# SCIENTIFIC DISCUSSION

## 1. Introduction

Age-related macular degeneration (AMD) is a progressive degenerative macular disease attacking the region of highest visual acuity (VA), the macula. AMD is the major cause of vision loss in the elderly population in the Western world. Although the disease rarely results in complete blindness and peripheral vision may remain unaffected, central vision is gradually blurred, severely affecting ordinary daily activities.

AMD is a disease occurring in older patients. Population-based epidemiologic studies have provided estimates of prevalence and incidence of AMD among various racial/ethnic groups around the world. These studies have shown that AMD is rare before 55 years of age - being more common in persons 75 years of age or older, and that it is less common in blacks than in whites.

AMD is classified into two different types: the non-exudative (or dry) form and the exudative (wet or neovascular) form. The dry form is the most prevalent, accounting for 90% of the cases. The onset and progression of either type do not follow any particular pattern. It is not uncommon that the dry form develops into the wet form of AMD in which new choroidal vessels are developed. The latter form causes the worst incapacity and accounts for approximately 90 % of severely impaired vision in AMD. In this process, the oxygen supply to the macula is disrupted and as a response to ischaemia, new, immature, leaky blood vessels are formed. These may grow through breaks of the membrane behind the retina, towards the macula, often lifting the retina and causing haemorrhage in the sub-retinal space. Eventually, the lesions may turn into scars resulting in destruction of the macula and loss of central vision.

The angiographic classification of AMD lesions includes determination of the lesion size, the proportion of the entire AMD lesion that consists of 'classic' and 'occult' choroidal neovascularisation (CNV).

The process of angiogenesis is multi-factorial and highly complex, but vascular endothelial growth factor (VEGF) is considered critical both in physiological and in pathological angiogenesis, such as in AMD. Even though overexpression of VEGF is not likely to be the sole factor behind AMD, elevated levels of VEGF have been found in pathological neovascularisation, both in experimental models and in AMD. Of the four major isoforms, $VEGF_{165}$ seems to be the predominant isoform in these processes, at least in animal studies. There are also a considerable number of publications showing that by antagonising VEGF, angiogenesis and vascular permeability can be prevented.

A certain percentage of patients with exudative AMD can benefit from laser treatment with traditional photocoagulation laser or photodynamic therapy (PDT) and more recently, therapy to block vascular endothelial growth factor (VEGF) has been approved. Still, there is no curative treatment for AMD as available treatment only slows down the disease progress and for a large number of patients, only low vision rehabilitation remains. Consequently, it is an area with an unmet medical need.

Lucentis is a new medicinal product containing a biotechnology-derived protein (ranibizumab) as drug substance. Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by standard recombinant DNA technology and is targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to VEGF-A isoforms generated by alternative mRNA splicing, e.g. VEGF121, VEGF165, and their biologically active proteolytic cleavage product VEGF110. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors VEGFR-1 and VEGFR-2 on the surface of endothelial cells. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular (wet) form of age-related macular degeneration, one of the leading causes of legal blindness.

The applicant submitted a complete independent application according to Article 8.3 of Directive 2001/83/EC, as amended.

The indication and posology proposed by the applicant for Lucentis was: *for the improvement and maintenance of visual acuity and function, and for the reduction of vascular leakage and retinal oedema, in patients with neovascular age-related macular degeneration (AMD). The recommended dose for Lucentis is 0.3 mg (0.05 ml) administered once a month as an intravitreal injection.*

## 2. Quality aspects

*Nomenclature*

| | |
|---|---|
| INN Name: | Ranibizumab |
| Compendial Name: | Not Applicable |
| Chemical Name: | Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ-chain |
| Laboratory Code: | rhuFab V2 |
| USAN/BAN/JAN Name: | Ranibizumab |
| CAS Registry Number: | 347396-82-1 |
| WHO Number: | 8313 |

*Description of the drug substance*

Ranibizumab results from the insertion of murine anti-VEGF-A complementary-determining regions (CDRs) into a consensus human IgG1 framework. Amino-acid substitutions were made in order to increase the binding affinity to VEGF-A.

The 214-residue light-chain linked by a disulfide bond at its C-terminus extremity to the 231-residue N-terminal segment of the heavy chain. The molecular weight of ranibizumab is approximately 48 kDa (23 kDa and 25 kDa for the light and heavy chain, respectively).
Ranibizumab contains 10 cysteine residues forming 4 intra-chain and 1 inter-chain disulfide bonds.
As a Fab fragment, ranibizumab does not contain the Fc region that is involved in antibody-mediated effector functions.

Manufacture

Genentech, South San Francisco, California, USA is responsible for the preparation of the Master Cell Bank (MCB) and Working Cell Bank (WCB) and the manufacture of the drug substance. This site was last inspected by the German inspectorate in May 2006. It is considered that this site is operated in accordance to current EU Good Manufacturing Practices (EU cGMP), with standard operating procedures in place to describe all procedures and controls.

*Development genetics:*
Ranibizumab was originally derived from a murine monoclonal antibody (muMAb A4.6.1), which was produced at Genentech using hybridomas generated from mice immunised with the predominant 165-residue form of recombinant human vascular endothelial growth factor (rhuVEGF165) conjugated with keyhole limpet hemocyanin.

The cDNAs encoding the muMAb A.4.6.1 variable light (VL) and variable heavy (VH) chains were isolated using reverse transcriptase-polymerase chain reaction (RT-PCR) from hybridoma cells producing muMAb A.4.6.1. These cDNAs were cloned and fused to human constant light (CL) and human constant heavy (CH1) domains. Several framework residue substitutions near the CDRs were made to improve binding to the VEGF antigen. The heavy and light chains were then moved into a phage display vector.

Site-directed mutagenesis of the CDRs was used to improve antibody/antigen binding.

The final expression plasmid pY0317xaptet contains the light-chain gene and the heavy-chain gene linked in tandem, a *pho*A promoter for the transcription of each gene into a single dicistronic mRNA, a tetracycline resistance gene, an origin of replication and a beta-lactam resistance gene.

To generate a ranibizumab-producing cell line, *E. coli* 60E4 cells were transformed with pY0317xaptet and selected for tetracycline resistance. A purified culture of the transformed cells was used to prepare the MCB.

The light and heavy chains fold into their native conformations after secretion into the periplasm and are covalently joined by a disulfide bond.

*Cell bank system:*
A two-tiered cell banking system of MCB and WCB has been developed and maintained in accordance to cGMP and ICH guidelines.

One vial containing transformed *E. coli* 60E4/ pY0317xaptet cells was used to inoculate a 1 L flask. The shake flask is incubated at 30°C after which DMSO is added.
The WCB was prepared from one vial of MCB, based on the same principles as for the MCB. The MCB is stored in liquid nitrogen refrigerators and WCB is stored in mechanical freezers.

Procedures followed in the preparation of MCB and WCB have been appropriately described. An extensive range of tests has been performed for their characterisation, in accordance with ICH guidelines, including identity, viability, stability, presence of adventitious agents (bacteria, fungi, bacteriophage that may be associated with *E. coli* production cultures). A validated non-host contamination test and a validated bacteriophage assay is performed on MCB and WCB culture vials.

The applicant satisfactorily justified why the stability of the MCB will not be tested per a pre-determined protocol in case a number of years have passed without preparing a WCB. However, an ampoule of MCB will be tested in case the viability of the WCB has declined for more than 2 logs.

*Fermentation process:*
One ampoule from either the MCB or the WCB is thawed and is inoculated in a 2 L shake flask. The flask is incubated (primary inoculum), after which the culture is transferred to a 10 L bioreactor to generate the secondary inoculum. The primary and secondary inoculum stages are performed to provide enough cell mass to transfer to the production bioreactor.

The first part of the production culture stage consists of cell mass accumulation and rapid cell growth, which depletes the media in phosphate. This depletion triggers the second part, which is the product induction phase. The two subunits accumulate in the periplasmic space and assemble to form the Fab fragment.

The purpose of the following steps is to release ranibizumab from the cells, to separate ranibizumab from the cell debris and to prepare a stable clarified feedstock for the first chromatography step. The cells are ruptured by homogenization, which releases soluble ranibizumab into the liquid phase of the product stream. A heated hold step follows, to induce the precipitation of impurities and flocculate insoluble cell debris. After that, heating is discontinued and the homogenate is diluted with purified water and then pH adjusted, if necessary, to meet the load criteria for the cation-exchange chromatography step. Finally, the product stream is clarified by centrifugation followed by normal flow filtration.

Cell culture conditions and in-process controls have been sufficiently described and are considered appropriate.

*Purification process:*
Purification is performed by a series of 4 chromatography steps, successively. The purpose of these chromatography steps is to reduce impurities, which includes cell substrate-derived impurities, small molecules, product-related aggregates, charge variants and fragments. The pH-adjusted anion-

exchange pool is centrifuged and formulated. After UF/DF, the pool is diluted and adjusted with conditioning buffer to achieve the bulk drug substance formulation.
The bulk drug substance is then filtered, filled into storage vessels and stored at 5ºC or at <-20ºC until shipment to the filling facility.

The purification process has been adequately described. Columns sizes and run conditions, including maximum protein load and elution criteria, are specified as well as acceptable ranges. Critical process parameters are identified and the in-process control limits that have been set are appropriately justified.

Tryptone, N-Z amine type A are the only materials of animal origin used in the manufacturing process. Both are derived from bovine casein and lactose (N-Z amine only) sourced from milk from healthy animals and considered fit for human consumption. The milk is obtained from cows from Australia, New Zealand and Canada. Porcine starting materials, which are part of the manufacturing process for tryptone and N-Z amine, are sourced from Canada and USA. Yeast extracts are also used in the manufacturing process. Before use in the manufacturing process, tryptone, N-Z amine type A and yeast extracts undergo a validated heat sterilisation process.

*Manufacturing process development and process validation:*
Several process versions were used during development, which have been described in sufficient detail. Manufacturing changes included change to the cell line, changes to the cell culture conditions, fermentation process parameters, various changes to the purification process, change to the finished product formulation.

The rationale for the proposed changes was explained. An extensive comparability exercise was performed, which includes a comprehensive physicochemical characterisation, non-clinical studies and clinical studies. The applicant chose an appropriate range of techniques from the characterisation studies for these comparability studies. Stability studies also confirmed comparability in the characteristics of the materials.

A prospective process validation programme was conducted in accordance with ICH guidelines to demonstrate the suitability and robustness of the manufacturing process and the consistent production of ranibizumab with the appropriate quality attributes.

Validation studies confirmed consistency of the cell culture and harvest processes and demonstrated that the purification process is robust and reproducible for removing cell substrate-derived impurities, process-related and product-related impurities. Hold times, buffer storage, cleaning and repeated use of columns and filter leachables were in addition addressed.

Overall, process validation was considered satisfactory.

*Characterisation:*

a) Elucidation of structure and other characteristics:
The drug substance has been comprehensively characterised, using state-of-the-art methods for physicochemical characteristics.

- Structural characterisation:
Edman degradation analysis showed that the light and heavy chains have the expected N-Terminal sequences.
Mass spectrometric analysis of carboxypeptidase Y-treated product confirmed the C-terminal sequence of the heavy chain.
The rest of the amino acid sequence was confirmed by peptide map analyses. Oxidation was also studied and consistent results were found.
The 5 expected disulfide bonds were identified. Additionally, free sulfhydryl content was consistently detected, indicating low levels of unpaired cysteine residues that are not assigned.

Evidence that the protein did not unfold or misfold has been provided.

- Physicochemical characterisation:
The molecular weight of ranibizumab (approximately 48 kDa), along with the isoelectric point and the extinction coefficient were determined.

Low levels of higher molecular weight species of ranibizumab, mainly dimer, were found. Trace amounts of fragments corresponding to the heavy and light chains were also identified.

- Biological characterisation:
Ranibizumab does not contain the Fc region and is therefore not expected to induce Fc-mediated cytotoxicity, to bind complement or to induce antibody-dependent cellular cytotoxicity.

It was shown that ranibizumab binds with high affinity to the three biologically active isoforms of VEGF: $VEGF_{165}$ (predominant form), $VEGF_{121}$ and $VEGF_{110}$.

A cell-based assay was chosen and validated as potency assay. The rationale for the use of this assay is based on the fact that the method is indicative of the inhibition of VEGF-induced proliferation (mimicking angiogenesis).
The biological properties of ranibizumab have been properly characterised and the potency assay that was chosen is considered adequate. Results demonstrated good consistency between lots.

b) Impurities:
Process-related impurities consist of cell substrate-derived impurities, including *E. coli* proteins (ECP) and DNA, cell culture-derived impurities and downstream-derived impurities.
A number of product-related impurities have been identified:
- Size variant: aggregates, fragments;
- Oxidized variants;
- Other variants including acetylation, glycation, methylation, Fab truncation.
Overall, impurities have been properly identified and characterised.

Specifications

A comprehensive set of tests has been developed and validated to assess the identity, purity, potency, content and other general parameters of the drug substance. The selection of tests was based on physicochemical and biological characterization, process validation, formulation development studies, the stability profile of the drug substance.

The drug substance specification limits have been provided and are considered acceptable. However, the applicant committed to re-evaluate the specification limits, including those for ECP, SEC, CE-SDS, IEC, after three post-approval commercial campaigns (comprising a minimum of 30 additional runs).

Stability

The design of the stability testing program, including the testing intervals and temperature storage conditions, are in accordance with current ICH guidelines.
The stability acceptance criteria for the tests used in the stability program are the same as those used for release of ranibizumab drug substance.
The stability data provided were within the specifications and support a shelf life of 36 months at ≤ −20°C and 90 days at 5°C including three freeze/thaw cycles.
A freeze-thaw study was initiated as part of the drug substance stability programme and the applicant committed to submit the results of this study.

**Drug Product**

Pharmaceutical Development

Early clinical trials were conducted using a lyophilised formulation. A liquid formulation was used from Phase III studies, with ranibizumab concentrations of 6 mg/ml and 10 mg/ml.

α,α-trehalose dihydrate (tonicity agent), a histidine buffer, polysorbate 20 (surfactant to minimise the risk of agitation-induced aggregation) are used in the commercial formulation of Lucentis. These excipients are commonly employed in medicinal products for parenteral administration whose drug substance is a protein.

Ranibizumab was found most stable in a solution at a range of pH 5 to pH 6. Therefore pH 5.5 was chosen.

No incompatibility was identified between these excipients and ranibizumab, as demonstrated by the long-term stability studies.

Water for injection is also used as solvent in the formulation.

The proposed container for Lucentis is a single-use type I glass vial, with an overfill of 0.25 ml. Lucentis is supplied with a filter needle for withdrawal of the vial content, a 1 ml syringe and an injection needle.

Manufacture of the product

The drug product is manufactured by Novartis Pharma Stein AG, Stein Switzerland. This facility was last inspected by Swissmedic in July 2005 and is operated in accordance to current EU-cGMP.

The frozen drug substance is thawed at 5°C and diluted in the sterile filtered formulation buffer. The drug product is then pre-filtered and sterile filtered (0.22 μm filter), which is followed by the aseptic filling into vials, stoppering, capping and crimping steps.
Reprocessing may be performed and allowable circumstances for a maximum of 3 refiltrations have been described.

The media fill and process validation results, lot-to-lot consistency data and critical process controls have shown that the sterile filtration and aseptic filling process are robust and well controlled and that the drug product can be consistently manufactured.

Specifications

The control of the drug product relies to a large extent on the same analytical methods as those used for the control of the drug substance. The tests and rationale for the acceptance criteria for the drug product were considered acceptable.

Stability of the Product

Real-time and accelerated stability studies were initiated in accordance with ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of drug product. Based on the data provided, the approvable shelf life for the drug product is 18 months at 2-8°C.
Photostability studies showed that Lucentis drug product should be protected from light.

**Discussion on chemical, pharmaceutical and biological aspects**

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with the existing guidelines.

Information on the source and generation of the cell substrate and analysis of the expression construct are considered satisfactory.

The cell bank system used for the manufacture of the drug substance is adequately described and an appropriate range of tests has been performed.
The applicant satisfactorily justified why the stability of the MCB will not be tested per a pre-determined protocol in case a number of years have passed without preparing a WCB. However, an ampoule of MCB will be tested in case the viability of the WCB has declined for more than 2 logs.

In general, the cell culture process and purification process as well as the filling and storage of the drug substance have been described in sufficient detail and appropriate in-process controls and acceptance criteria are in place.
Validation data generally demonstrate that the process consistently produces the drug substance.

A number of changes were introduced during development in the drug substance manufacturing process. The extensive comparability exercise that was performed to support these changes was considered satisfactory.

The drug substance has been comprehensively characterised, using state-of-the-art methods for physicochemical characteristics. The biological properties of ranibizumab have been properly characterised and the potency assay that was chosen is considered adequate. Results demonstrated good consistency between lots.

RP-HPLC was used in the characterisation of the reference material and showed one significant side peak. The applicant provided sufficient evidence to support the fact that this side peak is an analytical artefact and therefore to rule out the possibility that it represents misfolded ranibizumab material.

Overall, impurities have been properly identified and characterised. Concerns that have been raised during the assessment regarding the multi-product ELISA assay used for the quantification of ECP, which included qualification of the critical reagents, have been satisfactorily addressed.

The drug substance specification limits have been provided and are considered acceptable. However, the applicant committed to re-evaluate the specification limits, including those for ECP, SEC, CE-SDS, IEC, after three post-approval commercial campaigns (comprising a minimum of 30 additional runs).

The stability data that was provided for the drug substance and drug product support the proposed shelf life of 36 months at ≤−20°C and 90 days at 5°C including three freeze/thaw cycles, and 18 months at 2-8°C, respectively.

The formulation development and manufacturing process development for the drug product have been adequately described.

In general, the validation program has confirmed that the manufacturing process is robust and suitable for routine use and that a drug product of an appropriate quality can be consistently manufactured.

The control of drug product relies to a large extent on the same analytical methods as those used for the control of the drug substance. Therefore, most points for clarification raised during the assessment relating to the control of the drug substance apply to the drug product. The drug product specifications are considered acceptable.

The viral safety and safety concerning other adventitious agents, including TSE, have been sufficiently assured.

The last inspection of the drug substance and drug product manufacturing facilities showed compliance to EU cGMP.

Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the quality of Lucentis has been adequately demonstrated.

## 3. Non-clinical aspects

### Introduction

### Pharmacology

- Primary pharmacodynamics

The process of angiogenesis is multi-factorial and highly complex, but VEGF is considered critical both in physiological and in pathological angiogenesis, such as in AMD. VEGF has shown to promote growth of vascular endothelial cells *in vitro* and induces a potent angiogenic response and vascular leakage in a variety of *in vivo* models. Elevated levels of VEGF have been found in pathological neovascularisation, both in experimental models and in AMD. Consequently, the approach to target VEGF in AMD is considered relevant.

Ranibizumab is the Fab moiety of a recombinant humanised monoclonal antibody rhuMAb accomplished by site directed mutagenesis of a human IgG1 framework (95%) with murine complementarity-determining regions (5%). Ranibizumab binds with high affinity to the VEGF-A isoforms (e.g. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$). The binding is strong (in the subnanomolar region), dissociates slowly and it is likely that once the ranibizumab-VEGF complex is formed, it is very stable.

Ranibizumab dose-dependently inhibited VEGF-induced proliferation in human umbilical vein endothelial cell (HUVEC), which are cells that express the VEGF-receptors, with $IC_{50}$ values below 1 nM. This is 10-20-fold over clinical $C_{max}$. Roughly approximated $IC_{10}$ levels were somewhat higher than the clinical $C_{max}$ values (1.7 ng/ml predicted at steady state, maximal individual level 2.4 ng/ml) and consequently, no significant systemic VEGF-inhibiting activity is expected in humans. A total inhibition of proliferation was observed at ranibizumab concentrations $\geq$ 1.3 nM. Ranibizumab inhibited $rhVEGF_{165}$-induced tissue factor up-regulation in a dose-dependent manner, with an $IC_{50}$ of 0.31 nM.

No studies were carried out with the other isoforms. VEGF is highly conserved between species, and it is shown that ranibizumab has a high, but 40-fold reduced, affinity towards rabbit VEGF in comparison with human VEGF. There is no information on the affinity of ranibizumab to monkey VEGF. Identification of the sequence differences between monkey and humans (99% sequence homology, alignment predicting the protein products) resulted in a prediction of a 100% homology between the species on a protein level. Still, it is not shown that the binding activity of ranibizumab to VEGF from the two species is identical. It is however agreed that it is likely that the monkey and human protein sequence are very similar, or even identical and a high activity on monkey VEGF is expected. For intraocular administration, this is considered sufficient.

The Applicant has generated *in vivo* studies that show that that intravitreal/intravitreous (IVT) injected ranibizumab blocks VEGF-induced vascular permeability in a modified Miles assay. The data indicate that a 90% inhibition of vascular permeability may be achieved when ranibizumab concentrations are approximately 4−7 times larger than VEGF concentrations. The *in vivo* disease model used was the well established model of laser-induced CNV, in this case, in monkeys. There was a lower incidence of CNV-development in animals treated with IVT injected ranibizumab before laser induction of CNV, giving some support for the anti-angiogenic effect in the eye. It was also shown that ranibizumab (0.5 mg every 2nd week) inhibited vascular leakage from the CNV-lesions. Verteporfin with PDT given before, after or concomitant with ranibizumab (2 mg every 2nd week) gave an additive effect on the inhibition of vascular leakage without any apparent increase in side effects. Additional *in vivo* models, like the retinopathy of prematurity model, more directly addressing the antiangiogenic properties of ranibizumab might have given additional support.

From a proof of principle point of view, the submitted studies, even though limited, are considered sufficient. However adequate support for the clinical dosing regimen has not been provided, the rationale was only briefly addressed in a submitted publication. This is however further addressed in the clinical part of the assessment, since at this stage of development this is considered to be most accurately studied in patients.

- Secondary pharmacodynamics

There were no specific secondary pharmacodynamic studies, but the Applicant has submitted a study confirming that no complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity is expected, which is consistent with the lack of Fc region in ranibizumab. Besides the expected binding to $VEGF_{165}$ (and the murine variant $VEGF_{164}$), the binding of ranibizumab to other members of VEGF family (human VEGF-B, mouse placental growth factor-2 (PlGF-2), human PlGF - the short-form PlGF, which is homologous to the receptor-binding domain of $VEGF_{165}$ where ranibizumab binds, human VEGF-C, and human VEGF-D) was negligible. Theoretically, ranibizumab could bind to an 'off-target' protein. However, since ranibizumab appears to be very specific for the VEGF-A variants, it is considered unlikely that ranibizumab should bind with a relevant affinity to other more distant relatives to VEGF, or to a non-related target. The full-length counterpart (GN1754) of ranibizumab did not however, show any specific staining to a panel of several normal human tissues. Some binding to VEGF, for example to vascular endothelial cells and to reproductive organs including the placenta, which is a tissue undergoing active angiogenesis, would have been expected and the value of this assay is uncertain.

- Safety pharmacology

No safety pharmacology studies were performed. This was justified by the incorporation of safety pharmacology endpoints in repeat-dose toxicity studies, and the human systemic exposure being below levels where any meaningful effect of a VEGF-related activity is expected. The absence of systemic toxicity at exposure levels highly above maximum clinical exposure (see Toxicology) is further reassuring and the lack of formal safety pharmacology studies is accepted.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed and no justification for omitting such studies was submitted. Besides the probability that Lucentis will be combined with PDT, which has been addressed, other potential interactions require that a sufficient exposure is achieved. Therefore it is considered that the justification for not performing any pharmacokinetic interactions is considered valid also with respect to pharmacodynamic interactions (see below).

**Pharmacokinetics**

Overall, dose-dependent pharmacokinetics of ranibizumab is suggested after IVT injection where systemic levels are dependent of the relatively slow release of ranibizumab from the vitreous. In rabbits and monkeys, serum levels were >1000-fold lower than vitreous concentrations. The levels in aqueous humour and retina were 2.5 – 4-fold lower than the vitreous levels. All appeared to decline in parallel with the vitreous concentrations. Drug clearance from the vitreous is reported to be dependent on molecular size and the measured T½ of ~3 days is reasonable for a Fab fragment. The release from the eye is, in part, due to diffusion and species with bigger eyes, like humans, would be expected to have slower vitreous clearance. Other factors, like a more or less liquid vitreous may also affect the release. For example, rabbits have an almost liquefied vitreous, while in humans it is in a gel state. The Applicant has not presented any attempts to extrapolate animal data to humans. Even though this may be a challenge taking the differences above into account, such an attempt would have been desired.

The pharmacokintetics of ranibizumab manufactured by different processes and cell lines were comparable as studied in rabbits.

Ocular degradation is suggested to be limited, since the systemic bioavailability was 50 - 60% at 2 days post IVT injections to monkeys. At infinity, the systemic bioavailability is likely to be close to 100%. No studies on the metabolism of ranibizumab have been performed, but as with other proteins,

once reaching the systemic circulation, if not excreted, ranibizumab is most likely degraded in the liver or kidney.

Ranibizumab is distributed to aqueous humour, tissues in the anterior segment, to the retina and optic nerve. Immunohistochemistry and micro-autoradiography studies showed that ranibizumab is distributed through the retinal layers to the RPE (retinal pigment epithelium) and only low levels were found in the choroid, the target tissue. From the clinical efficacy data, ranibizumab had a convincing effect also in subjects with occult AMD, which occurs under the RPE. This indicates that sufficient amounts of ranibizumab affect tissues that lie below the retina.

Due to the low systemic levels of ranibizumab, systemic pharmacokinetic interactions are not expected. Likewise, since systemically or topically delivered drugs barely reach the posterior segment of the eye, also these interactions are of no concern. The potential for intraocular drug interaction with the use of ranibizumab in combination with PDT was however addressed. The pharmacokinetic profile of ranibizumab was not notably different when verteporfin with PDT was added to the treatment. This is further addressed in the clinical assessment.

**Toxicology**

All pivotal toxicity studies were performed according to GLP.

- Single dose toxicity

Single dose ocular toxicity (local tolerance) studies with IVT injections were performed in rabbits. In these studies, material from early processes and a formulation used in early clinical trials was compared with that of a later process /formulation for phase III clinical trials and the 26-week toxicity study. There were no major differences between the formulations in any study. Changes during manufacturing have been sufficiently addressed and there are no toxicological concerns regarding the impurity profile of Lucentis. Essentially, the effects observed in the single dose studies were restricted to ocular inflammation. The single dose studies were not according to present guidelines, and the maximum tolerated systemic dose was not determined. It is considered that with the present knowledge of the effects of VEGF-inhibition together with the information from repeat dose ocular toxicity studies, additional studies would not add to the safety evaluation of ranibizumab.

- Repeat dose toxicity (with toxicokinetics)

All repeat-dose toxicity studies were performed in Cynomolgus monkeys, a reasonable choice of species, in studies up to 26-weeks duration. Ranibizumab was administered bilaterally by 50 µl IVT injections every 2$^{nd}$ week at doses of up to 2.0 mg/eye. The control eyes received vehicle by the same method and regimen. The toxicokinetic profile was consistent with the data observed in the pharmacokinetic characterisation of ranibizumab, i.e. vitreous levels were generally > 1000-fold over serum levels. Repeated dosing did not indicate any accumulation of ranibizumab, either in serum or in vitreous. As in the pharmacokinetic part of the file, also in the toxicokinetic evaluation, a number of control and pre-dose animals had low, but measurable levels of ranibizumab. The Applicant suggests that ranibizumab binds to an unknown molecule in a non-specific manner and, consequently, the serum levels of ranibizumab may be overestimated, which would be most apparent at lower levels of ranibizumab. The performance of the ranibizumab-assay is not fully convincing, but the risk that control animals have been given ranibizumab appears low. Consequently, the low levels of ranibizumab found in control/pre-dose animals are not considered to jeopardise the integrity of the studies.

Besides the development of antibodies towards ranibizumab, there were no apparent systemic effects (assessment of body weights, food consumption, heart rate, rectal body temperature, respiration rate, haematology, coagulation, clinical chemistry tests, macroscopic observations and microscopy of extra-ocular tissues) in any study at systemic exposures of at least 1000-fold over the clinical maximal exposure. Since the ranibizumab ELISA used in the non-clinical part of the application measures free ranibizumab, while the electrochemiluminescence assay (ECLA) used for the clinical pharmacokinetic studies measures also ranibizumab bound to VEGF, the margin to clinical exposure could be larger than indicated by the toxicokinetic data. There were also no consistent decreases in ocular VEGF

levels in animals and no effects on serum VEGF-levels in humans. Consequently, from a systemic view-point there are sufficient margins of safety and therefore, the lack of standard systemic toxicology studies is acceptable. Only ocular findings are addressed below.

The NOEL or NOAEL were not identified in any of the studies, since all doses tested (0.25-2 mg) resulted in an ocular inflammation. Part of this inflammation was due to the injection procedure, but in ranibizumab-treated eyes, the inflammation was more pronounced and dose-related. The IVT injection procedure as such is not without risks for serious adverse events such as endophthalmitis, retinal detachments and increased intraocular pressure (IOP). These effects are well known and are handled in the Risk Management plan. Also in the monkey studies, injection of vehicle or ranibizumab induced a transient 2-5-fold increase in IOP and some cases of endophthalmitis were observed.

The anterior chamber ocular inflammation was dose-dependent, relatively rapid (peaked at day 2 post injection) and transient. In the vitreous, it was later (peaked at week 1 post injection) and more persistent. In shorter studies, the inflammation was most severe after the first injection and subsided thereafter. Pre- and post-dose treatment with oral and topical prednisone (9-week study) did not decrease the inflammatory response. In the 26-week study, the inflammatory response increased with the number of injections and a number of animals prematurely discontinued the study due to a dense vitreous inflammation severely impairing the view of the fundus. Data from these animals were handled according to the LOCF (last observation carried forward) approach, which is considered to be adequate. During recovery, anterior chamber inflammation decreased or disappeared, while a decrease in vitreous and tissue inflammatory cells was observed.

Two types of posterior segment changes were observed in ranibizumab-treated groups. The first form, observed in the 9- and 26-week studies, was characterised by single to multifocal, perivenous retinal haemorrhages typically with white centres in the far peripheral retina. These lesions usually appeared after the first dose, resolved by week 1 post dose, and were absent or diminished on subsequent injections, even if the dose was increased. The mechanism behind this finding is not clear, neither is the lack of this finding in the 4- and 13-week studies. The Applicant hypothesises that the haemorrhages may be related to dose, or to injection-related trauma, or to the increase in IOP. Since retinal haemorrhages occurred less frequently in ranibizumab-treated than in non-treated patients (which is consistent with ranibizumab's mode of action) in the pivotal clinical studies (MARINA, 2-year data and ANCHOR, 1 year data), the finding appears to be of limited clinical relevance.

The second form, a dose- and time-related focal to multifocal, perivascular sheathing (vasculitis) around peripheral retinal venules with inflammatory material over the optic disc surface was more chronic in nature and considered secondary to inflammation. These changes diminished, but did not resolve during recovery. Also a wide-spread ocular tissue inflammation that was dose and time-dependent was observed. From the 26-week study, it was suggested that an early onset of perivascular sheathing could be a marker for a later severe inflammatory response since all animals that were withdrawn from dosing due exhibited perivascular sheathing prior to withdrawal. However, there was no obvious correlation between the onset of the perivascular sheathing and the severity of the inflammatory response in monkeys. In clinical studies, most severe cases of inflammation were not preceded by vasculitis and occurrence of perivascular sheathing after the outbreak of severe inflammation has not been reported, possibly due to the difficulties to view the fundus in eyes with a severe inflammation. Therefore, the perivascular sheathing does not appear to be a useful marker for prediction of severe cases of inflammation in patients.

In the 26-week study, several cases of cataracts were observed. In all cases, cataract developed only after a relatively long period of intense inflammation suggesting that the lens changes were also secondary to a chronic inflammation.

Ranibizumab consists mainly of human protein. It is therefore not surprising that it is highly immunogenic in rabbits as shown in the single-dose ocular toxicity studies. A significant antigenicity was observed also in monkeys, even within the eye. The lack of information on whether the antibodies formed are neutralising, appears to be of minor importance since a clinical effect is shown. Most monkeys with perivascular sheathing were positive for antibodies towards ranibizumab, indicating an

immune-related effect which has not been observed clinically. The healthy eye is considered as an immunoprivileged site, but after repeated IVT injections, the blood-brain-barrier is disrupted. Further, in AMD, permeable vessels are a hallmark of the disease and it can not be excluded that antibodies towards ranibizumab may also be formed in the human eye. It is recognised that development of ocular antibodies can not be assessed in humans, but serum antibodies were found in 1-4% of treated subjects (and also in non-treated patients). The Applicant has reviewed the patient data (see Risk Management Plan), but no clear correlation between antibodies to ranibizumab and ocular inflammation or decrease in visual acuity in Lucentis-treated patients was found. However, a relation between antibody formation to ranibizumab and the development of intraocular inflammation cannot be completely ruled out. Therefore, monitoring of possible clinical signs attributable to intraocular antibody formation (such as intraocular inflammation) will be performed continuously.

The initial interspecies comparison addressed the previously filed 0.3 mg dose of Lucentis. Since the Applicant has decided to change the dose to 0.5 mg, the margins to clinical exposure are reduced. In the vitreous, only the lowest dose tested (1.0-fold the clinical 0.5 mg dose on a mg/ml vitreous basis) in the 13-week study gave an inflammatory response that subsided to levels comparable to those observed in vehicle-injected animals while the animals were still on treatment. In the 26-week study, from doses 1.9-fold the clinical dose (0.5 mg dose, mg/ml vitreous), the inflammatory response increased with the number of injections. Besides the issue of immunogenicity, the degree of inflammation could be affected by the frequent dosing (every 2$^{nd}$ week), not allowing sufficient time for recovery between injections. The Applicant was requested to discuss more in depth the aetiology of the inflammatory ocular reactions in cynomolgus monkeys and a plausible reasoning has been provided. The Applicant concludes that the available evidence suggests that inflammatory ocular reactions in cynomolgus are immune related responses linked to the administration of a humanised protein to animals and unlikely to occur at notable incidences in humans as shown by the clinical safety and antigenicity data collected. Furthermore, in the clinic, the ocular inflammation appears to be non-serious and easily manageable.

There is abundant evidence that VEGF has neuroprotective effects which raises concern when the biologically active isoforms of VEGF are blocked with ranibizumab. Therefore, it is reassuring that there were no apparent signs of nerve toxicity as evaluated with VEP (visual evoked potential) and ERG (electroretinogram). However, it was a full-field ERG, and small retinal lesions are not likely to be observed with this method. The lack of macular abnormalities was on the other hand confirmed with VEP. Histopathologically, besides inflammatory infiltrates in retinal tissues, there were no apparent degenerative effects on neural retinal or other ocular structures. In addition, clinically, a significant proportion of the patients actually gain vision, which would not be the case if the neural retina was impaired. Still, it can not be excluded that there may be long-term adverse effects of VEGF-inhibition.

By blocking VEGF, wound healing could be impaired. With respect to ranibizumab, the levels that reach the systemic circulation are considered to be below those that have a pharmacologically relevant effect. However, if ocular surgery is indicated, local wound healing may be impaired and a recommendation to withhold the next dose if intraocular surgery is planned is incorporated in the SPC section 4.4.

- Genotoxicity & carcinogenicity

There were no studies on genotoxicity or carcinogenicity. This is acceptable due to the nature of the compound.

- Reproduction Toxicity

No reproduction toxicology studies were performed. This was justified by the low systemic exposure of a compound for which the mechanism of action is well characterised during development, and the median age of the AMD-population (over 70 years). The justifications are considered to be acceptable, but if ranibizumab should be intended in an indication in a younger population, a segment II study is needed.

- Other toxicity studies

No additional studies were performed.

**Ecotoxicity/environmental risk assessment**

There is no environmental concern.

## 4. Clinical aspects

**Introduction**

In relation to this dossier, scientific advice has been obtained from the CHMP.

The submitted documentation consists of seven clinical studies including patients with neovascular AMD (see Table below).

**Table 1 Study overview**

| Study (Phase) | Design (Sites) | Population | Control | No. of Subjects Enrolled | Treatment Frequency and Duration | Ranibizumab Dose(s) | Status |
|---|---|---|---|---|---|---|---|
| **Pivotal Phase III Studies** | | | | | | | |
| FVF2598g **MARINA** (III) | Randomised, double-masked, sham-controlled (U.S.) | Subjects with minimally classic or occult subfoveal neovascular AMD | Sham injection | 716 | IVT inj. inj. every month, maximum of 24 total inj. over 2 years | 0.3 mg (n = 238), 0.5 mg (n = 240), sham inj. (n = 238) | Completed |
| FVF2587g **ANCHOR** (III) | Randomised, double-masked, double-sham, [b] active treatment–controlled (U.S., Europe, and Australia) | Subjects with predominantly classic subfoveal neovascular AMD | Verteporfin PDT (+ sham injection) | 423 | IVT inj.every month, maximum of 24 total inj. over 2 years, or verteporfin PDT every 3 months as needed | 0.3 mg (n = 140), 0.5 mg (n = 140), sham inj. (n = 143) | Ongoing to 2 years |
| FVF3192g **PIER** (IIIb) | sham-controlled (US) | Subjects with all lesion types of neovascular AMD in the active state | Sham | 184 | IVT inj every month trough Month 3, and then quarterly | 0.3 mg (n = 60 ), 0.5 mg (n = 61 ), sham inj. (n = 63) | Ongoing to 2 years |

| Study (Phase) | Design (Sites) | Population | Control | No. of Subjects Enrolled | Treatment Frequency and Duration | Ranibizumab Dose(s) | Status |
|---|---|---|---|---|---|---|---|
| **Phase I/II Studies** | | | | | | | |
| FVF2428g **FOCUS** (I/II) | Randomised, single-masked, sham-controlled, combination treatment (U.S.) | Subjects with predominantly classic neovascular AMD | Verteporfin PDT (+ sham injection) | 162 | IVT inj. every month, maximum of 24 total inj. over 2 years, in combi-nation with verteporfin PDT every 3 months as needed | 0.5 mg (n = 106), sham inj. (n = 56) | Ongoing |
| FVF2128g (I/II) | Randomised, open-label, dose-escalation (U.S.) | Subjects with classic neovascular AMD | Usual care [c] | 64 [d] | IVT inj. every 4 weeks, maximum of 8 total inj. over 28 weeks, or usual care with crossover to ranibizumab treatment after 14 weeks | 0.3 mg (n = 25), 0.3 mg initial dose escalated to 0.5 mg for subsequent doses (n = 28), usual care (n = 11) | Completed |
| **Phase I Studies** | | | | | | | |
| FVF2425g (I) | Randomised, open-label, multiple-dose escalating regimens (U.S.) | Subjects with neovascular AMD | None | 29 [d] | IVT inj. at 2- or 4-week intervals, maximum of 5, 7, or 9 total inj. over 16 weeks | 0.3 mg to 1.0 mg escalating regimen, 7 total inj. (n = 9), 0.3 mg to 2.0 mg escalating regimen, 9 total inj. (n = 10), 0.3 mg to 2.0 mg escalating regimen, 5 total inj. (n = 10) | Completed |
| FVF1770g (I) | Open-label, single-dose escalation (U.S.) | Subjects with neovascular AMD | None | 27 | Single IVT inj. | 0.05 mg (n = 6), 0.15 mg (n = 6), 0.30 mg (n = 6), 0.50 mg (n = 7), 1.0 mg (n = 2) | Completed |

Paediatric development of this therapeutic principle is not relevant, since AMD affects the elderly population only.

**GCP**
According to the applicant, the clinical development of ranibizumab was conducted in accordance with U.S. FDA regulations and with the principles of the EU Clinical Trial Directive (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001, e.g. ICH GCP and Declaration of Helsinki).

**Pharmacokinetics**
The pharmacokinetics of ranibizumab is of limited relevance due to the low clinical systemic exposure. Some aspects of the safety assessment may be addressed but generally, the pharmacokinetics is of secondary interest.

A total of six clinical trials (FVF1770g, FVF2425g, FVF2128g, FVF2428g, FVF2598g and FVF2587g) evaluated systemic ranibizumab concentrations in subjects who received doses ranging from 0.05 to 2.0 mg/eye either as a single dose or in a multiple-dose regimen at a frequency ranging from every 2 weeks to every month, for up to 12 months. All studies were conducted in subjects with neovascular AMD.

An ECLA for the quantitation of ranibizumab was developed and used in all studies. The minimum quantifiable concentration was 300 pg/ml. A few samples of vitreous fluid were obtained from subjects who underwent medically necessary vitrectomy. These samples were analyzed for ranibizumab by an ELISA.

Given the IVT route of administration for ranibizumab and the limited absorption into the systemic circulation, systemic pharmacokinetic data are sparse. Hence, the systemic pharmacokinetics of ranibizumab was best described in the population analysis using pooled data from five clinical trials (Studies FVF1770g, FVF2128g, FVF2425g, FVF2428g, and FVF2598g), as each study did not provide sufficient information for individual estimation of pharmacokinetic parameters. Serum concentration-time data from Study FVF2587g and the second year of Studies FVF2428g and FVF2598g were not available at the time of this analysis and was not included.

The base model was a one-compartment model with a linear rate of absorption from the vitreous compartment, and a proportional error. The full covariate model included CrCL as a predictor of clearance and concomitant verteporfin PDT treatment as a predictor of the rate of absorption. A total of 2993 serum samples were collected from 674 subjects, of which 675 samples from 238 subjects had measurable concentrations that were included in the data set. Rich sampling was applied in 89 of the subjects while the sampling was sparse in the remaining subjects.

The following information, which is mostly based on the population analysis, is available regarding the pharmacokinetics ranibizumab.

- Absorption

Following IVT administration, the time for ranibizumab to reach the maximum concentration in serum is 0.5 days, and the concentration of ranibizumab in the vitreous humour is estimated to be approximately 90,000 times of that in the systemic circulation. The systemic elimination half-life was estimated to be 2 hours, whereas the vitreous elimination half-life was estimated to be approximately 9 days. Because the rate of vitreous elimination is the rate-limiting step, the apparent half-life of ranibizumab in serum after IVT administration is equivalent to the vitreous elimination half-life.

- Distribution

The distribution of ranibizumab is limited to the volume of plasma (3 litres), which is expected as for drugs with high molecular weight.

The applicant compared the concentration of ranibizumab in vitreous samples collected from a limited number of subjects with simulated vitreous concentrations. Due to the small number of subjects, the validity of the simulated vitreous concentration-time profiles is difficult to assess.

- Elimination

The metabolism and the excretion of ranibizumab were not investigated. Based on data from Study FVF1770g, it is concluded that ranibizumab exhibits roughly proportional kinetics in the dose range 0.05-1 mg.

- Dose proportionality and time dependencies

Regarding exposure relevant for the safety evaluation, the predicted maximum serum concentration of ranibizumab at steady state, 1.7 ng/ml ($95^{th}$ percentile), is below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50%, 11-27 ng/ml, as assessed in an *in vitro* cellular proliferation assay.

- Special populations

The information regarding pharmacokinetics in special populations is based on the population analysis and suggests an increased exposure in patients with renal impairment and a lower systemic $C_{max}$ in subjects receiving concomitant verteporfin PDT without any significant influence of age, gender or total body weight. These findings are not considered clinically relevant as the decrease in CL/F was small in comparison to the inter-individual variability of this parameter and the change in $k_a$, will only lower the systemic $C_{max}$ and not affect the systemic AUC of ranibizumab.

- Pharmacokinetic interaction studies

No formal interaction studies have been performed, which is acceptable as the interaction potential is considered low. Considering that ranibizumab is a Fab and reaches only very low systemic levels after IVT administration, drug-drug interactions with ranibizumab outside of the ocular chamber are highly unlikely. Furthermore, since the vast majority of systemically or topically administered drugs barely penetrate the ocular chamber, drug-drug interactions with ranibizumab within the ocular compartment are also highly unlikely.

**Pharmacodynamic**

Ranibizumab is stated to exert inhibitory effects on angiogenesis and stabilising actions on vessel permeability through the blocking of $VEGF_{165, 121}$ and $_{110.}$ Proof of concept was sought in phase III where CNV membrane growth and leakage was explored as a secondary outcome measure with fluorescein angiography and to a lesser extent with ocular coherence tomography (OCT) as an exploratory analysis. The methods are deemed justified.

Pharmacodynamic data from the ranibizumab/verteporfin combination experiments, in which ranibizumab and verteporfin were administered concomitantly or sequentially, did not suggest *in vivo* pharmacological or pharmacokinetic interactions under "therapeutic" conditions.

No specific studies dedicated to pharmacodynamics have been performed. This is to some degree justifiable as no obvious biomarker exists that could allow for a reasonable interpretation of the pharmacodynamic studies. The pharmacodynamics hence relies on *in vitro* data, animal and human efficacy studies.

**Clinical efficacy**

The submitted documentation consists of seven clinical studies including patients with neovascular AMD (see Table above).

The 1-year results of the two pivotal Phase III studies (FVF2598g, MARINA, started in March 2003 and FVF2587g, ANCHOR, started in May 2003), including 378 randomised patients on the 0.3 mg dose and 380 patients on the 0.5 mg dose, constituted the main body of the dossier at the time of the initial submission.

The Applicant has now submitted, 2-year data from MARINA (FVF2598g), as well as one-year data from a study PIER (FVF3192) exploring a less frequent posology. The 2-year data from FVF 2587g (ANCHOR) and PIER (FVF3192) are pending.

- Dose response

A strong rationale for the dose level and dosing interval has from an efficacy point of view, has not been presented. *In vitro* and preclinical data identified 0.05 mg to 2 mg as a candidate dose range used in the phase I and I/II program, but the latter do not form a firm basis for further dose definition, other than providing a safety dossier indicating an acceptable adverse event profile besides the events of intraocular inflammation.

It was also a matter of concern that the two dose levels explored were close in strength and that no formal dose response studies were performed. It is therefore appreciated that ongoing study (FVF 3192g PIER) explores a less frequent dosing interval.

- Main studies

The 1-year results as well as the 2-year data of the pivotal study FVF 2598 MARINA (sham controlled study in patients with occult and minimally classic CNV lesions) as well as FVF 2587 ANCHOR (a PDT controlled study in patients with predominantly classic lesions) are described below. Both studies explored both 0.3 mg and 0.5 mg ranibizumab injected monthly IVT. The objectives were to show superiority vs. sham in FVF 2598 and non-inferiority vs. PDT in FVF 2587.

In addition, the 1-year data will be presented from FVF 3192 PIER (sham controlled including all lesions of neovascular AMD) exploring a 3-month dosing interval after a 3-month loading phase with monthly injections using the same doses.

METHODS

*Study Participants*
Inclusion criteria:
**Study FVF 2598 (ANCHOR)**
FVF2598g eligible patients had to fulfil among others that:

- age ≥ 50 years
- if classic CNV was present, the area of classic CNV had to be < 50% of the total lesion size
- total area of CNV (including both classic and occult components) encompassed within the lesion ≥ 50% of the total lesion area,
- total lesion area ≤ 12 disc areas (DA) in size and
- best corrected visual acuity (BCVA), using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye. (Only one eye was assessed in the study. If both eyes were eligible, the one with the better visual acuity was selected for treatment and study unless, based on medical reasons, the investigator deemed the other eye the more appropriate candidate for treatment and study).

**Study FVF 2587 (MARINA)**

- Same as the above outlined criteria regarding age, BCVA and selection of one eye only.
- CNV: Lesion needed to be active and have characteristics that qualified for treatment with verteporfin PDT in the study eye, according to the Visudyne product labelling and future treatment with verteporfin PDT anticipated or expected in the study eye.
- Total lesion size requirement: ≤ 5400 μm in greatest linear dimension.

Main exclusion criteria for FVF 2598 and FVF 2587:

- Previous treatment for neovascular AMD (PDT was however allowed in the fellow eye if performed > 1 wk before study start).
- Previous intraocular treatment of any sort in the study eye (except for extrafoveal laser photocoagulation in the study eye).

- As for lesion characteristics, patients with subretinal haemorrhage in the study eye that involved the centre of the fovea were disallowed if the size of the haemorrhage was either >50% of the total lesion area or >1 DA in size or if there was subfoveal fibrosis or atrophy in the study eye.
- In terms of concurrent ocular conditions, patients with disorders that would have an impact on visual function during the study course were excluded (e.g. ongoing infection, history of retinal detachment or macular hole, diabetic retinopathy, uveitis, uncontrolled glaucoma, previous corneal transplant, recent cataract surgery etc).

**Study FVF 3192 (PIER):** Same as above but all subtypes of lesions were included.

*Treatments*
Doses of 0.3 mg or 0.5 mg of ranibizumab, or in studies FVF 2587 and FVF 3192, a sham injection (a blunt syringe directed towards the sclera) were administered once every month. Following subconjunctival injection of anaesthetics, a 30-gauge, ½-inch needle, attached to a low-volume (e.g., tuberculin) syringe containing 50 µL of study drug solution, was inserted approximately 3.5–4.0 mm posterior to the limbus. The scleral site for subsequent IVT injections was rotated.

An antiseptic program including self-administration of antibiotics prior to and after the injection was implemented. Other features of the program were cleansing of the eyelid and the conjunctiva with antiseptics.

In FVF 2587, PDT and sham PDT (because of the dummy design) were treatment alternatives. Verteporfin PDT was administered in accordance with the Visudyne prescribing information. Sham PDT consisted of saline infusion followed by the actual laser irradiation in accordance with Visudyne prescribed procedure. Following Day 0, the evaluating physician determined the need for PDT every 3 months.

*Objectives*
The primary objective for studies FVF 2598 and FVF 2587 was to evaluate the efficacy of intravitreal injections of ranibizumab in preventing vision loss, as measured by the proportion of subjects who lost fewer than 15 letters in visual acuity at 12 months compared with baseline and to evaluate the safety and tolerability of intravitreal injections of ranibizumab administered monthly.

In study FVF2587g the previously mentioned objective the non-inferiority of ranibizumab to verteporfin PDT was evaluated; if non-inferiority was demonstrated, then the treatment differences between ranibizumab and verteporfin PDT were also to be evaluated for superiority.

The primary objective for study FVF3192 was to evaluate the efficacy and safety of IVT injections of ranibizumab when administered with a reduced dosing frequency.

Secondary objectives were among others to evaluate the efficacy of monthly intravitreal injections of ranibizumab in preventing vision loss as measured by the following: - The mean change from baseline in visual acuity over time up to 12 months, - The proportion of subjects who gained at least 15 letters in visual acuity at 12 months compared with baseline, - The proportion of subjects with a visual acuity Snellen equivalent of 20/200 or worse at 12 months, - To investigate the efficacy of the treatment, as measured by the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) and to evaluate the efficacy of ranibizumab on the size of choroidal neovascularisation and amount of leakage from CNV at 12 months, as assessed by fluorescein angiography.

*Outcomes/endpoints*
The **primary efficacy endpoint** for study FVF 2598 was to prove the superiority in efficacy of intravitreal ranibizumab vs. sham (FVF 2598) and for study and FVF 2587, non-inferiority vs. PDT (FVF2587) in preventing vision loss. This was measured by the proportion of subjects who lost < than 15 letters in the study eye (approximately 3 lines evaluated primarily using the BCVA score based on the ETDRS visual acuity chart) at 12 months compared with baseline, based on assessment at a starting test distance of 2 meters. At the request of the FDA the visual acuity score at a starting test distance of 4 meters was also assessed at selected timepoints.

As for FVF 3192, the primary endpoint was the mean change in VA from baseline. Apart from this difference, secondary endpoints were the same as for the above mentioned studies with the exception that proportion of patients opposing less than 15 letters was also a secondary endpoint.

The **secondary efficacy endpoint** measures assessed at 12 months were:

- Proportion of patients loosing < 15 letters on the ETDRS chart compared with baseline at a starting test distance of 4 meters
- The mean change from baseline in VA
- The proportion of subjects who gained at least 15 letters of VA from baseline
- The proportion of subjects with a VA Snellen equivalent of 20/200 or worse at 12 months compared with baseline
- Vision-related functions and well being assessment as measured with the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25) compared with baseline
- CNV size and amount of leakage as assessed by fluorescein angiography compared with baseline

In addition, a number of exploratory outcomes were investigated such as time to loss of more than 3 lines on the ETDRS chart, proportion of patients losing less than 30 letters and other vision parameters, various fluorescein angiographic features of the CNV, ocular coherence tomography (OCT) and contrast sensitivity testing.

*Sample size*

FVF2598

With a total sample size of 720 subjects (equally distributed between treatment arms) and an assumed difference of responders, 65% in each ranibizumab group vs. 50% in the control group, the analysis would have a 95% power to detect statistical significance in the ITT population and a 90% power in the subset of evaluable subjects, i.e. subjects who had at least baseline and month 12 VA examinations (= PP subset). The calculation was made assuming that 20% of the ITT subjects had missing VA data at Month 12.

FVF 2587

With a total sample size of 426 subjects (with a 1:1:1 distribution between the 3 treatment arms), the non-inferiority test had a > 99% power in the analysis based on randomised subjects and a > 98% power in the analysis based on evaluable subjects to show that one or both ranibizumab groups are non-inferior to the verteporfin PDT group (better or <7% worse) in the primary efficacy endpoint, using a one-sided normal approximation test.

To demonstrate superiority with an assumed difference in responders of 84% in each ranibizumab group and 67% in the verteporfin PDT group, the analysis would have a 96% power to detect a statistical significance in the ITT analysis and a 90% power in the analysis based on evaluable subjects. The calculation was made assuming that 20% of the randomized subjects had missing VA data at Month 12.

FVF 3192

With a total of 180 subjects in a 1:1:1 randomisation it was assumed that there would be a 90% to detect a difference in the mean change in VA between the active arms and sham in the ITT population using the Student's T-test with the Hochberg Bonferoni corrections for multiple comparisons. The analyses foresaw an ANOVA with stratification by lesion type (occult, minimally classic and predominantly classic) and by initial VA ($\leq$ 54 letters and $\geq$ 55 letters).

*Randomisation*

Eligible subjects were randomised in a 1:1:1 ratio to receive 0.5 mg ranibizumab, 0.3 mg ranibizumab, or a sham injection in the FVF2598g and FVF 3192 studies.

Eligible subjects were randomised in a 1:1:1 ratio to receive 0.3 mg ranibizumab and sham PDT with saline infusion, 0.5 mg ranibizumab and sham PDT with saline infusion, or sham injection of ranibizumab and active verteporfin PDT in the FVF2587g study.

*Blinding (masking)*
In order to ensure masking there was a minimum of two investigators per study site to fulfil the masking requirements of these studies. Investigators were designated as an "evaluating physician" (who was masked to the treatment assignment and conducted all ocular assessments) or an "injecting physician" (who was unmasked to the treatment assignment and performed the ranibizumab/sham injection and the active or sham PDT infusion procedures, but was masked to study drug dose (0.3 mg vs. 0.5 mg ranibizumab)).

Sham intravitreal injections were chosen instead of placebo intravitreal injections to avoid risk of ocular injury or endophthalmitis.

*Statistical methods*
The following efficacy analysis populations were defined for both pivotal studies FVF2598g and FVF2587g:

**Randomized Subjects:** This population was used for summaries of demographics and study conduct and for most summaries of efficacy. Treatment group assignment for this population was as randomised (i.e., intent to treat [ITT]).

**Per-Protocol Subjects:** A subset of randomised subjects who were considered more compliant with the protocol, i.e. having baseline and Month 12 VA assessments, not violating entry criteria, receiving the majority of treatments etc. This population was used for supportive analyses of visual acuity efficacy outcome measures at Month 12.

**Safety-Evaluable Subjects:** These were randomised subjects who received at least one treatment with study drug.

The primary, secondary, and most of the exploratory outcome measures were analysed based on the randomised subject population Missing data were imputed using the last-observation-carried-forward (LOCF) approach.

FVF2598
Comparisons of efficacy were performed between each ranibizumab dose group and the sham injection (control) group with the Cochran $\chi 2$ (categorical variables) or analysis of variance (ANOVA) or analysis of covariance (ANCOVA) models (continuous outcome measures). Comparisons included only two treatment groups (active vs. control) at a time. Multiple treatment comparisons of each ranibizumab dose group with the control group were managed with the Hochberg-Bonferroni multiple comparison procedure.

FVF2587
The same methods as described above were used, but for the non-inferiority assumption; a one-sided normal approximation test for the weighted average of the differences between two proportions over the strata was used, with baseline visual acuity score as the stratification variable. The Cochran-Mantel-Haenszel weights were used to calculate the weighted average or the overall stratified difference in proportions and the normal approximation test was performed by applying the procedure proposed by Blackwelder to stratified binomials

**Stratified Analyses** in both studies above and subsequent subgroup analyses of the primary efficacy endpoint were performed by categories of the following demographic and baseline variables:
sex, age ($\leq$ 74 vs. $\geq$75 yr), VA score in the study eye ($\leq$54 vs. $\geq$ 55 letters in FVF 2598 and $\leq$44 vs. $\geq$45 in FVF2587 ), CNV lesion characteristics and prior laser photocoagulation in the study eye (yes, no).

In study FVF 3192 the mean change in BCVA from baseline to 12 months was compared with the sham-injection control group using the t-test from an ANOVA model stratified by CNV classification at baseline. The Hochberg-Bonferroni multiple comparison procedure was used to adjust for

comparison of the two ranibizumab groups with the control group in order to maintain an overall type I error rate of 0.05.

Comparisons of efficacy were performed between each ranibizumab dose group and the sham injection (control) group with the Cochran $\chi 2$ test (secondary endpoint).

RESULTS

*Participant flow*

**Table 2 Subject Disposition and Reasons for Discontinuation: Randomised Subjects in Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT | Ranibizumab | |
| Status | Sham (n = 238) | 0.3 mg (n = 238) | 0.5 mg (n = 240) | (n = 143) | 0.3 mg (n = 140) | 0.5 mg (n = 140) |
| Received ranibizumab/sham ITV injection | 236 (99.2%) | 238 (100%) | 239 (99.6%) | 143 (100%) | 137 (97.9%) | 140 (100%) |
| Received verteporfin/sham PDT [a] | — | — | — | 143 (100%) | 137 (97.9%) | 140 (100%) |
| Completed Month 12 [b] | 212 (89.1%) | 226 (95.0%) | 226 (94.2%) | 127 (88.8%) | 128 (91.4%) | 131 (93.6%) |
| Discontinued treatment prior to Month 12 | 31 (13.0%) | 10 (4.2%) | 11 (4.6%) | 14 (9.8%) | 13 (9.3%) | 9 (6.4%) |
| Discontinued from study at or prior to Month 12 [c] | 21 (8.8%) | 6 (2.5%) | 6 (2.5%) | 10 (7.0%) | 10 (7.1%) | 5 (3.6%) |
| Primary reason for study discontinuation | | | | | | |
| Death | 0 | 1 (0.4%) | 2 (0.8%) | 1 (0.7%) | 3 (2.1%) | 2 (1.4%) |
| Adverse event | 5 (2.1%) | 0 | 2 (0.8%) | 4 (2.8%) | 2 (1.4%) | 1 (0.7%) |
| Lost to follow-up | 2 (0.8%) | 0 | 0 | 1 (0.7%) | 0 | 1 (0.7%) |
| Subject's decision | 11 (4.6%) | 5 (2.1%) | 2 (0.8%) | 3 (2.1%) | 2 (1.4%) | 1 (0.7%) |
| Physician's decision | 0 | 0 | 0 | 1 (0.7%) | 2 (1.4%) | 0 |
| Subject's non-compliance | 0 | 0 | 0 | 0 | 1 (0.7%) | 0 |
| Subject's condition mandated other therapeutic intervention | 3 (1.3%) | 0 | 0 | 0 | 0 | 0 |

ITV = intravitreal.

[a] Including only those specified as the study treatment.

[b] Defined as having a visual acuity score in the study eye at Month 12.

[c] Including subjects who discontinued from the study at Month 12 after assessments.

**Table 3 Subject Disposition and Reasons for Discontinuation: Randomised Subjects in Studies FVF3192g**

| | Study 3192g | | |
|---|---|---|---|
| | | Ranibizumab | |
| Status | Sham (n = 63) | 0.3 mg (n = 60) | 0.5 mg (n = 61) |
| Received study drug/sham | 62 (98.4%) | 59 (98.3%) | 61 (100%) |
| Completed Month 12 | 54 (85.7%) | 59 (98.3%) | 58 (95.1%) |
| Discontinued treatment prior to Month 12 | 17 (27.0%) | 4 (6.7%) | 4 (6.6%) |
| Discontinued study on or prior to Month 12 | 8 (12.7%) | 1 (1.7%) | 2 (3.3%) |
| Subject's decision [a] | 5 (7.9%) | - (0%) | - (0%) |
| Subject's non-compliance | 1 (1.6%) | 1 (1.7%) | 131 (93.6%) |
| Subject's condition mandated other therapeutic intervention | 2 (3.2%) | - (0%) | - (0%) |

*Recruitment*

FVF 2598: The first subject was enrolled into the study on 28 March 2003, and the last subject completed Month 12 of the study on 28 December 2004.

FVF 2587: The first subject was randomised into the study on 10 June 2003, and the last subject completed Month 12 of the study on 13 September 2005.

FVF3192g: The first subject was enrolled into the study on 7 September 2004, and the last subject completed Month 12 of the study on 15 March 2006.

*Conduct of the study*

The protocol of the study **FVF2598g** (MARINA) was amended six times the most important changes being; minor modifications in the inclusion and exclusion and dose-holding criteria, an unscheduled collection of a vitreous sample was added for subjects who underwent posterior vitrectomy surgery and the incorporation of procedures for concomitant treatment with verteporfin PDT for subjects who converted from minimally classic or occult lesion classification to predominantly classic. Later it was even decided that patients could have PDT regardless of lesion characteristics without being excluded from the study. The sixth amendment, dated 9 September 2005, allows subjects in the sham-injection group to cross over and receive ranibizumab. Subjects who cross over would receive monthly injections of 0.5 mg ranibizumab for the last 2 (n= 7) and 3 (n = 5) months of the treatment period. Data observed after crossover of these subjects were reviewed separately.

Of note, the need to increase the interval between verteporfin treatment and study drug injections if a subject converted to predominantly classic CNV in the study eye was addressed in the protocol because of ocular serious adverse events reported in Study FVF2428g. The Statistical Analysis Plan was amended to ensure consistency with the changes made to the protocol and across the ranibizumab clinical program.

In general, treatment compliance was good in FVF2598, with 89% or more of subjects treated at each visit. However, the treatment rate was slightly lower in the sham-injection group as a result of the greater number of drop-outs; the lowest treatment rate was 83.6% at 12 months. For most visits, the proportion of subjects treated was slightly larger in the 0.3-mg group than in the 0.5-mg group.

The **FVF2587** protocol was amended 5 times. These alterations did not profoundly influence the study design except for the change pertaining to the p-value of the one-sided test for the primary endpoint, which was reduced to 0.024 from 0.049. The protocol of the FVF2587g study was first amended on 21 October 2003 to clarify methods of administering verteporfin PDT or sham PDT in order to minimize the risk of infection. A few minor amendments were included afterwards. The amendment of

December 2005 allowed patients with sham injections to switch over to active treatment with ranibizumab 0.3 mg.

Treatment compliance with ranibizumab (or sham) in FVF2587 was also generally good, with 87% or more of randomised subjects receiving a ranibizumab (or sham) injection at each treatment visit. Likewise, treatment compliance with verteporfin/sham PDT was generally good, with 87% or more of subjects receiving either verteporfin or sham PDT at each of the appropriate visits or having no treatment administered if deemed unnecessary by the investigator.

In study **FVF3192g**, the protocol was amended twice. The first protocol amendment, dated 12 May 2005, specified pegaptanib sodium as an excluded medication, included additional antimicrobials for pre- and post-injection use, clarified that the method of IOP measurement used for a subject was to be consistent throughout the study and the time frame for determining whether an adverse event was sight threatening was clarified. Finally, the protocol was also revised to be consistent with the protocols of the other Phase III studies. The second amendment (27 February 2006) was done after review of the 12-month data from the two pivotal Phase III studies allowing subjects to cross-over to active treatment after the Month 12 visit.

**Protocol Deviations:** In the FVF2598g two overdose incidents during Year 1 of the study occurred. One subject (131006) (0.3-mg group, Month 1) was injected with four times the amount of study drug designated in the protocol. Another subject (196003) (0.5-mg group, Day 0) was reported as having a possible overdose of up to 2 mg and was unmasked to the treatment assignment (but not to dose level).

*Baseline data*
Baseline parameters were balanced with a few exceptions. Most importantly VA was slightly better and CNV dimensions slightly smaller in the ranibizumab arms in FVF 2587. In addition, a somewhat longer duration of active AMD was seen in control arms vs. ranibizumab arms in studies FVF 2598 and 2587 while in FVF 3192, the active arms contained more patients with occult lesions than the sham arm (48 – 49% vs. 32%) and the overall proportion of patients with predominantly classic lesions were few. The strata used in the analyses included baseline VA (and in FVF 3192 lesion type) which should compensate for these minor differences.

**Table 4 Demographic and baseline characteristics**

| Demographic | Study FVF2598g (MARINA) | | | Study FVF2587g (ANCHOR) | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT (n=143) | Ranibizumab | |
| | Sham (n=236) | 0.3 mg (n=238) | 0.5 mg (n=239) | | 0.3 mg (n=137) | 0.5 mg (n=140) |
| **Age (yr)** | | | | | | |
| Mean (SD) | 77.1 (6.6) | 77.4 (7.6) | 76.8 (7.6) | 77.7 (7.8) | 77.3 (7.3) | 76.0 (8.6) |
| Range | 56–94 | 52–95 | 52–93 | 53–95 | 54–96 | 54–93 |
| Sex | | | | | | |
| Male | 79 (33.5%) | 85 (35.7%) | 88 (36.8%) | 64 (44.8%) | 71 (51.8%) | 75 (53.6%) |
| **Race/ethnicity** | | | | | | |
| White | 229 (97.0%) | 229 (96.2%) | 231 (96.7%) | 140 (97.9%) | 134 (97.8%) | 136 (97.1%) |
| **Visual acuity** [a] | | | | | | |
| Number of letters, mean (SD) | 54.0 (13.4) | 53.1 (12.9) | 53.7 (12.8) | 45.5 (13.1) | 47.1 (12.8) | 47.1 (13.2) |
| Number of letters, range | 16–84 | 19–78 | 17–79 | 3–68 | 19–76 | 6–75 |
| Approximate Snellen equivalent, median | 20/80 | 20/80 | 20/80 | 20/100 | 20/100 | 20/125 |
| **CNV classification** | | | | | | |
| Predominantly classic | 0 | 1 (0.4%) | 1 (0.4%) | 141 (98.6%) | 131 (95.6%) | 135 (96.4%) |
| Minimally classic | 86 (36.4%) | 86 (36.1%) | 91 (38.1%) | 2 (1.4%) | 5 (3.6%) | 5 (3.6%) |
| Occult without classic | 150 (63.6%) | 151 (63.4%) | 147 (61.5%) | 0 | 1 (0.7%) | 0 |
| **Total area of CNV (DA)** | | | | | | |
| Mean (SD) | 4.28 (2.41) | 4.13 (2.47) | 4.28 (2.50) | 1.48 (1.25) | 1.42 (1.25) | 1.31 (1.24) |
| Range | 0.20–11.75 | 0.02–11.80 | 0.12–12.00 | 0.07–5.55 | 0.11–6.80 | 0.05–7.50 |
| **Total area of leakage from CNV plus intense progressive RPE staining (DA)** | | | | | | |
| Mean (SD) | 3.53 (2.46) | 3.59 (2.50) | 3.48 (2.63) | 3.06 (1.81) | 2.91 (1.83) | 2.92 (2.08) |
| Range | 0.00–12.85 | 0.00–11.95 | 0.00–13.50 | 0.20–8.20 | 0.20–11.00 | 0.25–9.00 |

DA=disc areas; RPE=retinal pigment epithelium.

[a] Visual acuity assessment based on a starting test distance of 2 meters. Number of letters was of 0–100.

**Table 5 Disease Duration and Prior Therapies for AMD in the Study Eye: Randomised Subjects in Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT (n=143) | Ranibizumab | |
| | Sham (n=238) | 0.3 mg (n=238) | 0.5 mg (n=240) | | 0.3 mg (n=140) | 0.5 mg (n=140) |
| **Year since first diagnosis of neovascular AMD** | | | | | | |
| n | 235 | 238 | 238 | 142 | 140 | 140 |
| Mean (SD) | 0.8 (1.3) | 0.6 (1.6) | 0.7 (1.3) | 0.4 (0.9) | 0.3 (0.6) | 0.3 (0.8) |
| Range | 0.0–10.9 | 0.0–18.9 | 0.0–13.3 | 0.0–5.4 | 0.0–5.4 | 0.0–7.3 |
| **Prior therapy for AMD** | | | | | | |
| n | 238 | 238 | 240 | 143 | 140 | 140 |
| Any prior therapy | 134 (56.3%) | 140 (58.8%) | 137 (57.1%) | 64 (44.8%) | 63 (45.0%) | 58 (41.4%) |
| Laser photocoagulation | 22 (9.2%) | 13 (5.5%) | 14 (5.8%) | 19 (13.3%) | 23 (16.4%) | 20 (14.3%) |

**Table 6 Study FVF 3192**

| Characteristics | Sham (n = 63) | Ranibizumab 0.3 mg (n = 60) | Ranibizumab 0.5 mg (n = 61) |
|---|---|---|---|
| Years since first diagnosis of neovascular AMD | | | |
| Mean (SD) | 0.3 (0.5) | 0.7 (1.6) | 0.7 (1.2) |
| Range | 0.0–3.0 | 0.0–9.1 | 0.0–5.0 |
| Visual acuity | | | |
| Number of letters (0–100) | | | |
| Mean (SD) | 55.1 (13.9) | 55.8 (12.2) | 53.7 (15.5) |
| Range | 25–76 | 18–79 | 13–79 |
| Approximate Snellen equivalent | | | |
| Median | 20/63 | 20/63 | 20/80 |

As for allowed concomitant PDT in FVF2598, 26 (3.6%) received one or more treatments with PDT in the study eye during the first treatment year: 25 subjects in the sham-injection group (10.5%) and 1 subject in the 0.3-mg group (0.4%).

Comorbility conditions

In studies FVF 2598 and 2587, > 80% of subjects had a history of cardiovascular conditions and > 60% of subjects had a history of musculoskeletal/rheumatic conditions.

*Numbers analysed*

**FVF 2598 (MARINA)**

**Table 7 FVF2598g Analysis Populations: Randomised Subjects**

| Analysis Population | Sham (n=238) | Ranibizumab 0.3 mg (n=238) | Ranibizumab 0.5 mg (n=240)[a] |
|---|---|---|---|
| Randomized subjects (ITT) | 238 (100%) | 238 (100%) | 240 (100%) |
| Per-protocol subjects (for the analysis of) | | | |
| 2-meter visual acuity at Month 12 | 183 (76.9%) | 208 (87.4%) | 205 (85.4%) |
| 4-meter visual acuity at Month 12 | 176 (73.9%) | 200 (84.0%) | 196 (81.7%) |
| Randomized subjects in the OCT subset | 16 (6.7%) | 23 (9.7%) | 14 (5.8%) |
| Randomized subjects in the HUI® subset | 19 (8.0%) | 16 (6.7%) | 13 (5.4%) |
| Safety-evaluable subjects | 236 (99.2%) | 238 (100%) | 239 (99.6%) |
| Pharmacokinetic-evaluable subjects | 218 (91.6%) | 226 (95.0%) | 225 (93.8%) |

ITT=intent to treat; HUI®=Health Utilities Index®; OCT=optical coherence tomography.

[a] Subject 119009 was randomized twice (to the 0.5 mg ranibizumab group in both cases) and was included as only 1 subject in all analyses.

**FVF 2587 (ANCHOR)**

**Table 8 FVF2587g Analysis Populations: Randomised Subjects**

| Analysis Population | Verteporfin PDT (n=143) | Ranibizumab 0.3 mg (n=140) | Ranibizumab 0.5 mg (n=140) |
|---|---|---|---|
| Randomized subjects (ITT) | 143 (100%) | 140 (100%) | 140 (100%) |
| Per-protocol subjects (for the analysis of) | | | |
| 2-meter visual acuity at Month 12 | 116 (81.1%) | 109 (77.9%) | 109 (77.9%) |
| 4-meter visual acuity at Month 12 | 114 (79.7%) | 101 (72.1%) | 103 (73.6%) |
| Randomized subjects in the OCT subset | 17 (11.9%) | 26 (18.6%) | 18 (12.9%) |
| Randomized subjects in the HUI® subset | 21 (14.7%) | 25 (17.9%) | 19 (13.6%) |
| Safety-evaluable subjects | 143 (100%) | 137 (97.9%) | 140 (100%) |
| Pharmacokinetic-evaluable subjects | 136 (95.1%) | 135 (96.4%) | 137 (97.9%) |

ITT=intent to treat; HUI®=Health Utilities Index®; OCT=optical coherence tomography.

## FVF 3192 (PIER)

### Table 9 FVF3192 Analysis Populations: Randomised Subjects

Analysis Populations:
Randomized Subjects

| Analysis Population | Sham (n=63) | Ranibizumab 0.3 mg (n=60) | Ranibizumab 0.5 mg (n=61) |
|---|---|---|---|
| Randomized subjects (ITT) | 63 (100.0%) | 60 (100.0%) | 61 (100.0%) |
| Per-protocol subjects | 53 (84.1%) | 59 (98.3%) | 58 (95.1%) |
| Randomized subjects in the OCT subset | 42 (66.7%) | 39 (65.0%) | 42 (68.9%) |
| Safety-evaluable subjects | 62 (98.4%) | 59 (98.3%) | 61 (100.0%) |
| Pharmacokinetic-evaluable subjects | 63 (100.0%) | 60 (100.0%) | 61 (100.0%) |

ITT=intent to treat; OCT=optical coherence tomography.
Source: Table 14.1/7.

*Outcomes and estimation*

- Primary endpoints

**1-year data from studies from FVF2598g (MARINA) and FVF2587g (ANCHOR)**

**Table 10 Visual Acuity at 12 Months: Randomised Subjects in Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT (n=143) | Ranibizumab | |
| Visual Acuity at 12 Months | Sham (n=238) | 0.3 mg (n=238) | 0.5 mg (n=240) | | 0.3 mg (n=140) | 0.5 mg (n=140) |
| At a Starting Test Distance of 2 Meters | | | | | | |
| n | 238 | 238 | 240 | 143 | 140 | 139 |
| **Loss of < 15 letters** | 148 (62.2%) | 225 (94.5%) | 227 (94.6%) | 92 (64.3%) | 132 (94.3%) | 134 (96.4%) |
| **p-value (vs. control)** | | **< 0.0001** | **< 0.0001** | | **< 0.0001** | **< 0.0001** |
| Gain of ≥15 letters | 11 (4.6%) | 59 (24.8%) | 81 (33.8%) | 8 (5.6%) | 50 (35.7%) | 56 (40.3%) |
| **p-value (vs. control)** | | **< 0.0001** | **< 0.0001** | | **< 0.0001** | **< 0.0001** |
| Change from baseline (letters), mean (SD) | -10.5 (16.6) | 6.5 (12.7) | 7.2 (14.4) | −9.5 (16.4) | 8.5 (14.6) | 11.3 (14.6) |
| Approximate Snellen equivalent: 20/200 or worse | 102 (42.9%) | 29 (12.2%) | 28 (11.7%) | 86 (60.1%) | 31 (22.1%) | 23 [a] (16.4%) |
| At a Starting Test Distance of 4 Meters | | | | | | |
| n | 229 | 229 | 230 | 141 | 133 | 139 |
| **Loss of < 15 letters** | 138 (60.3%) | 213 (93.0%) | 209 (90.9%) | 93 (66.0%) | 126 (94.7%) | 136 (97.8%) |
| **p-value (vs. control)** | | **< 0.0001** | **< 0.0001** | | **< 0.0001** | **< 0.0001** |
| Gain of ≥15 letters | 14 (6.1%) | 42 (18.3%) | 72 (31.3%) | 15 (10.6%) | 37 (27.8%) | 51 (36.7%) |
| Change from baseline (letters), mean (SD) | −11.0 (17.9) | 5.4 (13.4) | 6.3 (14.1) | −8.5 (17.8) | 7.2 (15.3) | 11.0 (15.8) |
| Approximate Snellen equivalent; 20/200 or worse [b] | 102 (43.0%) | 29 (12.2%) | 28 (11.7%) | 81 (56.6%) | 32 (23.0%) | 23 (16.4%) |

[a] n = 140.

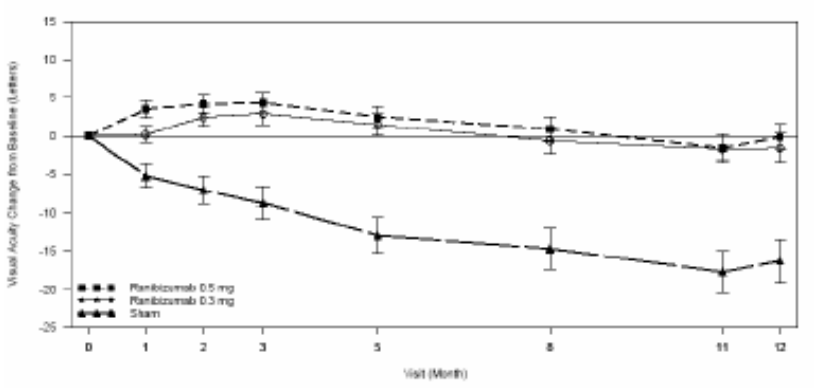
[b] n = 237, 237, 240, 143, 139, and 140 for the sham, 0.3-mg, and 0.5-mg groups in Study FVF2598g and the verteporfin PDT, 0.3-mg, and 0.5-mg groups in Study FVF2587g, respectively.

All treatment comparisons versus sham for Study FVF2598g and verteporfin PDT for Study FVF2587g were highly statistically significant according to the prespecified criteria for assessing significance, while accounting for multiplicity ($p < 0.0001$ for all comparisons except one: $p = 0.0003$ for the 0.3-mg group versus verteporfin PDT in the gain of ≥ 15 letters endpoint [4 meters] for Study FVF2587g). In both studies visual acuity results assessed at a starting test distance of 4 meters were comparable to those assessed at a starting test distance of 2 meters.

**1-year data from study FVF3192 (PIER)**

**Figure 1**

Mean Change from Baseline over Time in Visual Acuity of the Study Eye at a Starting Test Distance of 4 Meters: Randomized Subjects




Note: The LOCF method was used to impute missing data. Vertical bars are ±1 standard error of the mean.

p-values active vs. sham < 0.00001

*Ancillary analyses*

- Secondary endpoints

**Figures 2 - 3 Mean Change from Baseline over Time up to 12 Months in Visual Acuity: Randomized Subjects in Studies FVF2598g and FVF2587g**

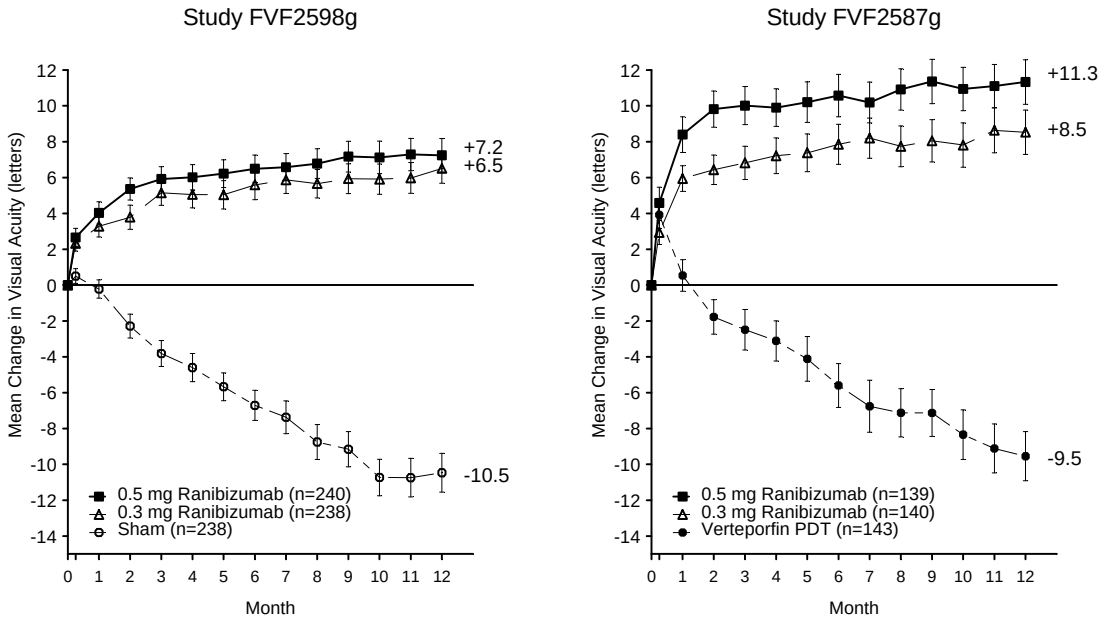


**Table 11 Gain in VA at 12 months**

| Gain of ≥15 Letters at 12 Months | Control | Ranibizumab 0.3 mg | Ranibizumab 0.5 mg |
|---|---|---|---|
| **Study FVF2598g (MARINA)** | | | |
| n | 238 | 238 | 240 |
| Response rate | 11 (4.6%) | 59 (24.8%) | 81 (33.8%) |
| 95% CI of the percentage | (2.0%, 7.3%) | (19.3%, 30.3%) | (27.8%, 39.7%) |
| p-value (vs. control) | | <0.0001 | <0.0001 |
| **Study FVF2587g (ANCHOR)** | | | |
| n | 143 | 140 | 139 |
| Response rate | 8 (5.6%) | 50 (35.7%) | 56 (40.3%) |
| 95% CI of the percentage | (1.8%, 9.4%) | (27.8%, 43.7%) | (32.1%, 48.4%) |
| p-value (vs. control) | | <0.0001 | <0.0001 |

Notes: Strata were defined using baseline CNV classification (minimally classic vs. occult) and VA score (2 meters, ≤54 vs. ≥55 letters) in Study FVF2598g and baseline VA score (2 meters, ≤44 vs. ≥45 letters) in Study FVF2587g.

**FVF 3192 (PIER)**

**Table 12**

Table 19
Visual Acuity in the Study Eye at 12 Months at a Starting Test Distance of 4 Meters: Randomized Subjects

| Visual Acuity at 12 Months | Sham (n=63) | Ranibizumab 0.3 mg (n=60) | Ranibizumab 0.5 mg (n=61) |
|---|---|---|---|
| Loss of <15 letters from baseline | | | |
| n | 31 (49.2%) | 50 (83.3%) | 55 (90.2%) |
| 95% CI for percentage [a] | (36.9%, 61.6%) | (73.9%, 92.8%) | (82.7%, 97.6%) |
| Difference in % (vs. sham) [b] | | 34.0% | 37.0% |
| 95% CI for difference [b] | | (19.2%, 48.8%) | (22.5%, 51.5%) |
| p-value (vs. sham) [c] | | <0.0001 | <0.0001 |
| Gain of ≥15 letters from baseline | | | |
| n | 6 (9.5%) | 7 (11.7%) | 8 (13.1%) |
| 95% CI for percentage [a] | (2.3%, 16.8%) | (3.5%, 19.8%) | (4.6%, 21.6%) |
| Difference in % (vs. sham) [b] | | 0.9% | 2.1% |
| 95% CI for difference [b] | | (−9.8%, 11.7%) | (−8.2%, 12.4%) |
| p-value (vs. sham) [c] | | 0.8674 | 0.7080 |
| Snellen equivalent of 20/200 or worse | | | |
| n | 33 (52.4%) | 14 (23.3%) | 15 (24.6%) |
| 95% CI for percentage [a] | (40.0%, 64.7%) | (12.6%, 34.0%) | (13.8%, 35.4%) |
| Difference in % (vs. sham) [b] | | −32.5% | −26.9% |
| 95% CI for difference [b] | | (−47.5%, −17.5%) | (−41.6%, −12.3%) |
| p-value (vs. sham) [c] | | 0.0002 | 0.0011 |
| Distribution, n | | | |
| 20/200 or worse | 33 (52.4%) | 14 (23.3%) | 15 (24.6%) |
| Better than 20/200 but worse than 20/40 | 23 (36.5%) | 28 (46.7%) | 29 (47.5%) |
| 20/40 or better | 7 (11.1%) | 18 (30.0%) | 17 (27.9%) |

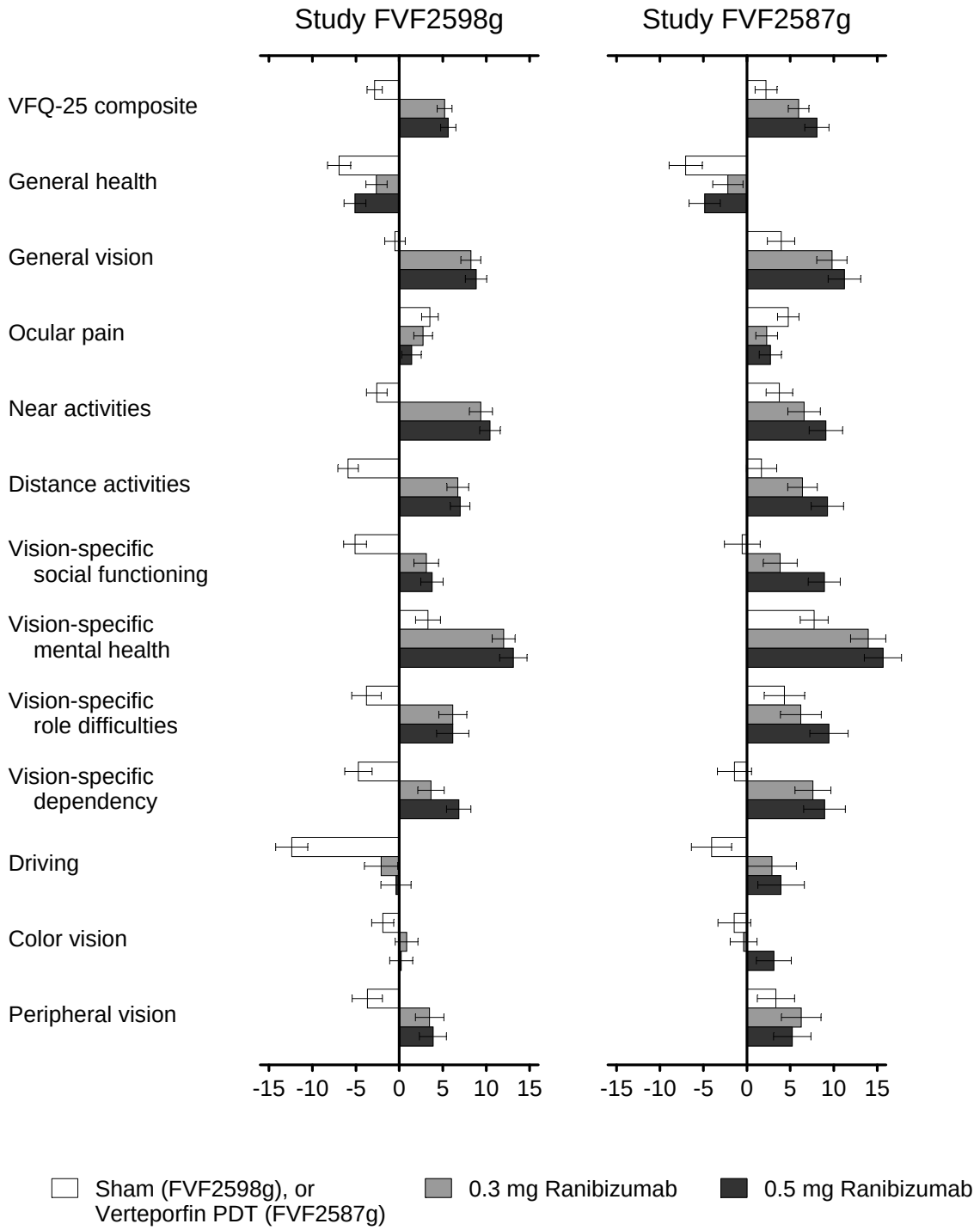
LS=least squares.
Note: The LOCF method was used to impute missing data. Strata were defined using two factors: baseline CNV classification (minimally classic vs. occult without classic vs. predominantly classic) and baseline visual acuity score (≤54 vs. ≥55 letters).
[a] By normal approximation.
[b] Weighted estimates adjusting for the strata by using the Cochran-Mantel-Haenszel weights.
[c] From Cochran $\chi^2$ tests adjusted for the strata.

LOCF analyses were only one type of analyses performed for studies FVF2598g (MARINA) and FVF2587g (ANCHOR). In addition, the CSRs for the two Phase III studies include a number of sensitivity analyses.

Using observed cases only, the proportion of patients losing fewer than 15 letters from baseline at 12 months in study FVF2598g (MARINA) was 95.2% on 0.3 mg, 95.6% on 0.5 mg, and 65.6% on sham treatment ($p<0.0001$ for both ranibizumab doses vs. sham). In study FVF2587g (ANCHOR), the corresponding proportions were 96.3% on 0.3 mg, 97.2% on 0.5 mg, and 61.2% on verteporfin PDT ($p<0.0001$ for both ranibizumab doses vs. PDT). For both studies, the results were very similar to those of the LOCF analyses. Even when missing data were accounted for in the most conservative way, i.e. by imputing every missing observation with the worst possible outcome (i.e. loss of > 15 letters), the results of the primary efficacy endpoints were not substantially altered: 90.8% on 0.3 mg, 88.8% on 0.5 mg, and 54.6% on sham treatment in study FVF2598g (MARINA); 88.6% on 0.3 mg, 91.4% on 0.5 mg, and 54.5% on verteporfin PDT in study FVF2587g (ANCHOR); $p<0.0001$ for both ranibizumab doses vs. control in both studies.

The above-mentioned results of the sensitivity analyses are not considered to be surprising given the low percentage of missing 12-month values particularly in the ranibizumab groups (5% on 0.3 mg, 6% on 0.5 mg, 11% on sham treatment in study FVF2598g/MARINA; 9% on 0.3 mg, 7% on 0.5 mg, 11% on verteporfin PDT in study FVF2587g/ANCHOR). Under these circumstances LOCF analyses, which assume stable vision in early dropouts from the control groups, may be more conservative than observed cases analyses.

**Figure 4 Mean change from baseline in VFQ-25 composite score and subscales at 12 Months: Randomised subjects in studies FVF2598g and FVF2587g**




Notes: Horizontal lines are ±1 standard error of the mean. The LOCF method was used for imputation of missing data.

No formal statistical comparisons were performed for the mean change from baseline over time up to 12 months for each of the following outcomes: Loss of < 30 Letters in Visual Acuity, Time to Loss of ≥ 15 Letters in Visual Acuity, Visual Acuity at 4 Meters, Change in Contrast Sensitivity. Change in Retinal Thickness, VFQ-25, SF-36 Health Survey. However, there is a notable trend toward an improvement, on average, for ranibizumab-treated subjects, whereas control-treated subjects had some decline. The robustness of the efficacy results in favour of ranibizumab is supported by different exploratory analysis.

Stratified analyses indicated a more pronounced effect in patients with fair VA at study start (≥ 55 and ≥45 letters, respectively). Subgroup analyses were also performed in patients with a baseline visual acuity < 20/200 (according to the definition of 'legal blindness' in the US), which indicated a true benefit of Ranibizumab for patients with poor VA at treatment onset.

- Exploratory analyses

A number of exploratory analyses were conducted regarding VA and CNV assessments, and Foveal Retinal Thickness. The most important ones are presented below.

CNV

The effect on the size and leakage of CNV is a measure of the treatment effect of a drug on neovascular AMD. The total size of CNV lesions was stabilized and the CNV leakage as estimated by fluorescein angiography was reduced with ranibizumab treatment in both study FVF2587g (ANCHOR) and study FVF2598g (MARINA), while the same parameters increased for the control groups.

Foveal Retinal Thickness

For OCT, which was performed only in small subgroup of the patients, the trend was similar in both study FVF2587g (ANCHOR) and study FVF2598g (MARINA). Among the subset of subjects with OCT assessments at baseline (a total of 46 subjects in Study FVF2598g and a total of 53 in Study FVF2587g), a significant mean reduction in foveal retinal thickness of the study eye from baseline was seen at Day 7 and maintained up to 12 months in ranibizumab-treated subjects. The number of patients with OCT data in the Phase III studies was however too small to allow reliable estimates of the correlation between OCT and visual acuity scores.

Change in Contrast Sensitivity in FVV 2587

At 12 months, ranibizumab-treated subjects had a mean gain of 1.9 and 2.1 letters from baseline in the 0.3- and 0.5-mg groups, respectively; this is statistically significant ($p < 0.0001$) vs. control.

Use of active PDT and sham PDT in FVF2587

The control group received an average of 3.1 treatments (SD, 1.3) with verteporfin PDT, and the 0.3-mg and 0.5-mg ranibizumab groups received an average of 1.9 (SD, 1.3) and 1.8 (SD, 1.1) sham-PDT treatments, respectively.

Analysis performed across trials (pooled analyses and meta-analysis)

Data from Phase III studies were not pooled, due to the differences in patient population (different study entry criteria as regards CNV features) and control group.

- Clinical studies in special populations

Subgroup analyses to explore the primary outcome measure (proportion of subjects losing < 15 letters from baseline at 12 months) and of the mean change from baseline in visual acuity at month 12 were performed using the following baseline characteristics: age (≥ 75 years vs. age ≤ 74 years), sex, visual acuity score in the study eye at 2 meters (baseline VA ≤54 letters vs VA ≥ 55 letters in FVF2598 or < 44 vs. 45 letters in FVF2587), CNV classification (minimally classic vs. occult lesions), lesion size (baseline lesion size ≤ 4 DA vs > 4 DA), and prior laser photocoagulation in the study eye.

Enhanced proportions of responders with ranibizumab treatment were demonstrated in the substratum of patients with a better baseline VA vs. those with a poorer baseline VA. This indicates that intervening early on in the disease process is clearly advantageous.

- Supportive studies

**FVF 2428 (FOCUS)** is an ongoing 2-year phase I/II study. It is a single-masked study with monthly 0.5 mg intravitreal ranibizumab vs. sham injection 1 week after PDT at study start and then with PDT as a possible add-on procedure as needed.

Patients with active predominantly classic CNV were recruited as in pivotal study FVF 2587 but in this study previous PDT was allowed unless delivered less than 3 months before study start and unless the extent of previous PDT exceeded three sessions. Active treatment was assigned on a 2:1 basis vs. sham. Patients and examiners of VA and angiography images were masked to the treatments.

The primary efficacy endpoint was the same as in the pivotal MARINA and ANCHOR studies. Secondary efficacy endpoints were mean VA change from baseline, proportions of patients gaining 15 letters and proportions of patients with VA 20/200 or worse.

Two formulations of drug were administered during the study to each subject randomised to ranibizumab: lyophilised and the liquid formulation intended for marketing. All subjects randomised to ranibizumab received the lyophilized formulation through at least the Month 12 visit. Subjects at each study site transitioned from the lyophilised to the liquid formulation once the last study subject enrolled and still receiving study treatment at the site had been evaluated at the Month 12 visit.

With a sample size of 112 subjects who received ranibizumab in combination with verteporfin PDT and 56 subjects who received a sham injection in combination with verteporfin PDT, the study had approximately 80% power to detect a statistical difference between the two treatment groups, assuming a rate of 86% responders for the verteporfin PDT + ranibizumab group and a rate of 67% for the control group. Missing data were managed with the LOCF principle.

Baseline demographic data were balanced in terms of age between the sham and the active group (mean age 73 vs 75 years) but not in terms of gender (54% vs. 43% males).

VA was slightly worse in the active group (45 vs. 48 letters). Unlike both Phase III studies, a subject's lesion eligibility for enrolment in Study FVF2428g was determined solely by investigators. Based on the reading center's post-hoc assessments of the fluorescein angiograms and fundus photographs, predominantly classic lesions were found to be present in 66.1% in the sham group and in 65.7% in the active group. The corresponding figures for minimally classic were 26.8% and 30.5% respectively. Disease duration was somewhat longer in the active arm than in the sham arm (0.8 vs. 0.6 years). Previous PDT had been given in 51.8% of sham patients and 45.3% of actively injected individuals. More than 10 out of a possible 13 injections were given to 89.5% in the active group as compared to 82.2% in the sham group.

Sub-group analyses revealed a larger difference in favour of ranibizumab if no previous PDT had been given while the spurious inclusion of minimally classic lesions did not seem to have an impact on the results.

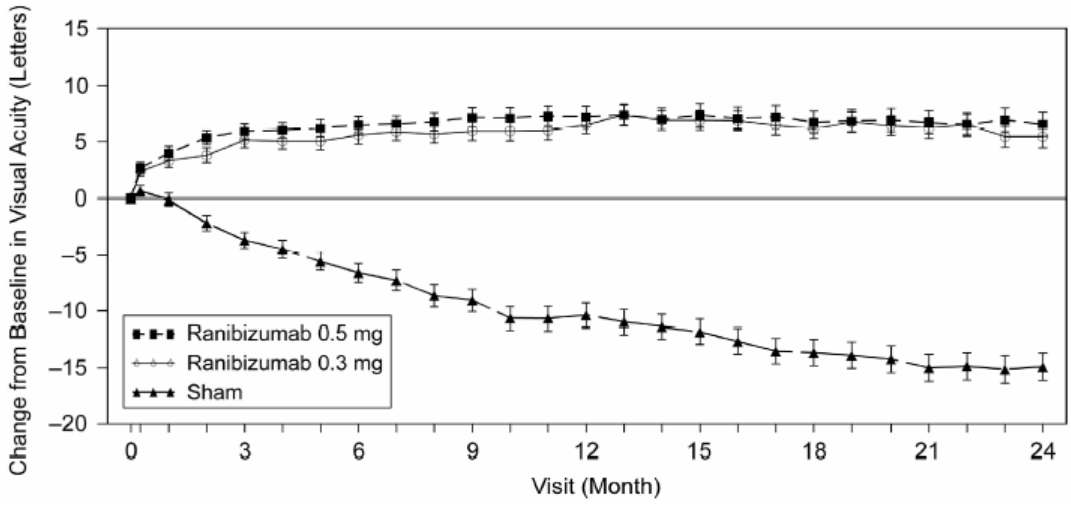
Although being differently designed in a number of aspects, FVF 2428 demonstrates a comparable efficacy for the primary and secondary outcome results for the 0.5 mg dose of ranibizumab to those found in the pivotal program, i.e. 90-95 % of ranibizumab-treated patients loose < 15 letters from baseline at 12 Months. The study also seems to show that patients with a history of PDT may benefit from ranibizumab, at least with the 0.5 mg dose. An additional study (CRFB002B2201, PROTECT) exploring the same-day administration of PDT and the liquid formulation of ranibizumab 0.5 mg is currently ongoing. Once the study is finalised and the data have been submitted for assessment, additional information may be implemented in the SPC.

- Discussion on clinical efficacy

**Choice of dose; 0.5mg dose vs 0.3mg dose**

Two-year data from study FVF2598g (MARINA)

**Figure 5 Study FVF2598g (MARINA): Mean BCVA change from baseline (letters)**




Note: The LOCF method was used to impute missing data. Vertical bars are ±1 standard error of the mean.

The 2-year efficacy data of FVF 2598 (MARINA) further show an impressive and sustained efficacy with a somewhat better outcome for the 0.5 mg dose, while the sham treated patients continued to loose visual function, albeit at a less pronounced pace than during the 1st year. At the end of the 2nd year of the study FVF2598g (MARINA), the data show that even though the proportion of patients with stable vision (proportion of patients loosing ≤ 15 letters, primary endpoint) was similar between the two doses, the difference in mean BCVA change from baseline, tended to be in favour of the 0.5 mg dose. Furthermore, the proportion of patients that gained ≥ 15 letters from baseline was ~ 7 % higher in the 0.5 mg dose group during the first and the 2nd year of treatment.

At the end of the 1st year, of study FVF2587g (ANCHOR), the data show that the difference in mean BCVA change from baseline, was slightly in favour of the 0.5 mg dose: a larger proportion of a poor initial VA (20/200 or worse) gained benefit from treatment with the 0.5 mg dose and the proportion of patients that gained ≥ 15 letters from baseline was ~ 4 % higher in the 0.5 mg dose group during the first year of treatment. The mean increase in VA in the 0.5-mg group was slightly greater than those in the 0.3-mg group at all monthly time points (see Figure 3).

At the end of the 1st year, of the study FVF 3192 (PIER), the data show that the proportion of patients with stable vision was 7% higher in the 0.5 mg dose group.

In addition, in ancillary analyses such as contrast sensitivity measurements (ANCHOR) and VFQ-25 composite score (MARINA and ANCHOR), the outcome of the 0.5 mg dose was consistently in favour of the lower dose.

Despite the fact that no statistically significant differences between the doses are obtained and that some of the parameters that were in favour of the 0.5 mg dose were too marginal to be of clinical importance, the proposal to switch from the 0.3 mg dose to the 0.5 mg dose is endorsed due to the consistency of the trends in an increased benefit from the higher dose across all the pivotal trials.

**Indication**

The presented data supports the indication wording. However, it is detailed in the SPC, section 5.1 that patients with lesions with typical signs of inactivity such as scar formation and subretinal fibrosis of the macula are not likely to respond to treatment with Lucentis.

**Posology**

The somewhat reduced efficacy but enhanced safety and patient convenience of the PIER regime called for a reappraisal of the initially proposed monthly posology, and the concept of the later applied for individualised regimen was generally seen to be acceptable. On a mean patient basis, the beneficial effect seemed to peak at 3 months (injections month 0, 1 and 2) where after a plateau was reached. However, it was not clear whether this plateau is reached in the responder population only, or whether this group of patients may gain additional benefit if monthly injections are given for a longer period of time. Further analysis, separating initial responders from non-responders showed that, independently of whether defining responders as those who lost < 15 letters, gained ≥ 0, or gained ≥ 5 letters of VA at month 3 compared with baseline, a plateau in VA was reached after three monthly injections. All analyses were based on observed values only without substituting for missing observations through LOCF.

Even though a slight, approximately 2 letter additional VA gain was observed after the first three months, this is considered to be of low clinical relevance, especially when taking the need for monthly injections into account. Consequently, the data strengthens the rationale for the present posology with three monthly initial loading injections, followed by a VA-guided flexible dosing.

More of a challenge is the substantial, initial drop in VA seen in the non-responders (as part of one of the definitions, where responders loose ≤ 15 letters). Per analysis definition, the loss ≥ 15 letters in VA is observed at Month 3, which is similar to the average loss in the sham-treated patients after 2 years (MARINA, minimally classic, occult AMD lesions) and more than the average 1-year loss of VA acuity (~ 10 letters) in ANCHOR (predominantly classic lesions). However, the non-responders were few and the variations were large. Consequently, on basis of the data presently available, it is difficult to conclude whether there are any patients with particular characteristics that should not be treated, or whether specific treatment recommendations should be given for patients that experience an initial drop in VA after treatment with Lucentis. Therefore, the Applicant will collect and analyse non-responder data from all ongoing studies (detailed in the RMP) including the finalised MARINA-study in an attempt to define characteristics of patients that are likely to lose initial VA. The Applicant should, if possible, suggest treatment recommendations for this group of patients. Data should be reported back to the CHMP on an ongoing yearly basis until the studies are completed (last study to be completed Q4, 2008, FUM).

The 2-year data from FVF 2587 (ANCHOR, due later this year) and FVF 3192 (PIER, due next year) will be submitted post-approval. This is all the more important given the few patients with predominantly classic lesions (n = 35 in total and only 21 actively treated) included in the PIER study.

**Patient monitoring**

The proposed regimen includes an initial loading phase of 3 monthly injections followed by a maintenance phase in which patients should be monitored for visual acuity on a monthly basis. A loss of greater than 5 letters in visual acuity is proposed as re-treatment criterion for the maintenance therapy with ranibizumab. A loss of greater than 5 letters was chosen because smaller changes are likely to be indistinguishable from measurement errors (Rosser et al, 2003). With the proposed flexible (visual acuity-guided) ranibizumab posology, the treatment frequency in the maintenance phase will be adjusted and individualised for each patient.

The criteria for treatment discontinuation has been debated and the non-responders in the active arms in the MARINA and ANCHOR studies, i.e. those who at any time during the 1st treatment year lost > 15 letters, are to be specifically analysed post-approval to provide information whether continued treatment in the 2nd year led to a reversal of disease progression or had no impact on a subsequently deteriorating course. This analysis should aid in defining criteria on when to stop treatment if no initial

improvement in vision has been achieved. It is recognised that in the case of ANCHOR, 2-year data are still due and that this analysis can only be completed when these data are available (FUM).

**Clinical safety**

The safety dossier includes data from seven clinical studies in neovascular AMD: the three pivotal Phase III studies (FVF2598g, FVF2587g and FVF3192g) and the four Phase I and Phase I/II studies which used the lyophilised formulation of ranibizumab (FVF2428g, FVF2128g, FVF2425g, and FVF1770g). The safety assessments focused on ocular adverse events and visual function effects as well as on systemic adverse events.

In the pivotal studies FVF 2598, FVF 2587 and FVF3192g (and to some extent in FVF 2428) the liquid formulation of ranibizumab intended for marketing was used whereas the phase I and I/II trials in this application were performed with a lyophilised formulation of ranibizumab.

No analyses based on pooled data are presented because of the differences between the studies in the patient populations studied and the control groups used.

- Patient exposure

Overall, the safety file includes safety data from 1608 subjects, 1096 of whom received treatment with ranibizumab.

**Table 13 Subjects Contributing Safety Information: Studies Included in the SCS**

| Phase | Study | Study Duration Included in SCS | Number of Subjects Control | Ranibizumab | All Subjects |
|---|---|---|---|---|---|
| III | FVF2598g | 2 years | 236 | 477 | 713 |
| III | FVF2587g | 1 year | 143 | 277 | 420 |
| III | FVF3192g | 1 year | 62 | 120 | 182 |
| I/II | FVF2428g | 1 year | 56 | 105 | 161 |
| I/II | FVF2128g | 210 days [a] | 11 | 62 [b] | 64 |
| I | FVF2425g | 140 days [a] | 0 | 29 | 29 |
| I | FVF1770g | 90 days [c] | 0 | 27 | 27 |
| | Total | | 508 | 1096 [d] | 1604 [d] |

[a] Subjects who did not subsequently enroll in a separate extension study (FVF2508g) had long-term follow-up safety visits approximately 26 and 52 weeks after the final study visit.

[b] Included in the 62 subjects are 53 subjects who were treated during Part 1 of the study and 9 subjects who crossed over from usual care to receive ranibizumab during Part 2 of the study.

[c] Included a treatment period (a single injection) and a 90-day follow-up period.

[d] One subject (14205) enrolled in Study FVF2425g was also enrolled previously in Study FVF1770g (as Subject 601).

Safety data from the first treatment year of the two pivotal trials with monthly dosing represent a large proportion of the total safety database and include 1133 subjects, 754 whom received treatment with ranibizumab. During the first treatment year, more than 9200 ranibizumab injections and 4400 sham injections were administered.

**Table 14 Extent of Study Drug Exposure (1-Year): Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT (n = 143) | Ranibizumab | |
| | Sham (n = 236) | 0.3 mg (n = 238) | 0.5 mg (n = 239) | | 0.3 mg (n = 137) | 0.5 mg (n = 140) |
| Number of injections [a] | | | | | | |
| Total | 2765 | 2952 | 2929 | 1711 | 1669 | 1692 |
| Mean (SD) [b] | 11.7 (2.7) | 12.4 (1.9) | 12.3 (2.2) | 12.0 (2.5) | 12.2 (2.1) | 12.1 (2.2) |
| Frequency [b] | | | | | | |
| < 10 | 27 (11.4%) | 10 (4.2%) | 15 (6.3%) | 17 (11.9%) | 9 (6.6%) | 13 (9.3%) |
| 10–12 | 55 (23.3%) | 36 (15.1%) | 40 (16.7%) | 21 (14.7%) | 29 (21.2%) | 29 (20.7%) |
| 13 | 154 (65.3%) | 192 (80.7%) | 184 (77.0%) | 105 (73.4%) | 99 (72.3%) | 98 (70.0%) |
| Treatment duration (days) [c] | | | | | | |
| Mean (SD) | 332.7 (80.0) | 350.6 (54.7) | 346.2 (61.5) | 337.1 (75.0) | 346.2 (61.8) | 345.6 (59.7) |

[a] Intravitreal ranibizumab injection or sham injection.
[b] Number of injections per subject, of 13 scheduled injections from Day 0 to the Month 12 visit.
[c] Number of days from the first injection to the last injection on or prior to the Month 12 visit.

In Study FVF2587g, during the first treatment year, the control group received an average of 3.1 treatments (SD, 1.3) with verteporfin PDT, and the 0.3-mg and 0.5-mg ranibizumab groups received an average of 1.9 (SD, 1.3) and 1.8 (SD, 1.1) treatments, respectively, with sham PDT with saline infusions.

The two-year data from study FVF2598 (MARINA) show that a little more than 90% of patients on the 0.3 mg dose received 18-23 injections and almost 54% received all 24. The corresponding figures for the 0.5 mg dose were 89% and 54%.

In study FVF 3192g with the reduced dosing frequency, 59 patients on the 0.3 mg dose received a mean of 5.9 injections and 61 patients on the 0.5 mg dose received an average of 5.8 injections during the 1st year of treatment.

In Study FVF2428g, subjects in both treatment groups received protocol-specified therapy with verteporfin in the study eye 7 days (± 2 days) prior to the first injection (ranibizumab or sham). During the first treatment year, the average number of treatments with verteporfin PDT was 3.4 (range, 1–5) in the verteporfin PDT group and 1.3 (range, 1–5) in the verteporfin PDT + ranibizumab group.

Together with the 2-year data, the extent of exposure is sufficient for the labelling applied for.

- Adverse events

Non-serious ocular events:

**Table 15 Ocular Adverse Events in the Study Eye during the First Treatment Year (Occurring in ≥ 10% of Subjects in Any Group): Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT | Ranibizumab | |
| **Preferred Term** | **Sham (n = 236)** | **0.3 mg (n = 238)** | **0.5 mg (n = 239)** | **(n = 143)** | **0.3 mg (n = 137)** | **0.5 mg (n = 140)** |
| **Total ocular**[a] | 229 (97.0%) | 233 (97.9%) | 233 (97.5%) | 138 (96.5%) | 129 (94.2%) | 132 (94.3%) |
| Blepharitis | **14 (5.9%)** | **16 (6.7%)** | **26 (10.9%)** | 6 (4.2%) | 6 (4.4%) | 7 (5.0%) |
| CNV | *27 (11.4%)* | *2 (0.8%)* | *3 (1.3%)* | *14 (9.8%)* | *2 (1.5%)* | *5 (3.6%)* |
| Conjunctival haemorrhage | 139 (58.9%) | 169 (71.0%) | 168 (70.3%) | 65 (45.5%) | 92 (67.2%) | 87 (62.1%) |
| Detachment of RPE | 30 (12.7%) | 24 (10.1%) | 17 (7.1%) | 5 (3.5%) | 2 (1.5%) | 5 (3.6%) |
| Eye irritation | 43 (18.2%) | 34 (14.3%) | 36 (15.1%) | 8 (5.6%) | 6 (4.4%) | 14 (10.0%) |
| Eye pain | **57 (24.2%)** | **77 (32.4%)** | **71 (29.7%)** | **24 (16.8%)** | **33 (24.1%)** | **34 (24.3%)** |
| Eye pruritus | 20 (8.5%) | 18 (7.6%) | 27 (11.3%) | 7 (4.9%) | 10 (7.3%) | 12 (8.6%) |
| Foreign body sensation | 27 (11.4%) | 41 (17.2%) | 39 (16.3%) | 15 (10.5%) | 8 (5.8%) | 10 (7.1%) |
| IOP increased | **7 (3.0%)** | **38 (16.0%)** | **39 (16.3%)** | **10 (7.0%)** | **21 (15.3%)** | **22 (15.7%)** |
| Lacrimation increased | 30 (12.7%) | 32 (13.4%) | 27 (11.3%) | 6 (4.2%) | 9 (6.6%) | 8 (5.7%) |
| Macular degeneration | *125 (53.0%)* | *88 (37.0%)* | *86 (36.0%)* | *89 (62.2%)* | *50 (36.5%)* | *50 (35.7%)* |
| Retinal disorder | **15 (6.4%)** | **20 (8.4%)** | **26 (10.9%)** | **2 (1.4%)** | **8 (5.8%)** | **7 (5.0%)** |
| Retinal haemorrhage | *101 (42.8%)* | *46 (19.3%)* | *40 (16.7%)* | *76 (53.1%)* | *20 (14.6%)* | *26 (18.6%)* |
| Subretinal fibrosis | *24 (10.2%)* | *18 (7.6%)* | *10 (4.2%)* | *27 (18.9%)* | *15 (10.9%)* | *18 (12.9%)* |
| VA reduced | 23 (9.7%) | 15 (6.3%) | 16 (6.7%) | 21 (14.7%) | 10 (7.3%) | 5 (3.6%) |
| Vitreous detachment | 30 (12.7%) | 39 (16.4%) | 40 (16.7%) | 26 (18.2%) | 21 (15.3%) | 19 (13.6%) |
| Vitreous floaters | **14 (5.9%)** | **59 (24.8%)** | **53 (22.2%)** | **6 (4.2%)** | **16 (11.7%)** | **25 (17.9%)** |

IOP = intraocular pressure.

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

[a] Represents the number of subjects with at least one ocular adverse event in the study eye.

Due to a variety of classification terms, no single adverse event with a preferred term iritis, iridocyclitis reached a 10% incidence, but taken together these episodes amounted to a rate > 10%. There was a slight overall increase of this AE in the higher dose group.

**Table 16 Intraocular inflammation Adverse Events in the Study Eye**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin PDT | Ranibizumab | |
| | Sham (n=236) | 0.3 mg (n=238) | 0.5 mg (n=239) | (n=143) | 0.3 mg (n=137) | 0.5 mg (n=140) |
| Total [a] | 23 (9.7%) | 26 (10.9%) | 34 (14.2%) | 4 (2.8%) | 14 (10.2%) | 21 (15.0%) |
| By severity [b] | | | | | | |
| Mild | 22 (9.3%) | 20 (8.4%) | **30 (12.6%)** | 4 (2.8%) | 12 (8.8%) | **17 (12.1%)** |
| By preferred term [c] | | | | | | |
| Iridocyclitis | 2 (0.8%) | 1 (0.4%) | 2 (0.8%) | 0 | 0 | **4 (2.9%)** |
| Iritis | 16 (6.8%) | 15 (6.3%) | 15 (6.3%) | 2 (1.4%) | 7 (5.1%) | **10 (7.1%)** |
| Uveitis | 2 (0.8%) | 0 | 1 (0.4%) | 0 | 0 | 1 (0.7%) |
| Vitritis | **7 (3.0%)** | **13 (5.5%)** | **22 (9.2%)** | **2 (1.4%)** | **8 (5.8%)** | **12 (8.6%)** |

[a] Represents the number of subjects with at least one intraocular inflammation adverse event in the study eye during the first treatment year.

[b] Subjects with multiple adverse events were counted once at the maximum severity of the events experienced.

[c] Represents the number of subjects with at least one adverse event of the preferred term specified.

Over 24 months (study FVF2598, MARINA), the most common ocular adverse events in the study eye observed more frequently in the ranibizumab groups than in the sham-injection group were; conjunctival haemorrhage, vitreous floaters, ocular inflammation and increased IOP.

Endophthalmitis events in the study eye were uncommon in ranibizumab-treated subjects and reported at a cumulative rate of 0.8% over 24 months for both the 0.3-mg and 0.5-mg ranibizumab groups (or 1.3% for the 0.5-mg ranibizumab group, including a presumed endophthalmitis case that was reported as uveitis).

The cumulative 24-month frequency of reported intraocular inflammation adverse events in the study eye was higher in the 0.3-mg (13.9%) and 0.5-mg (18.0%) ranibizumab groups compared with sham-injection group (10.6%). Serious intraocular inflammation was seen only in the ranibizumab groups, however at a low incidence for both dose groups (≤ 1.7% cumulative rate over 24 months).

**Table 17 Study FVF 3192, the following table displays major AEs.**

| Category of Adverse Events | Sham (n=62) | Ranibizumab 0.3 mg (n=59) | Ranibizumab 0.5 mg (n=61) |
|---|---|---|---|
| Ocular events: study eye | | | |
| All adverse events | 57 (91.9%) | 51 (86.4%) | 47 (77.0%) |
| Serious adverse events | 9 (14.5%) | 5 (8.5%) | 3 (4.9%) |
| Adverse events that led to discontinuation [a] | 9 (14.5%) | 0 | 1 (1.6%) |
| Endophthalmitis | 0 | 0 | 0 |
| Intraocular inflammation [b] | | | |
| Total | 2 (3.2%) | 3 (5.1%) | 3 (4.9%) |
| Serious | 0 | 0 | 0 |
| Ocular events: fellow eye | | | |
| All adverse events | 35 (56.5%) | 28 (47.5%) | 36 (59.0%) |
| Serious adverse events | 0 | 1 (1.7%) | 2 (3.3%) |
| Adverse events that led to discontinuation [a] | 2 (3.2%) | 0 | 2 (3.3%) |
| Endophthalmitis | 0 | 1 (1.7%) [c] | 0 |
| Intraocular inflammation [b] | | | |
| Total | 0 | 1 (1.7%) | 0 |
| Serious | 0 | 0 | 0 |
| Non-ocular events | | | |
| All adverse events | 40 (64.5%) | 46 (78.0%) | 40 (65.6%) |
| Serious adverse events | 6 (9.7%) | 8 (13.6%) | 7 (11.5%) |
| Adverse events that led to discontinuation [a] | 0 | 0 | 0 |

Note: Multiple occurrences of the same event in a subject were counted once in the overall incidence.

[a] Discontinuation from either treatment or study.

[b] Intraocular inflammation reported included the preferred terms of iritis, iridocyclitis, and vitritis.

[c] Vitreous culture obtained showed growth.

Ocular events are given in the following Table 18. The most striking finding is the dose dependent increase in IOP elevations.

**Table 18**

Ocular Adverse Events in the Study Eye during the First Treatment Year (Occurring in ≥ 10% of Subjects in Any Group): Safety-Evaluable Subjects

| MedDRA Preferred Terms | Sham (n=62) | Ranibizumab 0.3 mg (n=59) | Ranibizumab 0.5 mg (n=61) |
|---|---|---|---|
| Total [a] | 57 (91.9%) | 51 (86.4%) | 47 (77.0%) |
| Conjunctival hemorrhage | 18 (29.0%) | 27 (45.8%) | 26 (42.6%) |
| Macular degeneration | 24 (38.7%) | 10 (16.9%) | 14 (23.0%) |
| Retinal hemorrhage | 23 (37.1%) | 11 (18.6%) | 12 (19.7%) |
| Visual acuity reduced | 15 (24.2%) | 10 (16.9%) | 4 (6.6%) |
| Eye pain | 7 (11.3%) | 10 (16.9%) | 11 (18.0%) |
| Intraocular pressure increased | 3 (4.8%) | 5 (8.5%) | 13 (21.3%) |
| Vitreous detachment | 11 (17.7%) | 4 (6.8%) | 6 (9.8%) |
| Subretinal fibrosis | 8 (12.9%) | 0 | 5 (8.2%) |
| CNV | 8 (12.9%) | 3 (5.1%) | 0 |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

[a] Represents the number of subjects with at least one ocular adverse event in the study eye.

Source: Table 14.3/6.1.

**Table 19**

Ocular Serious Adverse Events in the Study Eye during the First Treatment Year: Safety-Evaluable Subjects

| MedDRA Preferred Terms | Sham (n=62) | Ranibizumab 0.3 mg (n=59) | Ranibizumab 0.5 mg (n=61) |
|---|---|---|---|
| Total[a] | 9 (14.5%) | 5 (8.5%) | 3 (4.9%) |
| Visual acuity reduced | 4 (6.5%) | 1 (1.7%) | 1 (1.6%) |
| Macular degeneration | 1 (1.6%) | 1 (1.7%) | 1 (1.6%) |
| Retinal hemorrhage | 2 (3.2%) | 1 (1.7%) | 0 |
| Macular edema | 1 (1.6%) | 1 (1.7%) | 0 |
| CNV | 1 (1.6%) | 0 | 0 |
| Eye hemorrhage | 0 | 1 (1.7%) | 0 |
| Incorrect route of drug administration | 0 | 0 | 1 (1.6%) |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.

[a] Represents the number of subjects with at least one ocular serious adverse event in the study eye.

Source: Table 14.3/12.1.

In FVF3192g, almost no AEs led to a discontinuation.

In FVF 2428 FOCUS (phase I/II), in contrast, there were generally high incidences of intraocular complications: retinal detachment (16% vs. 11%), retinal haemorrhage (39% vs. 15%), and subretinal fibrosis (14% vs. 9%) reported more frequently in the verteporfin PDT group than in the verteporfin PDT + ranibizumab group. The safety problems that were observed with the (initial) combination treatment of PDT and ranibizumab in study FVF2428g (FOCUS) could have been related to the lyophilised formulation rather than the time window of 7 (+ 2) days between the 2 treatments, but the frequent occurrence remains an enigma, given that they were even more common in the PDT treated group. Preliminary data from an ongoing study CRFB002B2201, PROTECT, indicate however that the same-day administration of PDT and the liquid formulation of ranibizumab 0.5 mg appears well tolerated. The wording of the SPC may need to be reconsidered once the study is finalised and the data have been submitted for assessment.

Serious ocular adverse events

**Table 20 Serious ocular events in the pivotal studies during the 1st study year**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin | Ranibizumab | |
| **Adverse Event Category** | **Sham (n = 236)** | **0.3 mg (n = 238)** | **0.5 mg (n = 239)** | **PDT (n = 143)** | **0.3 mg (n = 137)** | **0.5 mg (n = 140)** |
| Ocular events, study eye | | | | | | |
| All adverse events | 229 (97.0%) | 233 (97.9%) | 233 (97.5%) | 138 (96.5%) | 129 (94.2%) | 132 (94.3%) |
| Adverse events that led to discontinuation | 8 (3.4%) | 3 (1.3%) | 4 (1.7%) | 1 (0.7%) | 2 (1.5%) | 4 (2.9%) |
| Serious adverse events | 12 (5.1%) | 15 (6.3%) | 15 (6.3%) | 6 (4.2%) | 6 (4.4%) | 8 (5.7%) |
| Key serious adverse events | | | | | | |
| Cataract traumatic | 0 | 0 | 0 | 0 | 0 | 0 |
| Endophthalmitis | 0 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 1 (0.7%) |
| Intraocular inflammation | 0 | 2 (0.8%) | 2 (0.8%) | 0 | 0 | 1 (0.7%) |
| IOP increased | 0 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 0 |
| Retinal artery occlusion | 0 | 0 | 0 | 0 | 0 | 0 |
| Retinal detachment [a] | 0 | 1 (0.4%) | 0 | 1 (0.7%) [b] | 1 (0.7%) | 0 |
| Retinal tear | 0 | 1 (0.4%) | 1 (0.4%) | 0 | 0 | 0 |
| Vitreous haemorrhage | 0 | 1 (0.4%) | 1 (0.4%) | 0 | 1 (0.7%) | 0 |
| Non-ocular events | | | | | | |
| All adverse events | 192 (81.4%) | 212 (89.1%) | 200 (83.7%) | 114 (79.7%) | 103 (75.2%) | 119 (85.0%) |
| Adverse events that led to discontinuation | 5 (2.1%) | 2 (0.8%) | 5 (2.1%) | 6 (4.2%) | 5 (3.6%) | 2 (1.4%) |
| Serious adverse events | 39 (16.5%) | 43 (18.1%) | 44 (18.4%) | 28 (19.6%) | 20 (14.6%) | 28 (20.0%) |

IOP = intraocular pressure.

Notes: Table entries are number (%) of subjects with at least one adverse event of the type specified. Discontinuation refers to discontinuations from either treatment or study. Intraocular inflammation includes the preferred terms of iritis, vitritis, iridocyclitis, uveitis, and anterior chamber inflammation.

[a]Includes one case of exudative retinal detachment in Study FVF2598g and three cases of rhegmatogenous retinal detachments in 2 subjects in Study FVF2587g., [b]Subject experienced two episodes.

**Non-Ocular Events**

According to the applicant there was no notable imbalance among treatment groups except for one in Study FVF2587g, in which a higher percentage of subjects treated with verteporfin PDT experienced back pain compared with subjects treated with ranibizumab; back pain is a known adverse reaction associated with verteporfin (Visudyne® SmPC).

**Table 21 Non-Ocular Adverse Events during the First Treatment Year (Occurring in ≥ 5% of Subjects in Any Group): Studies FVF2598g and FVF2587g**

| | Study FVF2598g | | | Study FVF2587g | | |
|---|---|---|---|---|---|---|
| | | Ranibizumab | | Verteporfin | Ranibizumab | |
| Preferred Term | Sham (n = 236) | 0.3 mg (n = 238) | 0.5 mg (n = 239) | PDT (n = 143) | 0.3 mg (n = 137) | 0.5 mg (n = 140) |
| Total [a] | 192 (81.4%) | 212 (89.1%) | 200 (83.7%) | 114 (79.7%) | 103 (75.2%) | 119 (85.0%) |
| Anemia | 8 (3.4%) | 6 (2.5%) | 10 (4.2%) | 4 (2.8%) | 5 (3.6%) | 7 (5.0%) |
| Anxiety | 1 (0.4%) | 6 (2.5%) | 8 (3.3%) | 8 (5.6%) | 5 (3.6%) | 3 (2.1%) |
| Arthralgia | 14 (5.9%) | 15 (6.3%) | 10 (4.2%) | 9 (6.3%) | 4 (2.9%) | 8 (5.7%) |
| Arthritis | 14 (5.9%) | 7 (2.9%) | 10 (4.2%) | 5 (3.5%) | 2 (1.5%) | 2 (1.4%) |
| Back pain | 13 (5.5%) | 14 (5.9%) | 13 (5.4%) | 13 (9.1%) | 5 (3.6%) | 2 (1.4%) |
| Blood pressure increased | 14 (5.9%) | 14 (5.9%) | 11 (4.6%) | 3 (2.1%) | 4 (2.9%) | 6 (4.3%) |
| Bronchitis | 12 (5.1%) | 15 (6.3%) | 13 (5.4%) | 9 (6.3%) | 5 (3.6%) | 10 (7.1%) |
| Cough | 10 (4.2%) | 20 (8.4%) | 16 (6.7%) | 8 (5.6%) | 12 (8.8%) | 4 (2.9%) |
| Diarrhea | 12 (5.1%) | 10 (4.2%) | 5 (2.1%) | 6 (4.2%) | 6 (4.4%) | 4 (2.9%) |
| Dizziness | 16 (6.8%) | 11 (4.6%) | 5 (2.1%) | 4 (2.8%) | 3 (2.2%) | 7 (5.0%) |
| Gastroesophageal reflux disease | 6 (2.5%) | 6 (2.5%) | 6 (2.5%) | 8 (5.6%) | 4 (2.9%) | 5 (3.6%) |
| Headache | 15 (6.4%) | 24 (10.1%) | 14 (5.9%) | 7 (4.9%) | 11 (8.0%) | 11 (7.9%) |
| Hypertension | 23 (9.7%) | 20 (8.4%) | 20 (8.4%) | 12 (8.4%) | 3 (2.2%) | 9 (6.4%) |
| Nasopharyngitis | 23 (9.7%) | 21 (8.8%) | 18 (7.5%) | 15 (10.5%) | 21 (15.3%) | 14 (10.0%) |
| Nausea | 10 (4.2%) | 14 (5.9%) | 13 (5.4%) | 7 (4.9%) | 6 (4.4%) | 6 (4.3%) |
| Sinusitis | 9 (3.8%) | 13 (5.5%) | 14 (5.9%) | 9 (6.3%) | 7 (5.1%) | 7 (5.0%) |
| Upper respiratory tract infection | 15 (6.4%) | 15 (6.3%) | 11 (4.6%) | 6 (4.2%) | 8 (5.8%) | 8 (5.7%) |
| Urinary tract infection | 12 (5.1%) | 12 (5.0%) | 10 (4.2%) | 9 (6.3%) | 9 (6.6%) | 8 (5.7%) |

Note: Multiple occurrences of the same event for a subject were counted once in the overall incidence.
[a] Represents the number of subjects with at least one non-ocular adverse event.

- Serious adverse event/deaths/other significant events

With regard to potential side effects related to systemic VEGF inhibition over 24 months, no imbalance in hypertension was observed and no adverse events of proteinuria were reported. The small, dose-dependent trend in increased APTC (Antiplatelet Trialists' Collaboration 1994) arterial thromboembolic events seen in both studies MARINA and ANCHOR, in ranibizumab-treated groups, noted during the first treatment year was reduced in the cumulative data over the 2-year treatment period (MARINA study). The rates of APTC arterial thromboembolic events during the 2-year treatment period were similar in all three treatment groups, with 9 (3.8%), 11 (4.6%), and 11 (4.6%) subjects experiencing these events in the sham-injection, 0.3-mg, and 0.5-mg ranibizumab groups, respectively. Consequently, the concern raised from the 1-year data regarding a dose-dependent increase in these events is no longer an issue.

Numbers of deaths were low and within the expected range of this age group but still somewhat more common in ranibizumab-treated patients.

**Special safety issues**

A number of safety topics were subject to more extensive analyses in the pivotal trials, either because of the nature, mechanism of action and procedure of administration of ranibizumab, or either those which represent potential systemic anti-VEGF (irrespective of whether or not reported as serious). These areas were:

Endophthalmitis:

Across the two pivotal trials endophthalmitis was reported in 3 patients; two ranibizumab-treated subjects (0.4%) in Study FVF2598g and one ranibizumab-treated subject (0.4%) in Study FVF2587g. All three events were reported as serious. The overall rate of endophthalmitis considering the ranibizumab injections administered during the first treatment year (9200) was 0.03% per injection for the ranibizumab treated patients (0.03% for both doses). For presumed endophthalmitis, the overall rate was 0.05%. (0.03% and 0.07% for each ranibizumab dose respectively). The overall incidence of endophthalmitis in this studies was low and below the rate of the incidence available in published literature (endophthalmitis rate of 0.2% per injection. Jager et al. 2004) which is reassuring. Nevertheless, as the authors of the referred article concluded, "careful attention to injection technique and appropriate postinjection monitoring are essential because uncommon injection-related complications may be associated with permanent vision loss", the specific measures outlined in the SPC and in the RMP are considered necessary.

Intraocular inflammation or uveitis (includes the MedDRA terms of iritis, iridocyclitis, vitritis, uveitis and anterior chamber inflammation):

In Study FVF2598g, the frequency of reported intraocular inflammation in the study eye was higher in the 0.5-mg ranibizumab group (14.2%) compared with a 9.7% in the sham-injection group and a 10.9% in the 0.3-mg ranibizuamb group. Four ranibizumab-treated subjects, two in each dose experienced at least one serious event. In Study FVF2587g, the frequency was higher in the ranibizumab groups (10.2% in the 0.3-mg group and 15.0% in the 0.5-mg group) than in the verteporfin PDT group (2.8%). Overall, across the two studies, there appears to be a trend in intraocular inflammation towards higher rates in the 0.5-mg groups compared with the control and 0.3-mg groups. However, most cases were non-serious and manageable. In study FVF3192 with the reduced dosing frequency, the incidence of ocular inflammation was substantially lowered.

The cumulative 2-year frequency of reported intraocular inflammation in the MARINA study (including the MedDRA preferred terms iritis, iridocyclitis, vitritis, uveitis, hypopyon, and anterior chamber inflammation) was higher in the 0.3 mg (13.9%) and 0.5 mg (18.0%) ranibizumab groups than in the sham injection group (10.6%), i.e. slightly increased as compared to the corresponding figures for during the first treatment year. The various events of intraocular inflammation tended to decrease somewhat over time which does not indicate a sensitisation to the Ranibizumab.

Serious intraocular inflammation was seen only in the ranibizumab groups, but was uncommon for both doses ($\leq$ 1.7% cumulative rate over 2 years).

Cataract:

During the first treatment year, the frequency of the cataract adverse event reported in Study FVF2598g was 10.2%, 8.0% and 10.0% of patients in the sham, 0.3-mg, and 0.5-mg groups. In the Study FVF2587g the percentages were 7.0%, 10.9% and 12.9% for the subjects in the verteporfin PDT, 0.3-mg and 0.5-mg groups respectively. Most of the events were mild in severity, however it is worth noting that the incidence of moderate-severity cataract was highest in the 0.5-mg treatment group.

During the second year, in study FVF 2598 (MARINA), a notable proportion of ranibizumab-treated subjects showed changes in lens status during the 2-year treatment period. Of subjects who were phakic in the study eye at baseline and whose post-baseline lens status was known at Month 24, 6 (5.1%) in the 0.3-mg ranibizumab group and 8 (7.2%) in the 0.5-mg ranibizumab group became pseudophakic by Month 24 compared with none in the sham-injection group. This is of course of some concern, but cataract surgery is generally successful and safe in this population.

Elevation in IOP:

Across patients from Study FVF2598, 22 subjects in the 0.3-mg group (9.2%) and 31 subjects in the 0.5-mg group (13.0%) experienced IOP $\geq$ 30 mmHg in the study eye at some time point during the first treatment year, compared with 6 sham-treated subjects (2.5%). Most cases occurred following the study drug injection and were reversible. Two of the cases in the Study FVF2598g one each in the 0.3 and 0.5 mg groups, were reported as serious adverse events and anterior chamber paracentesis was

performed. In study FVF2587g, 8.8% of patients in the 0.3-mg group and 10.0% of patients in the 0.5-mg group experienced IOP ≥ 30 mmHg, compared to 4.2% of verteporfin with PDT-treated patients. Very few postdose IOP measurements were ≥ 40 mmHg.

The number of subjects who experienced any post-injection IOP ≥ 30 mmHg during the 2-year treatment period was higher in both ranibizumab groups (12.6% in the 0.3-mg group, 16.3% in the 0.5-mg group) than in the sham-injection group (2.5%); however, during the 2nd year also, very few measurements were made for IOP > 40 mmHg (1.7% for 0.3-mg and 2.9% for 0.5-mg vs. none for sham).

In summary, increases in IOP were reported more frequently in the active treatment arms, especially in the 0.5 mg group. Noteworthy is the fact that this was the only AE with a notably (1.7%-6.5%) higher incidence in ranibizumab-treated patients during the last 3 months of the treatment year compared with the first 3 months of treatment, however, the incidence of elevated IOP did not increase during the 2nd year of treatment.

Adverse Events potentially related to systemic VEGF inhibition:

In the pivotal studies with monthly dosing (MARINA and ANCHOR), serious AEs potentially associated with systemic VEGF inhibition were somewhat more common with the active treatments (control 0.8 – 2.1%, 0.3 mg 2.9 – 3.4%, 0.5 mg 3.8 – 5.7%), specifically with ranibizumab 0.5 mg, driven by haemorrhages and thromboembolic events (control 0.8 – 2.1%, 0.3 mg 1.3 – 2.2% and 0.5 mg 2.1 – 4.3%). However, over 24 months (MARINA study), no imbalance in hypertension was observed and no adverse events of proteinuria were reported. The rates of APTC (Antiplatelet Trialists' Collaboration 1994) arterial thromboembolic events during the 2-year treatment period were similar in all three treatment groups, with 9 (3.8%), 11 (4.6%), and 11 (4.6%) subjects experiencing these events in the sham-injection, 0.3-mg, and 0.5-mg ranibizumab groups, respectively. The small trend toward ranibizumab groups noted during the first treatment year for APTC arterial thromboembolic events was consequently reduced in the cumulative data over the 2-year treatment period and the initial concern regarding effects of systemic VEGF-inhibition is no longer an issue.

The potential administration of ranibizumab to both eyes has not been addressed in clinical studies although it is likely to happen in clinical practice. Based on the results of the pharmacokinetic simulation of the serum concentrations for unilateral and bilateral intravitreal administration of ranibizumab 0.5 mg, it seems that the maximum serum levels of ranibizumab would be under the systemic-threshold for VEGF-related adverse events. Reassuring evidence is available from the 2-year MARINA study data that has demonstrated that those events that were considered of specific concern (i.e. arterial thromboembolic events) are more balanced between sham and active arms.

- Laboratory findings

During the 1st year of treatment, slight changes in haematology analyses were documented overall with a tendency for more pronounced abnormalities in the ranibizumab groups. During the 2nd year of the MARINA study, more patients in the active arms showed increased eosinophilia than in the sham arm (5.4% in the 0.5 mg arm, 2.7% in the 0.3 mg arm vs. 0.5% in the sham group).

The noted abnormalities in blood chemistry at year 1, especially glucose levels in all treatment arms, were confirmed in the 2-year data with 22.1% of subjects in the sham-injection group, 19.0% in the 0.3-mg group, and 19.8% in the 0.5-mg group experiencing an elevation during the 2-year treatment.

Immunological events:

Indications of immunoreactivity were detected in particular in FVF 2598 (MARINA) where an increase was noted during the course of the study. Oddly enough, the test was positive also in a few control subjects and the relevance of the findings may be questioned. The incidence of patients with antibodies towards ranibizumab appeared to increase during the 2nd year of treatment. The Applicant has reviewed the patient data, but no clear correlation between antibodies to ranibizumab and ocular inflammation or decrease in visual acuity in Lucentis-treated patients was found. Still, a relation between antibody formation to ranibizumab, and the development of intraocular inflammation cannot

be completely ruled out. Therefore, monitoring of possible clinical signs attributable to intraocular antibody formation (such as intraocular inflammation) will be continuously performed (see Risk Management Plan).

- Safety in special populations

**Intraocular Inflammation Adverse Events by Subgroups**

The effect of ranibizumab treatment on the incidence of intraocular inflammation adverse events did not differ in a meaningful way between the subgroups based on age (< 75, ≥ 75 years), sex, race (White, non-White), baseline lesion subtype (predominantly classic, minimally classic, occult), and baseline lesion size (≤ 4, > 4 DA), although some of the subgroups contained a small number of subjects.

**History of Increased IOP**

Based on a review of reported medical history, approximately 16% of subjects (111 of 713) in Study FVF2598g and 14% of subjects (58 of 420) in Study FVF2587g were found to have a history of increased IOP (in either one or both eyes).

While the number of subjects with a history of increased IOP in each treatment group is relatively small, the percentage of subjects who experienced an adverse event of increased IOP was generally higher in subjects with a history of increased IOP compared with those without a history of increased IOP. This effect was more pronounced in ranibizumab-treated subjects than in control subjects.

**Table 22 Adverse Events of Increased IOP in the Study Eye during the First Treatment Year by History of Increased IOP: Studies FVF2598g and FVF2587g**

| | | Ranibizumab | |
|---|---|---|---|
| **Subgroup** | **Control** | **0.3 mg** | **0.5 mg** |
| Study FVF2598g | | | |
| History of increased IOP | 2/41 (4.9%) | 7/36 (19.4%) | 10/34 (29.4%) |
| No history of increase IOP | 5/195 (2.6%) | 31/202 (15.3%) | 29/205 (14.1%) |
| Study FVF2587g | | | |
| History of increased IOP | 1/17 (5.9%) | 4/18 (22.2%) | 4/23 (17.4%) |
| No history of increase IOP | 9/126 (7.1%) | 17/119 (14.3%) | 18/117 (15.4%) |

Note: Cell counts represent number of subjects with one or more adverse events of increased IOP in the study eye/number of subjects in the subgroup (%).

- Safety related to drug-drug interactions and other interactions

Regarding concomitant use of Lucentis and PDT/verteporfin, the data from study FVF 2428 (FOCUS) indicated potential safety problems, perhaps due to the use of a lyophilised formulation not intended for marketing. However, once finalised, data from the ongoing CRFB002B2201, PROTECT study will give further guidance.

- Discontinuation due to adverse events

Adverse events in the study eye that led to discontinuation in the pivotal studies:

The highest proportion of ocular events was found in the sham group of FVF 2598 (3.4%), whereas the figures for the ranibizumab groups were from 1.3% to 2.9%, always slightly higher in the 0.5 mg arm.

As for non-ocular events leading to discontinuation, ranibizumab treatment groups had a slightly lower frequency than the control arm (sham: 2%, 0.3 mg: 1%, 0.5 mg 2% in FVF 2598/ PDT: 4%, 0.3mg: 4%, 0.5mg: 1% in FVF 2587). Incidents involved heart, cerebral and airway events.

In study FVF3192 (PIER), no actively treated patients in any dose group and 3.2 % of sham injected patients discontinued the study due to adverse events.

- Post marketing experience

As ranibizumab had not been approved for market in any country at the time of submission, no postmarketing data were available for assessment.

- Discussion on clinical safety

The major ocular safety signals associated with IVT ranibizumab emerging during the first treatment year are intraocular inflammation and increased IOP. These safety problems tended to be more common in the 0.5 mg treatment group. It is reassuring to find that key ocular serious adverse events of endophthalmitis, intraocular inflammation, retinal detachment, retinal tear and traumatic cataract were uncommon in ranibizumab-treated subjects (< 1% for each event).

The 2-year data submitted for study FVF2598 (MARINA) show that in general terms, AEs such as increased intraocular inflammation, endophthalmitis, cataract operations and raised IOP > 30 mmHg were more frequent than with sham, however, the events were more or less of the expected kind and are considered to be outweighed by the sustained effect of the active treatment. Compared to patients treated with the initially filed 0.3 mg dose, with the exception of a slightly higher incidence in ocular inflammation and an elevation in IOP, there are no specific additional concerns regarding the higher, 0.5 mg dose. However, the observed intraocular inflammation and elevated IOP were manageable, easily monitored and generally not serious.

During the 1st treatment year, a small trend in serious non-ocular adverse events potentially related to systemic VEGF inhibition was observed toward the ranibizumab-treated groups, particularly in the 0.5-mg dose group, reflecting serious arterial thromboembolic events and non-ocular haemorrhages. However, the rates of arterial thromboembolic events during the 2-year treatment period were similar in all three treatment groups and no specific concerns remain.

Numbers of deaths were low and within the expected range of this age group but still somewhat more common in ranibizumab-treated patients.

It is recognised that from the 2-year data submitted from study FVF 2598 (MARINA), the incidence of AEs appears rather low and seemingly not increasing over the two years. However, there is a need to study the occurrence of selected AEs (including endophthalmitis, retinal detachment, vitreous haemorrhage, retinal tears, cataracts warranting operation, uveitis, and elevated IOP) post-marketing, when the injections of Lucentis are given in the clinical setting. In addition, AEs in patients that may have an impaired retinal blood flow, e.g. patients with atherosclerosis and diabetes, should be carefully monitored as well as bilateral use and compliance to the SPC. The Applicant has therefore committed to perform a European epidemiological cohort study to provide information about practice patterns and patient characteristics in Europe and to follow the incidence of selected adverse events.

The safety data (ocular and systemic) of long term use of Lucentis are unknown. Therefore the Applicant has committed to perform open-label extension phase of relevant studies in order to obtain long term safety data. The Applicant has committed to submit the study synopsis by the end of December 2006.

The Applicant has also committed to investigate the possibility of developing a more suitable delivery form of Lucentis and a summary of the measures taken to develop such a delivery system will be submitted within 6 months after approval.

## 5. Pharmacovigilance

**Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

**The Risk Management Plan**

The Applicant submitted a risk management plan, which included a risk minimisation plan. The updated version of the Risk Management Plan has taken into account the comments and recommendations and is now considered to be acceptable.

**Table 23 Summary of activities in the EU-RMP**

## Summary of the risk management plan for Lucentis

| Safety concern | Proposed pharmacovigilance activities | Proposed risk minimisation activities |
|---|---|---|
| IVT injection related AEs:<br>▪ Endophthalmitis<br>▪ Intraocular inflammation<br>▪ Ret. detachment<br>▪ retinal tear<br>▪ traumatic cataract<br>▪ IOP | ▪ Routine pharmacovigilance<br>▪ Targeted safety surveillance<br>▪ Background epidemiological studies[2]<br>▪ European epidemiological cohort study[4]<br>▪ Long-term extension study | ▪ Contraindications for patients with active or suspected ocular or periocular infections, and patients with active severe intraocular inflammation in section 4.3 of the SPC<br>▪ Warning in section 4.4. of the SPC<br>▪ List of AEs in section 4.8 of the SPC<br>▪ Warning in section 2 "Before use Lucentis" and section 4 "Possible side effects" of the Package Leaflet<br>▪ Educational package to ophthalmologists[6,7] |
| Systemic VEGF-inhibition | ▪ Routine pharmacovigilance<br>▪ Targeted safety surveillance<br>▪ European epidemiological cohort study[4]<br>▪ Long-term extension study | ▪ In section 4.4 of the SPC "Special warning and precautions for use"<br>▪ In section 4.6 of the SPC "Pregnancy and lactation"<br>▪ In section 4.8 of the SPC "Undesirable effects"<br>▪ In section 5.2 of the SPC "Pharmacokinetic properties"<br>▪ Educational package to ophthalmologists[7] |
| Systemic AEs related to overdose or bilateral treatment | ▪ Routine pharmacovigilance<br>▪ Expedited reporting<br>▪ Targeted safety surveillance<br>▪ European epidemiological cohort study[4]<br>▪ Long-term extension study | ▪ Warning in section 4.4. of the SPC<br>▪ Precaution in section 4.9 of the SPC "Overdose"<br>▪ Educational package to ophthalmologists[7] |
| AEs related to off-label use | ▪ Routine pharmacovigilance<br>▪ Targeted safety surveillance | |
| Intraocular AEs[1] | ▪ Routine pharmacovigilance<br>▪ Targeted safety surveillance<br>▪ European epidemiological cohort study[4]<br>▪ Long-term extension study | ▪ Contraindications for patients with active severe intraocular inflammation in section 4.3 of the SPC<br>▪ Warning in section 4.4. of the SPC<br>▪ List of AEs in section 4.8 of the SPC<br>▪ Educational package to ophthalmologists[7] |
| Serious hypersensitivity | ▪ Routine pharmacovigilance<br>▪ Targeted safety surveillance<br>▪ European epidemiological cohort study[4]<br>▪ Long-term extension study | ▪ Contraindications for patients with hypersensitivity to the active substance or to any of the excipients in section 4.3 of the SPC<br>▪ Warning in section 2 "Before use Lucentis" of the PL<br>▪ Educational package to ophthalmologists[7] |

1. Intraocular AEs related to antibody formation
2. Observational study in US healthcare claims database (to be performed)
3. Observational study in US databases to gain better understanding on background incidence rates of MI and CVA (completed)
4. Prospective epidemiological cohort study
5. Long-term extension study
6. Video, pictogram (poster)
7. Product monograph

******

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

Educational plan to ensure that all physicians who are expected to prescribe/use Lucentis are provided with physician information pack containing the following:
- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:
- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection, to minimise risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- Key signs and symptoms of IVT injection related adverse events
- Management of IVT injection related adverse events

The patient information pack should be provided in both a form of patient information booklet and audio-CD that contain following key elements:
- Patient information leaflet
- How to prepare for Lucentis treatment
- Which are the steps following treatment with Lucentis
- Key signs and symptoms of serious adverse events
- When to seek urgent attention from the health care provider

The Marketing Authorisation Holder must implement this educational plan nationally, prior to marketing, and as agreed with the competent authorities in the Member States.

## 6. Overall conclusions, risk/benefit assessment and recommendation

**Quality**

In general, the different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the drug substance, have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics, using state-of the-art methods, and appropriate specifications have been set. The manufacturing process of the drug product has been satisfactorily described and validated. The quality of the drug product is controlled by adequate test methods and specifications. The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured. Except for a number of quality points, which will be addressed as part of post-approval follow-up measures, the overall quality of Lucentis is considered acceptable.

**Non-clinical pharmacology and toxicology**

From a proof of principle point of view, the pharmacology studies submitted, even though limited, are considered sufficient.

The majority of adverse effects of ranibizumab are considered related to the ocular inflammation. Since the inflammation increased with time in the 26-week monkey study, non-clinical data can give no assurance to the long-term clinical use. The severe inflammation in monkeys is worrying, but is believed to be due to the exaggerated dosing and ranibizumab being a human protein. However, the ocular inflammation was not alarming and easy to follow in the clinic, and reassurance has been given

with the 2-year clinical data**.** In addition, the lack of any apparent ocular toxicity, or any effects on the neural retinal, is further reassuring.

**Efficacy & Safety**
Efficacy was convincingly demonstrated in three pivotal clinical studies with a trend towards a more pronounced efficacy with the 0.5 mg dose. Efficacy was clearly maintained throughout the 24-month period (MARINA study).

Additional analyses showed that regardless of whether initial responders lost < 15 letters, gained ≥ 0, or ≥ 5 letters of VA, a plateau in VA was reached after three monthly injections. The slight, additional gain in VA obtained after the first three months is considered to be of little clinical relevance, especially when taking the need for monthly injections into account. Consequently, the rationale for the individualised posology with three monthly initial loading injections, followed by a VA-guided flexible dosing is strengthened. However, a FUM is aimed to obtain guidance on whether to, or how to treat initial non-responders.

The proportion of patients experiencing important AEs, such as increased intraocular inflammation, raised IOP > 30 mmHg (both tended to be dose-related) and endophthalmitis was evidently higher in the active treatment arms with a slightly higher incidence in ocular inflammation and an elevation in IOP in the 0.5 mg dose group. No major increases in incidence of these AEs were however observed during the 2nd treatment year. Overall, the intraocular inflammation and elevated IOP were manageable, easily monitored and generally not serious. Importantly, the rates of arterial thromboembolic events during the 2-year treatment period were similar in all three treatment groups. Therefore, these adverse events are clearly outweighed by the superior efficacy of the study drug. In addition, even though a reduced efficacy was observed with a reduced dosing frequency (PIER), safety was enhanced. This, together with an increased patient convenience, further strengthens the concept of an individualised dosing regimen. The presented pharmacovigilance measures are acceptable and apart from issues that could be resolved post-approval, the submitted dossier supports the 0.5 mg dose in the present indication claim and wording.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 of this CHMP Assessment Report adequately addressed these.

- User consultation

A user test was presented as a summary, nevertheless enough information was available to assess the test, and to be assured that the package leaflet had been tested in an appropriate way.

Some comments regarding the layout have been provided, especially about the ease of reading for partially sighted people. These problems should be addressed even further when printing (i.e. letter size, colour and contrast and paper thickness). No information was given about the time for the interview, instructions for the recruiter and quantitative information if the information was easy to find, where the patients found it etc. However the test seemed clear enough and covered the relevant topics as to why these points were not of decisive importance.

Effort has been made between the two test rounds through using easier and shorter words and stylistic amendments. The package leaflet is found to be acceptable and so is the user test.

The Applicant commits to perform national submissions for evaluation of the key elements of the educational material for physicians and patients before launch of Lucentis in the respective countries.

**Risk-benefit assessment**

Efficacy was convincingly demonstrated in the three pivotal clinical studies with a trend towards a more pronounced efficacy with the 0.5 mg dose. Efficacy was clearly maintained throughout the 24-month period (MARINA study). The proportion of patients experiencing important AEs, such as increased intraocular inflammation, raised IOP > 30 mmHg (both tended to be dose-related) and

endophthalmitis was evidently higher in the active treatment arms. However, these problems are clearly outweighed by the superior efficacy of the study drug. In addition, even though a reduced efficacy was observed with a reduced dosing frequency (PIER), safety was enhanced. Together with an increased patient convenience, the concept of an individualised dosing regimen is therefore considered to be acceptable. The presented pharmacovigilance measures are acceptable and apart from issues that could be resolved post-authorisation, the submitted dossier supports the 0.5 mg dose in the present indication claim and wording.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and that the following additional risk minimisation activities were required:

- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information pack

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection, to minimise risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection
- Key signs and symptoms of IVT injection related adverse events
- Management of IVT injection related adverse events

The patient information pack should be provided in both a form of patient information booklet and audio-CD that contain following key elements:

- Patient information leaflet
- How to prepare for Lucentis treatment
- Which are the steps following treatment with Lucentis
- Key signs and symptoms of serious adverse events
- When to seek urgent attention from the health care provider

The MAH must implement this educational plan nationally, prior to marketing, and as agreed with the competent authorities in the Member States.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Lucentis in the treatment of neovascular (wet) age-related macular degeneration (AMD) was favourable and therefore recommended the granting of the marketing authorisation.