%	76	42.9%	161	43.8%
Missing	14		25		39	

N = total number of patients, n = number of patients within specified class, % = number of patients in specified class/total number of patients per visit*100

Fluid-free macula at each visit

At baseline, nearly none of the patients had a fluid-free macula. After treatment with Ranivisio or Lucentis gradually higher proportions of patients with a fluid-free macula were observed from Week 4 onwards, reaching about half of the patients (Ranivisio: 48.0%, Lucentis: 51.8%) with fluid-free macula at the Final Visit.

Table 40

Table 2.5.4-10: Number and percentage of patients assessed for fluid-free macula by analysis visit (FAS population)

Analysis Visit	FYB201 (N = 215)		Lucentis (N = 214)		Total (N = 429)	
Fluid-free macula?	n	%	n	%	n	%
Baseline						
Yes	0	0.0%	1	0.5%	1	0.2%
No	214	100.0%	211	99.5%	425	99.8%
Missing	1		2		3	
Week 4						
Yes	40	19.2%	35	17.3%	75	18.3%
No	168	80.8%	167	82.7%	335	81.7%
Missing	7		12		19	
Week 8						
Yes	62	30.5%	59	28.6%	121	29.6%
No	141	69.5%	147	71.4%	288	70.4%
Missing	9		8		17	
Week 12						
Yes	77	37.4%	71	34.3%	148	35.8%
No	129	62.6%	136	65.7%	265	64.2%
Missing	6		7		13	
Week 24						
Yes	74	35.9%	94	45.4%	168	40.7%
No	132	64.1%	113	54.6%	245	59.3%
Missing	3		4		7	
Final visit/Week 48						
Yes	98	48.0%	102	51.8%	200	49.9%
No	106	52.0%	95	48.2%	201	50.1%
Missing	1		5		6	

N = total number of patients, n = number of patients within specified class

NEI VFQ-25 Questionnaire

The effect of treatment with ranibizumab on quality of life was a secondary efficacy objective, which was to evaluate and compare change in vision-related functioning and well-being measured by NEI VFQ-25 questionnaire at Week 24 and 48 compared to baseline in the FAS population.

The same ANCOVA model as specified for the primary endpoint was used to derive the CIs for the LS means difference between both treatment groups, but without formal hypothesis testing.

Subscale score

In general, the mean vision-targeted sub-scale scores of general vision, near activities, distance activities, and vision-specific mental health and role difficulties were 6 to 8 points higher at Week 48 compared to baseline. For the sub-scales (general health, ocular pain, driving, colour vision, peripheral vision and vision-specific social functioning and dependency) the mean changes from baseline to the Final Visit were 0 to 4 points higher.

Composite score

At Week 24 the mean (SD) change from baseline in NEI VFQ-25 composite score reached 3.44 (9.851; median: 2.35) points for Ranivisio and 3.71 (11.676; median: 2.24) points for Lucentis. At Week 48 a mean (SD) change from baseline in NEI VFQ-25 composite score of 5.31 (12.006; median: 2.95) points for Ranivisio and of 3.67 (13.374; median: 2.58) points for Lucentis was reached.

Table 41

Table 11-29 Absolute change from baseline in NEI VFQ-25 composite score – FAS_US and FAS_EU

	FYB201	Lucentis	Total
FAS_EU	**(N = 215)**	**(N = 214)**	**(N = 429)**
At analysis visit V7/Week 24			
N*	209	211	420
n	207	206	413
Missing	2	5	7
Mean (SD)	3.44 (9.851)	3.71 (11.676)	3.57 (10.787)
Median	2.35	2.24	2.27
Interquartile range (Q1–Q3)	-2.16 – 8.04	-1.59 – 9.50	-1.88 – 8.52
Range (min–max)	-27.5 – 40.4	-35.5 – 52.8	-35.5 – 52.8
At Final Visit/Week 48			
N*	205	202	407
n	203	198	401
Missing	2	4	6
Mean (SD)	5.31 (12.006)	3.67 (13.374)	4.50 (12.711)
Median	2.95	2.58	2.83
Interquartile range (Q1–Q3)	-1.63 – 11.06	-2.78 – 9.50	-2.17 – 9.92
Range (min–max)	-30.3 – 48.0	-43.5 – 58.0	-43.5 – 58.0

Abbreviations: NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, FAS_US = full analysis set for the US, FAS_EU = full analysis set for the EU, 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
Source: Post-text table 14.2.3.16.1 and 14.2.3.16.2

Based on the ANCOVA estimates, the LS means difference for the change from baseline in NEI VFQ-25 composite score between Ranivisio and Lucentis at Week 24 was 0.01 points with a 95% CI of [-1.88; 1.91] points and at Week 48 it was 2.02 points with a 95% CI of [-0.12; 4.16] points.

Table 42

Table 11-30 ANCOVA for the change from baseline in NEI VFQ-25 composite score – FAS_US and FAS_EU

	n	Missing	Arithmetic mean	LS mean[1]	SE LS mean	CI
FAS_EU						**95% CI**
At analysis visit V7/Week 24						
FYB201	207	2	3.44	3.64	0.733	[2.20; 5.09]
Lucentis	206	5	3.71	3.63	0.745	[2.16; 5.09]
Difference						
FYB201 - Lucentis			-0.27	0.01	0.962	[-1.88; 1.91]
At Final Visit/Week 48						
FYB201	203	2	5.31	5.11	0.824	[3.49; 6.73]
Lucentis	198	4	3.67	3.09	0.840	[1.44; 4.74]
Difference						
FYB201 - Lucentis			1.64	2.02	1.088	[-0.12; 4.16]

[1] Estimates are adjusted for pooled country and baseline NEI VFQ-25.

Abbreviations: NEI VFQ-25 = National Eye Institute Visual Function Questionnaire, ANCOVA = Analysis of Covariance, CI = confidence interval, FAS_US = full analysis set for the US, FAS_EU = full analysis set for the EU, LS = Least squares, n = number of patients with non-missing assessment, Missing = number of patients with missing assessment, SE = standard error, V = visit

Notes: Two-sided 90% and 95% confidence intervals based on normal approximation.

Source: Post-text table 14.2.3.17.1, 14.2.3.17.2, 14.2.3.18.1, 14.2.3.18.2

Overall, comparability of Ranivisio to Lucentis was demonstrated for all secondary efficacy endpoints. Results were consistent over the time for all variables. Improvement of macula function in terms of BCVA demonstrated after 8 weeks was maintained until the end of the observation period.

Ancillary analyses

Subgroup analyses

For robust demonstration of similar efficacy, the applicant was requested to provide subgroup analyses of the primary EP by prognostic factors at BL.

A forest plot has been provided for the FAS-EU analysis set, for subgroups defined by total lesion area (≤ 4 disc area versus > 4 disc area) and by Snellen equivalent (Snellen equivalent from 20/32 to 20/63 indicating mild visual impairment versus 20/80 to 20/100 indicating moderate visual impairment).

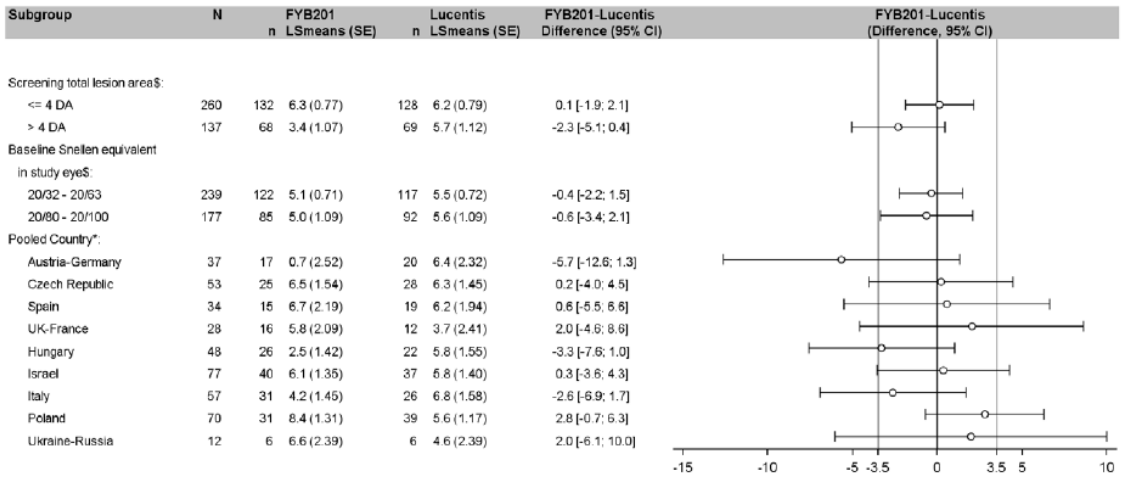


Figure 8 Forest Plot for Change from Baseline in BCVA (ETDRS letters) at Week 8 -FAS_EU

Source: Attachment to question 100, Figure 1

FAS_EU = Full Analysis Set for the EU, BCVA = Best-corrected visual acuity, ETDRS = Early Treatment Diabetic Retinopathy Study, N = number of patients with non-missing BCVA assessment at analysis visit 3/Week 8 overall in each subgroup, n = number of patients with non-missing BCVA assessment at analysis visit 3/Week 8 within each subgroup and treatment group, LS = least square, SE = standard error, CI = confidence interval, DA = disc area (4 DA = 10.16 mm²). $ ANCOVA includes pooled country and baseline BCVA [letters] and treatment group as independent variables. * ANCOVA includes baseline BCVA [letters] and treatment group as independent variables. Two-sided 95% confidence interval based on normal approximation.

The corresponding two-sided 95% CIs for the subgroup analyses by Snellen equivalent and by total lesion area ≤ 4 were within the equivalence margin. The subgroup of patients who had a total lesion area of more than 4 DA (n=137 patients), however, fell not within the pre-defined equivalence margin of ± 3.5 letter. Here, the estimated difference was -2.3 ETDRS letters with a 95% CI of [-5.1; 0.4].

In addition, the applicant provided subgroup analyses by country region. Here, the estimated mean differences for the primary EP between the two treatment arms within each country region were nearly all within the equivalence interval of [-3.5; 3.5] letters. However, for the region Austria-Germany, the estimated difference was -5.7 ETDRS letters, with a 95% CI of [-12.6; 1.3]. No reasonable explanation has been provided for this finding, except for the small number of patients from this country region (n=37; n=17 for Ranivisio, n=20 for Lucentis). With their responses to the D180 LoOI, the applicant has provided additional analyses and data for the subgroup Austria-Germany, such as baseline disease characteristics and results for secondary efficacy endpoints, as requested.

First of all, it is pointed out by the applicant that, in this overall small subgroup (n=17 patients in the Ranivisio arm, n=21 patients in the Lucentis arm), there was a difference of n=4 subjects between both study arms (n=3 for the primary analysis, due to a missing BCVA assessment at Wk 8 for 1 patient from the Lucentis arm).

With regard to major protocol deviations, there were no imbalances detected between both treatment arms in the AUT-GER subgroup.

As for patient demographics, there was a distinctly higher proportion of female patients enrolled in the Ranivisio arm (n=15/17; 88.2%) than in the Lucentis arm of the AUT-GER subgroup (n= 12/21; 57.1%). However, this imbalance cannot explain the lower efficacy observed in the Ranivisio arm from the AUT-GER subgroup, since various studies exploring the impact of gender as an influencing factor on the effectiveness of anti-VEGF therapy came to the conclusion that gender had no demonstrable effect on visual outcome (Gill et al, Ophthalmology and Therapy 9, 725-737, 2020).

Another marked imbalance between the study arms in the AUT-GER subgroup was observed with regard to iris colour: only 4/17 patients in the Ranivisio arm (23.5%) had light iris colour, whereas 9/21 patients in the Lucentis arm (42.9%) had light iris colour. However, this lower proportion of patients with light iris colour cannot account for the lower efficacy seen in the Ranivisio arm, since the opposite was reported in literature: The gain of functional recovery under anti-VEGF therapy was significantly higher in dark-coloured eyes (Brockman et al, Eye 27, 1169-1173, 2013).

Regarding ophthalmological history, slight numerical imbalances were observed between the treatment arms in the AUT-GER subgroup, however not satisfactorily explaining the observed lower efficacy in the biosimilar arm.

When looking at the marked difference for the primary efficacy EP between the treatment arms in this subgroup (estimated difference in BCVA of -5.7 ETDRS letters, 95% CI -12.6; 1.3), no specific patients could be identified as "outliers", according to the applicant. Indeed, the number of patients with a BCVA of less than 60 letters at baseline was balanced (n=5 in each treatment arm). However, two patients in the Ranivisio arm experienced a pronounced drop in BCVA despite anti-VEGF treatment (i.e. BCVA values below 20 letters). This was not seen in any patient of the Lucentis arm of the AUT-GER subgroup and might thus account for the observed worse efficacy in the biosimilar arm.

In summary, no clear explanation has been provided by the applicant for the lower efficacy of Ranivisio compared to the originator Lucentis in the AUT-GER subgroup.

Overall, taking into account that equivalence with regard to efficacy between Ranivisio and Lucentis was shown in the entire study population and that the AUT-GER subgroup is indeed rather small and has a numerical imbalance between the treatment arms (n=17 vs n=21), the observed lower efficacy for Ranivisio in this single subgroup is considered not to be of clinical relevance.

Post-hoc correlation between BCVA and FCP

With a protocol amendment, the primary efficacy endpoint for the EU/ EMA was changed from 'Change in FCP retinal thickness from BL at Week 4' to 'Change in BCVA from BL at Week 8'.

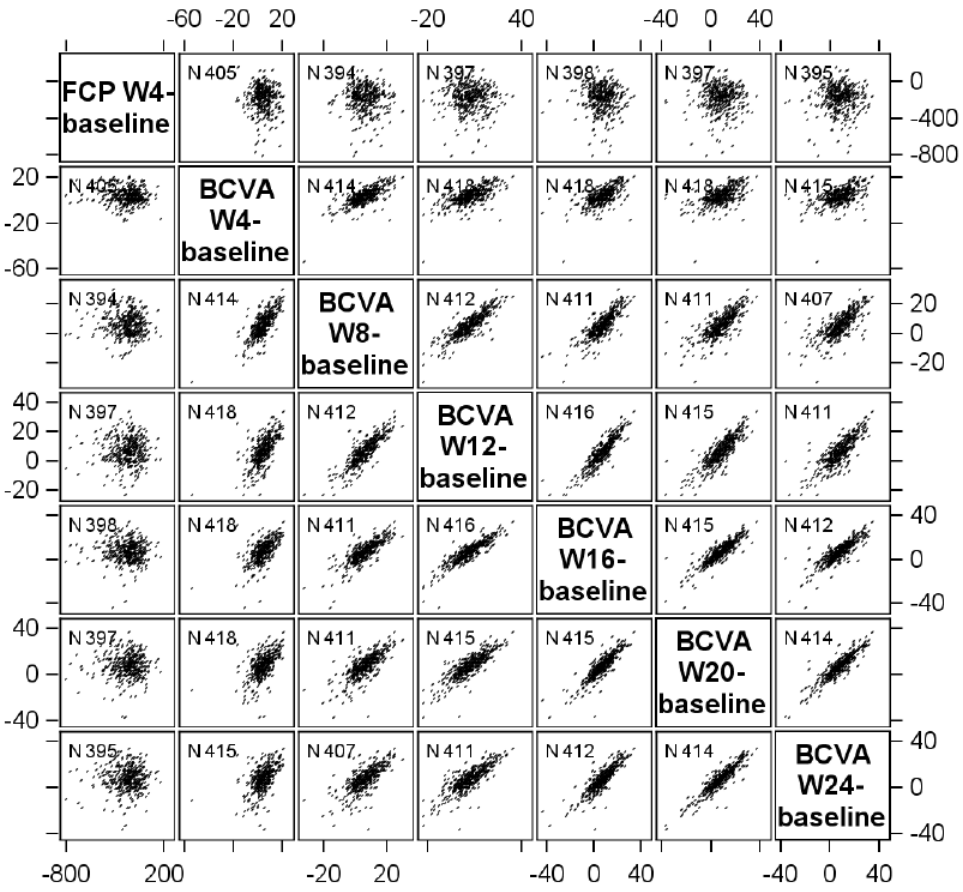
During the EMA pre-submission meeting in June 2020, this change in the primary EP was also discussed. Within this context, the EMA recommended to perform a post-hoc correlation analysis of BCVA-FCP results for all patients. Following this advice, after study completion the applicant conducted post-hoc analyses to investigate the possible correlation between FCP and BCVA changes from BL.

FCP change from baseline to Week 4 versus BCVA change from baseline to Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24

The first analysis simply plots the change from baseline to Week 4 in FCP against the changes from baseline to Weeks 4, 8, 12, 16, 20, and 24 in BCVA. No correlation between changes in FCP and changes in BCVA (both from baseline) could be observed (see first line and first columns of Figure 1).

Figure 1 shows that the results are in line with the previously submitted plots that had as basis considerably fewer data. The Figure is based on all 429 patients that were included in the Full Analysis Set for the EU Analysis. A subset of patients with available data is included in the corresponding plot displayed by "N".

Figure 1 Scatterplot of change from baseline to Week 4 in FCP vs change from baseline to Weeks 4, 8, 12, 16, 20 and 24 in BCVA



The relationship between the primary efficacy endpoint (the absolute change from baseline to Week 8 in BCVA) and the secondary endpoint (the absolute change from baseline to Week 4 in FCP) was further investigated using three possible regression models: linear regression, quadratic regression and regression to polynomials of 5th degrees.

Correlation between change from BL of BCVA to Week 8 and change from BL of FCP to Week 4

1) *Regression analysis with FCP as response*

Figure 2 Linear regression

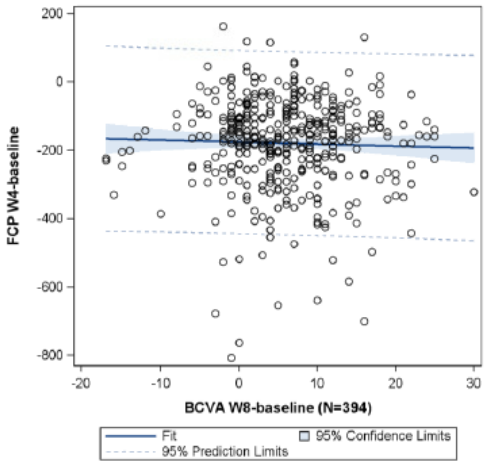


Figure 3 Quadratic regression

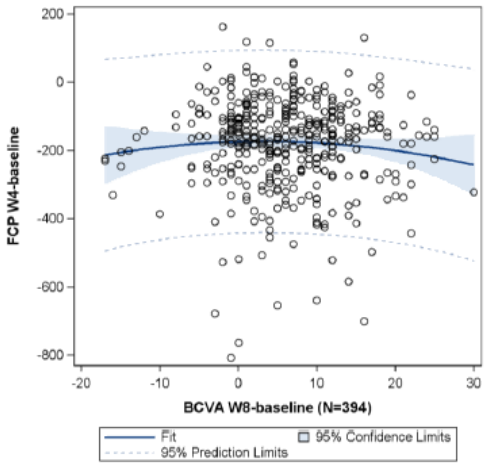
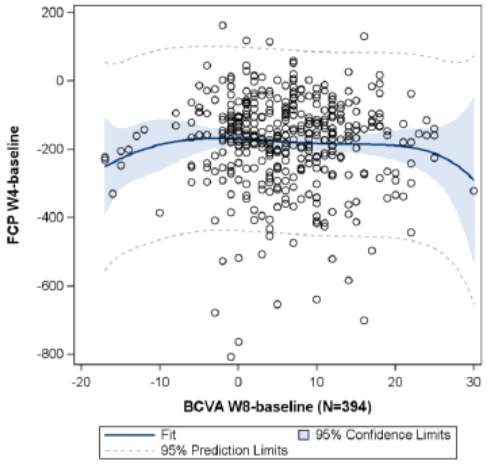


Figure 4 Regression to polynomial of 5th degree



2) Regression analysis with BCVA as response

Figure 5 Linear regression

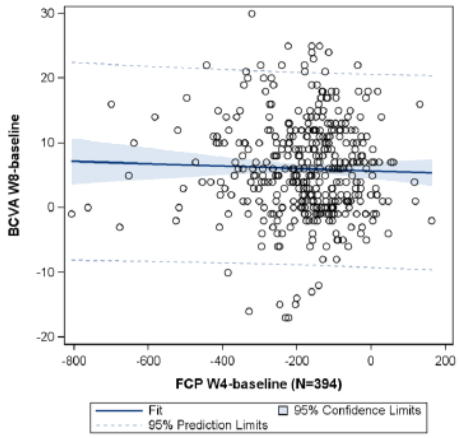


Figure 6 Quadratic regression

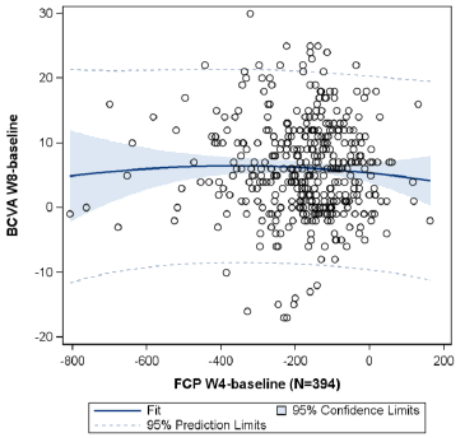
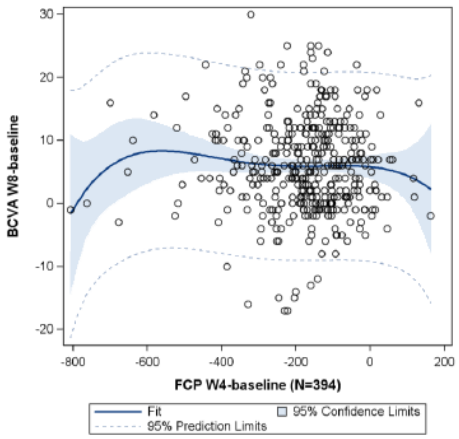


Figure 7 Regression to polynomial of 5th degree



According to the applicant, the figures depicted above illustrate that various regressions of BCVA change to FCP change or regressions of FCP change to BCVA change could not reveal a functional relationship between the two endpoints.

The coefficient of determination R^2 explains the proportion of variance in the response variable that can be predicted from the model (based on the explaining variable). It ranges from 0 to 1 with 0 meaning the model can explain nothing of the variability and 1 meaning that the model can explain 100%.

In all performed regression models, less than 1% of the variability could be explained. This indicates that there is no correlation between the changes from baseline for the two parameters at Week 8. Nevertheless, there might be any unknown model behind, but by using polynomials until the 5th degree, the applicant states that he has already covered a wide range of models.

Table 43

Table 1 Coefficient of determination R^2 for FCP Change from baseline to Week 4 versus BCVA change from baseline to Week 8

FCP W4 – baseline as response, BCVA W8 – baseline as explaining variable			BCVA W8 – baseline as response, FCP W4 – baseline as explaining variable		
Linear regression	Quadratic regression	Regression to polynomial of 5th degree	Linear regression	Quadratic regression	Regression to polynomial of 5th degree
0.001068 (≈0.1%)	0.005132 (≈0.5%)	0.007770 (≈0.8%)	0.001068 (≈0.1%)	0.002446 (≈0.2%)	0.007980 (≈0.8%)

The applicant has presented the correlation of the two endpoints over time as requested by the EMA. The correlation is not informative. However, given that both endpoints were independently met, this analysis is not deemed critical. It should be noted that a distinct correlation between a highly specific, "isolated" morphological endpoint reflecting retinal thickness only and a more "broad" and complex functional endpoint such as BCVA would not have been necessarily expected during the early treatment phase.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 44 Summary of efficacy for trial COLUMBUS-AMD (FYB201-C2015-01-P3)

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)		
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778	
Design	12-month (48-week), Phase III, randomised, active-controlled, evaluation-masked, parallel-group, multi-centre study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable not applicable
Hypothesis	Equivalence	

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
Treatments groups	Ranivisio (ranibizumab biosimilar)		Ranivisio IVT at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) for 12 months (48 Weeks, Q4W) starting at Visit 1 (Week 0) through Visit 12 (Week 44) (total of 12 injections) 238 patients randomised
	Reference product: US-Lucentis (ranibizumab)		US-Lucentis IVT at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) for 12 months (48 Weeks, Q4W) starting at Visit 1 (Week 0) through Visit 12 (Week 44) (total of 12 injections) 239 patients randomised
Endpoints and definitions	Primary endpoint	BCVA (Wk 8)	Mean change from baseline in BCVA by ETDRS letters after 2 months (8 weeks) of treatment. For the EU, this EP was evaluated in the group of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent (FAS_EU) For the US, this EP was evaluated in the entire FAS with a baseline BCVA between 20/32 and 20/100 Snellen equivalent Equivalence margin of ± 3.5 letters

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
	Secondary endpoint	BCVA (12 months)	- 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 [Wk 40], 11 [Wk 44] and 12 [Wk 48])
	Secondary endpoint	FCP /FCS	Changes from baseline in FCP retinal thickness and FCS retinal thickness over time
	Secondary endpoint	CNV leakage	Percentage of patients with active CNV leakage at Month 12
	Secondary endpoint	Fluid-free macula	Percentage of patients with fluid-free macula at each visit
	Secondary endpoint	Total lesion area	Change from baseline in total lesion area at Month 12
	Secondary endpoint	NEI VFQ-25	Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 at Month 12
Database lock	01-Oct-2018		
Results and Analysis			
Analysis description	**Primary Analysis**		

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
Analysis population and time point description	Full Analysis Set for EU/FAS_EU (including 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 20/40 and 20/100 Snellen equivalent in the study eye) n=429 patients, time point: 8 weeks		
Descriptive statistics and estimate variability	Treatment group	Ranivisio	US-Lucentis
	Number of subjects	215	214
	Change from BL in BCVA at Wk 8, mean (letters)	5.2 letters	6.0 letters
	SD	(7.75)	(8.42)
Effect estimate per comparison	Primary endpoint: Change from BL in BCVA at Wk 8 with margin ± 3.5	Comparison groups	Ranivisio versus US-Lucentis
		Difference between groups (LS means)	-0.7 letters
		95% CI	(-2.3, 0.9)
		EQ margin = ± 3.5	-2.3 > 3.5, 0.9 < 3.5
Notes	Model: ANCOVA: change in BCVA between baseline and Week 8 as dependent variable, baseline BCVA as covariate, country and treatment group as fixed effects.		

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
Analysis description	**Sensitivity analysis for primary EP**		
Analysis population and time point description	Per Protocol Set for EU/PPS_EU (including all patients who belonged to the FAS_EU who had no major protocol deviations until Visit 3 after 8 weeks that would interfere with the interpretation of BCVA efficacy data) n=402 patients, time point: 8 weeks		
Descriptive statistics and estimate variability	Treatment group	Ranivisio	US-Lucentis
	Number of subjects	200	202
	Change from BL in BCVA at Wk 8, mean (letters)	5.3 letters	6.2 letters
	SD	(7.82)	(8.39)
Effect estimate per comparison	Primary endpoint: Change from BL in BCVA at Wk 8 with margin ± 3.5	Comparison groups	Ranivisio versus US-Lucentis
		Difference between groups (LS means)	-0.8 letters
		95% CI	(-2.4, 0.8)
		EQ margin = ± 3.5	-2.4 > -3.5, 0.8 < 3.5

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Full Analysis Set for EU/FAS_EU (including 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 20/40 and 20/100 Snellen equivalent in the study eye) n=429 patients, time point: 48 weeks		
Descriptive statistics and estimate variability	Treatment group	Ranivisio	US-Lucentis
	Number of subjects	215	214
	Change from BL in BCVA after 12 months (averaged over Months 10 [Wk 40], 11 [Wk 44] and 12 [Wk 48]) mean (letters)	7.9 letters	8.4 letters
	SD	(11.64)	(11.07)
Effect estimate per comparison	Secondary EP: Change from BL in BCVA after 12 months	Comparison groups	Ranivisio versus US-Lucentis
		Difference between groups (LS means)	-0.2 letters
		95% CI	(-2.4, 2.0)
Descriptive statistics and estimate variability	**Change from BL in FCP at 12 months** mean (µm)	-218.76 µm	-218.49 µm

Title: Efficacy and Safety of the Ranibizumab biosimilar Ranivisio in Comparison to Lucentis in Patients with Neovascular Age-Related Macular Degeneration (COLUMBUS-AMD)			
Study identifier	Study code: FYB201-C2015-01-P3 Eudra CT-No.: 2015-001961-20 Clinicaltrials.gov No.: NCT02611778		
	SD	(160.440)	(150.769)
Effect estimate per comparison	Secondary EP: Change from BL in FCP at 12 months	Comparison groups	Ranivisio versus US-Lucentis
		Difference between groups (LS means)	9.02 µm
		95% CI	(-14.93, 32.98)
Descriptive statistics and estimate variability	**Change from BL in FCS at 12 months** (µm) mean (SD)	-188.15 (131.353)	-196.55 (127.650)
	CNV leakage at month 12 (yes)	55.5%	57.1%
	Fluid-free macula at month 12 (yes)	48.0%	51.8%
	Change from BL in total lesion area at month 12 (mm^2) mean (SD)	-0.6603 (4.84466)	-1.0827 (5.26262)
	Change from BL in NEI VFQ-25 composite score mean (SD)	5.31 (12.006)	3.67 (13.374)

2.4.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme was set up to demonstrate biosimilarity with regard to efficacy between Ranivisio and US-Lucentis and is based on one single pivotal Phase III trial. COLUMBUS-AMD was a randomised, active-controlled, evaluation-masked, parallel-group, multicentre study in patients with neovascular age-related macular degeneration. It is acceptable that no further clinical studies have been conducted to demonstrate similarities in efficacy between Ranivisio and Lucentis in other indications approved for EU Lucentis. The selected patient population is considered a relevant and sensitive study population for the detection of potential differences between Ranivisio and the reference product and was endorsed by the EMA. US-Lucentis was chosen as comparator in the Phase III study, which might be sufficient for submission of MAA, if an acceptable bridging could be demonstrated on analytical level.

477 patients from 75 study sites were randomised 1:1 to receive either Ranivisio or US-Lucentis. The study was conducted globally in 12 countries with 9 EU member states. The applicant states confirms that this study was performed in compliance with ICH guidelines on GCP as well as the ethical principles of the latest revision of the Declaration of Helsinki. No issues regarding GCP have been identified. The COLUMBUS-AMD study has been inspected by the Gesundheitsamt Düsseldorf. The GCP inspection report has been provided, as requested. No critical issues were identified during the inspection.

Eligible randomised patients received either Ranivisio or US-Lucentis on Day 1 every 4 weeks into the study eye. Treatment was repeated up to Week 44 for a total of 12 doses of study drug. Study duration was 48 weeks. Treatment was withheld and not resumed earlier than the next scheduled treatment in the event of decrease in BCVA of ≥ 30 letters compared with the last assessment of visual acuity, an intraocular pressure of ≥ 30 mmHg, a retinal break, a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area, and in the event of performed or planned intraocular surgery within the previous or next 28 days (except in case of cataract surgery, which required withdrawal from the study, see below). A patient was withdrawn from the study if informed consent was withdrawn, if prohibited concomitant medication had been used, in the case of cataract surgery in the study-eye, concurrent illness, AEs, major protocol deviations, the need of alternative treatment, pregnancy or loss to follow-up.

Overall, the design of the pivotal Phase III study is considered adequate and generally in line with previous EMA-scientific advices. The inclusion and exclusion criteria were in line with those in the clinical trials performed with Lucentis and are overall considered adequate. An upper BCVA boundary of 20/40 was recommended for study inclusion by the CHMP during prior SA (instead of 20/32, as defined by the applicant in the inclusion criteria), in order to ensure that the study population is sensitive enough to BCVA changes. This was not followed by the applicant. However, the primary EP analysis for EMA submission was conducted in the subgroup of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent, in order to fulfil CHMP/ EMA recommendations. This is considered acceptable.

Total area of whole lesion was set among the inclusion criteria. According to the study protocol, it had to be equal or less than 12 disc areas. Reducing the upper limit of lesion size for study inclusion was recommended by the CHMP during the prior SA to improve the homogeneity of the population. However, the applicant decided to stay in line with the MARINA and PIER studies of the originator product in respect of the inclusion criterion baseline lesion size ≤12 disc areas. The applicant provided analysis of patients, who had a lesion size between 9 and 12 disc areas: only 8 patients (1.9%) (4 Ranivisio [1.9%] and 4 Lucentis [1.9%]) in the

FAS_EU analysis set, and 7 patients (1,7%) (4 Ranivisio [2.0%] and 3 Lucentis [1.5%]) in the PPS_EU analysis set. As the number of patients who had a lesion size between 9 and 12 disc areas was very low (N=8, 1.9%), no effect on the homogeneity of the study is expected.

Uncontrolled hypertension or glaucoma in the study eye defined as intraocular pressure (IOP) ≥ 30 mm Hg was set among the exclusion criteria. Ranibizumab may cause a further increase in intraocular pressure. IOP ≥ 30 mm Hg is at the limit of the value, when the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of an intraocular pressure is ≥30 mmHg, as stated in the SmPC of Lucentis. The applicant was invited to specify, how many patients experienced the increase of IOP to ≥ 30 mm Hg during the study and how it was dealt with them during the study. According to the applicant, no patient experienced the increase of pre-injection IOP to ≥30 mmHg during the study. Therefore, no action regarding withholding the dose had to be taken as stated in the SmPC of Lucentis. The increase of post-injection IOP to ≥ 30 mmHg was observed during the whole study, however, in line with the SmPC of Lucentis the transient increases in IOP have been seen within 60 minutes of injection of ranibizumab.

The applied treatment regimens for ranibizumab were in line with the Lucentis labelling. The most common reasons for premature discontinuation (before Week 48) were consent withdrawal and adverse events. 6.7% in each treatment arm discontinued study treatment prior to the final Week 48 analysis. Up to week 24, there was an imbalance between treatment arms with regard to study treatment discontinuation (n=7 in the Ranivisio arm vs. n=3 in the Lucentis arm). The applicant provided the reasons for treatment discontinuation prior to Wk 24 and stated that there might be a higher probability of an uneven distribution without reason with such small numbers. This is acknowledged, against the background that, overall up to final analysis, the number of patients who discontinued treatment was similar in both treatment arms (n=16 in each arm).

The focus of a clinical comparability trial is to demonstrate similar efficacy and safety compared to the reference product. Comparability margins have to be pre-specified and justified based on clinical relevance. Adequate data on the effect size should be taken into account to support the selection of the margin. The biosimilarity margin for the main efficacy endpoint need to be justified on both clinical and statistical grounds, in order to ensure that there is no clinically relevant differences in efficacy and to prove that prove that there is no important loss of efficacy if the test product is used instead of reference.

With regard to demonstration of similar efficacy between Ranivisio and US-Lucentis, an equivalence margin of ± 3.5 letters was chosen. This margin has not been agreed with the EMA/ CHMP in advance, against the background that, originally, a different endpoint (i.e. CPT at Week 8) had been proposed by the applicant for the pivotal trial (see below). Thus, a justification for the chosen equivalence margin, based on a comprehensive meta-analysis, was requested. The applicant clarified that the chosen equivalence margin of ± 3.5 ETDRS letters was agreed in a FDA scientific advice meeting.

Within this context, a meta-analysis comprising 3 study publications was conducted and presented with the response to the D120 LoQ. It was explained that, from this meta-analysis, the estimated mean difference between ranibizumab IVT treatment and sham control was 9.9 letters, with a 95% CI of [7.06; 12.69]. Thus, an equivalence margin of ± 3.5 letters would preserve around 50% of the treatment effect when the lower bound of the 95% CI is used. This is considered acceptable.

The applicant was requested to explain 1) how dynamic allocation method works and 2) if randomisation scheme is the same for each centre as randomisation is stratified by site. Randomisation process used in study FYB201-C2015-01-P3 was considered from article Pocock, Simon (1975): Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial, Biometrics 31, 103-115. This

process used dynamic allocation to individual treatments as randomisation was stratified by best corrected visual acuity (BCVA) (mild, i.e. 20/32 Snellen equivalent, vs. moderate/severe, i.e. 20/40-20/100 Snellen equivalent) and centre. The applicant provided an example in response to a question from the CHMP. Patient with mild BCVA in was considered and was to be randomised either to Ranivisio treatment (Ranivisio) or Lucentis treatment (Lucentis). Value of function G‘(t) was calculated separately for t=1 which represented Ranivisio and for t=2 which represented Lucentis. Value for G‘(t) was obtained as sum of current number of patients with mild BCVA and current number of patients within centre 3 for t=1 (Ranivisio) and t=2 (Lucentis), respectively. If G‘(1)<G‘(2) then there was higher probability to be assigned into Ranivisio (t=1) than into Lucentis (t=2). If G‘(2)<G‘(1) then there was higher probability to be assigned into Lucentis (t=2) than into Ranivisio (t=1). If G‘(1)=G‘(2) then probability of assignment was equal both for Ranivisio and for Lucentis. This can be considered as acceptable randomisation procedure.

Efficacy endpoints

The primary endpoint is the ‘Change from baseline in BCVA at Week 8’ in the FAS_EU population. The Per Protocol population was used as a supportive population by the applicant for evaluation of the sensitivity of the primary efficacy analysis, but from a regulatory perspective in an equivalence setting, the PP set is equally important, and similarity has to be shown in both analysis sets (see ICH E9).

For the EU, the primary endpoint was evaluated in the subgroup of patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent (i.e. the FAS_EU population), in order to fulfil CHMP/ EMA recommendations obtained during EMA SA. For the FDA, the primary analysis was conducted in the entire FAS population with a baseline BCVA between 20/32 and 20/100 Snellen equivalent.

Originally, two independent primary endpoints had been proposed for the COLUMBUS-AMD study: Change from BL in BCVA by ETDRS letters after 12 months for the FDA, and Change from BL in foveal centre point (FCP) retinal thickness by SD-OCT at Week 4 for the EMA.

The choice of this morphological endpoint for the EU was overall endorsed and agreed with CHMP during EMA SA, against the background that visual function endpoints did not detect differences in clinical trials (e.g. the CATT study) when comparing ranibizumab to bevacizumab, in contrast to morphological endpoints for which ranibizumab outperformed bevacizumab, thus being able to sensitively detect product-related differences. During EMA SA, it was also stated by the CHMP that retinal thickness outcomes were expected to correlate with visual acuity in the early treatment phase, to support this morphological endpoint.

Based on this recommendation, the applicant conducted a blinded visual review of the two endpoints in a subset of patients, indicating only limited individual correlation between functional (BCVA) and anatomical (FCP) parameter. This obviously led to a protocol amendment (08 March 2017), with which the primary EU and US endpoints were “harmonised”, i.e. only one primary endpoint for both EU and US, was defined; namely the change in BCVA between baseline and Week 8. However, this rather late shift of the primary endpoint for the EU was not discussed with the CHMP during any SA procedure; it was communicated to the EMA via notification only. During the EMA pre-submission meeting in June 2020, this change in the primary EP was also discussed. Within this context, the EMA recommended to perform a post-hoc correlation analysis of BCVA-FCP results for all patients.

The applicant was requested to justify this late shift in the primary endpoint, since this was not explicitly addressed in the study protocol and might pose a challenge for the intended robust demonstration of similar efficacy. With his response, the applicant clarified that this change in the primary endpoint was deemed necessary by the applicant, as the underlying assumption for choosing FCP, i.e. that a correlation between FCP retinal thickness and BCVA could be demonstrated, was proven difficult if not impossible to demonstrate.

In addition, it was emphasised that a retrospective analysis showed that also the initially proposed primary EP, the change from BL in FCP retinal thickness up to Wk 4, was met.

The secondary efficacy endpoints include BCVA change from BL over time, as well as Change from BL in BCVA after 12 Months (averaged over Months 10, 11 and 12).

Additionally, morphological outcomes (changes in FCP and FCS retinal thickness, active CNV leakage, retinal fluid as well as total lesion area) and Quality of Life were explored as secondary endpoints, both at Week 24 and at Week 48, allowing investigation of the comparability of the maintenance of a comparable benefit over the time.

A responder analysis of patients who lost fewer than 5, 10, 15 letters/gained 5, 10, 15 letter or more in BCVA compared with baseline was requested in test and reference treatment arm to further support the biosimilarity between Ranivisio and the reference medicinal product Lucentis. In general, the results indicated similar proportions of responders in each of the observed parameter between test product and Lucentis. Slightly more responders were recorded in parameters Gain of 5 or more ETDRS letters in V3/Week 8 (50.5% responders in test arm vs. 55.1% responders in Lucentis arm) and Gain of 10 or more ETDRS letters in V3/Week 8 (27.8% in test arm vs. 33.2% in Lucentis arm) in the Lucentis arm in comparison with test arm in the FAS_EU analysis set. However, it can be concluded that the outcomes were represented in similar manner between treatment arms without impact on biosimilarity conclusion.

Overall, the applicant´s development programme to demonstrate similarity between Ranivisio and US-Lucentis with respect to efficacy is considered adequate to support this application: study design, study population, inclusion/exclusion criteria, and dose regimen were performed in line with the guidance on similar biological products and were in compliance with scientific advice obtained from the EMA. The chosen primary endpoint is overall considered adequate for the demonstration of similar efficacy.

Baseline data

Demographics and baseline disease characteristics were overall comparable between the treatment arms. However, morphological BL characteristics of the study participants, such as CST and CPT, as well as IOP and total lesion area at baseline were missing in the initial submission. This information has been provided, as requested. CST, CPT, IOP and total lesion area at BL were overall comparable between both treatment arms, in all three analysis sets.

Furthermore, no information has been provided with regard to the mean interval since first diagnosis of neovascular AMD at baseline for both treatment arms. The requested information has been provided: The time since first diagnosis of nAMD was calculated in two analyses. Since the date of the nAMD diagnosis was not fully provided for 66 patients (26 in the Ranivisio and 40 patients in the Lucentis arm, respectively), for one analysis the time since diagnosis was estimated. In the other analysis, patients without complete information were excluded. When excluding estimated data, the mean time since first nAMD diagnosis was 40.8 days in the Ranivisio arm versus 30.8 days in the Lucentis arm. When estimated data were included, the difference between study arms was smaller: 72.1 days versus 65.9 days.

Efficacy data and additional analyses

For the primary endpoint 'Change from Baseline BCVA by ETDRS letters at Week 8' in the FAS-EU population, a mean change (SD) from baseline of 5.2 (7.75) ETDRS letters was observed for Ranivisio, compared to 6.0 (8.42) letters for Lucentis.

The primary analysis was performed via ANCOVA: the change in BCVA between baseline and Week 8 was included as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects.

Biosimilarity was shown by the LS means difference between both treatments of -0.7 ETDRS letters with a 95% CI of [-2.3; 0.9] ETDRS letters, which was completely contained within the predefined equivalence margin of ±3.5 letters. Thus, formal similarity of efficacy with regard to the primary efficacy endpoint was demonstrated. This was supported by sensitivity analyses: Similar LS means differences were also observed using the PPS as sensitivity analysis and in the MMRM using the FAS with 95% CIs within the predefined equivalence margin.

The primary analysis was conducted as pre-specified, but the provided boxplots raised the question whether the ANCOVA assumptions were all met. Additional diagnostic plots were provided by the applicant to investigate the assumption of normality and homogeneity of the residuals to support the ANCOVA assumptions. Another sensitivity analysis was also requested and Hodges-Lehmann estimate for treatment difference was provided. Based on this sensitivity analysis, equivalence was concluded both for FAS_EU and PPS_EU. Anyway, Hodges-Lehmann estimate was not entirely acceptable as other important effects included in "original" ANCOVA model (pooled country, baseline BCVA value) were omitted. Consequently, additional sensitivity analysis, which could deal with this, was requested. The applicant provided Poisson regression and quantile regression. Based on quantile regression, equivalence was concluded for FAS_EU but not for PPS_EU if median was considered. Anyway, as "original" ANCOVA model applied on data of primary endpoint was acceptable (i.e. assumptions on data distribution were verified) and equivalence was concluded both for FAS_EU and PPS_EU, equivalence between Ranivisio and Lucentis was concluded.

Results from the FDA-specific analysis of the primary endpoint (i.e. in the entire FAS population with a baseline BCVA between 20/32 and 20/100 Snellen equivalent) were supportive: Biosimilarity of Ranivisio to Lucentis was shown at Week 8 by the LS means difference between both treatments of -0.4 ETDRS letters with a 90% CI of [-1.6; 0.9] ETDRS letters, which was contained within the predefined equivalence margin.

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of biosimilarity between Ranivisio and Lucentis.

The change from baseline in BCVA for Ranivisio and Lucentis over time using the endpoints analysis Week 24, Week 48, and the average over Week 40, Week 44 and Week 48, showed overall comparable efficacy of both treatments in the FAS_EU population.

A sustained higher BCVA from Week 4 onwards was observed. At Week 24 the changes from baseline in BCVA reached about 7 ETDRS letters and at the Final Visit/Week 48 about 8 ETDRS letters in the FAS_EU population. The respective CIs for the difference between both treatments were similar, showing sensitive results using the PPS_EU populations.

The mean changes from BL in BCVA were numerically lower at all time points for the Ranivisio arm than for the comparator arm receiving Lucentis (Week 24: mean 7.1 versus 7.6 ETDRS letters, Week 48: mean 7.9 vs. 8.5 ETDRS letters, averaged over Wk 40/44/48: mean 7.9 versus 8.4 ETDRS letters). The same numerically lower mean BCVA changes from BL were observed in the PPS. However, the results for the differences in change from BL in BCVA between the treatment arms were entirely within the 95% CI, both in the FAS-EU and PPS_EU analysis populations.

A sustained lower retinal thickness in terms of FCP and FCS was observed in the FAS_EU population from analysis V2/Week 4 onwards.

At Week 24, a mean (SD) change from baseline in FCP of -207.59 (146.937; median: -184.50) µm for Ranivisio and of -212.99 (147.289; median: -191.00) µm for Lucentis was reached. Based on the ANCOVA estimates, the LS means difference for the change from baseline in FCP retinal thickness between Ranivisio and Lucentis at Week 24 was 9.02 µm with a 95% CI of [-14.93; 32.98] µm for the FAS_EU population.

At the Final Visit/Week 48, a mean (SD) change from baseline in FCP of -218.76 (160.440; median: -194.00) µm for Ranivisio and of -218.49 (150.769; median: -202.50) µm for Lucentis was reached. Based on the ANCOVA estimates, the LS means difference for the change from baseline in FCP retinal thickness between Ranivisio and Lucentis at Week 48 was 10.66 µm with a 95% CI of [-13.47; 34.79] µm for the FAS_EU population.

For FCP retinal thickness, also the PPS_EU population was analyzed for sensitivity. The ANCOVA for the sensitivity analysis using the PPS_EU population showed an LS means difference for the change from baseline in FCP retinal thickness between Ranivisio and Lucentis of 6.07 µm with a 95% CI of [-18.72; 30.86] µm at Week 24 and of 12.35 µm with a 95% CI of [-12.77; 37.48] µm at Week 48.

The results for FCS retinal thickness were consistent with those for FCP: At the Final Visit/Week 48 a mean (SD) change from baseline in FCS retinal thickness of -188.15 (131.353; median: -172.75) µm for Ranivisio and of -196.55 (127.650; median: -190.50) µm for Lucentis was observed. Based on the ANCOVA estimates, the LS means difference for the change from baseline in FCS retinal thickness between Ranivisio and Lucentis at Week 48 was -8.97 µm with a 95% CI of [-12.24; 30.18] µm for the FAS_EU population.

Total lesion area was evaluated as an additional anatomical EP and was compared between treatment arms at Week 24 and Week 48. Results revealed that the mean change from BL in total lesion area in mm^2 was well comparable across the Ranivisio and Lucentis treatment arms (Ranivisio: -0.5224 mm^2, Lucentis: -0.7252 mm^2 at Week 24; Ranivisio: -0.6603 mm^2, Lucentis: -1.0827 mm^2 at Week 52). The LS means difference between Ranivisio and Lucentis at Week 24 was 0.221 mm^2 with a 95% CI of [−0.728, 1.171] and at Week 48 was –0.328 mm^2 with a 95% CI of [−0.754, 1.401] for the FAS_EU population.

Active CNV leakage at Week 24 was comparable between the treatments (51.7% versus 49.0% in the Ranivisio and Lucentis arm, respectively). At the end of the study (Week 48), the proportion of patients with active CNV leakage continued to be comparable between the treatment arms (55.5% versus 57.1% in the Ranivisio and Lucentis arm.

At baseline, nearly none of the patients (0.2% from FAS_EU) had a fluid-free macula. After treatment with Ranivisio or Lucentis, gradually higher proportions of patients with a fluid-free macula were observed from Week 4 onwards (Week 4 - Ranivisio: 19.2%, Lucentis: 17.3%), reaching about half of the patients (Ranivisio: 48.0%, Lucentis: 51.8%) with fluid-free macula at the Final Visit/Week 48 in the FAS_EU population. Ranivisio and Lucentis showed similar numbers and percentages of patients with fluid-free macula after 24 weeks and 48 weeks of treatment in the FAS_EU population.

An increase in the mean change from BL in NEI VFQ-25 composite score was observed in the FAS_EU population at Week 24 and Week 48 in both treatment groups (Ranivisio: 3.44, Lucentis: 3.71 at Week 24; Ranivisio: 5.31, Lucentis: 3.67 at Week 48). Overall, the mean change in the NEI VFQ-25 composite score was comparable between treatment arms.

Overall, comparability of Ranivisio to Lucentis was demonstrated for all secondary efficacy endpoints. Results were consistent over the time for all variables. Improvement of macula function in terms of BCVA demonstrated after 8 weeks was maintained until the end of the observation period.

In addition, Quality of life as assessed by the NEI VFQ-25 questionnaire composite score increased slightly with both IVT treatments.

For robust demonstration of similar efficacy, the applicant was requested to provide subgroup analyses of the primary EP by prognostic factors at BL.

A forest plot has been provided for the FAS-EU analysis set, for subgroups defined by total lesion area (≤ 4 disc area versus > 4 disc area) and by Snellen equivalent (Snellen equivalent from 20/32 to 20/63 indicating mild visual impairment versus 20/80 to 20/100 indicating moderate visual impairment).

The corresponding two-sided 95% CIs for the subgroup analyses by Snellen equivalent and by total lesion area ≤ 4 were within the equivalence margin. The subgroup of patients who had a total lesion area of more than 4 DA (n=137 patients), however, fell not within the pre-defined equivalence margin of ± 3.5 letter. Here, the estimated difference was -2.3 ETDRS letters with a 95% CI of [-5.1; 0.4].

In addition, the applicant provided subgroup analyses by country region. Here, the estimated mean differences for the primary EP between the two treatment arms within each country region were nearly all within the equivalence interval of [-3.5; 3.5] letters. However, for the region Austria-Germany, the estimated difference was -5.7 ETDRS letters, with a 95% CI of [-12.6; 1.3]. With his responses to the D180 LoOI, the applicant has provided additional analyses and data for the subgroup Austria-Germany, such as baseline disease characteristics and results for secondary efficacy endpoints, as requested.

When looking at the marked difference for the primary efficacy EP between the treatment arms in this subgroup (estimated difference in BCVA of -5.7 ETDRS letters, 95% CI -12.6; 1.3), no specific patients could be identified as "outliers", according to the applicant. Indeed, the number of patients with a BCVA of less than 60 letters at baseline was balanced (n=5 in each treatment arm). However, two patients in the Ranivisio arm experienced a pronounced drop in BCVA despite anti-VEGF treatment (i.e. BCVA values below 20 letters). This was not seen in any patient of the Lucentis arm of the AUT-GER subgroup and might thus account for the observed worse efficacy in the biosimilar arm.

Overall, taking into account that equivalence with regard to efficacy between Ranivisio and Lucentis was shown in the entire study population and that the AUT-GER subgroup is indeed rather small and has a numerical imbalance between the treatment arms (n=17 vs n=21), the observed lower efficacy for Ranivisio in this single subgroup is considered not to be of clinical relevance.

2.4.7. Conclusions on the clinical efficacy

The clinical data provided suggest similarity with regard to efficacy between Ranivisio and the US reference product.

In the pivotal comparative efficacy study COLUMBUS-AMD in nAMD patients, equivalence between Ranivisio and US-Lucentis was demonstrated for the primary efficacy endpoint, both in the FAS and in the PPS population. This was supported by sensitivity analyses.

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of similar efficacy between Ranivisio and Lucentis.

Overall, comparability of Ranivisio to Lucentis was demonstrated for all efficacy endpoints.

2.4.8. Clinical safety

One pivotal Phase III study including a total of 477 patients diagnosed with neovascular AMD (randomised 1:1) was conducted, in order to compare the safety profiles of Ranivisio and Lucentis.

Neovascular AMD is considered a sufficiently sensitive population to investigate clinical biosimilarity in terms of safety, as there is comparability for ranibizumab across indications with regard to target receptor, mode of action and safety across authorised indications, i.e., DME, RVO, CNV and PDR. In addition, immunogenicity of ranibizumab was reported to be overall low across indications (up to 9%).

Safety was assessed by monthly visits, continuous monitoring of AEs (categorised by SOC and PT and coded by MedDRA), clinical laboratory evaluations (at baseline, Week 24, and Week 48/ final visit), monthly ophthalmic assessments as well as immunogenicity sampling (see AR Section 2.2.3 for details).

The Q4W administration of the study drugs is in agreement with the anticipated posology in patients with the highest treatment need. From a safety perspective, a monthly schedule is most sensitive, as higher exposure levels can be expected in comparison with a treat and extend regimen and is thus supported.

Study duration was 12 months, with 12 monthly injections. A study duration of 12 months is considered a relevant time period to assess safety and immunogenicity in a biosimilarity exercise.

Per treatment arm, 238 (Ranivisio) and 239 (US-Lucentis) patients were included, respectively.

In general, to characterise the ADR pattern over time, the cohort of exposed subjects should be large enough to observe also less frequently occurring events. To detect a common AE (appearing in ≥1% of patient) with sufficient precision, at least 300 subjects need to be treated. Further, as per ICH E1, 100 patients exposed to a study drug for a minimum of one year is considered acceptable, and 300-600 patients should be treated for 6 months with the drug at the intended dose level.

It is overall acknowledged that this is a biosimilarity exercise. Thus, the present sample size is sufficiently large to conclude on comparability in terms of common or very common adverse effects. However, it is too small to draw robust conclusions as regards comparability in terms of less frequently occurring adverse events. This seems especially important to note with regard to the evaluation of the more serious, less common adverse reactions such as endophthalmitis, blindness, retinal detachment, retinal tear, iatrogenic traumatic cataract or systemic AEs such as arterial thromboembolic events or non-ocular haemorrhages.

Overall, in view of Ranivisio and its clinical background (proposed indication and target population), the sample size of enrolled patients is considered sufficient to allow the evaluation of safety profile.

Patient exposure

Comparative safety data from the pivotal phase III study COLUMBUS-AMD involved 477 randomised patients (Ranivisio: n=238, US-Lucentis n=239), most of whom (n=452, 94.8%) completed the scheduled study period (44 weeks of treatment, last assessment at Week 48).

Overall, the numbers of patients per treatment arm treated for one year comply with the ICH E1 guideline (usually comparative date from at least 100 patients exposed for a minimum of one-year would be expected) and are acceptable.

For demographic and baseline characteristics, please refer to Results on Clinical Efficacy for further details and assessment. Overall, baseline characteristics were balanced between treatment arms, and the population

that was investigated was sufficiently sensitive for the evaluation of similarity from a safety (and efficacy) perspective.

The number of patients who completed the study were overall comparable between treatment arms. The most common reasons for premature discontinuation (before Week 48) were consent withdrawal and adverse events. There were overall 25 patients (Ranivisio: 12 patients; Lucentis: 13 patients) who discontinued the study. Reasons for study discontinuation were: withdrawal by patient (Ranivisio: 2 patients, Lucentis: 8 patients), lost to follow-up (Ranivisio: 3 patients, Lucentis: 1 patient), AE (Ranivisio: 1 patient, Lucentis: 2 patients), major protocol deviation (Ranivisio: 1 patient, Lucentis: no patients), need for alternative treatment (Ranivisio: 1 patient, Lucentis: no patients), and other reasons (Ranivisio: 4 patients, Lucentis: 2 patients).

4 patients in the Ranivisio arm and 2 patients in the US-Lucentis arm discontinued the study prematurely due to "other reasons" (see Table 10-1 in CSR). Three patients died (Ranivisio: 2;; Lucentis:2). One patient (Lucentis) moved. One patient (Ranivisio) was incorrectly enrolled into the study in error and subsequently discontinued the study. One patient (Ranivisio) was withdrawn by the investigator due to multiple adverse events and thus discontinued the study.

Up to week 24, there was an imbalance between treatment arms with regard to study treatment discontinuation (n=7 in the Ranivisio arm vs. n=3 in the Lucentis arm). The applicant provided the reasons for treatment discontinuation prior to Wk 24 and stated that there might be a higher probability of an uneven distribution without reason with such small numbers. This is acknowledged, against the background that, overall up to final analysis, the number of patients who discontinued treatment was similar in both treatment arms (n=16 in each arm).

The exposure to study drug was overall comparable. Most patients received all planned 12 injections up to the final analysis (338 patients; 81.3%; Ranivisio: 83.6% versus US-Lucentis: 79.1%), 47 patients (9.9%; Ranivisio: 9.2% versus US-Lucentis: 10.5%) received 11 injections, 15 patients (3.1%) received 10 injections, 5 patients (1.0%) received 9 injections and less than 1.0% of the patients received less than 8 injections, respectively. Hence, the vast majority of the patients received all scheduled injections or only missed 1 or 2 injections. Only few patients missed 3 or more injections. The number of missed injections was overall balanced between both treatment groups.

Table 45

Table 10-20 Study and treatment duration – SAF

	FYB201 (N = 238)	Lucentis (N = 239)	Total (N = 477)
Treatment duration [Days]			
n	238	239	477
Missing	0	0	0
Mean (SD)	298.614 (48.6490)	299.671 (37.7674)	299.144 (43.4955)
Median	307.974	307.983	307.979
Interquartile range (Q1–Q3)	307.072–308.979	307.875–308.951	307.833–308.958
Range (min–max)	0.00–356.00	0.00–331.96	0.00–356.00
Study duration [Days]			
n	238	239	477
Missing	0	0	0
Mean (SD)	344.983 (60.0110)	347.021 (43.6257)	346.004 (52.3998)
Median	347.000	347.000	347.000
Interquartile range (Q1–Q3)	344.000–352.000	344.000–356.000	344.000–354.000
Range (min–max)	30.00–709.00	46.00–587.00	30.00–709.00

Abbreviations: N = total number of patients, 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,
Notes: Treatment duration [days] is calculated as date/time of last injection – date/time of first injection. If time of first or last injection is missing, the treatment duration is calculated as date of last injection – date of first injection + 1. Study duration [days] is calculated as date of last contact – date of screening + 1.
Source: Post-text tables 14.3.1.1

Table 10-18 Total number injections per patient, interruptions and premature treatment discontinuations – SAF

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Patients receiving						
1 Injection	3	1.3%	1	0.4%	4	0.8%
2 Injections	1	0.4%	0	0.0%	1	0.2%
3 Injections	1	0.4%	1	0.4%	2	0.4%
4 Injections	2	0.8%	1	0.4%	3	0.6%
5 Injections	0	0.0%	1	0.4%	1	0.2%
6 Injections	0	0.0%	4	1.7%	5	1.0%
7 Injections	1	0.4%	2	0.8%	3	0.6%
8 Injections	0	0.0%	3	1.3%	3	0.6%
9 Injections	2	0.8%	3	1.3%	5	1.0%
10 Injections	6	2.5%	9	3.8%	15	3.1%
11 Injections	22	9.2%	25	10.5%	47	9.9%
12 Injections	199	83.6%	189	79.1%	388	81.3%
Patients with at least 1 treatment interruption	25	10.5%	38	15.9%	63	13.2%
Patients with premature treatment discontinuation	16	6.7%	16	6.7%	32	6.7%

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
Source: Post-text table 14.3.1.4

Table 46

Table 10-21 Exposure to study drug– SAF

	FYB201 (N = 238)	Lucentis (N = 239)	Total (N = 477)
Cumulative total amount [mg] of study medication up to Week 24			
n	238	239	477
Missing	0	0	0
Mean (SD)	2.91 (0.361)	2.94 (0.265)	2.92 (0.317)
Median	3.00	3.00	3.00
Interquartile range (Q1–Q3)	3.00–3.00	3.00–3.00	3.00–3.00
Range (min–max)	0.5–3.0	0.5–3.0	0.5–3.0
up to Week 48			
n	238	239	477
Missing	0	0	0
Mean (SD)	5.75 (0.882)	5.72 (0.774)	5.74 (0.829)
Median	6.00	6.00	6.00
Interquartile range (Q1–Q3)	6.00–6.00	6.00–6.00	6.00–6.00
Range (min–max)	0.5–6.0	0.5–6.0	0.5–6.0
Administered total amount relative to total planned amount of study medication [%] up to Week 24			
n	238	239	477
Missing	0	0	0
Mean (SD)	96.92 (12.049)	98.05 (8.825)	97.48 (10.561)
Median	100.00	100.00	100.00
Interquartile range (Q1–Q3)	100.00–100.00	100.00–100.00	100.00–100.00
Range (min–max)	16.7–100.0	16.7–100.0	16.7–100.0
up to Week 48			
n	238	239	477
Missing	0	0	0
Mean (SD)	95.83 (14.701)	95.36 (12.908)	95.60 (13.819)
Median	100.00	100.00	100.00
Interquartile range (Q1–Q3)	100.00–100.00	100.00–100.00	100.00–100.00
Range (min–max)	8.3–100.00	8.3–100.00	8.3–100.00

Abbreviations: N = total number of patients, 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,
Notes: The cumulative total amount is calculated as the sum of amounts of study medication [mg] administered at each injection up to and including the injection at eCRF Visit 6 by patient for analyses up to Week 24 and including all injections by patient for analyses up to Week 48.
The percentage of total administered study medication relative to the amount of total planned study medication is calculated by total amount of administered study medication [mg]/ total amount of planned study medication [mg]. The total amount of planned study medication up to and including all ophthalmologic assessments at Week 24 is 3 mg, and at Week 48 it is 6 mg.
Source: Post-text tables 14.3.1.7, 14.3.1.8, 14.3.1.9, 14.3.1.10

Administration of cumulative study treatment closely followed the schedule which was also reflected by the median ratio of the administered vs. planned cumulative amount of study medication which was 100.0% up to Week 24 and Week 48.

An injection at Week 48 (final visit) was not scheduled in the protocol, but for 6 patients (Ranivisio: n=5, US-Lucentis: n=1) the visit schedule was delayed so that the injection administered at Visit 12/Week 44 was assigned to the final analysis visit according to the respective study day. This is not considered to be of concern.

Adverse events

Introduction

All safety analyses were performed for the SAF (Safety Set). The SAF comprised all patients who had received at least one injection with study drug. The safety set was used as general analysis set for all kinds of safety and tolerability data. Patients were analysed according to the treatment they actually received irrespective of their randomised 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 analysed.

Treatment-emergent AEs (TEAEs) were defined as all AEs starting after the first injection of study medication and occurring during the course of the study. Only those AEs were reported by the applicant, both by overall number of events and by percentage of study participants experiencing a TEAE.

Adverse events overview

A total of 321 patients (67.3%) reported 1106 TEAEs at any time after the first dose of the study drug until the End of Study (EOS). The incidence and severity of the reported TEAEs were generally comparable between the Ranivisio and US-Lucentis treatment arms (Table 12-1 below).

- Number of patients with TEAEs: Ranivisio - 154 (64.7%) / US-Lucentis - 167 (69.9%)
- Total number of TEAEs reported: Ranivisio - 509 / US-Lucentis - 597
- Number of patients with serious TEAEs: Ranivisio – 19 (8.0%) / US-Lucentis – 32 (13.4%)
- Severity TEAEs: The majority of TEAEs were mild or moderate in intensity, severe TEAEs were reported in 11 patients (4.6%) treated with Ranivisio and in 22 patients (9.2%) treated with Lucentis. See below for detailed analysis of TEAE severity.
- Unrelated/related TEAEs: The majority of the TEAEs were not related to the study drugs – only 70 events out of a total of 1106 events were considered related (Ranivisio: 33 events, US-Lucentis: 37 events).
- Three patients died during the study; 2 patients in the Ranivisio group (PTs: Chronic obstructive pulmonary disease and Cardiopulmonary failure) and 1 patient (PT: Respiratory failure) in the Lucentis group.

Table 47

Table 12-1 Overview of treatment-emergent adverse events up to Week 48 – SAF

	FYB201 (N = 238)			Lucentis (N = 239)			Total (N = 477)		
	Ev	n	%	Ev	n	%	Ev	n	%
TEAEs	509	154	64.7%	597	167	69.9%	1106	321	67.3%
Local (study eye)	221	86	36.1%	214	97	40.6%	435	183	38.4%
Systemic	288	123	51.7%	383	147	61.5%	671	270	56.6%
Serious TEAEs (SAEs)	30	19	8.0%	45	32	13.4%	75	51	10.7%
Local (study eye)	2	2	0.8%	3	3	1.3%	5	5	1.0%
Systemic	28	17	7.1%	42	29	12.1%	70	46	9.6%
Severe TEAEs	19	11	4.6%	32	22	9.2%	51	33	6.9%
Local (study eye)	2	2	0.8%	4	4	1.7%	6	6	1.3%
Systemic	17	9	3.8%	28	18	7.5%	45	27	5.7%
Fatal TEAEs	2	2	0.8%	1	1	0.4%	3	3	0.6%
Non-fatal serious SAEs	28	18	7.6%	44	31	13.0%	72	49	10.3%
Related TEAEs to study drug									
TEAEs	33	20	8.4%	37	25	10.5%	70	45	9.4%
Serious TEAEs	3	3	1.3%	3	3	1.3%	6	6	1.3%
Severe TEAEs	1	1	0.4%	7	5	2.1%	8	6	1.3%
Related TEAEs to IVT injection procedure		51	21.4%		66	27.6%		117	24.5%
TEAEs leading to withdrawal of study drug	8	6	2.5%	8	6	2.5%	16	12	2.5%

Abbreviations: N = total number of patients, Ev = number of TEAEs of specified AE type, 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, TEAE = treatment-emergent adverse event, IVT = intravitreal,
Notes: Related TEAEs to study drug are all TEAEs which are "probably" or "possibly" related to study drug. Local TEAEs are defined as TEAEs occurring in the study eye, Systemic TEAEs are TEAEs not occurring in the study eye.
Source: Post-text tables 14.3.2.1, 14.3.2.18

TEAEs by SOC and PT

The overall number and percentage of TEAEs was comparable between the two treatment groups: 64.7% of the patients in the Ranivisio group experienced 509 TEAEs and 69.9% of the patients in the Lucentis group experienced 597 TEAEs, with numerically more TEAEs in the US-Lucentis arm.

The most commonly affected SOCs in both treatment groups in at least 2.0% of patients in the SAF were Eye disorders, Infections and infestations, Investigations, and Musculoskeletal and connective tissue disorders.

Overall, the SOC Eye disorders was the most commonly affected SOC for both treatment arms in the SAF; at least 1 TEAE within this SOC was observed for 100 patients (42.0%) in the Ranivisio arm and also for 100 patients (41.8%) in the US-Lucentis arm. The most commonly affected PTs in this SOC were Neovascular age-related macular degeneration (Ranivisio: n=19 [8.0%]; US-Lucentis: n=22 [9.2%]), Conjunctival haemorrhage (Ranivisio: n=14 [5.9%]; US-Lucentis: n=19 [7.9%]), and Punctate keratitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=12 [5.0%]).

Other commonly affected PTs were Nasopharyngitis from SOC Infections and Infestations (Ranivisio: n=12 [5.0%], US-Lucentis: n=16 [6.7%]) and IOP from SOC Investigations (Ranivisio: n=11 [4.6%]; US-Lucentis: n=12 [5.0%]).

Table 48

Table 12-2 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)		Total (N = 477)	
PT	n	%	n	%	n	%
Any	154	64.7%	167	69.9%	321	67.3%
Eye disorders						
Overall	100	42.0%	100	41.8%	200	41.9%
Neovascular age-related macular degeneration	19	8.0%	22	9.2%	41	8.6%
Conjunctival haemorrhage	14	5.9%	19	7.9%	33	6.9%
Punctate keratitis	8	3.4%	12	5.0%	20	4.2%
Visual acuity reduced	6	2.5%	11	4.6%	17	3.6%
Eye pain	9	3.8%	6	2.5%	15	3.1%
Cataract	1	0.4%	11	4.6%	12	2.5%
Lacrimation increased	9	3.8%	2	0.8%	11	2.3%
Choroidal neovascularisation	6	2.5%	4	1.7%	10	2.1%
Conjunctival hyperaemia	4	1.7%	6	2.5%	10	2.1%
Retinal haemorrhage	7	2.9%	3	1.3%	10	2.1%
Vitreous detachment	6	2.5%	4	1.7%	10	2.1%
Infections and infestations						
Overall	55	23.1%	57	23.8%	112	23.5%
Nasopharyngitis	12	5.0%	16	6.7%	28	5.9%
Bronchitis	9	3.8%	5	2.1%	14	2.9%
Upper respiratory tract infection	8	3.4%	6	2.5%	14	2.9%
Conjunctivitis	9	3.8%	2	0.8%	11	2.3%
Investigations						
Overall	32	13.4%	39	16.3%	71	14.9%
Intraocular pressure increased	11	4.6%	12	5.0%	23	4.8%
C-reactive protein increased	10	4.2%	5	2.1%	15	3.1%
Musculoskeletal and connective tissue disorders						
Overall	17	7.1%	29	12.1%	46	9.6%
Back pain	5	2.1%	8	3.3%	13	2.7%
Nervous system disorders						
Overall	10	4.2%	26	10.9%	36	7.5%
Headache	4	1.7%	9	3.8%	13	2.7%
Gastrointestinal disorders						
Overall	13	5.5%	22	9.2%	35	7.3%
Vascular disorders						
Overall	10	4.2%	23	9.6%	33	6.9%
Hypertension	3	1.3%	14	5.9%	17	3.6%
Injury, poisoning and procedural complications	13	5.5%	18	7.5%	31	6.5%

[*Table 50* from CSR]

TEAEs by severity

Most TEAEs were of mild or moderate intensity: few TEAEs were severe (19 TEAEs in 11 patients in the Ranivisio arm and 32 TEAEs in 22 patients in the US-Lucentis arm). Severe TEAEs were recorded in twice as many patients in the Lucentis arm, but without clinically relevant differences or increased frequency in particular SOCs.

Table 49

Table 12-3 Frequency of patients with TEAEs up to Week 48 by MedDRA SOC, PT and maximum severity in ≥0.4% patients – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Severity						
Any TEAE	154	64.7%	167	69.9%	321	67.3%
Mild	77	32.4%	81	33.9%	158	33.1%
Moderate	66	27.7%	64	26.8%	130	27.3%
Severe	11	4.6%	22	9.2%	33	6.9%
Severe TEAEs by MedDRA SOC and PT in ≥0.4% patients						
Any	11	4.6%	22	9.2%	33	6.9%
Cardiac disorders						
Overall	4	1.7%	5	2.1%	9	1.9%
Atrial fibrillation	2	0.8%	1	0.4%	3	0.6%
Myocardial infarction	1	0.4%	2	0.8%	3	0.6%
Myocardial ischaemia	1	0.4%	1	0.4%	2	0.4%
Eye disorders						
Overall	2	0.8%	3	1.3%	5	1.0%
Neovascular age-related macular degeneration	1	0.4%	2	0.8%	3	0.6%
Infections and infestations						
Overall	2	0.8%	3	1.3%	5	1.0%
Endophthalmitis	1	0.4%	2	0.8%	3	0.6%
Respiratory, thoracic and mediastinal disorders						
Overall	3	1.3%	2	0.8%	5	1.0%
Respiratory failure	1	0.4%	1	0.4%	2	0.4%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.4%	2	0.8%	3	0.6%
Nervous system disorders	0	0.0%	3	1.3%	3	0.6%
Gastrointestinal disorders	0	0.0%	2	0.8%	2	0.4%
Metabolism and nutrition disorders	0	0.0%	2	0.8%	2	0.4%
Renal and urinary disorders						
Overall	2	0.8%	0	0.0%	2	0.4%
Acute kidney injury	2	0.8%	0	0.0%	2	0.4%
Vascular 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: Adverse events for one patient were counted with the worst severity per PT. MedDRA version 19.0 was used. Source: Post-text table 14.3.2.21, 14.3.2.7

[*Table 51* from CSR]

Ocular/ non-ocular (systemic) TEAEs

The applicant classified all AEs occurring in the study eye or in both eyes as "local AEs". Those local TEAEs observed were presented together ("as one") instead of separately. This is not considered adequate. It should clearly be separated between ocular and non-ocular (i.e. systemic) adverse events instead, in accordance with the Lucentis safety profile depicted in the product information. It is known from Lucentis marketing experience that the majority of AEs reported following administration of Lucentis are ocular events related to the intravitreal injection procedure. This would also be expected for Ranivisio. Thus, it is of importance for demonstration of similar safety to get a clear picture about the local (ocular) safety profile of Ranivisio with regard to the study eye to which Q4W IVT injections have been administered. As a consequence, local (i.e. ocular) TEAEs should be presented separately for the study eye as well as for the fellow eye for both treatment arms.

In addition, systemic TEAEs have been defined by the applicant as all TEAEs not meeting the definition of "local AEs" (i.e. all AEs not occurring the study eye). Here, the applicant was requested to present instead a revised tabulated summary of non-ocular (systemic) TEAEs.

To sum up, the applicant was requested to provide revised tabulated summaries regarding ocular TEAEs, separately for study eye and fellow eye, as well as regarding systemic, non-ocular TEAEs by treatment arm.

Furthermore, a tabulated comparison between arms listing all ocular (separately for study eye and fellow eye) and systemic, non-ocular TEAEs that were considered related by SOC and PT were requested to be provided.

In addition, a tabulated comparison including only the severe TEAEs (ocular [study eye; fellow eye]; non-ocular/ systemic) by SOC and PT were requested to be provided.

The applicant has provided the requested revised adverse event analyses clearly differentiating between ocular AEs (in study eye as well as in fellow eye) and systemic AEs.

Based on these analyses, no distinct differences between treatment arms can be detected with regard to incidences of ocular TEAEs, related ocular TEAEs, severe ocular TEAEs, related severe TEAEs, serious ocular TEAEs and related serious ocular TEAEs, neither in the study eye nor in the fellow eye.

With regard to systemic TEAEs, there were 104 (43.7%) patients in the Ranivisio treatment arm who reported 238 systemic TEAEs compared to 130 (54.4%) patients in the Lucentis treatment arm who reported 326 systemic TEAEs. This numerical imbalance was also observed for severe systemic TEAEs (16 events in n=8 Ranivisio patients vs. 26 events in n=16 Lucentis patients) as well as for serious systemic TEAEs (28 events in n=17 patients vs. 41 events in n=28 patients). However, when considering causality assessment, the imbalance between the study arms was less pronounced for all types of systemic TEAEs.

Table 27 Overview of treatment-emergent adverse events up to Week 48 – SAF

	FYB201			Lucentis			Total		
	(N = 238)			(N = 239)			(N = 477)		
	Pat.n	Pat.%	Ev.n	Pat.n	Pat.%	Ev.n	Pat.n	Pat.%	Ev.n
All TEAEs	154	64.7%	509	167	69.9%	597	321	67.3%	1106
Systemic TEAEs	104	43.7%	238	130	54.4%	326	234	49.1%	564
Ocular TEAEs in the SE	86	36.1%	221	97	40.6%	214	183	38.4%	435
Ocular TEAEs in the FE	50	21.0%	73	57	23.8%	88	107	22.4%	161
Ocular TEAEs in both eyes	17	7.1%	23	23	9.6%	31	40	8.4%	54
TEAEs to related study medication	20	8.4%	33	25	10.5%	37	45	9.4%	70
Systemic TEAES	3	1.3%	6	7	2.9%	9	10	2.1%	15
Ocular TEAEs in the SE	17	7.1%	27	20	8.4%	26	37	7.8%	53
Ocular TEAEs in the FE	4	1.7%	5	2	0.8%	3	6	1.3%	8
Ocular TEAEs in both eyes	4	1.7%	5	1	0.4%	1	5	1.0%	6
Severe TEAEs	11	4.6%	19	22	9.2%	32	33	6.9%	51
Systemic TEAEs	8	3.4%	16	16	6.7%	26	24	5.0%	42
Ocular TEAEs in the SE	2	0.8%	2	4	1.7%	4	6	1.3%	6
Ocular TEAEs in the FE	1	0.4%	1	2	0.8%	2	3	0.6%	3
Severe related TEAEs	1	0.4%	1	5	2.1%	7	6	1.3%	8
Systemic TEAEs	1	0.4%	1	2	0.8%	4	3	0.6%	5
Ocular TEAEs in the SE	0		0	3	1.3%	3	3	0.6%	3
Ocular TEAEs in the FE	0		0	0		0	0		0
Severe not related TEAEs	11	4.6%	18	17	7.1%	25	28	5.9%	43
Systemic TEAEs	8	3.4%	15	14	5.9%	22	22	4.6%	37
Ocular TEAEs in the SE	2	0.8%	2	1	0.4%	1	3	0.6%	3
Ocular TEAEs in the FE	1	0.4%	1	2	0.8%	2	3	0.6%	3
Serious TEAEs	19	8.0%	30	32	13.4%	45	51	10.7%	75
Systemic TEAEs	17	7.1%	28	28	11.7%	41	45	9.4%	69
Ocular TEAEs in the SE	2	0.8%	2	3	1.3%	3	5	1.0%	5
Ocular TEAEs in the FE	0		0	1	0.4%	1	1	0.2%	1
Serious related TEAEs	3	1.3%	3	3	1.3%	3	6	1.3%	6
Systemic TEAEs	2	0.8%	2	2	0.8%	2	4	0.8%	4
Ocular TEAEs in the SE	1	0.4%	1	1	0.4%	1	2	0.4%	2
Ocular TEAEs in the FE	0		0	0		0	0		0

Source: Attachment to question 110 and CSR in-text table 12-1;

SAF = Safety analysis set, TEAE = Treatment-emergent adverse event, SE = study eye, FE = fellow eye, N = total number of patients, Pat.n = number of patients with at least one AE of specified AE type, Pat.% = number of patients with at least one AE of specified AE type/total number of patients*100, Ev.n = number of TEAEs of specified AE type, Related TEAEs to study medication are all TEAEs which are "probably" or "possibly" related to study medication.

Local TEAEs (as presented by the applicant)

Local TEAEs were defined as TEAEs that occurred in the study eye or in both eyes.

Frequency and type of "local" (study eye or both eyes) TEAEs were overall comparable between both treatment groups, and no clinically relevant differences were identified. However, a revised tabulated comparison between treatment arms regarding ocular TEAE, presented separately for study eye and fellow eye, was requested and provided. See above.

As presented by the applicant, frequent PTs in SOC Eye disorders were Conjunctival haemorrhage (Ranivisio: n=13 [5.5%]; US-Lucentis: n=18 [7.5%]), Punctate keratitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=12 [5.0%]), Visual acuity reduced (Ranivisio: n=5 [2.1%]; US-Lucentis: n=10 [4.2%]). Frequent local TEAEs were also recorded in SOC Investigations (Ranivisio: n=17 [7.1%]; US-Lucentis: n=15 [6.3%]) with most frequent PT Intraocular pressure increased (in 10 patients in each treatment arm [4.2%]) and in SOC

Infections and infestations (Ranivisio: n=10 [4.2%]; US-Lucentis: n=7 [2.9%]) with most frequent PT Conjunctivitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=2 [0.8%]).

Ocular adverse events that were expected to occur (very) commonly (according to the Lucentis SmPC) were overall comparable between treatment arms in the present study, although it is notable that some AEs occurred at lower than expected rates (such as IOP increased, Conjunctival haemorrhage).

Table 50

Table 12-4 Frequency of local TEAEs up to Week 48 in ≥0.8% of patients by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any	86	36.1%	97	40.6%	183	38.4%
Eye disorders						
Overall	76	31.9%	82	34.3%	158	33.1%
Conjunctival haemorrhage	13	5.5%	18	7.5%	31	6.5%
Punctate keratitis	8	3.4%	12	5.0%	20	4.2%
Visual acuity reduced	5	2.1%	10	4.2%	15	3.1%
Eye pain	9	3.8%	5	2.1%	14	2.9%
Lacrimation increased	9	3.8%	2	0.8%	11	2.3%
Cataract	1	0.4%	9	3.8%	10	2.1%
Conjunctival hyperaemia	4	1.7%	5	2.1%	9	1.9%
Vitreous detachment	5	2.1%	4	1.7%	9	1.9%
Corneal erosion	4	1.7%	4	1.7%	8	1.7%
Retinal pigment epithelial tear	2	0.8%	6	2.5%	8	1.7%
Vitreous floaters	3	1.3%	5	2.1%	8	1.7%
Retinal haemorrhage	4	1.7%	3	1.3%	7	1.5%
Eye irritation	3	1.3%	3	1.3%	6	1.3%
Eyelid oedema	2	0.8%	4	1.7%	6	1.3%
Metamorphopsia	3	1.3%	2	0.8%	5	1.0%
Vision blurred	4	1.7%	1	0.4%	5	1.0%
Blepharitis	1	0.4%	3	1.3%	4	0.8%
Ocular hypertension	1	0.4%	3	1.3%	4	0.8%
Visual impairment	1	0.4%	3	1.3%	4	0.8%
Investigations						
Overall	17	7.1%	15	6.3%	32	6.7%
Intraocular pressure increased	10	4.2%	10	4.2%	20	4.2%
Visual acuity tests abnormal	4	1.7%	5	2.1%	9	1.9%
Infections and infestations						
Overall	10	4.2%	7	2.9%	17	3.6%
Conjunctivitis	8	3.4%	2	0.8%	10	2.1%
General disorders and administration site conditions						
Overall	9	3.8%	3	1.3%	12	2.5%
Pain	5	2.1%	1	0.4%	6	1.3%
Injury, poisoning and procedural complications	6	2.5%	2	0.8%	8	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: Local TEAEs were defined as TEAEs occurring in the study eye or in both eyes. MedDRA version 19.0 was used.

Source: Post-text table 14.3.2.10

Systemic TEAEs (as presented by the applicant)

Systemic TEAEs were defined as all remaining TEAEs which did not occur in the study eye.

The frequency of reported systemic TEAEs was higher in the US-Lucentis arm (147 patients; 61.5%) than in the Ranivisio arm (123 patients; 51.7%). However, a revised tabulated comparison between treatment arms including only systemic, non-ocular TEAE was requested and provided by the applicant.

As presented by the applicant, at SOC level, the most frequent systemic TEAEs were Infections and infestations with comparable incidences in both treatment arms (20.6 [Ranivisio] vs. 22.6% [US-Lucentis] of patients). For the SOCs Eye disorders (14.3% vs. 16.7%), Investigations (8.0% vs. 11.7%) and Musculoskeletal and connective tissue disorders (6.7% vs. 12.1%), numerical differences in favour of Ranivisio were seen.

Frequent PTs were Neovascular age-related macular degeneration in the fellow eye (Ranivisio: 18 patients, 7.6%; US-Lucentis: 21 patients, 8.8%), Nasopharyngitis (Ranivisio: 12 patients, 5.0%; US-Lucentis: 16 patients, 6.7%) and C-reactive protein increased (Ranivisio: 10 patients, 4.2%; Lucentis: 5 patients, 2.1%).

Per Lucentis SmPC, the non-ocular adverse events that are expected to occur most frequently are headache, nasopharyngitis and arthralgia. Indeed, nasopharyngitis was a frequently reported TEAE and occurred with comparable incidence for both arms. Conversely, headache was reported at lower than expected rates in the present study (Ranivisio: n=4 [1.7%]; US-Lucentis: n=9 [3.8%]). Arthralgia, however, was reported as TEAE only in 5 patients (2.1%) from the US-Lucentis arm.

Table 51

Table 12-5 Frequent systemic TEAEs up to Week 48 in ≥2.0% of patients by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any	123	51.7%	147	61.5%	270	56.6%
Infections and infestations						
Overall	49	20.6%	54	22.6%	103	21.6%
Nasopharyngitis	12	5.0%	16	6.7%	28	5.9%
Bronchitis	9	3.8%	5	2.1%	14	2.9%
Upper respiratory tract infection	8	3.4%	6	2.5%	14	2.9%
Eye disorders						
Overall	34	14.3%	40	16.7%	74	15.5%
Neovascular age-related macular degeneration	18	7.6%	21	8.8%	39	8.2%
Choroidal neovascularisation	6	2.5%	4	1.7%	10	2.1%
Investigations						
Overall	19	8.0%	28	11.7%	47	9.9%
C-reactive protein increased	10	4.2%	5	2.1%	15	3.1%
Musculoskeletal and connective tissue disorders						
Overall	16	6.7%	29	12.1%	45	9.4%
Back pain	5	2.1%	8	3.3%	13	2.7%
Gastrointestinal disorders	13	5.5%	22	9.2%	35	7.3%
Nervous system disorders						
Overall	10	4.2%	23	9.6%	33	6.9%
Headache	4	1.7%	9	3.8%	13	2.7%
Vascular disorders						
Overall	10	4.2%	21	8.8%	31	6.5%
Hypertension	3	1.3%	14	5.9%	17	3.6%
Respiratory, thoracic and mediastinal disorders						
Overall	15	6.3%	9	3.8%	24	5.0%
Cough	5	2.1%	5	2.1%	10	2.1%
Injury, poisoning and procedural complications	7	2.9%	16	6.7%	23	4.8%
General disorders and administration site conditions	9	3.8%	10	4.2%	19	4.0%
Cardiac disorders	8	3.4%	10	4.2%	18	3.8%
Blood and lymphatic system disorders	8	3.4%	4	1.7%	12	2.5%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	2.1%	7	2.9%	12	2.5%
Renal and urinary disorders	5	2.1%	6	2.5%	11	2.3%

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 all remaining TEAEs not occurring in the study eye. MedDRA version 19.0 was used. Source: Post-text table 14.3.2.12

TEAE related to study drug

A TEAE was considered to be related to the study drug if the Investigator had judged the relationship as 'probable' or 'possible'.

Study drug-related TEAEs occurred in 20 patients in the Ranivisio arm (8.4%; with 33 events) and in 25 patients in the Lucentis arm (10.5%; with 37 events). Frequent PTs for study drug related TEAEs were recorded in SOC Eye disorders with PT Cataract (Ranivisio: no patient; US-Lucentis: 5 patients, 2.1%), Retinal pigment epithelial tear (Ranivisio: 1 patient, 0.4%; Lucentis: 3 patients, 1.3%), Visual acuity reduced (Ranivisio: no patient; Lucentis: 3 patients, 1.3%), Punctate keratitis (Ranivisio: no patient; Lucentis: 2

patients, 0.8%), Pain (Ranivisio: 2 patients, 0.8%; Lucentis: no patient) and Intraocular pressure increased (Ranivisio: 3 patients, 1.3%; Lucentis: 2 patients, 0.8%).

Table 52

Table 12-6 Frequency of TEAEs related to study drug 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	%
Any	20	8.4%	25	10.5%	45	9.4%
Eye disorders						
Overall	11	4.6%	17	7.1%	28	5.9%
Cataract	0	0.0%	5	2.1%	5	1.0%
Retinal pigment epithelial tear	1	0.4%	3	1.3%	4	0.8%
Visual acuity reduced	0	0.0%	3	1.3%	3	0.6%
Punctate keratitis	0	0.0%	2	0.8%	2	0.4%
Vitreous haemorrhage	1	0.4%	1	0.4%	2	0.4%
Cataract nuclear	0	0.0%	1	0.4%	1	0.2%
Chromatopsia	0	0.0%	1	0.4%	1	0.2%
Colour blindness	1	0.4%	0	0.0%	1	0.2%
Corneal erosion	0	0.0%	1	0.4%	1	0.2%
Eye disorder	1	0.4%	0	0.0%	1	0.2%
Eye pain	1	0.4%	0	0.0%	1	0.2%
Iridocyclitis	1	0.4%	0	0.0%	1	0.2%
Macular pigmentation	1	0.4%	0	0.0%	1	0.2%
Macular scar	0	0.0%	1	0.4%	1	0.2%
Neovascular age-related macular degeneration	1	0.4%	0	0.0%	1	0.2%
Photopsia	1	0.4%	0	0.0%	1	0.2%
Retinal degeneration	1	0.4%	0	0.0%	1	0.2%
Retinal pigment epitheliopathy	1	0.4%	0	0.0%	1	0.2%
Vision blurred	1	0.4%	0	0.0%	1	0.2%

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Vitreous detachment	1	0.4%	0	0.0%	1	0.2%
Vitreous floaters	0	0.0%	1	0.4%	1	0.2%
Investigations						
Overall	4	1.7%	4	1.7%	8	1.7%
Intraocular pressure increased	3	1.3%	2	0.8%	5	1.0%
Gamma-glutamyltransferase increased	1	0.4%	1	0.4%	2	0.4%
Blood creatinine increased	1	0.4%	0	0.0%	1	0.2%
Blood urea increased	1	0.4%	0	0.0%	1	0.2%
Blood uric acid increased	1	0.4%	0	0.0%	1	0.2%
Visual acuity tests abnormal	0	0.0%	1	0.4%	1	0.2%
Nervous system disorders						
Overall	1	0.4%	4	1.7%	5	1.0%
Cerebrovascular accident	0	0.0%	1	0.4%	1	0.2%
Head discomfort	0	0.0%	1	0.4%	1	0.2%
Neuralgia	0	0.0%	1	0.4%	1	0.2%
Syncope	0	0.0%	1	0.4%	1	0.2%
Transient ischaemic attack	1	0.4%	0	0.0%	1	0.2%
General disorders and administration site conditions						
Overall	3	1.3%	0	0.0%	3	0.6%
Pain	2	0.8%	0	0.0%	2	0.4%
Injection site pain	1	0.4%	0	0.0%	1	0.2%
Infections and infestations						
Overall	1	0.4%	1	0.4%	2	0.4%
Conjunctivitis	1	0.4%	0	0.0%	1	0.2%
Endophthalmitis	0	0.0%	1	0.4%	1	0.2%
Vascular disorders						
Overall	0	0.0%	2	0.8%	2	0.4%
Circulatory collapse	0	0.0%	1	0.4%	1	0.2%
Hypertension	0	0.0%	1	0.4%	1	0.2%
Cardiac disorders						
Overall	1	0.4%	0	0.0%	1	0.2%
Myocardial infarction	1	0.4%	0	0.0%	1	0.2%
Gastrointestinal disorders						
Overall	0	0.0%	1	0.4%	1	0.2%
Vomiting	0	0.0%	1	0.4%	1	0.2%
Skin and subcutaneous tissue disorders						
Overall	0	0.0%	1	0.4%	1	0.2%
Blister	0	0.0%	1	0.4%	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: Related TEAEs were defined as all TEAEs which are 'probably' or 'possibly' related to study drug. MedDRA version 19.0 was used. Source: Post-text table 14.3.2.17

TEAEs related to IVT injection procedure

A TEAE was considered to be related to the IVT injection procedure if the investigator had judged the relationship to the IVT injection procedure as 'probable' or 'possible'.

IVT procedure related TEAEs occurred in 21.4% of patients in the Ranivisio group (n=51) and in 27.6% of the patients in the Lucentis group (n=66). Frequent PTs for IVT procedure related TEAEs were reported in SOC Eye disorders for PTs Conjunctival haemorrhage (Ranivisio: n=13 [5.5%]; US-Lucentis: n=19 [7.9%]) and Punctate keratitis (Ranivisio: n=6 [2.5%]; US-Lucentis: n=11 [4.6%]) and in SOC Investigations for PT Intraocular pressure increased (Ranivisio: n=8 [3.4%], US-Lucentis: n=9 [3.8%]).

Overall, TEAEs related to study drug as well as to the IVT injection procedure were observed at numerically higher frequencies in the US-Lucentis group than for Ranivisio. The same holds true for severe TEAE, which were recorded in twice as many patients in the Lucentis arm.

Table 12-7 Frequency of TEAEs related to the IVT injection procedure up to Week 48 in ≥0.6% of patients by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	N	%	n	%	n	%
Any	51	21.4%	66	27.6%	117	24.5%
Eye disorders						
Overall	42	17.6%	55	23.0%	97	20.3%
Conjunctival haemorrhage	13	5.5%	19	7.9%	32	6.7%
Punctate keratitis	6	2.5%	11	4.6%	17	3.6%
Eye pain	8	3.4%	5	2.1%	13	2.7%
Corneal erosion	4	1.7%	4	1.7%	8	1.7%
Lacrimation increased	6	2.5%	2	0.8%	8	1.7%
Vitreous floaters	3	1.3%	4	1.7%	7	1.5%
Conjunctival hyperaemia	3	1.3%	3	1.3%	6	1.3%
Vitreous detachment	3	1.3%	3	1.3%	6	1.3%
Cataract	0	0.0%	5	2.1%	5	1.0%
Eyelid oedema	2	0.8%	3	1.3%	5	1.0%
Eye irritation	2	0.8%	2	0.8%	4	0.8%
Visual impairment	1	0.4%	3	1.3%	4	0.8%
Eye disorder	2	0.8%	1	0.4%	3	0.6%
Foreign body sensation in eyes	2	0.8%	1	0.4%	3	0.6%
Ocular hyperaemia	2	0.8%	1	0.4%	3	0.6%
Retinal tear	0	0.0%	3	1.3%	3	0.6%
Vision blurred	2	0.8%	1	0.4%	3	0.6%
Investigations						
Overall	9	3.8%	9	3.8%	18	3.8%
Intraocular pressure increased	8	3.4%	9	3.8%	17	3.6%
General disorders and administration site conditions						
Overall	7	2.9%	1	0.4%	8	1.7%
Pain	5	2.1%	0	0.0%	5	1.0%
Injection site pain	2	0.8%	1	0.4%	3	0.6%
Infections and infestations						
Overall	4	1.7%	3	1.3%	7	1.5%
Endophthalmitis	1	0.4%	2	0.8%	3	0.6%
Nervous system disorders						
Overall	1	0.4%	6	2.5%	7	1.5%
Headache	1	0.4%	3	1.3%	4	0.8%
Injury, poisoning and procedural complications	3	1.3%	2	0.8%	5	1.0%

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, IVT = intravitreal

Notes: TEAEs related to IVT injection procedure were TEAEs which were 'probably' or 'possibly' related to IVT injection procedure. MedDRA version 19.0 was used.
Source: Post-text table 14.3.2.18

In summary, all differences in TEAEs between treatment arms concern only low numbers of patients and events; nevertheless, a trend towards a better tolerability of Ranivisio compared to the reference product seems notable.

For AEs according to ADA status, please refer to Overview Section 3.3.1.2 "Pharmacodynamics".

Serious adverse events, deaths, and other significant events

Introduction

Analyses will be presented by SOC and PT.

- Overall SAEs
- Local SAEs (occurring in the study eye or in both eyes)
- Systemic SAEs (all remaining SAEs, not occurring in the study eye)
- Deaths

In Section 9.7.7 of the CSR, it is stated that SAEs were classified as "local AEs" that had occurred in the study eye or in both eyes and as "systemic AEs" representing all remaining AEs that had not occurred in the study eye.

In contrast, in Section 12.2.2.1, it is stated that local SAEs were SAEs "occurring in the study eye" only.

Serious adverse events

The frequency and the type of serious adverse events (SAEs) which were reported up to Week 48 was numerically in favour of the Ranivisio arm; 30 SAEs were reported for 19 patients (8.0%) in the Ranivisio arm, whereas 45 events were reported for 32 patients (13.4%) in the US-Lucentis arm.

According to the applicant (CSR Section 9.7.7), SAEs were classified in "local AEs" that had occurred in the study eye or in both eyes and "systemic AEs" representing all remaining AEs that had not occurred in the study eye. However, in Section 12.2.2.1 it is stated that local SAEs were SAEs "occurring in the study eye" only. The applicant provided an explanation regarding the definition of the term "local TEAEs" which was followed in the CSR. Under this term, all the TEAEs which occurred in the study eye were involved.

In accordance with the requested revised tabulated comparisons for ocular and systemic (i.e. non-ocular) TEAEs by treatment arm, the applicant was requested to provide tabulated summaries by SOC/ PT regarding ocular SAEs, both for the study eye and for the fellow eye, as well as regarding systemic, non-ocular SAEs per treatment arm. In this tabulated summary, the number of events that were observed should also be presented. According to the submitted overviews, the SAEs (as per individual subcategories) observed in the treatment arms (Ranivisio vs. Lucentis) were overall balanced.

Ocular/ non-ocular (systemic) SAEs

Local SAEs (as presented by the applicant)

Only few ocular SAEs in the study eye were reported: 2 patients in the Ranivisio experienced Endophthalmitis and Iridocyclitis, and 3 patients in the US-Lucentis arm experienced Cataract (1 patient) and Endophthalmitis (2 patients). 1 Endophthalmitis case was judged as related to study drug and to IVT procedure, the other 2 cases were judged as related to the IVT procedure only. The case of Cataract was assessed related to the IVT procedure, too; and the Iridocyclitis case was judged realted to both study drug and IVT procedure. Only for 1 patient in the Lucentis arm, the Endophthalmitis led to interruption of study drug. All patients recovered from the local SAEs.

Table 12-8 Number and percentage of patients with serious local TEAEs 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	%
Any	2	0.8%	3	1.3%	5	1.0%
Infections and infestations						
Overall	1	0.4%	2	0.8%	3	0.6%
Endophthalmitis	1	0.4%	2	0.8%	3	0.6%
Eye disorders						
Overall	1	0.4%	1	0.4%	2	0.4%
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.
Source: Post-text table 14.3.2.13

Systemic SAEs (as presented by the applicant)

The frequency of systemic SAEs was somewhat higher in the Lucentis group with 29 patients (12.1%) compared to 17 patients (7.1%) in the Ranivisio group.

Most frequently systemic serious TEAEs were recorded in SOC Cardiac disorders (Ranivisio: n=7 [2.9%]; US-Lucentis: n=5 [2.1%]) followed by SOC Nervous system disorders (Ranivisio: n=2 [0.8%]; US-Lucentis: n=5 [2.1%]) and SOC Respiratory, thoracic and mediastinal disorders (3 patients in each arm [1.3%]). Systemic serious TEAEs were also frequently observed in SOC Musculoskeletal and connective tissue disorders (Ranivisio: n=1 [0.4%]; US-Lucentis: n=4 [1.7%]) and SOC Renal and urinary disorders (2 patients in each arm [0.8%]).

With the initial submission, no information has been provided with regard to causality assessment for systemic SAEs. A tabulated comparison between treatment arms listing all systemic SAEs by causality (related/ not related), by SOC and PT, was provided with the responses to the D120 LoQ. Overall, 6 of the serious TEAEs reported in 6 patients were judged as related to study medication. Among these were 4 systemic related SAEs, two in the Ranivisio group (Myocardial infarction and Transient ischaemic shock) and two in the Lucentis group (Cerebrovascular accident and Circulatory collapse).

Table 12-9 Frequency of serious systemic TEAEs up to Week 48 in ≥0.4% of patients by MedDRA SOC and PT – SAF

MedDRA SOC	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
PT	n	%	n	%	n	%
Any	17	7.1%	29	12.1%	46	9.6%
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.
Source: Post-text table 14.3.2.15

Deaths

Three patients died during the course of the study; two patients were exposed to Ranivisio and one patient was exposed to US-Lucentis.

The Investigators judged these fatal SAEs as unlikely related to study drug or to the IVT procedure.

One patient treated with Lucentis for 28 weeks experienced "Respiratory failure". This severe SAE resulted in the death of the patient. The Investigator judged the SAE as unlikely related to the study drug or to the IVT injection procedure, any actions taken with study drug were not applicable.

One patient treated with Ranivisio for 4 weeks reported a "Worsening bronchiectasis" and experienced a "Worsening of a severe obstructive pulmonary disease". This severe SAE resulted in the death of the patient. The SAE was considered to be unlikely related to the study drug or to the IVT injection procedure by the Investigator and any actions taken with study drug were not applicable.

One patient treated with Ranivisio for 28 weeks experienced "Cardiopulmonary failure". This severe SAE resulted in the death of the patient. The Investigator judged the SAE as unlikely related to the study drug or to the IVT injection procedure and any actions taken with study drug were not applicable.

Laboratory findings

Clinical chemistry

Clinical chemistry assessment was done at V0/ Screening, V7/Week 24, and at Final Visit/Week 48. In addition, the absolute change from screening at V7/Week 24 and at Final Visit/Week 48 was evaluated.

Overall, the vast majority of clinical chemistry values up to Week 48 were within normal ranges or not clinically significant above or below normal ranges. The number of patients who developed clinically significant abnormalities in clinical chemistry parameters throughout the study up to Week 48 was low, and no clinically relevant differences between the two treatment groups were identified. Clinical chemistry was considered normal, since most clinically significantly elevated values were related to kidney and liver function, glucose homeostasis and immune function reflecting the geriatric patient population.

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. Most values were within the normal range for each parameter.

Potassium changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 4 patients (Ranivisio: 1 patient; Lucentis: 3 patients).

Creatinine changed from normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 2 patients, from above normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 1 patient, and 1 patient had clinically significant increased creatinine values throughout up to Week 24. Creatinine changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 5 patients, from above normal to clinically significant above normal in 3 patients, and 1 patient had clinically significant increased creatinine values throughout up to Week 48. Five patients in the Ranivisio group and 4 patients in the Lucentis group had clinically significant above normal creatinine values at the Final Visit/Week 48.

Gamma-glutamyl transferase changed from above normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 3 patients. Gamma-glutamyl transferase changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 1 patient, and from above normal at screening to clinically significant above normal in 2 patients. One patient in the Ranivisio group and 2 patients in the Lucentis group had clinically significant above normal gamma-glutamyl transferase values at the Final Visit/Week 48.

Uric acid changed from normal at screening to clinically significant above normal in 1 patient and from above normal to clinically significant above normal in 2 patients at analysis visit V7/Week 24. Uric acid changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 1 patient, and from above normal at screening to clinically significant above normal in 3 patients. One patient in the

Ranivisio group and 3 patients in the Lucentis group had clinically significant above normal uric acid values at the Final Visit/Week 48.

Urea (blood urea nitrogen) changed from normal to clinically significant above normal in 3 patients at analysis visit V7/Week 24, from above normal to clinically significant above normal in 5 patients, and 1 patient had clinically significant increased urea (blood urea nitrogen) values throughout the study up to Week 24. Urea (blood urea nitrogen) changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 3 patients, and from above normal at screening to clinically significant above normal in 6 patients, and 1 patient had clinically significant increased urea (blood urea nitrogen) values throughout the study up to Week 48. Six patients in the Ranivisio group and 4 patients in the Lucentis group had clinically significant above normal urea (blood urea nitrogen) values at the Final Visit/Week 48.

Alanine aminotransferase changed from above normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 1 patient and 1 patient had clinically significant above normal values at screening and a value within normal ranges at analysis visit V7/Week 24 and at the Final Visit/Week 48. No patient had clinically significant alanine aminotransferase values at the Final Visit/Week 48.

Aspartate aminotransferase changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 2 patients in the Lucentis group.

Alkaline phosphatase changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 1 patient in the Ranivisio group, and from above normal at screening to clinically significant above normal in 1 patient in the Lucentis group.

Lactate dehydrogenase changed from normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 1 patient. Lactate dehydrogenase changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 2 patients, and from above normal at screening to clinically significant above normal in another 2 patients. One patient in the Ranivisio group and 3 patients in the Lucentis group had clinically significant above normal lactate dehydrogenase values at the Final Visit/Week 48.

C-reactive protein changed from normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 4 patients, from above normal to clinically significant above normal in 7 patients, and 3 patients had clinically significant above normal values throughout the study up to Week 24. C-reactive protein changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 5 patients, from above normal to clinically significant above normal in 6 patients, and 1 patients had clinically significant above normal values throughout the study up to Week 48. Nine patients in the Ranivisio group and 3 patients in the Lucentis group had clinically significant above normal C-reactive protein values at the Final Visit/Week 48.

Glycosylated haemoglobin changed from above normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 3 patients, 1 patient had clinically significant above normal values throughout the study up to Week 24. Glycosylated haemoglobin changed from normal at screening to clinically significant above normal at the Final Visit/Week 48 in 1 patient, from above normal to clinically significant above normal in 3 patients, and 1 patient had clinically significant above normal values throughout the study up to Week 48. Two patients in the Ranivisio group and 3 patients in the Lucentis group had clinically significant above normal glycosylated haemoglobin values at the Final Visit/Week 48.

Haematology

The per patient haematology results have been summarised descriptively for the absolute values of each laboratory parameter for V0/ Screening, V7/Week 24, Final Visit/Week 48, and for the absolute change from screening at V7/Week 24 and at Final Visit/Week 48.

Overall, the vast majority of haematology values up to Week 48 were within normal ranges or not clinically significantly above or below normal ranges. An exception was the neutrophil band count, which was below the normal range for the majority of patients. Similarly, the eosinophil count was below normal at analysis visit V7/Week 24 for 100 patients and at the Final Visit/Week 48 for 102 patients in the SAF. The number of patients who developed clinically significant abnormal haematology values throughout the study up to Week 48 was low, and no clinically relevant differences between the two treatment groups were identified.

Considering the elderly patient population under investigation in this clinical study, haematology was considered normal.

The white blood cell count changed from normal at screening to clinically significant above normal at analysis visit V7/Week 24 in 2 patients, changed from normal at screening to clinically significant below normal in 1 patient, and was clinically significant above normal throughout the study up to Week 24 for 1 patient. The white blood cell count changed from normal to clinically significant above normal at the Final Visit/Week 48 in 1 patient in the Ranivisio group.

Concerning white blood cell count differentials, the following changes were observed: The neutrophil count was clinically significant above normal throughout the study up to Week 24 for 1 patient. None of the patients had clinically significant above or below normal neutrophil counts at the Final Visit/Week 48. The neutrophil band count changed from below normal at screening to clinically significantly above normal at analysis visit V7/Week 24 for 1 patient. None of the patients had clinically significant above or below normal neutrophil band counts at the Final Visit/Week 48. The lymphocyte count decreased from below normal at screening to clinically significantly below normal at analysis visit V7/Week 24 in 1 patient in the Lucentis group. None of the patients had clinically significant above or below normal lymphocyte counts at the Final Visit/Week 48. The monocyte count decreased from normal at screening to clinically significantly below normal at the Final Visit/Week 48 for 1 patient in the Lucentis group. The eosinophil count increased from above normal at screening to clinically significantly above normal at analysis visit V7/Week 24 in 1 patient in the Ranivisio group. None of the patients had clinically significant above or below normal eosinophil counts at the Final Visit/Week 48. No clinically significant basophil counts were observed for any of the patients in the SAF.

The red blood cell count decreased from normal at screening to clinically significantly below normal at analysis visit V7/Week 24 for 1 patient, and from below normal to clinically significantly below normal for 2 patients. None of the patients had clinically significant above or below normal red blood cell counts at the Final Visit/Week 48.

Haemoglobin decreased from normal at screening to clinically significantly below normal at analysis visit V7/Week 24 for 4 patients, and from below normal to clinically significantly below normal for 2 patients. Haemoglobin decreased from normal at screening to clinically significantly below normal at the Final Visit/Week 48 for 2 patients, and from below normal to clinically significantly below normal for 1 patient. One patient in the Ranivisio group and 2 patients in the Lucentis group had haemoglobin values clinically significantly below normal ranges at the Final Visit/Week 48.

Haematocrit measurements decreased from normal at screening to clinically significantly below normal at analysis visit V7/Week 24 and from below normal to clinically significantly below normal for 2 patients, respectively. Haematocrit changed from normal at screening to clinically significantly below normal at the Final Visit/Week 48 for 1 patient in the Lucentis group.

The platelet count increased from above normal at screening to clinically significantly above normal at analysis visit V7/Week 24 for 1 patient in the Lucentis group. The platelet count increased from above normal at screening to clinically significantly above normal at the Final Visit/Week 48 for 1 patient in the Ranivisio group.

Coagulation profile

The coagulation profiles at screening were not clinically significantly abnormal for all patients. No clinically relevant differences between the two treatment groups were identified.

Vital signs

No clinically important findings were detected up to Week 48, and the vital signs measurements were balanced between both treatment groups. No clinically significant radial pulse assessments were reported for all patients in the SAF at screening and at analysis visit V7/Week 24, and two clinically significant assessments were reported at the final analysis visit/Week 48. For two patients, a clinically significant systolic blood pressure result was reported at screening and at analysis visit V7/Week 24, respectively, and for four patients at the final analysis visit/Week 48. One clinically significant diastolic blood pressure result was reported for 1 patient at screening and for two patients at the final analysis visit/Week 48.

Physical examination findings

Physical examinations were performed at screening, at analysis visit V7/Week 24 and at the Final Visit/Week 48. All clinically relevant findings were documented as medical history or as adverse events. Beyond that, no clinically important findings were detected up to Week 48.

Other observations related to safety

The intraocular pressure (IOP) was assessed in both eyes at screening and at the Final Visit/Week 48 as well as pre- and post-injection in the study eye at Visit 1 to Visit 12. In general, the IOP increased from pre- to post-injection at every treatment visit, but the magnitude of this increase was balanced between both treatment groups and no clinically relevant differences were identified. IOP values ≥30 mmHg were observed for few patients in both treatment groups and were closely followed up. They occurred only post-injection and normalised until the next treatment visit.

The anterior chamber was examined for inflammatory activity using the slit lamp before dilation of both eyes at screening and at the Final Visit and for the study eye at Visit 1 to Visit 12. The anterior chamber activity was zero for almost all patients throughout the study up to Week 48. An activity of 0.5+ was observed for 1 patient (0.2%) at Visit 3, 4, 5, 8, 9, and 11, respectively, and an activity of 1+ was observed for 1 patient (0.2%) at Visit 5 and the Final Visit, respectively. No relevant differences between the treatment groups were observed.

The lens status was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit. The lens status was phakic or pseudo-phakic for almost all patients throughout the study up to Week 48. An aphakic lens status was documented for 1 patient (0.2%) in the fellow eye at screening, and for

- 1 patient in the study eye at Visits 1, 3, 6, and 8, respectively
- 3 patients (0.6% - 0.7%) in the study eye at Visits 4, 5, 7, and 10; and in the fellow eye at the Final Visit
- 4 patients (0.9%) in the study eye at Visit 11

- 2 patients (0.5%) in the study eye at Visit 12.

No relevant differences were observed between the two treatment groups.

Cataract severity was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. Throughout the study up to Week 48, a gradable cataract was assessed for about 91% of the patients, no cataract was assessed for about 8% of the patients and mature or Morgagnian cataracts were assessed for about 1% of the patients. For about 170 patients, the cataract severity was not determinable at every analysis visit, respectively, and missing assessments were documented. The numbers varied slightly across the analysis visits. The number and percentage of patients within each category of cataract severity were balanced between the treatment groups.

Nuclear grade was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. The nuclear grade in the study eye was not determinable for about 140-150 patients at each analysis visit, and missing assessments were documented. At every analysis visit, most of the patients had a nuclear grade of 1, followed by a nuclear grade of 0 and a nuclear grade of 2. Only few patients had a nuclear grade of 3 or higher. The number and percentage of patients within each category of nuclear grade were balanced between the two treatment groups.

Posterior Subcapsular Cataract (PSC) grade was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. PSC grade in the study eye was not determinable for about 140-150 patients at each analysis visit and missing assessments were documented. Most of the patients had a PSC grade of 0 (> 80.0%), followed by a PSC grade of 1 (10.0%-15.0%). A PSC grade of 2 or higher was only assessed for few patients. The number and percentage of patients within each category of PSC grade were balanced between the two treatment groups.

Cortical grade was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. Cortical grade was not determinable for about 140-150 patients at each analysis visit and missing assessments were documented. For most of the patients a cortical grade of 0 was documented, followed by a cortical grade of 1 and 2, respectively. A cortical grade of 3 or higher was documented only for few patients. The frequency of the cortical grade categories by analysis visit was balanced between the two treatment groups.

Vitreous haze was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. A vitreous haze of 0 was assessed for most of the patients (> 90.0%), and a vitreous haze of 1 was documented for all other patients. A vitreous haze of 3 was only documented for 1 patient at Visit 9 and Visit 12; and a vitreous haze of 2 in the fellow eye for 2 patients at screening and for 1 patient in the study eye and for 2 patients in the fellow eye at the Final Visit. The number of patients within each vitreous haze category was balanced between the two treatment groups at all analysis visits.

Vitreous haemorrhage was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. There was no vitreous haemorrhage for almost all patients at every analysis visit. Present vitreous haemorrhage was only documented for 1 patient (0.2%) at Visits 1 and 2; and for 2 patients (0.4%) at Visit 8, 9 and in the study eye at the Final Visit. Only few missing assessments were documented. The number of patients with present and absent vitreous haemorrhage was balanced between both treatment groups at all analysis visits.

Posterior vitreous detachment was assessed for both eyes at screening and at the Final Visit and for the study eye at Visit 1 – Visit 12. An "absent" posterior vitreous detachment was assessed for about 60% of the patients, a "complete" posterior vitreous detachment was assessed for about 30% of the patients, and an

"incomplete" posterior vitreous detachment was assessed for about 10% of the patients at all analysis visits and in both treatment groups. Only few patients had an "indeterminate" or missing posterior vitreous detachment and none of the patients had a "present" posterior vitreous detachment. Hence, all categories were well balanced between the two treatment groups and no relevant differences were identified.

At the Final visit, diagnosis of the fellow eye for the presence of AMD or other ocular diseases was performed. A total of 253 (58.2%) patients out of 435 patients with non-missing assessments had no late AMD (no atrophy/ no CNV) in the fellow eye, with slightly more patients in the Lucentis arm (63.3%, 136 of 215 patients) than in the Ranivisio arm (53.2%, 117 of 220 patients). About one fourth of the patients had AMD with a neovascular component (24.8%, 108 of 435 patients with non-missing assessments), with slightly more patients in the Ranivisio arm (28.2%, 62 of 220 patients) than in the Lucentis arm (21.4%, 46 of 215 patients). Other diagnostic parameters: AMD with no active component (scar, regressed CNV), Pure geographic atrophy (any atrophy no matter of location within the macula) and Other diagnosis, and also the number of missing, not applicable or not gradable diagnoses were roughly similar regarding proportion and numbers of patients affected.

Overall, the clinical Phase III study COLUMBUS-AMD showed comparable patterns of safety laboratory, vital signs and physical examination assessments between Ranivisio- and US-Lucentis-treated patients. The vast majority of reported laboratory results were within normal ranges, or not clinically significantly below or above normal ranges. The number of patients with clinically significant laboratory results was low in general, and no clinically meaningful laboratory abnormalities were identified which could not be explained by a geriatric patient population.

The results from other safety assessments resulting from ophthalmological examinations and tonometry (including basic assessments of iris, macula, optic nerve, etc., lens, anterior chamber activity and vitreous body, safety check after intravitreal injection) were also balanced between the two treatment arms.

Overall, the results did not indicate any relevant differences between the two treatment arms.

In vitro biomarker test for patient selection for safety

N/A

Safety in special populations

N/A

Immunological events

Please refer to Overview Section 3.3.1.2 "Pharmacodynamics" for immunogenicity results and assessment.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Of the 477 subjects who were randomised, 452 (94.8%) subjects completed 48 weeks of the study (up to the final analysis). Up to the final analysis, 12 patients (5.0%) in the Ranivisio group and 13 patients (5.4%) in the Lucentis group discontinued the study prematurely; 16 patients (6.7%) in each group discontinued treatment. Reasons for premature study discontinuation recorded in both treatment groups appeared balanced, with withdrawal by patient (Ranivisio: 2 patients, Lucentis: 8 patients), AE (Ranivisio: 1 patient,

Lucentis: 2 patients), lost to follow-up (Ranivisio: 3 patients, Lucentis: 1 patient), and other (Ranivisio: 4 patients, Lucentis: 2 patients). In the Ranivisio group, one additional patient had a major protocol deviation and another patient needed alternative treatment.

Adverse events leading to study discontinuation

Three patients prematurely discontinued the study due to a TEAE; 1 patient treated with Ranivisio had worsening of nAMD, 1 patient treated with Lucentis was diagnosed with benign pancreatic neoplasm, and 1 patient treated with Lucentis was diagnosed with malignant tongue neoplasm of unspecified stage.

The patient who was diagnosed with benign pancreatic neoplasm recovered completely from the event. The events of worsening of nAMD and of malignant tongue neoplasm of unspecified stage in the other 2 patients were ongoing at the time of database cut.

The Investigator judged the event of worsening of nAMD as related to study drug, the other two events were judged as not related to study drug or to the IVT procedure.

Short narratives:

One patient treated with Ranivisio for 12 weeks (up to Study day 83) experienced moderate non-serious "neovascular age-related macular degeneration", which can be considered as worsening of his pre-existing nAMD (diagnosed on 27-Feb-2017). The study drug was permanently withdrawn after Visit 4/Week 12 after 4 of the 12 planned injections were administered, and the patient permanently discontinued the study due to AEs. The event was suspected to be possibly related to study drug and was suspected to be unlikely related to the IVT injection procedure. The event was ongoing at the time of database cut.

Patient treated with Lucentis developed a moderate "Benign pancreatic neoplasm" which required (prolonged) hospitalisation. The patient permanently discontinued the study due to this event. The SAE was not suspected to be related to the study drug or to the IVT injection procedure, but study drug was permanently withdrawn for this patient. The patient received only the initial injection of study medication at baseline (Study day 1). The patient recovered completely from this event.

Patient treated with Lucentis was diagnosed with "Malignant tongue neoplasm of unspecified stage". This severe SAE was life-threatening and the patient did not recover from this event as it was ongoing at database cut. The SAE was not suspected to be related to the study drug or to the IVT injection procedure. The patient was treated with Lucentis for 16 weeks (up to Visit 5/Week16) and permanently discontinued treatment afterwards. Previously, study drug was interrupted at Visit 4/Week 12 and in total, 4 of the 12 planned injections were administered. The patient discontinued the study due to adverse events.

Adverse events leading to permanent or temporary withdrawal of study drug

During the study, 32 patients (6.7%; n=16 in each treatment arm) permanently discontinued treatment (Table 10-18). No clinically relevant differences with regard to these permanent discontinuations of treatment between the two treatment groups were identified.

During the study, 63 patients (13.2%) had at least 1 treatment interruption, with 25 patients (10.5%) in the Ranivisio group and 38 patients (15.9%) in the Lucentis group (Table 10-18).

Table 10-18 Total number injections per patient, interruptions and premature treatment discontinuations – SAF

	FYB201 (N = 238)		Lucentis (N = 239)		Total (N = 477)	
	n	%	n	%	n	%
Patients receiving						
1 Injection	3	1.3%	1	0.4%	4	0.8%
2 Injections	1	0.4%	0	0.0%	1	0.2%
3 Injections	1	0.4%	1	0.4%	2	0.4%
4 Injections	2	0.8%	1	0.4%	3	0.6%
5 Injections	0	0.0%	1	0.4%	1	0.2%
6 Injections	0	0.0%	4	1.7%	5	1.0%
7 Injections	1	0.4%	2	0.8%	3	0.6%
8 Injections	0	0.0%	3	1.3%	3	0.6%
9 Injections	2	0.8%	3	1.3%	5	1.0%
10 Injections	6	2.5%	9	3.8%	15	3.1%
11 Injections	22	9.2%	25	10.5%	47	9.9%
12 Injections	199	83.6%	189	79.1%	388	81.3%
Patients with at least 1 treatment interruption	25	10.5%	38	15.9%	63	13.2%
Patients with premature treatment discontinuation	16	6.7%	16	6.7%	32	6.7%

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
Source: Post-text table 14.3.1.4

[Table 10-18 from CSR]

16 TEAEs (8 TEAEs in 6 patients in each treatment group) led to permanent or temporary withdrawal of study drug up to Week 48. (Tables 12-1, 12-10)

Table 12-1 Overview of treatment-emergent adverse events up to Week 48 – SAF

	FYB201 (N = 238)			Lucentis (N = 239)			Total (N = 477)		
	Ev	n	%	Ev	n	%	Ev	n	%
TEAEs leading to withdrawal of study drug	8	6	2.5%	8	6	2.5%	16	12	2.5%

[Table 12-1 from CSR]

Table 12-10 Patients with TEAEs leading to withdrawal of study drug up to Week 48 by MedDRA SOC and PT – SAF

Patient	Age	M /F	MedDRA PT (Study day start–stop)	Serious (Intensity)	Relationship to study drug	Relationship to IVT procedure	Outcome
FYB201: 6 patients							
[redacted]			Upper respiratory tract Infection [redacted]	No (mild)	Unlikely	Unlikely	Recovered / Resolved[2]
			Upper respiratory tract Infection [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Conjunctivitis [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Conjunctivitis [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Chalazion [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved
			Conjunctivitis [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Neovascular age-related macular degeneration Verbatim: nAMD worsening-treatment failure [redacted]	No (moderate)	Possibly	Unlikely	Not recovered/ Not resolved (study drug permanently withdrawn)[1]
			Conjunctivitis allergic [redacted]	No (moderate)	Unlikely	Unlikely	Recovered/ Resolved (study drug permanently withdrawn)
Lucentis: 6 patients							
[redacted]			Blepharospasm [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Visual acuity reduced [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Vascular anastomosis [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Eye complication associated with device [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Viral infection [redacted]	No (mild)	Unlikely	Unlikely	Recovered/ Resolved[2]
			Endophthalmitis [redacted]	Yes (severe)	Unlikely	Possibly	Recovered/ Resolved[2]
			Benign pancreatic neoplasm [redacted]	Yes (moderate)	Unlikely	Unlikely	Recovered/ Resolved (study drug permanently withdrawn)[1]
[redacted]			Tongue neoplasm malignant stage unspecified [redacted]	Yes (severe)	Unlikely	Unlikely	Not recovered/ Not resolved (study drug permanently withdrawn)[1,2]

[1] Patient prematurely discontinued the study due to AE on [redacted]

[2] Patient interrupted treatment due to AE

Abbreviations: F = Female, M = Male, IVT = intravitreal MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term

Notes: MedDRA version 19.0 was used

Source: Post-text table 14.3.2.9, Patient data listings 16.2.1.3, 16.2.7.9, 16.2.4.1,

[Table 12-10 from CSR]

Ranivisio

In the Ranivisio group 3 patients had interruption of treatment due to mild non-serious TEAEs; 2 events of upper respiratory tract infection, 2 events of conjunctivitis and 1 event of conjunctivitis, these patients recovered from the events. One had a short event (5 days) of Chalazion for which the study drug was

withdrawn, at the subsequent visit the patient had fully recovered and treatment was resumed, without omitting an IVT injection.

Another patient had an event of moderate Conjunctivitis allergic for which the study drug was withdrawn, the patient did not resume treatment and did not receive the last planned IVT injection, the patient recovered from the event.

The Investigators judged these events as not related to study drug or to the IVT procedure (Table 12-10).

One patient permanently discontinued treatment and the study for nAMD worsening-treatment failure (PT: Neovascular age-related macular degeneration), the event was ongoing at the time of database cut and the Investigator judged the event as related to study drug (Table 12-10, short patient narrative above).

US-Lucentis

In the US-Lucentis arm, 6 patients had an interruption of treatment, 3 patients for mild non-serious TEAEs; 2 events of Blepharospasm and Visual acuity reduced, 1 event of Vascular anastomosis, 2 events of Eye complication associated with device and Viral infection. The patients recovered from these events, and the Investigator judged these events as not related to study drug or to the IVT procedure (Table 12-10).

Also in the Lucentis group, serious TEAEs were observed in 3 patients: Patient experienced severe Endophthalmitis in her study eye (**local SAE**), for which the patient interrupted treatment, the Investigator judged this event as related to the IVT procedure, the patient recovered from the event; Patient was diagnosed with moderated Benign pancreatic neoplasm, for which the patient discontinued the study (see narrative above), the Investigator judged this event as not related to study drug or IVT procedure, the patient recovered from the event; Patient was diagnosed with severe Tongue neoplasm malignant stage unspecified, the patient had interruption of treatment and finally discontinued the study due to this event (see narrative above), the event was ongoing at database cut, the Investigator judged this event as not related to study drug or to the IVT procedure.

Post marketing experience

This section is not applicable, since Ranivisio has not been marketed yet in any country worldwide. There is wide overall clinical experience with ranibizumab (Lucentis) in the approved therapeutic indications, and a positive efficacy and safety record has been established.

2.4.9. Discussion on clinical safety

One pivotal Phase III study including a total of 477 patients diagnosed with neovascular AMD (randomised 1:1) was conducted, in order to compare the safety profiles of Ranivisio and Lucentis.

Neovascular AMD is considered a sufficiently sensitive population to investigate clinical biosimilarity in terms of safety, as there is comparability for ranibizumab across indications with regard to target receptor, mode of action and safety across the authorised indications, i.e., DME, RVO, CNV and PDR. In addition, immunogenicity of ranibizumab was reported to be overall low across indications (up to 9%).

The Q4W administration of the study drugs is in agreement with the anticipated posology in patients with the highest treatment need. From a safety perspective, a monthly schedule is most sensitive, as higher exposure levels can be expected in comparison with a treat and extend regimen, and is thus supported.

Per treatment arm, 238 (Ranivisio) and 239 (US-Lucentis) patients were included, respectively.

In general, to characterise the ADR pattern over time, the cohort of exposed subjects should be large enough to observe also less frequently occurring events. To detect a common AE (appearing in ≥1% of patient) with sufficient precision, at least 300 subjects need to be treated. Further, as per ICH E1, 100 patients exposed to a study drug for a minimum of one year is considered acceptable, and 300-600 patients should be treated for 6 months with the drug at the intended dose level.

However, it is overall acknowledged that this is a biosimilarity exercise. Thus, the present sample size is sufficiently large to conclude on comparability in terms of common or very common adverse effects. However, it is too small to draw robust conclusions as regards comparability in terms of less frequently occurring adverse events. This seems especially important to note with regard to the evaluation of the more serious, less common adverse reactions such as endophthalmitis, blindness, retinal detachment, retinal tear, iatrogenic traumatic cataract or systemic AEs such as arterial thromboembolic events or non-ocular haemorrhages.

Overall, the numbers of patients per treatment arm treated for one year comply with the ICH E1 guideline (usually comparative date from at least 100 patients exposed for a minimum of one-year would be expected) and are acceptable for in the context of a biosimilarity exercise.

The number of patients who completed the study were overall comparable between treatment arms. The most common reasons for premature discontinuation (before Week 48) were consent withdrawal and adverse events. There were overall 25 patients (Ranivisio: 12 patients; Lucentis: 13 patients) who discontinued the study. Reasons for study discontinuation were: withdrawal by patient (Ranivisio: 2 patients, Lucentis: 8 patients), lost to follow-up (Ranivisio: 3 patients, Lucentis: 1 patient), AE (Ranivisio: 1 patient, Lucentis: 2 patients), major protocol deviation (Ranivisio: 1 patient, Lucentis: no patients), need for alternative treatment (Ranivisio: 1 patient, Lucentis: no patients), and other reasons (Ranivisio: 4 patients, Lucentis: 2 patients). Here, the applicant was requested to clarify what those "other reasons" were. Three patients died Ranivisio: 2;; Lucentis: 2). One patient (Lucentis) moved. One patient (Ranivisio) was incorrectly enrolled into the study in error and subsequently discontinued the study. One patient (Ranivisio) was withdrawn by the investigator due to multiple adverse events and thus discontinued the study.

Up to week 24, there was an imbalance between treatment arms with regard to study treatment discontinuation (n=7 in the Ranivisio arm vs. n=3 in the Lucentis arm). The applicant provided the reasons for treatment discontinuation prior to Wk 24 and stated that there might be a higher probability of an uneven distribution without reason with such small numbers. This is acknowledged, against the background that, overall up to final analysis, the number of patients who discontinued treatment was similar in both treatment arms (n=16 in each arm).

The exposure to study drug was overall comparable. Most patients received all planned 12 injections up to the final analysis (338 patients; 81.3%; Ranivisio: 83.6% versus US-Lucentis: 79.1%), 47 patients (9.9%; Ranivisio: 9.2% versus US-Lucentis: 10.5%) received 11 injections, 15 patients (3.1%) received 10 injections, 5 patients (1.0%) received 9 injections and less than 1.0% of the patients received less than 8 injections, respectively. Hence, the vast majority of the patients received all scheduled injections or only missed 1 or 2 injections. Only few patients missed 3 or more injections. The number of missed injections was overall balanced between both treatment groups.

An injection at Week 48 (final visit) was not scheduled in the protocol, but for 6 patients (Ranivisio: n=5, US-Lucentis: n=1) the visit schedule was delayed so that the injection administered at Visit 12/Week 44 was assigned to the final analysis visit according to the respective study day. This is not considered to be of concern.

TEAEs by SOC/PT

The overall number and percentage of TEAEs was comparable between the two treatment groups: 64.7% of the patients in the Ranivisio group experienced 509 TEAEs and 69.9% of the patients in the Lucentis group experienced 597 TEAEs, with numerically more TEAEs in the US-Lucentis arm.

Overall, the SOC Eye disorders was the most commonly affected SOC for both treatment arms in the SAF; at least 1 TEAE within this SOC was observed for 100 patients (42.0%) in the Ranivisio arm and also for 100 patients (41.8%) in the US-Lucentis arm. The most commonly affected PTs in this SOC were Neovascular age-related macular degeneration (Ranivisio: n=19 [8.0%]; US-Lucentis: n=22 [9.2%]), Conjunctival haemorrhage (Ranivisio: n=14 [5.9%]; US-Lucentis: n=19 [7.9%]), and Punctate keratitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=12 [5.0%]).

Other commonly affected PTs were Nasopharyngitis from SOC Infections and Infestations (Ranivisio: n=12 [5.0%], US-Lucentis: n=16 [6.7%]) and IOP from SOC Investigations (Ranivisio: n=11 [4.6%]; US-Lucentis: n=12 [5.0%]).

TEAEs by severity

Most TEAEs were of mild or moderate intensity: few TEAEs were severe (19 TEAEs in 11 patients in the Ranivisio arm and 32 TEAEs in 22 patients in the US-Lucentis arm). Severe TEAEs were recorded in twice as many patients in the Lucentis arm, but without clinically relevant differences or increased frequency in particular SOCs.

Ocular/ non-ocular (systemic) TEAEs

The applicant classified all AEs occurring in the study eye or in both eyes as "local AEs". Those local TEAEs observed were presented together ("as one") instead of separately. This was not considered adequate. It should clearly be separated between ocular and non-ocular (i.e. systemic) adverse events instead, in accordance with the Lucentis safety profile depicted in the product information. It is of importance for demonstration of similar safety to get a clear picture about the local (ocular) safety profile of Ranivisio with regard to the study eye to which Q4W IVT injections have been administered. As a consequence, local (i.e. ocular) TEAEs should be presented separately for the study eye as well as for the fellow eye for both treatment arms.

In addition, systemic TEAEs have been defined by the applicant as all TEAEs not meeting the definition of "local AEs" (i.e. all AEs not occurring the study eye). Here, the applicant was requested to present instead a revised tabulated summary of non-ocular (systemic) TEAEs.

Furthermore, a tabulated comparison between arms listing all ocular (separately for study eye and fellow eye) and systemic, non-ocular TEAEs that were considered related by SOC and PT were requested to be provided.

In addition, a tabulated comparison including only the severe TEAEs (ocular [study eye; fellow eye]; non-ocular/ systemic) by SOC and PT were requested to be provided.

The applicant has provided the requested revised adverse event analyses clearly differentiating between ocular AEs (in study eye as well as in fellow eye) and systemic AEs.

Based on these analyses, no distinct differences between treatment arms can be detected with regard to incidences of ocular TEAEs, related ocular TEAEs, severe ocular TEAEs, related severe TEAEs, serious ocular TEAEs and related serious ocular TEAEs, neither in the study eye nor in the fellow eye.

With regard to systemic TEAEs, there were 104 (43.7%) patients in the Ranivisio treatment arm who reported 238 systemic TEAEs compared to 130 (54.4%) patients in the Lucentis treatment arm who reported 326 systemic TEAEs. This numerical imbalance was also observed for severe systemic TEAEs (16 events in n=8 Ranivisio patients vs. 26 events in n=16 Lucentis patients) as well as for serious systemic TEAEs (28 events in n=17 patients vs. 41 events in n=28 patients). However, when considering causality assessment, the imbalance between the study arms was less pronounced for all types of systemic TEAEs.

Local TEAEs (as presented by the applicant)

Frequency and type of "local" (study eye or both eyes) TEAEs were overall comparable between both treatment groups, and no clinically relevant differences were identified.

As presented by the applicant, frequent PTs in SOC Eye disorders were Conjunctival haemorrhage (Ranivisio: n=13 [5.5%]; US-Lucentis: n=18 [7.5%]), Punctate keratitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=12 [5.0%]), Visual acuity reduced (Ranivisio: n=5 [2.1%]; US-Lucentis: n=10 [4.2%]). Frequent local TEAEs were also recorded in SOC Investigations (Ranivisio: n=17 [7.1%]; US-Lucentis: n=15 [6.3%]) with most frequent PT Intraocular pressure increased (in 10 patients in each treatment arm [4.2%]) and in SOC Infections and infestations (Ranivisio: n=10 [4.2%]; US-Lucentis: n=7 [2.9%]) with most frequent PT Conjunctivitis (Ranivisio: n=8 [3.4%]; US-Lucentis: n=2 [0.8%]).

Ocular adverse events that were expected to occur (very) commonly (according to the Lucentis SmPC) were overall comparable between treatment arms in the present study, although it is notable that some AEs occurred at lower-than-expected rates (such as IOP increased, Conjunctival haemorrhage), which might raise a concern on the suitability/sensitivity of the safety monitoring.

Systemic TEAEs (as presented by the applicant)

The frequency of reported systemic TEAEs was higher in the US-Lucentis arm (147 patients; 61.5%) than in the Ranivisio arm (123 patients; 51.7%).

As presented by the applicant, at SOC level, the most frequent systemic TEAEs were Infections and infestations with comparable incidences in both treatment arms (20.6 [Ranivisio] vs. 22.6% [US-Lucentis] of patients). For the SOCs Eye disorders (14.3% vs. 16.7%), Investigations (8.0% vs. 11.7%) and Musculoskeletal and connective tissue disorders (6.7% vs. 12.1%), numerical differences in favour of Ranivisio were seen.

Frequent PTs were Neovascular age-related macular degeneration in the fellow eye (Ranivisio: 18 patients, 7.6%; US-Lucentis: 21 patients, 8.8%), Nasopharyngitis (Ranivisio: 12 patients, 5.0%; US-Lucentis: 16 patients, 6.7%) and C-reactive protein increased (Ranivisio: 10 patients, 4.2%; Lucentis: 5 patients, 2.1%).

Per Lucentis SmPC, the non-ocular adverse events that are expected to occur most frequently are headache, nasopharyngitis and arthralgia. Indeed, nasopharyngitis was a frequently reported TEAE and occurred with comparable incidence for both arms. Conversely, headache was reported at lower-than-expected rates in the present study (Ranivisio: n=4 [1.7%]; US-Lucentis: n=9 [3.8%]). Arthralgia, however, was reported as TEAE only in 5 patients (2.1%) from the US-Lucentis arm.

TEAEs related to study drug/ IVT injection procedure

Study drug-related TEAEs occurred in 20 patients in the Ranivisio arm (8.4%; with 33 events) and in 25 patients in the Lucentis arm (10.5%; with 37 events). Frequent PTs for study drug related TEAEs were

recorded in SOC Eye disorders with PT Cataract (Ranivisio: no patient; US-Lucentis: 5 patients, 2.1%), Retinal pigment epithelial tear (Ranivisio: 1 patient, 0.4%; Lucentis: 3 patients, 1.3%), Visual acuity reduced (Ranivisio: no patient; Lucentis: 3 patients, 1.3%), Punctate keratitis (Ranivisio: no patient; Lucentis: 2 patients, 0.8%), Pain (Ranivisio: 2 patients, 0.8%; Lucentis: no patient) and Intraocular pressure increased (Ranivisio: 3 patients, 1.3%; Lucentis: 2 patients, 0.8%).

IVT procedure related TEAEs occurred in 21.4% of patients in the Ranivisio group (n=51) and in 27.6% of the patients in the Lucentis group (n=66). Frequent PTs for IVT procedure related TEAEs were reported in SOC Eye disorders for PTs Conjunctival haemorrhage (Ranivisio: n=13 [5.5%]; US-Lucentis: n=19 [7.9%]) and Punctate keratitis (Ranivisio: n=6 [2.5%]; US-Lucentis: n=11 [4.6%]) and in SOC Investigations for PT Intraocular pressure increased (Ranivisio: n=8 [3.4%], US-Lucentis: n=9 [3.8%]).

Overall, TEAEs related to study drug as well as to the IVT injection procedure were observed at numerically higher frequencies in the US-Lucentis group than for Ranivisio. The same holds true for severe TEAE, which were recorded in twice as many patients in the Lucentis arm.

In summary, all differences in TEAEs between treatment arms concern only low numbers of patients and events; nevertheless, a trend towards a better tolerability of Ranivisio compared to the reference product seems notable.

Importantly, the requested tabulated analyses with regard to ocular (study eye; fellow eye) and systemic, non-ocular TEAEs as well as to causality and severity were provided by the applicant to allow for further and conclusive assessment regarding comparability of safety.

SAEs

Frequencies of SAEs reported up to Week 48 were overall low and numerically in favour of the Ranivisio treatment group. 30 SAEs were reported for 19 patients (8.0%) in the Ranivisio arm, whereas 45 events were reported for 32 patients (13.4%) in the US-Lucentis arm.

As already done for TEAEs, SAEs were classified as "local AEs" that had occurred in the study eye or in both eyes and "systemic AEs" representing all remaining AEs that had not occurred in the study eye.

In accordance with the requested revised tabulated comparisons for ocular and systemic (i.e. non-ocular) TEAEs by treatment arm, the applicant was requested and provided tabulated summaries by SOC/ PT regarding ocular SAEs, both for the study eye and for the fellow eye, as well as regarding systemic, non-ocular SAEs per treatment arm. In this tabulated summary, the number of events that were observed was presented.

Ocular/ non-ocular (systemic) SAEs

Local SAEs (as presented by the applicant)

Only few ocular SAEs in the study eye were reported: 2 patients in the Ranivisio experienced Endophthalmitis and Iridocyclitis, and 3 patients in the US-Lucentis arm experienced Cataract (1 patient) and Endophthalmitis (2 patients). 1 Endophthalmitis case was judged as related to study drug and to IVT procedure, the other 2 cases were judged as related to the IVT procedure only. The case of Cataract was assessed related to the IVT procedure, too; and the Iridocyclitis case was judged related to both study drug and IVT procedure. Only for 1 patient in the Lucentis arm, the Endophthalmitis led to interruption of study drug. All patients recovered from the local SAEs.

Systemic SAEs (as presented by the applicant)

The frequency of systemic SAEs was higher in the Lucentis group with 29 patients (12.1%) compared to 17 patients (7.1%) in the Ranivisio group.

Most frequently systemic serious TEAEs were recorded in SOC Cardiac disorders (Ranivisio: n=7 [2.9%]; US-Lucentis: n=5 [2.1%]) followed by SOC Nervous system disorders (Ranivisio: n=2 [0.8%]; US-Lucentis: n=5 [2.1%]) and SOC Respiratory, thoracic and mediastinal disorders (3 patients in each arm [1.3%]). Systemic serious TEAEs were also frequently observed in SOC Musculoskeletal and connective tissue disorders (Ranivisio: n=1 [0.4%]; US-Lucentis: n=4 [1.7%]) and SOC Renal and urinary disorders (2 patients in each arm [0.8%]).

With the initial submission, no information has been provided with regard to causality assessment for systemic SAEs. A tabulated comparison between treatment arms listing all systemic SAEs by causality (related/ not related), by SOC and PT, was provided with the responses to the D120 LoQ. Overall, 6 of the serious TEAEs reported in 6 patients were judged as related to study medication. Among these were 4 systemic related SAEs, two in the Ranivisio group (Myocardial infarction and Transient ischaemic shock) and two in the Lucentis group (Cerebrovascular accident and Circulatory collapse).

Deaths

Three patients died during the course of the study; two patients were exposed to Ranivisio and one patient was exposed to US-Lucentis. The Investigators judged these fatal SAEs as unlikely related to study drug or to the IVT procedure.

As the above imbalances are mostly events reported at low rates, they are difficult to interpret and need to be considered in the context of the overall safety profile and the totality of evidence (e.g., also consider quality/PK/immunogenicity findings).

With regard to the rather limited number of patients in the safety database (n=238 for Ranivisio vs. 239 for US-Lucentis), there is the possibility that the study might be insensitive to detect differences in the incidence of more uncommon AEs. In this regard, an integrated discussion should be provided by the applicant, evaluating whether the tendency of a favourable safety profile for Ranivisio compared to US-Lucentis might be attributable to a lower systemic exposure. It should be comprehensively justified that the observed differences in PK and safety do not impair the establishment of biosimilarity. The tendency of an inferior efficacy profile as well as a trend towards lower efficacy in ADA positive subjects should also be included in this discussion. In summary, the data set from the initial submission has been presented once again, without providing a genuine discussion of the imbalances regarding PK and safety. Overall, since the imbalances are rather numerical by nature and since equivalence in terms of efficacy has been demonstrated, those issues will not be further pursued.

Immunogenicity

Overall, the total number of patients with positive ADAs in blood serum was low and comparable between treatment arms. 28 patients out of 477 (5.9%) in the SAF (Ranivisio, 14/238 [5.9%] and Lucentis 14/239 patients [5.9%]) had at least one confirmed positive ADA assessment between baseline and after the first administration of study treatment up to 48 weeks. This is considered to be acceptable.

Out of theses 28 patients with positive ADAs, only one ADA sample (one patient) in the Ranivisio treatment group at the final visit was detected positive for neutralizing ADA. All other samples were nAb negative.

Based on the current limited available data, only one mild severity event of drug hypersensitivity was reported in each of the treatment groups. In both cases the patients were ADA negative throughout the

treatment period. Since no TEAE (drug hypersensitivity, anaphylaxis or intra-ocular inflammation) were reported for ADA positive patients, the safety risk due to clinically relevant treatment-emergent ADAs is assumed to be low.

2.4.10. Conclusions on the clinical safety

In summary, a trend towards a better tolerability of FYB201 compared to the reference product seems apparent in the data. However, since these imbalances are less pronounced when considering causality/ relationship to treatment, the safety evidence is compatible with biosimilarity.

2.5. Risk Management Plan

2.5.1. Safety concerns

3. Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infectious endophthalmitis Intraocular inflammation Retinal detachment and retinal tear Intraocular pressure increase

3.1.1. Pharmacovigilance plan

In line with the originator, no additional pharmacovigilance activities are proposed.

3.1.2. Risk minimisation measures

4. Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Infectious endophthalmitis	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8, 6.6	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 6.6 where advice is given on how to administer an IVT injection and information for physicians and patients on how to manage this event. PL sections 2, 3 and 4. Pack size: one single-use vial Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Targeted follow-up checklist Additional pharmacovigilance activities: None
Intraocular inflammation	Routine risk minimisation measures: SmPC sections 4.3 and 4.4. PL sections 2 and 4. Pack size: one single-use vial. Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Retinal detachment and retinal tear	Routine risk minimisation measures: SmPC sections 4.4 and 4.8. PL sections 2 and 4. Pack size: one single-use vial. Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Intraocular pressure increase	Routine risk minimisation measures: SmPC sections 4.4, 4.8 and 4.9.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.4 where advice is given on monitoring IOP and the perfusion of the optic nerve head. PL sections 2 and 4. Pack size: one single-use vial. Legal status: Prescription only medicine Additional risk minimisation measures: Educational plan for adult patients (for indications of nAMD, CNV, DME, RVO and PDR)	Additional pharmacovigilance activities: None

5.1.1. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

5.2. Pharmacovigilance

5.2.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

5.2.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

5.3. Product information

5.3.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

6. Biosimilarity assessment

6.1. Comparability exercise and indications claimed

Ranivisio is developed as a biosimilar to the reference product Lucentis. The administration route (intravitreal) and posology are in accordance with the reference product as described in the Lucentis SmPC.

The marketing authorisation is claimed for the following indications in adult patients:

•The treatment of neovascular (wet) age-related macular degeneration (AMD)

•The treatment of visual impairment due to diabetic macular oedema (DME)

•The treatment of proliferative diabetic retinopathy (PDR)

•The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)

•The treatment of visual impairment due to choroidal neovascularisation (CNV)

6.2. Results supporting biosimilarity

Quality

In summary, the presented analytical data show similarity of the proposed biosimilar Ranivisio and the reference medicinal product Lucentis. Quality attributes related to the mechanism of action of Ranivisio were similar. The analytical differences observed for several quality attributes have been appropriately addressed by the applicant and justified with regard to their potential impact on clinical performance of the product.

Clinical

Pharmacokinetics:

The maximum concentrations of both the treatments [Ranivisio and Lucentis] were well below the concentration range of ranibizumab that was necessary to inhibit the biological activity of vascular endothelial growth factor by 50%.

Pharmacodynamics:

As there is no obvious PD biomarker that could allow for a reasonable interpretation of the PD studies, PD relies on *in vitro* data and the human efficacy study.

Efficacy:

In the pivotal comparative efficacy study COLUMBUS-AMD in nAMD patients, equivalence between Ranivisio and US-Lucentis was demonstrated for the primary efficacy endpoint, 'Change from Baseline BCVA by ETDRS letters at Week 8', both in the FAS and in the PPS population. The difference between both treatments was -0.7 ETDRS letters (95%CI: -2.3; 0.9) for the FAS population; the two-sided 95% CI was entirely within the pre-defined equivalence margin of ± 3.5 letters. This was supported by the sensitivity analysis in the PPS population (difference of -0.8 letters, with a 95% CI of -2.4; 0.8) - the results were consistent with the primary analysis.

Several functional and anatomical parameters were assessed as secondary efficacy endpoints, in order to support demonstration of similar efficacy between Ranivisio and Lucentis. Overall, comparability of Ranivisio to Lucentis was demonstrated for all secondary efficacy endpoints.

Safety:

The safety analyses for the pivotal Phase III study comprised 48 weeks safety data from 477 subjects. Based on this dataset, the incidences, types and severities of TEAEs and SAE were overall comparable between Ranivisio and US-Lucentis, and were in line with the safety profile for ranibizumab (SmPC Lucentis). No new safety signals have been identified so far.

Immunogenicity:

The total number of patients treated with Ranivisio and Lucentis with positive ADAs in blood serum were low and similar between both treatments. As only one mild severity event of drug hypersensitivity was reported in each treatment group (both ADA negative patients) and no events of drug hypersensitivity, anaphylaxis or intra-ocular inflammation were reported for ADA positive patients, the immunogenicity of Ranivisio and a safety risk due to clinically relevant treatment-emergent ADAs is assumed to be low.

6.3. Uncertainties and limitations about biosimilarity

Quality

Some differences with regard to binding to VEGF isoform VEGF-A111 was observed. However, these differences could be sufficienty justified and do not preclude biosimilarity as such.

Clinical

Pharmacokinetics:

In study FYB201-C2015-01-P3, the number of patients enrolled in the pharmacokinetics analysis set (PKS) is limited (n=59). An imbalance in the baseline characteristics of age, iris color and Snellen was observed between the Lucentis group and the Ranivisio group in the pharmacokinetics analysis set. Although, the systemic concentrations of ranibizumab measured close to Cmax after the 1st and 6th IVT injections were broadly similar in both treatment groups for all measurement time points, the geometric mean of Ranivisio was lower than the geometric mean of Lucentis, for both visits (V1a and V6a). It is possible that the observed imbalance may have affected comparability. However, the data are too limited to make an entire conclusion of the clinical relevance of these differences.

Pharmacodynamics:

The clinical evaluation of similarity for Ranivisio is based on clinical endpoints used in study FYB201-C2015-01-P3 rather than a PD endpoint which is judged acceptable since no obvious PD endpoint is known.

Efficacy:

With the initial submission, no subgroup analyses were presented for the primary EP (except for subgroup analysis by ADA status). Therefore, subgroup analyses by prognostic factors at BL, such as total lesion area and Snellen equivalent, had been requested. They were provided by the applicant and were overall supportive.

In addition, the applicant provided subgroup analyses by country region. For the region Austria-Germany, the estimated difference was -5.7 ETDRS letters, with a 95% CI of [-12.6; 1.3 With their responses to the D180 LoOI, the applicant has provided additional analyses and data for the subgroup Austria-Germany, such as baseline disease characteristics and results for secondary efficacy endpoints, as requested.

When looking at the marked difference for the primary efficacy EP between the treatment arms in this subgroup (estimated difference in BCVA of -5.7 ETDRS letters, 95% CI -12.6; 1.3), no specific patients could be identified as "outliers", according to the applicant. Indeed, the number of patients with a BCVA of less than 60 letters at baseline was balanced (n=5 in each treatment arm). However, two patients in the Ranivisio arm experienced a pronounced drop in BCVA despite anti-VEGF treatment (i.e. BCVA values below 20 letters). This was not seen in any patient of the Lucentis arm of the AUT-GER subgroup and might thus account for the observed worse efficacy in the biosimilar arm.

Overall, taking into account that equivalence with regard to efficacy between Ranivisio and Lucentis was shown in the entire study population and that the AUT-GER subgroup is indeed rather small and has a numerical imbalance between the treatment arms (n=17 vs n=21), the observed lower efficacy for Ranivisio in this single subgroup is considered not to be of clinical relevance.

Safety:

With regard to systemic adverse events, there are numerical imbalances between biosimilar and originator, in favour of the biosimilar. However, since these imbalances diminish when considering causality/ relationship to treatment, they are not considered to be of critical relevance.

Immunogenicity:

For all efficacy endpoints (BCVA, FCP/FCS retinal thickness and total lesion area) investigated over time in study FYB201-C2015-01-P3, a trend was observed that the ADA status may have an impact on efficacy. Moreover, there is a tendency for the biosimilar (Ranivisio) to have a higher number of treatment-induced and persistent ADAs. These persistent ADAs could lead to a reduction in the efficacy of the biosimilar. However, based on the currently available data, no numerically significant difference between the treatment groups was observed and the number of patients with positive ADAs was generally low.

Based on the limited provided data (54 patient samples) for the PK Subgroup Analysis Set (PKS) no meaningful conclusion, whether the ADA status (Ranivisio: 2 ADA positive patients, Lucentis: 3 ADA positive patients) has an impact on the pharmacokinetic, can be made for this subpopulation.

6.4. Discussion on biosimilarity

Overall, the design of the analytical similarity exercise is considered adequate. The results of the analytical similarity exercise between Ranivisio and EU-Lucentis demonstrate similarity. Also, the data indicate that EU-Lucentis and US-Lucentis are comparable for the perspective of pharmaceutical quality.

The pivotal comparative efficacy study in nAMD patients comparing Ranivisio and US-Lucentis was overall adequately designed, and the primary and secondary efficacy outcomes and similarity criteria are considered acceptable. Equivalence was demonstrated for the primary endpoint, the change from baseline in BCVA at Week 8 in the FAS population. This was supported by sensitivity analyses for the primary EP in the PPS population, as well as by secondary efficacy endpoints reflecting functional and anatomical outcomes.

With the initial submission, no subgroup analyses were presented for the primary EP (except for subgroup analysis by ADA status). Therefore, subgroup analyses by prognostic factors at BL, such as total lesion area and Snellen equivalent, had been requested. They were provided by the applicant and were overall supportive.

In addition, the applicant provided subgroup analyses by country region. For the region Austria-Germany, the estimated difference was -5.7 ETDRS letters, with a 95% CI of [-12.6; 1.3]. No clear explanation has been provided by the applicant for the lower efficacy of Ranivisio compared to the originator Lucentis in the AUT-GER subgroup.

It can be assumed that the two patients in the Ranivisio arm who experienced a pronounced drop in BCVA despite ranibizumab treatment have contributed to the observed lower efficacy in the biosimilar arm in this subgroup.

Overall, taking into account that equivalence with regard to efficacy between Ranivisio and Lucentis was shown in the entire study population and that the AUT-GER subgroup is indeed rather small and has a numerical imbalance between the treatment arms (n=17 vs n=21), the observed lower efficacy for Ranivisio in this single subgroup is considered not to be of clinical relevance.

The other efficacy concerns from the D120 LoQ, mainly related to the late shift in the primary EP, justification of the chosen equivalence margin, missing morphological BL characteristics and statistical issues, were resolved.

With regard to safety, the applicant provided revised safety analyses, differentiating between ocular and systemic adverse events, by study arm. Overall, the revised AE analyses confirm a comparable ocular safety profile for Ranivisio compared to Lucentis, with no new safety signals detected. With regard to systemic adverse events, there are numerical imbalances between biosimilar and originator. However, since these imbalances are less pronounced when considering causality/ relationship to treatment, they should be interpreted with caution. In addition, it has to be taken into account that they are rather favourable for Ranivisio.

Against the background that equivalence with regard to efficacy was demonstrated, this trend towards a better tolerability of Ranivisio compared to Lucentis is considered overall acceptable.

Based on the limited data provided, immunogenicity appears to be low and comparable between both treatments (Ranivisio and Lucentis). Although, a potential impact of the ADA status on the efficacy in patients treated with Ranivisio, and thus on biosimilarity cannot be completely excluded based on the limited data available at present, it is not considered that the differences alter the benefit-risk ratio to an extent that would raise major efficacy/safety concerns and thus an apparent dissimilarity between both products.

6.5. Extrapolation of safety and efficacy

The indications granted for the reference product Lucentis for adults were applied for Ranivisio. Ranibizumab binds to VEGF-A to prevent binding to corresponding receptors, thereby suppressing neovascularisation. The mode of action of ranibizumab is considered to be the same across all approved indications of Lucentis. The biological activities related to the mode of action have been comprehensively evaluated in the analytical similarity exercise.

Extrapolation to other indications of the reference product than neovascular age-related macular degeneration is considered acceptable, since similarity of Ranivisio to the ranibizumab reference EU-Lucentis was demonstrated.

6.6. Conclusions on biosimilarity and benefit risk balance

Based on the review of the submitted data, Ranivisio is considered biosimilar to Lucentis. Therefore, a benefit/risk balance comparable to the reference product can be concluded.

7. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ranivisio is favourable in the following indication(s):

Ranivisio is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)

- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)
- The treatment of visual impairment due to choroidal neovascularisation (CNV)

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.