CONFIDENTIAL

CLINICAL STUDY PROTOCOL

EFFICACY AND SAFETY OF THE BIOSIMILAR RANIBIZUMAB FYB201 IN COMPARISON TO LUCENTIS IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (COLUMBUS-AMD)

Study code:	FYB201-C2015-01-P3	Study development phase:	Phase III
EudraCT number:	2015-001961-20	Investigational medicinal product:	FYB201
		Indication:	Neovascular age-related macular degeneration
Version:	9.0, incorporating Amendment 7	Date:	29 August 2017
Previous version:	7.0, incorporating Amendment 6		
Coordinating Investigator:	[redacted]		
Sponsor Signatory:	Bioeq GmbH Bergfeldstraße 9 83607 Holzkirchen Germany		

This study will be conducted in compliance with the protocol and in accordance with Good Clinical Practice (GCP) and International Conference of Harmonisation (ICH) guidelines associated with the conduct of clinical studies.

1 SYNOPSIS

Name of the Sponsor/Company: Bioeq GmbH	**Study Code:** FYB201-C2015-01-P3
Name of Investigational Medicinal Product: FYB201	**EudraCT No.:** 2015-001961-20
Development Phase of the Study: Phase III	

TITLE OF THE STUDY:

EFFICACY AND SAFETY OF THE BIOSIMILAR RANIBIZUMAB FYB201 IN COMPARISON TO LUCENTIS IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (COLUMBUS-AMD)

OBJECTIVES:

Primary objective:

Evaluate and compare functional changes in best corrected visual acuity (BCVA) after 2 months (8 weeks) of treatment with FYB201 or Lucentis, compared to baseline BCVA

Secondary objectives:

- Evaluate and compare functional changes of the retina by BCVA over time
- Evaluate and compare changes in foveal center point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness over time
- Evaluate and compare presence of active choroidal neovascularization (CNV) leakage at Month 6 and 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 6 and Month 12 compared to baseline
- Evaluate and compare systemic ranibizumab concentrations close to C_{max} 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 Months 6 and 12 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)

OVERALL STUDY DESIGN:

The COLUMBUS-AMD study is a parallel-group, 1:1 randomized, active-controlled, evaluation-masked, multicenter study to demonstrate clinical equivalence in terms of clinical efficacy, pharmacology, and safety of FYB201 with Lucentis over 12 months of treatment in patients with subfoveal nAMD.

All patients will receive monthly intravitreal (IVT) injections over a time period of approximately 12 months (48 weeks). Patients will receive FYB201 or Lucentis at a dose of 0.5 mg (0.05 mL of a 10 mg/mL solution) as monthly (every 4 weeks) IVT injections starting at Visit 1 (Week 0) through Visit 12 (Week 44) (total of 12 injections).

Systemic ranibizumab concentration close to C_{max} after first and sixth IVT injections (24 hours post-dose [±3 hours]) and ADA formation one week after first IVT injection will be assessed in a subgroup of up to 60 patients (up to 30 each for Lucentis and FYB201) of selected study centers.

INVESTIGATIONAL MEDICINAL PRODUCT:

FYB201 – ranibizumab biosimilar (International Nonproprietary Name [INN]: ranibizumab) 10 mg/mL solution for IVT injection

COMPARATOR DRUG

Lucentis (INN: ranibizumab), US-licensed, 10 mg/mL solution for IVT injection

NUMBER OF PATIENTS:

460 patients are planned to be randomized. Inclusion will be 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].

NUMBER OF STUDY CENTERS:

Approximately 80 study centers in Europe, Russia and Israel.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

General

1. Age ≥ 50 years of either gender
2. Signed informed consent form must be obtained before any study-related procedure is performed
3. Willingness and ability to undertake all scheduled visits and assessments
4. Women must be 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 age-related macular degeneration (AMD)
    a. All subtypes of wet AMD CNV lesions are eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Active primary CNV must be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by spectral domain optical coherence tomography (SD-OCT) or retinal pigment epithelium (RPE) detachment)
    b. Total area of whole lesion must be equal or less than 12 disc areas
    c. Total CNV area encompasses equal or more than 50% of total lesion area based on fluorescein angiography (FA), including all subtypes of wet AMD

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 standardized Early Treatment Diabetic Retinopathy Study (ETDRS) testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent
8. FCP retinal thickness at Screening ≥ 350 µm. (FCP thickness is defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea)

Ocular (Fellow Eye)

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

Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the study:

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 are legally institutionalized

Prior or current ocular treatment

2. Any prior treatment with IVT anti-vascular endothelial growth factor (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 (photodynamic therapy), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the study eye
6. Topical ocular corticosteroids administered for at least 30 consecutive days within three months prior to Screening
7. Any other intraocular surgery (including cataract surgery) in the study eye within three months prior to Screening

CNV lesion characteristics

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

Current ocular conditions

11. Retinal pigment epithelial tear involving the macula in the study eye
12. History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT imaging of any size) in the study eye
13. History of retinal detachment in the study eye
14. Current vitreous hemorrhage in the study eye
15. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
16. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot 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 is 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 may confound interpretation of study results and compromise 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 require surgical intervention during the study to prevent or treat visual loss that might result 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 is 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 may bias 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.

ENDPOINTS

Primary Endpoint:

- 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.

Secondary Endpoints:

- 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 6 and Month 12
- Percentage of patients with fluid-free macula at each visit
- Change from baseline in total lesion area at Month 6 and Month 12
- Systemic ranibizumab concentrations close to C_{max} after the first and sixth IVT injections (24 hours post-dose [±3 hours]) in a subgroup of up to 60 patients (up to 30 per arm)
- Change from baseline in vision-related functioning and well-being measured by NEI VFQ-25 at Month 6 and Month 12
- Number of patients with anti-drug antibodies over time
- Frequency of local and systemic AEs and SAEs

STATISTICAL METHODS

Primary endpoint:

The change from baseline to Week 8 in the ETDRS BCVA will be calculated and compared between FYB201 and Lucentis based on the following hypotheses:

Null hypothesis: H_0: $|\mu_{BCVA,FYB201} - \mu_{BCVA,Lucentis}| \geq 3.5$

Alternative hypothesis: H_1: $|\mu_{BCVA,FYB201} - \mu_{BCVA,Lucentis}| < 3.5$,

where $\mu_{BCVA,FYB201}$ and $\mu_{BCVA,Lucentis}$ are the mean changes of ETDRS letters from baseline to Week 8.

An analysis of covariance (ANCOVA) model will be used with the change in BCVA between baseline and week 8 as the dependent variable, the baseline BCVA as covariate, and the country and treatment group as fixed effects.

For the US specific analysis, the endpoint will be evaluated in all patients with a baseline BCVA between 20/32 and 20/100 Snellen equivalent and a 90% confidence interval (CI) for the treatment difference will be calculated using Least Square Means.

For the EU specific analysis, the endpoint will be evaluated in all patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent and a 95% CI for the treatment difference will be calculated using Least Square Means.

If the respective confidence interval is completely contained in the interval]-3.5; 3.5[letters, equivalence of FYB201 and Lucentis can be concluded (rounded to the next integer, this corresponds to an equivalence margin of 3 letters).

Secondary endpoints:

All secondary endpoints will only be analyzed descriptively.

All values for BCVA, FCP, and FCS retinal thickness as well as total lesion area will be summarized by visit and treatment, including change from baseline. The change from baseline to Week 24 and Week 48 for all three variables will be compared between treatment groups using the ANCOVA model as used for the primary endpoint to derive the confidence intervals for the difference between the treatment groups, but without formal hypothesis testing. For the Week 48 analysis of the change in BCVA, the patient-wise average of Weeks 40, 44, and 48 will be used to reduce the intrinsic variability of these measurements.

NEI VFQ-25 scores will be determined as described in the official manual. Values will be summarized by visit and treatment, including change from baseline.

The number and proportion of patients who have binding anti-drug antibodies in serum (including identification and quantitation of nAbs) will be determined at Visit 1 (pre-dose), as a part of baseline evaluation, Week 1 (Subgroup only), Week 4, Week 12, Week 24 and Week 48 (or final visit).

Furthermore, all efficacy endpoints will be analyzed on all patients with either a screening BCVA between 20/40 and 20/100 Snellen equivalent, and on patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent as well as by country/country group.

PLANNED SAMPLE SIZE

The sample size of 460 patients is calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 10 ETDRS letters. The calculation considers that application of a 90% CI for the US and a 95% CI for the EU is required for assessing biosimilarity.

The required sample size for the EU specific analysis based on a power of at least 90% is sufficient to provide at least 95% power for the US specific analysis based on all patients randomized and using a 90% confidence interval.

STUDY PERIOD:

The total study period for each patient will be approximately 12 months (48 weeks).

Planned start of the study (First Patient First Visit [FPFV]): Quarter 4 2015

Planned end of the study (Last Patient Last Visit [LPLV] Final visit): Quarter 2 2018

Table 1 Schedule of Study Events - Visits for ALL patients

	V0 Screening	V1 Baseline	V1a**	V1b**	V2	V3	V4	V5	V6	V6a**	V7	V8	V9	V10	V11	V12	Final Visit
Week (Day)	W-4–W-1 (-28 to -1)	W0 (0)	D1 (1±3 h)	W1 (7±1)	W4 (28±3)	W8 (56±3)	W12 (84±3)	W16 (112±3)	W20 (140±3)	W20+24 h (±3 h)	W24 (168±3)	W28 (196±3)	W32 (224±3)	W36 (252±3)	W40 (280±3)	W44 (308±3)	W48 (336±3)
Patient information / informed consent	x																
Demographics information	x																
Medical History	x																
Prior treatments	x																
Physical assessment, vital signs[1]	x										x						x
BCVA[2,3]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
Tonometry[3,4,5]/ ophthalmological examination[3,6]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
Inclusion/Exclusion	x	x[12]															
Randomization		x															
Fluorescein angiography*[3]	x										x						x
Color Fundus Photography[3]	x										x						x
SD-OCT[3]	x	x			x	x	x	x	x		x	x	x	x	x	x	x
NEI VFQ-25[7]		x									x						x
Laboratory tests	x										x						x
Pregnancy (serum HCG) *(only women)*	x																
PK[/8]**		x**	x**							x**							
ADAs[9]		x		x**	x		x				x						x

	V0 Screening	**V1 Baseline**	**V1a****	**V1b****	**V2**	**V3**	**V4**	**V5**	**V6**	**V6a****	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**Final Visit**
Week (Day)	W-4 – W-1 (-28 to -1)	W0 (0)	D1 (1±3 h)	W1 (7±1)	W4 (28±3)	W8 (56±3)	W12 (84±3)	W16 (112±3)	W20 (140±3)	W20+24 h (±3 h)	W24 (168±3)	W28 (196±3)	W32 (224±3)	W36 (252±3)	W40 (280±3)	W44 (308±3)	W48 (336±3)
Concomitant med.		x	x**	x**	x	x	x	x	x	x**	x	x	x	x	x	x	x
AEs[10]	x	x	x**	x**	x	x	x	x	x	x**	x	x	x	x	x	x	x
IVT treatment[11]		x			x	x	x	x	x		x	x	x	x	x	x	
3-Day Post-Injection Telephone Safety Check		x			x	x	x	x	x		x	x	x	x	x	x	

* Additional fluorescein angiography may be performed at any time at the discretion of the Masked Investigator/s.

** Subgroup only.

1 Before any blood sample collection on the same day.

2 Refraction and VA testing must be performed prior to any other visual examination that requires eye drops (i.e. ophthalmological examination, FA, color fundus photography and SD-OCT) using ETDRS charts.

3 Ocular assessments at Screening and Final visit are performed on both eyes (OU). Ocular assessments at all other study visits are performed on the study eye (SE) only.

4 Goldmann applanation tonometry must be performed at Screening. The Tonopen or Perkins Tonometer, may be used at other times, however Goldmann applanation tonometry must be used to verify any IOP ≥30 mm Hg.

5 Tonometry should be measured prior to the injection and at least 30 minutes after the injection.

6 A complete ophthalmic examination should be performed prior to the IVT injection. For details and examinations after the IVT injection please see Section 10.4.

7 Before any invasive procedure.

8 Evaluation of systemic ranibizumab concentration only

9 In case of confirmed anti-drug antibodies, the titer and neutralizing capacity of ADAs (nAbs titer) will be evaluated

10 AEs starting after signing the informed consent must be recorded on relevant AE page.

11 A safety check will be performed just after the injection.

12 No significant anatomical change in the study eye compared to screening and visual acuity in the study eye within the defined inclusion criteria range (Snellen equivalent20/32 [0.63] to 20/100 [0.2]) and within 5 letters of the Screening BCVA.

ADA: Anti-drug antibody, AE: Adverse event, BCVA: Best-corrected visual acuity, D: day, ETDRS: Early treatment diabetic retinopathy study, h: hours, HCG: Human chorionic gonadotropin, IOP: Intraocular pressure, IVT: Intravitreal, nAb: neutralizing antibody, NEI VFQ-25: National eye institute visual function questionnaire 25, OU: Both eyes, PK: Pharmacokinetic, SD-OCT: Spectral domain optical coherence tomography, V: Visit, VA: Visual acuity.

VISIT WINDOWS:
It is essential that patients adhere to their scheduled study visits within the following visit windows:
- **Visits 1a and 6a (Subgroup only): 24 hours after first and sixth IVT injections (respectively) ± 3 hours**
- **Visit 1b (Subgroup only): ± 1 day**
- **Visit 2 to Visit 12 (all patients): ± 3 days**

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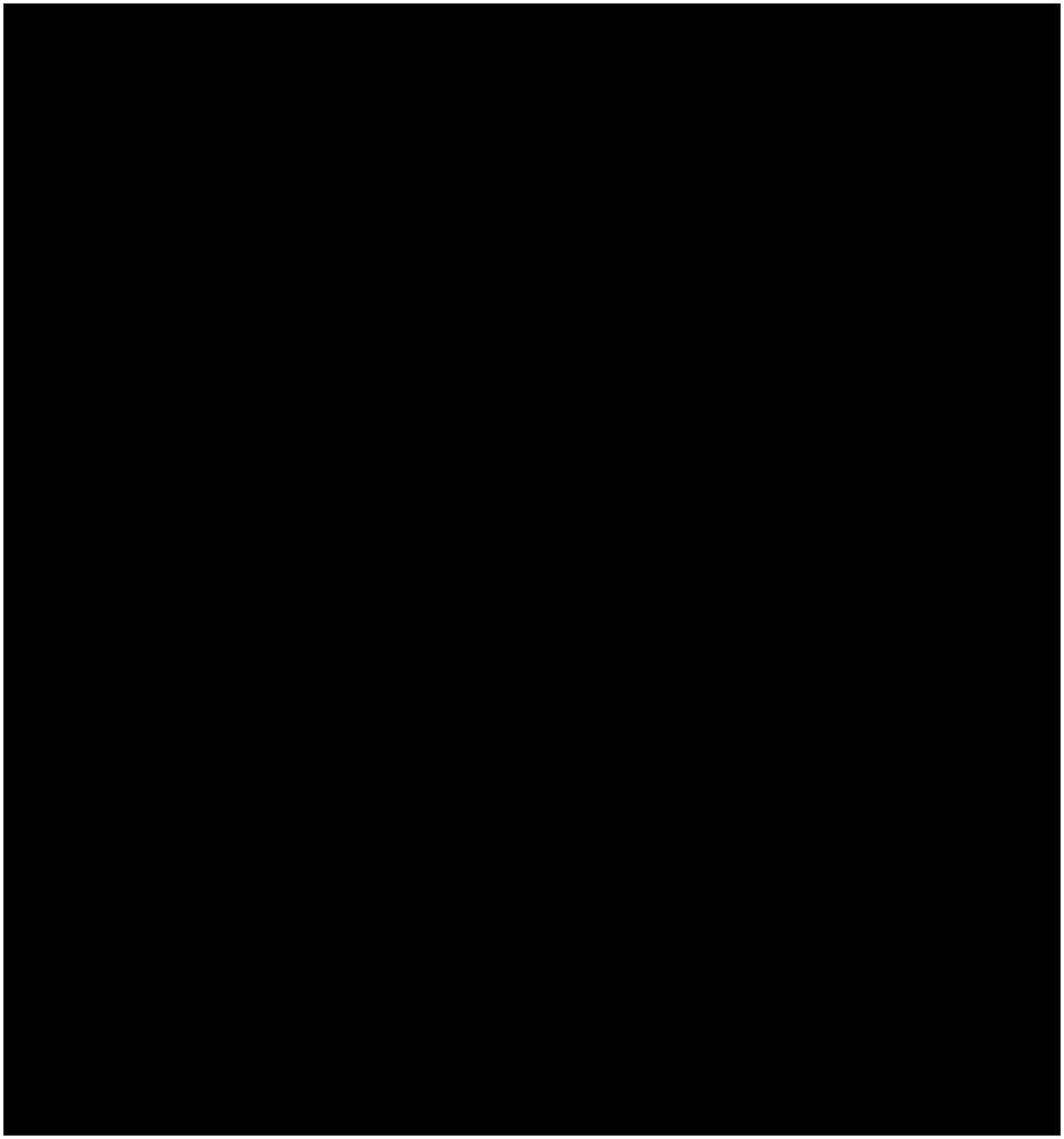
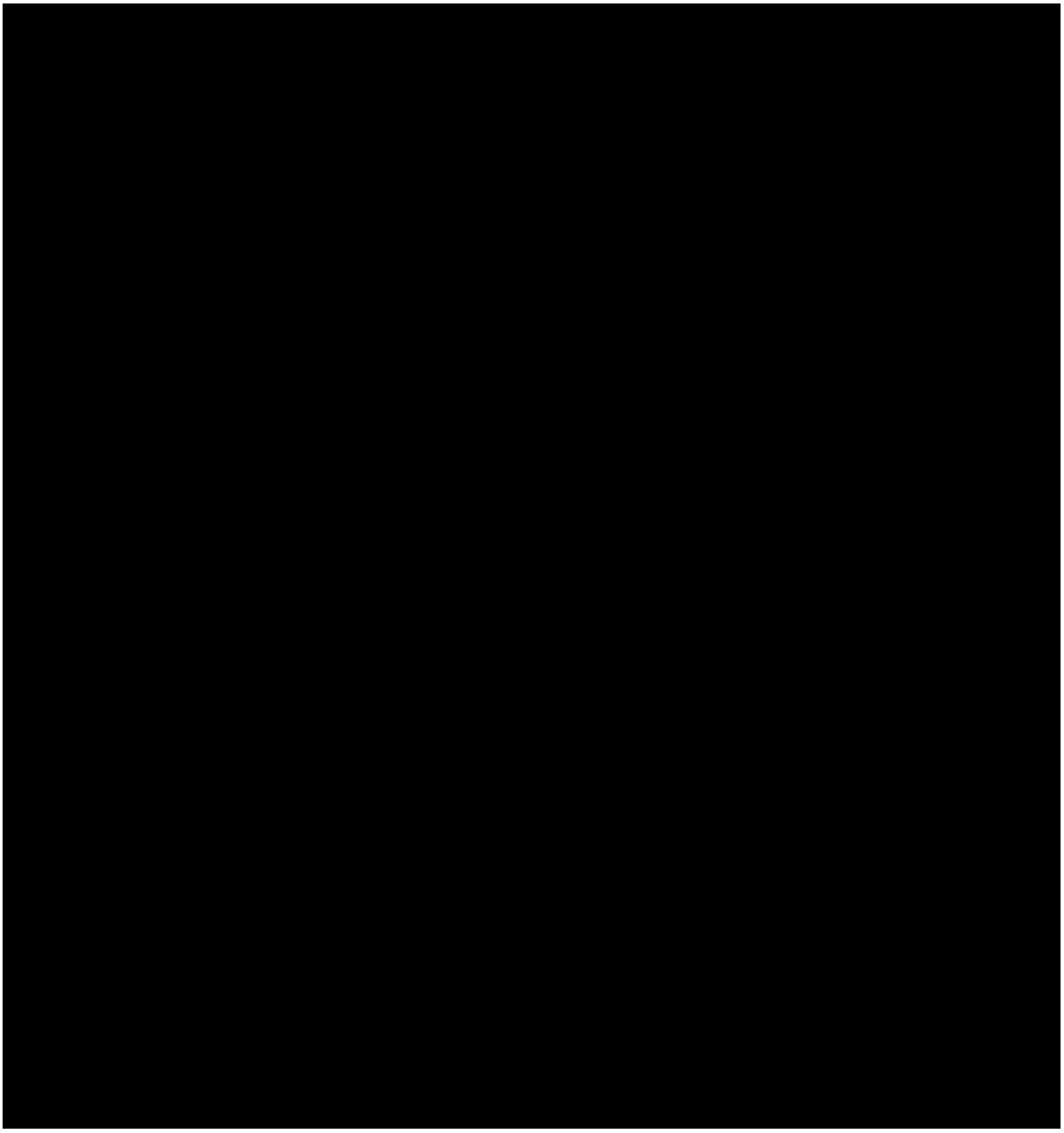
3 LIST OF ABBREVIATIONS

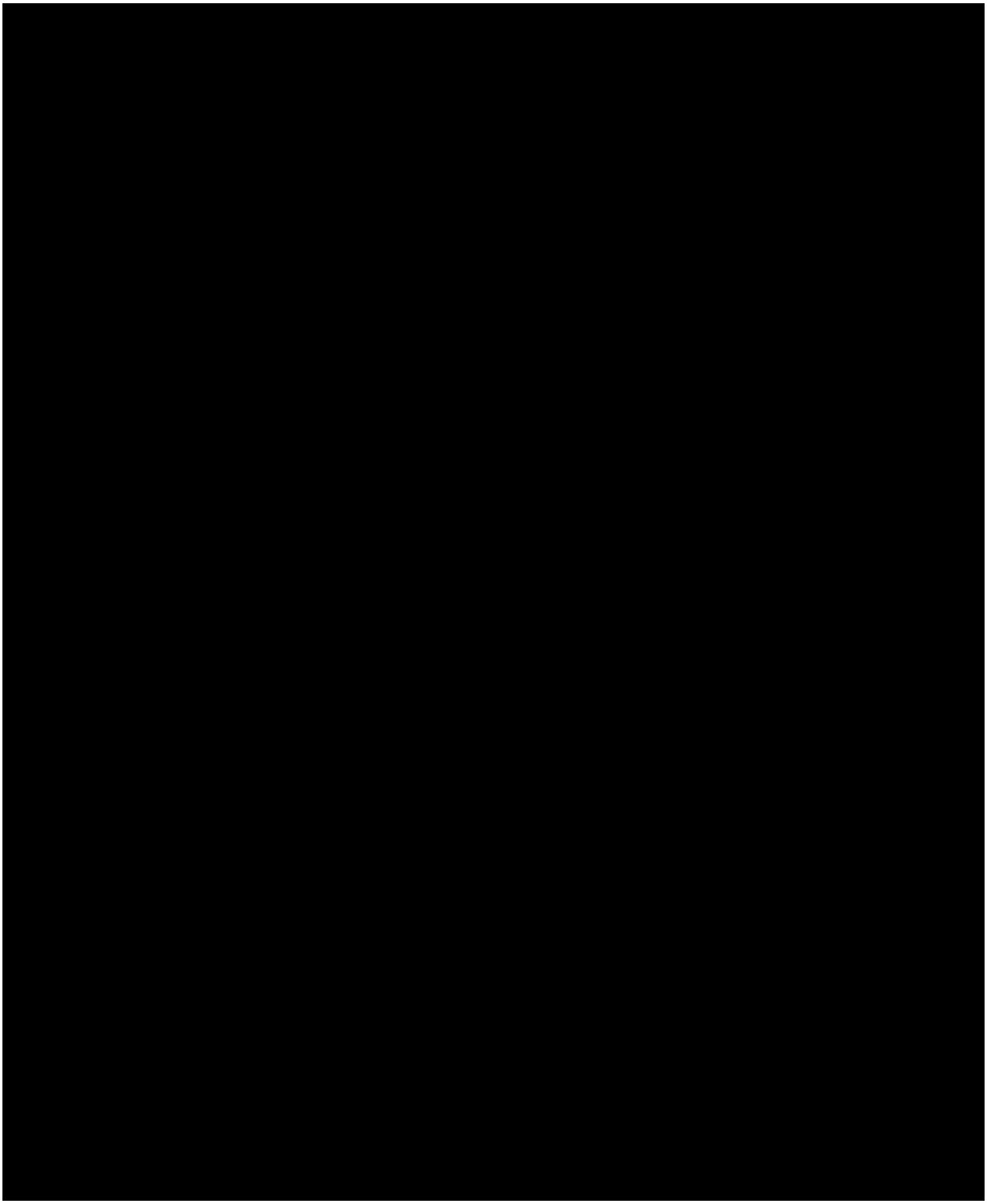
ADA	Anti-Drug Antibody
AE	Adverse Event
AMD	Age-Related Macular Degeneration
ANCOVA	Analysis of Covariance
BCVA	Best-corrected Visual Acuity
CA	Competent Authority
CATT	Comparison of AMD Treatments Trials
CI	Confidence Interval
C_{max}	Maximum concentration
CNV	Choroidal Neovascularization
CRC	Central Reading Center
CRO	Contract Research Organization
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
Fab	Antigen-binding fragment
FAS	Full Analysis Set
FCP	Foveal Center Point
FCS	Foveal Central Subfield
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HCG	Human Chorionic Gonadotropin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Nonproprietary Name
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intention-to-treat
IVT	Intravitreal
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
nAb	Neutralizing Antibody
nAMD	neovascular AMD
NEI VFQ-25	National Eye Institute Visual Function Questionnaire
OCT	Optical Coherence Tomography
OU	Both eyes
PK	Pharmacokinetic
PP	Per Protocol
PRN	Pro Re Nata
PDT	Photodynamic Therapy
Q25	Percentile of 25%
Q75	Percentile of 75%
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAEs	Treatment-emergent Adverse Events
[redacted]	
US	United States
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor

4 STUDY ADMINISTRATIVE STRUCTURE







5 INTRODUCTION

5.1 Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a progressive degenerative disease of the central retina affecting the region of highest visual acuity (VA) of the eye. Characteristically, it is a disease affecting individuals over 50 years of age and is the leading cause of visual loss in developed countries [1,2,3,4,5,6].

A recent meta-analysis revealed that the prevalence of AMD in the European population aged between 65 and 75 years old is between 9% and 25% [7]. In the United States, the prevalence of AMD in people aged 65-74 is estimated to be approximately 6%, and in those older than 75 years of age [8], prevalence is 20%. With increasing life expectancy in many countries, the elderly population is expected to grow at a greater rate in coming decades. According to United States (US) Census Bureau projections, the number of Americans over 65 years of age will grow to 80 million by the middle of this century [9].

Therefore, in the absence of adequate prevention or treatment, the number of cases of AMD with visual loss is expected to grow correspondingly.

A population-based meta-analysis has shown that in Caucasian populations over 40 years of age the prevalence of early and late stage AMD is around 6.8% and 1.5%, respectively [10]. The effect of ethnicity on the incidence of AMD is not clear. The results of the Baltimore Eye Survey showed that the prevalence of advanced clinical forms of AMD was nine-fold higher in Caucasians than in African–Americans [11]. Recently, the prevalence of the advanced AMD has been found to be similar between Asians and Caucasians [5].

Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities. AMD is classified into one of two general subgroups: the non-neovascular (non-exudative or dry) form of the disease and the neovascular (exudative or wet) form of the disease. The non-neovascular form of AMD is more prevalent, accounting for approximately 85%-90% of all AMD cases, and is often characterized by a slow degeneration of the macula resulting in atrophy of the central retina with gradual vision loss over a period of years. By contrast, neovascular AMD (nAMD), although less prevalent, accounting for only 10%-15% of clinical forms, commonly causes sudden, often substantial, loss of central vision and is responsible for most cases of severe loss of VA in patients with this disease [12]. This type of AMD results from abnormal proliferation of blood vessels (neovascularization) under and/or within the retina. The neovascular form appears due to an angiogenic process in which newly formed choroidal vessels (choroidal neovascularization; CNV) invade the macular area, which results in rapid loss of vision and often total blindness [13,14]. The end stage of the disease is scarring with irreversible destruction of the central retina. In the non-neovascular form, the pathophysiological mechanism has yet to be clarified, but it is thought that the mechanism may be chronic inflammation involving several factors associated with the activation pathways of complement factors and oxidative stress [14,15].

Treatment of Age-Related Macular Degeneration

Today there is ample scientific evidence to suggest that vascular endothelial growth factor (VEGF) plays a key role in the pathophysiology of wet AMD [16,17,18]. VEGF is an endothelial cell survival factor and a mitogen, thus promoting the growth of endothelial cells, which are a key component of neovascular tissue. These findings have led to the development and use of anti-angiogenic drugs in a new era of treatment of CNV, based on a better understanding of the cellular and molecular mechanisms associated with disease. These anti-angiogenic drugs, which block the various stages of VEGF action, represent a major advance in the treatment of wet AMD. The introduction of anti-VEGF in the treatment of AMD has resulted in clear therapeutic effects such as an improvement of visual acuity, compared with other therapies. Thus, anti-VEGF therapy is now a front line treatment for nAMD. The primary mechanism of action of these anti-VEGF agents is to decrease the volume of intraretinal and subretinal fluid accumulations associated with abnormal, hyperpermeable blood vessels. Currently, anti-VEGF therapy remains the mainstay and the gold standard for the treatment of wet AMD [19].

The current Food and Drug Administration (FDA)/ European Medicines Agency (EMA) approved pharmacologic therapies for wet AMD all target and inhibit VEGF and are administered by the intravitreal (IVT) route. These include Lucentis® (ranibizumab), Eylea® (aflibercept), and Macugen® (pegaptanib sodium) [20,21,22].

Pegaptanib sodium (Macugen®) was the first drug developed for IVT treatment of wet AMD. It is a polyethylene glycolaptamer synthesized from RNA oligonucleotides which binds selectively with high affinity and specificity to the VEGF-A165 isoform, thus preventing recognition of VEGF by its receptor [24].

Bevacizumab (Avastin®) is a humanized recombinant monoclonal antibody (RhuAbV2), which also inhibits all isoforms of VEGF-A in a nonselective manner. Although the use of this drug is approved for intravenous treatment of some advanced and metastatic carcinomas, it has been shown that repeated IVT administration in wet AMD reduces vascular exudation and prevents CNV [25]. Bevacizumab (Avastin®) is used as an off-label treatment.

More recently, aflibercept (Eylea®) a fusion protein with specific high affinity binding to VEGF-A and VEGF-B receptors and to the placental growth factors PlGF-1 and PlGF-2, has been shown to safely and effectively suppress CNV in patients with nAMD with similar durability of action relative to other IVT anti-VEGF agents [26].

Ranibizumab (Lucentis®) was first approved in 2006 for IVT administration in the treatment of all subtypes of nAMD, based on the results of three large-scale double-masked randomized controlled studies. Lucentis® works on the principle of competitive VEGF inhibition in extracellular space owing to penetration into all retinal layers and affinity to all VEGF isoforms. Ranibizumab is an antigen-binding fragment (Fab) of recombinant humanized monoclonal anti-body (RhuFabV2) targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to VEGF-A isoforms (e.g. VEGF110, VEGF121, VEGF165), thus preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. The binding of ranibizumab to VEGF-A prevents endothelial cell proliferation and neovascularization, as well as vascular leakage, thus blocking progression to exudative AMD [27]. Lucentis® (48 kDa) is a fragment of murine MAb Anti-VEGF-A (~150 kDa) that achieves 5-20 times higher affinity to VEGF compared to the antibody from which it derived. It combines higher penetration into all retinal layers with reduced cytotoxicity and inflammatory potential. Furthermore, the shorter half-life minimized systemic effects of this medication. Due to its lower molecular weight (~48 kDa), following IVT administration results in rapid penetration through the layers of the retina where it exerts an inhibitory effect on vascular permeability and angiogenesis [28].

Ranibizumab in the Treatment of Age-Related Macular Degeneration

Clinical safety and efficacy of ranibizumab were evaluated in three randomized, double-masked, placebo or active-controlled studies during 24 months with patients suffering from wet AMD (MARINA - Minimally Classic/Occult Study of the Anti-VEGF Antibody Ranibizumab in the Treatment of nAMD [29], ANCHOR - Anti-VEGF antibody for the treatment of predominantly classic CNV in AMD [30], and PIER - A phase IIIb multi-center randomized double-masked sham injection-controlled study of the efficacy and safety of ranibizumab in patients with sub-foveal neovascularization with or without classic CNV [31]). These studies of a total of 1,323 patients (879 active and 444 control) showed that ranibizumab was efficacious and could be used for all types of wet AMD. The studies demonstrated that ranibizumab led to stabilization of VA in over 90% of the patients (94.6% of patients in the MARINA study who were receiving 0.5 mg ranibizumab), and to improvement in 41% of the patients (in the ANCHOR study).

These studies have resulted in a paradigm shift in the treatment of exudative AMD, from a condition in which vision loss could only be slowed or stabilized to one in which there is a real possibility of improved VA. Clinicians are now attempting to maximize VA while minimizing the number of retreatments to eyes with exudative AMD. The PIER study tested three monthly injections of ranibizumab followed by quarterly injections over a 24-month interval. The 3-month results mirrored MARINA and ANCHOR; however, VA gains declined once quarterly dosing began. The PIER data suggest that quarterly injections are less effective than monthly. Patients treated with ranibizumab achieved rapid and significant improvement in VA during the initiation phase, but VA began to decline thereafter, falling to just below baseline at 12 months, and remaining below baseline through to Month 24 [31,32].

Fixed quarterly dosing was also investigated in the more recent EXCITE study that randomized patients to quarterly dosing with ranibizumab 0.3 or 0.5 mg or to a control group receiving monthly ranibizumab 0.3 mg [33]. Outcomes for the quarterly dosing arms in EXCITE were better than those in PIER, with patients maintaining a mean gain from baseline VA of 4 to 5 letters at Month 12. But the treatment benefit was superior in the control patients who received monthly injections with a mean VA gain of 8.3 letters.

In clinical practice, most ophthalmologists and retina specialists, use an induction phase, usually with three monthly injections, followed by an as-needed or pro re nata (PRN) phase based on visual

response, clinical examination, and imaging results. Several studies have attempted to compare this as-needed approach to the results found in MARINA and ANCHOR.

The “Prospective optical coherence tomography (OCT) Imaging of Patients with nAMD Treated with Intra-Ocular Lucentis® (PrONTO) Study” was a small, uncontrolled open-label study that treated patients with three monthly ranibizumab injections followed by monthly follow-up and redosing on an as-needed basis. PrONTO was the first prospective study to investigate PRN anti-VEGF treatment of nAMD. The VA improvements remained near the level of MARINA and ANCHOR, but the average number of injections dropped to 5.6 over the first 12 months and to 4.3 in the second year [34].

SAILOR, started in 2005, was the first large, industry-sponsored study to investigate PRN treatment with ranibizumab [35]. Outcomes were not as good as in PrONTO, and that has been attributed to use of less frequent follow-up and less stringent retreatment criteria in SAILOR, criteria that would be considered inadequate by today’s standards. In the first year of SAILOR, patients received an average of only 4.9 injections and had 9 office visits, and mean VA declined continuously after patients completed the three-dose initiation phase.

Results from other published studies, such as the European SUSTAIN study [36] which was also initially based on three monthly injections and PRN retreatment thereafter for nine months, showed an improvement in VA of 5.8 letters at Month 3 compared to baseline, however this slightly decreased between Months 3 and 6 and remained stable by Month 12 at 3.6 letters. Other studies, such as CATT - Comparison of AMD Treatments Trials [23,37] and HARBOR [38] studies, showed equivalence in the results obtained with a PRN ranibizumab regimen vs. monthly ranibizumab treatment, minimizing the risk of unnecessary injections.

Other clinicians are adopting the "treat and extend" approach, where patients are treated with three sequential monthly ranibizumab injections followed by gradually extending the interval between subsequent injections until fluid reaccumulates. If a time pattern of recurrence develops, tailored treatments can be adopted [39,40]. Two such studies have demonstrated results similar to MARINA and ANCHOR with this approach [41,42].

The HORIZON extension study, including patients from MARINA, ANCHOR, and FOCUS, documented adverse events (AEs) and VA results in patients treated with ranibizumab over four or more years. Rates of AEs, including stroke and myocardial infarction continued to be low with long-term treatment. Some VA gains achieved with monthly treatment during the initial phases of the studies were lost as patients were followed and treated less frequently during the latter years of the HORIZON study [43].

IVT administration of ranibizumab had promising results worldwide, with the absence of retinal toxicity, with no serious systemic and local ophthalmological adverse effects related to the IVT administration of the medication. Complications that can occur during ranibizumab administration are rare local effects that reflect complications associated with all medications administered intravitreally, such as anterior uveitis, transient increases in intraocular pressure (IOP), cataract; and less frequently retinal detachment, vitreous hemorrhage, and very rarely endophthalmitis. Systemic complications are very serious, but rare, and a causal relationship has not been established [44]. Reported complications include cardiovascular events such as acute myocardial infarction with a possibility of lethal outcome and cerebrovascular accidents ranging from mild transient ischemic attack to serious cerebrovascular insult [27,43,45].

There is however still an unmet need for an affordable, highly effective treatment for nAMD. Furthermore, the approved reference product Lucentis is approaching patent expiration. For these reasons the Sponsor is developing a ranibizumab biosimilar version to Lucentis.

5.2 Biosimilar ranibizumab (FYB201)

A biosimilar medicine is a biological medicine that is designed to be similar to an existing biological medicine (the ‘reference medicine’). Biological medicines are medicines that are made by or derived from a biological source, such as a bacterium, yeast or mammalian cells. Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines. The active substance of a biosimilar and its reference medicine is essentially the same biological substance, though there may be minor differences due to their complex nature and production methods.

Biosimilars can only be introduced to the market once the period of data exclusivity and patent protection on the original 'reference' biological medicine have expired. Biosimilars in general increase access to effective therapies for patients who require them.

Like Lucentis, FYB201 is produced in *E. coli* by periplasmic expression. Ranibizumab, which consists only of a Fab moiety and a single binding site, so it is not considered to be a highly complex protein.

Ranibizumab is targeted against human VEGF-A. It binds with high affinity (Kd in subnanomolar range) to VEGF-A isoforms which are either generated by alternative splicing (e.g. VEGF-A165, VEGF-A121) or by proteolytic cleavage (i.e. VEGF-A110) (EPAR, FDA Summary Basis of Approval [46,47]).

The Sponsor had developed *in-vitro* pharmacology assays for biosimilarity assessment which are based on the *in-vitro* studies conducted to support Lucentis marketing approval. The assessment of binding and biological activity includes analysis of binding kinetics for VEGF-A165/121/110 using Bio-layer interferometry, analysis of inhibition of VEGF-A165/121/110 mediated proliferation, and of inhibition of VEGF-A165 mediated tissue factor expression. These in vitro assays broadly cover the functional aspects of ranibizumab, reflect the well-established mode of action, and are sensitive enough to detect differences between FYB201 and Lucentis. Since ranibizumab is a Fab antibody fragment that lacks the Fc part of a full antibody, investigation of Fc receptor functions or complement binding seems unnecessary. In addition, since the immunological properties regarding antigen and epitope binding including non-binding to target-related proteins (e.g. the other members of the VEGF family) as well as tissue cross-reactivity were already defined by the originator, no additional studies are planned to analyze the epitope on VEGF-A, non-binding to target related proteins and the tissue cross-reactivity of FYB201.

As qualitative and quantitative formulation, strength, route of administration, posology and storage conditions of FYB201 will be the same as for the reference product Lucentis, and provided that quality data and the in vitro pharmacology data of FYB201 have demonstrated sufficient evidence of comparability between the biosimilar and the originator product, additional comparative toxicity studies are not considered necessary for the similarity assessment.

5.3 Clinical Safety

Data of Lucentis has demonstrated that the IVT dose of 0.5 mg ranibizumab/eye has a well-established safety profile in patients suffering from retinal diseases. Clinically relevant safety information for ranibizumab is documented on manufacturer´s prescribing information (see that approved on 2017-01-05 for Lucentis®, BLA no. 125156/S111). Information regarding ocular and systemic safety of Lucentis will serve as guidance for the Investigators in this planned phase III study.

Regarding immunogenicity of ranibizumab, incidence rates of anti-drug antibodies (ADAs) are assumed to be in the range of 3% to 6%. It is known from the relevant literature that incidence rates of anti-ranibizumab antibodies do not significantly change over time. Additionally, in the case of FYB201 or Lucentis it is expected that a potential formation of neutralizing antibodies (nAbs) and ADAs against ranibizumab will not be accompanied by severe adverse events (SAEs). The Fab-fragment ranibizumab is not an endogenous protein. The results of the HARBOR study showed that ADAs had no effect on PK and pharmacodynamics or treatment efficacy demonstrating that ADAs for ranibizumab are of little concern [38]. Furthermore, no clear correlation between antibodies to ranibizumab and ocular inflammation or decrease in VA in Lucentis-treated patients has been found so far. It should also be noted that alternative anti-VEGF treatment options are available in the event of immunogenic reactions occurring with the use of ranibizumab.

5.4 Study Rationale

The prevalence of nAMD in the US and European Union (EU) will increase in the coming years due to an aging population with higher life expectancy, combined with a high incidence of known risk factors including smoking and uncontrolled hypertension [48]. For these reasons, the World Health Organization has identified AMD as a priority eye disease requiring treatment to prevent vision loss in developed countries. The introduction of anti-VEGF therapy has substantially improved the prognosis of the disease, allowing recovery of visual function and preventing vision loss in the vast majority of patients. However, not all patients are able to access approved anti-VEGF therapy. The availability of biosimilar FYB201 could offer an alternative to Lucentis to a broader patient population and improve patient access to anti-VEGF therapy.

The rationale of this study is to demonstrate clinical equivalence in terms of efficacy and safety of FYB201 and the reference product (Lucentis) in the treatment of patients with nAMD. Since the qualitative and quantitative formulation, strength and route of administration of FYB201 is the same as for the reference product, also the dosage regimen and treatment duration is as for Lucentis.

Systemic concentrations of ranibizumab at 24 hours post-first dose (close to C_{max}) and at 24 hours post-sixth dose (close to C_{max}) will be also compared in a subpopulation of patients to show comparable systemic exposure with a resulting similar safety profile.

In order to demonstrate biosimilarity, and after consultation with both the EMA and the FDA the change in BCVA from baseline to Week 8 was chosen as the primary endpoint due to its high sensitivity to detect any potential differences between the two products without the need for de novo proof of patient benefit.

5.5 Potential Risks and Benefits

The Investigational Medicinal Products (IMPs) (FYB201 and Lucentis) and procedures in this study are potentially associated with risks, discomforts, and side effects. The risk to patients in this study will be minimized by compliance with the inclusion/exclusion criteria, compliance with the recommendations found in the Summary of Product Characteristics (SmPC) for Lucentis and close clinical monitoring. Participants receiving an injection of FYB201 or Lucentis may experience some side effects that may be related to the pre-injection preparation procedure or the injection itself. For FYB201 a similar side effect profile to that of the comparator can be assumed which is well characterized and taken from the SmPC.

The majority of adverse reactions reported following administration of Lucentis are related to the IVT injection procedure. The most frequently reported ocular adverse reactions following injection of Lucentis are: eye pain, ocular hyperemia (or an excess of blood in the white of the eyes), increased IOP, inflammation in the vitreous, vitreous detachment, vitreous hemorrhage (abnormal bleeding in the vitreous), visual disturbance, vitreous floaters, conjunctival hemorrhage, eye irritation, foreign body sensation in eyes, increased tear secretion, inflammation of the eyelid, dry eye, and itching in the eye.

The most frequently reported non-ocular adverse reactions are headache, common cold and joint pain. Less frequently reported, but more serious, adverse reactions include inflammation in the cavity of the eye, blindness, retinal detachment, retinal tear and cataract caused by the treatment. Although not common, injections into the eye can cause side effects such as infections (endophthalmitis), retinal detachment (retina separates from the back of the eye), or bleeding.

The occurrence of non-ocular adverse reactions and unexpected AEs or interactions will be carefully monitored.

The expected benefits for patients with nAMD would be an improvement in their condition with ranibizumab treatment, either with the approved reference product Lucentis (considered the “gold standard” in a group of anti-angiogenic drugs) or its biosimilar candidate version FYB201.

6 STUDY OBJECTIVES

6.1 Primary Objective

- Evaluate and compare functional changes in best corrected visual acuity (BCVA) after 2 months (8 weeks) of treatment with FYB201 or Lucentis, compared to baseline BCVA

6.2 Secondary Objectives

The secondary objectives are to:

- Evaluate and compare functional changes of the retina by BCVA over time
- Evaluate and compare changes in foveal center point (FCP) retinal thickness and change in foveal central subfield (FCS) retinal thickness over time
- Evaluate and compare presence of active choroidal neovascularization (CNV) leakage at Months 6 and 12 compared to baseline
- Evaluate and compare the absence of disease activity (fluid-free macula) over time
- Evaluate and compare total lesion size at Months 6 and 12 compared to baseline
- Evaluate and compare systemic ranibizumab concentrations close to C_{max} 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 Months 6 and 12 compared to baseline
- Evaluate and compare the immunogenic profile (ADAs) in serum
- Evaluate and compare local and systemic AEs and SAEs

6.3 Primary Endpoint

- 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 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.

6.4 Secondary Endpoints

Secondary endpoints of the study include:

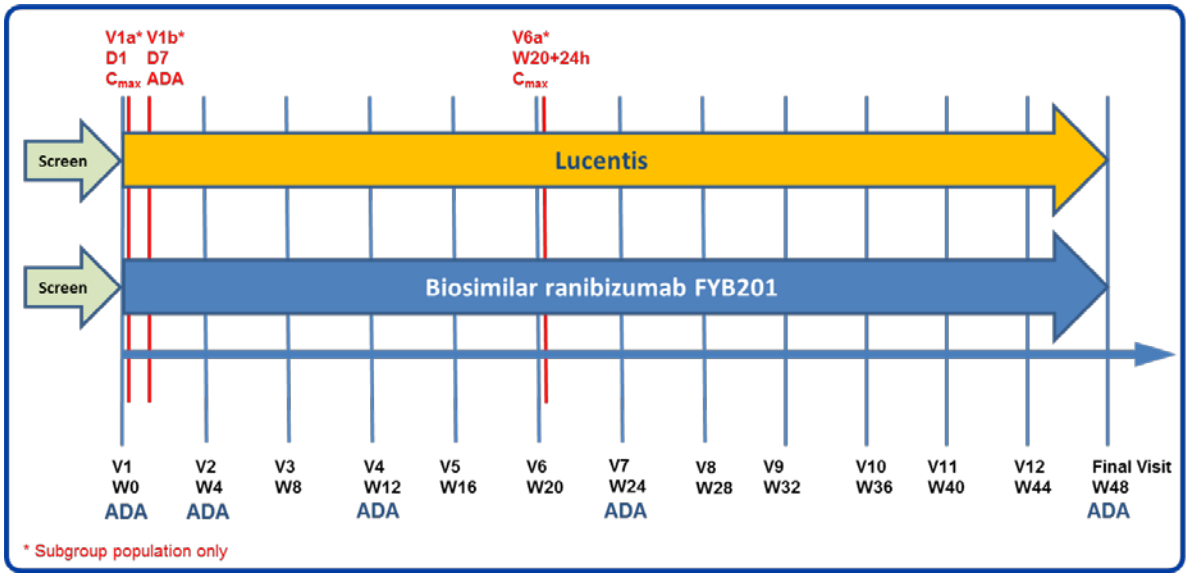
- Change from baseline in BCVA by ETDRS letters over time
- Change from baseline in BCVA by ETDRS letters after 12 months (averaged over Months 10 [Week 40], 11 [Week 44] and 12 [Week 48]
- Changes from baseline in FCP retinal thickness and FCS retinal thickness over time
- Percentage of patients with active CNV leakage at Month 6 and Month 12
- Percentage of patients with fluid-free macula at each visit
- Change from baseline in total lesion area at Month 6 and Month 12
- Systemic ranibizumab concentrations close to C_{max} after the first and the sixth doses (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 and Month 12
- Number of patients with anti-drug antibodies over time
- Frequency of local and systemic AEs and SAEs

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a 12-month, phase III, randomized, active-controlled, evaluation-masked, parallel-group, multicenter study to demonstrate clinical equivalence in terms of clinical pharmacology, efficacy and safety of FYB201 with Lucentis in the treatment of patients with subfoveal nAMD.

Figure 1 Overall Study Design



The study is planned to randomize approximately 460 patients at approximately 80 study centers in Europe, Russia and Israel. Inclusion will be 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].

All patients will receive monthly IVT injections for a period of approximately 12 months (48 weeks).

Before participating in the active treatment phase of the study, patients will undergo an examination for eligibility during the Screening period, which will have a maximum duration of 28 days. As part of the screening process, the central reading center will receive the patient's retinal images in order to provide an independent, masked assessment of patient eligibility regarding FCP, lesion classification, lesion size and area of CNV. Patients must meet all eligibility criteria at the screening visit, including positive evaluation of the screening retinal images performed by the central reading center. After all eligibility requirements are confirmed, patients who are found to be eligible will be randomized into one of the two treatment groups in a 1:1 ratio (FYB201:Lucentis) using an interactive voice response system (IVRS) or interactive web response system (IWRS).

Patients will receive FYB201 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).

This study is designed to be evaluation-masked, neither the patient nor the investigator(s) who perform the evaluations will know which treatment the patient receives.

In each center there will be **at least 2 Masked Staff members** (one of whom will be the Principal Investigator and the other will be the VA Examiner) and **1 Unmasked Injector** (who will administer the IMP). There may 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 may also have a back-up person and/or designated assistant(s), if needed (e.g. pharmacist).

The Principal Investigator (or his/her masked study team to whom tasks have been delegated) will do all pre- and post-injection assessments (Tonometry and Ophthalmologic Examination, SD-OCT, fluorescein angiography [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 will also assess the relationship of all AEs to IMP, including those noted by the Unmasked Injector.

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

Only the Unmasked Injector will perform IVT injections (see Section 10.4). He/she can also perform the post-dose safety check or tonometry, according to the clinical practice of the study site.

Neither patients nor masked study personnel will be given information about the treatment administered (see Section 0).

Retinal images of study visits will be sent to the Central Reading Center (CRC) for grading by trained personnel (and masked to the patient's treatment).

AEs will be recorded from the time that the patient has signed the informed consent form.

An independent Data Safety Monitoring Board (DSMB) will review safety data on a regular basis and ad hoc if needed (see Section 11.6).

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

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

PK SUBGROUP

Systemic ranibizumab concentration close to C_{max} after first and sixth IVT injections, (24 hours post IVT injection), and ADA formation at one day and one week after first IVT injection will be assessed in a subgroup of up to 60 patients at selected sites randomly assigned in a ratio 1:1 to either FYB201 or Lucentis.

Samples obtained pre-first dose, at 24 ± 3 hours after first IVT injection (close to C_{max}) and at 24 ± 3 hours after sixth IVT injection (close to C_{max}) will be used to measure systemic concentration of ranibizumab. Another sample one week after first IVT injection will be used to determine ADAs.

7.2 Study Procedures

7.2.1 Schedule of Study Events

The schedule of all study events is shown in Table 1. All study assessments are described in detail in section 10.

7.2.1.1 Visit 0 (Screening Visit)

Before their participation in the study patients will be informed both verbally and in writing about the purpose of the study, its procedures and any risks or discomforts involved with participation. Informed consent will be obtained for the patient before any study specific procedures can take place. Only those patients who fulfil all eligibility criteria will be entered into the study.

However, if a routine procedure (e.g. FA, SD-OCT) is performed to diagnose AMD independent of this clinical study, and subsequently the patient provides informed consent for this study, procedures performed prior to informed consent may be used as Screening assessments for this study, provided the 28-day period of Screening evaluations is respected. In addition, the assessments must meet the standards defined in this protocol and SD-OCT images must be obtained by [redacted] certified SD-OCT operators and evaluated by the CRC.

At Visit 0 (Screening Visit), the following activities and assessments will be performed within 28 days prior to Visit 1:

- Informed consent
- Verification of inclusion and exclusion criteria
- Demographic information
- Height and weight
- Medical history and ophthalmological history (both eyes [OU])
- Prior ocular treatments and prior non-ocular treatments within six months previous to signature of informed consent
- Vital signs **(before any blood sample collection, if done the same day)**
- Physical assessment
- Protocol refraction and BCVA (4 meters, then 1 meter if applicable) using ETDRS chart (OU) **(before ophthalmological examination, FA, color fundus photography and SD-OCT, if done the same day)**
- Ophthalmologic examination (slit lamp and indirect ophthalmoscope) and Goldmann applanation tonometry (OU)
- FA (OU)
- Color fundus photographs (OU)
- SD-OCT (OU)
- Laboratory tests (biochemistry, hematology, coagulation)
- Pregnancy test, serum human chorionic gonadotropin (HCG) (female patients only)
- AEs recorded from the day the informed consent was signed

Images obtained with FA, color fundus photographs and SD-OCT will be transferred to the CRC (according to the manual) in a timely manner. Patients can only be randomized after the CRC has confirmed that the patient fulfills all the corresponding selection criteria (see Sections 8.2.2 and 8.2.3).

7.2.1.2 Visit 1 / Baseline (Day 0)

To remain eligible for randomization at Visit 1 (Day 0), the following three criteria must be met:

1) There is **no significant anatomical change** in the study eye following ophthalmological and SD-OCT examination between the Screening visit and Visit 1 (i.e. large subretinal hemorrhage, retinal pigment epithelial (RPE) tear, pigment epithelial detachment).
2) Visual acuity in the study eye is **within the defined inclusion criteria range** (using ETDRS testing Snellen equivalent 20/32 [0.63] to 20/100 [0.2]) and **within 5 letters** (better or worse) of the Screening VA. Thus:
    - If difference in BCVA is greater than 5 ETDRS letters (better or worse) between Screening and Visit 1, the patient must NOT be randomized.
    - If the Snellen equivalent at Visit 1 is no longer within the inclusion criteria (Snellen equivalent 20/32 to 20/100), the patient must NOT be randomized.
3) No diagnosis and/or signs of nAMD requiring immediate treatment with an IVT anti-VEGF agent in the fellow eye (e.g. aflibercept, bevacizumab, ranibizumab)

After completing the Screening period and being confirmed eligible for participation in the study by the CRC and the Masked Investigator, patients will be centrally randomized, using the screening BCVA value, via IVRS/IWRS into one of two study groups in 1:1 ratio (FYB201:Lucentis).

At Visit 1, the following activities and assessments will be performed:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection

- Protocol refraction and visual acuity (4 meters, then 1 meter if applicable) using ETDRS chart (study eye [SE]) **(before ophthalmological examination and SD-OCT)**
- NEI VFQ-25 **(before any invasive procedure)**
- Tonometry and complete ophthalmologic examination (SE)
- SD-OCT (SE)
- Randomization
- Blood sampling for ADAs
- Blood sampling for systemic ranibizumab baseline concentration (Subgroup only)

IVT-injection

- Biosimilar ranibizumab FYB201 or Lucentis administration by Unmasked Injector

Post-IVT injection

- Safety check just after the injection (SE) for all patients
- Tonometry: at least 30 minutes after the injection (SE) for all patients
- Basic ophthalmologic examination: at least 30 minutes after the injection, if required

7.2.1.3 Visit 1a (Day 1) (24±3 hours) (Subgroup only)

- Blood sampling for ranibizumab concentration (C_{max})
- AEs
- Concomitant medications

7.2.1.4 Telephone Safety Call (3-Days Post-Visit 1) (±1 day)

A telephone call will be made at Day 3 by study center staff to the patient for an AE assessment to determine if there are any signs or symptoms of retinal detachment or endophthalmitis. Should a potential AE be suspected, the Masked Investigator or delegated staff member will be responsible for further patient assessments (either by phone or in person).

7.2.1.5 Visit 1b (Day 7) (±1 day) (Subgroup only)

- Blood sampling for ADAs
- AEs
- Concomitant medications

7.2.1.6 Visit 2 (Week 4) and Visit 4 (Week 12) (±3 days)

The following activities and assessments will be performed:

<u>During the visit:</u>

- Concomitant medications
- AEs

<u>Pre-IVT injection</u>

- Protocol refraction and VA (4 meters, then 1 meter if applicable) using ETDRS chart (SE) **<u>(before ophthalmological examination and SD-OCT)</u>**
- Tonometry and complete ophthalmologic examination (SE)
- SD-OCT (SE)
- Blood sampling for ADAs

<u>IVT-injection</u>

- Biosimilar ranibizumab FYB201 or Lucentis administration by Unmasked Injector

<u>Post-IVT injection</u>

- Safety check just after the injection (SE) for all patients
- Tonometry: at least 30 minutes after the injection (SE) for all patients
- Basic ophthalmologic examination: at least 30 minutes after the injection, if required

7.2.1.7 Telephone Safety Calls (3-Days Post-Visits 2 and 4) (±1 day)

A telephone call will be made 3-Days post each injection at Visits 2 and 4 by study center staff to the patient for an AE assessment to determine if there are any signs or symptoms of retinal detachment or endophthalmitis. Should a potential AE be suspected, the Masked Investigator or delegated staff member will be responsible for further patient assessments (either by phone or in person).

7.2.1.8 Visit 3 (Week 8), Visit 5 (Week 16), Visit 6 (Week 20), Visit 8 (Week 28), Visit 9 (Week 32), Visit 10 (Week 36), Visit 11 (Week 40) and Visit 12 (Week 44) (±3 days)

The following activities and assessments will be performed in each visit:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection

- Protocol refraction and VA (4 meters, then 1 meter if applicable) using ETDRS chart (SE) **(before ophthalmological examination and SD-OCT)**
- Tonometry and complete ophthalmologic examination (SE)
- SD-OCT (SE)

IVT-injection

- Biosimilar ranibizumab FYB201 or Lucentis administration by Unmasked Injector

Post-IVT injection

- Safety check just after the injection (SE) for all patients
- Tonometry: at least 30 minutes after the injection (SE) for all patients
- Basic ophthalmologic examination: at least 30 minutes after the injection, if required

7.2.1.9 Telephone Safety Calls (3-Days Post-Visits 3, 5, 6, 8, 9, 10, 11 and 12) (±1 day)

A telephone call will be made 3-Days post each injection at Visits 3, 5, 6, 8, 9, 10, 11 and 12 by study center staff to the patient for an AE assessment to determine if there are any signs or symptoms of retinal detachment or endophthalmitis. Should a potential AE be suspected, the Masked Investigator or delegated staff member will be responsible for further patient assessments (either by phone or in person).

7.2.1.10 Visit 6a (24-Hours Post-Visit 6) (±3 hours) (Subgroup only)

- Blood sampling for ranibizumab concentration (C_{max})
- AEs
- Concomitant medications

7.2.1.11 Visit 7 (Week 24) (±3 days)

The following activities and assessments will be performed:

During the visit:

- Concomitant medications
- AEs

Pre-IVT injection

- Protocol refraction and VA (4 meters, then 1 meter if applicable) using ETDRS chart (SE) **(before ophthalmological examination, FA, color fundus photography and SD-OCT)**
- NEI VFQ-25 **(before any invasive procedure)**
- Vital signs **(before any blood sample collection)** / physical assessment
- Tonometry and complete ophthalmologic examination (SE)
- FA (SE)

- Color fundus photographs (SE)
- SD-OCT (SE)
- Laboratory tests (biochemistry, hematology)
- Blood sampling for ADAs

IVT-injection

- Biosimilar ranibizumab FYB201 or Lucentis administration by Unmasked Injector

Post-IVT injection

- Safety check just after the injection (SE) for all patients
- Tonometry: at least 30 minutes after the injection (SE) for all patients
- Basic ophthalmologic examination: at least 30 minutes after the injection, if required

7.2.1.12 Telephone Safety Call (3-Days Post-Visit 7) (±1 day)

A telephone call will be made by study center staff to the patient for an AE assessment to determine if there are any signs or symptoms of retinal detachment or endophthalmitis. Should a potential AE be suspected, the Masked Investigator or delegated staff member will be responsible for further patient assessments (either by phone or in person).

7.2.1.13 Final Visit (Week 48) (±3 days)

The Final Visit will be performed four weeks (±3 days) after the last injection at Visit 12 (Week 44). For patients who prematurely terminate the study, the Masked Investigator should attempt to complete the assessments of the Final Visit at the moment of early termination.

The following activities and assessments will be performed during the visit:

- Protocol refraction and VA (4 meters, then 1 meter if applicable) using ETDRS chart (OU) **(before ophthalmological examination, FA, color fundus photography and SD-OCT)**
- NEI VFQ-25 **(before any invasive procedure)**
- Vital signs **(before any blood sample collection)** / physical assessment
- Tonometry and complete ophthalmologic examination (OU)
- FA (OU)
- Color fundus photographs (OU)
- SD-OCT (OU)
- Laboratory tests (biochemistry, hematology)
- Blood sampling for ADAs
- Concomitant medications
- AEs

Any AE that is ongoing at the Final Visit or when the patient is withdrawn from the study should be followed up until the AE is resolved or the Masked Investigator, or delegated staff member, decides that the AE is stable and needs no further follow-up. The date when the Masked Investigator or delegated staff member considers that one of these outcomes has occurred will be considered the last visit for that patient and the last status (resolution or stable situation) should be recorded in the electronic Case Report Form (eCRF).

7.2.1.14 Unscheduled visits

Unscheduled visits may be performed for safety follow-up. Any observed AEs have to be recorded accordingly, including eCRF documentation.

7.2.2 Schedule of Study Events

The schedule of study events is shown in Table 1 in Section 1.

7.3 Discussion of Study Design

This study was designed in accordance with the current EMA and FDA guidelines for biosimilars and the choice of the primary objective was made after consultation with both EMA and FDA.

Justification of comparator (US-licensed Lucentis)

Analytical characterization of FYB201 has demonstrated that it is identical to Lucentis with respect to amino acid sequence and highly similar in protein structure. In addition, qualitative and quantitative formulation, strength, route of administration, posology and storage conditions of FYB201 are the same as for the reference product. In vitro pharmacology assays and quality data of FYB201 have demonstrated sufficient evidence of similarity between the biosimilar and the reference product. [redacted]

Justification of primary study objective

[redacted] the relevant primary study endpoint will be the change in BCVA after 2 months. This is due to the fact that an early 2-month time point minimizes the potential impact of confounding factors later in the study. In addition, the time point is in the ascending part of the BCVA time-response curve, which will allow the sensitive detection of potential clinically relevant differences on visual function between the biosimilar candidate and the approved reference product.

7.4 Study Period

The expected start of recruitment is Q4 2015 and the planned LPLV (Final visit) is Q2 2018.

7.5 End of Study

The end of study is defined as the date of the LPLV (Final visit).

8 SELECTION OF STUDY POPULATION

8.1 Number of Patients

This study will be conducted in Europe, Russia and Israel, approximately 10-14 countries, at approximately 80 study centers. It is anticipated that a total of approximately 460 patients will be randomized into the study. Inclusion will be 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]. For details regarding sample size calculation see Section 12.3.

At Screening, a unique number will be given to identify the country, the study center, and the patient, as described in the randomization procedure in Section 9.2.

8.2 Inclusion Criteria

The patients have to meet all of the following criteria to be eligible to enter the study:

General

1. Age ≥ 50 years of either gender
2. Signed informed consent form must be obtained before any study related procedure is performed
3. Willingness and ability to undertake all scheduled visits and assessments
4. Women must be 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 wet AMD CNV lesions are eligible (classic, occult, some classical component, retinal angiomatous proliferation lesions). Active primary CNV must be subfoveal or juxtafoveal with subfoveal component related to CNV activity (such as sub- or intraretinal fluid by SD-OCT or RPE detachment)
    b. Total area of whole lesion must be equal or less than 12 disc areas
    c. Total CNV area encompasses equal or more than 50% of total lesion area based on FA, including all subtypes of wet AMD

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 standardized ETDRS testing, between 20/32 (0.63) and 20/100 (0.2) Snellen equivalent

8. FCP retinal thickness at Screening ≥ 350 µm. (FCP thickness is defined as the distance between the vitreoretinal interface and Bruch's membrane at the geometric center of the fovea)

Ocular (Fellow Eye)

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

8.3 Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the study:

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 are legally institutionalized

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

Current ocular conditions

11. Retinal pigment epithelial tear involving the macula in the study eye
12. History of full-thickness macular hole (stage 2 and above by clinical examination or full thickness macular hole by SD-OCT imaging of any size) in the study eye
13. History of retinal detachment in the study eye
14. Current vitreous hemorrhage in the study eye
15. Spherical equivalent of the refractive error in the study eye demonstrating more than 8 diopters of myopia
16. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye cannot 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 is 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 *a*ctive 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 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 may confound interpretation of study results and compromise 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 require surgical intervention during the study to prevent or treat visual loss that might result 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 is 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 may bias 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.

8.4 Withholding Study Treatment

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

- A decrease in best-corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity
- An intraocular pressure of ≥30 mmHg
- A retinal break
- A subretinal hemorrhage involving the center of the fovea, or, if the size of the hemorrhage 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 will require withdrawal from the study, see Section 8.5)

The Masked investigator finally decides on withholding an IVT injection or withdrawing a patient from the study on a case by case basis.

8.5 Removal of Patients from Therapy or Assessment

Patients are free to discontinue their participation in the study at any time. Withdrawal from the study will not affect or prejudice the patient's further care or treatment. Patients may be withdrawn from study treatment and assessments at any time, if deemed necessary by the Masked Investigator or Sponsor.

Potential reasons for withdrawal of patients from this study are:

- The decision of a patient to withdraw from the study (including if the patient withdraws informed consent)
- Administration of concomitant medication prohibited by this protocol
- Cataract surgery in the study-eye
- Concurrent illness
- AEs
- Major protocol deviations
- Need of alternative treatment
- Pregnancy
- Patient is lost to follow-up

The reason and date the patient is withdrawn from the study will be documented in the eCRF (e.g. lost to follow-up, consent withdrawn, incorrect enrolment, AEs, lack of efficacy, etc.). If a patient is withdrawn from further treatment with the IMP, the Masked Investigator should attempt to complete the final study assessments as outlined in the Section 7.2.1. Patients who withdraw due to an AE should be followed until resolution of the AE, or the Masked Investigator or delegated staff member decides that the AE is stable and needs no further follow-up. All AEs should be followed up according to Section 11.2.

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

8.6 Premature Termination of the Study

The Sponsor may terminate this study prematurely for any reasonable cause. The Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) and Competent Authority(ies) (CAs) should be informed in accordance with applicable regulations.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study, or potential study patients
- A decision on the part of the Sponsor to suspend or discontinue development of FYB201

If the study is prematurely terminated or suspended for any reason, the Masked Investigator/institution should promptly inform the study patients and should ensure appropriate therapy and follow-up for the patients. The Masked Investigator should also attempt to complete the final study assessments as outlined in the Section 7.2.1. Patients with an ongoing AE should be followed until resolution of the AE, or the Masked Investigator or delegated staff member decides that the AE is stable and needs no further follow-up. All AEs should be followed up according to Section 11.2.

9 TREATMENT OF PATIENTS

9.1 Investigational Medicinal Products

The Investigational Medicinal Products (IMPs) are FYB201 and Lucentis.

The term experimental product refers to the biosimilar FYB201 (biosimilar ranibizumab).

The term comparator refers to the reference product Lucentis (ranibizumab)

9.1.1 Treatment Regimens

Patients will receive FYB201 or Lucentis at a dose 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).

9.1.2 Identity of Experimental Product

Biosimilar ranibizumab FYB201:

- INN name: Ranibizumab
- Biosimilar ranibizumab FYB201 10 mg/mL solution for IVT injection
- One mL contains 10 mg ranibizumab
- Each single-use glass vial is designed to provide 0.05 mL for IVT injection
- List of excipients: α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injection
- Pharmaceutical form: solution for injection (IVT); clear, colorless to pale yellow aqueous solution

9.1.3 Identity of Comparator

US licensed Lucentis:

- INN name: Ranibizumab
- Lucentis: 10 mg/mL solution for IVT injection
- One mL contains 10 mg ranibizumab
- Each single-use glass vial is designed to provide 0.05 mL for IVT injection
- List of excipients: α,α-trehalose dihydrate; histidine hydrochloride, monohydrate; histidine; polysorbate 20; water for injection
- Pharmaceutical form: solution for injection (IVT); clear, colorless to pale yellow aqueous solution

9.1.4 Packaging and Labelling

Packaging and labelling of IMP will comply with Annex 13 of the European Union Good Manufacturing Practice (GMP) regulations and local regulatory requirements.
The comparator Lucentis will be the US licensed product, which will be imported into the EU by [redacted] Then, it will be unlabeled and re-labelled with a label similar to that of the experimental product (FYB201) (booklet label on vial). Primary and secondary packaging will be similar.

Primary packaging:

Biosimilar ranibizumab FYB201 and Lucentis will be supplied as solution for IVT injection in single-use glass vials (type I glass). The vials are tightly closed with rubber stoppers and sealed with a crimp containing a flip-off cap.

Secondary packaging:

Biosimilar ranibizumab FYB201 and Lucentis will be packed in a cardboard box containing 1 vial inside. The cardboard box will carry a tear off label, which will be used for drug accountability.
The medical devices needed for preparation and administration by IVT (a 5 µm filter needle (18G x 1½″, 1.2 x 40 mm), a 1 mL sterile syringe and an injection needle (30G x ½″, 0.3 mm x 13 mm)) will be provided with the pack.

9.1.5 Storage and Handling of Experimental Product and Comparator

Detailed instructions for storage and handling will be provided within a separate Study Drug Manual (IMP Handling Manual).

The Principal Investigator, or designated representative (e.g. pharmacist), will ensure that all IMP is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Store biosimilar ranibizumab FYB201 and Lucentis under standard refrigeration conditions (2-8°C; 36-46°F); do not freeze. All vials should be protected from light and stored in the IMP clinical kit, as provided, until the time of use. Vials should be removed from refrigerated storage before use. During storage of IMP the vial should be stored in upright position.

9.2 Method of Assigning Patients to Treatment Groups

At Screening the study center will register each patient within the IVRS or IWRS and provide information about his/her eligibility for participation in the study and, if applicable, in the Subgroup.

The IVRS or IWRS will inform the center about the assigned patient number. Patient numbers will consist of 8 digits, for example; 01-001-001, where the first 2 digits identify the country, the 3rd to 5th digits identify the study center and the last 3 digits identify the patient (Country-study center-Patient). This number will be used as the patient identifier in the study. Patients from the Subgroup will follow the same numbering system as the overall group.

Once assigned to a patient, the patient number will neither be replaced nor used a second time.

At Visit 1, once the patient has completed the Screening procedures and eligibility has been reconfirmed (no significant anatomical change and visual acuity within the defined inclusion criteria range and within 5 letters of the Screening VA), the patient will be randomized using the IVRS or IWRS. Randomization will be 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 will be allocated to one of the two treatment groups in a ratio 1:1. Once a maximum of 48 patients with a screening BCVA of 20/32 (0.63) are enrolled, randomization to this stratum will be stopped. The IVRS or IWRS will specify a unique medication number which will correspond to the package number of IMP that will be dispensed to the patient. Only the unmasked personnel who will open the IMP package might be able to distinguish between FYB201 and Lucentis.

At Visits 2-12, the study personnel (either masked or unmasked) will contact the IVRS or IWRS to obtain the medication number which will correspond to the number on the IMP package to be dispensed to the patient. Medication numbers will be different for each IMP package.

9.3 Selection of Dose

The IVT dose of 0.5 mg ranibizumab/eye has a well-established efficacy and safety profile in patients suffering from retinal diseases as demonstrated by the originator Lucentis. As FYB201 is being assessed for biosimilarity to Lucentis the approved dose of 0.5 mg ranibizumab/eye was chosen for this study.

9.4 Administration of IMP

Biosimilar ranibizumab FYB201 and Lucentis must be administered by a qualified ophthalmologist/site staff experienced in IVT injections (Unmasked Injector), and who must not be the Masked Investigator/s. For full details on preparation see Appendix E.

The vial, injection needle, filter needle and syringe are for single use only and must not be re-used. Re-use may lead to infection or other illness/injury. All components are sterile. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact.

For preparation and IVT injection the following medical devices for single use are needed (provided within the IMP kit):

- a 5 µm filter needle (18G x 1½″, 1.2 x 40 mm, 5 µm)
- a 1 mL sterile syringe
- an injection needle (30G x ½″, 0.3 mm x 13 mm)

The method for IVT administration of biosimilar ranibizumab FYB201 or Lucentis is described in detail in Appendix E.

The Unmasked Injector will perform the FYB201 or Lucentis injections (see Section 10.4). He/she can also perform the post-dose tonometry, according to the clinical practice of the study site. Before the Unmasked Injector or Unmasked Assistant breaks the seal on the cardboard box of the masked drug kit, the masked staff must leave the room. Only unmasked clinical staff will remain in the injection room until the injection has been given and the drug kit and components (i.e. the empty vial, the colored flip-off cap, the syringe and the needles) have been disposed of by the Unmasked Injector/unmasked assistant; only the empty drug kit box and the tear-off part of the box label are saved. The empty vial and the flip-off cap should be disposed of immediately while ensuring that no masked staff are within visible range of the disposal.

9.5 Masking

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

In each center there will be **at least 2 Masked Staff members** (one of whom will be the Principal Investigator and the other will be the VA Examiner) and **1 Unmasked Injector** (who will administer the IMP). There may 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 may also have a back-up person and/or designated assistant(s).

The Principal Investigator (or his/her masked study team to whom tasks have been delegated) will do 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 will also assess the relationship of all AEs to IMP, including those noted by the Unmasked Injector.

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

Only the Unmasked Injector will perform IVT injections (see Section 10.4). He/she can also perform the safety check or post-dose tonometry, according to the clinical practice of the study site.

Measures will be taken to ensure that neither the patient nor the masked study personnel will become aware of the treatment administered. Site staff will monitor the receipt, storage, dispensing, and accounting of all IMPs. FYB201 and Lucentis will have the same secondary packaging, and will be indistinguishable. The unmasked clinic staff will not discuss the treatment administered with the masked staff.

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 may decide to unmask a patient's treatment, if it is judged to be essential for the clinical management or welfare of the patient.

Emergency unmasking is performed using the IVRS or IWRS. The Masked Investigator or the Unmasked Injector must contact the system and provide the patient number and the IMP kit number. The person contacting the IVRS or IWRS for unmasking will then receive details of the drug treatment for the specified kit number and a fax or email confirming this information. The system will automatically inform the monitor, the Sponsor and the medical monitor that the masking has been broken without revealing the treatment arm.

The person contacting the IVRS or IWRS for unmasking must also record the date and reason for unmasking the kit in the eCRF.

If a report requires expedited regulatory reporting to a CA, the report will identify the patient's treatment assignment. When this is the case, the unmasking will be performed by [redacted] Drug Safety. Patients, study center staff, the Masked Investigator/s, the masked [redacted] personnel and the Sponsor will not be informed of the treatment assignment. Hence, the patient will not be considered unmasked with regard to statistical analysis. When applicable, a masked copy of the regulatory report may be sent to the Masked Investigator in accordance with relevant regulations.

9.6 Prior and Concomitant Therapy

9.6.1 Prior Therapy and Treatment

Prior vitrectomy, macular surgery or other surgical intervention for AMD in the study eye is not permitted. Any other intraocular surgery (including cataract surgery) within three months prior to Screening is not allowed.

Prior treatment with anti-VEGF agents in either eye as e.g. bevacizumab, aflibercept, ranibizumab is not allowed.

Intravitreal or periocular injections of corticosteroids or device implantation in the study eye within six months prior to Screening are not permitted.

Topical ocular corticosteroids administered for at least 30 consecutive days within three months prior to Screening are not permitted.

Prior treatment with verteporfin (PDT), transpupillary thermotherapy, radiation therapy, or retinal laser treatment (e.g. focal laser photocoagulation) in the study eye is not allowed.

Any treatment with any investigational drug within 30 days or 5 half-lives prior to Screening, whichever is longer is not permitted.

Current treatment at inclusion for active systemic infection is also not allowed.

Systemic treatment with high doses of corticosteroids (administration of >10 mg/day of prednisolone equivalent) or any intraocular treatment with long acting steroids during the last six months prior to Screening is not permitted.

Prior ocular treatments and prior non-ocular treatments within six months previous to signature of informed consent must be recorded in the appropriate sections of the eCRF.

9.6.2 Concomitant Therapy and Treatments

The Masked Investigator should instruct the patient to report any new medication taken after the study has begun.

All medications (other than the IMP) and significant non-pharmacological therapies (including physiotherapy and blood transfusions) administered after the patient starts treatment with the IMP, must be recorded in the eCRF in the concomitant medication/non-pharmacological therapies section.

Patients who need anti-VEGF treatment for AMD in the fellow eye during the course of the study must be treated with commercially available Lucentis (Lucentis is prohibited in the fellow eye until V1 [included]). Patients in the PK substudy should not receive fellow eye treatment within 7 days prior to Visit 6 and not until after the PK blood sample at Visit 6a has been taken.

If a treatment is given due to an AE, proper cross-reference to the corresponding AE section of the eCRF must be created.

<u>Prohibited medications</u>

Ranibizumab is not to be administered concurrently with any other anti-VEGF agent (systemic or ocular) [except for commercially available Lucentis in the fellow eye after V1].

Intravitreal or periocular injections of corticosteroids or high doses of systemic (oral or IV) corticosteroids (administration of >10 mg/day of prednisolone equivalent), are not allowed.

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 are not allowed.

The use of prohibited medications may interfere with the assessment of safety, tolerability and/or efficacy of the IMP and may lead to premature discontinuation / withdrawal of the patient.

If a patient takes any prohibited medication this must be reported to the Sponsor/DSMB for a decision on whether the patient should continue further study participation.

Medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Masked Investigator or the Unmasked Injector (only during the injection procedure).

However, prohibited medication administered during the study may lead to withdrawal of the patient from the study (see Section 8.5).

The use of all medication by the patient must be recorded in the appropriate sections of the eCRF.

9.7 Treatment Compliance

Each injection will be administered at the study center and documented in medical notes, eCRF, and drug accountability log.

9.8 Drug Accountability

IMP (Biosimilar ranibizumab FYB201 and Lucentis) will be supplied by the Sponsor. It is the responsibility of the Principal Investigator and the delegated study team to supervise accurate monitoring of the receipt, storage, dispensing, and accounting of all IMPs according to accepted medical and pharmaceutical practice.

The Site staff must confirm the receipt/shipment of IMP using the IVRS/IWRS and must report the condition of the kits upon delivery. In addition, a temperature evaluation after transport will be performed to indicate kits are ready for use. Damaged kits should be quarantined and not allocated to patients; only kits that are fine to use can be allocated to patients.

Copies of all IMP delivery notes must be retained. Accurate, original study center records of IMP inventory and dispensing must be maintained e.g. by using the forms provided. All shipment, accountability, and dispensing records must be made available for inspection by the Sponsor or the designated Contract Research Organization (CRO) upon request.

Each study center must keep all used empty flattened kit packages and tear-off labels and unused original kit packages until the unmasked Study Monitor has performed Drug Accountability. If any unused kits remain at the end of the study, they will be accounted for at the study center Close-Out Visit in the presence of the Study Monitor, who will provide instructions on their return or disposal. If the Study Monitor directs the study center to dispose of IMP or empty kits, disposal should be according to the institution’s standard operating procedures and all applicable local and national regulations. Documentation of disposal has to be filed in the study documentation.

10 STUDY ASSESSMENTS

The following assessments will be performed during the study.

10.1 Optical Coherence Tomography

Morphologic changes of retina FCP with FYB201 and Lucentis treatment will be evaluated by SD-OCT. OCT will be performed at all visits as shown in Table 1 and described in Section 7.2.1.

A Heidelberg Spectralis® OCT scanner must be used for OCT.

The CRC will provide a separate manual to the study center with instructions for the OCT procedures, including specification of the OCT raw data to be sent to the CRC.

Prior to any evaluation of patients (including screening), SD-OCT operators and systems will be certified by the CRC as specified in the reading center manual.

All images should be transferred to the CRC (according to the manual) within 72 hours. Prior to randomization of a patient the screening image needs to be evaluated by the CRC and eligibility confirmed.

All the FCP retinal thickness images will be evaluated centrally by trained personnel of the CRC [redacted] who will be masked to the patient's treatment. Two independent readers will perform grading; in case of discrepancy (cut off 25 µm) a third reader will be consulted for arbitration.

The FCP retinal thickness will be defined as the retinal thickness in the very center of the fovea as determined on the single central B scan according to standard definitions as follows:

- Upper boundary: Vitreoretinal Interface (internal limiting membrane)
- Lower boundary: Lower border of band 4 (Bruch's membrane)

10.2 Procedures for Refraction and Best Corrected Visual Acuity Testing

Functional changes of the retina after monthly treatment with FYB201 or Lucentis will be assessed by determining BCVA using ETDRS charts at the visits shown in Table 1 and described in Section 7.2.1.

In each visit, BCVA will be assessed **prior to any other visual examination that requires eye drops (i.e. ophthalmological examination, FA, color fundus photography and SD-OCT)**.

BCVA refers to VA in the study eye based on scores obtained using Retroilluminated Ferris-Bailey ETDRS VA charts and assessed at a starting test distance of 4 meters, then repeated at a test distance of 1 meter if necessary (see Appendix C).

The format of the ETDRS chart is an anti-glare white high impact polystyrene piece measuring 64.8 cm wide by 62.2 cm high containing 5 letters on each line, with logarithmic proportional spacing between letters on the rows and between the rows themselves. The letters on each line are 25% larger than those on the following line. In general, the patient should read from the first row down until they reach a line that makes it difficult to read a minimum of 3 letters. The results are obtained on a logarithmic scale, which has its equivalent on the Snellen chart and in meters. For example, a VA of 1.0 is equivalent to 20/20, 6/6, or, in everyday language, 100% vision. They can be also expressed as the sum of ETDRS letters that the patient is able to read (VA score).

Standard ETDRS charts will be used in all countries except Russia and the Ukraine. In Russia and the Ukraine, the validated modified ETDRS European-wide charts will be used [49]. In these modified ETDRS charts, the Roman letters C, D, N, R, S, V and Z (contained in the standard ETDRS chart) are substituted with E, P, X, B, T, M and A (common to Latin, Greek and Cyrillic), respectively.

Visual acuity is defined as the total number of letters that the patient can correctly identify on the ETDRS charts. VA score (ETDRS letters) will be computed by the VA Examiner and recorded on the Visual Acuity Worksheets provided to the sites.

Refraction and BCVA measurements will be performed only by certified VA Examiners masked to the patient's treatment assignment as well as the patient's previous BCVA results. VA Examiners will not be permitted to have any further roles in obtaining data from a patient; however, they may perform additional study support tasks such as e.g. read-out of the temperature logger.

The study center's staff performing the VA assessments will be certified prior to study start by VA certifiers. A Study Operations manual for performing VA examinations and a BCVA worksheet to calculate overall BCVA score will be provided to each study center.

10.3 Tonometry

Tonometry will be performed at visits as shown in Table 1 and described in Section 7.2.1. All tonometry at IVT injection visits should be performed shortly before the IVT injection and at least 30 minutes after IVT injection. For the post-injection tonometry, proper care should be taken to minimize the risk of contamination.

Pre-dose IOP in the study eye will be assessed by the Masked Investigator/s or trained technician at every scheduled visit (except at Visits 1a, 1b and 6a of the Subgroup). Post-dose IOP will be assessed either by the Unmasked Injector or by the Masked Investigator/s or trained technician after injection in the study eye. The values will be recorded in mmHg and will be entered into the eCRF. The IOP of both eyes will be measured at Screening and Final Visit.

Goldmann applanation tonometry must be performed at Screening. The Tonopen or Perkins Tonometer may be used at other times; however, Goldmann applanation tonometry must be used to verify any IOP ≥30mm Hg.

In the event that there is a non-transient increase in IOP ≥30 mmHg in the study eye, at any time during the study period, the Masked Investigator/s should treat and closely monitor the IOP until it is reduced to baseline values. In this case, the IVT procedure is not recommended unless normalization of the IOP has been achieved. The Masked Investigator/s should treat the increased IOP if the patient is to be continued in the study.
In addition, at the discretion of the Masked Investigator and/or according to the local requirements/practices, monitoring of optic nerve head perfusion may be appropriate within 30 minutes after injection. Results of these procedures will be recorded in the source documents. Only if the findings constitute an AE they have to be recorded in the eCRF.

10.4 Ophthalmologic Examination

The following examinations will be performed by one of the Masked Investigators **before the IVT injection (comprising a complete exam)** at visits as shown in Table 1 and described in Section 7.2.1.

- Inspection of the eyelids and conjunctiva
- Inspection of the cornea
- Examination of the anterior chamber for inflammation (Appendix A)
- Examination of the pupils
- Examination of the iris
- Inspection of the lens (cataract grading: WHO cataract grading system [50])
- Inspection of the vitreous body (Appendix B)
- Inspection of the retina and optic disc

The following examinations will be performed **after the IVT injection** at visits as shown in Table 1 and described in Section 7.2.1.:

Safety check (just after the injection)

- Examination of vision with hand movement or counting fingers
- If there is no perception of hand movements or finger counting, an ophthalmoscopy should be performed to confirm that the central retinal artery is perfused and to assess any complications. If there is an absence of perfusion of the central retinal artery (that would be due to extensive IOP elevation following the IMP injection), immediate measures must be taken to lower IOP

After at least 30 minutes

- Tonometry

- If the central retinal artery was not adequately perfused, or if there was reduced vision at the safety check just after the IMP injection, a basic ophthalmological examination (performed by one of the Masked Investigators) should be performed to verify the status of the central retinal artery

10.5 Fundus Photography and Fluorescein Angiography

Color fundus photographs and FA will be performed by one of the Masked Investigators, or a trained technician, at visits as shown in Table 1 and described in Section 7.2.1. All color fundus photographs and FA images that are collected at protocol-specified times must be sent to the CRC for central evaluation. The CRC will provide instructions for color fundus photography and FA procedures. Color fundus photography and FA systems must undergo certification by the CRC before any evaluation of study patients (including screening). Please note that any not-study related indocyanine green angiography should not be performed simultaneously to FA as it may have an impact on the quality of the results for FA.

10.6 Visual Function Questionnaire-25

The NEI VFQ-25 is a 25-question quality of life questionnaire created by the National Eye Institute to measure the influence of visual disability on general health and functioning. The NEI VFQ-25 will be administered by one of the Masked Investigators or Site staff members, in local language versions. The questionnaire will be completed at visits as shown in Table 1 and described in Section 7.2.1.

The NEI VFQ-25 is a widely used and extensively studied instrument to measure vision-targeted health-related quality of life among patients with chronic eye conditions. The questionnaire assesses the influence of visual disability and visual symptoms on general health domains such as emotional well-being and social functioning, in addition to task oriented domains related to daily visual functioning.

The NEI VFQ-25 consists of 25 items combined into 11 subscales: general vision, ocular pain, near activities, distance activities, driving, color vision, peripheral vision and vision-specific social functioning, mental health, role difficulties and dependency. A single-item general health rating also is included (26th item) (see Appendix D).

Given the visual impairment of patients, the questionnaire will be interviewer–administered to patients. Interviewers will require approximately 10 minutes for completing this form. Each item of the NEI VFQ-25 is converted into a 0-100 scale; thus, the lowest and highest possible scores are set at 0 and 100 points. Higher scores represent better functioning, and scores decrease with worsening VA.

Efforts should be made to ensure complete and accurate completion of the questionnaire before the study treatment is applied. It is also recommended that this assessment be performed before any invasive procedure (i.e. blood sampling, SD-OCT, FA, color fundus photography). The patient shouldn't be accompanied by a family member/friend during the interview.

10.7 Pharmacokinetic Assessments

A blood sample will be collected in a subgroup of patients at selected clinical study centers at visits as shown in Table 1 and described in Section 7.2.1 (Subgroup) to assess systemic ranibizumab concentrations pre-first dose, at 24 hours (±3 hours) post-first dose (close to C_{max}), and at 24 hours (±3 hours) post-sixth dose (close to C_{max}).

Instructions regarding the preparation, handling and shipping of samples will be provided in the laboratory manual.

The amount of blood needed for these assessments will be 4 mL at each time point.

10.8 Immunological Response Assessments

A blood sample will be collected for anti-drug antibodies (ADAs) assessments at visits as shown in Table 1 and described in Section 7.2.1. Instructions regarding the preparation, handling and shipping of samples will be provided in the laboratory manual.

The amount of blood needed for these assessments will be 12 mL at Visit 1 (Week 0) and 8 mL at the other time points.

10.9 Demographic and Other Baseline Characteristics

10.9.1 Demographic and Baseline Data

The following demographic and baseline data will be collected at the Screening visit/Visit 0:

- Date of birth (if authorized by local regulation)
- Sex
- Race (if authorized by local regulation)
- Weight and height

10.9.2 Medical History

Medical history including ophthalmologic history will be recorded at the Screening visit/ Visit 0.

10.9.3 Prior Treatments

Prior ocular treatments and prior non-ocular treatments within six months previous to signature of informed consent will be recorded at the Screening visit/ Visit 0.

10.10 Safety Assessments

The following safety variables will be measured in addition to recording AEs:

- Physical assessment
- Vital signs
- Laboratory tests

10.10.1 Physical Assessment

All patients will undergo verbal health status assessments. The timing of the assessments is described in Section 7.2.1 and Table 1. Additionally, at any time, other physical assessments may be performed at the Masked Investigators' discretion.

The assessment will consist of a routine interrogation of the patients' general health. The assessment is divided into nine categories: general appearance; head, eye, ear, nose, and throat (HEENT); chest; cardiovascular; abdominal; genitourinary; musculoskeletal; skin; and neurological. The findings will be recorded as either "normal" or "abnormal" for each category and any abnormal findings will be described.

10.10.2 Vital Signs

The following vital signs will be monitored: radial pulse [beats per minute] and systolic and diastolic blood pressure [mmHg].

- Resting systolic and diastolic blood pressure (mmHg), after 5 minutes sitting
- Resting *pulse/heart* rate (beats per minute), after 5 minutes sitting

The observed values will be recorded and assessed as "normal" or "abnormal". Abnormal findings will be assessed as "clinically significant" or "not clinically significant".

The timing of the assessments is described in Section 7.2.1 and Table 1. Vital signs must be measured before any blood sample is collected.

10.10.3 Laboratory Tests

The laboratory safety analyses (hematology, clinical chemistry and coagulation) will be performed by [redacted]

The following laboratory safety parameters will be measured (Table 2):

Table 2 Laboratory Safety Parameters

Category	Laboratory Parameter
Hematology	white blood cell count, red blood cell count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, bands, lymphocytes, eosinophils, monocytes, basophils and other cells)
Clinical chemistry	sodium, potassium, chloride, creatinine, total protein, albumin, total bilirubin, gamma-glutamyl transferase, uric acid, urea (blood urea nitrogen), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, calcium, C-reactive protein, glycosylated hemoglobin
Coagulation profile (screening only)	prothrombin time, partial thromboplastin time
Other tests (Screening only, female patients only)	Serum pregnancy test (HCG)

Laboratory values outside of the normal range will be assessed as “clinically significant” or “not clinically significant” by the Masked Investigator. If an abnormal laboratory value is judged as clinically significant, the Masked Investigator will repeat the laboratory determination as judged appropriate to ensure the validity of the abnormal result. If any clinically significant abnormal results are noted, the tests are to be repeated until the results are normal, are no longer considered clinically significant by the Masked Investigator, or an explanation for the change is obtained.

The timing of the assessments is described in Section 7.2.1 and Table 1.

The amount of blood needed for these assessments will be 12 mL at Screening and 8 mL at the other time points.

10.11 Total blood volume

The total volume of blood collected for the study will be approximately 74 mL spread over 48 weeks (6 mL x 3 = 18 for biochemistry; 3 mL x 3 = 9 mL for hematology; 3 mL x 1 = 3 mL for coagulation; 12 mL + (8 mL x 4) = 44 mL for ADAs).

In the Subgroup, the additional blood samples (4 mL x 3 = 12 mL for PK; 8 mL for ADAs at visit 1b) increase the total volume of blood up to 94 mL.

10.12 Appropriateness of Measurements

Standardized methods for measurements of efficacy and safety will be used. The visual function testing and ophthalmological examinations are accepted standard clinical evaluations for the assessment of patients with nAMD. The laboratory analyses of ranibizumab concentrations and ADA titers will be performed by the respective central laboratories using validated assays.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject which does not necessarily have a causal relationship with a medicinal product.

Treatment-emergent adverse event (TEAE): any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

11.1.2 Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting Masked Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

11.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorized IMP or summary of product characteristics for an authorized product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

11.1.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Life-threatening in the definition of a SAE or serious adverse reaction refers to an event in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical judgement should be exercised in deciding whether an adverse event/reaction is deemed serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

11.2 Reporting of Adverse Events

All study patients will be carefully monitored for the occurrence of AEs during the study period **from the time that the informed consent is signed through to the completion of the final visit**. The Masked Investigator will collect AEs with a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by patients. The Unmasked Injector will collect AEs occurring during or right after the injection procedure.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

All AEs including but not limited to events reported by the patient, or reported in answer to an open question by the Masked Investigator or delegated staff member, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding IMP
- Opinion on causality
- Seriousness
- Outcome

SEVERITY

Severity describes the intensity of an event, and will be assessed as:

Mild

The AE does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance.

Moderate

The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe

The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient.

If an AE changes in severity, the worst severity should be reported.

CAUSALITY

AEs are assessed as either related to the IVT injection procedure (eyelid speculum, anesthetic drops, antibiotic drops, povidone-iodine or equivalent drops or flush, subconjunctival injection of anesthetic, IVT injection), termed "injection procedure-related", or to IMP (FYB201 or Lucentis)

The relationship to the IVT injection procedure or to IMP will be assessed **by the Masked Investigator** using the following definitions.

Causality will be assessed as:

Probable

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, but which could also be explained by concurrent disease or other drugs or chemicals. Information on IMP withdrawal may be lacking or unclear.

Unlikely

A clinical event, including laboratory test abnormality, with a temporal relationship to IMP administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

Any AE that is ongoing at the Final Visit or when the patient is withdrawn from the study should be followed up until the AE is resolved or the Masked Investigator, or delegated staff member, decides that the AE is stable and needs no further follow-up. The date when the Masked Investigator or delegated staff member considers that one of these outcomes has occurred will be considered the last visit for that patient and the last status (resolution or stable situation) should be recorded in the eCRF.

ABNORMAL LABORATORY VALUES/VITAL SIGNS

The reporting of abnormalities as both laboratory/vital signs findings and AEs should be avoided.

An asymptomatic abnormal laboratory/vital sign finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE or if it causes the patient to discontinue the study.

If an abnormal laboratory/vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory/vital sign result should be considered additional information.

11.3 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to [redacted] immediately, but in any event no later than 24 hours of any study center staff becoming aware of the event. Initial reports should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify patients by unique code numbers assigned in the study. The patients' names, personal identification numbers, and/or addresses must not be included. The following information is **mandatory** for the initial report:

- Patient study ID
- Study treatment (masked, if applicable)
- Start date (time, if relevant) of the study treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the Investigator should supply [redacted] and the IEC/IRB (if applicable) with any additional requested information (e.g. autopsy reports and terminal medical reports).

SAE REPORTING CONTACT DETAILS

SAEs will be reported to [redacted] via the web-based eCRF system. If the web system is down, a paper SAE report form should be used and sent by e-mail or fax to the Drug Safety Unit at [redacted]

[redacted]

Note: If there is local legislation requiring Investigators to report AEs to the CAs or the IEC/IRB, the Investigator should also comply with this legislation. If any such reporting is planned, this must be stated in the SAE report, and once the reporting has been performed, a copy of the reporting documentation must be enclosed with the follow-up SAE report to [redacted]

11.4 Reporting of Suspected Unexpected Serious Adverse Reactions

[redacted] is responsible for informing the CA(s)/IEC/IRB(s) of any individual case reports of SAEs that are determined to be reportable (i.e. suspected unexpected serious adverse reactions [SUSARs]). The Investigator will ensure that all relevant information is provided to [redacted] to allow [redacted] to meet their obligations to report the SUSAR to the CA and IEC/IRB. For a SUSAR that is fatal or life-threatening, this should be reported as soon as possible and not later than 7 days after [redacted] was first advised, for any other SUSAR this should be within 15 days.

11.5 Pregnancy

Female patients will be instructed to notify the Masked Investigator immediately if they become pregnant during the study. Male patients will be instructed to notify the Masked Investigator immediately if their partner becomes pregnant. Pregnant patients will be withdrawn from further study treatment.

The Masked Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs (Section 11.3). The pregnancy report form should be used instead of the SAE form.

The pregnant patient or partner will, if possible, be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth

defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

11.6 Data Safety Monitoring Committee

In order to assess safety during the conduct of the trial, a DSMB will be appointed to review all relevant safety data from the trial as defined in the board charter. The board for the trial will be comprised of a limited number of external personnel. The members of the board will not otherwise be involved directly in the conduct of this study or other FYB201 development studies. The membership of the DSMB and the responsibilities of the DSMB will be defined in a separate 'Data Safety Monitoring Board Charter'. The Charter will include information about purpose and timings of DSMB meetings, evaluation of safety and efficacy parameters, communication strategy, procedures for ensuring confidentiality, and procedures to maintain masking of the board.

12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1 Statistical and Analytical Plans

There will be two analyses within this study for which separate statistical analysis plans (SAP) will be written in order to describe details of the statistical evaluation.

1. Unblinded main analysis after all patients randomized have either completed the Week 24 assessments or have discontinued the study
2. Final analysis after all patients randomized have either completed the Week 48 assessments or have discontinued the study

The documents for the main and final analyses will be finalized prior to trial unblinding. In particular, changes of planned analyses outlined in the trial protocol have to be documented in the SAP. Deviations from the SAP will be documented in the clinical study report.

12.1.1 Datasets to be Analyzed

Safety Set (SAF)

The safety population includes all patients who received at least one injection with IMP.

It will be used as general analysis set for all kinds of safety and tolerability data.

With regard to the **efficacy analysis**, the following trial populations are considered:

For the EU: All patients who have a baseline BCVA between 20/40 and 20/100 Snellen equivalent.

For the US: All patients who have a baseline BCVA between 20/32 and 20/100 Snellen equivalent.

Within these trial populations, the following analysis sets are defined:

Full Analysis Set (FAS)

This analysis set is based on the “Intention to Treat” (ITT) principle and includes all patients

- who received at least one injection of study medication
- for whom efficacy results at least after 1 month are available.

"Per-Protocol" (PP) Analysis Set

This analysis set includes all patients

- who belong to the analysis set "Full Analysis Set"
- who have no major protocol deviations until V3 (visit after 8 weeks) that would interfere with the interpretation of BCVA efficacy data.

PK Subgroup analysis set

This analysis set includes all patients

- who received the initial injection of study medication
- who have a valid measurement of C_{max} post-first dose
- who have no major protocol deviations that would interfere with the interpretation of ranibizumab concentration data.

he primary efficacy analyses will be based on the FAS and sensitivity analyses will be performed using the PP population.

12.1.2 Statistical Issues

The assessments performed at Visit 1 (Day 0) will be considered the baseline values (unless there is no assessment at Visit 1 – e.g. FA, color fundus photography –; for these variables, the Screening assessments will be considered the baseline values).

Handling of missing values

Data from subjects who prematurely terminate the trial will be used to the maximum extent possible. With the readouts for the primary endpoint being early in the trial, the impact of missing BCVA data is considered limited. However, the pattern and reasons for missing data will be carefully examined and appropriate imputation strategies will be described in the statistical analysis plans prior to unblinding and any analyses, if needed.

No other procedures for replacing missing data are intended.

Handling of protocol deviations

All protocol deviations will be listed. The deviations will be assessed as major or minor during the blind data review with regard to their influence on any of the primary efficacy or pharmacokinetic variables prior to locking the database. If applicable, the reasons for exclusion of subjects from any of the analysis sets will be listed and, where relevant, the data of these subjects will be described separately.

12.1.3 Summary Statistics

If not stated otherwise, all efficacy data will be summarized descriptively by treatment group and visit. Categorical data will be presented as counts and percentages. Continuous data will be presented as number of patients, arithmetic mean, standard deviation (SD), minimum, Q25, median, Q75 and maximum. The mean time-course for all continuous efficacy variables which are measured every month is presented by appropriate plots.

Individual patient data will be listed, sorted by treatment arm, center ID, patient ID and visit. All derived data (e.g., change from baseline) will be included in the data listings.

Statistical descriptions and analyses will be carried out using SAS statistical analysis software (SAS Institute, Inc., Cary, North Carolina, USA).

12.2 Efficacy Analysis

12.2.1 Primary Efficacy Analyses

The primary endpoint is defined as change from baseline in ETDRS BCVA calculated for the data after Week 8 with an equivalence margin of 3.5 letters.

Statistical hypothesis, model and method of analysis

The primary endpoint will be evaluated in all patients with a baseline BCVA between 20/32 and 20/100 Snellen equivalent for the US specific analysis and in all patients with a baseline BCVA between 20/40 and 20/100 Snellen equivalent for the EU specific analysis. The change from baseline in ETDRS BCVA at Week 8 will be calculated. The equivalence margin of 3 ETDRS letters (as rounded to the nearest integer) will be tested by the following hypotheses:

Null hypothesis: H_0: $|\mu_{BCVA,FYB201} - \mu_{BCVA,Lucentis}| \geq 3.5$

Alternative hypothesis: H_1: $|\mu_{BCVA,FYB201} - \mu_{BCVA,Lucentis}| < 3.5$,

where $\mu_{BCVA,FYB201}$ and $\mu_{BCVA,Lucentis}$ are the mean changes of ETDRS letters from baseline to Week 8.

An analysis of covariance (ANCOVA) model will be used for the analysis with the change in BCVA between baseline and Week 8 as the dependent variable, the baseline BCVA as covariate, and the country and the treatment group as fixed effects. The model can be expressed as

$$\mu_{BCVA,i} = \mu + \alpha * b_i + c_j + t_k + e_{ijk}$$

where:

$\mu_{BCVA,i}$: Change of BCVA from baseline to Week 8 in patient i.

μ: Intercept

α: Regression parameter for effect of baseline BCVA

b_i: Baseline value of BCVA of patient i

c_j: Effect of country j

t_k: Effect of treatment k = 1 (FYB201), 2 (Lucentis)

e_{ijk}: Residual Error: N (0, σ_e^2)

For the comparison between the treatment groups, the 90% (US) and 95% (EU) CIs for the treatment difference $t_1 - t_2$ will be calculated using Least Square Means. If the respective confidence interval is completely contained in the interval]-3.5 ; 3.5[letters, equivalence of FYB201 and Lucentis can be concluded.

The main analysis set for this analysis is the FAS including pre-defined criteria for the imputation of missing data as described in the SAP. A sensitivity analysis using the PP will also be performed.

Depending on the extent of missing data, additional sensitivity analyses in analogy to the primary analyses may be conducted. These will be pre-specified in the SAP.

12.2.2 Secondary Efficacy Analyses

All values for BCVA, FCP, and FCS retinal thickness as well as total lesion area will be summarized by visit and treatment, including change from baseline. The change from baseline to Week 24 and to Week 48 for all three variables will be compared between treatment groups using the ANCOVA model as used for the primary endpoint to derive the CIs for the difference between the treatment groups, but without formal hypothesis testing. For the Week 48 analyses of the change in BCVA, the patient-wise average of Weeks 40, 44, and 48 will be used to reduce the intrinsic variability of these measurements.

NEI VFQ-25 scores will be determined as described in the official manual. Values will be descriptively summarized by visit and treatment, including change from baseline. The analysis set for these analyses will be the FAS.

Furthermore, all efficacy endpoints will be analyzed taking the stratification factors into consideration. Efficacy results will be tabulated by patients with a screening BCVA between 20/40 and 20/100 Snellen equivalent (population for the EU specific analysis) and on patients with a screening BCVA between 20/32 and 20/100 Snellen equivalent (population for the US specific analysis) as well as stratified by country by pooling the sites within each country. If only few patients are randomized in a particular country, clustering of countries may be necessary for the analyses and the corresponding strategy will be described in the SAP, if needed.Details regarding any additional subgroup analyses will be described in the Statistical Analysis Plan.

12.2.3 Analysis of systemic ranibizumab concentrations

The mean ranibizumab concentrations at 24 hours after the first and the sixth doses will be calculated.

This analysis will be performed on the PK Subgroup population.

Descriptive statistics (arithmetic and geometric means, ranges, SDs and coefficient of variation [%]) will be generated for each treatment group.

12.2.4 Immunogenicity Analysis

The number and proportion of patients who have binding anti-drug antibodies in serum (including identification and quantitation of nAbs) will be provided by treatment group for Visit 1 (pre-dose), Week 1 (PK Subgroup only), Week 4, Week 12, Week 24 and Week 48 (or final visit).

12.2.5 Demographic and Other Baseline Characteristics

All patients' demographic data and baseline characteristics will be listed and tabulated. Summary statistics (number of patients, arithmetic mean, SD, minimum, Q25, median, Q75 and maximum) will be

provided for quantitative data. For qualitative data frequency tables (including counts and percentages) will be provided. Descriptive statistics will be presented for each of the analysis populations by treatment group and additionally by country and by visual acuity randomization strata.

12.2.6 Exposure to Treatment

The number of IVT injections of the study medication will be summarized according to treatment group for the SAF population.

A flowchart will be produced detailing the number of patients screened, randomized, receiving IMP, and the number of patients withdrawing from the study and completed.

In addition, the number and percent of patients who withdraw from the study and their reasons for withdrawal will be tabulated. The distribution of withdrawals will be displayed for each visit.

A list of patients who discontinue from study will be documented including the following information: treatment group, center ID, patient ID, date of discontinuation, reason for discontinuation and specification.

The fulfilment status of inclusion and exclusion criteria will be listed together with treatment group, center ID, patient ID and criteria.

12.2.7 Concomitant Treatment

Concomitant medication and concomitant therapy will be summarized as number of patients being treated with each type of medication/therapy classified according to ATC level 3 and World Health Organization Drug Dictionary preferred term. The SAF population will be used for this presentation.

12.2.8 Adverse Events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). A listing will be provided linking the original and coded terms.

An overview over all treatment-emergent adverse events (TEAEs) (original term) will be generated including onset relative to start of treatment, duration, intensity, and relationship to the study medication, action taken and outcome.

The total number of patients with at least one TEAE and the total number of TEAEs will be presented.

The incidence of TEAEs will be summarized by treatment using MedDRA terms grouped by preferred terms and by system organ classes. Separate frequency tables for incidence of TEAEs by worst severity and worst relationship to study medication will be presented by treatment. Furthermore, a frequency table for all patients with TEAEs leading to withdrawal from the study will be provided. The frequency tables will include the number and percentage of patients who experienced TEAEs. Counts will not be done by event.

A listing of all AEs will be presented, whether treatment emergent or not. Non-TEAEs will be flagged in this listing.

Deaths, serious adverse events, severe adverse events and adverse events leading to study discontinuation will additionally be listed separately (if applicable).

12.2.9 Other Safety Assessments

All safety data will be listed, sorted by treatment group, center ID, patient ID and visit. All data collected will be included in the data listings.

Physical Assessment

Physical assessment data will be summarized by treatment group.

Vital Signs

Vital signs will be summarized by treatment group, together with changes from baseline.

All vital signs will be listed by patient. All values outside the normal reference ranges and clinically significant abnormal values will be flagged in this listing. In addition, all patients with clinically significant

abnormal values will be listed in a separate listing. The number of patients with at least one clinically significant abnormal value will be tabulated by treatment group and visit.

Ophthalmic Variables

Ophthalmic examination, incl. IOP will be summarized by treatment group, together with changes from baseline.

Laboratory Safety Assessments

Listings for laboratory values will be generated. Laboratory values outside the normal range will be flagged.

Summary statistics will be produced for observed values and for changes from baseline to each visit.

All laboratory values outside the normal range and assessed as clinically significant will be listed as absolute values and multiples of the lower or upper normal limit in separate listings displaying the entire individual time course. The number of abnormal and clinically significant observations will be tabulated for each treatment group by visit.

12.3 Determination of Sample Size

12.3.1 Sample size calculation for the primary endpoint

The required sample size for the primary endpoint is calculated on the basis of a 1:1 randomization ratio and a standard deviation (SD) of 10 ETDRS letters. The calculation is based on using a 95% confidence interval, i.e. a two-sided significance level of 2.5%, to establish equivalence in line with EMA requirements.

Requesting a power of the trial of 90%, assuming no difference between the treatment groups, and using an equivalence margin of 3.5 requires a total of 412 evaluable patients (206 patients each to be treated with FYB201 and Lucentis, respectively). Since the EU specific analysis will be limited to patients with a screening Snellen equivalent of 20/40 or worse and assuming that approximately 10% of all patients randomized will be in the 20/32 strata, a total of 460 patients will need to be enrolled.

A sample size of 460 is also sufficient for the US specific analysis. In particular, 230 patients per treatment group will provide at least 95% power for assessing equivalence in the change in BCVA using a 90% confidence interval, a standard deviation of 10 letters, no expected difference between the treatment groups, and an equivalence margin of 3.5 letters.

12.3.2 Sample size consideration for other endpoints

Incidence rates concerning immunogenicity are assumed to be in the range of 3% to 6%.The comparison between the two groups will only be descriptive and will be based on confidence intervals for the difference between the antibody incidences in each group without formal hypothesis testing. The planned sample size of 460 patients will be sufficient to estimate the difference between the two groups with a precision of less than ± 4.5% which is considered adequate given the low immunogenic potential of ranibizumab.

Furthermore, systemic ranibizumab concentration analyses are intended as an additional safe guard to detect potential excessive systemic exposure. Therefore, samples close to C_{max} (24 hours post-dose [±3 hours]) after the first injection and after the sixth injection will be analyzed in a subgroup of up to 60 patients (up to 30 each for FYB201 and Lucentis). This sample size is deemed sufficient for descriptive purposes. No formal statistical testing to demonstrate similarity in ranibizumab concentration will be performed.

12.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any deviation(s) from the original statistical analysis plans (as described in the study protocol or in the SAP) will be described and justified in a protocol amendment and/or in a revised SAP and/or in the clinical study reports, as appropriate.

12.5 Interim Analysis

No formal interim analysis will be performed.

12.6 Main Analysis

The main analysis will be performed when all randomized patients have either completed the Week 24 assessments or have discontinued the study. At this point, all data will be cleaned and the database will be locked for unblinding. All analyses involving all data collected up to Week 24 will be described in the clinical study report (six month report).

To ensure an objective assessment of the ongoing trial, investigational sites and patients will remain blinded to the treatment assignments and the medical/safety review will be performed by independent blinded personnel.

12.7 Final Analysis

The final analysis will be performed when all randomized patients have either completed the Week 48 assessments or have discontinued the study. At this point, all data will be cleaned and the database will be locked for the analyses. The analyses and the corresponding clinical study report (12 month report) will cover the whole study period, i.e. all data generated over the course of the whole study.

13 INVESTIGATOR/SPONSOR RESPONSIBILITIES

13.1 Ethics

13.1.1 Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

This protocol and any amendments will be submitted to a properly constituted IEC/IRB, in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval/favorable opinion of the study.

For studies conducted in the USA, the Investigator will additionally ensure adherence to the basic principles of “Good Clinical Practice” as outlined in the current version of 21 CFR, subchapter D, part 312, “Responsibilities of Sponsors and Investigators”, part 50, “Protection of Human Patients”, and part 56, “Institutional Review Boards”.

Approval/favorable opinion must be obtained in writing from the IEC/IRB before the first patient can be recruited.

13.1.2 Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, regulatory requirements, good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

13.1.3 Patient Information and Consent

All patients will receive written and verbal information regarding the study at an interview prior to any study procedure. This information will emphasize that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

Before any study-related procedures, the informed consent form will be signed and personally dated by the patient (or their legally acceptable representative) and witness, as applicable) and by the person who conducted the informed consent discussion.

The informed consent must contain all of the elements prescribed by the relevant regulatory authorities and must be appropriately signed, dated and witnessed by an impartial witness (not a member of the study team). A witness is not required unless the participant is unable to read (such as blind or illiterate) or unless required by state or local laws. If a witness is present, however, the witness must observe the entire informed consent process, including participant’s signature.

The consent includes information that data will be recorded, collected, processed and may be transferred to European Economic Area (EEA) or non-EEA countries. In accordance with the European Union Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the study.

A copy of the patient information including the signed consent form and other documents (e.g. insurance conditions, if required by national regulations) will be provided to the patient.

13.2 Patient Records and Source Data

The origin of source data in the study will be specified in a separate document (“Origin of Source Data”).

It is the responsibility of the Principal Investigator and all study personnel to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the patient is in a clinical study
- The identity of the study e.g. Study code
- Patient number
- That informed consent was obtained and the date
- Diagnosis

- Dates of all visits during the study period and if a study injection was given
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination

The Principal Investigator and all study personnel are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Signed sections of eCRFs will be monitored on a regular basis.

13.3 Access to Source Data and Documentation

The Principal Investigator and all study personnel should guarantee access to all applicable source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the IEC/IRB, if required.

13.4 Monitoring

The monitor will visit the study center on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as CRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs
- The IMP is being stored correctly and drug accountability is correct and being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The Principal Investigator and all study personnel are receiving sufficient information and support throughout the study

Moreover, during monitoring visits the data recorded in the eCRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data are reliable and robust and have been processed correctly i.e. source data verification.

13.5 Data Management

All data will be recorded in an electronic data capture system. eCRFs will be provided by [redacted] or its designee.

The Masked Investigator or study personnel will complete the appropriate eCRF pages within a reasonable time frame following completion of each procedure or evaluation.

Data management and handling of data will be conducted according to the study specific Data Management Plan and with ICH guidelines and [redacted] standard operating procedures (SOPs).

An eCRF system will be used to capture data from the study. Validation and data queries will be handled by the [redacted] Data Management Team. The data will be subjected to validation according to [redacted] SOPs in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the study center by the Masked Investigator or study center personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Prior to the database closure for the main and for the final analysis, a reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

13.6 Quality Assurance and Audit

Audits or inspections, including, but not limited to a review of protocol adherence, compliance with applicable regulations and guidelines, essential documentation (including source data verification), may be performed by representatives of [redacted] Bioeq GmbH, a CA and/or an IEC/IRB.

13.7 Record Retention

The Principal Investigator/institution should maintain essential documents (as defined in ICH E6 GCP, Section 8) as required by the applicable regulatory requirement(s).

The Principal Investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where Bioeq GmbH intends to apply for approval.

It is the responsibility of Bioeq GmbH to inform the Principal Investigator/institution in writing as to when the documents no longer need to be retained.

13.8 Protocol Deviations

The classification of protocol deviations in major or minor deviations will be mutually agreed between Bioeq GmbH and [redacted] at the start of the study. Deviations to the study protocol will be documented in a Protocol Deviation Log.

Protocol deviations will be reviewed during a meeting before database lock in order to allocate the patients into the different analysis sets.

Any serious breaches that substantially affect the integrity or the safety of the patients or the scientific validity of the study will be reported to the relevant authorities in accordance with local regulatory requirements.

13.9 Insurance

Insurance will be provided by Bioeq GmbH who will indemnify the Investigator/the institution against legal and financial costs of claims arising from the study, unless the claims arise from malpractice, negligence or non-compliance with the protocol.

13.10 Report and Publication

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by [redacted] in close collaboration with the coordinating Investigator and the Sponsor. The final report will be signed by the coordinating Investigator and by the Sponsor.

All publications and presentations must be based upon the clinical study report.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development

activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences.

The Sponsor may choose to publish or present data from this study. If an Investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

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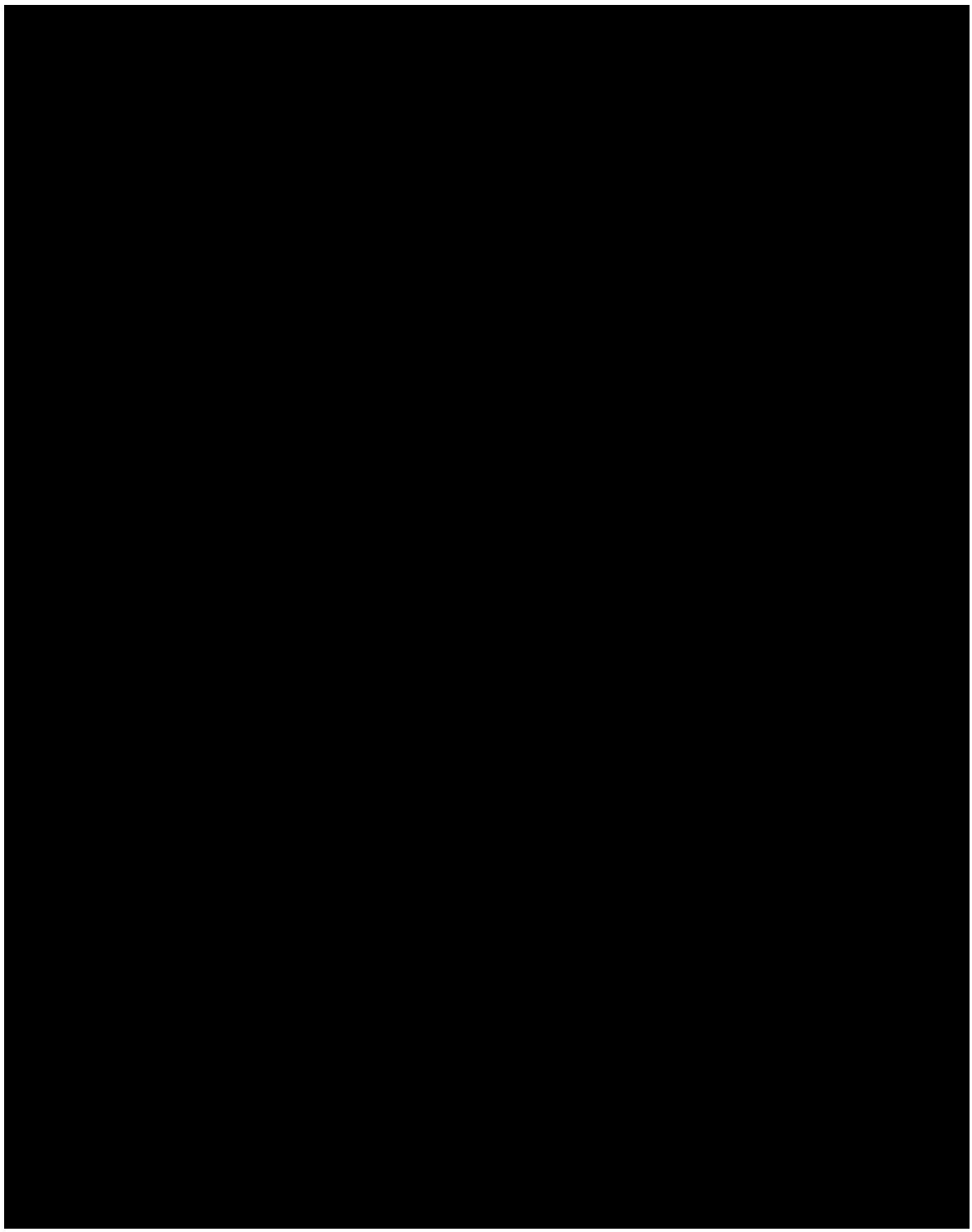
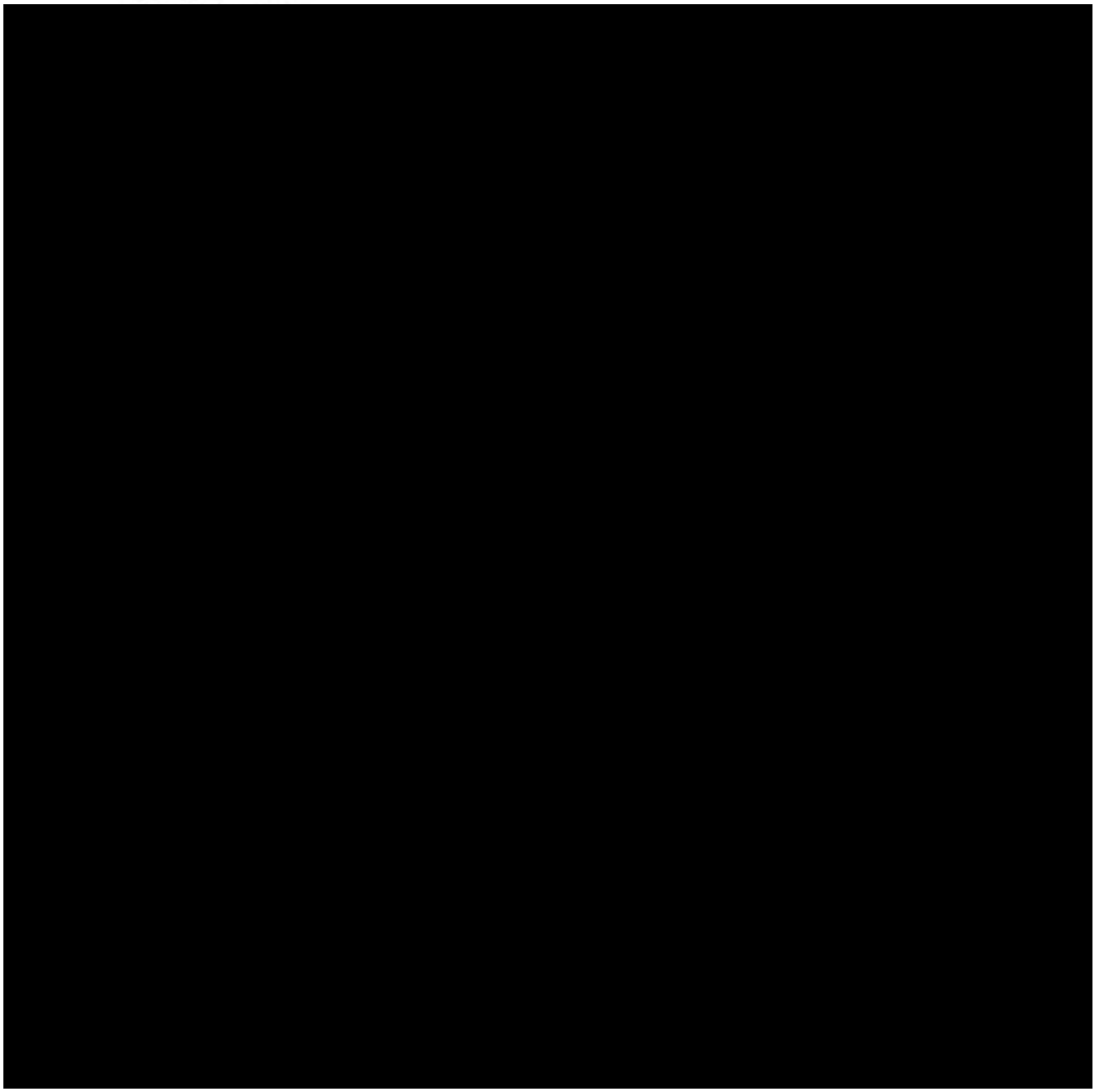
15 SIGNATURES

This Clinical Study Protocol is approved by:





16 CLINICAL STUDY PROTOCOL AGREEMENT FORM

I have read the clinical study protocol entitled: EFFICACY AND SAFETY OF THE BIOSIMILAR RANIBIZUMAB FYB201 IN COMPARISON TO LUCENTIS IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (COLUMBUS-AMD)

and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- my staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations.

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

Principal Investigator: _____

Date: _____

Signature: _____

17 APPENDICES

Appendix A: Method for Evaluating Anterior Chamber Inflammatory Activity

Appendix B: Method for Evaluating Vitreous Inflammatory Activity

Appendix C: Procedures for Refraction and Vision Testing

Appendix D: Visual Function Questionnaire-25

Appendix E: Intravitreous Administration Protocol

APPENDIX A METHOD FOR EVALUATING ANTERIOR CHAMBER INFLAMMATORY ACTIVITY

Slit Lamp Examination

The viewing of several eye structures is enhanced by the use of the slit lamp. The examination is optimized by viewing through a dilated pupil. However, assessment of anterior chamber cells and flare should be accomplished prior to dilation.

The examination of the anterior chamber involves observing with high-magnification (25-40x) while directing a small, intense 1x1mm beam obliquely through the aqueous, following relative dark adaptation. Anterior chamber cells and/or flare are visible, owing to the Tyndall effect of the bright beam. A grading system for flare and cells is shown in Table 1.[1,2] Clinicians should strive to develop consistency in their grading.

Table 1 Grading of Flare and Cells*

Grade	Flare	Cells
0	Complete absence	< 1 cell per field
0.5+[3]	----------	1 to 5 cells per field
1+	Faint flare (barely detectable)	6 to 15 cells per field
2+	Moderate flare (iris and lens details clear)	16 to 25 cells per field
3+	Marked flare (iris and lens details hazy)	26 to 50 cells per field
4+	Intense flare (fixed, coagulated aqueous humor with considerable fibrin)	50+ cells per field

* Field size is a 1x1mm slit beam.

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APPENDIX B METHOD FOR EVALUATING VITREOUS INFLAMMATORY ACTIVITY

All patients will have a complete dilated fundus examination seeking for vitreous inflammatory activity. By using a slit lamp, a fundus examination will be performed to examine the following eye structures:[1,2]

1. Peripheral retina
2. Macula
3. Optic nerve head
4. Retinal vessels
5. Evaluation of the choroid.

The examination will allow to determine to grade the vitreous inflammatory activity according to a scale graded from 0 to 5 (see Table 2):[3]

Table 2: Grading Scheme for Vitreous Haze[4]

Score	Description	Clinical findings
0	Nil	None
1	Minimal	Posterior pole clearly visible
2	Mild	Posterior pole details slightly hazy
3	Moderate	Posterior pole details very hazy
4	Marked	Posterior pole details barely visible
5	Severe	Fundal details not visible

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APPENDIX C PROCEDURES FOR REFRACTION AND VISION TESTING

Best Corrected Visual Acuity Examination

SCOPE
Best-corrected visual acuity (BCVA) will be measured by trained and certified personnel at the study sites. Visual acuity examiners are "masked" to previous visual acuity testing results, patient's medical chart and to the patient treatment assignment. The VA examiner will have no access to a patient's previous VA scores; the VA examiner may only know the patient's previous visits' refraction data (previous refraction should be made available). The VA examiner is not permitted to perform any other tasks involving direct patient care except for trial frame refraction, BCVA. VA will be measured at the intervals specified in the protocol (see Table 1 and Section 7.2.1 of the protocol).

EQUIPMENT
The following is needed at minimum to conduct the examination:

- Examination lane of adequate dimensions to allow testing at required distances (4 meters and 1 meter)
- 1 meter rigid measuring stick (for the 1 meter VA testing)
- Standard chair with a firm back
- Set of three Precision VisionTM or Lighthouse distance acuity charts (Standard Early Treatment Diabetic Retinopathy Study [ETDRS] Charts 1, 2, and R or European-Wide Modified ETDRS Charts 1, 2, and 3 (Russia and Ukraine only))
- Retro-illuminated light box and stand
- Trial frame
- Full Aperture trial lens set (with black occluding lens and - 0.37 lens). Jackson Cross Cylinder lenses (0.25, 0.50 and 1.00D)

Refraction

Previous to visual acuity testing, refraction (myopia, hyperopia, astigmatism, presbyopia) should be conducted.[1]

REFRACTION AND VISUAL ACUITY EXAMINATION

Refraction
The analysis of refractive error incorporates objective and subjective assessment of the patient's refractive correction needs. The goal is to determine the lens correction needed to provide optimal visual acuity for all viewing distances.[2,3] During this component of the examination, the refractive error is determined and the patient's need for a specific reading or other near point prescription is assessed, particularly if the patient is presbyopic.[4] The refractive analysis may include:[5-11]

- Measurement of the patient's most recent optical correction
- Measurement of the anterior corneal curvature (e.g., keratometry, corneal topography)
- Objective measurement of refractive status
- Subjective measurement of monocular and binocular refractive status at distance and near or at other specific working distances.

Visual acuity

Visual acuity is performed with the aid of letters on the ETDRS chart, decreasing in size from top to bottom.[12,13] The following are requirements concerning the ETDRS charts, its illumination, and the reading distance:[1,14]

- The ETDRS chart has an optimal contrast: black optotypes on a white background.
- Ensure uniform illumination.[15] Avoid distracting reflections on the chart. The illumination in the examination room must be subdued (not dark), such that the pupil opening of the patient is 2-4 mm and is required to be ≦ 161.4 Lux (15 foot candles). The patient should sit directly in front of the sight chart and the eyes should not be narrowed.
- The starting distance between the patient and the chart should be 4 meters, for the purposes of this study, for at this distance the eye is not normally accommodated.
- For persons known to have a refractive disorder the visual acuity examination always takes place with the current correction. If the patient wears spectacles, the general practitioner should take a look through the spectacles prior to the visual acuity. Spectacles that magnify have positive lenses, indicating that the patient is hyperopic. Spectacles that reduce have negative lenses, indicating that the patient is myopic.

Procedure:[1]

- BCVA will be tested in both eyes (study eye and fellow eye) at screening, and the final visit. The procedure will be done in the study eye only during the rest of the study visits.
- BCVA will be performed in one eye while the other eye is covered by lightly patching with an eye-pad or folded tissue with tape and by inserting a black occluding lens into the trial frame. The measured vision should be noted immediately by circling the letters read correctly on the Visual Acuity Worksheet provided for this study.
- The patient should be asked to read across the rows starting from the upper left-hand corner of the chart. The patient should be asked to read slowly (at a rate not faster than about one letter per second) in order to achieve the best identification of each letter and to not proceed until they have given a definite response.

  Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test. Instead, a sheet of white paper or clip board may be used to guide the patient to the proper location on the chart.
- Each letter is circled on the Visual Acuity Worksheet, if read correctly. Once a patient has identified a letter with a definite single-letter response and has read the next letter, a correction of the previous letter cannot be accepted. If the patient changes a response aloud (e.g., “That was a ‘C,’ not an ‘O’.”) before he or she has read aloud the next letter, then the change should be accepted.
- <u>If 3 letters or less are read correctly on any row, stop testing.</u>
- If an eye is able to read a total of ≤ 19 letters on the chart at 4 meters distance, then patient’s eye continues to be tested at a 1-meter distance.
- If no letters are read correctly at either the 4-meter distance or the 1-meter distance, the 4-meter BCVA letter score is 0 and Low Vision testing would be conducted, including: counting fingers, hand motion, and light perception.
- All scores are recorded on the Visual Acuity Worksheets provided for this study.

TRAINING AND CERTIFICATION

A VA Specifications document, procedure manual, and other training material will be provided to the investigational sites, and VA examiner certification will be required. The VA examination room also must be certified before any VA examinations are performed for this study. If new VA personnel or VA rooms are added to the study, certification must be obtained prior to performing study assessments.

All visual acuity examiners will be provided with a detailed study specific Refraction and Visual Acuity manual.

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APPENDIX D VISUAL FUNCTION QUESTIONNAIRE-25

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

- 1 - ***version 2000***

Instructions:

I'm going to read you some statements about problems which involve your eyesight or feelings that you have about your eye condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. As the purpose of this survey is to improve our knowledge about eyesight problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as if you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND EYESIGHT

1. In general, would you say your health is*:

(Circle One)

READ OUT THE CATEGORIES:	**Excellent**	**1**
	Very Good	**2**
	Good	**3**
	Fair	**4**
	Poor	**5**

2. At the present time, would you say your eyesight in both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor, or are you completely blind?

(Circle One)

READ OUT THE CATEGORIES:	**Excellent**	**1**
	Good	**2**
	Fair	**3**
	Poor	**4**
	Very Poor	**5**
	Completely Blind	**6**

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

3. How often are you concerned about your eyesight?

(Circle One)

READ OUT THE CATEGORIES:		
	None of the time	1
	A little of the time	2
	Some of the time	3
	Most of the time	4
	All of the time	5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?

(Circle One)

READ OUT THE CATEGORIES:		
	None	1
	Mild	2
	Moderate	3
	Severe	4
	Very severe	5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for those activities.

5. How much difficulty do you have reading ordinary print in newspapers?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

6. **How much difficulty do you have doing work or hobbies that require you to see well close up, such as cooking, sewing, fixing things around the house, or using hand tools?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

7. **Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

8. **How much difficulty do you have reading street signs or the names of shops?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

10. Because of your eyesight, how much difficulty do you have noticing objects on the side while you are walking along?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

12. **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

13. **Because of your eyesight, how much difficulty do you have meeting people in their homes, at parties, or in restaurants?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

14. **Because of your eyesight, how much difficulty do you have going out to see films, plays, or sports events?**
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF THE RESPONDENT GAVE UP DRIVING, ASK: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING, ASK: How much difficulty do you have driving during the daytime in familiar places?

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have driving at night?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight?	**5**
Have you stopped doing this for other reasons or are you not interested in doing this?	**6**

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during the rush hour, on the motorway, or in city traffic?
(READ OUT THE CATEGORIES)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight?	**5**
Have you stopped doing this for other reasons or are you not interested in doing this?	**6**

PART 3 - RESPONSES TO EYESIGHT PROBLEMS

The next questions are about how your eyesight may affect the things you do. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ OUT THE CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like to because of your eyesight?	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your eyesight?	1	2	3	4	5
19. How often does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing?.....	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not sure	Mostly False	Definitely False
20. I stay at home most of the time because of my eyesight	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me.....	1	2	3	4	5
24. I need a lot of help from others because of my eyesight	1	2	3	4	5
25. I am concerned about doing things that might embarrass myself or others, because of my eyesight	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

APPENDIX E INTRAVITREOUS ADMINISTRATION PROTOCOL

This protocol applies to IVT injections of biosimilar ranibizumab FYB201 or Lucentis.

Injections must be performed by the Unmasked Injector (ophthalmologist) at the clinical study center, neither the patient nor the Masked Investigator team will know which treatment the patient receives.

Only a qualified ophthalmologist who is experienced with intravitreous injections may perform the intravitreous injections under aseptic conditions.

Patients will receive FYB201 or Lucentis at a dose 0.5 mg (0.05 mL of a 10 mg/mL solution) as twelve (12) monthly (every 4 weeks) IVT injections starting at Visit 1 (Week 0) to Visit 12 (Week 44).

In addition to the procedures outlined, any additional safety measures in adherence to specific institutional policies associated with IVT injections should be utilized.

NOTE: Prior to intravitreous injection, direct ocular massage using a sterile cotton-tip applicator at the intended site of injection may be utilized at the Injector´s discretion. However, a paracentesis MAY NOT be performed prior to injection of the intravitreous drug.

NOTE: Pre-operative antibiotic drops are NOT required prior to the scheduled injection(s) of intravitreous drug. In addition, peri-operative and post-operative antibiotic drops are NOT required at the time of the procedure or after the procedure, respectively. However, if it is considered the standard of care at the individual institution (center), appropriate broad spectrum topical antibiotics may be prescribed for subject use at the discretion of the Injector.

How to prepare and administer FYB201/Lucentis

Before IVT injection administration:

Few days before the injection the Injector or their staff will call the patient to remind him/her the day of the injection visit. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the IVT procedure.

The day of IVT injection administration:

Each vial should only be used for the treatment of a single eye

FYB201 / Lucentis should be inspected visually for particulate matter and discoloration prior to administration.

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). Adequate anesthesia and a broad-spectrum microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior the injection, in accordance with local practice, standard practice at the center and at discretion of the Injector.

To prepare and administer FYB201/Lucentis for intravitreal administration, please adhere to the following instructions:

All necessary devices are provided within the IMP Kit:

- A 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm, 5 µm)
- A 1 mL sterile syringe
- An injection needle (30G x ½″, 0.3 mm x 13 mm)

The vial, injection needle, filter needle and syringe are for single use only. Re-use may lead to infection or other illness/injury. All components are sterile. Any component with packaging showing signs of damage or tampering must not be used. The sterility cannot be guaranteed unless the component packaging seal remains intact.

1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble the 5 µm filter needle (18G x 1½″, 1.2 mm x 40 mm, 5 µm) onto the 1 mL syringe using aseptic technique. Push the blunt filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial.
3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle.

   The filter needle should be discarded after withdrawal of the vial contents and must not be used for the IVT injection.
6. Aseptically and firmly assemble the injection needle (30G x ½″, 0.3 mm x 13 mm) onto the syringe.
7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

   Note: Grip at the yellow hub of the injection needle while removing the cap.
8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL mark on the syringe. The syringe is ready for injection.

   Note: Do not wipe the injection needle. Do not pull back on the plunger.

   The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 mL is then delivered; a different scleral site should be used for subsequent injections.

   After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

Safety check: Just after IVT injection

1. Cover opposite eye and assess whether the patient can count fingers held directly in front of him/her and/or can detect hand movement. If there is no perception of hand movements or finger counting, verify the presence of central retinal artery perfusion by indirect or direct ophthalmoscopy. If there is an absence of perfusion of the central retinal artery (that would be due to extensive IOP elevation following the IMP injection), immediate measures must be taken to lower IOP.
2. Remove the eyelid speculum.
3. Rinse the eye with 3 mL 0.9% sodium chloride, repeat two more times.

Special considerations for IMP administration:

Prior to and 30 minutes following the intravitreal injection, patients should be monitored for elevation in intraocular pressure using tonometry. Monitoring may also consist of a check for perfusion of the central retinal artery immediately after the injection. Patients should also be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection.

For further details on how to prepare and administer ITV injections, special precautions for disposal and other handling, please see the Lucentis 10 mg/mL solution for injection [ranibizumab injections] prescribing information.