13 October 2016
EMA/757247/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lucentis

International non-proprietary name: ranibizumab

Procedure No. EMEA/H/C/000715/II/0061

Note

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

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Table of contents

List of abbreviations

AE	adverse event
wAMD	wet age-related macular degeneration
ANCOVA	analysis of covariance
AS	angioid streaks
BCVA	best corrected visual acuity
CI	Confidence Interval
CNV	choroidal neovascularisation
CS	corticosteroids
CSC	Central Serous Chorioretinopathy
CSFT	Central subfield thickness
CSFV	Central subfield volume
DME	diabetic macular oedema
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescence angiography
FAS	full analysis set
IC	idiopathic chorioretinopathy
IOP	intraocular pressure
IVT	intravitreal
LOCF	last-observation-carried-forward
LS	Least Square
M	miscellaneous
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	Mixed-Effect Model Repeated Measure
MV-LOCF	mean value-last observation carried forward
NEI-VFQ-25	National Eye institute Visual Function Questionnaire 25
OCT	optical coherence tomography
PCV	polypoidal choroidal vasculopathy
PDT	photodynamic therapy
PIR	post inflammatory retinochoroidopathy
PM	pathological myopia
PP	per-protocol set
PSUR	Periodic Safety Update Report
PXE	pseudoxanthoma elasticum
RAP	Retinal Angiomatous Proliferation
RMP	Risk Management Plan
RPE	retinal pigment epithelium
RVO	retinal vein occlusion
SAE	serious adverse events
SD	standard deviation
SOC	system organ class
VA	visual acuity
VEGF	vascular endothelial growth factor
(v)PDT	(verteporfin) photodynamic therapy

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 9 February 2016 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of visual impairment due to choroidal neovascularization (CNV) based on data from the pivotal study CRFB002G2301 (MINERVA). Consequential changes were proposed to SmPC sections 4.1, 4.2, 4.8 and 5.1 and the Package Leaflet was proposed to be updated accordingly. The application included an updated RMP version 16.0.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0185/2014 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 20 September 2012 (EMA/CHMP/SAWP/561217/2012). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder Co-Rapporteur: Concepcion Prieto Yerro

Timetable	Actual dates
Submission date	9 February 2016
Start of procedure	27 February 2016
CHMP Co-Rapporteur Assessment Report	3 May 2016
CHMP Rapporteur Assessment Report	21 April 2016
PRAC Rapporteur Assessment Report	21 April 2016
PRAC members comments	3 May 2016
Updated PRAC Rapporteur Assessment Report	4 May 2016
PRAC Outcome	13 May 2016
CHMP members comments	17 May 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 May 2016
Request for supplementary information (RSI)	26 May 2016
CHMP Rapporteurs' joint response Assessment Report	13 September 2016
PRAC Rapporteur response Assessment Report	13 September 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	29 September 2016
CHMP members comments	3 October 2016
Updated CHMP Rapporteurs' Assessment Report	6 October 2016
Opinion	13 October 2016

2. Scientific discussion

2.1. Introduction

Lucentis (ranibizumab) has been approved in the European Union (EU)/ European Economic Area via the Centralised Procedure for the treatment of neovascular (wet) age related macular degeneration (wAMD) in 2007, for the treatment of visual impairment due to diabetic macular oedema (DME) and retinal vein occlusion (RVO) in 2011 and for choroidal neovascularisation (CNV) secondary to pathologic myopia (PM) in 2013.

Ranibizumab is a recombinant humanised immunoglobulin IgG1 κ isotype monoclonal antibody fragment that selectively binds and neutralises vascular endothelial growth factor A (VEGF-A). Binding of VEGF-A to its receptors on the surface of endothelial cells triggers angiogenesis and neovascularisation by promoting vascular endothelial cell proliferation and migration. It also causes increased vascular permeability.

Abnormal growth of new blood vessels below the sub-retinal pigment epithelium or into the subretinal space characterises CNV and may lead to exudation of intra- and subretinal fluids with subsequent atrophic changes (e.g. wAMD and PM) as well as macular oedema (DME and RVO), all of which can lead to visual impairment. By inhibiting VEGF, ranibizumab prevents angiogenesis and decreases vascular permeability, thereby preventing vision loss, restoring vision, and/or improving visual function.

Lucentis is administered as monthly injections until maximum visual acuity is achieved and/or there are no signs of disease activity. Initially, at least 3 monthly intravitreal (IVT) injections may be needed for treatment of wet AMD, DME and RVO, while for PM one or two injection in the first year might be sufficient. Patients should be monitored and treatment resumed when disease activity occurs.

Problem statement

With the present application, the MAH proposed an extension of the indication of Lucentis to the 'umbrella' indication treatment of visual impairment due to CNV. This indication would also cover the previously approved use in CNV secondary to PM, while AMD was proposed to remain as stand-alone indication.

For wAMD and CNV due to PM, the two most common causes of CNV, a treatment benefit of Lucentis has previously been demonstrated. Based on the same mechanism of action, ranibizumab is thought to also have a potential in the treatment of CNV due to any cause. Other causes than wAMD and CNV are usually rare and include angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy (CSC), idiopathic CNV, and other miscellaneous diseases. They typically occur in young, working age persons, and can be multifocal, binocular, and recurrent. CNV may cause vision loss from the exudation of intra- or subretinal fluid, haemorrhage or fibrosis.

For many of these rare conditions no or only suboptimal treatment options are available and there is no established standard of care.

For CNV secondary to angioid streaks, argon-laser treatment, photodynamic therapy (PDT) with verteporfin, or a combination of the IVT application of triamcinolone with PDT all failed to show clear effectiveness; furthermore, increased or persistent subretinal haemorrhage following PDT has been reported. Thus, the prognosis for CNV due to angioid streaks remains particularly poor.

The core treatment of uveitis/ocular inflammation is based on suppression of the inflammation, generally using steroids with or without immunosuppressants. CNV in younger patients is an uncommon complication associated with uveitis involving the posterior segment. Treatments that have been reported for the CNV

associated with uveitis include photocoagulation, PDT, and surgical removal, usually once the ocular inflammation has been controlled with anti-inflammatory agents.

CSC is a disease hallmarked by presence of serous detachment of the neurosensory retina in the posterior pole, sometimes associated with a serous retinal pigment epithelium (RPE) detachment. Chronic CSC can be complicated by CNV. Different treatment modalities including PDT with verteporfin, and submacular surgery have been reported, with variable success. Anti-VEGF agents have been reported to be used and effective in the treatment of CSC patients with CNV complication (Carneiro et al 2011).

Idiopathic CNV patients are currently treated with laser photocoagulation or surgical removal of subfoveal CNV, however neither intervention appears to show a clear benefit. It has been demonstrated that these patients may benefit from anti-VEGF therapy with a mean gain of visual acuity up to 2.2 lines (11 letters on ETDRS chart) at 6-month follow-up (Gunther and Altawheel 2009; Heier et al 2011; Fan et al 2014).

In addition, anti-VEGF therapy has been investigated in several case (series) reports to treat CNV associated with rare causes such as adult-onset vitelliform dystrophy (Mimoun et al 2013), atypical choroidal nevus (Cavalcante et al 2014), blunt-head trauma (Artunay et al 2009) or macular telangiectasia type II (Kovach and Rosenfield 2009). Based on its anti-VEGF mechanism of action, any CNV lesion may also potentially benefit from treatment with ranibizumab, including CNV associated with these rare conditions.

Development program

In order to support this application, the MAH submitted one pivotal, 12-months phase III study (study CRFB002G2301, hereafter also referred to as study G2301 or MINERVA) investigating efficacy and safety of 0.5 mg ranibizumab in the treatment of visual impairment due to CNV (due to other causes than wet AMD and PM). Supportive data from an observational study (CRFB002GFR01, hereafter also referred to as study GFR01) in patients with ocular complications secondary to a pseudoxanthoma elasticum (PXE) was provided as well. The development program has previously been discussed in a scientific advice and covering the broad label of CNV in a common development program was agreed with a caveat regarding heterogeneity of the patient population and sham as comparator was essentially agreed by the CHMP.

Despite a PIP waiver had been granted to all subsets of the paediatric population, study G2301 was open for inclusion of adolescent patients in an open-label separate cohort where all subjects received treatment. By submitting the full study report (12-months) data, the MAH fulfilled the requirement as per Article 46 of the Paediatric Regulation.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

In line with the Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 corr 2), since ranibizumab is a protein and unlikely to result in a significant risk to the environment, there is no need for ERA studies.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

The MAH confirmed that the clinical trials were performed in accordance with GCP.

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

- Tabular overview of clinical studies

Study	Objective, population	No. of treated patients	Treatment frequency, dose and duration
G2301 (MINERVA)	Randomized, double-masked, sham-controlled, multicenter study in adult patients, with a non-randomized, open-label group in adolescent patients*, to evaluate the efficacy and safety of ranibizumab 0.5 mg intravitreal injections in patients with visual impairment due to CNV	Arm 1: 119 (ranibizumab 0.5 mg); Arm 2: 59 (sham up to Month 2)	IVT injections of ranibizumab 0.5 mg or sham on Day 1, followed by individualized treatment regimen based on evidence of disease activity From Month 2, patients in arm 2 were switched to open-label treatment with ranibizumab 0.5 mg, where individualized treatment continued based on evidence of disease activity. As of Month 2, treatment was open-label. Planned end of treatment was at Month 11.
GFR01	Observational study of the efficacy, tolerance, and usage conditions of Lucentis in patients with ocular complications secondary to a pseudoxanthoma elasticum	75 enrolled 72 analysed	Ranibizumab 0.5 mg, individualised regimen. Up to 4 years.

* The study also enrolled 5 adolescent patients, whose results have been reported with the final study report.
IVT= intravitreal

2.3.2. Pharmacokinetics

No new pharmacokinetic data have been provided to support this application.

However, blood samples have previously been collected in patients with AMD in several clinical trials with ranibizumab as well as in trials for other conditions. Following monthly IVT administration of ranibizumab

0.5 mg/eye to patients with wAMD, serum concentrations of ranibizumab were generally <5 ng/ml and thus below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (IC_{50} = 11 to 27 ng/ml). Serum ranibizumab concentrations in DME and RVO patients were similar to those observed in wAMD patients.

Tong et al (2006) compared aqueous humour concentrations of VEGF in patients with active macular polypoidal choroidal vasculopathy, patients with CNV related to AMD, patients with CNV secondary to PM, and control subjects. VEGF concentrations were significantly higher in the three disease states versus control. The rank order of mean VEGF concentrations from lowest to highest was control < PCV < PM < AMD. Likewise, Chan et al. (2008) observed higher baseline aqueous VEGF concentrations in patients with CNV of AMD compared to patients with myopic CNV before treatment.

From these cross-indication comparisons, the MAH drew the following conclusions:

(1) aqueous humor VEGF concentrations in patients with CNV of PM were not higher than those in patients with CNV of AMD, and

(2) serum ranibizumab concentrations were similarly low for patients treated with ranibizumab for AMD, DME, and RVO.

Consequently, vascular permeability and ranibizumab transfer from the vitreous to the serum in patients with visual impairment due to CNV of PM should not be greater than what has been previously measured in other diseases (AMD, DME, RVO).

Immunogenicity

No new data has been provided.

In AMD studies, the pre-treatment incidence of immunoreactivity to ranibizumab across treatment groups was 0% to 3%. After monthly dosing with ranibizumab for 12 to 24 months, antibodies to ranibizumab were detected in approximately 1% to 8% of AMD patients. In a DME study, the pre-treatment incidence of antibodies to ranibizumab across treatment groups was 0% to 2% and after monthly dosing with ranibizumab for 12 months, antibodies to ranibizumab were detected in approximately 2% to 4% of DME patients. In RVO studies, the pre-treatment incidence of antibodies to ranibizumab across treatment groups was 2% to 3% and after monthly dosing with ranibizumab for 12 months, antibodies to ranibizumab were detected in approximately 4% to 5% of RVO patients. The clinical significance of pre-existing anti-ranibizumab antibodies is unclear.

Given the low incidence and lack of a relationship to clinical outcome, immunogenicity to ranibizumab was not assessed in the clinical program to support the use of ranibizumab in the treatment of visual impairment due to CNV.

2.3.3. Pharmacodynamics

Mechanism of action

The mechanism of action of ranibizumab is to bind and neutralise VEGF, thereby decreasing permeability of leaking blood vessels and reducing neovascularisation. This basic mechanism of action is valid independent on whether targeting choroidal vessels in AMD, in PM or in other cases of visual impairment due to CNV. No additional pharmacology studies have been conducted and none are needed.

2.3.4. Discussion and conclusion on clinical pharmacology

No additional pharmacokinetic or pharmacodynamic studies have been performed in support of this application. No relevant differences in the pharmacokinetics of ranibizumab are expected in the new population (patients with CNV) with respect to the patient populations previously studied (wAMD, DME, RVO, PM). Dose and method of administration are the same as for other approved indications. With this in mind, and in view of the common mechanism of action, and the low and similar systemic exposure across the previously investigated conditions, the lack of additional studies was considered acceptable by the CHMP.

2.4. Clinical efficacy

The main support for the efficacy of ranibizumab in the treatment of visual impairment due to CNV was derived from the randomised controlled phase III trial G2301 (MINERVA).

2.4.1. Dose response studies

No new dose finding studies have been conducted by the MAH. The rationale for the dose (0.5 mg) and posology used in study G2301 was based on previous experience in AMD, DME, and RVO.

The MAH stated that the 0.5 mg/injection dose has been shown to have the best benefit-risk balance in previous wAMD and RVO dose-finding studies. It is approved dose for all indications of Lucentis (RVO, AMD, DME, and CNV secondary to PM). Evidence from previously conducted AMD, DME, and RVO studies suggested that there were individual differences in treatment response and need for re-treatment. To allow for a balance of efficacy, safety and treatment burden for patients and taking into consideration the heterogeneity of the associated CNV aetiologies, an individualized ranibizumab treatment regimen was chosen for the ranibizumab treatment arm based on disease activity.

The minimum dosing interval of 1 month (4 weeks) is based on pharmacokinetic data for ranibizumab and previously collected clinical data of patients with AMD and is the same as approved for the other indications.

2.4.2. Main study

Study CRFB002G2301 (MINERVA): A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven choroidal neovascularization (CNV).

2.4.2.1. Methods

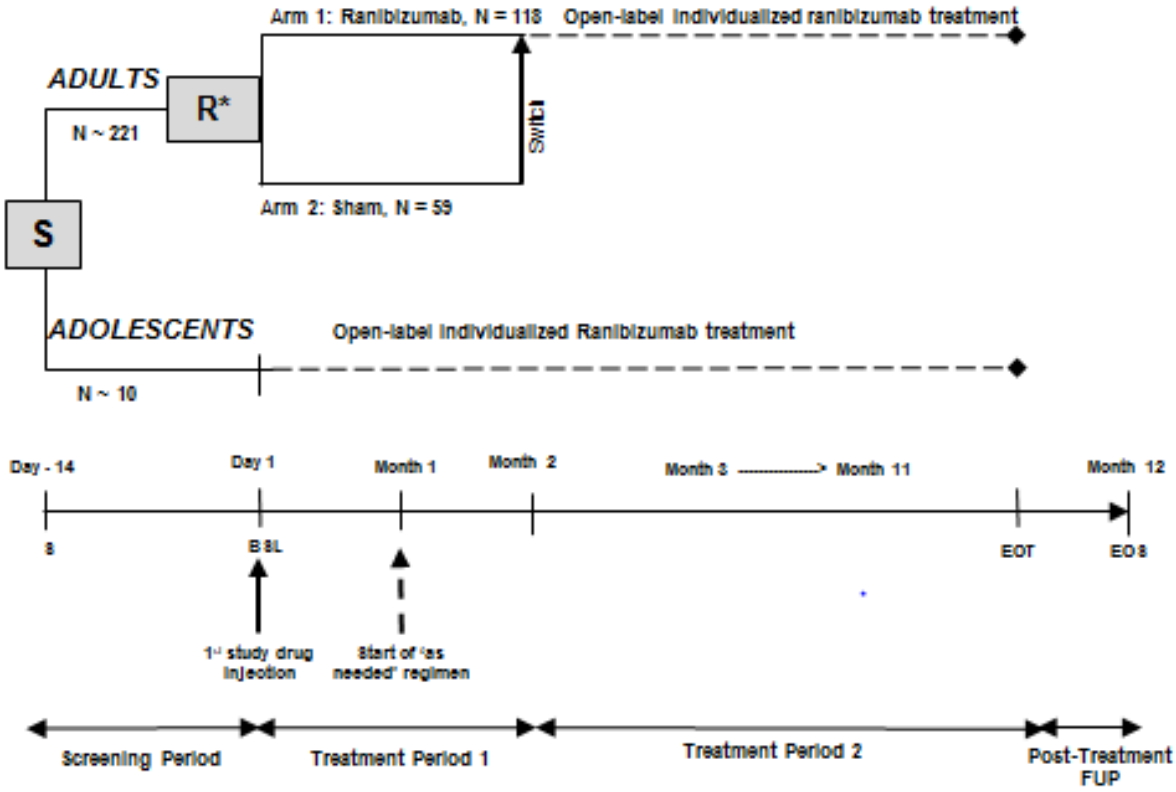
MINERVA was a 12-month, randomized, double-masked, sham-controlled, multicentre study in adult patients with visual impairment due to CNV, including a non-randomized, open-label group of adolescent patients.

The study was divided into four periods (see also Figure 1):

- Screening period,
- Treatment period 1 (double-masked for adults; open-label for adolescents),
- Treatment period 2 (open-label for adults and adolescents),
- Post-treatment follow-up period.

Consenting patients participated in an up to 14 day screening period. In addition to screening and baseline, there was a visit on Day 8, followed by monthly visits from Month 1 to Month 12.

Treatment period 2 commenced at Month 2, when all adult patients assigned to the sham arm switched to ranibizumab open-label treatment. Thus, as of Month 2, both adult and adolescent patients received open-label individualized ranibizumab IVT injections.



S = screening; R* = randomization at 2:1, including stratification by type of underlying ocular pathophysiologic mechanisms (angioid streaks vs. others); BSL = baseline; EOT = end of treatment; EOS = end of study.

Figure 1 – Schematic illustration of study G2301 design

Study participants

Main inclusion criteria

- For adults: Male or female patients ≥18 years of age; for adolescents: male or female patients ≥ 12 years of age and < 18 years of age.
- Diagnosis of active CNV secondary to any causes (for adult patients: except wAMD, polypoidal choroidal vasculopathy [PCV] or PM), with the CNV or its sequelae affecting the fovea, confirmed by at least one of the three following criteria:
    - Presence of posterior pole changes compatible with active CNV seen by fundus ophthalmoscopy and/or biomicroscopy,
    - Presence of leakage from CNV seen by fluorescein angiography (FA),
    - Presence of intra- or subretinal fluid seen by optical coherence tomography (OCT).
- At least one of the following CNV lesion in the study eye: subfoveal, juxtafoveal, extrafoveal, margin of the optic disc

- Best correct visual acuity (BCVA) ≥ 24 letters and ≤ 83 letters on Early Treatment Diabetic Retinopathy Study (ETDRS) chart.
- Visual loss in the study eye mainly due to the presence of any eligible types of CNV (for adult patients: non-wAMD and non-PM) based on ocular clinical, as well as FA and OCT findings.

Main exclusion criteria

Systemic

- History of stroke, presence of confirmed systolic/diastolic blood pressure > 160 and > 100 mmHg, respectively.
- Uncontrolled systemic inflammation or infection, related directly to the underlying causal disease of CNV.

Ocular

- Active diabetic retinopathy, active ocular/periocular infectious disease or active severe intraocular inflammation (eg, anterior chamber cells >2+ and/or vitreous haze >2+).
- Confirmed intraocular pressure (IOP) ≥ 25 mmHg for any reason.
- Neovascularization of the iris or neovascular glaucoma.
- Inability to obtain fundus photographs, fluorescein angiograms or OCT images of sufficient quality to be analysed.
- CNV secondary to wAMD, PCV or PM (for adult patients only). Retinal Angiomatous Proliferation (RAP) lesions are exclusionary in patients ≥ 50 years.
- Ocular disorders that could confound interpretation of study results, compromise visual acuity (VA) or require medical or surgical intervention during the 12-month study period.
- CNV conditions with a high likelihood of spontaneous resolution.
- History of laser photocoagulation with involvement of the macular area (study eye) at any time.
- History of intraocular treatment with any anti-VEGF therapy or IVT corticosteroids (CS) within 6 month of baseline visit. Verteporfin photodynamic therapy (vPDT) or intravitreal implants at any time (study eye).
- History of vitreoretinal surgery at any time (standard cataract surgery not an exclusion criterion) (study eye).
- Prior treatment with other anti-angiogenic drugs (including any anti-VEGF agents other than ranibizumab) within 3 months prior to baseline (fellow eye).

Treatments

Patients recruited in the study received one of the following treatments in the study eye:

- Ranibizumab 0.5 mg/0.05 mL via IVT injection,
- Sham for adult patients only; Sham injection refers to the imitation of an IVT injection using an injection syringe without a needle. Ranibizumab sham consisted of an empty vial.

Adult patients started study treatment with a 0.5 mg ranibizumab IVT or sham at baseline, followed by an individualized treatment regimen based on evidence of disease activity (see re-treatment criteria below). Patients were monitored every 4 weeks (+/- 7 days). All adolescent patients received open-label

ranibizumab 0.5 mg/0.05 mL from baseline. At Month 2, all adult patients randomized into the sham group switched to as-needed treatment with open-label ranibizumab.

Study eye: If both eyes were eligible at screening and baseline, the eye selected as the study eye was the one the investigator deemed to be more appropriate for study treatment and the study, based on the most appropriate active CNV lesion characteristics in addition to visual impairment.

Re-treatment criteria: Patients could receive additional treatment based on evidence of disease activity as judged clinically or based on morphology / imaging (e.g. VA impairment, intra-/sub-retinal fluid, haemorrhage or leakage).

Rescue therapy: vPDT could be administered to adult subjects only at Month 1, according to standard clinical practice according to the decision of the evaluating (masked) investigator, if the patient had VA loss of >5 letters due to disease activity from baseline to Month 1. 'Rescued' patients continued in the study and could obtain study treatment (ranibizumab) at Month 2. Adolescent patients did not receive protocol-specified rescue since they received ranibizumab from baseline.

Prohibited concomitant medication included, for example, systemic CS for > 15 days, systemic anti-angiogenic drugs, IVT or peri-ocular pharmacological treatment for CNV.

Objectives

The primary objective was to demonstrate that an individualized regimen of IVT injection of 0.5 mg ranibizumab has superior efficacy compared to sham treatment in adult patients with visual impairment due to VEGF-driven CNV.

The secondary objectives were to evaluate the efficacy of ranibizumab by additional assessments of changes in BCVA, changes in central subfield thickness (CSFT), central subfield volume (CSFV) and presence of intra-/sub-retinal fluid by OCT, presence of active chorioretinal leakage by FA, requirement for rescue treatment Month 1, number of ranibizumab treatments, reasons for treatment decisions and safety. This included the evaluation the efficacy of ranibizumab by original treatment assignment by assessing data up to Months 12.

Exploratory objectives included evaluation of functional and anatomical outcomes of ranibizumab treatment by the underlying categories of ocular pathophysiologic mechanisms, by baseline BCVA and age, patient reported outcomes and the efficacy and safety in adolescent patients.

Outcomes / endpoints

The primary efficacy endpoint was the change in BCVA from baseline to Month 2.

The secondary endpoints based on BCVA were:

- BCVA change from baseline by visit up to Month 2.
- Average BCVA change from baseline to Month 1 through Month 6 and 12.
- Proportion of patients with gain or loss in BCVA ≥ 1, ≥ 5, ≥ 10 and ≥ 15 letters or reaching 84 letters from baseline at Month 2 and 6 and 12.

BCVA (tested at all visits) was tested at 4 meters starting distance using ETDRS charts.

Secondary efficacy parameters based on anatomical markers were:

- Change in CSFT (within 1 mm around the foveal centre) and central subfield volume (3 mm field centred around the fovea) assessed by OCT from baseline over time to Month 2 and by visit.

- Presence of intra-/sub-retinal fluid (yes/no) assessed by OCT at Month 2, 6 and 12.
- Presence of active chorioretinal leakage (yes/no) assessed by FA at Month 2, 6 and 12.

Anatomical parameters were evaluated by a central reading centre.

Other secondary efficacy parameters included:

- Requirement for rescue treatment at Month 1.
- The number of ranibizumab treatments and re-treatments.
- Reasons for treatment decision.

Exploratory variables evaluated changes in health-related quality of life with the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) vs. baseline.

Subgroups analyses by baseline BCVA (≤60, >60 letters), age (≤60, >60 years), type of underlying ocular pathophysiological mechanism/baseline aetiology in study eye (Angioid Streaks, Central Serous Chorioretinopathy, Idiopathic Chorioretinopathy, Post-inflammatory Retinochoroidopathy, Miscellaneous), and by type of OCT-machine used ((time domain vs. spectral domain) were conducted.

Exploratory subgroup analyses of anatomical outcomes based on the above criteria were also conducted.

Sample size

Literature data formed the basis for the sample size calculation. To allow for an identification of an 8-letter (ETDRS) treatment difference between treatment arms, assuming a standard deviation (SD) of 15 letters in both treatment arm (Cordero Coma et al 2007; Arevalo et al 2009; Weiss et al 2009; Carneiro et al 2011), and using a randomisation ratio of 2:1, an alpha of 0.025 for a single, and one-sided comparison, a sample size of 112 subjects in the ranibizumab treatment arm and 56 patients in the sham treatment arm would result in a power of 89.7%. The sample size was increased by 5% to account for missing data, i.e. the study population was planned to consist of approximately 177 adult patients.

Randomisation

Adult subjects were randomised in a 2:1 ratio (ranibizumab:sham) via interactive response technology. Randomization was stratified by the type of underlying ocular pathophysiologic mechanisms (angioid streaks versus others). All adolescent patients were assigned to receive treatment with open-label 0.5 mg ranibizumab IVT injections.

Masking

Masking was limited to the adult population. Patients, investigator staff (excluding the treating investigator, see below), and persons performing the assessments remained masked to the identity of the treatment from the time of randomization until database lock. The MAH's trial team was unmasked after the Month 6 database lock; however, masking to the original treatment assignment was maintained at the site level (including patients) until Month 12.

There were at least two investigators involved into the study: the masked (evaluating) investigator who performed all assessments and captured data in the electronic Case Report Forms and an unmasked (treating) investigator who administered the randomized study treatment when needed according to the protocol. The masked evaluating investigator performed all the monthly clinical and ancillary assessments during the course of the study. The treating investigator treated the patient based on the three re-treatment assessments provided by the evaluating investigator and the randomized treatment group.

Statistical methods

The results of the study were analyzed at two time points, i.e., after Month 6 and after Month 12:

1. Month 6 database lock included analyses from Day 1 to Month 2 and from Day 1 to Month 6.
2. Month 12 database lock included analyses from Day 1 to Month 2, from Day 1 to Month 6, and from Day 1 to Month 12.

Data were summarized with respect to demographic and baseline disease characteristics, efficacy, drug exposure, and safety observations and assessments. Descriptive statistics were provided by treatment group unless otherwise specified. Where appropriate, estimates of treatment group differences, confidence intervals and p-values were presented. Efficacy analyses were based on the study eye only.

Unless otherwise specified, confidence intervals (CIs) were 2-sided and at a 95% level and hypothesis tests were evaluated at a one-sided 0.025 level of significance.

The primary efficacy variable (change in BCVA from baseline to Month 2) was analysed using a Mixed-Effect Model Repeated Measure (MMRM) with treatment group, visit, type of underlying ocular pathophysiologic mechanism (angioid streaks versus others) as factors in the model. Baseline BCVA was fitted as a continuous covariate and the interaction terms 'treatment group by visit' and 'visit by baseline' were included. A term for visit was included in the repeated statement (in SAS PROC MIXED) and an unstructured correlation matrix was used thus allowing adjustment for correlations between time points within patients.

Secondary variables were either analysed using MMRM (changes in anatomical markers over time) or by using analysis of covariance (ANCOVA). For consistency with the MMRM model, the restricted likelihood method was used for the ANCOVA as this would give the same results as least squares (LS) provided all of the variables in the model were fixed effects. Efficacy variables recorded as binary and used for statistical inference were analysed using logistic binary regression containing important baseline variables (underlying pathophysiology, baseline BCVA) on the multiple imputation dataset or on observed data, if multiple imputation fails. Descriptive statistics were used for the estimation of ranibizumab use.

Descriptive statistics were used for exploratory variables.

Missing values were handled as follows:

- For continuous data, no imputation of missing data was made for the primary analysis (MMRM model to be valid if data are missing at random - MAR). If the number of patients with missing baseline data was large or severely unbalanced between treatment arms, the mean value-last observation carried forward (MV-LOCF) single imputation was included. MV-LOCF categorise missing data as monotone (no other measurements of that variable at any future visit) or non-monotone (at least one observation for that variable at a later visit). Monotone missing data were imputed by the LOCF value and non-monotone values were imputed by the mean of the last observed value before and the first observation after the missing data.
- For binary data, missing binary data used for statistical inference was imputed by multiple imputation assuming MAR.

Subgroup analyses (based on the FAS) were performed for adult patients only based on the following criteria:

- type of underlying ocular pathophysiologic mechanisms (angioid streaks, post-inflammatory retinochoroidopathy, CSC, idiopathic chorioretinopathy and miscellaneous),
- baseline BCVA (≤ 60 letters, > 60 letters), and
- age (≤ 60 and > 60 years).

Analysis sets

- The **Full Analysis Set (FAS)** comprised all randomized patients to whom treatment regimen had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment regimen they were assigned to at randomization.
- The **Per Protocol Set (PPS)** consisted of all patients in the FAS who followed the treatment regimen as randomized and completed the study period for the analysis of the primary variable without clinically important protocol deviations.
- The **Safety Set** consisted of all adult patients who received at least one application of study treatment and had at least one post-baseline safety assessment.
- The **Adolescent Full Analysis Set** consisted of all adolescent patients assigned to treatment.
- The **Adolescent Safety Set** consisted of all adolescent patients who received at least one application of study treatment and had at least one post-baseline safety assessment.

All efficacy evaluations were carried out on the full analysis set (FAS) and the Adolescent FAS. The analysis for the primary efficacy evaluation was carried out on both the FAS and the PPS. For the sensitivity analysis, the model options repeated the options for the main analysis for the primary variable for the PPS and FAS-MV-LOCF.

For exposure and safety, patients that were reported in the sham treatment arm for the period up to Month 2 were split into the sham with ranibizumab group and the sham without ranibizumab group for the period up to Month 6 and Month 12. Patients in the sham with ranibizumab group received at least 1 injection in the study eye at or after Month 2, while patients in the sham without ranibizumab group received no ranibizumab injection(s) in the study eye.

2.4.2.2. Results

Participant flow

Overall, 194 patients were screened. Of these, 16 patients were screening failures, mainly due to failure meeting the diagnostic/severity criteria (8 patients) followed by patients who had an unacceptable past medical history/concomitant diagnosis (3 patients) or withdrew consent to participate in the study (3 patients). Patient disposition is summarised in the below table.

Table 1 – Patient Disposition

Disposition Reason	Ranibizumab 0.5 mg N = 119 n (%)	Sham N = 59 n (%)	Total N = 178 n (%)
Randomized	119 (100)	59 (100)	178 (100)
Baseline to Month 2 (primary efficacy endpoint)			
Completed 2 Months	119 (100)	58 (98.3)	177 (99.4)
Discontinued study prior to Month 2	0 (0.0)	1 (1.7)	1 (0.6)
Physician's decision	0 (0.0)	1 (1.7)	1 (0.6)
Baseline to Month 6			
Completed study period (6 Months)	118 (99.2)	56 (94.9)	174 (97.8)
Discontinued study prior to Month 6	1 (0.8)	3 (5.1)	4 (2.2)
Adverse Event(s)	0 (0.0)	1 (1.7)	1 (0.6)
Patient withdrew consent	1 (0.8)	1 (1.7)	2 (1.1)
Physician's decision	0 (0.0)	1 (1.7)	1 (0.6)
Baseline to Month 12			
Completed study period (12 Months)	112 (94.1)	55 (93.2)	167 (93.8)
Discontinued study prior to Month 12	7 (5.9)	4 (6.8)	11 (6.2)
Adverse Event(s)	1 (0.8)	1 (1.7)	2 (1.1)
Patient withdrew consent	2 (1.7)	1 (1.7)	3 (1.7)
Lost to follow-up	1 (0.8)	0 (0.0)	1 (0.6)
Protocol deviation	1 (0.8)	0 (0.0)	1 (0.6)
Pregnancy	1 (0.8)	0 (0.0)	1 (0.6)
Physician's decision	1 (0.8)	2 (3.4)	3 (1.7)

Recruitment

The first patient was enrolled on 19 -Sep-2013 and the last patient completed the 12-month period on 11-Nov-2015 (last patient last visit).

The study recruited subjects from 60 centres from 13 EU countries, Australia, Canada, Peru, Russia, South Korea, Switzerland and Turkey.

Conduct of the study

The protocol was amended once (4 May 2014), primarily to align the protocol-specified re-treatment criteria with current medical practice for the management of patients with visual impairment due to VEGF-driven CNV and 2 additional CNV conditions considered sub-categories of wAMD, PCV and RAP lesions in patients ≥ 50 years were excluded. Thus, patients with these conditions were included in the study prior to the amendment. In addition, the eligibility criteria were relaxed and editorials changes were made. The amendment was made when 28 subjects had been recruited.

Baseline data

The mean age of the adult patient population was 53.7 years and 21% of all patients were younger than 40 years. The majority of patients (89.3%) were Caucasian and the ratio was approximately 1:1 males to females per treatment arm (see Table 2)

Table 2 – Demographics by treatment group (all randomised patients)

Demographic variable	Ranibizumab 0.5 mg N=119	Sham N=59	Total N=178
Age (years)			
Mean (SD)	54.6 (15.1)	51.9 (17.3)	53.7 (15.8)
Range	19-86	20-81	19-86
Age category (years) - n (%)			
< 40	20 (16.8)	17 (28.8)	37 (20.8)
40 - 60	52 (43.7)	19 (32.2)	71 (39.9)
> 60	47 (39.5)	23 (39.0)	70 (39.3)
Sex - n (%)			
Male	59 (49.6)	29 (49.2)	88 (49.4)
Female	60 (50.4)	30 (50.8)	90 (50.6)
Predominant race - n (%)			
Caucasian	110 (92.4)	49 (83.1)	159 (89.3)
Black	1 (0.8)	0 (0.0)	1 (0.6)
Asian	4 (3.4)	7 (11.9)	11 (6.2)
Other	4 (3.4)	3 (5.1)	7 (3.9)
Ethnicity - n (%)			
Hispanic/Latino	6 (5.0)	0 (0.0)	6 (3.4)
Other	113 (95.0)	59 (100)	172 (96.6)

Ocular baseline characteristics are summarised in

Table 3 - Ocular characteristics of the study eye at baseline

Characteristics	Ranibizumab 0.5 mg N=119	Sham N=59	Total N=178
Visual acuity (letters)			
Mean (SD)	62.4 (15.0)	61.8 (14.2)	62.2 (14.7)
Min, Max	24, 83	34, 82	24, 83
Visual acuity subgroup (letters) - n (%)			
<= 60	50 (42.0)	26 (44.1)	76 (42.7)
> 60	69 (58.0)	33 (55.9)	102 (57.3)
Intraocular pressure (mmHg)			
Mean (SD)	15.2 (3.0)	15.0 (2.7)	15.2 (2.9)
Min, Max	8, 24	9, 20	8, 24
Baseline aetiology - n (%)			
CNV-Angioid streaks	18 (15.1)	9 (15.3)	27 (15.2)
CNV-Post-inflammatory retinochoroidopathy	18 (15.1)	10 (16.9)	28 (15.7)
CNV-CSC	17 (14.3)	6 (10.2)	23 (12.9)
CNV-Idiopathic chorioretinopathy	37 (31.1)	26 (44.1)	63 (35.4)
CNV-Miscellaneous	29 (24.4)	8 (13.6)	37 (20.8)
Time since diagnosis of current ocular condition (months)			
Mean (SD)	0.7 (1.6)	0.7 (1.2)	0.7 (1.5)
Min, Max	0, 14	0, 6	0, 14
Time since diagnosis of current ocular condition (months) - n (%)			
< 2	108 (90.8)	54 (91.5)	162 (91.0)
2 - <3	3 (2.5)	1 (1.7)	4 (2.2)
3 - 9	7 (5.9)	4 (6.8)	11 (6.2)
> 9	1 (0.8)	0 (0.0)	1 (0.6)
Time since diagnosis of underlying disease (months)			
Mean (SD)	30 (85.7)	14 (38.7)	24 (73.8)
Min, Max	0, 623	0, 193	0, 623
OCT and FA characteristics			
CSFT (µm) Mean (SD)	392 (145.2)	414 (155.0)	400 (148.5)

Characteristics	Ranibizumab 0.5 mg N=119	Sham N=59	Total N=178
Missing n (%)	3 (2.5)	0 (0.0)	3 (1.7)
CSFV (macular volume)* (µl) Mean (SD)	2.72 (0.677)	2.79 (0.591)	2.75 (0.648)
Missing n (%)	3 (2.5)	0 (0.0)	3 (1.7)
Sub-retinal fluid - n (%)			
Absent	16 (13.4)	7 (11.9)	23 (12.9)
Definite	102 (85.7)	52 (88.1)	154 (86.5)
Missing	1 (0.8)	0 (0.0)	1 (0.6)
Intraretinal fluid** - n (%)			
Absent	72 (60.5)	34 (57.6)	106 (59.6)
Definite	46 (38.7)	25 (42.4)	71 (39.9)
Missing	1 (0.8)	0 (0.0)	1 (0.6)
Sub-retinal haemorrhage - n (%)			
Absent	66 (55.5)	29 (49.2)	95 (53.4)
Definite	52 (43.7)	30 (50.8)	82 (46.1)
Missing	1 (0.8)	0 (0.0)	1 (0.6)
Evidence of CNV by FA- n (%)			
Absent	6 (5.0)	3 (5.1)	9 (5.1)
Definite	113 (95.0)	56 (94.9)	169 (94.9)
CNV location - n (%)			
Subfoveal	70 (58.8)	31 (52.5)	101 (56.7)
Juxtafoveal	22 (18.5)	15 (25.4)	37 (20.8)
Extrafoveal	21 (17.6)	10 (16.9)	31 (17.4)
Missing	6 (5.0)	3 (5.1)	9 (5.1)
Active chorioretinal leakage*** - n (%)			
Absent	2 (1.7)	1 (1.7)	3 (1.7)
Definite	112 (94.1)	56 (94.9)	168 (94.4)
Missing	5 (4.2)	2 (3.4)	7 (3.9)
Area of lesion (mm^2) Mean (SD)	6.09 (5.576)	5.27 (5.179)	5.82 (5.443)
Area of CNV (mm^2) Mean (SD)	4.59 (4.325)	3.75 (4.021)	4.31 (4.232)

* - CSFV is recorded by the central reading centre as inner subfield volume of the field with 3mm diameter around the foveal center.
** - Recorded as recorded Intra-retinal edema by the central reading centre
*** - Active chorioretinal leakage is measured as CNV leakage.
Source: Table 14.1-3.4, 14.1-3.5

The treatment arms were generally well balanced with respect to baseline ocular characteristics of the study eye. In addition, subjects were fairly well balanced between treatment arms with regards to intraretinal fluids, intraretinal cysts and pigment epithelium detachment. Somewhat more subjects in the ranibizumab treatment arm compared to placebo (16 versus 10%) had evidence of vitreomacular traction. The majority of patients (78%) did not have the margin of the optic disc involved. All but 2 subjects that couldn't be graded (one per treatment arm) had no capillary loss. Similarly, all but 1 subject that couldn't be graded (ranibizumab arm) had no peripheral neovascularisation.

Medical history

The proportion of patients with a relevant ocular medical history of the study eye was 26.9% in the ranibizumab arm and 22.0% in the sham arm. The most frequent ocular medical history conditions (≥5% in any arm) were cataract (9.2% in ranibizumab and 11.9% in sham), cataract operation (6.7% in ranibizumab and 6.8% in sham), vitreous opacities (2.5% in ranibizumab and 5.1% in sham), and myopia (1.7% in ranibizumab and 5.1% in sham). The proportion of patients with active ocular medical conditions of the study eye was 15.1% in the ranibizumab arm and 20.3% in the sham arm. The most frequent active ocular

medical conditions (≥ 5% in any arm) were cataract (5.0% in ranibizumab and 8.5% in sham) and myopia (0.8% in ranibizumab and 5.1% in sham)

Overall, 65.2% of patients were reported with an active non-ocular medical condition, most frequently related to the system organ class (SOC) of vascular disorders (38.8%), metabolism and nutrition disorders (25.8%), and musculoskeletal and connective tissue disorders (18.0%). A total of 65 (36.5%) patients were reported with hypertension and 18 (10.1%) patients with hypercholesterolemia.

The 5 groups baseline aetiologies included the following diagnoses/ cause of CNV:

- Angioid streaks: Angioid Streaks.
- Post-inflammatory retinochoroidopathy: Serpiginous choroiditis/retinitis, Acute posterior multifocal placoid pigment epitheliopathy, Multifocal choroiditis, Retinochoroidpathy, Punctate inner choroidopathy.
- Central Serous Chorioretinopathy (CSC): Central serous chorioretinopathy/retinochoroidpathy, Secondary CSC, Central serous choriodopathy
- Idiopathic chorioretinopathy: Idiopathic Chorioretinopathy, Idiopathic choriocapillaropathy
- Miscellaneous: RAP, Morbus Stargadt, Choroidal nevus, Macular/juxtafoveal telangiectasia Type 2, Chorioretinitis by toxoplasma, Pattern dystrophy of RPE, Adult pseudoviteliform macular dystrophy, Polipoid choroidal vasculopathy, Trauma/scar (e.g. post laser), Familial dominant drusen, Best's disease, Choroidal rupture, Haemangioma chorioideae

Numbers analysed

A total of 32 patients (18.0%) were recorded with at least one protocol deviation up to Month 12, 20 patients in the ranibizumab arm and 12 patients in the sham arm. A total of 11 patients (ranibizumab 7, sham 4) recorded protocol deviations with impact on the analyses and were excluded from the PP set. Important deviations were: did not satisfy entry criteria (n=2), wrong treatment or incorrect dose (n=4), prohibited medication (n=1), procedural deviations (n=3) and accidental unmasking (n=1).

Overall, all but one randomised subject (99.4 %) completed 2 months and 97.8 of all patients completed 6 months. Two patients discontinued the study due to an adverse event (AE).

Table 4 - Analysis sets

Analysis sets	Ranibizumab 0.5 mg n (%)	Sham with Ranibizumab 0.5 mg n (%)	Sham without Ranibizumab 0.5 mg n (%)	Total n (%)
Randomized set	119 (100)		59 (100)	178 (100)
Full analysis set	119 (100)		59 (100)	178 (100)
Per protocol set	112 (94.1)		55 (93.2)	167 (93.8)
Safety				
Day 1 to Month 2	119 (100)		59 (100)	178 (100)
Day 1 to Month 6	119 (100)	52 (88.1)	7 (11.9)	178 (100)
Day 1 to Month 12	119 (100)	52 (88.1)	7 (11.9)	178 (100)

Outcomes and estimation

Extent of exposure

The mean number of ranibizumab or sham injections received in the study eye prior to Month 2 was similar with approximately 75% of patients in each treatment arm received 2 out of 2 possible injections. The number of patients treated with ranibizumab decreased over time in the ranibizumab group. A similar

pattern was observed for patients in the sham group once they started to receive ranibizumab injections from Month 2 onward.

Table 5 - Number of ranibizumab injections received (Safety Set)

	Ranibizumab 0.5 mg N=119	**Sham with Ranibizumab* 0.5 mg N=52**	**Sham without Ranibizumab** 0.5 mg N=7**
Number of treatments			
Up to **Month 2** Mean (SD)	1.7 (0.44)	1.8 (0.43)	-
Median	2	2	-
Min, Max	1, 2	1, 2	-
Frequency of treatments - n (%)			
1	31 (26.1)	14 (23.7)	-
2	88 (73.9)	45 (76.3)	-
Up to **Month 12** Mean (SD)	5.8 (3.7)	5.4 (3.1)	0.0 (0.0)
Median	5	5	0
Min, Max	1, 12	1, 10	0, 0
Frequency of injections - n (%)			
0	0 (0.0)	0 (0.0)	7 (100.0)
1	12 (10.1)	5 (9.6)	0 (0.0)
2	12 (10.1)	6 (11.5)	0 (0.0)
3	19 (16.0)	7 (13.5)	0 (0.0)
4	13 (10.9)	6 (11.5)	0 (0.0)
5	9 (7.6)	5 (9.6)	0 (0.0)
6	11 (9.2)	6 (11.5)	0 (0.0)
7	2 (1.7)	2 (3.8)	0 (0.0)
8	8 (6.7)	1 (1.9)	0 (0.0)
9	5 (4.2)	4 (7.7)	0 (0.0)
10	7 (5.9)	10 (19.2)	0 (0.0)
11	6 (5.0)	0 (0.0)	0 (0.0)
12	15 (12.6)	0 (0.0)	0 (0.0)

* Patients in the sham group that did received ranibizumab treatment in the study eye at or after Month 2.

** Patients in the sham group that never received ranibizumab treatment in the study eye.

Throughout the 12 months, 7 patients received injections in the fellow eye in the ranibizumab group, and 8 patients in the sham with ranibizumab group. The mean number of ranibizumab injections received in the fellow eye prior to Month 12 was 5.1 in the ranibizumab group and 3.8 in the sham with ranibizumab group.

Primary efficacy endpoint

For the primary efficacy variable, BCVA change from baseline to Month 2, statistical superiority of ranibizumab compared sham was shown (one-sided p-value <0.001), with a between-treatment difference of 9.9 letters.

Table 6 - BCVA of the study eye (letters): Change from Baseline to Month 2 (FAS)

Statistic	Ranibizumab 0.5 mg N = 119	Sham N = 59
n	118	57
LS mean (SE)	9.5 (0.95)	-0.4 (1.16)
95% CI for LS mean	(7.6, 11.4)	(-2.8, 1.9)
Difference in LS means (Ranibizumab minus Sham) (SE)	9.94 (1.502)	
95% CI for difference	(6.97, 12.91)	
One-sided p-value for treatment difference [(1)]	<0.001	

n is the number of patients with data available in the analysis: One patient in the ranibizumab arm and 2 patients in the sham arm did not have BCVA values recorded at either Month 1 or 2 and are not included in the analysis
[(1)] Analyzed using MMRM, which contains scheduled visit, the type of underlying pathophysiologic mechanism (angioid streaks vs others) and treatment group as fixed effect factors, centered baseline BCVA as a continuous covariate and treatment group by visit and visit by centered baseline BCVA interactions.

The outcomes of sensitivity analyses within the FAS with imputation for missing observations using MV-LOCF and in the PPS were consistent with the primary analysis. In the FAS/MV-LOCF and PPS analyses, the treatment effect sizes were 9.8 letters (95% CI: 6.9, 12.7; p<0.001) and 10.0 letters (95% CI: 6.9, 13.1; p<0.001), respectively.

For the subgroups (baseline BCVA, age, and CNV aetiology), a consistent positive treatment effect in favour of ranibizumab was observed throughout the analyses. The magnitude of the treatment effect (LS adjusted means) across the 5 different CNV aetiology subgroups ranged from a gain of 5.0 to 14.6 letters. Patients with a lower baseline BCVA score, as well as patients 60 years of age or younger, had larger treatment effect with ranibizumab at Month 2, see Figure below.

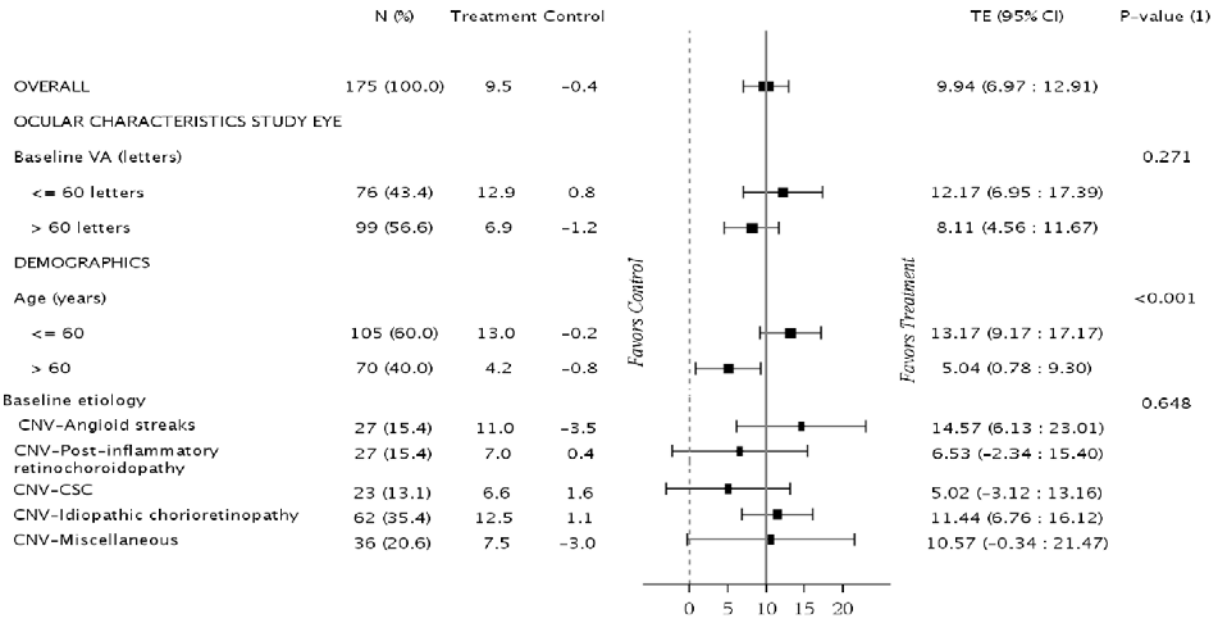


Figure 2 - Subgroup analyses of VA of the study eye (letters): Change from Baseline to Month 2 by ocular and disease characteristics (FAS)

Treatment: Ranibizumab 0.5 mg, Control: Sham, TE: Treatment effect, N:number of patients with data available in the analysis; Percentages are based on the number of patients available for the analysis.
(1) p-value is of the interaction between the subgroup and treatment.

Secondary efficacy endpoints

- Visual acuity

The mean BCVA change from baseline over time to Month 12 showed that the initial improvement in BCVA was maintained with a 11.0 letter change from baseline in the ranibizumab treatment group. In the sham arm, BCVA was unchanged at Month 2, after which patients could receive ranibizumab open-label. Thereafter BCVA improved up to Month 4 and the mean improvement was 9.3 letters at Month 12.

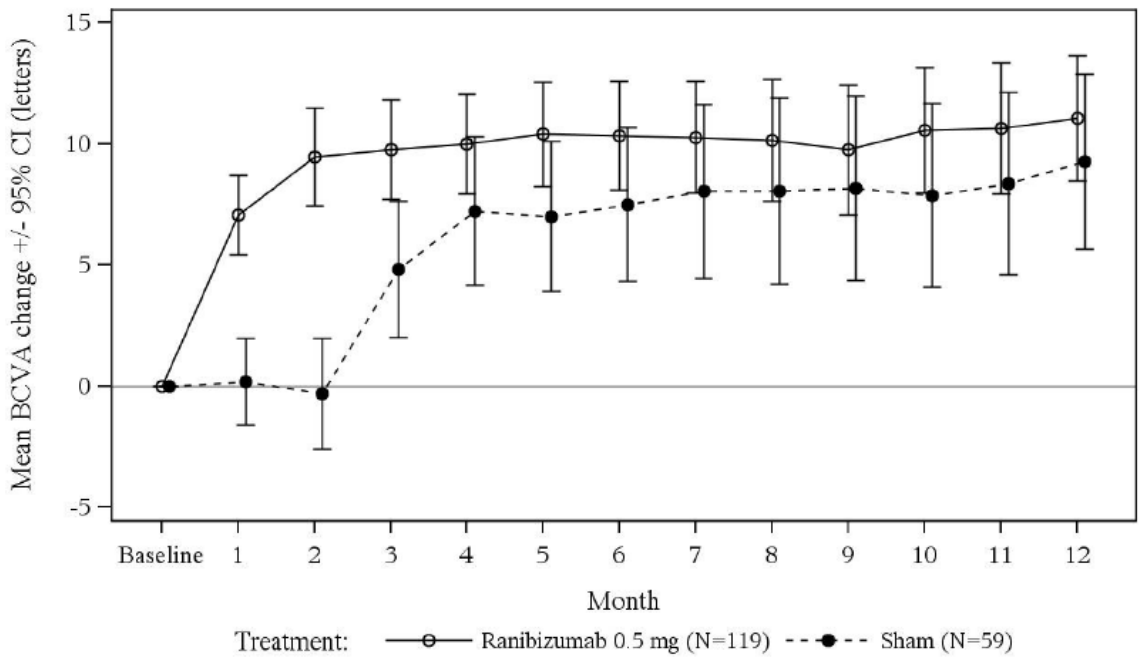


Figure 3 - VA of the study eye (letters): Change over time to Month 12 (FAS)

The average change (SD) in BCVA from baseline up to Month 12 was 6.6 (10.7) and 10.0 (11.5) in the sham and ranibizumab treatment groups, respectively.

Seven patients never received ranibizumab throughout the study. Among the 4 patients of these subjects that completed the study, 1 patient in the miscellaneous aetiology group has a stable BCVA without ranibizumab treatment, 2 idiopathic CNV patients and 1 CSC patient gained 27, 13 and 12 letters at Month 12 in comparison to baseline, respectively.

The categorised change from baseline in BCVA is summarised in the below table.

Table 7 - Categorised Change from Baseline in BCVA (FAS)

Visit	Parameter	Ranibizumab 0.5 mg N = 119 r/n (%) [95% CI](1)	Sham N = 59 r/n (%) [95% CI]
Categorised change from baseline at Month 2			
	Gain ≥ 15 letters(2)	37/118 (31.4) [23.13, 40.54]	7/57 (12.3) [5.08, 23.68]
	Gain ≥ 10 letters(2)	50/118 (42.4) [33.33, 51.81]	8/57 (14.0) [6.26, 25.79]
	Loss ≥ 10 letters	1/118 (0.8) [0.02, 4.63]	5/57 (8.8) [2.91, 19.30]
	Loss ≥ 15 letters	1/118 (0.8) [0.02, 4.63]	3/57 (5.3) [1.10, 14.62]
Categorised change from baseline at Month 6			
	Gain ≥ 15 letters(2)	53/118 (44.9) [35.75, 54.34]	20/54 (37.0) [24.29, 51.26]
	Gain ≥ 10 letters(2)	67/118 (56.8) [47.34, 65.87]	24/54 (44.4) [30.92, 58.60]
	Loss ≥ 10 letters	6/118 (5.1) [1.89, 10.74]	2/54 (3.7) [0.45, 12.75]
	Loss ≥ 15 letters	3/118 (2.5) [0.53, 7.25]	2/54 (3.7) [0.45, 12.75]
Categorised change from baseline at Month 12			
	Gain ≥ 15 letters(2)	55/113 (48.7) [39.16, 58.26]	23/55 (41.8) [28.65, 55.89]
	Gain ≥ 10 letters(2)	64/113 (56.6) [46.99, 65.93]	28/55 (50.9) [37.07, 64.65]
	Loss ≥ 10 letters	5/113 (4.4) [1.45, 10.02]	4/55 (7.3) [2.02, 17.59]
	Loss ≥ 15 letters	3/113 (2.7) [0.55, 7.56]	2/55 (3.6) [0.44, 12.53]

N: number of evaluable patients at the visit; r: number of patients satisfying the condition at the visit.
(1) Based on Clopper-Pearson exact method.
(2) Gained ≥10/15 letters or reached 84 letters in BCVA

- Anatomical variables

The central subfield thickness (CSFT) representing the average retinal thickness (Bruch's membrane to inner limiting membrane) of the circular area within 1 mm diameter around the foveal centre on OCT showed a statistically significantly greater mean reduction from baseline to Month 2 in the ranibizumab arm compared to sham (LS difference -87 µm; 95% CI for difference: -126, -48; p<0.001). At Month 6, the mean changes from baseline were -89 and -86 µm in the ranibizumab and previously sham treated subjects, respectively. At Month 12, the corresponding changes were -103 and -92 µm in the respective groups.

A summary of additional anatomical variables is provided in the following table.

Table 8 - Anatomical variables: Change from Baseline to Month 2 (FAS)

Variable	Ranibizumab 0.5 mg N = 119	Sham N = 59
N	**115**	**57**
Macular volume[1], µm		
LS mean (SE)	-0.4 (0.05)	0.0 (0.09)
Difference in LS mean, 95% CI for difference, p[2]	-0.40 (-0-60, -0-20), p<0.001	
Intra-retinal fluids[3], n		
Resolved/Present at baseline (%)	31/46 (67.4)	7/24 (29.2)
OR* (95% CI for OR), p	0.16 (0.067, 0.369), p<0.001	
Subretinal fluid[4], n		
Resolved/Present at baseline (%)	56/100 (56.0)	7/50 (14.0)
OR (95% CI for OR), p	0.12, (0.048, 0.283), p<0.001	
Active chorioretinal leakage, n		
Resolved/Present at baseline (%)	37/104 (35.6)	4/49 (8.2)
OR (95% CI for OR), p	0.20 (0.058, 0.575), p<0.001	

N: number of patients with data available in the analysis, n: number of patients meeting the analysis criteria
[1] Bruch's membrane to inner limiting membrane of the 3 mm field centred around the fovea
[2] One sided
[3] Non-cystoid fluid defined by OCT
[4] Fluid between photoreceptor outer segment tips and retinal pigment epithelium on OCT
*Adjusted for baseline covariates

The mean reduction in macular volume from baseline to Month 6 and 12 was similar in both treatment arms.

At Month 6, intra-retinal fluid present at baseline resolved in 75.6% of the patients in the ranibizumab arm and 59.1% in the sham arm. At Month 12, intra-retinal fluid present at baseline resolved in 75.6% of the patients in the ranibizumab arm and 65.2% in the sham arm.

At Month 6, subretinal fluid present at baseline resolved in 63.0% of patients in the ranibizumab arm and 60.4% in the sham arm. At Month 12, sub-retinal fluid present at baseline resolved in 67.4% of patients in the ranibizumab arm and 73.5% in the sham arm.

At Month 6, active chorioretinal leakage present at baseline resolved in 64 patients (60.4%) in the ranibizumab arm and 29 patients (64.4%) in the sham arm. At Month 12, active chorioretinal leakage present at baseline resolved in 80 patients (79.2%) in the ranibizumab arm and 37 patients (78.7%) in the sham arm.

- Other secondary and exploratory efficacy evaluations

One patient in the sham arm was given rescue treatment with vPDT as per protocol at Month 1. No patients in the ranibizumab arm required rescue treatment at Month 1.

The number of treatments is summarised in Table 5. For the majority of patients (approximately 90%), the primary reason for treatment up to Month 12 was abnormality as observed with OCT, as per assessment provided by the investigator.

The mean change (improvement, 95% CI) in the NEI-VFQ-25 composite score from baseline at Month 2 was 2.7 (1.24, 4.26) in the ranibizumab arm compared to -0.1 (-3.41, 3.13) in the sham arm. At Month 6, the corresponding figures were 5.4 (3.51, 7.31) and 3.2 (0.06, 6.25). At Month 12, the change in the composite score from baseline was 4.6 (2.47, 6.70) in the ranibizumab arm versus 2.7 (-0.58, 5.94) in the sham arm. Up to Month 2, ranibizumab was also favoured (~4 units difference or more between treatment arms) with regards to general health, near activities and driving. Smaller improvements, but numerically in favour of ranibizumab were observed for general vision, ocular pain, distance activities, social functioning, mental

health, role difficulties, colour vision and peripheral vision. Ranibizumab was not favoured with regards to dependency.

- Subgroup analyses

Subgroup analyses addressing the mean change in BCVA up to Month 2 (primary endpoint) are displayed in Figure 2. The below table summarises the mean change in BCVA up to Month 12 in subgroups by gender, baseline aetiology and location of the lesion.

Table 9 - VA of the study eye (letters): Subgroup analyses by gender, aetiology and lesion location for Change from Baseline to Month 6 and 12 (FAS)

	Month 6				Month 12			
	Ranibizumab 0.5 mg N=119		Sham N=59		Ranibizumab 0.5 mg N=119		Sham N=59	
Sub-group categories	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Gender								
Male	58	9.8 (11.06)	28	7.3 (11.26)	56	9.6 (14.25)	29	9.1 (12.59)
Female	60	10.8 (13.34)	26	7.7 (12.20)	57	12.4 (13.38)	26	9.4 (14.40)
Baseline aetiology								
CNV-AS	18	11.6 (13.12)	9	7.1 (7.62)	18	12.2 (14.79)	9	8.9 (7.03)
CNV-PIR	18	7.0 (14.65)	9	8.9 (7.32)	18	6.8 (20.20)	9	8.6 (13.24)
CNV-CSC	17	9.8 (7.13)	6	7.2 (7.73)	16	9.1 (8.67)	6	10.8 (8.04)
CNV-IC	36	13.5 (12.47)	23	10.3 (13.24)	34	14.3 (11.70)	24	11.9 (15.06)
CNV-MIS	29	8.0 (11.82)	7	-2.7 (13.97)	27	10.2 (12.93)	7	0.1 (15.91)
Lesion location								
Subfoveal	69	8.9 (12.13)	31	8.2 (13.51)	65	10.1 (12.58)	31	10.8 (14.60)
Juxtafoveal	22	12.1 (9.68)	10	10.9 (7.34)	21	11.9 (8.05)	11	14.7 (9.00)
Extrafoveal	21	13.6 (12.79)	10	3.6 (8.88)	21	12.9 (20.12)	10	2.3 (8.55)

CNV-AS=CNV-Angioid streaks, CNV-PIR=CNV-Post-inflammatory retinochoroidopathy, CNV-CSC=CNV-Central Serous Chorioretinopathy, CNV-IC=CNV-Idiopathic chorioretinopathy, CNV-MIS=CNV-Miscellaneous.
Baseline is defined as the last available non-missing value collected just prior to the start of treatment.
n: number of patients with a value for both baseline and the specific post-baseline visit for the given sub-group.

In the miscellaneous subgroup of patients (n=37), 15 different aetiologies were represented. Data from single or a few subjects were obtained for some of the aetiologies and in many cases, the randomisation to the two treatment groups was uneven. An overall benefit of ranibizumab was observed, but for a few of the aetiologies no or a very limited benefit was indicated.

The mean change in CSFT from baseline to Month 2 by subgroups that included baseline BCVA (≤60 and >60 letters) and the 5 CNV aetiology categories (including miscellaneous) were consistent with the analysis in the full data set and ranibizumab was favoured in all subgroups. The reductions in CSFT were larger in patients with baseline BCVA ≤60 letters. Across the 5 different CNV aetiologies, the mean changes ranged from -65 to -97 µm in ranibizumab arm, and the treatment effect (between-treatment difference) was between -60 and -167 µm.

With regards to macular volume, results in the subgroups were consistent with the outcome in the full data set and again ranibizumab was numerically favoured in all subgroups and there was a larger reduction in subjects with a baseline BCVA ≤60 letters.

For subretinal fluids, the data were too limited to draw any meaningful conclusions in subgroups.

Ancillary analyses

Not applicable (subgroup analyses are summarised above).

Summary of main study

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

Table 10 - Summary of Efficacy for Trial CRFB002G2301 (MINERVA)

Title: A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5 mg ranibizumab intravitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven choroidal neovascularization (CNV)			
Study identifier	Study code: CRFB002G2301 // EudraCT no.: 2012-005417-38		
Design	Adults: randomized, double-masked, sham-controlled Adolescents and adults after Month 2: open-label		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 months not applicable 10 months
Hypothesis	Superiority		
Treatments groups	Ranibizumab		0.5 mg ranibizumab IVT. After 1st injection, individualized treatment regimen based on disease activity no more frequent than every 4 weeks. Randomised: 119, completed Month 2:119, completed Month 6:118, completed Month 12: 112.
	Sham		As above, but sham injection without penetrating the eye globe. Randomised: 59, completed Month 2: 58, completed Month 6:56, completed Month 12: 55.
Endpoints and definitions	Primary endpoint	Mean change in BCVA Mo 2	Mean change in BCVA from baseline to Month 2 (letters).
	Secondary endpoint	Mean change in BCVA Mo 12	Mean change in BCVA from baseline to Month 12 (letters).
	Secondary endpoint	% of patients with ≥15 BCVA letter gain	Proportions of patients with a gain of ≥15 letters in BCVA from baseline to Month 2
	Secondary endpoint	Mean change in CSFT Mo 2	Mean change in central subfield thickness (µm) from baseline to Month 2.
Database lock	Month 6 database lock (Month 6): 21 May 2015. Last patient last visit (Month 12): 11 Nov 2015.		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	FAS (observed) 2 and 6 months		
Descriptive statistics and estimate variability	**Treatment group**	**Ranibizumab**	**Sham**
	Number of subject	**119**	**59**
	LS mean change in BCVA Mo 2 (letters)	9.5	-0.4
	95% CI	7.6, 11.4	-2.8, 1.9
	Mean change in BCVA Mo 12 (letters)	11.0	9.3

	SD	13.83	13.35
	% of patients with ≥15 BCVA letter gain, %	31.4	12.3
	95% CI	23.13, 40.54	5.08, 23.68
	Mean change in CSFT Mo 2 (µm)	-77	10
	95% CI	-94.5, -59.5	-25.6, 45.2
Effect estimate per comparison	Primary endpoint: LS mean change in BCVA Mo 2	Comparison groups	Ranibizumab vs. Sham
		Difference LS mean (letters)	9.94
		95% CI	6.97, 12.91
		P-value (one-sided)	<0.001
	Secondary endpoint: Mean change in CSFT Mo 2	Comparison groups	Ranibizumab vs. Sham
		Difference LS mean (µm)	-87
		95% CI for difference	-126.1, -47.5
		P-value (one-sided)	<0.001
Notes	Primary efficacy evaluation based on observed data without any imputation for missing data may be questioned, however, missing data and major protocol deviations very limited. Outcomes in sensitivity analyses based on MV-LOCF and the PP were essentially identical as in the primary analysis. The effects observed in the ranibizumab treatment arm at month 2 were maintained at month 6 and 12 and improvements were observed in the previously sham-treated patients after switching to ranibizumab, but with regards to the effects on BCVA, the magnitude of the effect was slightly inferior compared to subjects that received ranibizumab from baseline.		
Analysis description	**Subgroup analysis of primary endpoint by disease aetiology:** • CNV-angioid streaks (AS), • CNV – post inflammatory (PIR), • CNV-CSC (CSC), • CNV – idiopathic chorioretinopathy (IC), • CNV – miscellaneous (M)		
Analysis population and time point description	FAS (observed) 2 months		

	Treatment group	**Ranibizumab**					**Sham**				
Descriptive statistics and estimate variability		AS	PIR	CSC	IC	M	AS	PIR	CSC	IC	M
	Number of subject	18	18	17	37	28	9	9	6	25	8
	LS mean change in BCVA Mo 2 (letters)	11	7	7	12	8	-4	0	2	1	-3

Effect estimate per comparison	Secondary endpoint: Subgroups by disease aetiology	Comparison groups	Ranibizumab vs. Sham
		Difference (letters)	AS 14.6 PI 6.5 CSC 5.0 IC 11.4 M 10.6
		95% CI	AS 6.13, 23.01 PI -2.34, 15.40 CSC -3.12, 13.16 IC 6.76, 16.12 M -0.34, 21.47

Clinical studies in special populations

Study G2301 included a non-randomised, open-label group of adolescent patients who were 12 years of age and older. One of the exploratory objectives of the trial was to describe the efficacy and safety of ranibizumab in adolescent patients by assessing the same efficacy and safety objectives as planned for adult patients where applicable and depending on the number of adolescent patients enrolled.

For details on the study design and methodology see section 2.4.2.

Results

Overall, 5 adolescent patients were enrolled. All adolescent patients completed the 12-month study period and no patient discontinued from study drug. The age of adolescents ranged from 13 to 17 years at screening. Baseline aetiology was Best disease (CNV –miscellaneous) and idiopathic chorioretinopathy in 2 cases each and optic disc drusen (CNV –miscellaneous) in 1 case.

The results for change in BCVA and the key anatomical endpoint, CSFT (study eye) is shown below.

Table 11 - BCVA (letters) at baseline, Months 2, 6 and 12

Patient	Baseline	Month 2	Month 6	Month 12
#1	34	47	51*	55
#2	82	84	91	87
#3	63	73	77	77
#4	65	71	73	70
#5	46	61	81	84
Change from baseline				
Mean		9.2	16.6	16.6
Min		2	8	5
Max		15	35	38

* Month 6 visit not reported for this patient, hence Month 7 visit data presented.

Table 12 - Observed CSFT (micrometers) and change from baseline at Months 2, 6 and 12

Patient	Baseline	Month 2	Month 6	Month 12
#1	696	481	501*	490
#2	216	220	222	226
#3	245	246	247	254
#4	451	529	453	342
#5	520	495	267	234
Change from baseline				
Mean		-31.4	-87.6	-116.4
Min		-215	-253	-286
Max		78	6	10

*Month 6 visit not reported for this patient, hence Month 7 visit data presented.

Supportive study(ies)

A number of published, retrospective and prospective studies evaluating ranibizumab in the treatment of CNV secondary to other causes than AMD or PM have been provided by the MAH. Overall, they provide support for an effect on BCVA and retinal thickness.

In addition, the MAH provided the synopsis of study GFR01, an observational study of the efficacy, tolerance, and usage conditions of Lucentis in patients with CNV secondary to a pseudoxanthoma elasticum (PXE) conducted in France.

- **Study CRFB002GFR01**

Title of study: Observational study of the efficacy, tolerance, and usage conditions of Lucentis in patients with ocular complications secondary to a pseudoxanthoma elasticum

Efficacy Objectives:

- To describe the demographic and clinical characteristics of patients and of eyes with secondary to PXE that were treated with ranibizumab
- To describe the average number of ranibizumab injections, reasons for re-administration, the treatments other than ranibizumab and the average number of patient follow-up visits
- To describe the functional and anatomical changes in the patient/eye treated with ranibizumab (VA, spread of neovascularisation, retinal haemorrhages, retinal central thickness)

Methodology: This was a national, multicentre, observational historical/prospective and prospective/dynamic cohort study performed in France by ophthalmologists. The purpose of the study was to describe and monitor patients, under the conditions of current medical practice. Participation in the study was voluntary and treatments and follow-up were according to the physician discretion. Physicians participating in the study identified patients through medical record review (retrospective review from 7-Oct-2011, the date of temporary reimbursement), or prospectively during routine consultation.

Table 13 - Study scheme

Observation			Follow-up	
			Retrospective/prospective (consultation)	Prospective (assessment)
Diagnosis of CNV secondary to PXE	Period between diagnosis of CNV secondary to PXE and the first ranibizumab injection	First ranibizumab injection	For each routine consultation	3 months, then 6, 12 and 18 months after signing the consent form

Both eyes of each patient were followed-up in this study, even if only one eye was eligible.

No specific patient planned calculation was performed due to the observational study design. A total of 75 patients were enrolled and data for 72 patients were analysed. Patients were exposed from 7-Oct-2011 (historical part).

First patient enrolled: 05-Jun-2013, Last patient completed: 23-Sep-2014 (prospective part).

Diagnosis and main criteria for inclusion: Any patient with ocular complications secondary to PXE who had received at least one injection of ranibizumab no earlier than 7-Oct-2011 and signed the informed consent were eligible for inclusion. There were no specific exclusion criteria other than those who did not match those for inclusion.

Test product, dose and mode of administration: IVT injections of 0.5 mg ranibizumab

There was no primary efficacy endpoint for this study. Observational data was collected and descriptive analyses conducted on the “patient” and “eyes” populations.

Results

Demographic and background characteristics

The majority of patients were men (54.2%), the mean age was 59.6 ± 8.3 years at the time of the consent, and 44.4% had complications secondary to PXE other than ocular. Prior to the first injection of the first treated eye, the majority of patients had ocular symptoms (90.3 %) and angioid streaks (91.7%). At the time of the first injection of ranibizumab, the mean VA was 65.4 ± 19.4 ETDRS letters for the treated eye, 88.9 % of patients had CNV that were mainly subfoveal (37.5 %) and juxtafoveal (35.9 %), and 47.2% had ocular haemorrhages, of which 100% were retinal. On average, the initiation of first treatment with ranibizumab occurred within 1.4 years after the first ocular symptoms and within 0.9 years after the CNV diagnosis.

The reasons for initial treatment with ranibizumab in the "patient" population were mainly due to diagnosis of ocular complications secondary to PXE (58.3%), followed by growth of neovascular activity (34.7%) and signs of exudation (31.9%), loss of VA (25.0%), haemorrhages (22.2%) and the systematic treatment matching a treatment of "precaution" without formal signs of CNV (15.3%).

In the "eyes" population, overall, 35 eyes had received previous treatments prior ranibizumab initiation: 22.4% of eyes were treated with an anti-VEGF other than ranibizumab, 17.3% with Visudyne, 9.2% by thermal laser, and 5.1% with corticosteroids.

Efficacy results:

While 98 eyes were available for analysis at the first injection, the number of eyes available for analysis decrease over time (N=72 eyes at 1 year follow-up, N=60 eyes at 2 years of follow-up, and N=28 eyes at 4 years of follow up).

The median number of ranibizumab injections or any other treatment was 4 treatments per year for the "patient" population and 3 treatments per year for the "eyes" population. The median number of monitoring visits per year was 8.

The mean VA for the "eyes" population (N = 72) was relatively stable from first injection (64.6 ± 21.0 ETDRS letters) to the 2-year follow-up (N=58; 62.3 ± 20.4 ETDRS letters), and even up to 4-years of follow-up (N=24; 60.5 ± 20.3 ETDRS letters). Moreover, at 1 and 2 years, 59.7 % and 54.8 % of the "eyes" population, respectively, had a change in VA between -15 letters and 15 letters. The number of patients with blindness or visual impairment was limited to 29 patients during the course of the study. At the end of the study, 24 patients still had visual impairment, while VA was improved in 5 patients. Anatomically, the presence of CNV, angiographic leakage, and incidence of haemorrhages decreased during treatment with ranibizumab from the time of first injection through follow-up after 1, 2, and 4 years.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of ranibizumab for the treatment of visual impairment due to CNV due to any cause was supported by one single pivotal trial (study G2301, MINERVA).

Apart from wAMD and PM, which have been studied separately and were assessed previously, the incidence and prevalence of individual CNV conditions are very low. As VEGF is suspected to be the common factor playing a key role in their pathophysiology, patients with various CNV conditions were grouped into the MINERVA study. This approach of combining all patients into a single study has previously been agreed by the CHMP in a scientific advice. As the study population was expected to be highly heterogeneous, randomization was stratified by the type of underlying ocular pathophysiologic mechanisms (angioid streaks

versus others) and subgroups by aetiology and/or inflammatory status were predefined in order to at least have analysis groups with a potentially reduced heterogeneity. The subgroups included patients with CNV associated with angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic chorioretinopathy and miscellaneous. In the miscellaneous subgroup, subjects with, for example, retinal angiomateous proliferation, macular/juxtafoveal telangiectasia Type 2 and trauma were included. However, some of the underlying conditions within the miscellaneous subgroup were represented by single or very few patients. From these limited data, no robust conclusions regarding the treatment effect can be drawn (see also discussion on efficacy results below). On the other hand, the anti-VEGF mechanism of action of ranibizumab in the treatment of visual impairment due to CNV is well characterised, whereby ranibizumab targets choroidal vessels irrespective of the underlying disease aetiology including rare conditions. Based on this as well as the results of the MINERVA trial and previously conducted studies in AMD and PM, an extrapolation to the full CNV indication including very rare aetiologies was considered justified.

No dose-response study was conducted. Ranibizumab is intended to be administered in accordance with the dose (0.5mg) and method of administration (IVT) already included in the EU SmPC. No relevant PK differences were expected with respect to relevant groups of patients previously studied (i.e. AMD and PM populations) and the individualised posology (allowing monthly or less frequent injections) based on disease activity, as applied in the pivotal MINERVA study, was chosen to allow adjusting treatment to patients' needs as the different conditions underlying the CNV may require different frequency of injections for an optimum treatment effect. The CHMP agreed in principle to the individualised patient treatment as it would prevent from administration of unnecessary IVT injections and derived risks. However, it constitutes another source of variability at the time of analysis.

Overall, the inclusion criteria were considered acceptable, however, subjects without any visual impairment (83 letters) were allowed for inclusion and 4 such subjects were recruited (and randomised into the ranibizumab arm). According to the MAH, eligible patients also must have had active CNV with macular involvement, i.e. a condition that would be expected to lead to visual impairment, and that visual stabilisation is the treatment target in these patients. Visual stabilisation or a further improvement of BCVA was in fact achieved in the afore-mentioned 4 subjects. While not fully logical to include these subjects, it would not have affected the study outcome in favour of ranibizumab, nor does it impact on the proposed indication "treatment of visual impairment due to CNV".

The exclusion criteria were in line with those applied in previous studies with ranibizumab and considered largely reasonable and thus agreed. Two additional CNV conditions (PCV and RAP in subjects ≥50 years) were excluded in a protocol amendment since they were considered to be sub-categories of wAMD. Although the classification of these two conditions may not be clear cut, there are no objections to the strategy. The cut-off for previous treatment with intravitreal CS that may well have an effect on retinal thickness (and consequently VA) was set to 6 months which seems short in view of the long-lasting effect of available formulations of IVT fluocinolone acetonide (≥12 months) and the early evaluation of efficacy in MINERVA. However, no such prior use was reported for the study eye.

As in previous studies with ranibizumab, patients in the control arm were given an imitation of an IVT injection using an injection syringe without a needle (sham). From Month 2, the sham-treated patients were allowed to switch to as-needed treatment with open-label ranibizumab, resulting in a rather short controlled study period (see discussion on primary efficacy assessment below). The need for re-treatment was based on clinical, anatomical or functional criteria of disease activity (e.g. BCVA impairment, intra-/sub-retinal fluid, haemorrhage or leakage). The strategies for treatment, re-treatment and rescue therapy (vPDT), were overall considered acceptable.

Primary and secondary efficacy endpoints were, as in previous trials based on BCVA and anatomical variables which was considered acceptable by the CHMP. Due to the short controlled duration of the trial, the

exploratory ranking of vision-related quality of life (NEI-VFQ-25) is reasonable. Standard methods were used to assess/measure the endpoints.

The evaluation of primary efficacy at Month 2 was early for a chronic condition and given the variable natural course of the different conditions involved in the trial a longer double-blind, controlled period would have been desirable. However, it is recognised that previous studies showed the onset of action of ranibizumab to be rapid and data for the previously approved CNV-associated conditions (wAMD and CNV) did not suggest that the effect would be of limited durability. The MAH's arguments relating to the risk of a rapid worsening of the condition and the feasibility issues related to a longer controlled period are also recognised. Taken together, the strategy is accepted.

A total of 178 patients were randomised (2:1) to the two treatment groups. Since no phase II study was performed, the sample size calculation was based on published data applying a 5% adjustment for missing data, which is endorsed in view of the primary efficacy evaluation at Month 2 (i.e. assuming only few missing data for such short time period). Measures to maintain masking are in line with previous trials with ranibizumab and acceptable. However, the fact that the majority of patients are expected to be on open-label ranibizumab from Month 2 onwards may make the benefit of the masking less reliable for follow-up visits as the patient may recognise the differences between a sham and a true IVT injection.

The choice of statistical methods, i.e. MMRM and additional sensitivity analyses using ANCOVA, both assuming MAR for the missing data, was considered acceptable. A more conservative sensitivity analysis for estimating the treatment effect, with baseline observations carried forward, would have been preferred. However, all but 1 patient (sham) completed the 2 months and at Month 6 and 12, only 4 (1 ranibizumab and 3 original sham patients) and 11 (7 ranibizumab, 4 sham) patients, respectively, had discontinued. Also, the number of critical protocol deviations was limited. The issue of multiple comparisons was not addressed in the protocol and there was no control for multiple testing. Formally, only the primary endpoint analysis can be considered confirmative. However, given that the secondary endpoints evaluating the anatomical variables were highly significant and consistency was observed with regards to other outcomes (see below), overall the conduct of the study was considered acceptable.

Baseline demographics as well as ocular characteristics were overall reasonably balanced between treatment arms. In view of the overall robust outcome of the study (see discussion below), the few imbalances observed were considered unlikely to alter the results to a major extent. Considering the diversity of the diagnoses included, it is difficult to conclude whether the study population fully represented the spectrum of the target population. It is on the other hand recognised that some of the disease aetiologies are very rare and as previously discussed, the study population was considered adequate to support an umbrella CNV indication. The most common CNV subtype was located subfoveal (57% of patients) which is consistent with a population with impaired VA. Finally, concomitant medication use was as expected for the study population.

Efficacy data and additional analyses

Two months after treatment initiation, statistically significant (at the one-sided alpha-level of 0.001) and clinically relevant differences were observed in favour of ranibizumab compared to sham. Mean changes of BCVA from baseline were +9.5 and -0.4 letters in the respective treatment arms [p (one-sided) < 0.001]. Sensitivity analyses confirmed the robustness of the data which would be expected in view of the limited number of premature withdrawals and major protocol deviations. After 2 months, the gain in BCVA essentially plateaued in the ranibizumab treatment group, and was maintained up to the end of the study at 12 months. In the previously sham-treated group (could receive ranibizumab from Month 2 onwards), the 12 months mean gain in BCVA did not fully reach the same magnitude as in patients treated from study start (11.0 vs. 9.3 letters). These results suggest an added value of early treatment initiation. However, the mean

difference between treatment arms at Month 12 was limited with less than 2 letters, and the clinical relevance of such difference is questionable.

The secondary efficacy outcomes related to VA also consistently favoured ranibizumab. The proportion of patients that experienced a clinically relevant gain in BCVA was larger in the ranibizumab treatment group with 19% and 28% more patients compared to sham gaining ≥15 and 10 letters in BCVA by Month 2. At Month 6 and 12, the proportions of patients with relevant gains in BCVA had increased further and almost half of the patients (45 and 49% at Month 6 and 12, respectively) that were treated with ranibizumab from study start had gained ≥15 letters in BCVA. Very few patients lost ≥10 or 15 letters in BCVA. However, some subjects in the sham group (8/57, >10%) had gained ≥10-15 letters (or reached 84 letters) at Month 2 although conditions with a high likelihood of spontaneous resolution were to be excluded. Further review of these subjects clarified that 4 of them gained ≥ 10 letters in BCVA without reaching 84 letters and 4 reached 84 letters. Furthermore, 5 of these subjects had close to normal BCVA at baseline (i.e. only a few letters change would be needed to reach the ceiling of 84 letters) and 5 needed treatment from Month 2 or later. This indicates that some subjects improved in BCVA without treatment despite the inclusion requirement of having an active CNV with macular involvement. Notably, there were 7 patients in the study, who never received ranibizumab during the study and 4 of them completed the study. For these patients, overall, the mean final gain in BCVA was similar compared to subjects from the sham-treatment group that did receive ranibizumab from Month 2. From the available data it was however not possible to identify a definite subgroup of patients who may improve without treatment. Also, the number of patients was very limited and variability was high and although these data provide some information on the BCVA pattern without treatment, no further conclusions can be drawn since any efficacy comparison between these non-randomised subgroups will be subject to bias. In any event, patients that do worse would be more likely to receive ranibizumab.

Overall, the CHMP considered that, while in some subsets of patients a prompt treatment might be indicated, it may not be critical to initiate treatment as soon as possible in all subjects. Rather, the available data suggest that some CNV patients may not require treatment in order to maintain good vision. The decision when to initiate treatment may be best left at the discretion of the treating physician, weighing the potential benefit of early treatment against exposure to unnecessary treatment. The individualised dosing regimen based on disease activity is expected to lower the risk of unnecessary injections and the CHMP was of the view that no further recommendation could be given at the time of this report. The SmPC already states that if, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued and this also applies to CNV of any cause.

With regards to anatomical variables such as central subfield thickness (CSFT), presence of intra-/sub-retinal fluids and active leakage, a treatment effect in favour of ranibizumab was observed at Month 2 and the observed treatment differences compared to sham were highly statistically significant ($p<0.001$). A mean reduction of approximately 80 µm in CSFT was observed between baseline and Month 2 in the ranibizumab-treatment group, which was of similar size as the reduction observed in the RADIANCE study, the pivotal trial supporting the use of ranibizumab in CNV secondary to PM. The initial declines in the CSFT, macular volume, intra- and subretinal fluids and leakage were maintained or slightly decreased further throughout the study. Analyses of the anatomical variables thus supported a beneficial effect of ranibizumab in CNV.

Ranibizumab was also clearly favoured over sham in all subgroups, irrespective of disease aetiology, thus showing overall internal consistency of the study. At Month 2, the difference in BCVA change between treatment groups was largest in the subgroups with angiod streaks (14.6 letters), idiopathic chorioretinopathy (11.4 letters) and miscellaneous (10.6 letters), but ranibizumab was also favoured in the group with post-inflammatory retinochoroidopathy (6.5 letters) and in subjects with central serous chorioretinopathy (5.0 letters). While ranibizumab remained clearly in favour over sham, a smaller effect size was observed in elderly patients (> 60 years, 5 letter difference between treatment arms) compared to

younger patients (13.2 letters in the subset ≤ 60 years) and in those with higher baseline VA (8.1 letter difference in subjects with a baseline BCVA > 60 letters versus 13.7 letters in subjects with a baseline BCVA ≤ 60 letters). These results were within the range observed in the RADIANCE study for the PM indication. Further, additional analyses of the 6 and 12 months data, maintenance of the benefit of ranibizumab was confirmed in all investigated subgroups and consistency across subgroups based on gender, disease characteristics and lesion location has been shown. The CHMP however noted that in the subgroup of patients with CNV - miscellaneous and in subjects with an extrafoveal location of the lesion, the initially sham-treated subjects appeared on average to have no, or a very limited effect of treatment after receiving ranibizumab from Month 2 onwards. But these data represents a rather limited number of patients and the variability was high. Therefore, it is not possible to conclude that these subsets represent populations where treatment should be initiated at the time of diagnosis.

Among the 15 different baseline aetiologies in the heterogeneous CNV-miscellaneous subgroup of patients (n=37), while overall a benefit of ranibizumab over sham was observed, for a few of the aetiologies no or a very limited beneficial effect was seen. However, these are data based on a single or few subjects and there were inconsistencies with regards to response to treatment and the randomisation to the treatment groups was uneven. Therefore, it is not possible to draw any conclusions from these data applicable to a specific aetiology. As previously discussed, based on the underlying pathophysiology of abnormal growth of leaky vessels which is common to CNV irrespective of the cause and the anti-VEGF mechanism of action of ranibizumab, a broad CNV indication is still considered acceptable. The CHMP furthermore agreed to the MAH's proposal for SmPC section 4.1; that is to list separately indications for wAMD and CNV (including PM), as compared to most of the other CNV conditions, wAMD occurs in an older population with additional risk factors and requires intense treatment.

With regards to treatment frequency, on average half of the maximum number of injections was administered over the 12 months period of the trial, but the range was large. Some subjects received only one injection, while 13% (ranibizumab treatment group) to 19% (initially sham-treatment group) of subjects received monthly treatment. The CHMP was therefore of the view that section 4.2 of the SmPC should be updated to reflect the fact that some patients may only need one injection during the first 6 months, while others may need monthly treatment.

While maintenance of efficacy of ranibizumab has been shown for a duration of 12 months, given that at least in some subsets of patients, a chronic treatment might be required, long-term data beyond 12 months would have been desirable. The MAH argued however that the ongoing LUMINOUS study has and will provide long-term data in patients with wAMD and CNV due to PM. The 3-year observational CRFB002F2401 study will provide further data for patients with CNV secondary to PM. In addition, the observational PIXEL study study (CRFB002GFR01) provided data on 72 patients with ocular complications secondary to a pseudoxanthoma elasticum (with CNV being one of them) who received IVT ranibizumab for more than 1 year under standard medical practice conditions. Overall, patients were observed to have stable VA up to 2 years after study start based on functional observation (ETDRS), and in a smaller subset (n=24) up to 4 years. CNV regression and/or stabilization was observed, as well as a decrease in angiographic leakage, and a decrease in the incidence of ocular haemorrhages during treatment with ranibizumab from the time of first injection through follow-up up to 4 years. The results suggest a beneficial effect of ranibizumab and were considered supportive in the context of this application. But given the existing differences between the PIXEL study population and the target population of the new indication as well as the uncontrolled design of the PIXEL study, the results should be interpreted with caution. Finally, the MAH referred to available long-term data in the scientific literature and emphasised the common role of VEGF in CNV independent on underlying aetiology. In view of the substantial experience gained with ranibizumab in subjects with CNV (although mainly from patients with wAMD) so far, the CHMP agreed that no further study was needed.

Finally, with regards to the group of 5 adolescent patients, it would be expected that the efficacy profile would be largely in line with that in adults since the eye is fully developed in adolescent patients and the

underlying disease mechanism are expected to be similar. While the data were to limited to draw firm conclusions, the observed mean gain in BCVA was almost 17 letters at Month 6 and 12 (with a range from 5 to 38 letter gain at Month 12), which exceeded the number of letters gained in adults and was thus encouraging. The reduction in CSFT and SCFV was similar as in the adult population. Relevant data in the adolescent population were reflected in SmPC sections 4.2 and 5.1.

2.4.4. Conclusions on the clinical efficacy

Overall, the CHMP was of the view that, despite some limitations, the available data supported a robust and clinically relevant effect of ranibizumab in the treatment of adult patients with visual impairment due to CNV when administered based on disease activity and when using an individualised treatment regimen. The observed gain in vision in the primary analysis of the pivotal MINERVA trial was highly convincing and further supported by secondary analyses addressing other aspects of functional outcomes as well as anatomical variables. Consistency among the different disease aetiologies as well as maintenance of the effect up to 12 months has been shown. The CHMP therefore concluded that the available evidence for clinical efficacy was adequate to support the present application.

2.5. Clinical safety

Introduction

Lucentis has been approved and is marketed in the EU since 2006. The overall safety profile of Lucentis is well characterised. The majority of adverse reactions reported following administration of Lucentis are related to the IVT injection procedure. Based on previously conducted clinical trials, the most frequently reported (very common) ocular adverse reactions are vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus and intraocular pressure (IOP) increased. The most frequently reported (very common) non-ocular adverse reactions are nasopharyngitis, headache and arthralgia. Less frequently reported (common), but more serious, ocular adverse reactions include retinal detachment, retinal tear and iatrogen traumatic cataract. Less frequently reported (common) non ocular adverse reactions are urinary tract infection, anaemia, hypersensitivity, anxiety, cough, nausea and allergic reactions. Rarely reported (uncommon) ocular adverse reactions include endophthalmitis, blindness, hypopyon, hyphamia, keratopathy, iris adhesion, corneal deposits, corneal oedema, corneal striae, injections site pain, injection site irritation, abnormal sensation in eye and eyelid irritation.

There is also a theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction, following IVT use of VEGF inhibitors. In the wAMD phase III studies, non-ocular haemorrhages, an adverse event potentially related to systemic VEGF inhibition, was slightly increased in ranibizumab-treated patients compared to sham, however, without a consistent pattern among the different haemorrhages. An increased risk for death, cardiovascular accident and vascular death following monthly dosing of ranibizumab in DME patients compared to sham and laser treatment, has been shown (studies RIDE and RISE, and Avery et al., 2015).

The safety evaluation of the present application was conducted based on the known safety profile of Lucentis and the main new data assessed were derived from G2301 (MINERVA). Supportive data from the observational PIXEL study (GFR01) were also taken into consideration.

Safety assessments in study G2301 consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug and/or ocular injection, and pregnancies. They

included regular monitoring of ophthalmic examinations, haematology, blood chemistry and urine tests performed at central laboratory and regular assessments of vital signs. AEs were coded using the current MedDRA version available at the time of submission (Version 18.1).

All safety analyses were performed in patients in the safety set (see section 2.4.2.1. for study methods). Safety and tolerability of 0.5 mg ranibizumab were compared to safety and tolerability of sham injections up to Month 2. For exposure and safety, patients' data that were reported in the sham treatment arm for the period up to Month 2 were split into the sham with ranibizumab group and the sham without ranibizumab group for the period up to Month 6 and Month 12. Patients in the sham with ranibizumab group received at least 1 injection of ranibizumab in the study eye at or after Month 2, while patients in the sham without ranibizumab group received no ranibizumab injection(s) in the study eye.

Patient exposure

Exposure to ranibizumab over the course of study G2301 is summarised in Table 5. Briefly, 119 subjects have been treated with ranibizumab for up to 12 months, and of the 59 subjects who received sham up to 2 months, 52 patients were treated with ranibizumab between Month 3 and 12. Seven subjects did not receive any administration of ranibizumab in the study eye during the reporting period. Prior to Month 6 the mean number of injections in the study eye was 3.7 out of 6 possible injections in the ranibizumab group and 2.7 out of 4 possible injections in the sham with ranibizumab group. Up to Month 12, the mean number of injections in the study eye out of 12 possible injections was 5.8 in the ranibizumab group and 5.4 in the sham with ranibizumab group. Overall, 15 patients (12.6%) received the maximum possible 12 injections in the ranibizumab group, 10 patients (19.2%) received the maximum possible 10 injections in the sham with ranibizumab group, corresponding to monthly injections.

Prior to Month 6, 6 patients in the ranibizumab group, 5 patients in the sham with ranibizumab group, and none in the sham without ranibizumab group, received injections in the fellow eye. The mean number of ranibizumab injections received in the fellow eye prior to Month 6 was 3.8 in the ranibizumab group and 3.4 in the sham with ranibizumab group. In the ranibizumab group, 5 of the 6 patients received 1 to 6 injections in the fellow eye. In the sham with ranibizumab group, 5 of the 5 patients received 3 or 4 injections in the fellow eye. Up to Month 12, the mean number of injections in the fellow eye out of 12 possible injections was 5.1 in the ranibizumab group and 3.8 in the sham with ranibizumab group.

Patient disposition and baseline demographics of study G2301 are shown in Table 1 and Table 2. Baseline disease (ocular) characteristics are shown in Table 3. Baseline aetiology was dominated by CNV-idiopathic chorioretinopathy in both treatment groups (31.1% in ranibizumab group and 44.1% in sham group). The CNV-miscellaneous group was almost twice as large in the ranibizumab group (24.4%) as in the sham group (13.6%).

In study GFR01, 72 patients had an average duration of treatment with ranibizumab of 2.4 ± 2.2 years (median: 2.1 years) and the average number of injections was 4.1 ± 4.0 (median: 3).

Adverse events

Ocular adverse events

- Study eye

A total of 14 (11.8%) and 11 (18.6%) patients in the ranibizumab and sham arm, respectively, experienced ocular adverse events (AEs) in the study eye up to Month 2, regardless of study drug relationship.

At Month 12, the frequency of ocular AEs of the study eye was 25.2% (30 patients) in the ranibizumab group, 42.3% (22 patients) in the sham with ranibizumab group, and 42.9% in the sham without ranibizumab group.

Table 14 - Number (%) of patients with ocular AEs of the study eye up to Month 12 (≥5% in any group) by MedDRA preferred term (safety set)

Preferred term	Ranibizumab 0.5 mg N=119 n (%)	Sham with Ranibizumab 0.5 mg N=52 n (%)	Sham without Ranibizumab 0.5 mg N=7 n (%)	Total N=178 n (%)
Total	30 (25.2)	22 (42.3)	3 (42.9)	55 (30.9)
Conjunctival haemorrhage	7 (5.9)	6 (11.5)	0 (0.0)	13 (7.3)
Choroidal neovascularisation	3 (2.5)	0 (0.0)	1 (14.3)	4 (2.2)
Visual acuity reduced	3 (2.5)	1 (1.9)	1 (14.3)	5 (2.8)
Conjunctivitis	2 (1.7)	3 (5.8)	0 (0.0)	5 (2.8)
Foreign body sensation in eyes	1 (0.8)	1 (1.9)	1 (14.3)	3 (1.7)
Ocular hyperaemia	1 (0.8)	1 (1.9)	1 (14.3)	3 (1.7)
Photopsia	1 (0.8)	0 (0.0)	1 (14.3)	2 (1.1)
Eye inflammation	0 (0.0)	0 (0.0)	1 (14.3)	1 (0.6)
Macular oedema	0 (0.0)	0 (0.0)	1 (14.3)	1 (0.6)

AEs with start date on or after the date of first administration of study treatment in the study eye are included. A patient with multiple occurrences of a preferred term is counted only once in the preferred term row. Coded with MedDRA version 18.1.

- Fellow eye

A total of 11 patients were treated with ranibizumab in the fellow eye up to Month 6. Three patients (2 in the ranibizumab and 1 in the sham group) experienced ocular AEs. The AEs reported were conjunctival haemorrhage, IOP increase, lacrimation increased, ocular hyperaemia. A total of 15 patients were treated with ranibizumab in the fellow eye up to Month 12 (7 in the ranibizumab group and 8 in the sham with ranibizumab group). Six patients (5 in the ranibizumab group and 1 in the sham with ranibizumab group) experienced ocular AEs in the fellow treated eye.

Table 15 - Number (%) of patients with ocular AEs of the fellow treated eye up to Month 12 (≥5% in any group) by MedDRA preferred term (safety set)

Preferred term	Ranibizumab 0.5 mg N=119 n (%)	Sham with Ranibizumab 0.5 mg N=52 n (%)	Sham without Ranibizumab 0.5 mg N=7 n (%)	Total N=178 n (%)
Number of patients with fellow treated eye	7 (100)	8 (100)	0 (0.0)	15 (100)
Total	5 (71.4)	1 (12.5)	0 (0.0)	6 (40.0)
Conjunctival haemorrhage	1 (14.3)	0 (0.0)	0 (0.0)	1 (6.7)
Intraocular pressure increased	1 (14.3)	0 (0.0)	0 (0.0)	1 (6.7)
Iridocyclitis	1 (14.3)	0 (0.0)	0 (0.0)	1 (6.7)
Ocular hypertension	1 (14.3)	0 (0.0)	0 (0.0)	1 (6.7)
Retinal exudates	1 (14.3)	0 (0.0)	0 (0.0)	1 (6.7)
Lacrimation increased	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.7)
Ocular hyperaemia	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.7)
Retinal haemorrhage	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.7)
Retinal oedema	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.7)
Visual acuity reduced	0 (0.0)	1 (12.5)	0 (0.0)	1 (6.7)

AEs with start date on or after the date of first administration of study treatment in the fellow eye. A patient with multiple occurrences of a preferred term is counted only once in the preferred term row. Coded with MedDRA version 18.1.

- Relation to study drug

Up to Month 2, there were no ocular AEs of the study eye reported, which were suspected by the investigator to be related to study drug, neither in the ranibizumab arm nor the sham arms. From Month 2 to Month 6, 3 ocular AEs which were suspected to be related to study drug were reported for 2 patients in the ranibizumab group (retinal cyst, vitreous floaters, and IOP increased) and 1 ocular AE was reported for 1 patient in the sham with ranibizumab group (retinal pigment epithelial tear). No ocular AEs which were suspected to be related to study drug were reported in the sham without ranibizumab group. No ocular AEs of the fellow treated eye were suspected by the investigator to be related to study drug up to Month 6. Up to Month 12, no additional ocular AE suspected by the investigator to be related to study drug was reported.

- Relation to ocular injection

Up to Month 2, the most commonly reported (≥2%) ocular AE of the study eye, suspected to be related to ocular injection was conjunctival haemorrhage (4.2% vs 1.7% in the ranibizumab arm and sham arm, respectively). Up to Month 6, the most commonly reported (≥5% in any arm) ocular AE was conjunctival haemorrhage (5.9% and 9.6% of patients in the ranibizumab group and the sham with ranibizumab group, respectively and none were reported in the sham without ranibizumab group).

Up to Month 2, out of the 8 patients treated in the fellow eye, 2 patients experienced AEs related to ocular injection (conjunctival haemorrhage and increased IOP). Up to Month 6, 11 patients were treated with ranibizumab in the fellow eye including 6 in the ranibizumab group and 5 in the sham with ranibizumab group. Of these, 3 patients experienced ocular AEs in the fellow eye including 2 patients in the ranibizumab group (one with conjunctival haemorrhage and one with IOP increased) and 1 patient in sham group (lacrimation increased and ocular hyperaemia).

Up to Month 12, 12.6% of patients in the ranibizumab group, 23.1% of patients in the sham with ranibizumab group, and 14.3% of patients in the sham without ranibizumab group experienced an ocular AE of the study eye suspected by the investigator to be related to the ocular injection. The most commonly

reported (≥ 2%) ocular AE suspected to be related to the ocular injection was conjunctival haemorrhage (5.9% and 11.5% of patients in the ranibizumab and the sham with ranibizumab groups, respectively and none of the patients in the sham without ranibizumab group).

Up to Month 12, a total of 15 patients were treated in the fellow eye (7 in the ranibizumab group, 8 in the sham with ranibizumab group, and none in the sham without ranibizumab group). No additional ocular AEs were suspected by the investigator to be related to the ocular injection from Month 6.

- Severity

Ocular AEs of the study eye up to Month 2 and up to Month 12 were predominantly of mild severity, regardless of study drug relationship. Up to Month 6, 14.3%, 23.1% and 28.6% of patients experienced mild AEs in ranibizumab, sham with ranibizumab and sham without ranibizumab, respectively. Up to Month 6, 1 patient in the sham with ranibizumab group experienced severe reduced VA which was not suspected to be related to study drug. Up to Month 6, 1 patient in the ranibizumab group experienced severe retinal haemorrhage, which was not suspected to be related to study drug.

From Month 2 to Month 6, 1 patient in the ranibizumab group experienced severe diabetic retinal oedema in the fellow untreated eye. From Month 6 to Month 12, 1 patient in the ranibizumab group experienced severe retinal detachment in the fellow untreated eye. Neither was suspected to be related to study drug.

Non-ocular events

A total of 28 patients, including 18 patients (15.1%) in the ranibizumab arm and 10 patients (16.9%) in the sham arm, experienced non-ocular AEs up to Month 2, with no AE preferred term being observed in at least 5% of the patients in either treatment arm. The most frequently reported MedDRA system organ class (SOC) was gastrointestinal disorders (5.9% in the ranibizumab arm and none in the sham arm) with all AE frequencies <1%, followed by infections and infestations (3.4% in the ranibizumab arm and 6.8% in the sham arm) with all AE frequencies <2%. A total of 67 patients (45 [37.8%] in the ranibizumab group, 19 [36.5%] in the sham with ranibizumab group, and 3 [42.9%] in the sham without ranibizumab group) experienced non-ocular AEs up to Month 6. The most commonly reported preferred term (≥5% in any group) was nasopharyngitis (7.6%, 11.5%, and 14.3% in the ranibizumab, sham with ranibizumab, and sham without ranibizumab arms, respectively).

Back pain, hypertension, and headache were observed in at least 5% of the patients in the sham without ranibizumab group. Each of these three AEs was experienced by 1 patient (14.3%) in the sham without ranibizumab group (7 patients). In the other 2 groups (ranibizumab and sham with ranibizumab), the incidence of these events was <5%.

Non-ocular AEs observed in at least 5% of patients in the ranibizumab group experienced AEs originating from the SOC gastrointestinal disorder, musculoskeletal and connective disorders and nervous system disorders.

A total of 95 patients (67 [56.3%] in the ranibizumab group, 25 [48.1%] in the sham with ranibizumab group, and 3 [42.9%] in the sham without ranibizumab group) experienced non-ocular AEs up to Month 12 (see below table). The most commonly reported preferred term was nasopharyngitis (11.8%, 17.3%, and 14.3%, respectively). Influenza, back pain, sinusitis, and headache were also observed in at least 5% of the patients in the ranibizumab or sham with ranibizumab group.

Table 16 - Number (%) of patients with non-ocular AEs up to Month 12 (≥ 5% in any group)

Preferred term	Ranibizumab 0.5 mg N=119 n (%)	Sham with Ranibizumab 0.5 mg N=52 n (%)	Sham without Ranibizumab 0.5 mg N=7 n (%)	Total N=178 n (%)
Total	67 (56.3)	25 (48.1)	3 (42.9)	95 (53.4)
Nasopharyngitis	14 (11.8)	9 (17.3)	1 (14.3)	24 (13.5)
Influenza	9 (7.6)	0 (0.0)	0 (0.0)	9 (5.1)
Back pain	6 (5.0)	0 (0.0)	1 (14.3)	7 (3.9)
Hypertension	5 (4.2)	1 (1.9)	1 (14.3)	7 (3.9)
Sinusitis	2 (1.7)	3 (5.8)	0 (0.0)	5 (2.8)
Headache	1 (0.8)	3 (5.8)	1 (14.3)	5 (2.8)
Pneumonia	1 (0.8)	0 (0.0)	1 (14.3)	2 (1.1)

Adverse events with start date on or after the date of first administration of study treatment in the study eye are included. A patient with multiple occurrences of a preferred term is counted only once in the preferred term row. Coded with MedDRA version 18.1.

- Relation to study drug

No non-ocular AEs were suspected by the investigator to be related to study drug up to Month 2. Up to Month 6, 2 AEs were reported for 1 patient in the ranibizumab group (arrhythmia of moderate intensity and blood pressure increased of mild intensity) which were suspected by the investigator to be related to study drug. From Month 6 to Month 12, no additional non-ocular AE suspected by investigator to be related to study drug was reported.

- Relation to ocular injection

Up to Month 2 and up to Month 6, there were no non-ocular AEs reported for patients treated with ranibizumab, which were suspected by the investigator to be related to the ocular injection procedure. Up to Month 12, 1 non-ocular AE (headache) was reported for a patient in the sham without ranibizumab group, which was suspected by the investigator to be related to the ocular injection procedure.

- Severity

Up to Month 2, non-ocular AEs experienced by patients in the ranibizumab and the sham arm were predominantly of mild severity. One patient in the ranibizumab arm experienced a severe AE of foot fracture. No other severe AEs were reported up to Month 2.

Up to Month 6 and 12, the majority of non-ocular AEs experienced by patients in the ranibizumab group and the sham with ranibizumab group were of mild or moderate severity. From Month 2 to Month 6, 2 additional severe non-ocular AEs occurred in the ranibizumab group (1 patient with sciatica and 1 patient with parkinsonism, also reported as an SAE), and in 1 patient in the sham with ranibizumab group (fecaloma, also reported as an SAE). From Month 6 to Month 12, 2 additional severe non-ocular AEs occurred in the ranibizumab group and 1 additional AE occurred in the sham with ranibizumab group including peripheral artery stenosis, invasive lobular breast carcinoma and hepatocellular carcinoma.

Supportive safety data from study GFR01

Of the 72 study participants, 14 patients (19.4%) experienced at least one AE. The most frequent AEs observed by MedDRA SOC were eye disorders (10 patients, 13.9%), nervous system disorders (3 patients, 4.2%) and infections and infestations (2 patients, 2.8%). The most frequently reported AEs were ocular pain (3 patients, 4.2%) and decreased VA (2 patients, 2.8%). All other AEs occurred occasionally with a

frequency equal to 1.4% (1 patient). Six patients (8.3%) reported at least one SAE, including ischemic cerebral infarction, transient ischemic attack. No deaths were reported. The non-serious AEs (n = 14) were mainly ocular (13/14), the majority were mild in severity (12/14) and were considered unrelated to study drug by the ophthalmologists (for those for which causality was available). However, 7 of them were considered potentially related to the IVT procedure (amaurosis fugax, retinal artery spasm, conjunctival haemorrhage, 2 cases of eye pain, blurred vision, and eye irritation). Among the non-ocular AEs cerebral vascular events were reported in 2 subjects (vertebral artery occlusion, carotid artery stenosis, ischemic cerebral infarction, transient ischemic attack)

Serious adverse event / deaths / other significant events

Table 17 provides an overview of SAEs or AEs leading to permanent discontinuation of study drug reported in study G2301 up to Month 12.

Table 17 - Number (%) of patients who experienced SAEs or AEs leading to permanent discontinuation of study drug up to Month 12 (safety set)

Patients with serious or significant AEs	Ranibizumab 0.5 mg N = 119 r/n (%)	Sham with Ranibizumab 0.5 mg N = 52 r/n (%)	Sham without Ranibizumab 0.5 mg N = 7 r/n (%)	Total N = 178 r/n (%)
Death	0/119 (0.0)	0/52 (0.0)	0/7 (0.0)	0/178 (0.0)
SAEs	9/119 (7.6)	4/52 (7.7)	0/7 (0.0)	13/178 (7.3)
Study eye	0/119 (0.0)	0/52 (0.0)	0/7 (0.0)	0/178 (0.0)
Fellow treated eye	0/7 (0.0)	0/8 (0.0)	0/0	0/15 (0.0)
Fellow untreated eye	1/119 (0.8)	0/52 (0.0)	0/7 (0.0)	1/178 (0.6)
Non-ocular	8/119 (6.7)	4/52 (7.7)	0/7 (0.0)	12/178 (6.7)
Permanently discontinued study drug due to SAEs	2/119 (1.7)	0/52 (0.0)	0/7 (0.0)	2/178 (1.1)
Study eye	0/119 (0.0)	0/52 (0.0)	0/7 (0.0)	0/178 (0.0)
Fellow treated eye	0/7 (0.0)	0/8 (0.0)	0/0	0/15 (0.0)
Fellow untreated eye	0/119 (0.0)	0/52 (0.0)	0/7 (0.0)	0/178 (0.0)
Non-ocular	2/119 (1.7)	0/52 (0.0)	0/7 (0.0)	2/178 (1.1)
Permanently discontinued study drug due to AEs	2/119 (1.7)	0/52 (0.0)	1/7 (14.3)	3/178 (1.7)
Study eye	0/119 (0.0)	0/52 (0.0)	1/7 (14.3)	1/178 (0.6)
Fellow treated eye	0/7 (0.0)	0/8 (0.0)	0/0	0/15 (0.0)
Fellow untreated eye	0/119 (0.0)	0/52 (0.0)	0/7 (0.0)	0/178 (0.0)
Non-ocular	2/119 (1.7)	0/52 (0.0)	0/7 (0.0)	2/178 (1.1)

N = Number of patients in the treatment group
r/n: r is the number of the patients with at least one AE in the corresponding category; n is the number of patients in the safety set in the specific treatment group except for (i) ocular AE of the treated fellow eye, where n is the number of patients with a treated fellow eye, and (ii) ocular AE of the untreated fellow eye, where n is the number of patients with an untreated fellow eye.

Serious Adverse Events (ocular and non-ocular events)

No SAEs were reported in any treatment group up to Month 2. Up to Month 6, a total of 6 patients experienced non-ocular SAEs, 3 patients in the ranibizumab group and 3 patients in the sham with ranibizumab group. Two of these SAEs, Parkinsonism and fecaloma, were severe in intensity; none of the SAEs were suspected to be related to study treatment or ocular injection. Up to Month 12, there were no ocular SAEs in the study eye or in the fellow treated eye. One patient experienced an ocular SAE (retinal

detachment) in the fellow untreated eye judged as not suspected to be related to the study drug and ocular injection. Up to Month 12, a total of 12 patients experienced non-ocular SAEs, 8 patients in the ranibizumab group and 4 patients in the sham with ranibizumab group.

Deaths

There were no deaths in the study up to Month 12 or during the study.

Other significant events

All AEs of the study eye which occurred up to Month 2 and that were related to ocular safety concerns are summarized, based on AEs defined as safety concerns in the risk management plan (RMP), are presented below.

Table 18 - Key risks up to Month 6 and 12 based on RMP vers. 14 Jan 2015 (safety set)

	6 Months		12 Months	
	Ranibizumab 0.5 mg N=119		Ranibizumab 0.5 mg N=119	
Risk category	n (%)	95% CI[1]	n (%)	95% CI[1]
Ocular risks (study eye)				
Infectious endophthalmitis	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Intraocular inflammation	3 (2.5)	[0.5, 7.2]	3 (2.5)	[0.5, 7.2]
Traumatic cataract	0 (0.0)	[0, 2.5]	0 (0)	0, 2.5
Intraocular pressure increased	3 (2.5)	[0.5, 7.2]	4 (3.4)	[0.9, 8.4]
Retinal detachment and retinal tear	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Retinal pigment epithelial tear	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Vitreous haemorrhage	1 (0.8)	[0, 4.6]	1 (0.8)	[0, 4.6]
Glaucoma	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Non-ocular risks				
Myocardial infarction	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Non ocular haemorrhage	0 (0.0)	[0, 2.5]	0 (0.0)	[0, 2.5]
Non-myocardial arterial thromboembolic events	1 (0.8)	[0, 4.6]	1 (0.8)	0, 4.6
Venous thromboembolic events	0 (0.0)	[0, 2.5]	0 (0)	[0, 2.5]
Hypertension	6 (5.0)	[1,.9, 10.7]	7 (5.9)	[2.4, 11.7]

Multiple occurrences of the same event in a patient were counted only once. Coded with MedDRA version 18.1.
[1] Based on Clopper-Pearson exact method.

Immunological events

Hypersensitivity reactions were reported in 1.7% of the patients in the ranibizumab group and 3.4% in the sham group up to Month 2. Up to Month 6, 1 patient reported contrast media allergy in the ranibizumab group.

Supportive safety data from study GFR01

A total of 10 SAEs (recurrence of chronic macular oedema, ischemic cerebral infarction, transient ischemic attack, bicuspid aortic valve, aortic dilatation, vertebral artery occlusion, carotid artery stenosis, endophthalmitis, pilonidal cyst and visual acuity reduced) were reported in 6 patients. Five of the 10 SAEs (cerebral protuberance ischemic infarction, aortic dilatation, vertebral artery occlusion, carotid artery stenosis, and endophthalmitis) were severe in intensity. The causality of one SAE cerebral protuberance ischemic infarction was considered to be related to ranibizumab. The case of endophthalmitis was considered to be possibly related to the IVT procedure. None of these SAEs were attributed to the use of other treatment. No death was reported during the study.

Laboratory findings

Overall, no shifts in haematology parameters were observed. One patient reported low platelets (criterion: <50x10E9/L) in the ranibizumab arm at baseline but they recovered during treatment.

There were also no shifts in biochemistry values: In the ranibizumab arm, 1 patient had low sodium values (criterion: <120 mmol/L) at baseline which returned to normal post-baseline. An additional patient had high potassium values (criterion: >6.0 mmol/L) at baseline, which recovered with treatment at Month 2, but was elevated again at Month 6.

Only sporadic changes were found in the urinalysis parameters over time.

Vital signs, electrocardiogram and other observations related to safety

Low pulse and high systolic and diastolic blood pressure values were observed in three patients in the ranibizumab arm up to Month 6. No electrocardiograms were performed in the study. No notable changes in vital signs were observed up to Month 12.

Intraocular pressure

Three patients in the ranibizumab arm met the criteria of IOP of 30 mmHg or greater of the study eye at any time post-baseline, with one of these incidents being reported post-baseline but pre-injection. There were no patients with IOP of 30 mmHg or greater in the fellow eye at any time post-baseline.

Safety in special populations

Paediatrics

Safety data for the 5 adolescent patients recruited into study G2301 are summarised below. The exposure in the study eye of the adolescent patients is presented in Table 19.

Table 19 - Exposure of study medication in the study eye

Patient	#1	#2	#3	#4	#5
Treatment received at	Baseline, Months 1, 2	Baseline, Month 9	Baseline, Months 1, 3	Baseline, Month 1	Baseline, Months 1, 2, 4, 5

Patient #1 also received 4 ranibizumab injections at Months 3, 4, 7 and 10 in the fellow eye diagnosed with CNV due to Best disease at baseline (same CNV aetiology as in the study eye).

No patient died. No SAEs, no severe AEs and no AEs suspected to be related to study drug were reported.

Ocular AEs of the study eye and the fellow eye and non-ocular adverse events by patient are displayed in the below table.

Table 20 - Treatment emergent ocular (study and fellow eye) and non-ocular AEs by patient up to Month 12 by MedDRA preferred term

Patient	#1	#2	#3	#4	#5
Ocular adverse events					
Study eye	Ocular discomfort (S) Conjunctival haemorrhage (S) Eye pain (S) Ocular hyperaemia Eye swelling Vision blurred	Conjunctival haemorrhage (S) Visual impairment CNV	Dry eye (S) Conjunctival haemorrhage (S) Scratch (S)	N/A	N/A

	Conjunctival hyperaemia				
Fellow eye	Vision blurred Lacrimation increased (S)	Visual impairment	N/A	N/A	N/A
Non-Ocular adverse events					
	Headache (S) Pyrexia Dizziness Weight increased Tendonitis Vertigo	Epistaxis Abdominal pain lower	Toxoplasmosis Nasopharyngitis	N/A	N/A

S: at least one episode with suspected relationship to ocular injection

No clinically notable abnormal vital signs and no positive pregnancy tests were identified.

There were no patients with IOP of ≥ 30 mmHg in the study eye at any time post-baseline.

Aetiology subgroups

Based on baseline aetiology, there were no AEs which occurred up to Month 2 that constituted ocular safety concerns in 2 of the 5 subgroups: patients with angioid streaks and post-inflammatory retinochoroidopathy CNV. In patients with CNV-CSC and with idiopathic chorioretinopathy, 1 patient each in the ranibizumab and the sham arm experienced intraocular inflammation up to Month 2 (CNV-CSC: 5.9% and 16.7%; Idiopathic chorioretinopathy: 2.7% and 3.8%, respectively). In the subgroup of patients with miscellaneous disorders, 1 patient (3.4%) in the ranibizumab arm experienced a non-ocular risk of non-myocardial arterial thromboembolic events up to Month 2.

Pregnancy and lactation

There was one pregnancy reported during the 12 Month period of study G2301. The patient was discontinued accordingly. Pregnant women were excluded from the study as were women of childbearing potential unless they used effective methods of contraception during dosing of study drug.

Discontinuation due to adverse events

An overview of discontinuations due to AEs is given in Table 17. Up to Month 2, one patient with idiopathic chorioretinopathy CNV, in the sham arm reported ocular AEs (macular oedema and reduced visual acuity) in the study eye on Day 4 of the study. The patient was discontinued from the study. The events resolved 80 days later. The investigator considered these AEs not to be related to study drug. There were no patients who discontinued from the study due to non-ocular AEs up to Month 2.

Up to Month 6, overall 3 patients discontinued permanently due to an SAE or AE. One patient discontinued permanently from study drug due to a non-ocular SAE in the ranibizumab group (benign pituitary tumour, assessed by investigator as unrelated to study drug). Two patients discontinued permanently from study drug due to AE, one patient discontinued due to an ocular event in the study eye in sham without ranibizumab group, and one patient discontinued due to a non-ocular AE in the ranibizumab group.

No further patients discontinued from the study due to an AE up to Month 12.

Post marketing experience

There is no post-marketing experience from use of Lucentis in the broad CNV indication including angioid streaks, post-inflammatory retinochoroidopathy, CSC, idiopathic choroidopathy and CNV-miscellaneous. Lucentis (ranibizumab) is approved for the treatment of wAMD since 2007, for the treatment of visual impairment due to DME and RVO since 2011 and for CNV secondary to PM since 2013. The estimated

cumulative post-marketing patient exposure since the International Birth Date i.e. from 30 June 2006 through to 31 December 2014 is 3.7 million patient years (based on the number of ranibizumab vials and ranibizumab pre-filled syringes sold worldwide, PSUR 12).

2.5.1. Discussion on clinical safety

The main support for the safety evaluation of the present application was derived from the 12 months data of the pivotal controlled trial G2301 (MINERVA), including comparative data (ranibizumab versus sham) for the first 2 months of the study. The safety database comprised a total of 178 patients with visual impairment due to CNV and the vast majority of these (167 patients, 93.8%) completed Month 12. The submitted 12 Month data also included data from five adolescent patients receiving open-label ranibizumab. In addition, supportive safety data from the observational study GFR01 (PIXEL) in patients with ocular complications secondary to PXE was submitted. Patients included in this study are closely related to some of the conditions covered by the MINERVA study and the proposed new indication of CNV, and a relevant number of subjects have been recruited and continued in the study up to 4 years. Thus, the data were considered supportive for the purpose of this application.

Generally, the ocular AEs reported in the MINERVA study were few and mild in severity, usually occurring in single patients with a frequency of <5%, except for injection related conjunctival haemorrhage, reported up to Month 6 in 5.9%, 9.6% and 0.0% of the patients in the ranibizumab, the sham with ranibizumab (i.e. patients originally assigned to sham with at least 1 ranibizumab treatment at or after Month 2) and the sham without ranibizumab group (i.e. patients originally assigned to the sham group with no ranibizumab treatment at or after Month 2), respectively. Up to Month 12, the pattern for conjunctival haemorrhage remained unchanged. In addition, conjunctivitis was reported in 3 patients (5.8%) in the sham with ranibizumab group compared to 2 patients (1.7%) and no patients in the ranibizumab and sham without ranibizumab group, respectively. Both conjunctival haemorrhage and conjunctivitis are known adverse reactions of Lucentis with a very common and common frequency, respectively.

Cases of increased IOP were rare and the increase in pressure was transient. IOP increase is a very common adverse reaction of IVT ranibizumab and is an important identified risk addressed in the RMP of Lucentis.

Overall, no new ocular adverse events or any change to known ocular adverse reactions of Lucentis were detected. However, the SmPC includes a warning in section 4.4 concerning risk factors associated with the development of a retinal pigment epithelial tear after ant-VEGF therapy for wet AMD, including a large and/or high pigment epithelial retinal detachment. Pigment epithelial detachment is not uncommon in many disorders underlying CNV e.g. chorioretinopathy, high myopia, angioid streaks, central serous chorioretinopathy, and polypoidal choroidal vasculopathy, which may well be complicated by a retinal pigment epithelial tear. Thus, the risk factor applicable to wAMD may also be valid to the CNV indications and the CHMP was of the view that the warning should be updated by adding reference to other forms of CNV.

Non-ocular AEs in MINERVA were generally few and mild in severity and reported in <5% of patients, except for nasopharyngitis. At Month 12 nasopharyngitis was reported in 11.8%, 17.3% and 14.3 in ranibizumab, sham with ranibizumab and sham without ranibizumab treated patients, respectively. Nasopharyngitis is already included in section 4.8 of the SmPC of Lucentis as a very common adverse reaction.

Hypersensitivity reactions were reported (1.7% in ranibizumab vs 3.4% in the sham group) to a similar extent as in previous clinical trials. The significance of immunogenicity assessments is unknown since intraocular sampling for local immunogenicity is not acceptable and, consequently, no correlations to intraocular inflammation can be made. No increased risk for immunogenicity would be expected for the CNV population. The lack of additional assessment of immunogenicity is therefore found acceptable.

The arterial thromboembolic events reported by one patient and the case of non-myocardial arterial thromboembolic event in the ranibizumab group were of interest in light of the previously recognised theoretical risk of arterial thromboembolic events, including stroke and myocardial infarction with IVT anti-VEGF inhibitors. However, no further conclusions could be drawn based on the limited data in this application.

No deaths were reported. By the end of the MINERVA study, 12 patients experienced SAEs, all of which were non-ocular events including 8 patients in the ranibizumab group and 4 patients in sham groups. None of the events was considered related to the drug.

There was one pregnancy reported during the 12-months period of the study. The patient was discontinued accordingly, but the outcome has not been reported. VEGF is a major angiogenic factor involved in the formation of new blood vessels during embryonic and foetal development and placentation, and ranibizumab can reach the systemic circulation and inhibit VEGF systemically. Although the systemic exposure of ranibizumab is low the target population of CNV includes women in child-bearing age. Ranibizumab should not be used during pregnancy and it is recommended that women wait at least 3 months after last dose before conceiving a child. This is adequately addressed in the SmPC. The MAH should report the outcome of the pregnancy in next PSUR.

With regards to the safety in the 5 adolescent patients, the data presented were far too limited to draw any conclusions on possible differences in the AE profile between adults and adolescents. It would be expected that the safety profile would be largely in line with that in adults since the eye is fully developed in adolescent patients, the systemic exposure of ranibizumab is overall low, and the underlying disease mechanism is expected to be similar. Overall, the AEs reported in the adolescents were mainly due to the injection procedure, which is in line with what has been observed with the use of Lucentis adults. This was considered reassuring.

The clinical safety profile in the observational PIXEL study in patients with PXE was generally in line with the known safety profile of Lucentis, with the majority of AEs being ocular and potentially related to the injection procedure. Among the non-ocular AEs, cerebral vascular events were reported in 2 patients (vertebral artery occlusion, carotid artery stenosis, ischemic cerebral infarction, transient ischemic attack). According to the MAH, as cardiovascular impairment and haemorrhages are part of the vascular manifestations of the disease, an increased risk of vascular events in patients with PXE treated with VEGF inhibitors cannot be ruled out. This may be a specific source of concern in this population. Furthermore, closely related terms such as hypertension, myocardial infarction, non-myocardial ATE and venous thromboembolic events are important potential risks in the RMP of Lucentis. No immediate action was required; the issue should be followed in future PSURs.

Overall, no new AEs were identified. Ocular and non-ocular key safety concerns are few and AEs were consistent throughout the study periods. Although the data are limited due to the small size of the studies and number of injections, the data was considered by the CHMP generally reassuring. However, there were too few exposed subjects per condition for a reasonable detection of common AES. Aetiology subgroup data is limited and uncertainties remained if there was varying vulnerability of the different aetiological subgroups. In light of the low prevalence of some of the conditions the CHMP considered that the issue would best followed up in future PSURs.

The CHMP also noted that Lucentis has been approved for more than 10 years including for use in wAMD (since 2006) and PM (since 2013), the most common causes of CNV. From previous clinical trial and post-marketing data, substantial knowledge of the safety of the use of Lucentis in these conditions, in particular wAMD, has been gained. Compared to the already approved CNV related indication wAMD, the broad CNV population proposed with the present application (i.e. CNV due to any cause) is generally younger and fewer IVT injections are expected to be administered. Although CNV due to any cause is heterogeneous with mixed aetiologies (some isolated eye disorders, whereas others include systemic disorders), with some

of the underlying conditions being rare, overall, the CHMP agreed that the safety data base consisting of the newly presented clinical data from MINERVA and PIXEL, together with the experience of the use of Lucentis in the already approved indications, was sufficient to support the present application.

As already discussed in section 2.4.3, further long-term safety data beyond 12 months would have been desirable given the need for chronic treatment in at least some subgroups of CNV patients. The LUMINOUS study including patients of all indications is ongoing but at a late stage, so that the new indication could not be included. Given the substantial experience gained with ranibizumab in subjects with CNV (although mainly from patients with wAMD) so far, and since VEGF plays a key-role in the pathophysiology of CNV, the CHMP agreed that no further study was needed.

Finally, the need for additional Pharmacovigilance measures with regards to the RMP safety concern of AEs related to paediatric off-label use was reviewed. While previously a PIP waiver had been agreed with regards to CNV, as it was not considered feasible to recruit a sufficient number of children in a clinical study with Lucentis in this indication, concerns remained about the safety of IVT injections in children, which are known to occur in clinical practice. A cumulative review of known cases of use of Lucentis in paediatric patients provided by the MAH, showed retinopathy of prematurity as the dominating indication in almost 50% of the patients treated. A study is already ongoing to investigate the use for ranibizumab in neonates with retinopathy of prematurity, which was considered reassuring as these patients represent a very vulnerable population in which the eye is not fully developed. To improve the reporting of cases, the Pharmacovigilance and Risk Assessment Committee (PRAC) furthermore decided on implementing a targeted follow-up questionnaire as part of the routine pharmacovigilance activities including age of child, condition being treated, dose regimen used, and any efficacy data if available. The results should be reported in future PSURs. Other means to gather additional data such as a prospective registry or a drug utilisation study were considered not feasible and potentially even promotional. The CHMP endorse the PRAC position.

2.5.2. Conclusions on clinical safety

The safety assessment was based on limited data due to the small size of the study, limited study duration and number of injections. Also, the CNV population is heterogeneous with several different aetiologies of CNV, some of which are very rare. However, no new safety concerns were detected and, despite the limitation of the data, the safety profile of Lucentis in CNV patients appeared to be broadly in line with that reported in the previously approved indications.

In conclusion, the CHMP was of the view that the available safety data were sufficient to support the application for extending the indication of Lucentis to treatment of adult patients with visual impairment due to CNV. Considering the limitations of a small heterogeneous population, the CHMP was furthermore of the view that the safety profile should continue to be monitored in future PSURs.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC outcome on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 16.2 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to

h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 16.2 with the following main changes (in bold) for each relevant part of the RMP:

Safety concerns

Only missing information section is updated as follows:

Missing information	Systemic AEs related to bilateral treatment and overdose
	AEs related to off-label use, including potential local and systemic AEs related to pediatric off-label use
	Long-term safety two years and beyond
	Intraocular antibody formation
	Potential effect on DR of stopping periodic anti-VEGF injections (DME)
	Systemically unstable patients (DME)
	Age greater than 75 years (DME)
	Ethnicities other than Caucasian (DME and RVO)
	Long term effects on the progression of the condition **(CNV including PM)**
	Visudyne (verteporfin-PDT) or laser photocoagulation given in combination with ranibizumab (PM)

Pharmacovigilance plan

Only the 2 following sections are updated as follows:

AEs related to off-label use including potential local and systemic AEs related to pediatric off-label use – missing information

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Any new signals in off-label indications	Routine pharmacovigilance activities **including targeted follow-up using targeted checklist**	To collect reports of AEs in patients being treated with ranibizumab for off-label indications and in other off-label uses and to monitor these reports for evidence of increased safety risks in these patient populations.

Long term effects on the progression of the condition (CNV including PM) – missing information

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Effect of long-term treatment with ranibizumab on **CNV including** PM condition.	Routine pharmacovigilance activities. Long-term observational study CRFB002A2406 (LUMINOUS) Long-term observational study CRFB002F2401 (CNV secondary to PM)	To assess whether there are any long term effects on the progression of **CNV including** PM

Risk minimisation measures

Only the 2 following risks are updated as follows:

Safety concern	**Routine risk minimization measures**	**Additional risk minimization measures**
Important identified risks		
RPE tear	Routine risk minimization (labelling in the SmPC, Annex 2): Risk factors associated with the development of a RPE tear after anti-VEGF therapy for nAMD **and potentially also other forms of CNV,** include a large and/or high pigment epithelial retinal detachment. When initiating ranibizumab therapy, caution should be used in patients with these risk factors for RPE tears (SmPC Section 4.4) RPE tear is identified as a common undesirable effect in SmPC Section 4.8 The SmPC may be updated if new patterns develop during on-going safety reviews	None
Missing information		
Long term effects on the progression of the condition (**CNV including PM**)	No safety concerns have been observed from the clinical trials. This potential safety risk will continue to be monitored according to routine pharmacovigilance practices. The SmPC may be updated if new patterns develop during on-going safety reviews.	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated (see below) and the Package Leaflet has been updated accordingly. Changes to SmPC sections 4.1, 4.2 and 4.4 are shown below (additions are shown in **bold und underlined**, deletions are shown a ~~strike-through~~). For all other changes, please refer to attachment 1 of this report.

SmPC section 4.1

Lucentis is indicated in adults for:

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

SmPC section 4.2

(…)

The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 6 months; others may need monthly treatment. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year (see section 5.1).

~~In the treatment of visual impairment due to CNV secondary to PM, many patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see section 5.1).~~

(…)

Paediatric population

The safety and efficacy of Lucentis in children and adolescents below 18 years of age have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described in section 5.1.

~~The safety and efficacy of Lucentis in children and adolescents below 18 years of age have not been established. No data are available.~~

SmPC section 4.4

(…)

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD **and potentially also other forms of CNV.** include a large and/or high pigment epithelial retinal detachment. When initiating Lucentis therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

(…)

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Lucentis PI. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Wet AMD followed by PM are the most common causes of CNV. Other causes of CNV, e.g. angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic CNV, and other miscellaneous diseases are rare. They typically occur in young, working age persons, and can be multifocal, binocular, and recurrent. Although a highly heterogeneous group of patients in which different rates of progression would be expected, CNV irrespective of the underlying aetiology is associated with abnormal leaky vessel formation as well as vision loss by disturbing the retinal neurosensory structure, due to exudation of intra- or subretinal fluid, haemorrhage, and fibrosis formation. Currently, treatments for CNV related to these various conditions include submacular surgery, laser photocoagulation, and off-label photodynamic therapy with verteporfin and locally administered VEGF-inhibitors. While published data in the scientific literature suggest a beneficial effect of VEGF-inhibitors, the efficacy with the other treatment modalities is reported as limited. There is thus a clear need for effective treatment options.

Amongst other indications, ranibizumab is currently authorised in the EU for the treatment of wAMD as well as visual impairment due to PM. For these indications, efficacy of ranibizumab has been demonstrated in three (wAMD) and one (PM) pivotal controlled clinical trials. Based on its anti-VEGF activity, since VEGF is suspected to be the common factor playing a key role in the pathophysiology of CNV in general, ranibizumab is also thought to be effective in CNV due to other causes than wAMD and PM. To support this claim, the MAH conducted one pivotal 12-months study (study G2301, MINERVA) comparing IVT ranibizumab with sham in patients with various CNV conditions.

Benefits

Beneficial effects

In the pivotal MINERVA trial, ranibizumab was superior to sham at Month 2 in the primary efficacy endpoint, change of BCVA compared to baseline. Ranibizumab-treated patients had a mean (LS) gain in BCVA of 9.5 EDTRS letters at Month 2 compared to a loss of 0.4 letters in patients receiving sham. The difference between treatments was 9.94 letters (one-sided p-value <0.001). Sensitivity analyses confirmed the robustness of the primary analysis data which is not surprising given the limited number of premature withdrawals and major protocol deviations. In the ranibizumab treatment group, the gain in BCVA essentially reached maximum levels at Month 2 and was maintained for the total duration of the study up to 12 months. In the previously sham-treated group, i.e. patients who received sham up to Month 2 and thereafter ranibizumab, a gain in BCVA of 9.3 letters was achieved by Month 12.

The secondary efficacy outcomes consistently favoured ranibizumab and at Month 2, 31.4% (37/118) of patients treated with ranibizumab experienced a ≥15 letters improvement in BCVA versus 12.3% (7/57) of patients on sham. At 12 months, the proportions with relevant gains in BCVA had increased further and close to half of the patients (55/128, 48.79%) that were treated with ranibizumab from study start and slightly less (23/55, 41.8%) in patients who initially received sham had gained ≥15 letters.

With regards to anatomical variables such as central subfield thickness, presence of intra-/sub-retinal fluids and active leakage, ranibizumab was consistently favoured over sham and the effects were highly statistically significant (p<0.001, one-sided). Ranibizumab was further consistently favoured in the

subgroups by various CNV conditions, by age (≤60 years, >60 years) and baseline BCVA (≤60 letters, > 60 letters). The differences between treatment groups were largest in the subgroups with angioid streaks (14.6 letters), idiopathic chorioretinopathy (11.4 letters) and miscellaneous (10.6 letters), but ranibizumab was also favoured in the group with post-inflammatory retinochoroidopathy (6.5 letters) and in subjects with central serous chorioretinopathy (5.0 letters). The treatment effect was maintained over time in all subgroups.

Finally, given that the anti-VEGF mechanism of action of ranibizumab is valid regardless of the underlying cause of CNV, data from previous studies with ranibizumab in the approved indications, and in particular in patients with wAMD and visual impairment due to PM, were considered of relevance for understanding the treatment of CNV due to various aetiologies and supportive in the context of the present application.

Uncertainty in the knowledge about the beneficial effects

This application was based on a single pivotal study of limited size (178 randomised patients). Considering the diversity of the aetiologies included, it was difficult to conclude whether the study population was fully representative of the spectrum of the target population. However, given that some of the conditions are very rare, the approach to group all aetiologies into a single study was agreed by the CHMP. Furthermore, in light of the consistent results across all aetiology subgroups as well as previous studies in wAMD and PM, all of which favouring ranibizumab over sham, and since the inhibition of VEGF is thought to be the common mechanism of action in CNV regardless of the underlying cause, the CHMP considered the available data sufficient to support a broad CNV indication.

This was despite the fact that within the 15 different disease aetiologies represented in the CNV subgroup miscellaneous, for a few of the aetiologies no or only a very limited benefit was indicated. However, some of these findings were based on a single or very few subjects and there were uneven randomisation to treatment and inconsistencies in the treatment effects observed, so that it was not possible to draw firm conclusions. It is however of importance to avoid unnecessary treatment. In this context, the CHMP noted that a number of subjects in the sham group (14%) had gained ≥10-15 letters or reached normal BCVA (84 letters) at Month 2 despite evidence of an active CNV with macular involvement and despite exclusion of CNV conditions with a high likelihood of spontaneous resolution. Similarly, over the course of the study, a few subjects who did not receive ranibizumab after Month 2 maintained or gained BCVA over the course of the study. However, from the available data it was not possible to identify a definitive subgroup of patients who may improve without treatment. The patient population represents a heterogeneous group of patients with not necessarily similar clinical pictures regarding clinical manifestations, prognosis or expected response to treatment. Data from patients initially receiving sham, in fact suggest a benefit of early treatment initiation. In the previously sham-treated group the 12 months mean gain in BCVA did not reach the same magnitude (+9.3 letters) as in patients receiving ranibizumab from study start (+ 11.0 letters). However, the mean difference between treatment arms at Month 12 was limited with less than 2 letters, and the clinical relevance of such difference is questionable. The individualised dosing regimen based on disease activity was considered appropriate for a heterogeneous patient population like this, as it will allow the physician to decide on a case by case basis when best to initiate treatment. At the same time, although it cannot be excluded that some unnecessary treatment may be given, the individualised dosing regimen is expected to lower this risk. The SmPC (section 4.2) already states that, if, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued, a recommendation also considered valid for CNV due to any cause.

The study period was another source of uncertainty. An early switch of patients in the control arm to active treatment was made and from Month 2 onwards all patients received ranibizumab. Thus, only 2 months active comparison of ranibizumab versus sham was available. In light of the variable natural course of the different conditions involved in the trial a longer double-masked, active controlled period would have been

desirable as long-term treatment is foreseen in many of these patients. However, given the rapid onset of action of ranibizumab and the favourable effect shown over placebo across the efficacy analyses, the 2 months data were overall considered satisfactory.

In terms of long-term data, the MINERVA study was limited to a maximum 12 months observation period and seeing that, at least in some subsets of patients, chronic treatment may be needed, data beyond this period would be desirable. A substantial experience of the long-term use of ranibizumab has however been obtained in patient with wAMD. Additional data in patients with CNV due to PM are under way in LUMINOUS and in the 3-year observational study. Given the common role of VEGF in CNV irrespective of the underlying aetiology, long-term data in patients with wAMD and PM were considered by the CHMP to be also relevant for CNV due to any cause. Further, some additional, although mainly safety related data has been generated through the PIXEL study as well as from published data where subjects relevant for the now targeted CNV indication have been treated with ranibizumab for up to 4 years. Altogether, the data were considered reassuring and no further studies were considered necessary.

Unfavourable effects

Risks

The most commonly reported adverse events up to Month 12 in the MINERVA trial were conjunctival haemorrhage and nasopharyngitis. Conjunctival haemorrhage was reported up to Month 12 in 5.9%, 11.5% and 0.0% in ranibizumab, sham with ranibizumab and sham without ranibizumab group, respectively. Nasopharyngitis was reported in 11.8%, 17.3% and 14.3% in ranibizumab, sham with ranibizumab and sham without ranibizumab group, respectively.

Overall the safety profile observed in MINERVA was consistent with the known safety profile of Lucentis. The main concerns of IVT use of ranibizumab relate to important identified ocular risks including endophthalmitis, ocular inflammation, retinal detachment and tear, retinal pigment epithelial tear, vitreous haemorrhage as well as IOP increased and cataract. Further, because of the theoretical risk of arterial thromboembolic events with IVT anti-VEGF inhibitors, relevant important potential risks are myocardial infarction and non-myocardial arterial thromboembolic events. Within the safety database relevant to the present application, i.e. clinical trials in patients with CNV secondary to PM (RADIANCE) and due to any cause other than wAMD and PM (MINERVA), AEs for most of these risks were only observed in few or in no patents at all. However, the limited size of the safety database in CNV patients precludes the detection of rare events and realistic frequency estimations.

Uncertainty in the knowledge about the unfavourable effects

The broad, heterogeneous population of patients with CNV have not been studied before, and some of the conditions are potentially linked to risk factors for ocular safety concerns; for example, the experience of ranibizumab use in post-inflammatory conditions is especially limited. There are too few exposed subjects per individual condition for a reasonable detection of common AEs and there may be differences in incidence and severity between the different aetiologies. However, no obvious clustering of any AE in a specific aetiology group was observed and thus a higher vulnerability in any aetiology subgroup was not shown. However, considering the limited data of the respective subgroup in the study and the low prevalence of these conditions, no firm conclusions can be drawn. Further surveillance in PSURs is expected. This also includes monitoring of patients with PXE, i.e. patients that already have an increased risk of vascular events.

In general, the safety database was limited due to the small study size, limited duration up to 12 months and limited number of injections. However, given the substantial experience gained with ranibizumab in subjects with CNV (although mainly from patients with wAMD) so far, and since VEGF plays a key-role in the pathophysiology of CNV, regardless of the cause, the CHMP agreed that the data were sufficient to support this application.

Effects Table

Table 21 – Effects Table for Lucentis for the Treatment of Adult Patients with Visual Impairment due to CNV

Effect	Short Description	Unit	Ranibizumab 0.5 mg N=118	Sham[1] N=59	Uncertainties/ Strength of evidence
Favourable Effects					
BCVA improvement	Mean change from baseline to	Letters (95% CI)			Strength: Convincing from clinical and statistical view (p< 0.001, one-sided). Limited amount of missing data, few major protocol deviations. Consistency was shown across the 5 subgroups by CNV diagnosis as in other pre-specified subgroups. Limitation: Short duration of controlled phase, early timing of evaluation of primary efficacy when long-term treatment is foreseen. Previously sham-treated patients (ranibizumab from month 2) gained slightly less in BCVA.
	- Month 2		9.5 (7.6, 11.4)	-0.4 (-2.8, 1.9)	
	- Month 12		11.0 (8.5, 13.6)	9.3 (5. 6, 12.9)	
	Rate of patients with BCVA gain of ≥ 15 letters or reaching 84 letters at	%			Convincing from a clinical view. Previously sham-treated patients (ranibizumab from month 2[2]) gained somewhat less in BCVA.
	- Month 2		31.4	12.3	
	- Month 12		48.7	41.8	
Reduction in CSFT	Mean change from baseline to Month 2	µm	77.0	-9.8	Convincing from clinical and statistical view (p< 0.001, one-sided).
Unfavourable Effects[2]					
Ocular risks in study eye	Endophthalmitis	Incidence over 12 months % (n/N)	0 (0/343)	N/A	
	Intraocular inflammation		2.9 (10/343)		3 events in MINERVA, 7 events in RADIANCE
	Retinal detachment & retinal tear		0.9 (3/343)		All events observed in RADIANCE
	Retinal pigment epithelial tear		0 (0/343)		
	Vitreous haemorrhage		0.3 (1/343)		1 event in MINERVA
	IOP increased		4.1 (14/343)		4 events in MINERVA, 10 events in RADIANCE
	Traumatic cataract		0 (0/343)		
Non-ocular risks	Myocardial infarction		0 (0/343)		
	Non-myocardial arterial thromboembolic events		0.9 (3/343)		1 event in MINERVA, 2 events in RADIANCE

BCVA=best corrected visual acuity, CI=Confidence Interval, CSFT= central subfield thickness, IOP=intraocular pressure, n= number of events, N=Number of patients

(1) Patients in the sham group received double-blind sham up to Month 2 and thereafter switched to open-label ranibizumab 0.5 mg as needed. All but 7 sham-treated patients received ranibizumab at or after Month 2.

(2) The limited size of the safety database in CNV patients precludes the detection of rare events and realistic frequency estimations. The unfavourable effects displayed above therefore represents the integrated data for the CNV indication including the 12-month data from study F2301 (RADIANCE) for CNV secondary to PM, i.e. a total of 343 patients. Due to the difference of the comparator period (MINERVA study had primary endpoint assessment at Month 2 and F2301 at Month 3), and it's limited duration, a comparison of the 12-month data is provided.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The pivotal MINERVA trial showed a mean difference of 10 letters in BCVA between ranibizumab and sham after 2 months of treatment based on disease activity in this rare and heterogeneous patient population. This beneficial effect on vision was mirrored by the rate of patients with a relevant gain in vision under treatment (≥15 EDTRS letters in BCVA) with 31.4% (37/118) of patients receiving ranibizumab compared to 12.3% (7/57) of sham treated patients. These clinically relevant gains in VA were maintained until the end of the study, i.e. up to Month 12. Furthermore, the observed functional improvements in vision were supported by clear effects on anatomical variables including a reduction in central subfield thickness with a -86.79 µm difference between treatment groups at Month 2, which shows that ranibizumab reduces fluid accumulation in the retina, the main cause of vision loss in CNV patients. The observed effects were statistically compelling and of clear clinical value in particular for those conditions for which no or only suboptimal treatment options were available, e.g. CNV due to angioid streaks. The consistent effect of ranibizumab across all subgroups including those by disease aetiology further supports robustness of the study outcome. While some of the underling conditions were too rare to demonstrate a beneficial effect, in light of the totality of the available data including previous studies in wAMD and PM, all of which favouring ranibizumab over sham, and since the inhibition of VEGF is thought to be the common mechanism of action in CNV regardless of the underlying cause, the CHMP considered the available data sufficient to support a broad CNV indication.

Despite some limitations of the safety database supporting this application, due to the limited number of patients and injections, study duration and the rarity of some of the CNV aetiologies, the safety profile as observed in MINERVA was reassuring and consistent with the previously reported safety profile of Lucentis. The overall safety profile of Lucentis is well characterised. With treatment, there is a risk of injection-related adverse events that may be serious (e.g. endophthalmitis, retinal detachment). However, in the new CNV patient population, the mean number of injections administered would be expected to be fewer than in previously studied conditions including wAMD. There is also a risk of serious non-ocular adverse events, potentially related to systemic VEGF-inhibition.

Benefit-risk balance

The observed benefits of ranibizumab in the treatment of visual impairment due to CNV, namely an improvement of visual acuity by an average of 10 letters and a reduction in retinal thickness and fluid accumulation, outweigh the risks of mainly ocular adverse reactions which were largely related to the injection procedure.

Uncertainties arising from the rarity of some of the aetiologies and the limited study size were at least to some extent addressed by the well characterised anti-VEGF mechanism of action of ranibizumab which is common to the treatment of conditions involving growth of abnormal leaky vessels including wAMD and CNV secondary to PM, indications in which a positive benefit-risk balance of ranibizumab has previously been demonstrated. Furthermore, an individualised dosing regimen by disease activity will allow physicians to adjust treatment to the needs of a heterogeneous patient population, including early treatment initiation in

patients at risk of vision loss. At the same time, such treatment regimen would be expected to reduce the risk of unnecessary injections.

The CHMP furthermore agreed to list separately indications for wAMD and CNV due to other causes (including PM). Compared to most of the other CNV conditions, wAMD occurs in an older population with additional risk factors and requires intense treatment.

Discussion on the Benefit-Risk Balance

Not applicable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of visual impairment due to choroidal neovascularization (CNV) based on data from the pivotal study CRFB002G2301 (MINERVA). Consequential changes have been implemented in SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 and the Package Leaflet has been updated accordingly. An updated RMP version 16.2 was agreed during the procedure.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).