EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 September 2012
EMA/646256/2012 corr
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

aflibercept

Procedure No.: EMEA/H/C/002392/

Note

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

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List of abbreviations

Ab	Antibody
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AEI	AE of interest
ALT	Alanine aminotransferase
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Anti-Platelet Trialists' Collaboration
ATE	Arterial thromboembolic events
AUC	Area under the drug concentration-time curve
BCVA	Best corrected visual acuity
BLA	Biologic License Application
BMI	Body mass index
Capped PRN	Term used for flexible-dosing phase in the VIEW 1 and VIEW 2 studies
CI	Confidence interval
Cmax	Maximum observed plasma drug concentration
CNV	Choroidal neovascularization
CRF	Case report form
CR/LT	Central Retinal Lesion Thickness
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
CSR	Clinical study report
CVA	Cerebrovascular accident
DA	Disc area (4 DA =10.16 mm2)
DLT	Dose limiting toxicity
DME	Diabetic macular edema
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FAS	Full analysis set
Fc	Fragment, crystallizable region or constant
FDA	Food and Drug Administration
Fixed-dosing phase	Fixed protocol- specified schedule
Flexible-dosing phase	Based on specific retreatment criteria "PRN" (as needed) phase
FSH	Follicle-stimulating hormone
GLP	Good Laboratory Practice
Ig	Immunoglobulin
INR	International normalized ratio
IOP	Intraocular pressure
IV	Intravenous
IVT	Intravitreal
LOAEL	Lowest-observable-adverse-effect level
LOCF	Last observation carried forward
LSMean	Least-square mean
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NEI-VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire
NOAEL	No-observed-adverse-effect level
NSCLA	Non-small-cell lung adenocarcinoma
NYHA	New York Heart Association
OCT	Optical coherence tomography

PD	Pharmacodynamic
PDT	Photodynamic therapy
PFS	Pre-filled syringe
PK	Pharmacokinetics
PIGE	Placental growth factor
PMDA	Pharmaceutical and Medical Devices Agency
PPS	Per protocol set
PPT	Partial thromboplastin time
PT	Preferred term
PRN	As need (*pro re nata*)
QOL	Quality of life
RAAS	Renin angiotensin aldosterone system
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard deviation
SOC	System organ class
SPA	Special Protocol Assessment
TEAE	Treatment-emergent adverse event
TJA	Transient ischemic attack
ULN	Upper limit of normal
UPCR	Urine/protein creatinine ratio
US	United States
VEGF-A	Vascular endothelial growth factor – A
VEGFR	VEGF receptor
VA	Visual acuity
VTE	VEGF Trap (formulation for IVT injection
WBC	White blood cell
WET AMD	Neovascular age-related macular degeneration
WHO	World Health Organization
WOCF	Worst observation carried forward

DOSE GROUPS ABBREVIATIONS

Phase-2 Study VGFT-OD-0508	
0.5Q4	0.5 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
2Q4	2 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
0.5Q12	0,5 mg VEGF Trap dosed on a quaterly basis (ie, every 12 weeks)
2Q12	2 mg VEGF Trap dosed on a quaterly basis (ie, every 12 weeks)
4Q12	4 mg VEGF Trap dosed on a quaterly basis (ie, every 4 weeks)
Phase-3 Studies VIEW 1 (VGTF OD 605), VIEW 2 (A36355) – Integrated analysis POOL 1	
RQ4	0.5 mg ranibizumab dosed on a monthly basis (ie, every 4 weeks)
2Q4	2 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
0.5Q4	0.5 mg VEGF Trap dosed on a monthly basis (ie, every 4 weeks)
2Q8	2 mg VEGF Trap dosed every two months (ie, every 0 weeks) after three initial monthly doses

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Pharma AG submitted on 31 May 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eylea, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment of neovascular (wet) age-related macular degeneration (AMD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMEA/56/2008) on the granting of a class waiver.

New active Substance status

The applicant requested the active substance aflibercept contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

Several Scientific Advices were given by the EMA and other regulatory authorities.

EU Scientific Advices
March and June 2007: MPA advice on clinical questions for the planned Phase 3 trial design and non-clinical development programme;

July and August 2007: CHMP advice on the same aspects as discussed with MPA;

May – July 2010: National agency meetings with Denmark, Germany, Spain, Sweden on clinical aspects of the submission package for the MAA;

November 2010: EMA pre-submission meeting on regulatory aspects of the MAA;

January 2011: Rapporteur / Co-Rapporteur meeting on specific issues around the clinical data package for the MAA.

US (FDA)
March 2007: Special Protocol Assistance (SPA) for Phase-3 study design VIEW1 support filing.

July 2007: Second SPA for Phase-3 study VIEW1 agreements on amended Phase-3 study design, including a change in the VEGF Trap dose regimens

September 2010: Pre-Biologic License Application (BLA) meeting on specific clinical questions.

Japan (PMDA)
August 2007: Scientific advice meeting with Pharmaceutical and Medical Devices Agency (PMDA) on Phase-3 study design.

Overall, the clinical development programme appears fairly in compliance with the CHMP and national agencies scientific advices. The design/analysis of pivotal studies was widely discussed across these consultations. Some topics were thoroughly discussed with the CHMP (e.g. choice of primary variable and non-inferiority margin in pivotal studies) as they were slightly controversial. Region-specific feedback on each aspect has been implemented as protocols' local, or if relevant, as general amendments to both pivotal studies. Finally, although some preliminary advices were not always fully taken into account by the MAA, there were acceptable justifications for such deviations.

Licensing status

Eylea has been given a Marketing Authorisation in The USA in 2011 and in Colombia and Australia in 2012.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Philippe Lechat**

Co-Rapporteur: **Robert James Hemmings**

CHMP Peer reviewer: Conception Prieto Yerro

The EMA Product Team Leader: Francesca Cerreta

The application was received by the EMA on 31 May 2011.

The procedure started on 22 June 2011.

The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 September 2011 (Annex 2).

During the meeting on 20 October 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 October 2011 (Annex 3).

The applicant submitted the responses to the CHMP consolidated List of Questions on 18 April 2012.

The Rapporteurs circulated the Joint Assessment Reports on the applicant's responses to the List of Questions to all CHMP members on 6 June 2012 (Annex 4).

During the CHMP meeting on 18-21 June 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant (Annex 5).

The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2012.

The Rapporteurs circulated the Joint Assessment Reports on the applicant's responses to the List of Outstanding Issues to all CHMP members on 4 September 2012 (Annex 6).

The Rapporteurs circulated the updated Joint Assessment Reports to all CHMP members on 14 September 2012 (Annex 7).

During the meeting on 17-20 September 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Eylea on 20 September 2011.

2. Scientific discussion

2.1. Introduction

Neovascular age-related macular degeneration (AMD) is a common cause of irreversible blindness among the elderly worldwide. Vision loss results from the abnormal growth and leakage of blood vessels in the macula. Increasing incidence is reported with increasing age (it is suggested that 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD). The main factor of progression remains age, besides genetics and smoking.

AMD is a disease of the photoreceptors and the retinal pigment epithelium (RPE). In the aging eye, Bruch's membrane composition changes, and RPE function diminishes. As a consequence of reduced RPE function, drusen deposits at the level of the RPE and photoreceptors accumulate. Drusen contain lipofuscin and other toxic waste products of metabolism.

There are two forms of AMD, the dry (atrophic) and the wet (i.e. neovascular or exudative) form.

Dry AMD

The dry form is more benign and accounts for 90% of all AMD cases, but only for 10% of cases of blindness due to AMD. In the dry form, no abnormal vascularisation occurs in the subretinal space and drusen deposits are clustered in and around the macula, and these become larger and more numerous over time. Nevertheless, dry AMD with drusen only is generally asymptomatic. If, in addition to drusen, RPE cells degenerate and undergo apoptosis, geographic atrophy develops which can, if involving the fovea, significantly reduce near and distance vision. Eventually, the RPE atrophies. This results in a loss of vision due to the loss of photoreceptor function.

Patients suffering from an atrophic form of AMD do not benefit from the same therapeutic options than wet AMD. Although less progressive, dry AMD is of bad prognosis. Nowadays, treatments remain based on optic systems and re-education. There is no drug therapy for dry AMD.

Wet AMD

Only about 10% of AMD patients have the wet form; however, 80% to 90% of patients with severe vision loss due to AMD have wet AMD. In wet AMD, Bruch's membrane ruptures, and this is associated with a localized inflammatory response and release of VEGF (Vascular endothelial growth factor), which induces choroidal neovascularization (CNV). The CNV is a membrane of abnormal and leaky blood vessels, growing from the choroid through the defects in Bruch's membrane underneath the RPE and the retina. These new, immature blood vessels leak lipids, fluid and blood. This causes edema and elevation of the retina, resulting in blurring and distortion of vision. Onset of visual dysfunction in wet AMD is acute and progresses within a few weeks or even faster, particularly if bleeding occurs. With bleeding under the retina or persistent edema, the loss of central vision becomes permanent.

CNV is characterized clinically, using fluorescein angiography (FA), as occult, mixed or classic/visible CNV. Occult CNV is usually limited to the space beneath the RPE, and the degree of vision loss is usually mild compared with classic CNV. Classic CNV often penetrates the pigment epithelium and grows into the subretinal space with possible retinal serous.

In addition to the gold standard fluorescein angiography test, optical coherence tomography (OCT) is a complementary useful tool to make a diagnosis of wet AMD and identify the presence of subretinal fluid and the central retinal thickness.

Wet AMD Treatments:

Vascular endothelial growth factor-A (VEGF-A) is involved in many forms of angiogenesis, both physiological and pathological. The role of VEGF-A in promoting pathological neovascularization and/or abnormal and excessive vascular permeability in several diseases affecting the eye is now well established.

The VEGF / platelet-derived growth factor gene family includes other members (VEGFB, VEGFC, VEGFD, VEGFE and PlGF). The activity of VEGF-A is mediated primarily by binding to and activation of two transmembrane receptor tyrosine kinases, VEGFR1 and VEGFR2. A third related receptor, VEGFR3, binds VEGFC and VEGFD, and to a lesser extent VEGF-A, and is mainly involved in the regulation of lymphatic vessel development. VEGFA is thought to induce its effects on the vascular endothelium primarily by signalling through VEGFR2.

Intravitreal (IVT) anti-VEGF treatments for wet AMD have been introduced in recent years, first with Pegaptanib (Macugen; Pfizer), and shortly after with Ranibizumab (Lucentis; Genentech-Roche/Novartis). Intravitreal anti-VEGF therapy is nowadays the standard of care in the treatment of neovascular (wet) AMD.

About the product

Aflibercept (also referred to in this document as "VEGF Trap") is intended to be marketed as an intravitreal injection under the name EYLEA.

VEGF Trap belongs to the pharmacological class of VEGF inhibitors: it is a recombinant protein created by fusing the second Ig domain of human VEGFR1 with the third Ig domain of human VEGFR2, which is in turn fused to the constant region of human IgG1.

Aflibercept is a potent, specific inhibitor of VEGF that is active in animal models of ocular neovascularisation after systemic and IVT administration. Aflibercept interferes with the biological actions of VEGF-A by binding to VEGF-A, preventing it from interacting with its receptors.
It also binds to other VEGFR1 ligands, notably PlGF.

Other drugs of this class include, as previously noted, two currently approved treatments for AMD, ranibizumab (Lucentis) and pegaptanib sodium (Macugen).

VEGF Trap showed some differences over other VEGF blockers, which might have been expected to prolong the interval between two IVT injections up to two or three months, to decrease the number of injections needed by year compared to the current regimens:

-a higher affinity (~ 0.5 pM dissociation constant for VEGF165 and VEGF121) than a humanized monoclonal antibody,

-a longer circulating half-life compared to soluble receptor constructs which have been studied in animals.

-a binding to the related factors Placental Growth Factor 1 and 2 (PLGF1 and PLGF2), thought to be advantageous in certain disease situations, including retinal neovascularizations.

2.2. Quality aspects

2.2.1. Introduction

The drug substance aflibercept is a novel biotechnological product, engineered to act as a decoy VEGF receptor. It is a fully human, recombinant fusion protein consisting of sequences derived

from vascular endothelial growth factor (VEGF) receptor extracellular domains fused to the Fc portion of immunoglobulin G1(IgG1). Aflibercept is a member of the pharmacological class of VEGF inhibitors formulated for intravitreal (IVT) use.

Its proposed indication is for the treatment of neovascular (wet) age-related macular degeneration in adults.

The drug product is an iso-osmotic sterile solution of 40 mg/mL Aflibercept for IVT injection in an aqueous buffered solution. The drug product is presented either in single dose vials or single use prefilled syringes.

During clinical development, the drug product was supplied primarily in vials.

A pre-filled syringe was developed in order to improve the ease of drug delivery for retinal physicians, and by design of the syringe, to ensure delivery of the correct drug volume to the patient.

Following consultation with regulatory authorities and in accordance with the medical practice as well as guidance for administration of ophthalmologic products, a pre-filled syringe that is terminally sterilised was developed.

2.2.2. Active Substance

Aflibercept is a recombinant fusion protein consisting of two identical polypeptide chains, each comprising the second Ig domain of the human vascular endothelial growth factor (VEGF) receptor 1 and the third Ig domain of the human VEGF receptor 2, with both polypeptide chains fused to the Fc domain of human IgG1. This fusion protein is synthesized by Chinese Hamster Ovary (CHO) cells as a dimeric, secreted, soluble protein.

Aflibercept functions as a decoy receptor that binds to VEGF ligand, thus inhibiting VEGF from binding to its receptor and subsequent stimulation.

Fusion with the Fc region of IgG1 allows prolonging the *in-vivo* half-life of the molecule.

Manufacture

Manufacturer

The drug substance (DS) is manufactured and released by Regeneron Pharmaceuticals Inc., New-York, USA.

Description of manufacturing process and process controls

The upstream process consists on expansion of a single vial of Working Cell Bank (WCB) and production phase into a bioreactor. It is a fed batch fermentation process using step-wise feeding strategy and harvesting.

The downstream process consists of several chromatography steps (protein A affinity chromatography, Cation exchange, Anion exchange, Hydrophobic Interaction and Size Exclusion chromatographies), viral steps (low pH virus inactivation, one nanofiltration) and ultrafiltration-diafiltration steps.

No reprocessing is claimed for the standard manufacturing of the product.

The DS contains sodium phosphate- pH6.2 and is supplied in 1 L polycarbonate (PC) bottle.

During purification, a DS intermediate can be stored frozen at ≤-20°C up to 9 months in two different containers (EVA bags or PC bottles).

The manufacturing process does not directly use any materials of biological origin other than the foetal bovine serum used in the freezing medium for the Master Cell Bank (MCB). The development of the producer cell line and the construction and control of the MCB and WCB are adequate.

In general, the in process controls are appropriate and adequate, including those designed to prevent or reduce bioburden, mycoplasma and adventitious viruses.

Process Validation

The process validation followed a traditional approach and was performed in two stages on four consecutive DS intermediates lots and on four consecutive lots of DS manufactured from the P3 process at commercial scale. The process, including the clearance of potential process-related impurities, was considered acceptably validated.

Manufacturing process development

The manufacturing process evolved over the course of development through three process changes (designated P1, P2 and P3). The P1 material was used in early toxicology and Phase 1 clinical studies. This process was subsequently scaled up and designated P2, while the later replacement of the viral filter with one with a tighter porosity and further minor refinements led to the validated commercial P3 process.

Extensive bioanalytical testing studies have shown that aflibercept produced from all three processes are comparable and the changed processes are not expected to impact the assessment of pre-clinical or clinical studies performed with different process lots. In early 2011, several minor changes were made to the upstream cell culture process to implement process improvements identified subsequent to the validation of the conformance lots. These minor changes to the validated process did not result in changes to the validated performance in terms of cell growth or protein production and no difference in the quality of the product pre- and –post changes was detected.

Specification

Characterization

Aflibercept was well characterised in terms of mass, extinction coefficient, primary sequence, disulphide bond formation, glycosylation, size variants (truncated forms and aggregates), charge variants, process-related impurities, degradation products (fragmented forms, oxidised species and deamidation products) and secondary and tertiary structure.

The DS is a homodimeric glycosylated protein. The primary structure consists of 432 aminoacids for each polypeptide chain. There is 6 methionines, two of which proned to oxidation, and 6 asparagines proned to deamidation.

The secondary structure is stabilised by 4 intra-chain disulfide bridges in each polypeptide.

The protein chain is glycosylated. The monosaccharide contributing to carbohydrate structures are N-acetyl-glucosamine, fucose, galactose, mannose and sialic acids. The N-linked oligosaccharides consist of mainly bi-antennary structures with zero, one or two terminal sialic acids.

Impurities

Impurities are separated into potential product-related impurities identified in forced degradation studies (molecular variants of aflibercept resulting from various types of degradation) and process-related impurities.

Control of Drug Substance

The analytical procedures used to characterise and control aflibercept quality were appropriately validated.

The proposed specifications are in line with international guidance on the setting of specifications (ICH Q6B - Note for Guidance on "Specifications: test procedures and acceptance criteria for biotechnological products").

Routine testing is performed at release for HCP, DNA, Protein A, bioburden, endotoxins. The purity is tested by SDS-PAGE and Size Exclusion HPLC, while charge heterogeneity is monitored by Isoelectric Focusing. Deamidation is also monitored on a routine basis by enzyme-linked detection of isoaspartate with reversed-phase HPLC.

A cell based assay was designed to evaluate potency.

Reference standards or materials

The reference standards used throughout the process development and manufacturing are traceable and well documented.

Stability

Long-term stability data were provided up to 36 months for batches from the P3 process.

The shelf-life has been re-evaluated following a requested re-evaluation of the release specifications and trending analysis for potency.

All data support a storage of 36 months under the proposed conditions at -80°C and protected from light.

2.2.3. Finished Medicinal Product

The drug product (DP) is presented as a solution for intravitreal injection containing 40 mg/ml Aflibercept, sodium phosphate, sodium chloride, sucrose and PS20 at pH 6.2.

The DP appears in two presentations differing in terms of primary container type: 2 ml type I glass vials and 1ml pre-filled syringes.

All presentations are single dose/partial use presentations. There is an overfill in the vial and syringe presentations compared to the volume required to deliver the appropriate dose i.e. 50 µl. These overfills have been justified in both cases as the minimum volumes required in order to consistently achieve accurate dosing (user testing by trained individuals) and the fill volume does not allow preparing 2 doses. The wording of the SmPC highlights overfills, and that excess solution should be discarded.

Pharmaceutical Development

The commercial formulation was designated IVT-2, while an earlier formulation (ITV-1), was used in Phase 1 and Phase 2 clinical studies. IVT-2 was developed to provide greater thermal stability and resistance to agitation-induced aggregate formation, while maintaining isotonicity.

During clinical development, drug product was supplied primarily in vials. In 2007, a pre-filled syringe has been developed. In 2009, an external sterilization step was added to the proposed pre-filled syringe manufacturing process after secondary packaging to render the external surface of the syringe and the internal surface of the blister as sterile.

Comparability studies have been performed comparing:

- Commercial vials to vials from the clinical development site. Un-sterilised syringes to vials from the clinical development site,
- Un-sterilised syringes to syringes sterilised at the commercial site and syringes sterilised at a development site,
- Syringes sterilised at the development site and at the commercial site

The data provided support the comparability of the products tested.

Manufacture of the product

The manufacturing process of the drug product includes manufacture of formulated bulk intermediate (thawing of DS, pooling, formulation, bioburden reduction filtration, and storage at -30°C up to 36 months), filling of vials or syringes (thawing of formulated bulk, pooling, bioburden reduction filtration, sterile filtration, filling) and sterilisation of blister packs of syringes. Only vials and PFS externally sterilised are intended to be used for commercial supply.

The manufacturing process was well described and appropriately validated.

Product specification

Control of drug product

The analytical procedures used to characterise and control the DP quality were appropriately validated.

The proposed specifications are in line with international guidance on the setting of specifications.

Testing for sterility and endotoxin content is routinely performed at release.

As for the DS, the purity is tested by SDS-PAGE and Size Exclusion HPLC, while charge heterogeneity and deamidation are monitored by Isoelectric Focusing and enzyme-linked detection of isoaspartate with reversed-phase HPLC, respectively.

Potency is determined using a cell-based assay.

Stability of the product

36-month supportive real-time stability data are available for the clinical vials and for PFS that were not subjected to a terminal sterilisation step. Long-term stability data have been updated with 24-month data for prefilled syringes externally sterilised and vials.

In general, the results support the shelf-life of 24 months and storage conditions (2-8°C protected from light) as defined in the SPC, for both the PFS and vial presentations.

Adventitious agents

The overall viral safety of Eylea is considered satisfactory based on the fact that:

- No product of biological origin is used during the production process,

- Cell banks were extensively controlled and no viral particles other than retroviral-like particles normally seen in these cell types were observed,

- The starting materials from animal origin are mainly used indirectly or before the establishment of the cell banks,

- The manufacturing process includes several steps shown to be efficient to clear adventitious viruses (two chromatography steps, low pH treatment and nanofiltration). Global reduction factors reported were satisfactory regarding the virus removal/inactivation for enveloped viruses as well as for non-enveloped viruses.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major objections were raised during the assessment of the quality part of the dossier.

The Applicant has responded satisfactorily to all of the other quality concerns and questions identified in the Day 120 List of Questions and in the Day 180 List of Outstanding Issues.

Concerning the specifications for both the DS and DP, the approach to determine acceptance criteria was discussed during the procedure. A re-evaluation together with a review of historical drug substance intermediates and DS batches was performed and most specifications were subsequently tightened by the Applicant. Likewise, the DP specifications were re-evaluated during the course of the procedure and most acceptance limits were tightened.

Osmolality of the solution is monitored as part of the formulated bulk in-process controls. Although below the osmolality in vitreous humor, the lower limit was clinically qualified and the proposed acceptance limits were supported by batch data.

The choice of the ligand in the cell based bioassay was justified by the Applicant during the course of the evaluation.

Regarding the sterilisation of the DP in pre-filled syringes, two external sterilisation methods were initially developed. A single method has been retained for marketing and only vials and PFS externally sterilised by the selected method will be used for commercial supply.

In conclusion, information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the manufacture and control of the aflibercept drug substance and the Eylea drug product are considered acceptable.

The Quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in satisfactory way.

Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

VEGF Trap interferes with the biological actions of VEGF-A by tightly binding to it, and preventing VEGF-A from interacting with its receptors. 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. VEGF Trap can also bind to other VEGFR-1 ligands, notably PlGF.

In order to provide proof of concept and clarify the mode of action, the binding of VEGF Trap and effect of phosphorylation of VEGFR-2 have been characterised in a number of in vitro and in vivo studies. The effects of VEGF Trap have also been evaluated in vascular leak and/or neovascularisation in animal models of ocular vascular disease.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A number of in vitro studies have been performed to examine the binding of VEGF Trap to human VEGF-A165 and to human PIGF-2. As the protein sequence for Cynomolgus monkey VEGF-A is identical to that from humans, the binding affinities can be assumed to also be nearly identical, and this has been supported by additional data provided in the Applicant's responses:

- potential glycosylation sites (Asn and Ser/Thr) in VEGFA are well-conserved among species, are not located in VEGFR-1 and VEGFR-2 binding interfaces, and have no effect on VEGF function but are required for efficient secretion;

- sequence alignment of VEGF-A/PlGF indicates that key residues of VEGF-A/PlGF located in the receptor binding interfaces are strictly conserved among species;

- VEGF-A is conserved across species with a sequence homology of approximately 85% between human and rodent VEGF-A. Thus, given the sequence identity between monkey and human VEGF-A, very similar binding affinity of VEGF Trap to monkey VEGF-A is expected.

- VEGF Trap binds to both human and monkey VEGF, at concentrations relevant to support pharmacological and toxicological assessment of VEGF Trap.

- an efficacy study of VEGF Trap in a laser induced-choroidal neovascularisation (CNV) model in Cynomolgus monkeys further supports the presumption of high affinity of VEGF Trap to monkey VEGF.

VEGF Trap displayed binding affinities with human VEGF-A165 and to human PlGF-2 in the pico-molar range, for human VEGF-A165 the KD was calculated as 0.497 pM. For human PIGF-2 the KD was 38.8 pM. VEGF Trap was also shown to bind to VEGF and PlGF isoforms from non-human species such as the mouse, rat and rabbit with similar affinities, and this supported the use of these species in non-clinical studies during the development of VEGF Trap. There is high binding affinity of VEGF Trap to VEGF-A for human, rat, mouse and rabbit, KD values were very low, in the pM range. Binding to PlGF-2 was also high for human and murine PlGF.

VEGF Trap does not bind other VEGF family ligands, VEGF-C and VEGF-D, which bind primarily to the closely related receptor VEGFR3. Thus it can be concluded that the binding of VEGF Trap is selective, even within the VEGF family of ligands. Binding of VEGF Trap to 'non-target' protein ligands is unlikely. PDGF family is closely related to the VEGF family, although PDGFs and VEGFs have been shown to be selective for their own receptors. The difference is consistent with the low sequence homology and the conformational variability of the ligand: receptor binding interfaces between PDGFs and VEGFs. EGF, HGF and NGF are even more distantly related to VEGF, such that there is no basis in the literature, or theory that would lead one to expect that they might interact with VEGFRs.

In vitro, VEGF Trap was shown to completely block VEGF-mediated phosphorylation of VEGFR-2 on HUVEC, at molar concentrations ≥1:1. VEGF Trap exhibited high affinity binding to VEGFA from human, mouse, rat and rabbit with subpicomolar K_D values.

VEGF Trap has been found to effectively inhibit neovascularisation and/or pathological vascular leak in all animal models of ocular neovascular disease and vascular leak tested to date. VEGF Trap inhibits the development of pathological neovascularisation and/or edema in rodent models of diabetic and ischemic retinopathy, and corneal injury, as well as in rodent and primate models of CNV that resemble the neovascular or 'wet' form of age-macular degeneration (AMD). Of particular relevance, intravitreal (IVT) administration of VEGF Trap has been shown to rapidly resolve existing vascular leak in the retinas of diabetic rodents, and in primates with active, laser-induced CNV. Moreover, VEGF Trap ameliorated the associated ocular inflammation. The anti-inflammatory effect of VEGF Trap is likely attributable to its ability to bind VEGF-A and/or PlGF, which are known to mediate leukocyte chemotaxis via VEGFR-1 expressed on the surface of subpopulations of leukocytes, particularly macrophages and neutrophils. VEGF Trap was found to be effective whether administered directly into the vitreous of the eye, or systemically (e.g. by subcutaneous (SC), intraperitoneal (IP) or intravenous (IV) routes).

VEGF Trap prevented the development of active CNV when given IVT at doses of 50, 250 or 500 µg/eye every other week, as effectively as 3 mg/kg or 10 mg/kg given IV weekly. In mice, VEGF Trap was shown to suppress the growth of most tumour xenografts only at doses ≥2.5 mg/kg (SC, twice weekly), with maximal suppression of tumour growth generally seen at doses ≥10 mg/kg (SC, twice weekly). Similarly, SC doses of VEGF Trap ≥10 mg/kg were required to achieve maximal elevations in blood pressure in telemetered rats. VEGF Trap did not produce detectable elevations in blood pressure at doses < 0.5 mg/kg.

The diabetic retina can cause retinal oedema and ischemia-induced retinal neovascularisation. These effects were demonstrated by using i) a single IVT dose of VEGF Trap (3 µg/eye) which resulted in normalisation of retinal vascular permeability in streptozotocin-treated, diabetic male Sprague Dawley rats; ii) a single IVT dose of VEGF Trap (0.5 or 0.24 µg) prevented the development of pathological retinal neovascularisation in a mouse model of oxygen-induced ischemic retinopathy. VEGF Trap (single dose of 12.5 mg/kg IP) also suppressed CNV and reduced the inflammatory response in mice with induced corneal injury.

Secondary pharmacodynamic studies

VEGF Trap at doses greater than 2.5 mg/kg (given s.c, twice weekly) administered to SCID mice bearing subcutaneously implanted mouse B16F1 melanoma, human A673 rhabdomyosarcoma, or mouse MMT mammary carcinoma, were sufficient to achieve maximally attainable VEGF Trap complex concentrations (1-2 µg/ml). Free VEGF Trap concentrations were ≥10 µg/ml at these doses and this appeared to have a significant impact in inhibiting tumour growth in these animal models.

VEGF Trap elevates blood pressure in both rats and mice in a manner that is dose dependent in both amplitude and duration of effect. This effect is also closely tied to circulating levels of free VEGF Trap. In both species, maximal increases in blood pressure were evident at doses which produced peak circulating levels of free VEGF Trap in the excess of 6 µg/ml, and in both species blood pressure remained elevated above baseline until the concentration of VEGF Trap in the serum fell below approximately 1 µg/ml. The expected level of free VEGF Trap following IVT administration in humans is expected to be 0.0193 µg/ml; this is a 50-fold lower level than that determined from the rodent studies.

Blood pressure data taken after systemic single administration of VEGF-Trap from telemetered rodents were sensitive enough (rats>mice) to show a blood pressure increasing effect of VEGF Trap thereby revealing a good correlation with the well known blood pressure increasing mode of action of a VEGF inhibitor. This was in contrast to the data obtained in toxicity studies with physically or chemically restrained Cynomolgus monkeys in which blood pressure was measured with an indirect method, the conventional oscillometric cuff system. VEGF Trap plasma levels in Cynomolgus

monkeys exceeded those in rodents. The lack of an effect of VEGF Trap on blood pressure is most probably due to the effects of chemical/physical restraint on the cardiovascular system of the Cynomolgus monkeys and the limited sensitivity of indirect blood pressure measurement systems as compared to direct, e.g. radiotelemetry techniques which has been used in rodents.

Safety pharmacology programme

In vitro safety pharmacology studies with VEGF Trap have not been carried out, as they are considered to be irrelevant for high molecular weight proteins such as VEGF Trap. CNS safety pharmacology has been reviewed from the repeat dose systemic toxicity studies in Cynomolgus monkeys dosed subcutaneously and intravenously with VEGF Trap. The studies did not reveal any adverse effect on the CNS in monkeys following administration with VEGF Trap.

In vitro cardiovascular safety studies with VEGF Trap were not conducted. The in vivo examination in monkeys treated with the VEGF Trap in the systemic toxicity studies in Cynomolgus monkeys for up to 26 consecutive weeks showed an absence of ECG abnormalities. Based on the overall in vivo results in monkeys, VEGF Trap is not expected to exert a cardiotoxic effect.

The potential effects of VEGF Trap on venous and arterial thrombus formation were evaluated in New Zealand White rabbits after electrolytic injury. The animals were treated with VEGF Trap at doses of 0.3, 3.0, and 30 mg/kg by 30 minute infusion. There was no significant effect on venous and arterial thrombus formation following VEGF Trap treatment.

In line with ICH S6(R1), respiratory effects have been examined as part of the toxicity studies. Following intravenous infusion of VEGF Trap over 30 minutes at 10, 50 or 250 mg/kg in male Sprague-Dawley rats had no effects on the respiratory function up to 7 days after administration.

The effects of VEGF Trap on wound repair and healing were evaluated in the New Zealand White rabbit incisional and excisional wound healing models. Wound repair and healing in the rabbit incisional model was inhibited after repeat administration with VEGF-Trap at dose levels of 0.3, 3, and 30 mg/kg as demonstrated by a reduction in blood vessel density and tensile strength evaluation. There was reduced fibrous response, neovascularisation and epidermal hyperplasia, resulting in larger wound areas following repeat administration with VEGF-Trap in the excisional wound healing model. In both models, the effects of VEGF Trap resulted in delayed wound repair and healing.

Pharmacodynamic drug interactions

Data from formal pharmacodynamic drug-drug interaction studies of VEGF Trap with ophthalmic anaesthetic agents, antimicrobial agents and mydriatics is not available. Because topical ocular medications do not reach the posterior segment, drug-drug interactions with VEGF Trap within this ocular compartment are highly unlikely. In addition, the clinical experience during the clinical development program for VEGF Trap Eye included prior administration of topical mydriatic agents and concomitant topical administration of anaesthetics and disinfectant antimicrobials with intravitreal injection of VEGF Trap Eye. The administration of these topical medications concomitantly with VEGF Trap was well-tolerated.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetic (PK) profiles of free VEGF Trap were determined following single dose IV and SC administration to mice, rats, and Cynomolgus monkeys and following single dose IVT administration to rabbits. As part of repeated-dose toxicology studies in monkeys, plasma and vitreous free VEGF Trap and plasma VEGF Trap complex concentrations were determined after IVT

administration to assess drug exposure as well as to develop additional understanding of the in vivo disposition of the free and bound forms of VEGF Trap.

Enzyme-linked immunosorbent assays (ELISA) were developed for determining the concentration of free VEGF Trap in mouse, rat and monkey serum and in rabbit and monkey plasma from pharmacology, pharmacokinetic and toxicology studies conducted in these species. The methods for determining the concentration of free and bound VEGF-trap in rabbit and monkey vitreous humour, choroïd and retinal were not evaluated.

The percentage of recovery and the coefficient of variation were calculated using vitreous humour and various eye tissues as matrix for analyzed quality control samples. From these data, it may be concluded that these assays have been performed with good precision, accuracy, and reproducibility.

Following IV administration to mice, rats and monkeys, VEGF Trap displayed a multicompartmental PK plasma or serum profile, as inferred from the serum or plasma concentration vs. time profiles. Clearance was slow, $t_{1/2}$ and MRT long and the V_{ss} was slightly greater than the volume of the central compartment. VEGF Trap SC bioavailability was good in mice (94%) and monkeys (85%) and moderate in rats (33%). Following IVT administration to monkeys, VEGF Trap systemic absorption appears to be relatively high

Tissue distribution following IV administration of [^{125}I]-VEGF Trap to rats supported the assertion that distribution was limited primarily to the circulation. As expected for a protein-based therapeutic, the highest concentration of tissue radioactivity was localized in the liver, followed by other highly perfused tissues. Following IVT dosing of VEGF Trap, distribution to the systemic circulation is slow and prolonged, resulting in the transfer of a substantial fraction of each IVT dose into the blood.

The applicant has performed a number of studies to examine the distribution of radio-labelled VEGF Trap administered systemically to rats. Other studies investigated the distribution of VEGF Trap after IVT administration to rabbits and monkeys. The bio-distribution of ^{125}I-labeled VEGF Trap after IV administration was investigated in female Sprague-Dawley rats.

However, the PK profile of ^{125}I-labeled VEGF Trap differed from VEGF Trap, and so these findings may not be representative of the actual product. Approximately 75% of the total dose of radioactivity was found in the serum at 5 minutes post-dosing and steadily declined to approaching zero by 168 hours. Radioactivity was highest in the organs of clearance and other highly perfused tissues, predominately in the liver (11.4%), but also the kidney, spleen, lung and heart. The decline seen in serum was also replicated in these organs: at 168 hours post-dosing, only 0.16% of the total radioactive dose was detected in the liver. This indicates rapid clearance and limiting the distribution of the labelled VEGF Trap to the circulation.

The distribution of free VEGF Trap in the choroid, retina, vitreous, and plasma after IVT administration was investigated in male, pigmented New Zealand rabbits. The free VEGF Trap mean $t_{1/2}$ was 115 hours in the vitreous and 157 hours in plasma following IVT administration; free VEGF Trap plasma concentrations were also detected for up to 28 days post dose. Vitreous humour contained the majority of VEGF Trap (compared to retina, choroid and plasma), suggesting accumulation in this compartment. Free VEGF Trap in plasma was only detected 72 hours after dosing, displaying a slow distribution from the vitreous to the plasma in systemic circulation.

The vitreous and plasma concentrations of free VEGF Trap and the plasma concentrations of VEGF Trap complex were determined in 4 separate toxicology studies following single or repeated (either monthly or every 6 weeks) IVT dosing to male and female Cynomolgus monkeys. Peak concentration of free VEGF Trap was approximately 24 hours post-dose, levels of free VEGF Trap peaked at 1 week in the vitreous, and results were dose proportional. Approximately 5.5-16% of

applied dose was detectable after 1 week in the vitreous humour. The estimated $t_{1/2}$ of free VEGF Trap in the vitreous ranged from approximately 40 to 68 hours and was independent of the dose applied.

Plasma free VEGF Trap concentrations increased in a greater than dose proportional manner at IVT doses of up to 2000 µg/eye, with concentrations becoming slightly less than dose proportional at a doses higher than this. This shows that at lower doses, the lower levels of plasma free VEGF Trap concentrations are due to VEGF Trap binding to endogenous VEGF.

In plasma, concentrations of the VEGF Trap complex increased with increasing dose. Seven days following dosing the total concentration of bound VEGF Trap ranged from 100% (50 µg/eye) to 26-34% (4000 µg/eye). Clearance of the bound VEGF Trap was slow as it was detected well into the recovery phase unlike the free VEGF Trap.

There were no specific non-clinical studies conducted to examine metabolism of VEGF Trap. The expected metabolism of VEGF Trap is expected to be to small peptides and amino acids and so further classical biotransformation studies are not required.

Regarding the excretion, single 1 mg/kg IV doses were administered to functionally-nephrectomized and sham-operated female rats and serial VEGF. Comparison of the key indices of VEGF Trap exposure (C_{max}, time of maximum serum concentration (T_{max}), AUC, and $t_{1/2}$) revealed no apparent differences between the nephrectomized and sham-operated control animals, suggesting that renal excretion of VEGF Trap is insignificant.

Single 1 mg/kg IV doses were administered to functionally-nephrectomized and sham-operated female rats and serial VEGF. Comparison of the key indices of VEGF Trap exposure (C_{max}, time of maximum serum concentration (T_{max}), AUC, and $t_{1/2}$) revealed no apparent differences between the nephrectomized and sham-operated control animals, suggesting that renal excretion of VEGF Trap is insignificant.

There were no specific non-clinical studies conducted to examine potential pharmacokinetic drug interactions with VEGF Trap following IVT administration. No systemic pharmacokinetic drug interactions are expected following intravitreal administration with VEGF Trap since only very low concentrations of free and bound VEGF Trap will reach the systemic circulation.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity of VEGF Trap following IVT administration was evaluated in Cynomolgus monkeys. The evaluation did not reveal any signs of an adverse response. Single dose toxicity studies were performed by IV administration (at doses of 50, 150 and 500 mg/kg) to rats. Transient skin lesions and discoloration of the tail (administration site) were observed at a dose of 150 mg/kg. A moderate decrease in body weight gain was noted in both male and female rats at both dose levels, and was associated with a moderate decrease in food consumption in male rats at a dose of 500 mg/kg. The Minimum Lethal Dose and the Maximum Tolerated Dose were >500 mg/kg.

Repeat dose toxicity

The sub-chronic and chronic toxicity of VEGF Trap was evaluated in the most relevant species, the Cynomolgus monkey, using the clinically relevant IVT route of administration. Further systemic toxicity studies with VEGF Trap were undertaken in mice (SCID and CD-1), rats (Sprague Dawley and nude) and Cynomolgus monkeys by IV and SC routes.

IVT: A number of studies were carried out to examine the subchronic toxicity of VEGF Trap following IVT administration was evaluated in monkeys (dosing up to 13 weeks) and the chronic toxicity of the test article was evaluated in monkeys treated up to 8 months by the IVT route. Following IVT administration with VEGF Trap there was a level of inflammatory response characterised as inflammatory cells in the anterior chamber that occurred. This effect was seen predominately in VEGF Trap treated eyes and was not dose-related or treatment duration-related. The inflammatory response peaked at 2 days, and in all instances reversed within 3 weeks post-dosing. There were no angiographic or electroretinographic changes following IVT treatment, however increased ocular pressure was seen in either VEGF Trap or VEGF Trap Placebo treated animals. This effect is due to the increase in vitreal volume following intravitreal injection (volume of 50 µl/eye). Administration of a lower volume (25 µl) of the VEGF Trap test article usually resulted in a much smaller immediate post-dose increase in IOP. This effect was also reversible. In the pivotal 8-month repeat dose toxicity study in monkeys, at a dose of 2000 µg/eye there was increased incidence of epithelial erosion/ulceration of the respiratory epithelium of the nasal turbinates, often accompanied by chronic-active inflammation of the nasal turbinates. This effect is likely a result of local exposure of the nasal epithelium to the nasal cavity by way of anastomoses between the ophthalmic and nasal venous plexuses, or leakage from the IVT injection site into the nasal lacrimal duct. A NOAEL of 500 µg/eye was established based on the findings of epithelial erosion/ulceration of the nasal turbinates noted at the 2 and 4 mg/eye levels. Although the findings of anterior segment cells were present at all dose levels, this effect may be considered as mild and reversible so a tentative NOAEL is proposed. A LOAEL of 2 mg/eye is acceptable, and using this exposure ratios based upon the established LOAEL, Cmax and AUC determined from this toxicity study, was compared to the clinical exposure of VEGF Trap following IVT administration of 2 mg/eye. Exposure multiples were 231-fold higher (based on AUC and LOAEL values) and 708-fold higher (based on Cmax and LOAEL values).

The issue of only reaching 6-times the clinical exposure levels in the monkey intravitreal studies had been discussed in a CHMP advice to the Applicant. Limitations due to the formulation of the product, increasing volume or frequency of administration to the monkey eye were discussed in order to justify this lower safety margin.

No significant pharmacodynamic differences are expected between monkeys and humans because the VEGF molecules are identical in humans and monkeys. The high degree of conservation between species could also be demonstrated by the similar affinity (KD) of VEGF and PlGF from mice and humans. PlGF1 and PlGF2 molecules in monkeys and humans only differ by 2 amino acids that are located outside of the known sites relevant for receptor binding and therefore this difference should not affect binding to VEGF Trap to an appreciable degree.

Systemic: A comprehensive range of systemic toxicity studies were performed in mice, rats and monkeys. Due to the high immunogenicity in the rodent species, the Cynomolgus monkey was the preferred species. Exposure to free VEGF Trap was much higher in these studies compared to IVT administration, and allowed to determine systemic toxicities. Common effects in target organs included bone (interference with growth plate maturation of long bones and osteocartilaginous exostoses of vertebrae), kidney (frequently increased glomerular mesangial matrix, occasionally hyperplasia of parietal epithelium and periglomerular fibrosis), adrenals (decreased vacuolation with eosinophilia in the zona fasciculata), ovary (decreased number of maturing follicles, granulosa cells and/or theca cells), and nasal cavity (respiratory and olfactory epithelium of nasal turbinates). Further microscopic findings were seen in the 6 month monkey study, included vascular alterations in the choroid plexus (≥3 mg/kg) and digestive tract (≥10 mg/kg), vascular degeneration and fibrosis in several tissues (≥10 mg/kg) including the heart, and hepatic portal inflammation and periportal necrosis (30 mg/kg). No NOAEL could be determined in the systemic toxicity studies due to effects seen in each tested dose of VEGF Trap. Exposure ratios based upon the established LOAEL, Cmax and AUC determined from each toxicity study was compared to the clinical exposure

of VEGF Trap following IVT administration of 2 mg/eye. Exposure multiples ranged from 134- to 1546-fold (based on AUC and LOAEL values) and 503- to 4902-fold (based on Cmax and LOAEL values). It is also considered that following IVT VEGF Trap administration, levels of free VEGF Trap are unlikely to be seen at levels to cause systemic toxicity.

Genotoxicity

Due to the fact that this is a biotechnology-derived product, the range and type of genotoxicity studies routinely conducted for pharmaceuticals are generally not applicable, as it is unlikely that the administration of large levels of proteins would yield any meaningful results. It is agreed that VEGF Trap is unlikely to interact with DNA or chromosomal material.

Carcinogenicity

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals, and this is the case for VEGF Trap. This is in line with previous CHMP scientific advice obtained by the applicant (EMEA/CHMP/SAWP/310870/2007) and the requirements of ICH S6 (R1) guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals. Product specific assessment of carcinogenic potential may be required for products that act as growth factors or as an immunosuppressive. Studies conducted with VEGF Trap do not indicate that it acts in this way, and due to the high immunogenic potential of VEGF Trap to rodents, classical rodent carcinogenicity studies would be of little relevance. It is acceptable to not perform genotoxicity or carcinogenicity studies.

Reproduction Toxicity The effects of VEGF Trap on fertility were investigated in the context of the 6-month toxicity study in sexually mature Cynomolgus monkeys by IV administration. Results showed decreased sperm motility and increased spermatozoa morphological abnormalities in males and abrogation of ovarian function and follicular development in females during treatment with VEGF Trap, along with abrogation of normal menstruation. These findings were reversible after cessation of treatment. Decreases in ovary weights were noted. Moreover, some females given 30 mg/kg/dose had an evident reduction of maturing follicles compared to controls. Uterine endometrial and myometrial atrophy and vaginal epithelial atrophy also were common findings in VEGF Trap-treated animals. Following recovery, all VEGF Trap-treated females presented normal ovarian folliculogenesis and presence of medium to large size corpora lutea.

There were no test-article related effects on male reproductive hormone levels (FSH, LH, and testosterone) at any dose or time. Weights for the testis, epididymis, prostate and seminal vesicles were not different between treated and control groups, and no histopathological changes were evident in the male sex organs. There were profound effects on sperm motility and quality. In all doses of VEGF Trap there were decreased levels of sperm motility and increased number of abnormalities to sperm. Although these changes are reversible following up to 13 weeks recovery, a clear effect on reduced male fertility is apparent.

As no NOAEL for effects on ovary/ovarian hormones and to sperm could be determined from this study, the applicant has calculated potential exposure ratios based upon the toxicokinetic findings from this study and in comparison to Cmax and AUC determined from humans treated with 2 mg/eye (Study No. VGFT-OD-0702-PK). Exposure was 4902-fold (Cmax) and 1546-fold (AUC0-168h) higher in the monkey study after 3 mg/kg dosing, compared to the anticipated human dose.

The main embryo-foetal development study (Study No. VGFT-TX-06002, GLP) was conducted by administering doses of 0, 3, 15, or 60 mg/kg/administration of VEGF Trap to mated female New Zealand white rabbits once daily 30-minute i.v. infusions on gestational days (GD) 6, 9, 12, 15, and 18. Justification of the dose levels used has been provided by the results of the two range-finding studies in rabbits (VGFT-TX-05007 & VGFT-TX-06001). The doses were selected to

determine levels of maternal toxicity, to establish a dose-response relationship and to establish a NOAEL.

At doses of ≥3 mg/kg there were dose-related increases in fetal resorptions, pregnancy disruptions and numerous foetal (external, visceral and skeletal) malformations observed. Animals treated at the high dose level (60 mg/kg) resulted in abortions and increased levels of skeletal malformations in F1 generation.

A maternal NOAEL is considered to be 3 mg/kg, whereas the developmental NOAEL could not be identified. A calculation of potential exposure ratios based upon the toxicokinetic findings from this study and in comparison to Cmax and AUC determined from humans treated with 2 mg/eye (Study No. VGFT-OD-0702-PK). Exposure was 2907-fold (Cmax) and 678-fold (AUC0.5-72h) higher in the monkey study after 3 mg/kg dosing, compared to the anticipated human dose.

Recommendation that VEGF Trap should not be used during pregnancy is appropriate from the findings of increased disruption to pregnancy and foetal malformations; this has been included in the SmPC in section 4.6. Additional warning to women of child bearing potential to use effective contraception during treatment is appropriate.

For the indication of aged-related macular degeneration (AMD) and target population, pre- and post-natal development studies are not required.

Juvenile Toxicity
VEGF Trap was administered IV at doses of 0, 0.5, 3, or 30 mg/kg/administration once weekly for 3 months in young, skeletally immature Cynomolgus monkeys, with reversibility of systemic findings evaluated after an additional 5 month recovery phase. Effects were seen in bone, kidney, ovaries, adrenal glands and systemic vascular proliferation. A NOAEL was not determined. Based on C_{max} and $AUC_{0\text{-}168h}$ for free VEGF Trap observed at the 0.5 mg/kg IV dose, the lowest dose at which finding were observed, the exposure was 503-fold and 134-fold higher, respectively, than the systemic exposure observed in humans after an IVT dose of 2 mg/eye.

Toxicokinetic data

Local Tolerance

The local tolerance of the intended clinical formulation IVT was studied in the context of the pivotal 8-month study in monkeys after IVT administration. This formulation was well tolerated in the animals, and inflammation was mild and transient. The local tolerance of other formulations was studied in New Zealand White rabbits by other routes of administration at 24.4, 25 and 100 mg/mL (intravenous, intramuscular and subcutaneous routes). The findings resulted in decrease or absence of food intake associated with a minimal body weight loss or reduced body weight gain in animals receiving the 100 mg/mL solution by all of the routes of administration studied.

Other toxicity studies

The VEGF Trap formulation did not induce haemolysis and did not cause the formation of flocculants or precipitates in either serum or plasma. VEGF Trap was evaluated for possible binding to a panel of 33 human tissues. No specific staining was observed with any of the representative human tissues at concentrations of 5 or 25 µg/ml.

Immunogenicity
In preclinical IVT studies, very few animals were positive in the anti-drug antibody (ADA) assay and only 1 animal generated a response that appeared to impact PK. Animals with ADA responses that did not affect plasma drug levels did not exhibit these ocular findings. It is noted that immunogenicity in monkeys is not predictive of immunogenicity in humans, although the very low immunogenicity observed in monkeys was also observed in humans. Following extended intravitreal administration of VEGF Trap in clinical trials, positivity rates in the ADA assay were similar in patients regardless of treatment (VEGF Trap or ranibizumab). It is therefore agreed that, based on the available data, there is no indication that IVT administration of VEGF Trap in patients would elicit a serious immune response.

In some pregnant female rabbits, a total of five IV administrations resulted in the presence of anti-VEGF Trap antibodies associated with decreased levels of free VEGF Trap concentrations. In no case was toxicity in rabbits or monkeys associated with the presence of an anti-VEGF Trap antibody response.

No studies were conducted for dependence or with metabolites.

2.3.5. Ecotoxicity/environmental risk assessment

Aflibercept is exempted from an environmental risk assessment, because it is a protein and therefore unlikely to result in a significant environmental risk.

2.3.6. Discussion on non-clinical aspects

The nonclinical studies were designed to evaluate the pharmacology, pharmacokinetics, and toxicology of VEGF Trap in support of clinical intravitreal (IVT) treatment of VEGF Trap. Studies were conducted in vitro (PD) and in mice, rats, rabbit and monkeys, and their scope is considered to be extensive and adequate.

In order to provide proof of concept and mode of action, the binding of VEGF Trap and effect of phosphorylation of VEGFR-2 have been characterised in *in vitro* and *in vivo* studies.

The assumption that identical or near identical protein sequences are predictive of very similar, if not identical, binding affinities of monkey and human VEGF-A/PlGF has been supported by additional data provided by the Applicant in their responses to the CHMP questions.

The pharmacology studies were acceptable, and the Applicant has shown that the binding of VEGF Trap is selective, even within the VEGF family of ligands. It is agreed that binding of VEGF Trap to 'non-target' protein ligands is unlikely.

Regarding the safety pharmacology, VEGF Trap had no effect on respiratory function or thrombus formation, and no effects on the central nervous system were detected in toxicological studies, even when VEGF Trap was administered at high doses systemically for several months. Concerning the cardiovascular system, the effect of VEGF Trap on blood pressure was assessed after single subcutaneous injections of 2, 5 and 25 mg/kg in telemetered C57BL/6 mice (VGFT-MX-08018) and from 0.05 to 25 mg/kg in telemetered Wistar-Kyoto rats (VGFD-MX-08015). Administration of VEGF Trap resulted in a statistically significant increase in both systolic and diastolic blood pressure dose dependent and lasting several days. In the opposite, single or repeated subcutaneous or intravenous injection of VEGF Trap in Cynomolgus monkey do not change blood pressure levels. It was concluded that the lack of an effect of VEGF Trap on blood pressure is most probably due to the effects of chemical/physical restraint on the cardiovascular system of the Cynomolgus monkeys and the limited sensitivity of indirect blood pressure measurement systems as compared to direct, e.g. radiotelemetry techniques which have been used in rodents.

Data from formal pharmacodynamic drug-drug interaction studies of VEGF Trap with ophthalmic anaesthetic agents, antimicrobial agents and mydriatics is not available. This was considered acceptable, as topical ocular medications do not reach the posterior segment and drug-drug interactions with VEGF Trap within this ocular compartment are therefore unlikely. In addition, the clinical experience included prior administration of topical mydriatic agents and concomitant topical administration of anaesthetics and disinfectant antimicrobials with intravitreal injection of VEGF Trap Eye, which were well-tolerated.

Concerning the pharmacokinetic aspects, SC bioavailability was good in mice (94%) and monkeys (85%) and moderate in rats (33%). Following IVT administration to monkeys, VEGF Trap systemic absorption appears to be relatively high. Tissue distribution following IV administration of [^{125}I]-VEGF Trap to rats supported the assertion that distribution was limited primarily to the circulation. The highest concentration of tissue radioactivity was localized in the liver, followed by other highly perfused tissues. No studies were conducted on metabolism. Renal excretion of VEGF Trap is insignificant.

Regarding the toxicological aspects, the only treatment related post mortem findings observed in the chronic study by intravitreal administration to monkeys were epithelial erosions and/or ulcerations with chronic active inflammation of the nasal turbinates. The SmPC section 4.6 incorporates a warning about women of childbearing potential, following the findings in the rabbit reproductive studies.

The fact that it was possible to reach only 6-times the clinical exposure levels in the monkey intravitreal studies was discussed in CHMP scientific advice and considered acceptable due to the limitations in the formulation of the product, increasing volume or frequency of administration.

No significant pharmacodynamic differences are expected between monkeys and humans because the VEGF molecules are identical in humans and monkeys.

Regarding the antibody formation to VEGF Trap, in preclinical IVT studies, very few animals were positive in the ADA assay and only 1 animal generated a response that appeared to impact PK. Animals with ADA responses that did not affect plasma drug levels did not exhibit these ocular findings. It is noted that immunogenicity in monkeys is not predictive of immunogenicity in humans, although the very low immunogenicity observed in monkeys was also observed in humans. Following extended intravitreal administration of VEGF Trap in clinical trials, positivity rates in the ADA assay were similar in patients regardless of treatment (VEGF Trap or ranibizumab). The CHMP concluded that, based on the available data, there is no indication that IVT administration of VEGF Trap in patients would elicit a serious immune response.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, VEGF Trap had no effect on respiratory function or thrombus formation, and no effects on the central nervous system or cardiac function were detected in toxicological studies, even when VEGF Trap was administered at high doses systemically for several months. However, repeated systemic administration of VEGF Trap did impair the rate and/or extent of healing of both incisional and excisional wounds in rabbits, in a dose related manner, at all doses tested (0.3, 3 and 30 mg/kg/administration). Impairment of wound healing is also a class effect of VEGF inhibitors.

A pregnancy warning is included in Section 4.6 of the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

A GCP inspection was carried out at two investigator sites, one in Germany (14-17 November 2011) and in Hungary (28 November-2 December 2011), in relation to the conduct of trial protocol n. 311523. The final integrated inspection report was issued on 6 February 2012. According to the GCP final integrated inspection report, the outcome of this inspection is satisfactory. The inspected investigator sites appeared to be GCP compliant and it was nothing identified to suggest that the data collected at the sites are unreliable.

The Inspection report do not suggest that the deficiencies/findings observed during the course of inspections may impact on the results of the study and according to the recommendation for use of the inspected data, the inspected data of clinical trial 311 523 (VIEW 2) are of an acceptable quality to be used for the evaluation by the assessors in connection with the marketing authorisation application for Eylea.

- Tabular overview of clinical studies

Summary of clinical studies in age-related macular degeneration (AMD)

Phase	Study	Description	Route/Dose	Frequency	Subjects/Status
I	PDY6656	Phase I, single centre study to assess cardiovascular PD and PK	**IV**; 1, 2, 4 mg/kg, placebo	Single dose	48 healthy volunteers **Completed**
	PDY6655	Phase I, single-centre study to compare cardiovascular PD and PK	**IV & SC**; 2 mg/kg	Single dose	40 healthy volunteers **Completed**
	VGFT-OD-0305	Phase I, exploratory study of the safety, tolerability and biological activity	**IV**; 0.3, 1, 3, 5, 7, 10 mg/kg, placebo	Repeat dose (4 doses q2w)	26 AMD patients **Completed**
	VGFT-OD-0306	Phase I, safety and tolerability study (open label extension of VGFT-OD-0305)	**IV**; 0.3, 1, 3 mg/kg, placebo	Repeat dose (q2w)	7 AMD patients **Completed**
	VGFT-OD-0502 Part A, B, C (CLEAR-IT 1)	Phase I, exploratory study of the safety tolerability and biological effect	**IVT**; 0.05, 0.15, 0.50, 1, 2, 4 mg	Single and repeat dose (in Part C two doses q8w, with optional monthly dosing for 1 year extension period)	49 AMD patients **Completed**
	VGFT-OD-0603 (CLEAR-IT 1b)	Phase I study to assess the safety and tolerability of VEGF Trap in the ITV-1 and ITV-2 formulations	**IVT**; 4 mg	Repeat dose (3 doses q4w)	20 AMD patients **Completed**
II	VGFT-OD-0508 (CLEAR-IT 2)	Phase II study of the safety, tolerability and biological effect	**IVT**; 0.5, 2, 4 mg	Repeat dose (0.5/2 mg q4w, 0.5/2/4 mg q12w, prn dosing from Week 12 to Week 52)	157 AMD patients **Completed**
	VGFT-OD-0702	Phase I/II long-term safety extension study, with PK sub-study. Open to patients previously enrolled in VGFT-OD-0502, -508, and -0603.	**IVT**; 2 mg	Repeat dose (q8w for 39 months)	120 AMD patients **Completed**
III	VGFT-OD-0605 (VIEW 1)	Phase III, active controlled study of efficacy, safety, and tolerability	**IVT**; 0.5, 2 mg	Repeat dose (Year 1: 0.5/2 mg q4w or 2 mg q8w; Year 2 q4w-q12w)	1038 AMD patients **Completed**
	311523 (VIEW 2)	Phase III, active controlled study of efficacy, safety, and tolerability	**IVT**; 0.5, 2 mg	Repeat dose (Year 1: 0.5/2 mg q4w or 2 mg q8w; Year 2 q4w-q12w)	1025 AMD patients **Completed**
	VGFT-OD-0910	Phase III open label, long-term, safety extension of VIEW 1	**IVT**; 2 mg	Repeat dose 2 mg capped PRN (at least q12w)	323 AMD patients (target 960) **Ongoing**

In addition, one PK study and three efficacy and safety phase III studies using IVT route were not related to the claimed indication (DME : VGFT-OD-0307 and VGFT-OD-0706-DAVINCI / CRVO : VGFT-OD-0319-COPERNICUS and 14130-GALILEO)

2.4.2. Pharmacokinetics

Absorption, Distribution, Elimination

PKs of VEGF Trap could be considered well characterized based on the investigations performed by systemic (mainly IV but also SC) route as well as by IVT (intra-vitreal) routes. These investigations consisted in six Phase I, two Phase II and one Phase III studies. Studies by systemic route were performed in healthy volunteers and patients. Studies by IVT route were conducted in patients.

Analytical techniques. The analytical techniques used through the PK development programme were described and validated. The earlier colorimetric versions of the ELISA techniques used for the determination of free and bound VEGF Trap levels from clinical studies involving systemic

administration of VEGF Trap were modified to luminescence based ELISAs which were used to analyze systemic levels of free and bound VEGF Trap in AMD clinical studies involving IVT administration of VEGF Trap. The analytical techniques used in the IV and IVT were not formally cross-validated. Therefore, the inter-study comparisons should be regarded cautiously. Adequate methods were used for pharmacokinetic and statistical data analysis.

Analysis of different formulations and processes. During the development of VEGF Trap, to improve stability, the drug substance was manufactured using three different processes (IVT P1, P2 and P3) and two formulations of the drug product for IVT administration of VEGF Trap were developed. Subsequently, the different formulations were evaluated with respect to pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity, in order to demonstrate comparability between the various process and IVT formulations. Considering that VEGF Trap is intended for local administration, the contribution of the systemic exposure in the assessment of the comparability of the different process (active substance) and formulations (drug product) is limited. Reassuringly, the final formulation and process were used for the preparation of the lots tested in the pivotal phase III studies (VIEW1 and VIEW2). As a consequence, the comparability of early process (active substance) and formulations (drug product) was not of concern. The pharmacodynamic and clinical investigations (see relevant parts) revealed no difference between products issued from different process and formulations.

Systemic route. The investigation by systemic route confirmed that VEGF Trap PK behaviour is consistent with that generally observed with large proteins. The VEGF Trap Vd following IV administration is close to plasma volume. At plasma level, VEGF-trap binds to endogenous free VEGF with high affinity to form an inert complex. Due to the saturation of this binding to endogenous VEGF, Free VEGF-trap exhibits a non-linear PK. Data suggests that free VEGF Trap is cleared by relatively rapid, specific and saturable high-affinity binding to VEGF as well as via slower, non-saturable clearance mechanisms. These latter mechanisms are expected to be proteolytic catabolism processes, which affect both free and bound VEGF Trap. The terminal elimination half-life ($t_{1/2}$) of free VEGF Trap was approximately 1.9 days following an IV dose of 0.3 mg/kg, and increased with increasing doses, reaching $t_{1/2}$ estimates of 5 to 6 days after IV administration of doses of 2 to 4 mg/kg VEGF Trap. The systemic exposure to the free VEGF-Trap observed at the clinical MTD i.e. 1mg administered by the IV route is approximately 10 to 20 (µg/mL) for Cmax and 50-80 (day*µg/mL). The systemic exposure observed with the first toxic dose i.e. 2 mg by IV route is 45 ± 36 (µg/mL) for Cmax and 180 ±33 (day*µg/mL) approximately.

Intravitreal route. Since VEGF Trap is administered directly into the target site of pharmacological activity, the eye, the bioavailability within the target organ is assumed to be 100%. Following IVT administration of VEGF Trap, a fraction of the administered dose is expected to bind to free endogenous VEGF in the eye to form a stable, high affinity VEGF:VEGF-Trap complex. Excess free VEGF Trap is available to bind newly synthesized VEGF in the eye or endogenously available VEGF in the central compartment. VEGF Trap is slowly absorbed from the eye into the systemic circulation after IVT administration and is predominantly observed in the systemic circulation as an inactive, stable complex with VEGF. In most patients plasma levels of free VEGF-Trap were below the LLOQ. Some measurable plasma levels (up to 0.473 µg/mL) were actually observed in patients. Based on Cmax comparison the highest level observed in the clinical Phase III study VIEW2 is 200-250 times lower than that observed with the MTD (1 mg, IV route) and approximately 100 times lower than that observed with the first toxic dose (2 mg by IV route). Therefore, the level of this exposure is deemed to be too low to lead to significant systemic (non-ocular) side effects. However this needs to be confirmed by safety clinical data.

Dose proportionality and time dependencies

Data obtained with the IV route showed that Free VEGF Trap exhibits non-linear PK consistent with saturable, target-mediated drug disposition. However, this is not relevant for the IVT route.

Data from phase III study (VIEW 2) revealed no unexpected accumulation at plasma level of VEGF Trap after repeated IVT administration (up to 1 year).

Special populations

Age, sex, body mass index (BMI), renal function, hepatic function and ethnicity are not expected to influence the plasma concentrations of free and bound VEGF Trap.

Pharmacokinetic interaction studies

Considering the administration pathway (IVT) and the very low systemic level of VEGF trap, neither *in vitro* nor *in vivo* interactions studies have been performed.

Since the systemic exposure to both free and bound VEGF Trap following intravitreal injection is low, the potential for drug interactions is low. In addition, systemic or topically applied drugs usually reach the vitreous cavity in very low concentrations, so interactions within the eye are also unlikely. However, some clinicians may manage AMD with concomitant therapies, such as verteporfin with PDT or use off label intraocular steroids. The potential for such treatments to influence the intraocular effect of VEGF Trap has not been appropriately addressed in the documentation provided, therefore clarifying statements have been inserted in the section 4.5 of the SmPC.

Pharmacokinetics using human biomaterials

None.

2.4.3. Pharmacodynamics

No specific studies dedicated to human pharmacodynamics have been performed for aflibercept. The pharmacodynamics data derive from in vitro, animal and human efficacy studies.

VEGF Trap (aflibercept) exerts inhibitory effects on angiogenesis and stabilizing actions on vessel permeability through the blocking of VEGF-A.

IVT injection permits direct targeting of the areas of abnormal neovascularization in the retina, and this route of administration is considered as the more relevant for retinal pathologies. In addition, the IVT route of administration also permits to decrease systemic toxicity linked to anti-VEGF activity.

Mechanism of action

Aflibercept belongs to the pharmacological class of VEGF inhibitors. The role of VEGF in promoting pathological neovascularization and/or abnormal and excessive vascular permeability in several diseases affecting the eye is now well established.

Primary and Secondary pharmacology

Primary pharmacology:
The clinical pharmacology programme consists of phase I and II studies that were designed to explore, in patients suffering from wet AMD, the bioeffects of VEGF Trap on the retina. Central

retinal/lesion thickness and CNV lesion size were assessed using Optical coherence tomography (OCT), and fluorescein angiography (FA) as pharmacodynamic endpoints, concomitantly with evolution of visual acuity (according to the ETDRS Chart). Retinal thickness is an accepted PD marker for neovascular AMD, but it is known to have a variable correlation with visual acuity.

IV injections were firstly explored in studies VGTF OD 305-306-307; a favourable trend of improvements in central retinal thickness and visual acuity at the VEGF Trap dose levels of 1.0 and 3.0 mg/kg was identified in Study VGTF OD 305.

Single and repeated IVT injections of escalating doses of VEGF Trap (0.05 to 4 mg) were further explored in VGTF OD 502, VGTF OD 508 and VGFT-OD-0603 studies, and were shown to reduce both retinal thickness and the size of the CNV lesion, in a dose-proportional fashion.

In these studies central retinal thickness was not always well correlated with visual acuity. An important lack of correlation was specifically observed in study VGTF OD 508 at the end of the fixed dosing phase and at Week 16 for the 4 mg dose administered every 12 weeks. This is thought to be probably related to the high variability observed in the results for prolonged interval duration beyond 8-week.

Bioeffects were also explored as secondary or additional outcome measures using FA and OCT measurements, in pivotal studies VIEW 1 and VIEW 2. After treatment initiation, retinal thickness decreased > 100 microns and reduced mean CNV lesion size were observed, consistent with the results seen in phase I and II studies.

Secondary pharmacology:

Systemic VEGF inhibition is known to cause dose-related increases in systolic and diastolic blood pressure. Although this was observed in subjects following IV and SC dosing with VEGF Trap at all dose levels between 0.3 and 3 mg/kg, no such changes were detected when VEGF Trap was administered intravitreally. This is likely to be due to the low amounts of free VEGF Trap reaching the systemic circulation (approximately 50 ng/mL). The Michaelis-Menten constant (K_m – the concentration of free VEGF Trap corresponding to the half-maximal binding capacity) value was calculated to be 2.91 µg/mL for free VEGF Trap binding to human VEGF.

The Applicant considered that the increase risk of blood pressure in the target population is unlikely. However, 15-20% of aflibercept passes to the systemic circulation and during the pivotal studies, hypertension have been reported in 14.6% patients. The CHMP considered that systemic side effect on blood pressure should not be ruled out and need to be further monitored even if the product is locally administered. This is identified as an important potential risk in the RMP.

2.4.4. Discussion on clinical pharmacology

Intravitreal VEGF Trap has been shown to reduce both retinal thickness and CNV lesion size in patients with neovascular AMD in a dose-proportional fashion. Furthermore, the data suggest that dosing every 12 weeks may be insufficient to maintain these improvements, and that more frequent dosing may be required. Visual acuity results from the Phase II studies were more variable, and as a whole the data suggest no additional benefit of the 4 mg dose over a 2 mg dose. There is minimal systemic exposure to VEGF Trap following intravitreal administration, making systemic pharmacodynamic effects or interactions unlikely.

2.4.5. Conclusions on clinical pharmacology

The CHMP considers the following measures necessary to address the issues related to pharmacology:

The CHMP considered that, systemic side effect on blood pressure should not be ruled out and need to be further monitored even if the product is locally administered. This measure is included in the RMP.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Dose-response studies in patients suffering from neovascular age-related macular degeneration:

In the early development programme, IV injections of VEGF Trap (0.3, 1 and 3 mg/kg) were compared to placebo in Study VGTF OD 305 over an 8-week duration. These preliminary results suggested that the highest dose of 3.0 mg/kg provided the best improvements in visual acuity, retinal thickness and macular volume.

A direct head-to-head comparison of the two formulations of VEGF Trap (ITV-1, the first formulation and ITV-2, the new formulation used in pivotal clinical studies VIEW 1 and VIEW 2) at the same dose was provided in Study VGFT-OD-0603. The results suggested that the ITV-2 formulation (used in pivotal studies VIEW 1 and 2) would at least provide a similar effect level regarding reduction in retinal thickness or improvements in visual acuity than that observed for the VEGF Trap administered in the ITV-1 formulation (used for dose escalating studies VGFT-OD-502 and 508).

IVT route: Study VGFT-OD-0502 was the first study initiated for a clinical development of intravitreally (IVT) administered VEGF Trap in patients suffering from wet AMD. This was an open label, single escalating doses study (0.05 mg, 0.15 mg, 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg). The small sample size/group only allowed preliminary conclusions suggesting that better effects on visual acuity or on morphologic endpoints may be provided by higher doses (2, 4 mg) and that they may last until week 43.

IVT route: Study VGFT-OD-0508 was a Phase-2 dose-ranging study which comprised a 12-week fixed-dosing phase followed by a flexible-dosing phase up to week 52, designed to assess the efficacy in AMD patients of repeated IVT administration of VEGF Trap at different doses and dosing intervals.

In this study subjects who received monthly injections at the start of the study (in the 0.5 and 2 mg groups) generally had better outcomes at Week 52, supporting the proposal to administer 3 initial monthly injections of VEGF Trap prior to dosing every 8 weeks. An initial monthly dosing up to 12 weeks was therefore chosen for the design of pivotal VIEW 1 and VIEW 2 studies.

2.5.2. Main study(ies)

Studies VIEW 1 and VIEW 2: in patients suffering from neovascular age-related macular degeneration:

This application is supported by two pivotal trials of two-year duration and of identical design.

- Study VIEW 1 (Study VEGF-OD-605) was conducted from 02 August 2007 to 14 September 2010 (year 1 cut-off) at 154 sites in United States [US] and Canada.

- Study VIEW 2 (Study A36355) was conducted at 186 sites in Asia/Pacific, Europe, and South/Latin America (first patient 11 April 2008 – 16 September 2010 (year 1 cut-off).

The Study period covered from start of enrolment and last subject's last visit was from 31 Jul 2007 to 22 Jul 2011 (VIEW 1) and to 11 Aug 2011 (VIEW 2).

Both studies were multi-center, randomized, double-masked, active controlled (ranibizumab) non-inferiority designed, phase III studies.

The design of both studies is described below.

Methods

Study Participants

The inclusion/exclusion criteria were identical in the two Phase III studies.

Subjects eligible were Men and women ≥ 50 years of age had to have subfoveal CNV secondary to AMD. "Subfoveal" CNV was defined as the presence of subfoveal neovascularization, including juxtafoveal lesions that affect the fovea, documented through confirmed FA by an independent reading

center. Only one eye was designated as the study eye. For subjects who met eligibility criteria in both eyes, the eye with the worse visual acuity (VA) was selected as the study eye.

The Main exclusion Criteria included prior ocular or systemic treatment or surgery for neovascular AMD; total lesion size >12 disc areas (30.5 mm2, including blood, scars and neovascularization); any history of ocular retinal disease history other than AMD, Any intraocular or periocular surgery within 3 months of Day 1 on the study eye, prior trabeculectomy; Previous therapeutic radiation in the region of the study eye; history of corneal transplant or corneal dystrophy in the study eye; significant media opacities, including cataract; history or clinical evidence of diabetic retinopathy, diabetic macular edema or any retinal vascular disease other than AMD in either eye. Exclusions criteria were conventional and as expected for this class of product. Contra-indications for Lucentis as reported in the EU SPC were listed as exclusion criteria.

Treatments

Year-1: Fixed dose/fixed schedule regimens for the first year of the studies were chosen fairly in accordance to the results from phase I and II dose-finding studies. Subjects were randomised to one of the following regimen: 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses and compared to RQ4=ranibizumab 0.5 mg every 4 weeks. This posology corresponds to the original dosing regimen used in the pivotal studies Marina and Anchor for ranibizumab registration either in Europe or in the US. An aseptic procedure for IVT injection was recommended by the Applicant. Nevertheless, a degree of freedom was permitted to take into account the different practices that vary considerably among practitioners or countries.

Year-2: During the second year of the study, the subjects received IVT injection of study drug or comparator at intervals determined by the specific criteria for redosing at the same dose level as originally assigned. They were evaluated every 4 weeks. Injections could be given as frequently as every 4 weeks, but no less frequently than every 12 weeks (modified quarterly dosing schedule), according to the following re-dosing criteria, which were assessed by the investigator:

i) Increase in CRT ≥100 µm compared to the lowest previous value (OCT), or ii) A loss of ≥5 ETDRS letters from the best previous letter score in conjunction with recurrent fluid as indicated by OCT, or iii) New or persistent fluid as indicated by OCT, or iv)New onset classic neovascularization, or v) New or persistent leak on fluorescence angiography (FA), or vi) New macular hemorrhage, or vii) 12 weeks have elapsed since the previous injection.

Subjects and study personnel remained double masked with regard to the dose level but no sham injections were given in the second year for prolonged interval dosing.

Objectives

Objectives were identical across both phase-3 pivotal studies: VIEW 1 and VIEW 2

Primary Objective
The primary objective was to assess the efficacy of IVT administered VEGF Trap-Eye compared to ranibizumab, in a non-inferiority design, in preventing moderate vision loss (defined as a loss < 15 letters/3 lines of vision on the ETDRS chart at a distance of 4 meters) in subjects with all subtypes of neovascular AMD.

Secondary Objective(s)
The secondary objectives were:

1/to assess the safety and tolerability of repeated IVT administration of VEGF Trap-Eye in subjects with all sub-types of neovascular AMD for periods up to 2 years.

2/to assess the effect of repeated IVT administration of VEGF Trap-Eye on Vision-Related Quality of Life (QoL) in subjects with all subtypes of neovascular AMD, as assessed using the NEI VFQ-25 questionnaire.

Outcomes/endpoints

Primary and secondary efficacy criteria were identical in the two Phase-3 studies: VIEW 1 and VIEW 2

Three categories of end points were analysed: Visual, Quality of life and Morphologic

Primary Endpoint

• The primary efficacy variable was the proportion of subjects who maintained vision (ie, loss of fewer than 15 letters on the ETDRS chart compared to Baseline) at Week 52 as assessed in the PPS.

Visual function of the study eye was assessed using the ETDRS chart at 4 meters and a subject was classified as maintaining vision if the subject has lost fewer than 15 letters in ETDRS letter score compared to baseline.

Secondary Endpoints

• Mean change from baseline in BCVA as measured by ETDRS letter score at Week 52.

• Proportion of subjects who gain at least 15 letters of vision from baseline at Week 52 on the ETDRS chart.

Quality of life

• Mean change in total NEI VFQ-25 score from baseline to Week 52.

(Vision-related Quality Of Life is assessed using the National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25).

Morphologic end points

• Mean change in CNV area from baseline to Week 52 as assessed by fluorescein angiography (FA).

Sample size

Assuming that 90% of subjects treated with 0.5 mg ranibizumab and any VEGF Trap-Eye dose would maintain vision (defined as losing fewer than 15 letters of visual acuity) at Week 52 compared to Baseline, a one-sided alpha level of 0.025, a power of 90% and defining **the non-**

inferiority margin to be 10%, the sample size estimation resulted in 191 (VIEW1) / 190 (VIEW 2) subjects per treatment group. Assuming a dropout rate of 30% (a high dropout rate was assumed because of the availability of competing, approved therapies), enrolment of 300 subjects per group was determined to provide adequate power to achieve the study's objectives under the stated assumptions.

Randomisation

Subjects were randomly assigned in a 1:1:1:1 ratio to one of the four treatment groups.

Blinding (masking)

Studies were presented as double masked clinical trial, however a strict blinding was not readily feasible:all VEGF Trap-Eye study medication and sham treatments were packaged in identical packaging with identical labeling, except for the kit number. The comparator was supplied in commercial packaging with over labeling for local languages where necessary.

Study drug injection was to be performed by an unmasked physician. The unmasked physician did not play any role in the study beyond the receipt, tracking, preparation, destruction and administration of study drug, as well as assessing safety at 30-60 minutes post IVT injection.

A separate masked physician was assigned to 1) assess AEs and 2) supervise the masked assessment of efficacy. Visual acuity assessments were always masked to treatment assignment.

Statistical methods

The predefined non-inferiority margin was set at 10% and was justified by reference to the results of pivotal studies for ranibizumab. A conditional sequence of statistical evaluation of non-inferiority was used to control multiplicity (1) 2Q4; 2) 0.5Q4; 3) 2Q8 versus RQ4). A predefined test for superiority on secondary criteria was planned using again a conditional sequence of hypothesis to control multiplicity.

The following methods were used for sensitivity analyses: analysis repeated in FAS using LOCF and in FAS and PPS using Observed case analysis, Worst observed carried forward, Discontinued counted as non-responder, or Treatment failure counted as non-responder.

Results

Patient disposition (all randomized subjects):

Study VIEW 1	RQ4	2Q4	0.5Q4	2Q8	VEGF Trap-Eye Combined	Total
Screened*						2063
Randomized	306 (100)	304 (100)	304 (100)	303 (100)	911 (100)	1217 (100)
Treated[2] (safety set)	304 (99.3)	304 (100)	304 (100)	303 (100)	911 (100)	1215 (99.8)
FAS[1]	304 (99.3)	304 (100)	301 (99.0)	301 (99.3)	906	1210
PPS	269 (87.9)	285 (93.8)	270 (88.8)	265 (87.5)	820	1089
Completed Year 1	284 (92.8)	293 (96.4)	277 (91.1)	276 (91.1)	846 (92.9)	1130 (92.9)
Premature discontinuation within first year						
Total	22 (7.2)	11 (3.6)	27 (8.9)	27 (8.9)	65 (7.1)	87 (7.1)
Subject withdrawal	10 (3.3)	5 (1.6)	7 (2.3)	8 (2.6)	20 (2.2)	30 (2.5)
Adverse event	4 (1.3)	3 (1.0)	5 (1.6)	4 (1.3)	12 (1.3)	16 (1.3)
Death[a]	3 (1.0)	1 (0.3)	2 (0.7)	7 (2.3)	10 (1.1)	13 (1.1)
Lost to follow-up	1 (0.3)	2 (0.7)	4 (1.3)	4 (1.3)	10 (1.1)	11 (0.9)
Protocol deviation*	3 (1.0)	0	3 (1.0)	1 (0.3)	4 (0.4)	7 (0.6)
Treatment failure	0	0	2 (0.7)	2 (0.7)	4 (0.4)	4 (0.3)
Other	1 (0.3)	0	4 (1.3)	1 (0.3)	5 (0.5)	6 (0.5)
Completed study medication	279 91.2)	288 (94.7)	274 (90.1)	273 (90.1)	911 (100)	1114 (91.51)
Prematurely discontinued study medication	27 (8.8)	16 (5.3)	30 (9.9)	30 (9.9)	76 (8.3)	103 (8.5)
Withdrawal by Subject	12 (3.9)	8 (2.6)	9 (3.0)	9 (3.0)	_	38 (3.1)
Adverse event	4 (1.3)	3 (1.0)	5 (1.6)	6 (2.0)	14 (1.5)	18 (1.5)
Lost to follow-up	2 (0.7)	4 (1.3)	4 (1.3)	5 (1.7)	13 (1.4)	15 (1.2)
Death	3 (1.0)	1 (0.3)	2 (0.7)	6 (2.0)	9 (1.0)	12 (1.0)
Protocol deviation*	3 (1.0)	0 (0.0)	3 (1.0)	1 (0.3)	4 (0.4)	7 (0.6)
Treatment failure	1 (0.3)	0 (0.0)	2 (0.7)	2 (0.7)	4 (0.4)	5 (0.4)
Other	2 (0.7)	0 (0.0)	5 (1.6)	1 (0.3)	6 (0.7)	8 (0.7)

[a] An additional four deaths were reported during the study but not captured in the database as a reason for premature discontinuation.
[1] FAS :
RQ4 : 2 subjects excluded from FAS : 144-003 (no leakage) & 227-003 (no baseline value) and 1 subject maintained in FAS 195-001 (treated accidentally by 0.5Q4).
0.5Q4 : 3 subject excluded from FAS : 180-002 (not treated by investigator decision) and 227-006 and 171-005 (no post-baseline value). [2] SAS : 195-001 included.
2Q8 : 2 subject excluded from FAS : 152-003 and 171-004 (no post-baseline value).
*Protocol deviation i.e violation and Screened i.e. enrolled
RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses.

Recruitment

Study VIEW 1 was conducted from 2 August 2007 up to 14 September 2010.

Conduct of the study

Up to the database lock for the year-1 data, there were 3 amendments to the original study protocol in response to regulatory agency feedback.

Baseline data

Baseline demographics were balanced across the treatment groups except for sex that shown a more accentuated difference in the 2Q4 group (63.8% vs 58.8% for the total population); most patients were white, non Hispanic or Latino, there were more female (58.8 %) than male and the mean age was 78.1 years (range :from 49 to 99 years). The overall mean BMI was 27.40 kg/m2, the mean weight was 75.39 kg, and the mean height was 165.60 cm.

Disease characteristics were well balanced among groups. Mean BVCA score was 55.1 letters; retinal thickness was 266.6 microns; area of CNV 6.6 mm^2, lesion size 6.95 mm^2 and NEI VQF 25 total score 70.7. Lesion subtypes were also balanced across study groups as reported above with a predominance of occult lesions in all groups.

Numbers analysed

Disposition/Reason	Ranibizumab 0.5Q4 (N = 306)	VEGF Trap-Eye 2Q4 (N = 304)	0.5Q4 (N = 304)	2Q8 (N = 303)
Subjects Randomized	306 (100%)	304 (100%)	304 (100%)	303 (100%)
Safety Analysis Set [a]	304 (99.3%)	304 (100%)	304 (100%)	303 (100%)
Full Analysis Set [b]	304 (99.3%)	304 (100%)	301 (99.0%)	301 (99.3%)
Per Protocol Set [c]	269 (87.9%)	285 (93.8%)	270 (88.8%)	265 (87.5%)

Outcomes and estimation

One-year efficacy results

VIEW 1 Study: One-year efficacy results

All three hypothesis analyses met non-inferiority criteria in favour of the three VEGF Trap-Eye regimens showing upper limits of the 95.1% CI of the difference between each of the three tested dosing regimens and the comparator ≤ 3.1%.

VIEW 1 -Primary efficacy analysis-Proportion of Subjects who Maintained Vision at Week 52

Closed test procedure	Treatment Group[a]	Subjects who Maintained Vision at Wk 52; n (%)	Difference % (95.1% CI)[b]	Statistical Interpretation (LOCF, PPS)
First hypothesis	2Q4 (n=285) RQ4 (n=269)	271 (95.1) 254 (94.4)	**-0.7 (-4.4, 3.1)**	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis
Second hypothesis	0.5Q4 (n=270) RQ4 (n=269)	259 (95.9) 254 (94.4)	**-1.5 (-5.1, 2.1)**	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis
Third hypothesis	2Q8 (n=265) RQ4 (n=269)	252 (95.1) 254 (94.4)	**-0.7 (-4.5, 3.1)**	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued as confirmatory analysis

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4=2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
b: Difference is ranibizumab minus VEGF Trap-Eye. Negative values favour VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

The different methods used as sensitivity analyses provided consistent results with the primary analysis (upper limits ≤ 4.6% and 5.3% for the analyses in the PPS and in the FAS, respectively) although these values were less stringent than observed in the primary analysis.

All values stayed well below the pre-specified CI upper bound of 10% but also well below the 7% margin discussed with CHMP.

Secondary criteria related to visual acuity:

Since non-inferiority to ranibizumab was met for all VEGF Trap-Eye regimens, a test for superiority was authorized for secondary criteria in the FAS. The comparison of the change from baseline to Week 52 in BCVA letter score in the 2Q4 and RQ4 groups demonstrated a superior improvement from baseline for the 2Q4 regimen (mean =10.9 letters; LS mean =10.97 letters versus mean =8.1 letters; LS mean 7.82 letters; LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054).

The second conditional sequence of superiority was interrupted at the second authorized comparison (2Q4 versus RQ4 with respect to the proportion of patients' group gaining ≥ 15 letters) as analyses were no longer statistically significant.

The 0.5Q4 and 2Q8 regimens did not show difference with the RQ4 regimen (6.9 letters; p=0.479 and 7.9 letters; p=0.818, respectively).

VIEW 1 - Change from Baseline to Week 52 in ETDRS Letter Score (LOCF) (FAS)

Study View 1	RQ4	2Q4	0.5Q4	2Q8
n	304	304	301	301
Week 52 (change from baseline)				
Mean (SD)	8.1 (15.25)	**10.9 (13.77)**	6.9 (13.41)	7.9 (15.00)
Point estimate for the contrast[a]		**3.15**	-0.80	0.26
95.1% CI for difference		(0.92, 5.37)	(-3.03, 1.43)	(-1.97, 2.49)
p-value vs RQ4[b]		**0.0054**	0.4793	0.8179

a: Difference is VEGF Trap-Eye minus ranibizumab using least-square means (LSMeans). Positive values are in favour of VEGF Trap-Eye. CI=confidence interval calculated using normal approximation.
b: ANCOVA, main effect model using LSMeans.

The best result for the change in letter score from baseline, was observed with the VEGF Trap-Eye dosed monthly (2Q4 regimen) compared to ranibizumab dosed monthly. The 2Q4 regimen showed a superior improvement from baseline in the ETDRS letter score compared to the RQ4 group (a mean of 10.9 letters; LS mean 10.97 letters versus a mean of 8.1 letters; LS mean 7.82 letters; LS mean difference = 3.15; 95.1% CI = 0.92 to 5.37; p = 0.0054).

The analysis of the proportion of subjects gaining ≥ 15 letters from baseline showed numeric trend in favour of the 2Q4 regimen while the 2Q8 and RQ4 regimens were of similar pattern. All sensitivity analyses showed a similar picture.

VIEW 1 – Analysis of the Proportion of subjects gaining ≥ 15 letters from baseline to Week 52 (LOCF/FAS)

Treatment Group	RQ4	2Q4	0.5Q4	2Q8
n	304	304	301	301
Subjects [n (%)] gaining ≥ 15 letters	94 (30.9)	**114 (37.5)**	75 (24.9)	92 (30.6)
Difference [a] (95.1% CI) p-value vs. RQ4 [2]	—	**6.6** (-1, 14.1) 0.1042	-6.0 (-13.2, 1.2) 0.1037	-0.4 (-7.7, 7.0) 0.93

a: Mantel-Haenszel estimate for difference ranibizumab minus VEGF Trap-Eye (positive values are in favour of VEGF Trap- Eye); CI=Confidence interval calculated using normal approximation; [2] Pearson's Chi-Square Test (2-Sided)

Other secondary criteria (Visual Quality of life, CNV area)
By Week 52 in the FAS (LOCF), the improvement in visual quality of life (as assessed by the NEI VFQ-25 total score) was numerically larger in the 2Q4 group (mean change 6.7 points) than in the RQ4 group (mean change 4.9 points). Sensitivity analyses showed a similar trend of results.

By week 52, mean CNV area decreased in all treatment groups while better numeric results were observed again with the 2Q4 regimen (-4.6 mm^2) than with the RQ4 regimen (-4.2 mm^2).

Additional Efficacy Endpoints

By week 12, the greatest improvement in BCVA was seen in the 2Q4 group (a mean of 8.7 letters), while the RQ4 group reached a mean of 7.3 letters.

The proportion of subjects who gained ≥ 0, 10, or 30 letters was numerically higher and the proportion of subjects who lost ≥ 15 or 30 letters was lower in the 2Q4 group than in the RQ4, 0.5Q4, and 2Q8 groups.

The proportions of subjects with severe vision loss ≥ 30 letters were higher in the RQ4 and 2Q8 groups (3%) than in the 0.5Q4 and 2Q4 groups (1%).

VIEW 2 Study: One-year efficacy results

Similarly to VIEW 1 Study, primary criteria analysis met the non-inferiority for all VEGF Trap-eye regimens (all upper limits of the 95% CIs <2.6%). All the nine sensitivity analyses provided consistent results with the primary analysis showing upper limits of the 95% CI of the difference between all VEGF Trap-eye regimens and the comparator ≤ 3.65% and ≤ 8.5% for the analyses in the PPS and in the FAS, respectively.

VIEW 2 -Primary efficacy analysis-Proportion of Subjects who Maintained Vision at Week 52

Closed test procedure	**Treatment Group**[a]	**Subjects who Maintained Vision at Wk 52; n (%)**	**Difference % (95% CI)**[b]	**Statistical Interpretation** (LOCF, PPS)
First hypothesis	2Q4 (n=274) RQ4 (n=269)	262 (95.62) 254 (94.42)	-1.20 (-4.86, 2.46)	Non-inferiority of 2Q4 to RQ4 is statistically proven, test procedure can be continued
Second hypothesis	0.5Q4 (n=268) RQ4 (n=269)	258 (96.27) 254 (94.42)	-1.84 (-5.40, 1.71)	Non-inferiority of 0.5Q4 to RQ4 is statistically proven, test procedure can be continued
Third hypothesis	2Q8 (n=270) RQ4 (n=269)	258 (95.56) 254 (94.42)	-1.13 (-4.81, 2.55)	Non-inferiority of 2Q8 to RQ4 is statistically proven, test procedure can be continued

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses
b: Difference is ranibizumab minus VEGF Trap-Eye. Negative values favour VEGF Trap-Eye. CI=Confidence interval calculated using normal approximation.

The 0.5Q4 regimen showed the best numeric result according to proportion of patients who maintained vision (96.27%) in the primary analysis. It should be noted that the proportion of patients who maintained vision in the ranibizumab group was similar to that seen in VIEW 1 Study (94.4%) which is in good accordance with the results of Marina Study (by 12 months, 94.6%).

Numeric results for either the 2Q4 or the 2Q8 regimens were very similar (95.62 and 95.56).

In contrast to VIEW 1 results, no superiority was found in VIEW 2 Study for the first step of comparison, which failed to show a statistically significant treatment difference between the 2Q4 and the RQ4 groups (p=0.076).

Secondary criteria related to visual acuity:

VIEW 2 - Change from Baseline to Week 52 in ETDRS Letter Score (LOCF) (FAS)

Study View 2	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
Week 52 (change from baseline)				
n	291	309	296	306
Mean (SD)	9.4 (13.5)	7.6 (12.6)	**9.7 (14.1)**	8.9 (14.4)
Point estimate for the contrast[a]		-1.95	-0.06	-0.90
95% CI for difference		(-4.10; 0.20)	(-2.24; 2.12)	(-3.06; 1.26)
p-value vs RQ4[b]		0.076	0.956	0.413

a: Difference is VEGF Trap-Eye minus ranibizumab using LSMeans. CI=confidence interval calculated using normal approximation.
b: ANCOVA, main effect model using LSMeans.

Only one comparison was numerically in favour of VEGF Trap-Eye (0.5Q4 group: 9.7 letters versus RQ4 group: 9.4 letters); differences between the three VEGF Trap-Eye groups and the ranibizumab group were numerically slightly in favour of the ranibizumab group with a maximum difference observed in the comparison of 2Q4 vs RQ4 (-1.95 letters) but the 95% CIs for the treatment differences remained consistently included zero and all p-values were > 0.05. The PPS followed the

same trends. Overall, the results of the sensitivity analyses were consistent with the main analysis, except for the following comparisons which were in favour of ranibizumab were point estimate for the difference were (OV: 2Q4 – RQ4::-2.38 (95% CI: -4.61 to -0.14); p=0.0373 and WOCF: 2Q4 – RQ4: point estimate for the difference: -2.60 (95% CI: -4.78 to -0.42); p=0.0193).

VIEW 2 – Analysis of the Proportion of subjects gaining ≥ 15 letters from baseline to Week 52 (LOCF/FAS)

Treatment Group[a]	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
N	291	309	296	306
Subjects [n (%)] gaining 15 letters	99 (34.02)	91 (29.45)	**103 (34.80)**	96 (31.37)
Difference (95% CI)[b]	—	-4.57 (-12.02, 2.88)	**0.78** (-6.91, 8.46)	-2.65 (-10.18, 4.88)

a: RQ4=ranibizumab 0.5 mg every 4 weeks; 0.5Q4=0.5 mg VEGF Trap-Eye every 4 weeks; 2Q4= 2 mg VEGF Trap-Eye every 4 weeks; 2Q8=2 mg VEGF Trap-Eye every 8 weeks after three initial monthly doses

b: Mantel-Haenszel estimate for difference ranibizumab minus VEGF Trap-Eye; CI=Confidence interval calculated using normal approximation

At Week 52, 103 subjects (34.8%) in the 0.5Q4 group and 96 subjects (31.4%) in the 2Q8 group had gained ≥ 15 letters. In the PPS, results were consistent.

Other secondary endpoints: Overall, at Week 52, in the FAS/LOCF, the results for the NEI VFQ-25 total score numerically favoured ranibizumab and when using the LSmeans from the ANCOVA main effect model, a significant difference was observed in favour of the RQ4 regimen over the 2Q4 regimen, p=0.010). All baseline differences nonetheless, remained in the range (≥4-6) of clinical relevance as identified from Marina and Anchor published studies while ranibizumab provided the higher difference. The results of the sensitivity analyses supported these results.

The results for the change from Baseline to Week 52 in CNV Area numerically slightly favoured all VEGF Trap-eye regimens. The lowest mean decrease was observed in the RQ4 group (-4.16 mm2), the highest in the 2Q4 group (-5.95 mm2) followed by the 2Q8 (-5.16 mm2). When using the LSmeans from the ANCOVA main effect model, a significant difference was observed in favour of the 2Q4 regimen over the RQ4 regimen, p=0.004). The results of the sensitivity analyses (observed cases and WOCF) were consistent with the results obtained in the main analysis applying the LOCF method.

In conclusion, the primary criteria analysis met the non-inferiority for all VEGF Trap-eye regimens and all secondary endpoint analyses supported the comparability of the efficacy of ranibizumab with the three VEGF Trap-Eye treatment regimens. Sensitivity analyses in the FAS and in the PPS of primary and secondary endpoints also supported the main analyses.

Nevertheless, results in favour of the 2Q4 regimen observed in Study VIEW 1 were not replicated in Study VIEW 2. In contrast to the findings observed in VIEW 1 Study, no superiority was evidenced from the first conditional ordered test hypothesis. In addition, while results based on visual acuity measurements seemed to rather favour the 0.5Q4 regimen, results based on morphologic endpoints seemed in favour of the 2Q4 regimen and, to a lesser extent, in favour of the 2Q8 regimen showing the greatest mean decrease in classic CNV area.

Therefore, there were no clear tendencies of results in VIEW 2 Study to favour one dosing regimen of VEGF Trap-Eye over the others, apart the number of injections that is reduced in the 2Q8 regimen.

Ancillary analyses

Since all three VEGF Trap-Eye groups were shown to be non-inferior to ranibizumab on the primary endpoint, additional comparisons were authorized with respect to secondary endpoints, and these have been described above.

Summary of main studies

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

Summary of Efficacy for trial VIEW1

Title: **A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration**			
Study identifier	14393 (Bayer study ID); VGFT-OD-0605 (Regeneron study ID)		
Design	Multicenter, double-masked, randomized (1:1:1:1), active-controlled, parallel-group study		
	Duration of main phase:		52 weeks for primary efficacy
	Duration of Run-in phase:		21 day maximum screening period
	Duration of Extension phase:		1 year after week 52
Hypothesis	Non-inferiority (primary); superiority (secondary)		
Treatments groups	RQ4		During 1st year: Ranibizumab 0.5 mg every 4 weeks, 306 subjects randomized
	2Q4		During 1st year: VEGF Trap-Eye 2.0 mg every 4 weeks, 304 subjects randomized
	0.5Q4		During 1st year: VEGF Trap-Eye 0.5 mg every 4 weeks, 304 subjects randomized
	2Q8		During 1st year: VEGF Trap-Eye 2.0 mg every 8 weeks, 303 subjects randomized
Endpoints and definitions	Primary endpoint	Maintenance of vision	Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline
	Secondary endpoints	ETDRS change	Change from baseline in best corrected visual acuity (BCVA) as measured by ETDRS letter score at Week 52
		15-letter gain	Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52
		NEI VFQ-25 change	Change in total NEI VFQ-25 score from baseline to Week 52
		CNV change	Change in choroidal neovascularization (CNV) area from baseline to Week 52
Database lock	10 Nov. 2010 (for 1-year database)		

Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Per protocol set (PPS): All subjects in the full analysis set (see below) who received at least nine injections of study drug or sham and attended at least nine scheduled visits during the first year, except for those who were excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results. The PPS also included subjects without major protocol deviations who discontinued due to treatment failure at any time during the first 52 weeks of the study. Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment. At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject (PPS)	269	285	270	265
	Maintenance of vision [no. (%) of subjects]	254 (94.4%)	271 (95.1%)	259 (95.9%)	252 (95.1%)
Effect estimate per comparison	Primary endpoint **maintenance of vision**	Comparison groups	**2Q4 vs RQ4**		
		RQ4 minus 2Q4	-0.7		
		95.1% CI	-4.4, 3.1		
		P-value	*not applicable*		
		Comparison groups	**0.5Q4 vs RQ4**		
		RQ4 minus 0.5Q4	-1.5		
		95.1% CI	-5.1, 2.1		
		P-value	*not applicable*		
		Comparison groups	**2Q8 vs RQ4**		
		RQ4 minus 2Q8	-0.7		
		95.1% CI	-4.5, 3.1		
		P-value	*not applicable*		
Notes	Confidence intervals (CIs) were calculated using a normal approximation.				
Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	ETDRS change mean	8.1	10.9	6.9	7.9
	Standard deviation	15.25	13.77	13.41	15.00

Effect estimate per comparison	Secondary endpoint **ETDRS change**	Comparison groups	**2Q4 vs RQ4**		
		2Q4 minus RQ4 [LS mean]	3.15		
		95.1% CI	0.92, 5.37		
		P-value (ANCOVA)	0.0054		
		Comparison groups	**0.5Q4 vs RQ4**		
		0.5Q4 minus RQ4 [LS mean]	-0.8		
		95.1% CI	-3.03, 1.43		
		P-value (ANCOVA)	0.4793		
		Comparison groups	**2Q8 vs RQ4**		
		2Q8 minus RQ4 [LS mean]	0.26		
		95.1% CI	-1.97, 2.49		
		P-value (ANCOVA)	0.8179		
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.				
Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried-forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	15-letter gain [no. (%) of subjects]	94 (30.9%)	114 (37.5%)	75 (24.9%)	92 (30.6%)
Effect estimate per comparison	Secondary endpoint **15-letter gain**	Comparison groups	**2Q4 vs RQ4**		
		2Q4 minus RQ4 [LS mean]	6.6		
		95.1% CI	-1, 14.1		
		P-value (Chi-square)	0.1042		
		Comparison groups	**0.5Q4 vs RQ4**		
		0.5Q4 minus RQ4	-6		
		95.1% CI	-13.2, 1.2		
		P-value (Chi-square)	0.1037		
		Comparison groups	**2Q8 vs RQ4**		
		2Q8 minus RQ4	-0.4		
		95.1% CI	-7.7, 7		
		P-value (Chi-square)	0.93		
Notes	Confidence intervals (CIs) were calculated using a normal approximation.				

Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	NEI VFQ-25 change [mean]	4.9	6.7	4.5	5.1
	Standard deviation	14.01	13.50	11.87	14.74

Effect estimate per comparison	Secondary endpoint **NEI VFQ-25 change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	1.28
		95.1% CI	-0.73, 3.28
		P-value (ANCOVA)	0.2090
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	-0.67
		95.1% CI	-2.69, 1.35
		P-value (ANCOVA)	0.5128
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.60
		95.1% CI	-2.61, 1.42
		P-value (ANCOVA)	0.5579
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.		

Analysis description	**Analysis of secondary endpoints**				
Analysis population and time point description	**Full analysis set**				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	304	304	301	301
	CNV change [mean]	-4.2	-4.6	-3.5	-3.4
	Standard deviation	5.59	5.47	5.27	6.02

Effect estimate per comparison	Secondary endpoint **CNV change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-0.33
		95.1% CI	-1.04, 0.38
		P-value (ANCOVA)	0.3575
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	0.71
		95.1% CI	-0.01, 1.42
		P-value (ANCOVA)	0.0507
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	0.86
		95.1% CI	0.15, 1.58
		P-value (ANCOVA)	0.0173
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.		

Summary of Efficacy for trial VIEW2

Title: **A randomized, double masked, active controlled, phase 3 study of the efficacy, safety, and tolerability of repeated doses of intravitreal VEGF Trap-Eye in subjects with neovascular age-related macular degeneration (AMD)** **VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 2)**		
Study identifier	311523	
Design	Multicenter, double-masked, randomized (1:1:1:1), active-controlled, parallel-group study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	52 weeks for primary efficacy 21 day maximum screening period 1 year after week 52
Hypothesis	Non-inferiority (primary); superiority (secondary)	
Treatments groups	RQ4	During 1st year: Ranibizumab 0.5 mg every 4 weeks, 306 subjects randomized
	2Q4	During 1st year: VEGF Trap-Eye 2.0 mg every 4 weeks, 304 subjects randomized
	0.5Q4	During 1st year: VEGF Trap-Eye 0.5 mg every 4 weeks, 304 subjects randomized

	2Q8		During 1st year: VEGF Trap-Eye 2.0 mg every 8 weeks, 303 subjects randomized
Endpoints and definitions	Primary endpoint	Maintenance of vision	Proportion of subjects who maintained vision at Week 52, where a subject was classified as maintaining vision if the subject had lost fewer than 15 letters in the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score compared to baseline
	Secondary endpoints	ETDRS change	Change from baseline in best corrected visual acuity (BCVA) as measured by ETDRS letter score at Week 52
		15-letter gain	Proportion of subjects who gained at least 15 letters of vision from baseline to Week 52
		NEI VFQ-25 change	Change in total NEI VFQ-25 score from baseline to Week 52
		CNV change	Change in choroidal neovascularization (CNV) area from baseline to Week 52
Database lock	10 Nov. 2010 (for 1-year database)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Per protocol set (PPS): All subjects in the full analysis set (see below) who received at least nine injections of study drug or sham and attended at least nine scheduled visits during the first year, except for those who were excluded because of major protocol violations, where a major protocol violation is one that may affect the interpretation of study results. The PPS also included subjects without major protocol deviations who discontinued due to treatment failure at any time during the first 52 weeks of the study. Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment. At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject (PPS)	269	274	268	270
	Maintenance of vision [no. (%) of subjects]	254 (94.42%)	262 (95.62%)	258 (96.27%)	258 (95.56%)

Effect estimate per comparison	Primary endpoint **maintenance of vision**	Comparison groups	**2Q4 vs RQ4**
		RQ4 minus 2Q4	-1.20
		95% CI	-4.86; 2.46
		P-value	*not applicable*
		Comparison groups	**0.5Q4 vs RQ4**
		RQ4 minus 0.5Q4	-1.84
		95% CI	-5.40; 1.71
		P-value	*not applicable*
		Comparison groups	**2Q8 vs RQ4**
		RQ4 minus 2Q8	-1.13
		95% CI	-4.81; 2.55
		P-value	*not applicable*
Notes	Confidence intervals (CIs) were calculated using a normal approximation.		

Analysis description	**Analysis of secondary endpoints, pre-specified**			
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values			
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	ETDRS change mean	9.4	7.6	9.7	8.9
	Standard deviation	13.5	12.6	14.1	14.4

Effect estimate per comparison	Secondary endpoint **ETDRS change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-1.95
		95% CI	-4.10; 0.20
		P-value (ANCOVA)	0.076
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	-0.06
		95% CI	-2.24; 2.12
		P-value (ANCOVA)	0.956
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.90
		95% CI	-3.06; 1.26
		P-value (ANCOVA)	0.413

Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.

Analysis description	**Analysis of secondary endpoints, pre-specified**			
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried-forward (LOCF) principle for missing week 52 values			
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	15-letter gain [no. (%) of subjects]	99 (34.02%)	91 (29.45%)	103 (34.80%)	96 (31.37%)

Effect estimate per comparison	Secondary endpoint **15-letter gain**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-4.57
		95% CI	-12.02; 2.88
		P-value (Chi-square)	0.229

		Comparison groups		**0.5Q4 vs RQ4**	
		0.5Q4 minus RQ4		0.78	
		95% CI		-6.91; 8.46	
		P-value (Chi-square)		0.843	
		Comparison groups		**2Q8 vs RQ4**	
		2Q8 minus RQ4		-2.65	
		95% CI		-10.18; 4.88	
		P-value (Chi-square)		0.490	
Notes	Confidence intervals (CIs) were calculated using a normal approximation.				
Analysis description	**Analysis of secondary endpoints, pre-specified**				
Analysis population and time point description	Full analysis set (FAS): All randomized subjects who received any study drug and had a baseline and at least one post-baseline BCVA assessment At week 52 using last-observation-carried–forward (LOCF) principle for missing week 52 values				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	NEI VFQ-25 change [mean]	6.3	4.5	5.1	4.9
	Standard deviation	14.8	15.0	13.7	14.7
Effect estimate per comparison	Secondary endpoint **NEI VFQ-25 change**	Comparison groups		**2Q4 vs RQ4**	
		2Q4 minus RQ4 [LS mean]		-2.79	
		95% CI		-4.90; -0.68	
		P-value (ANCOVA)		0.010	
		Comparison groups		**0.5Q4 vs RQ4**	
		0.5Q4 minus RQ4 [LS mean]		-0.93	
		95% CI		-3.07; 1.20	
		P-value (ANCOVA)		0.392	
		Comparison groups		**2Q8 vs RQ4**	
		2Q8 minus RQ4 [LS mean]		-1.95	
		95% CI		-4.07; 0.17	
		P-value (ANCOVA)		0.072	
Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.				

Analysis description	**Analysis of secondary endpoints**				
Analysis population and time point description	**Full analysis set**				
Descriptive statistics and estimate variability	Treatment group	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
	Number of subject	291	309	296	306
	CNV change [mean]	-4.160	-5.950	-4.236	-5.160
	Standard deviation	5.900	6.116	6.129	5.866

Effect estimate per comparison	Secondary endpoint **CNV change**	Comparison groups	**2Q4 vs RQ4**
		2Q4 minus RQ4 [LS mean]	-1.180
		95% CI	-1.979; -0.382
		P-value (ANCOVA)	0.004
		Comparison groups	**0.5Q4 vs RQ4**
		0.5Q4 minus RQ4 [LS mean]	0.170
		95% CI	-0.632; 0.972
		P-value (ANCOVA)	0.678
		Comparison groups	**2Q8 vs RQ4**
		2Q8 minus RQ4 [LS mean]	-0.733
		95% CI	-1.534; 0.068
		P-value (ANCOVA)	0.073

Notes	Confidence intervals (CIs) were calculated using a normal approximation. Analysis of covariance (ANCOVA), main effect model. Difference is VEGF Trap-Eye minus Ranibizumab. The pairwise comparison is performed as contrast statement in the ANCOVA model with treatment group as fixed factor (all 4 treatment groups) and the baseline ETDRS letter score as covariate.

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

Due to similar design and inclusion criteria, data from VIEW 1 and VIEW 2 pivotal studies were pooled in accordance with the pre-defined analysis.

Statistical analyses of differences across studies or between treatment groups were not conducted in the integrated analysis data set.

One-year pooled efficacy results (VIEW 1+VIEW 2)

Data set analysed:

The PPS (used for primary efficacy endpoint) comprised 1089, 1081 or 2170 subjects in the VIEW 1, VIEW 2 studies and pooled population, respectively).

The FAS (used for the four main secondary analyses) comprised 1210, 1202 or 2412 subjects in the VIEW 1 and VIEW 2 and pooled population, respectively).

In both analysis sets, subjects were analyzed as randomized. A summary of the pooled results is provided below:

Primary efficacy analysis: Maintenance of vision at Week 52 – PPS Pooled Efficacy results

Integrated Analysis Treatment Group[a]	**RQ4**	**2Q4**	**0.5Q4**	**2Q8**
N	538	559	538	535
Subjects [n (%)] maintaining vision	508 (94.42)	533 (95.35)	**517 (96.10)**	510 (95.33)
Difference (95% CI)[b]	—	-0.9 (-3.5,1.7)	**-1.7 (-4.2 ,0.9)**	-0.9 (-3.5 ,1.7)

The results of the integrated analysis reflect the findings of the individual studies either for primary or secondary variables. The results of ancillary efficacy endpoints are supportive of the primary and secondary endpoints, showing comparable efficacy for all dosages of VEGF Trap-Eye with ranibizumab. Subgroup analyses showed that subjects who were younger, with poorer baseline vision and smaller lesions were more likely to maintain or gain vision. No important differences were seen between the ranibizumab and VEGF Trap-Eye 2Q8 groups in any subgroup. No geographical variations were observed in VIEW 2 (conducted in Europe, Asia, Australia and Latin America). In no particular group did the efficacy of VEGF Trap-Eye appear to be significantly worse than expected.

Data on certain subgroups are limited, due to the small number of patients: Black race subgroup, and history of hepatic impairment. However, this was not a significant concern. Neovascular AMD has a far higher prevalence in Caucasians than Black patients and there is no reason to suggest that efficacy would differ in the two groups. Systemic exposure to VEGF Trap-Eye following intravitreal injection is minimal, and the liver does not play an important role in the elimination of VEGF Trap, so hepatic impairment should not affect efficacy.

Two-year pooled efficacy results (VIEW 1+VIEW 2)

The applicant submitted results of Year 2 of the pivotal studies in which subjects underwent examinations every 4 weeks and were retreated with Eylea or ranibizumab according to a capped-PRN schedule. Injections could be given as frequently as every 4 weeks, but no less frequently than every 12 weeks. The retreatment criteria included an increase in CRT of ≥100 µm, a loss of ≥5 letters with recurrent fluid on OCT, new or persistent fluid, new onset classic CNV, new or persistent leak on FA, and new macular haemorrhage.

Subjects disposition and analysis sets for subjects entering in year 2

Of the 2457 randomized subjects, 2419 received at least 1 dose of randomized study medication in either VIEW 1 or VIEW 2. In both studies, 2235 (90.0%) of the subjects entered Year 2 (92.0% and 89.9%, in VIEW 1 and 2, respectively) and above 80% completed studies in all treatment groups.

Between randomisation and Week 96/100, the drop-out rate in VIEW 1 study was lower for subjects in the VEGF Trap-Eye 2Q4 arm and in VIEW 2 study, higher in the VEGF Trap-Eye 0.5Q4 arm.

During the 2-year study period, the overall discontinuation rate was 16.0% (394/2457 randomized subjects) and quite similar in both individual studies: 14.7% (179/1217) and 17.3% (215/1240) in VIEW 1 and 2, respectively.

The most frequent primary reasons for premature discontinuation were "withdrawal by subject" (4.9% for VIEW 1 and 6.3% VIEW 2) or "adverse event" (3.1% for VIEW 1 and 4.3% for VIEW 2) showing consistently higher proportions of subjects who discontinued from the study primarily due to adverse events in the VEGF Trap-Eye groups (4.2% - 6.8%) than in the ranibizumab group (1.3%).

In both studies, the treatment groups were well balanced with regard to group sizes, proportions of subjects continuing treatment in Year 2 and demographic baseline. Slight imbalances already present at randomization in VIEW 2 Study persist, in particular poorer baseline anatomical parameters, with greater larger total lesion and CNV areas.

The dosing subgroups were determined post-hoc.

No per-protocol population was defined for the analysis of the data of Year 2.

Efficacy results analysis

The number of injections given in Year 2 and the time between injections are shown in the table below.

When fixed dosing was changed to a capped-PRN schedule in Year 2, a similar mean number of injections (~4), with a similar mean interval duration between injections (~73 days), were observed for the 2Q4 and 2Q8 treatments; these appear also rather similar to ranibizumab (i.e. 4.7 injections and interval of 68 days). Therefore, a prolonged interval of around 10 weeks is observed for the majority of subjects in all treatment groups. This tends to confirm the trend observed in the dose–response study 508.

Integrated analysis: Number of injections in Year 2 (Year 2 completers)				
	R 0.5Q4	VTE		
	N=513	2Q4 N=529	0.5Q4 N=499	2Q8 N=511
Mean Number of Injections (SD) Median Min-max	4.7 (±2.2) 4.0 2-11	4.1 (±1.8) 3.0 2-11	4.6 (±2.2) 4.0 2-11	4.2 (±1.7) 4.0 2-11
Integrated analysis: Mean time between injections (Subjects entering in year 2)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
Mean Time between Injections, Days (SD) Median Min-max	67.9 (±20.3) 76.0 27-154	73.7 (±17.4) 82.7 28-125	68.2 (±19.8) 77.0 27-113	73.2 (±21.6) 77.3 28-311*
Integrated analysis: subjects receiving retreatment at least once in a 4-weeks interval in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	231 (41.5%)	166 (29%)	219 (40%)	201 (36%)
Integrated analysis: subjects receiving retreatment at intervals of 8 or 12-weeks in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	291 (52%)	373 (65%)	297 (54%)	326 (58%)
Integrated analysis: subjects receiving retreatment at intervals of 12-weeks in Year 2 (Year 2 completers)				
	0.5Q4 N=557	2Q4 N=571	0.5Q4 N=549	2Q8 N=558
N (%)	218 (39%)	285 (50%)	217 (39.5%)	245 (44%)

311* due to one subject: 440030046

Nevertheless, the VTE 2Q4 regimen shows the lower proportion of patients (29%) receiving retreatment at least once in a 4-weeks interval, and the higher (65%) receiving retreatment at intervals of 8 or 12-weeks in Year 2. This suggests that the 2Q4 regimen administered during the first year of treatment may yield at the end of Year 2 slightly better results than the 2Q8 regimen (36% and 58%) or the competitor ranibizumab (41.5% and 52%).

A similar picture is observed from the Integrated Analysis for post hoc dosing subgroups

(Year 2 study medication completers) as reported in the table below:

Subgroup	Ranibizumab	VEGF Trap-Eye		Total
	0.5Q4 (N = 513) n (%)	2Q4 (N = 529) n (%)	0.5Q4 (N = 499) n (%)	2Q8 (N = 511) n (%)	(N = 2052) n (%)
≤ 3 injections in Year 2	219 (42.7)	288 (54.4)	222 (44.5)	247 (48.3)	976 (47.6)
4-6 injections in Year 2	201 (39.2)	189 (35.7)	195 (39.1)	212 (41.5)	797 (38.8)
≥ 7 injections in Year 2	93 (18.1)	52 (9.8)	82 (16.4)	52 (10.2)	279 (13.6)
Re-treatment always at intervals of 8 or 12 weeks in Year 2 [a]	291 (56.7)	373 (70.5)	297 (59.5)	326 (63.8)	1286 (62.7)

[a] Includes subjects with minimum time between PRN injections of 12 weeks or longer.

Efficacy endpoint (primary endpoint for Year 1):

At week 96 results show a relevant maintenance of therapeutic effect in all treatment groups, although a slight drop off in the proportion of subjects who maintained vision is observed compared to week 52. The proportion of subjects maintaining vision was ≥90% in all treatment groups and comparable between studies. The 95% CIs for the difference in proportions between the VEGF Trap-Eye group and the RQ4 group were consistently well below the boundary of 10%. Results show the same trend when the LOCF method was repeated with the observed values only.

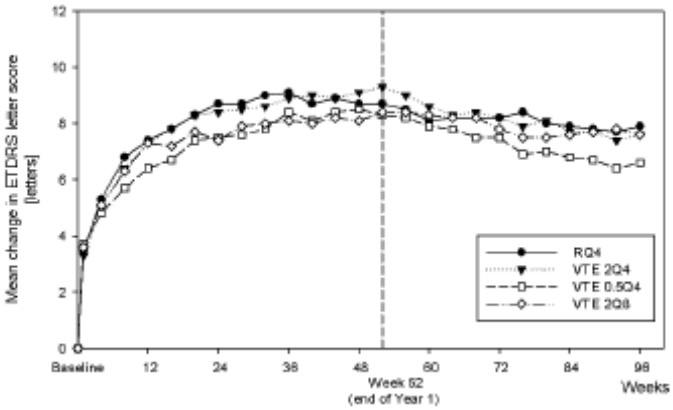
Integrated analysis: Proportion of subjects who maintained vision at Week 52 and 96 (LOCF-FAS)

Treatment Group	RQ4	2Q4	0.5Q4	2Q8
N	595	613	597	607
Subjects [n (%)] maintaining vision (W 52)	561 (94.3)	581 (94.78)	568 (95.14)	576 (94.89)
Difference (95% CI)	—	-0.5 (-3.1, 2.1)	-0.9 (-3.4, 1.7)	-0.6 (-3.2, 2.0)
Subjects [n (%)] maintaining vision (W 96)	545 (91.6)	565 (92.2)	546 (91.5)	561 (92.4)
Difference (95% CI)	—	-0.6 (-3.6, 2.5)	0.2 (-3.0, 3.3)	-0.8 (-3.8, 2.3)
p-value (Breslow-Day test		0.08	0.79	0.67

The largest differences between the two studies at week 96 were the treatment difference of the pairwise comparisons between RQ4 and 2Q4, which was numerically in favour of 2Q4 in VIEW 1 (FAS, LOCF, -3.3 [-7.7; 1.2]), but reversed in VIEW 2 (FAS, LOCF, 2.2 [-2.0; 6.5]). Therefore, the observed variability between VIEW 1 and 2 studies results at Year 1 still persists in Year 2.

Other efficacy endpoints (secondary endpoints for Year 1):

Integrated Analysis: Mean change from Baseline to Week 96 in ETDRS letter score (LOCF, FAS)



Decreases (by 1-2 letters) in mean ETDRS letter score occurred in the second year with a similar pattern in all treatment groups.

W52 mean changes in ETDRS letter score:
RQ4:8.7 (14.4); 2Q4: 9.3 (13.3); 0.5Q4: 8.3 (13.8); 2Q8: 8.4 (14.7)
W96 mean changes in ETDRS letter score:
RQ4:7.9 (16.1); 2Q4: 7.6 (15.5); 0.5Q4: 6.6 (15.3); 2Q8: 7.6 (16.2)
The mean change in visual acuity at W96 remained also similar between groups (increase of 7.6 or 7.9 letters for VTE 2mg and ranibizumab, respectively).

Integrated Analysis: Proportion of subjects who gained at least 15 letters of vision from Baseline to Week 52 and 96 (LOCF, FAS)

Treatment Group[a]	RQ4	2Q4	0.5Q4	2Q8
Integrated Analysis (N)	595	613	597	607
From Baseline to Week 52				
Subjects [n (%)] gaining at least 15 letters	193 (32.44)	205 (33.44)	178 (29.82)	188 (30.97)
Difference (95% CI)[b]	—	1.0 (-4.3, 6.3)	-2.7 (-7.9, 2.6)	-1.5 (-6.8, 3.8)
From Baseline to Week 96				
Subjects [n (%)] gaining at least 15 letters	188 (31.6)	191 (31.2)	168 (28.1)	203 (33.4)
Difference (95% CI)[b]	—	-0.4 (-5.6, 4.8)	-3.5 (-8.7, 1.7)	1.8 (-3.5, 7.1)
p-value (Breslow-Day test		0.04	0.12	0.85

Similarly, a slight decrease occurred in the second year in the proportion of patients who gained ≥ 15 letters.

Change in total NEI VFQ-25 score (0-100) from Baseline to Week 52 and 96 (LOCF, FAS):

During year 2, improvements remained in the same range for each individual studies (4-6 points) or integrated analysis (4-5 points) with nearly identical improvements in all groups.

Change in CNV area (mm^2) from Baseline to Week 52 and 96 (LOCF, FAS):

At the end of year 2, the decreases in mean CNV area observed at Year 1 (W52) were maintained in all groups but no additional improvement was reported.

Therefore, after a second year of treatment, as observed for the primary criteria, all secondary endpoints also show a similar effect for Eylea and ranibizumab, when criteria based re-dosing were applied.

Additional efficacy endpoints results at Week 96

1/Proportion of subjects with vision gain or loss:

According to the results of the integrated analysis at week 96, the proportion of subjects with *vision gains* ≥ 0 letters or ≥ 10 letters or ≥ 30 letters were maintained to approximately 75-77% or 42-51% or 5.2-7.3%. The higher proportion of subjects was observed in the 2Q8 group for gain ≥ 30 letters (7.3%) or ≥ 15 letters (33.4%) (LOCF, FAS).

The proportion of subjects with *vision loss* ≥ 5 letters or ≥ 30 letters were approximately 16-18% or 2.3-3.3% with the highest proportion in the 2Q8 group (3.3%) (LOCF, FAS).

2/Change from Baseline in central retinal thickness (FAS, LOCF):

At Week 52, the results of the pairwise comparisons were all numerically in favour of the VEGF Trap-Eye treatment. By Week 96, the absolute reduction in CRT from Baseline was also most pronounced in the 2Q8 groups (-121 ± 116 µm) compared to the RQ4 group (114 ± 110 µm) in VIEW 1 study and in the 2Q4 and 2Q8 groups (-146 ± 128 µm and 145 ± 118 µm, respectively) compared to the RQ4 group was -121 ± 130 µm. A similar trend was observed in VIEW 2.

Therefore the one year reductions were not completely maintained in all groups over the whole 2-year treatment period. The *largest increase in CRT from Week 52 to Week 96/100* was seen under RQ4 treatment (18.3 ± 76.0 µm) while the mean increase in the combined VEGF Trap-Eye 2 mg groups (2Q4 and 2Q8) was 8.2 ± 63.0 µm.

3/Proportion of subjects without intraretinal cystic edema and/or subretinal fluid (dry retina) on OCT:

In both studies, the proportions of subjects with retinal fluid increased between W52 and W96/100 by about 15-20% or 15% in VIEW 1 and VIEW 2 studies, respectively, showing that, overall, the proportion of subjects with dry retinal fluid status declined from Week 52 to Week 96. At Week 96 retinal fluid remains present in approximately 40-50% of the subjects.

Integrated Analysis: Proportion of subjects with dry retinal fluid status on OCT (W52 and 96 – OV FAS)

At W52: 2Q4, 72%; 2Q8, 68% vs RQ4, 62%

At W96/100: 2Q4, 54%; 2Q8, 50% vs RQ4, 45%

These results may suggest that the disease is progressing more during year 2. Since no fixed regimen was included as comparator arm for treatments through year 2, the link with the change in the schedule of administration (capped-PRN regimen applied in the second year) is not demonstrated.

4/Proportion of subjects receiving re-treatment within the first 12 weeks of the second year (*at Weeks 52 or 56 - subjects entering Year 2)* of the study

The proportion of subjects receiving their first re-treatment injections prior to the mandatory dose after 12 weeks in Year 2 was approximately 10% higher in the RQ4 and 0.5Q4 groups than in the VEGF Trap-Eye 2 mg groups (approximately 40% versus approximately 30%), reinforcing the choice of the 2 mg VTE dosing.

Post hoc dosing subgroup analysis (observed values; Year 2 study completers)

Additional analyses were performed on post-hoc determined dosing subgroups in the group of Year 2 study medication completers with regard to BCVA (changes in ETDRS letter score) and OCT data (changes in CRT and retinal fluid status): i) Subjects with ≤ 3 injections in Year 2; ii) Subjects with 4-6 injections in Year 2; iii) Subjects with ≥ 7 injections in Year 2; iv) Subjects with re-treatment always in the interval of 8 or 12 weeks in Year 2 (this subgroups was considered only in the integrated analysis).

In these dosing subgroups, as observed in the whole population, increases in BCVA from baseline to W96/100 are still observed ranging from 5.5 (2Q4; ≥7 injections) to 10.3 letters (RQ4; 4-6 injections). Although no meaningful differences between groups were identified, numeric BCVA values suggest that subjects receiving ≤ 3 injections or re-treatment every 8 or 12 weeks, in Year 2, may undergo meaningful improvements in vision with less re-treatments than the other dosing groups. The percentage of patients receiving re-treatment every 8 or 12 weeks in Year 2 was > 58%.

Vision gain and loss show a similar picture with more than 70% of patients gaining ≥ 0 letters, approximately 35-60% of patients gaining ≥ 10 letters and 25-40% of patients gaining ≥ 15 letters. Overall, visual gains seem to numerically favoured the 2Q8 regimen (year 1), except for the dosing group 4-6 injections that show numeric gains favouring RQ4 (83%, 60%, 38 %) vs the VEGF trap eye regimens (<76%; 51%; 35%). Less than 9% of subjects underwent vision gain ≥ 30 letters (except for 2Q8, ≥7 injections that reached 15%). Less than 4% of subjects underwent vision loss ≥ 30 letters in all groups.

Changes in CRT: in all treatment groups, subjects who received ≤ 3 injections in Year 2 and subjects who received re-treatment every 8 or 12 weeks in Year 2 had the largest decreases in mean CRT during the study (130-151 microns and 124-147microns, respectively). In both dosing subgroups, the highest decreases in CRT were observed in the 2Q8 treatment groups.

Changes in retinal fluid status: new or persistent fluid as indicated by OCT was the most frequent reason for retreatment (i.e. in approximately 50% of cases). Similarly to what observed for CRT changes, the subgroups of subjects who received ≤ 3 injections in Year 2 and those who received re-treatment always every 8 or 12 weeks in Year 2 also included the highest proportions of subjects without detectable retinal fluid.

Results on dosing subgroups are not surprising since these results may also reflect a more aggressive progression of the disease for these patients who need more frequent re-treatments, independently of the effect of the drug. Therefore, these results should be interpreted with caution.

Clinical studies in special populations

No special populations were formally studied. In the two pivotal studies and the integrated analysis, a number of subgroups were considered for efficacy and safety analyses based on demographics (eg, age, sex, race ..) and baseline disease characteristics (eg, visual acuity, lesion type, lesion size).

The only prognostic factor identified for maintaining vision was "age".

Differences between subgroups were not subjected to formal statistical testing. Overall, no clear tendency was identified among these analyses and no consistent pattern of clinically relevant differences compared to the analyses of the overall population was observed.

Supportive study(ies)

No formal supportive studies were performed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design and the conduct of clinical studies submitted for Eylea were in line with the requirement of the scientific advices which were sought by the Applicant and the historical development of previous AMD treatments.

A non-inferiority design with respect to prevention of moderate vision loss (loss < 15 letters of vision on ETDRS chart compared to baseline) versus monthly IVT injection of ranibizumab (Lucentis) was considered appropriate. The primary criterion selected allowed comparing identical study endpoints for VEGF Trap-Eye and ranibizumab since a similar criterion was used in both pivotal trials conducted with ranibizumab for European and US registrations (i.e. Marina and Anchor studies). In addition, this permitted also to compare data to the two other drugs registered in Europe (Macugen and Visudyne) to treat wet AMD. This criterion was also, according to the two pivotal placebo-controlled trials BPD OCR 002 A and B, the historical endpoint which was used for the first medication registered in Europe and the US to treat neovascular AMD (i.e. PDT with verteporfin (Visudyne).

However, this historical endpoint is based on a large vision loss (<15 letters) which doesn't anymore reflect the current expectations of practitioners. From a practitioners' view, a more stringent primary outcome would be the mean change from baseline in visual acuity at 1 year, with a suitable non-inferiority margin chosen and justified by the applicant.

Therefore, importantly, the Applicant integrated as first secondary criteria, the "Mean change from baseline in BCVA" as measured by ETDRS letter score, at Week 52. This criterion was used also as a basis for the first conditional ordered superiority analyses. The second important secondary criteria was the "proportion of subjects who gained ≥ 15 letters of vision" from baseline, at Week 52. Otherwise, "gain ≥ 30 letters or degradation ≥ 30 letters" in visual acuity were additional endpoints of importance.

The complete panel of examinations related to visual acuity or to the morphologic aspect of CNV lesions explored correlates well with the current clinical practice and the procedures used were relevant. The ETDRS procedure is a reliable method for BCVA measurement since it is well standardized (e.g. room lightening, optotype distance (4 meters)…) and was used in previous studies. In addition to the gold standard -fluorescein angiography examination- optical coherence tomography (OCT) is a standard practice of eye specialists to follow the progression of wet AMD and adapt the management of patients' care in case of retinal diseases.

The investigated population and the control treatment in the pivotal studies VIEW 1 and VIEW 2 were appropriate as well as the large number of patients exposed and the endpoints explored.

All deficiencies concerning the protocol or the choice or the management of statistics as identified during the early review of the one year results have been clarified and resolved by the Applicant. In the pivotal studies, the statistical methods used an acceptable ordered sequence of conditional tests. While the use of a non-inferiority design was appropriate, the chosen non-inferiority margin of 10% could have been considered too wide: however the final results were reassuring in showing observed non inferiority margins well below 10%.

The baseline characteristics of subjects in VIEW 2 suggested a slightly more severe disease at the beginning of the study than those in VIEW 1, which was accepted since the severity of disease in participants of both studies falls within the expected clinical scope of untreated AMD. This disparity between VIEW 1 and 2 was attributed by the MAA partly to differences in the methodology used for interpretation of the OCT images by the central reading centres in the assessment of CRT on OCT (readers used in VIEW 1 study a center-point thickness measurement while in VIEW 2, they used a central subfield approach). These appeared to have affected the results, but a reanalysis of VIEW 1 data by the applicant using the methodology utilised in VIEW 2 showed that the results were comparable when analysed with the same methodology.

Both studies demonstrated non-inferiority of Eylea 2Q8 versus ranibizumab, and it was accepted that differences in the baseline characteristics of subjects in the two studies did not preclude an integrated analysis of the results.

Efficacy data and additional analyses

One year results:
One year results from both pivotal studies supported a clinically relevant non-inferiority of all dosages and regimens of VEGF Trap-Eye over ranibizumab, administered monthly. The results were convincing in terms of preservation of visual acuity. Both trials were successful with regard to the primary endpoint using a non-inferiority margin of either 10% or 7%. 95-96% of subjects who received 2 mg VEGF Trap-Eye every 8 weeks maintained vision at Week 52, as compared to 94% of subjects who received ranibizumab.

The applicant provided a short discussion about the variability of results for the primary endpoint across the two pivotal studies, particularly when the most conservative analysis was considered (with all drop-outs counted as non-responders using the full analysis set) and has clarified that inconsistencies observed in the results of the sensitivity analysis in the FAS, counting drop-outs as non-responders, especially in the comparison of the 2Q4 dosing regimen of VEGF and ranibizumab,

are explained by the different drop-out rates of the 2Q4 VEGF Trap-Eye groups and ranibizumab groups between the studies. This was accepted by CHMP.

The clinically relevant result for the primary endpoint was backed up by secondary endpoints, which showed that subjects receiving VEGF Trap-Eye gained an average of 8-9 letters at Week 52, with 30-31% of subjects gaining at least 3 lines of vision. These results were comparable to those for subjects in the active comparator group who received ranibizumab. Visual function questionnaire test scores improved by 5 points for those on VEGF Trap-Eye, and CNV area was reduced by 3-5 mm^2, again comparable to ranibizumab.

The results of ancillary efficacy endpoints were generally supportive of the primary and secondary endpoints, showing comparable efficacy for VEGF Trap-Eye 2Q8, 2Q4 and 0.5Q4 with ranibizumab. The distribution of subjects with varying levels of vision loss and gain were comparable across groups and studies. In the VIEW studies a slightly greater proportion of Eylea 2Q8 subjects experienced a loss of vision from baseline in the first year than those treated with ranibizumab. However, this difference seemed to disappear in Year 2, when PRN treatment was initiated. The difference seen in Year 1 was small (around 4 percentage points at most), and was not considered relevant.

Two year results:
Since neovascular AMD is a chronic disease which requires ongoing treatment, the Year 1 results needed to be confirmed at two years.

The proportion of subjects maintaining vision were ≥ 90% in all treatment groups and was comparable between individual studies, although a slight drop off in the proportion of subjects who maintained vision was observed compared to week 52. Decreases (by 1-2 letters) in mean ETDRS letter score occurred in the second year with a similar picture in all treatment groups. Also, a slight decrease occurred in the second year in the proportion of patients who gained ≥ 15 letters.

Discussion on the number of injections received by patients during year two:
According to the integrated analysis of Year 2 completers, the mean number of injections was approximately similar in all treatments groups (around 4, range: 4.7 for RQ4 vs 4.1-4.2 for 2Q4 or 2Q8) with an interval of around 70 days (range: 67.9 for RQ4 vs 73.7-73.2 for 2Q4 or 2Q8), also approximately similar between groups.

About a third of subjects received at least one injection in Year 2 at an interval of one month from the previous injection. Of these, most patients received ≤ 6 injections while "4-week interval" was only an isolated event for these patients. Nevertheless, it could not be ruled out that a monthly regimen may help to stabilize vision in some patients in the long term. To elucidate this point, the CHMP requested that the applicant commit to a post authorisation study.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Eylea 2 mg in the treatment of wet AMD was demonstrated over the two years data.

The primary endpoint analysis met the non-inferiority margins for all VEGF Trap-eye regimens, and all secondary endpoint analyses support the comparability of the efficacy of ranibizumab with the three VEGF Trap-Eye treatment schedules.

According to study VIEW 1 results, the 2Q4 regimen showed the best results in term of vision, with superior gain in the number of letters read at Week 52; retinal morphology evolution showed also better results with the 2Q4 regimen than with the other regimens. In the VIEW 2 study however, the 52-week numeric results favoured the 0.5Q4 regimen while the 2Q4 and 2Q8 regimens were

very similar and still non inferior to ranibizumab. Wile this result confirmed the efficacy of Eylea in the proposed indication, it left a degree of uncertainty in the selection of the most appropriate dosage regimen. This was also shown by the year 2 data: the possibility of visual improvements with less than 3 injections by year is not excluded. Some patients did require occasional injections on a monthly basis in Year 2, but it is not clear in which circumstances this would be beneficial. As there were no clear tendencies of results to favour one dosing regimen of VEGF Trap-Eye over the others, the 2Q8 regimen was chosen as it reduces the number of injections.

Therefore the CHMP concluded that for the long term (after the first 12 months of treatment), patients should continue to be treated with Eylea every 2 months and that after the first 12 months of treatment with Eylea, the treatment interval could be extended based on visual and anatomic outcomes.

The CHMP also considered that there are still uncertainties regarding the choice of dosing schedule, as it was not demonstrated whether a proactive or a reactive approach was the most beneficial. The SmPC reflects the fact that there is no requirement for monitoring between injections and there is the possibility for the patients to receive monthly injections based on clinician evaluation. The Applicant also committed to submit a clinical study aimed to compare the proactive regimen with injection every 2 months with a reactive regimen based on visual and anatomic outcomes.

The approved indication reads as follows:

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microlitres.

Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

The CHMP considers the following measures necessary to address issues related to efficacy:

To perform a post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.

The final clinical study report should be submitted by December 31, 2017.

The protocol will be submitted for CHMP agreement by Q1, 2013.

2.6. Clinical safety

Patient exposure

The clinical safety analysis was based on data pooled from two phase 3 studies (VIEW 1 and VIEW 2 constituting pool 1) and phase 1/2 studies (pool 2). Overall, 11 ophthalmology studies were integrated in the safety analysis, including 7 studies in the requested indication of AMD; 3 of these studies are completed (phase 1 and 2) and 4 are still on-going (2 pivotal and 2 extension studies). VEGF Trap-Eye was administered intravitrealy in 3237 patients, including 2647 patients in the requested indication.

In pool 1 (pivotal studies), a total of 2457 subjects were distributed as follows: 609 subjects in the RQ4 group, 617 subjects in the 2Q4 group, 615 subjects in the 0.5Q4 group, and 616 subjects in the 2Q8 group. During the first year of treatment in the pool 1 studies, planned exposure to VEGF Trap-Eye in the study eye was 2 mg administered monthly (13 IVT injections, 26 mg/yr) or every 2 months (8 IVT injections, 16 mg/yr), or 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr), and planned exposure to ranibizumab was 0.5 mg administered monthly (13 IVT injections, 6.5 mg/yr). The mean number of injections administered was similar among the monthly dosing regimens (12.3 in the RQ4, 12.3 in the 2Q4, and 12.2 in the 0.5Q4 groups) and just over half of that in the 2Q8 treatment group (7.5). The total mean exposure was 6.08 mg (RQ4), 24.62 mg (2Q4), 6.08 mg (0.5Q4), and 14.93 mg (2Q8), over a mean duration of 347 to 353 day.

In pool 2, a total of 230 subjects were randomized (159 in VGFT-OD-0508, 51 in VGFT-OD-0502, and 20 in VGFT-OD-0603). A total of 102 subjects from the 3 studies in pool 2 were either randomized to receive VEGF Trap-Eye at a dose of 4 PRN (31 were from VGFT-OD-0508) or were eligible to receive 4 PRN of VEGF Trap-Eye in the extension phase of study VGFT-OD-0502. In addition in study VGFT-OD-0508, 64 subjects were randomized to receive 0.5 PRN and 64 subjects were randomized to receive 2.0 PRN during the first 12 weeks.

The mean number of injections administered to subjects in pool 2 ranged from 2.5 in the 4 mg VGFT-OD-0508 group to 3.6 in the combined 4 mg group, with an overall mean of 3.3 injections. The total mean amount of study medication received increased less than dose proportionally: 1.6 mg (0.5PRN), 6.0 mg (2PRN), 10.1 mg (4PRN) and 14.5 mg in the 4 combined PRN, and 8.1 mg in the pool 2 any dose groups.

Long-term safety data: the 2-Year data have been provided in the Response Document. From VIEW 1: of the 1217 randomized subjects, 1120 (92.0%) entered Year 2 of the study. Eighty-two (7.3%) of these 1120 subjects discontinued the study during the second year. From VIEW 2: of the 1240 randomized subjects, 1115 (89.9%) entered Year 2 of the study. Ninety (8.1%) of these 1115 subjects discontinued the study during the second year.

The long-term extension study VGFT-OD-910 was ongoing at the time of authorisation; safety data on SAEs and deaths have been provided for 202 subjects treated > 2 years; 15 subjects reported 23 SAEs; CIOMS forms have been provided. Final, complete data on this phase 3, long-term extension study will be provided post authorisation.

Adverse events

Pool 1: subjects were evaluated every 4 weeks for safety; safety assessments included ophthalmic examinations, monitoring of clinical treatment-emergent adverse events (TEAEs) (non-ocular, ocular study eye, and ocular fellow eye), and laboratory testing. Adverse event (AE) information were collected up until the termination visit or until 30 days after the last dose of study drug has been administered. Immunological response was monitored through sampling for potential development of anti-VEGF Trap antibodies. ECG and Potential nasomucosal side effects were investigated in a sub-set of subjects participating in the ENT sub-study in VIEW 2 trial only.

Overall, when safety results are pooled from the 2 pivotal studies, the rate of ocular and non-ocular TEAEs appears to be similar between VEGF Trap-Eye and comparator groups.

Overall Summary of Treatment-Emergent Adverse Events, Pool 1 (SafetyAnalysis Set)

	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Number (%) of subjects with:						
Any TEAE	538 (90.4%)	555 (90.5%)	535 (89.0%)	565 (92.6%)	1655 (90.7%)	2193 (90.7%)
Any non-ocular TEAE	415 (69.7%)	451 (73.6%)	437 (72.7%)	436 (71.5%)	1324 (72.6%)	1739 (71.9%)
Any study drug related TEAE	6 (1.0%)	12 (2.0%)	8 (1.3%)	11 (1.8%)	31 (1.7%)	37 (1.5%)
Any injection related TEAE	0	0	0	0	0	0
Maximum intensity for any non-ocular TEAE						
Mild	191 (32.1%)	229 (37.4%)	225 (37.4%)	217 (35.6%)	671 (36.8%)	862 (35.6%)
Moderate	174 (29.2%)	181 (29.5%)	151 (25.1%)	164 (26.9%)	496 (27.2%)	670 (27.7%)
Severe	50 (8.4%)	40 (6.5%)	59 (9.8%)	55 (9.0%)	154 (8.4%)	204 (8.4%)
Any ocular TEAE (study eye)	433 (72.8%)	419 (68.4%)	408 (67.9%)	436 (71.5%)	1263 (69.2%)	1696 (70.1%)
Any study drug related TEAE	39 (6.6%)	28 (4.6%)	34 (5.7%)	33 (5.4%)	95 (5.2%)	134 (5.5%)
Any injection related TEAE	275 (46.2%)	251 (40.9%)	241 (40.1%)	252 (41.3%)	744 (40.8%)	1019 (42.1%)
Maximum intensity for any ocular TEAE (study eye)						
Mild	280 (47.1%)	274 (44.7%)	283 (47.1%)	286 (46.9%)	843 (46.2%)	1123 (46.4%)
Moderate	134 (22.5%)	123 (20.1%)	98 (16.3%)	133 (21.8%)	354 (19.4%)	488 (20.2%)
Severe	19 (3.2%)	21 (3.4%)	27 (4.5%)	17 (2.8%)	65 (3.6%)	84 (3.5%)
Any ocular TEAE (Fellow Eye)	274 (46.1%)	261 (42.6%)	269 (44.8%)	266 (43.6%)	796 (43.6%)	1070 (44.2%)
Any study drug related TEAE	1 (0.2%)	3 (0.5%)	0	3 (0.5%)	6 (0.3%)	7 (0.3%)
Any injection related TEAE	18 (3.0%)	20 (3.3%)	12 (2.0%)	14 (2.3%)	46 (2.5%)	64 (2.6%)
Maximum intensity for any ocular TEAE (fellow eye)						
Mild	188 (31.6%)	175 (28.5%)	193 (32.1%)	174 (28.5%)	542 (29.7%)	730 (30.2%)
Moderate	71 (11.9%)	76 (12.4%)	64 (10.6%)	86 (14.1%)	226 (12.4%)	297 (12.3%)
Severe	13 (2.2%)	8 (1.3%)	10 (1.7%)	6 (1.0%)	24 (1.3%)	37 (1.5%)
Any TEAE leading to death [1,2]	7 (1.2%)	2 (0.3%)	3 (0.5%)	8 (1.3%)	13 (0.7%)	20 (0.8%)
Any TE SAE	103 (17.3%)	95 (15.5%)	97 (16.1%)	104 (17.0%)	296 (16.2%)	399 (16.5%)
Any non-ocular TE SAE	83 (13.9%)	76 (12.4%)	87 (14.5%)	89 (14.6%)	252 (13.8%)	335 (13.8%)
Any ocular TE SAE (Study Eye)	19 (3.2%)	13 (2.1%)	11 (1.8%)	12 (2.0%)	36 (2.0%)	55 (2.3%)
Any ocular TE SAE (Fellow Eye)	6 (1.0%)	9 (1.5%)	5 (0.8%)	5 (0.8%)	19 (1.0%)	25 (1.0%)
Any TEAE causing disc. of study drug	9 (1.5%)	15 (2.4%)	19 (3.2%)	13 (2.1%)	47 (2.6%)	56 (2.3%)
Any TEAE causing Disc. from the study	0	0	0	0	0	0
Any TEAE of interest	322 (54.1%)	311 (50.7%)	305 (50.7%)	315 (51.6%)	931 (51.0%)	1253 (51.8%)
Any TE SAE of interest	22 (3.7%)	22 (3.6%)	25 (4.2%)	26 (4.3%)	73 (4.0%)	95 (3.9%)
Any non-ocular TE SAE of interest	11 (1.8%)	15 (2.4%)	21 (3.5%)	18 (3.0%)	54 (3.0%)	65 (2.7%)
Any ocular TE SAE of interest (Study Eye) Any	9 (1.5%)	7 (1.1%)	5 (0.8%)	8 (1.3%)	20 (1.1%)	29 (1.2%)
ocular TE SAE of interest (Fellow Eye)	2 (0.3%)	0	2 (0.3%)	0	2 (0.1%)	4 (0.2%)

Note: This table is summarizing all subjects with treatment emergent adverse events starting post first injection
[1] SAEs resulting in death or AEs with fatal outcome.
[2] This table only includes deaths associated with fatal SAEs that began within 30 days of the last administration of study drug. A total of 26 subjects died in the 2 studies combined: 7, 5, 4, and 10 in the RQ4, 2Q4, 0.5Q4, and 2Q8 groups, respectively.

Ocular Treatment-Emergent Adverse Events (TEAEs)

In **pool 1**, 70.1% of subjects overall reported ocular TEAEs in the study eye, the frequency of which was similar across treatment groups: (72.8% [RQ4], 68.4% [2Q4], 67.9% [0.5Q4], and 71.5% [2Q8].

Ocular Treatment-Emergent Adverse Events in the Study Eye, Pool 1 (in 5% of Subjects in Any Treatment Group) (by SOC and PT) (Safety Analysis Set)

Primary system organ class Preferred term MedDRA Version 13.1	R 0.5 mg Q4 N=595 (100%)	VTE 2.0 mg Q4 N=613 (100%)	VTE 0.5 mg Q4 N=601 (100%)	VTE 2.0 mg Q8 N=610 (100%)	VTE total N=1824 (100%)	TOTAL N=2419 (100%)
Eye disorders						
Conjunctival hemorrhage	167 (28.1%)	133 (21.7%)	157 (26.1%)	161 (26.4%)	451 (24.7%)	618 (25.5%)
Eye pain	53 (8.9%)	66 (10.8%)	49 (8.2%)	43 (7.0%)	158 (8.7%)	211 (8.7%)
Macular degeneration	39 (6.6%)	43 (7.0%)	40 (6.7%)	40 (6.6%)	123 (6.7%)	162 (6.7%)
Retinal hemorrhage	48 (8.1%)	36 (5.9%)	47 (7.8%)	50 (8.2%)	133 (7.3%)	181 (7.5%)
Visual acuity reduced	40 (6.7%)	50 (8.2%)	57 (9.5%)	53 (8.7%)	160 (8.8%)	200 (8.3%)
Vitreous detachment	33 (5.5%)	44 (7.2%)	32 (5.3%)	34 (5.6%)	110 (6.0%)	143 (5.9%)
Vitreous floaters	44 (7.4%)	48 (7.8%)	30 (5.0%)	30 (4.9%)	108 (5.9%)	152 (6.3%)
Investigations						
Intraocular pressure increased	41 (6.9%)	38 (6.2%)	27 (4.5%)	30 (4.9%)	95 (5.2%)	136 (5.6%)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. All events reported by at least 5% of subjects are displayed.

TEAEs reported in the supportive phase 1 and phase 2 studies were consistent with those seen in the pivotal phase 3 studies. The most common ocular TEAEs occurring in the study eye for the pool 2 (non pivotal studies) any dose group were conjunctival haemorrhage (47 subjects; 23.2%), reduced VA (31 subjects; 15.3%), and increased IOP (26 subjects; 12.8%).

The 4 combined PRN group had a higher incidence than the other doses for eye pain, foreign body sensation in eyes, and lacrimation increased. The 0.5 PRN group had a higher incidence than the other doses of retinal haemorrhage and VA reduced. Otherwise, the TEAEs were reported with similar frequencies across dose groups.

Ocular Treatment-Emergent Adverse Events in the Study Eye, Pool 2 (in 5% of Subjects in Any Treatment Group) (by SOC and PT) (Safety Analysis Set)

	VGFT-OD-0508			VGFT-OD-0502 VGFT-OD-0508 VGFT-OD-0603	VGFT-OD-0502 VGFT-OD-0508 VGFT-OD-0603
Primary system organ class Preferred term MedDRA Version 13.0	**VTE 0.5 mg PRN N=62 (100%)**	**VTE 2.0 mg PRN N=60 (100%)**	**VTE 4.0 mg PRN N=30 (100%)**	**VTE 4.0 mg PRN TOTAL N=81 (100%)**	**VTE ANY DOSE TOTAL N=203 (100%)**
Eye disorders					
Blepharitis	0	3 (5.0%)	1 (3.3%)	2 (2.5%)	5 (2.5%)
Cataract cortical	0	3 (5.0%)	0	1 (1.2%)	4 (2.0%)
Cataract nuclear	2 (3.2%)	3 (5.0%)	0	1 (1.2%)	6 (3.0%)
Conjunctival hemorrhage	13 (21.0%)	16 (26.7%)	5 (16.7%)	18 (22.2%)	47 (23.2%)
Dry eye	2 (3.2%)	3 (5.0%)	0	1 (1.2%)	6 (3.0%)
Eye pain	2 (3.2%)	1 (1.7%)	1 (3.3%)	8 (9.9%)	11 (5.4%)
Foreign body sensation in eyes	1 (1.6%)	0	0	5 (6.2%)	6 (3.0%)
Lacrimation increased Photopsia	1 (1.6%)	0	1 (3.3%)	5 (6.2%)	6 (3.0%)
Punctate keratitis	1 (1.6%)	2 (3.3%)	2 (6.7%)	3 (3.7%)	6 (3.0%)
Retinal hemorrhage	0	3 (5.0%)	2 (6.7%)	2 (2.5%)	5 (2.5%)
Retinal edema	10 (16.1%)	3 (5.0%)	2 (6.7%)	3 (3.7%)	16 (7.9%)
Visual acuity reduced	4 (6.5%)	3 (5.0%)	0	1 (1.2%)	8 (3.9%)
Visual impairment	14 (22.6%)	6 (10.0%)	5 (16.7%)	11 (13.6%)	31 (15.3%)
Vitreous detachment	2 (3.2%)	0	2 (6.7%)	3 (3.7%)	5 (2.5%)
Vitreous floaters	2 (3.2%)	7 (11.7%)	0	3 (3.7%)	12 (5.9%)
General disorders and administration site conditions	4 (6.5%)	3 (5.0%)	0	3 (3.7%)	10 (4.9%)
Injections site hemorrhage	4 (6.5%)	0	0	3 (3.7%)	7 (3.4%)
Injection site pain	1 (1.6%)	1 (1.7%)	1 (3.3%)	5 (6.2%)	7 (3.4%)
Sensation of foreign vbody	0	0	1 (3.3%)	6 (7.4%)	6 (3.0%)
Investigations					
Intraocular pressure increased	9 (14.5%)	6 (10.0%)	4 (13.3%)	11 (13.6%)	26 (12.8%)

Note: At each level of subject summarization, a subject is counted once if the subject reported one or more events. All events reported by at least 5% of subjects are displayed.

In Pool 1, the number of *ocular drug-related TEAEs* was rather low (5.5% in total) and similar between treatment groups (6.6% ranibizumab vs 5.2% VTE). The most common drug-related TEAEs were vitreous floaters, visual acuity reduced and IOP increased with maximum of 1.2% of

rate. The majority of cases were sporadic with a rate < 1%. Of note, macular degeneration was observed in 11 (0.5%) patients in VEGF Trap-eye group compared to no case in ranibizumab group.

In pool 2, only 14 subjects reported *drug-related ocular treatment-emergent AEs* (6.9%) including 3% of IOP increased.

Non-ocular Treatment-Emergent Adverse Events

In Pool 1, 71.8% of subjects overall reported non-ocular TEAEs; the frequency of which was similar among treatment groups: (69.7% [RQ4], 73.4% [2Q4], 72.7% [O.5Q4], and 71.5% [2Q8].

The most common non-ocular TEAEs in pool 1 were nasopharyngitis (7.8% overall), hypertension (6.8% overall) headache (4.2% overall), bronchitis (3.9% overall), and urinary tract infection (3.6% overall]). Treatment-emergent adverse events occurred with similar frequency across all treatment groups, and were generally characteristic of patients in the age range studied.

Non-ocular TEAEs reported in pool 2 were consistent with those seen in pool 1. The most common non-ocular TEAEs observed in subjects in pool 2 were nasopharyngitis (14 subjects; 6.9%), urinary tract infection (13 subjects; 6.4%), bronchitis (11 subjects; 5.4%), and hypertension (10 subjects; 4.9%).

Cardiovascular Events:
(a) Arterial thromboembolic events (ATEs): the incidence of APTC ATEs was similar in the pivotal studies: 1.7% in ranibizumab group vs 1.8 in VEGF Trap-eye groups. In the long-term safety study (VGFT-OD-0702), 13 patients (8.3%) reported arterial thromboembolic events.

Arterial thromboembolic events, as defined by ApTC criteria, include nonfatal myocardial infarction, nonfatal stroke, or vascular death including deaths of unknown cause).

When TEAEs are analysed as TEAEs of interest in pool 1 (SOC and PT), the global rate of arterial thromboembolic events (refer to table 69 of Summary of Clinical Safety), was higher in VEGF Trap-eye groups (3.2%) when compared to the ranibizumab (1.8%) group. The CHMP listed arterial thromboembolic events as an important potential risk in the RMP and covered in section 4.8 of the SmPC.

(b) Hypertension. In pool 1, hypertension was frequently reported non-ocular TEAE, observed in 7.9% of patients in ranibizumab group and 6.5% in VEGF Trap-eye groups. In addition, hypertension has been reported in 23 (14.6%) patients in pool 2.

Taking into account the potential role of VEGF in the systemic cardiovascular events and the fact that almost 20% of drug substance goes through the systemic circulation, systemic effects of VEGF Trap-eye cannot be excluded.

2-Year Data

A similar number of subjects with any study drug-related adverse event, with any injection-related AE and any AE of interest has been reported in the study groups. However, more subjects discontinued the study due to adverse event in the VEGF Trap-Eye groups (2Q4 4.2%, 0.5Q4 6.5%, 2Q8 4.9%) compared to ranibizumab (3.5%). These AEs were in majority mild and moderate with however about 20% of severe AEs (21.7% in ranibizumab, 20.3% in VEGF Trap-Eye groups).

Table 67. Integrated analysis: Treatment-emergent adverse events during the entire study period from Baseline to Week 96/100 (SAF)

Number of subjects with:	Ranibizumab 0.5Q4 (N = 595) n (%)	VEGF Trap-Eye 2Q4 (N = 613) n (%)	VEGF Trap-Eye 0.5Q4 (N = 601) n (%)	VEGF Trap-Eye 2Q8 (N = 610) n (%)	VEGF Trap-Eye Combined (N = 1824) n (%)
Any TEAE	**567 (95.3)**	**587 (95.8)**	**566 94.2)**	**591 (96.9)**	**1744 (95.6)**
Any study drug-related AE	52 (8.7)	51 (8.3)	51 (8.5)	55 (9.0)	157 (8.6)
Any injection-related AE	297 (49.9)	276 (45.0)	276 (45.9)	287 (47.0)	839 (46.0)
Any AE of interest	353 (59.3)	354 (57.7)	333 (55.4)	354 (58.0)	1041 (57.1)
Any AE causing treatment discontinuation	21 (3.5)	26 (4.2)	39 (6.5)	30 (4.9)	95 (5.2)
Maximum intensity for any AE					
Missing	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (<0.1)
Mild	152 (25.5)	163 (26.6)	168 (28.0)	163 (26.7)	494 (27.1)
Moderate	286 (48.1)	313 (51.1)	266 (44.3)	299 (49.0)	878 (48.1)
Severe	129 (21.7)	111 (18.1)	131 (21.8)	129 (21.1)	371 (20.3)
Maximum intensity for any study drug related AE					
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mild	33 (5.5)	30 (4.9)	38 (6.3)	32 (5.2)	100 (5.5)
Moderate	17 (2.9)	18 (2.9)	10 (1.7)	16 (2.6)	44 (2.4)
Severe	2 (0.3)	3 (0.5)	3 (0.5)	7 (1.1)	13 (0.7)
Any Death	15 (2.5)	12 (2.0)	16 (2.7)	18 (3.0)	46 (2.5)
Any SAE	170 (28.6)	158 (25.8)	168 (28.0)	177 (29.0)	503 (27.6)
Any study drug related SAE	3 (0.5)	7 (1.1)	1 (0.2)	7 (1.1)	15 (0.8)
Any injection related SAE	12 (2.0)	8 (1.3)	3 (0.5)	3 (0.5)	14 (0.8)
Any SAE of interest	40 (6.7)	34 (5.5)	34 (5.7)	42 (6.9)	110 (6.0)
Any SAE causing Discontinuation of study drug	18 (3.0)	19 (3.1)	30 (5.0)	26 (4.3)	75 (4.1)

Source: Annex 3, Post-text table 14.3.1/3a

Table 70. Integrated analysis: Ocular TEAEs in the study eye occurring in ≥5.0% of the subjects at preferred term level in any treatment group during the entire study period from Baseline to Week 96/100 (SAF)

MedDRA preferred term	Ranibizumab 0.5Q4 (N = 595) n (%)	VEGF Trap-Eye 2Q4 (N = 613) n (%)	VEGF Trap-Eye 0.5Q4 (N = 601) n (%)	VEGF Trap-Eye 2Q8 (N = 610) n (%)	VEGF Trap-Eye Combined (N = 1824) n (%)
Any ocular TEAE (study eye)	486 (81.7)	475 (77.5)	467 (77.7)	483 (79.2)	1425 (78.1)
Conjunctival haemorrhage	178 (29.9)	145 (23.7)	171 (28.5)	171 (28.0)	487 (26.7)
Retinal haemorrhage	85 (14.3)	85 (13.9)	82 (13.6)	99 (16.2)	266 (14.6)
Visual acuity reduced	67 (11.3)	76 (12.4)	76 (12.6)	79 (13.0)	231 (12.7)
Eye pain	62 (10.4)	74 (12.1)	60 (10.0)	54 (8.9)	188 (10.3)
Macular degeneration	49 (8.2)	54 (8.8)	52 (8.7)	57 (9.3)	163 (8.9)
Vitreous detachment	48 (8.1)	61 (10.0)	46 (7.7)	47 (7.7)	154 (8.4)
Cataract	37 (6.2)	53 (8.6)	51 (8.5)	40 (6.6)	144 (7.9)
Vitreous floaters	58 (9.7)	59 (9.6)	40 (6.7)	39 (6.4)	138 (7.6)
Intraocular pressure increased	64 (10.8)	48 (7.8)	37 (6.2)	47 (7.7)	132 (7.2)
Retinal oedema	23 (3.9)	21 (3.4)	27 (4.5)	42 (6.9)	90 (4.9)
Retinal degeneration	27 (4.5)	32 (5.2)	26 (4.3)	23 (3.8)	81 (4.4)
Maculopathy	32 (5.4)	23 (3.8)	37 (6.2)	19 (3.1)	79 (4.3)
Ocular hyperaemia	31 (5.2)	24 (3.9)	23 (3.8)	14 (2.3)	61 (3.3)

Note: Preferred terms are sorted in descending order by frequency in the VEGF Trap-Eye combined group.
Source: Annex 3, post-text table 14.3.1/5a

With regards to ocular AEs, a similar number of events has been reported between the study groups. Conjunctival haemorrhage, retinal haemorrhage, visual acuity reduced and eye pain were very frequently reported in all groups. There were some slight differences between the recommended dose group (2Q8) and the comparator ranibizumab group in the rate of retinal

haemorrhage (16.2% vs 14.3%), visual acuity reduced (13% vs 11.3%) and eye pain (8.9% vs 10.4%).

Few of ocular AEs were considered as related to study treatment, 7.4% in ranibizumab group vs 6.7% in the VEGF Trap-Eye groups and the differences in the percentage are not significant.

The incidence of injection-related TEAEs was significantly higher in VIEW 1 when compared to VIEW 2 study. The applicant explained that this was due to the mode of peri-procedural anaesthesia that was different between the two studies.

Serious adverse event/deaths/other significant events

Severe ocular TEAEs

Pool 1: the number of severe ocular TEAEs is low and similar between the treated groups. However, more eye disorders were reported in VEGF Trap-eye groups (3%) compared to ranibizumab group (2%).

Endophtalmitis was reported in 0.5% of patients in ranibizumab and 2Q4 group, as well as IOP increased, retinal haemorrhage and conjunctival haemorrhage. Three cases of cataract were reported in VEGF Trap-eye groups and none in ranibizumab group. Severe eye pain occurred more frequently in VEGF treated groups (0.5%) compared to comparator group (0.3%).

Pool 2: Only 2 subjects reported severe ocular TEAEs in the study eye: in study VGFT-OD-0508, 1 subject in the 0.5 PRN group had severe uveitis and 1 subject in the combined 4 PRN group had severe retinal vascular disorder.

Severe non-ocular TEAEs

Pool 1: 204 (8.4%) subjects experienced severe non-ocular TEAEs: 50 (8.4%) subjects in the RQ4 group, 40 (6.5%) subjects in the 2Q4 group, 59 (9.8%) subjects in the 0.5Q4 group, and 55 (9.0%) subjects in the 2Q8 group. The percentage of subjects in each treatment group reporting severe non-ocular TEAEs was similar across the treatment groups.

The most common severe non-ocular TEAEs was myocardial infarction, and this occurred in 0.5% (12/2419) of subjects, overall. All other severe non-ocular TEAEs occurred in 0.3% of subjects.

One case of transient ischemic attack (TIA) was considered to be related to study drug in the 2Q4 group. In total, TIA was observed in 10 patients treated with VEGF Trap-eye while no cases occurred in comparator group.

Pool 2*:* Severe non-ocular TEAEs were reported in 7.4% (15) of subjects.The most commonly reported severe non-ocular TEAE was congestive cardiac failure (in 2 subjects; 1%). All other severe non-ocular TEAEs occurred in only 1 subject each.

Deaths. A total of 26 subjects died in Pool 1 during year 1 (7 subjects in the RQ4 group, 5 subjects in the 2Q4 group, 4 subjects in the 0.5Q4 group, and 10 subjects in the 2Q8 group) (cut-off date of 10 November 2010). None of the deaths was considered related to study drug.

The reported causes of death were consistent with what would be expected in the elderly population with AMD: cardiac disorders (cardiac arrest, myocardial infarction, cardiopulmonary failure), neoplasm (hepatic neoplasm malignant, leukaemia, lung cancer), cerebral haemorrhage.

Most cases of death occurred in the 2Q8 group (10). Slightly more deaths have been reported in 2Q8 group (1.5%) when compared to 2Q4 (0.7%) and 0.5Q4 (0.5%) groups during the

development programme. As cause of death, 2 cases of vascular disorders were observed in 2Q8 group, and none in other groups.

A total of 2 subjects died in Pool 2. One subject (in the 4 combined PRN group) with a pre-existing condition of pulmonary hypertension died 85 days after the last dose of study drug due to cardiac arrest. The other subject (in the 2PRN group) died due to pancreatic carcinoma diagnosed 112 days after receiving the last dose of study drug.

Long-term study (VGFT-OD-0702): 8 subjects died during the period from baseline of this study to the cut-off date. Two of the deaths occurred after the subjects had completed the initial study but before they had received study treatment in the long-term safety study.

A total of 3 deaths were reported during the first 6 months of **VGFT-OD-0706**, 1 subject each in the 0.5Q4 (multi-organ failure), 2Q4 (sudden death), and 2Q8 (convulsion) groups. None of the events that led to death in these subjects were judged by the investigator to be related to study drug.

2-Year Data

Deaths. Full 2-year data showed a total of 68 deaths (2.8%) reported in the 2 studies, including 20 deaths (3.3%) in 2Q8, 19 (3.2%), 13 (2.1%) and 16 (2.7%) in ranibizumab group. The trend in difference in number of deaths was not confirmed during the second year of treatment. Also, the total number in Eylea groups is comparable with the ranibizumab group.

Ocular serious TEAEs. In the integrated analysis, 91 study subjects (3.8%) were documented to have ocular SAEs in the study eye by the end of Year 2. As seen in the single studies, many of these events were likely procedure-related or AMD-related, with "visual acuity reduced" (19 study pool subjects [0.8%]), "retinal hemorrhage" (17 study pool subjects [0.7%])), and "cataract" (12 study pool subjects [0.5%]) being the prevailing events.

Five cases of endophtalmitis, including one case of pseudoendophtalmitis have been reported, 4 in VIEW 1 and one in VIEW 2 study. Two cases have been observed in the VEGF Trap-Eye groups (0.5Q4 and 2Q4) and 3 cases in ranibizumab group. All cases of endophtalmitis were considered related to the study drug procedure. This event is covered in sections 4.4. and 4.8. of the SmPC and is mentioned as an important identified risk in the RMP.

Non-ocular serious TEAEs. Non-ocular, drug-related treatment-emergent SAEs occurred at a higher frequency in Eylea-treated subjects, though the absolute numbers were low; 7 cerebrovascular events (0.8%) in Eylea-treated subjects (mostly in VIEW 2), none in ranibizumab-treated subjects. Furthermore, a higher frequency of TIAs was detected in Eylea-treated subjects in VIEW 1 than for ranibizumab: 18 events (2%) versus 1 (0.3%). This trend was not observed in VIEW 2, nor is a trend observed when arterial thromboembolic events are analysed according to the APTC criteria.

Laboratory findings

Chemistry

The incidences of pre-defined laboratory abnormalities were low and balanced among treatment groups for all clinical chemistry test parameters.

Hypercholesterolaemia was reported as a TEAE in 34 (1.4%) subjects in pool 1 during the first year of the studies (RQ4 1.3%; 2Q4 1.0%; 0.5Q4 1.5%; 2Q8 1.8%) and in 51 (2.1%) subjects in the 2nd year of treatment (RQ4 2.2%; 2Q4 1.5%; 0.5Q4 2.0%; 2Q8 2.8%). The occurrence of hypercholesterolemia is expected in this elderly population and its rate remains low.

No safety signal emerged from haematology and vital signs data.

The majority of the treated subjects (1371 and 131 subjects, respectively), had a medical history of hypertension. Blood pressure changes were presented as the mean and median values, showing no apparent trend over time in pool 1 and 2. No increases in SBP and DBP have been observed in the sub-group of patients with medical history of hypertension up to 2 years of treatment. However, according to the results of the PK studies, there is a possibility that aflibercept might increase blood pressure. As part of the pharmacovigilance activities, it is requested that the post-marketing and study reports which indicate hypertension should be followed up with a targeted questionnaire.

Safety in special populations

Intrinsic Factors

Subgroup analyses were conducted on the following safety variables for subjects in pool 1: gender; age (< 65 years, ≥ 65 years to < 75 years, ≥ 75 years); race (white, black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, or other); ethnicity (Hispanic or Latino [no / yes]); renal status (CLCR > 80 mL/min [normal], > 50 – 80 mL/min [mild impairment], > 30 - 50 mL/min [moderate impairment], 2 30 mL/min or requiring dialysis [severe impairment]), history of diabetes mellitus, cataracts, hypertension, CVA/stroke, and myocardial infarction.

The number of subjects in the following subgroups within pool 1 were too small to allow meaningful comparisons: race (other); renal impairment (severe impairment); hepatic impairment, and proteinuria; although there were few subjects in the subgroup of CVA/stroke, analyses were conducted as this is an adverse event of interest.

Overall, the results of the subgroup analyses of all TEAEs were similar to those seen in the entire study population. No clinically relevant imbalances or trends were seen among the treatment groups.

Extrinsic Factors

Pre-filled syringes vs. Vials

Although there where differences in the incidence of events comparing the vial to the PFS group, they appeared random and a pattern was not discerned between the 2 groups.

Pregnancy, Lactation and Fertility

Aflibercept produced embryo-foetal toxicity in rabbit and effects on male and female fertility in monkey after intravenous administration. However, there are large safety margins when compared to corresponding values observed in humans after an intravitreal therapeutic dose. Therefore, systemic effects are unlikely in patients, including pregnant women. In addition, exposure of a woman of childbearing potential to Aflibercept seems to be unlikely given the indication.

It is noted that products of the same therapeutic class are already marketed (Lucentis® and Macugen®), whose SmPCs indicate they should not be used during pregnancy unless there is a clear benefit. Similar recommendations regarding pregnancy, fertility and lactation were inserted in the Product Information.

Overdose

In clinical studies with VEGF Trap-Eye, isolated cases of overdose of up to 10-fold were generally well tolerated. One subject received a single dose of 20 mg VGFT Trap-Eye in 500 µL

volume (instead of the planned 2 mg in 50 µL), which was associated with increased injection volume and subsequently with a transient increase in IOP lasting 1 day. No other TEAE were observed. As of January 2011, all overdosed subjects recovered without sequelae.

The concentration of bound VEGF Trap in plasma following IVT administration of up to 4 mg/eye was about 20-fold lower than those following IV administration of 1 to 4 mg/kg. Since IV administration of VEGF Trap at doses ≥1 mg/kg every 2 weeks was required to completely saturate endogenous VEGF synthesized over the dosing interval, the IVT doses being investigated in this development programme did not appear to be able to saturate systemic VEGF. This conclusion is supported by the observation that the peak concentration of bound VEGF Trap continued to increase in a dose-dependent manner with increasing IVT doses.

Recommended treatment: overdoses of up to 20 mg/eye were generally well tolerated. Overdosing was associated with increased injection volume and subsequently with increased IOP. Therefore, when overdose is associated with increased volume, IOP should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

Drug Abuse

VEGF Trap-Eye will be administered by a qualified physician. The drug will not be prescribed for self-administration In addition, the method of VEGF Trap-Eye administration, IVT injection, is not conductive to drug abuse.

There has been no evidence of psychotropic properties associated with the study drug. Post-intraocular-injection, VEGF-Trap binds with VEGF-A to form a complex. As a protein molecule, VEGF-Trap and its complex are too large to cross the blood-brain barrier, which limits any possibility for centrally-mediated effects associated with drug abuse.

Withdrawal and Rebound

Age-related macular degeneration requires lifelong treatment. Cessation of treatment with VEGF Trap-Eye does not mean that the disease will not recur; VA may again decline over time, consistent with the disease process. There is a large variability in patient presentation, course of treatment, and need for re-treatment in cases of wet AMD.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

VEGF Trap-Eye is an ophthalmologic preparation intended to treat visually impaired patients. Subjects may experience temporary visual disturbances after an IVT injection with VEGF Trap- Eye and the associated eye examinations. As a result, they should not drive or use machinery until visual function has sufficiently recovered.

Elderly population

Table 3: Number of subjects with non-ocular treatment-emergent adverse event in the elderly population grouped by age (Year 1 data) - Amended

Age Group	< 65 years		≥ 65 – < 75 years		≥ 75 – < 85 years		≥ 85 years	
	Ranibizumab N=71 (100%)	VEGF Trap-Eye (Total) N=202 (100%)	Ranibizumab N=163 (100%)	VEGF Trap-Eye (Total) N=478 (100%)	Ranibizumab (N=274 (100%)	VEGF Trap-Eye (Total) N=861 (100%)	Ranibizumab N=87 (100%)	VEGF Trap-Eye (Total) N=283 (100%)
Any non-ocular TEAEs	**43 (60.6%)**	**144 (71.3%)**	**105 (64.4%)**	**335 (70.1%)**	**200 (73.0%)**	**623 (72.4%)**	**67 (77.0%)**	**222 (78.4%)**
Fatal (ie, deaths)	0	0	1 (0.6%)	1 (0.2%)	3 (1.1%)	5 (0.6%)	3 (3.4%)	7 (2.5%)
Serious	1 (1.4%)	15 (7.4%)	19 (11.7%)	48 (10.0%)	44 (16.1%)	117 (13.6%)	19 (21.8%)	72 (25.4%)
Withdrawals or discontinuations	0	4 (2.0%)	1 (0.6%)	6 (1.3%)	3 (1.1%)	14 (1.6%)	1 (1.1%)	9 (3.2%)
Any non-ocular TEAEs by AE grouping								
CNS (confusion/extrapyramidal)	1 (1.4%)	5 (2.5%)	6 (3.7%)	3 (0.6%)	5 (1.8%)	14 (1.6%)	1 (1.1%)	10 (3.5%)
AE related to falling	0	2 (1.0%)	5 (3.1%)	4 (0.8%)	16 (5.8%)	24 (2.8%)	5 (5.7%)	25 (8.8%)
Cardiovascular events	0	6 (3.0%)	1 (0.6%)	12 (2.5%)	11 (4.0%)	26 (3.0%)	8 (9.2%)	8 (2.8%)
Cerebrovascular events	0	0	0	5 (1.0%)	1 (0.4%)	10 (1.2%)	1 (1.1%)	20 (7.1%)
Infections and Infestations	23 (32.4%)	49 (24.3%)	54 (33.1%)	140 (29.3%)	96 (35.0%)	239 (27.8%)	27 (31.0%)	86 (30.4%)

Table 7: Number of subjects with non-ocular treatment-emergent adverse event in the elderly population grouped by age (2 Year data)

Age Group	< 65 years		≥ 65 – < 75 years		≥ 75 – < 85 years		≥ 85 years	
	Ranibizumab N= 71 (100%)	VEGF Trap-Eye (Total) N=202(100%)	Ranibizumab N= 163(100%)	VEGF Trap-Eye (Total) N= 478 (100%)	Ranibizumab (N= 274 (100%)	VEGF Trap-Eye (Total) N= 861(100%)	Ranibizumab N= 87 (100%)	VEGF Trap-Eye (Total) N= 283 (100%)
Any non-ocular TEAEs	**51 (71.8%)**	**166 (82.2%)**	**129 (79.1%)**	**393 (82.2%)**	**235 (85.8%)**	**732 (85.0%)**	**79 (90.8%)**	**251 (88.7%)**
Fatal ie, deaths	0	1 (0.5%)	2 (1.2%)	8 (1.7%)	6 (2.2%)	20 (2.3%)	7 (8.0%)	17 (6.0%)
Serious	5 (7.0%)	21 (10.4%)	29 (17.8%)	83 (17.4%)	80 (29.2%)	221 (25.7%)	32 (36.8%)	112 (39.6%)
Withdrawals or discontinuations	0	5 (2.5%)	2 (1.2%)	11 (2.3%)	7 (2.6%)	32 (3.7%)	4 (4.6%)	25 (8.8%)
Any non-ocular TEAEs by AE grouping								
CNS (confusion/extrapyramidal)	2 (2.8%)	8 (4.0%)	9 (5.5%)	8 (1.7%)	9 (3.3%)	26 (3.0%)	2 (2.3%)	15 (5.3%)
AE related to falling	0	6 (3.0%)	6 (3.7%)	8 (1.7%)	24 (8.8%)	49 (5.7%)	9 (10.3%)	47 (16.6%)
Cardiovascular events	3 (4.2%)	6 (3.0%)	8 (4.9%)	21 (4.4%)	18 (6.6%)	41 (4.8%)	9 (10.3%)	21 (7.4%)
Cerebrovascular events	0	2 (1.0%)	0	6 (1.3%)	9 (3.3%)	20 (2.3%)	3 (3.4%)	27 (9.5%)
Infections and Infestations	28 (39.4%)	63 (31.2%)	70 (42.9%)	182 (38.1%)	134 (48.9%)	360 (41.8%)	40 (46.0%)	123 (43.5%)
APTC events	1 (1.4%)	2 (1.0%)	2 (1.2%)	11 (2.3%)	11 (4.0%)	24 (2.8%)	5 (5.7%)	23 (8.1%)

Several tables on number of subjects with TEAEs, ocular TEAEs and non-ocular TEAEs in the elderly population grouped by age and including year 1 and 2-year data have been provided by the applicant.

No deaths related to ocular TEAEs have been reported in the elderly during 2 years. The rate of deaths from non-ocular TEAEs was comparable between the treatment groups during the first and the second year of treatment and increased with age.

Ocular TEAEs were related to the infections; in addition, 3 cases of blepharospasm have been observed in the VEGF Trap-Eye groups.

The number of cerebrovascular events was higher in the VEGF Trap-Eye groups (35) compared with ranibizumab (2 cases) in elderly, especially in the sub-group ≥ 85 years (20 vs 1 case), during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events in the VEGF Trap-Eye groups vs ranibizumab: 53 vs 12 (27 vs 3 in the sub-group ≥ 85 years). One death due to CVA in the 0.5Q4 group and one death due to ischemic stroke in the 2Q8 group were considered as treatment related.

Immunological events

As with all therapeutic proteins, there is a potential to develop immunogenicity towards VEGF Trap-Eye, and this is mentioned in section 4.4 of the SmPC. In order to monitor subjects for the potential appearance of anti-VEGF Trap antibodies, serum samples were collected at study-specific time points during each of the VEGF Trap clinical studies and examined for the presence of ADA (Anti-drug antibodies).

The resulting immunogenicity data reflects the percentage of subjects whose test results were considered positive for ADA in immunoassays and are highly dependent on the sensitivity and specificity of the assays. Early studies (pool 2) used a validated, direct ADA enzyme-linked immunosorbent assay (ELISA) to assess immunogenicity; no samples from these studies were confirmed positive for ADA. For the phase 3 studies (VIEW 1 and 2), a validated, titer-based, bridging ADA immunoassay, which is approximately 40-fold more sensitive than the original ADA ELISA, was used to assess immunogenicity. In these phase 3 studies the pre-treatment incidence of immunoreactivity to VEGF Trap-Eye was 1% to 3% across treatment groups. After dosing with VEGF Trap-Eye for 52 weeks, treatment-emergent positive responses in the assay were detected in a similar percentage range of subjects across treatment groups.

The observed low level of positive assay responses in subjects treated with ranibizumab was similar to the levels in subjects treated with VEGF Trap-Eye, suggesting that a majority of these positive assay responses may be due to pre-existing immunoreactivity in these subjects and, therefore, not due to an immune response to VEGF Trap-Eye.

The tables on proportion of subjects with maintained vision at week 52 and week 96 by negative or positive ADA results have been provided. These 2-year data showed that the majority of subjects with positive ADA results maintained their vision.

However, the analysis was based on the small number of subjects having positive ADA, especially during the first year of treatment (41 subjects in VIEW 1 and 38 in VIEW 2). At week 96, 86 subjects had positive ADA and the majority maintained the vision status (87% to 100%).

Safety related to drug-drug interactions and other interactions

No formal drug interaction studies have been performed with VEGF-Trap Eye.

Individuals with AMD are generally older and often have concomitant diseases that are characteristic of an older population. Study subjects in the VEGF Trap-Eye clinical development programme had a mean age of 76.0 years and a medical history characteristic of individuals in the target AMD population.The mean age of the population in the VEGF Trap-Eye clinical development programme is similar to that found in the MARINA study range = 52 – 95 years) (Rosenfeld 2006) and in the ANCHOR study (age=76.0, range = 53-97) (Brown 2006).

Concomitant topical medications (topical anesthetic and antibiotic) given during the injection of VEGF Trap-Eye do not penetrate the sclera and are not expected to interact with Eylea.

Free VEGF Trap binds VEGF to form a stable, inert complex. As with other large proteins, both free and bound VEGF are expected to be cleared by proteolytic catabolism. Hepatic and renal impairment do not impact clearance of the drug, nor does VEGF Trap-Eye interfere with drugs metabolized through the hepatic and renal systems.

Discontinuation due to adverse events

A total of 212 (8.6%) subjects discontinued from their study within the first year; the most common reason for discontinuation was withdrawal by subject (84 subjects [3.4%]). A total of 255 (10.4%) subjects prematurely discontinued the study medication within the first year; the most common reason was "withdrawal by subject" (94 [3.8%]).

Adverse events leading to withdrawal were generally consistent with events associated with disease progression or with the expected consequences of the IVT injection procedure, and were characteristic of AEs observed in the overall AMD subject population.

In **pool 1**, the most common TEAEs leading to withdrawal were retinal haemorrhage, reduced VA, retinal detachment, CVA, angina pectoris, and myocardial infarction, and were similar among the treatment groups.

In **pool 2**, the TEAEs leading to withdrawal were retinal detachment, abscess in a limb, osteomyelitis, sinusitis, constipation, colon cancer, and cutis laxa.

The AEs leading to withdrawal in the long-term safety study **VGFT-OD-0702** were comparable with those reported in pools 1 and 2 (macular degeneration, reduced VA, and metastatic non-small cell lung cancer). None of the AEs that led to permanent withdrawal of study drug was judged by the investigator to be related to study drug.

The incidence of TEAEs leading to premature treatment discontinuation in the integrated analysis over the entire study period of 2 years (116 [4.8%] of the 2419 study subjects) was 3.5% in the RQ4 group, 4.2% in the 2Q4 group, 6.5% in the 0.5Q4 group, 4.9% in the 2Q8 group, and 5.2% in the VEGF Trap-Eye combined group. Thus, the rate of subjects discontinuing treatment because of AEs over 2 years in the integrated analysis was slightly higher with VEGF Trap-Eye than on treatment with ranibizumab. However, the overall discontinuation rate and discontinuations due to an AE remain low in all study groups.

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

The exposure and safety database size are considered sufficient to allow the safety evaluation.

The safety assessment conducted by the applicant in the 2 pivotal studies is appropriate. When safety results are pooled from these studies, the rate of ocular and non-ocular TEAEs seems similar between VEGF Trap-Eye and comparator groups.

In term of ocular TEAEs, the rate of conjunctival hemorrhage, vitreous floaters and IOP increase was slightly higher in the comparator group in pool 1, while Visual acuity was more reduced in VEGF Trap Eye groups. The number of severe ocular TEAEs is low and similar between the treated groups in pool 1. Three cases of cataract were reported in VEGF Trap-eye groups and none in ranibizumab group.

Five cases of endophtalmitis, 2 for VEGF Trap-Eye and 3 for ranibizumab, have been observed. All were considered related to the study drug. This event is covered by sections 4.4. and 4.8. of the SmPC and is mentioned as an important identified risk in the RMP.

For vascular disorders, hypertension appeared with similar rates between the ranibizumab and VEGF Trap-eye groups (7.9% vs 6.5%). In pool 1 (SOC and PT), the overall rate of arterial thromboembolic events was higher in VEGF Trap-eye groups (3.2%) compared to 1.8% in ranibizumab group.

Taking into account the fact that almost 20% of drug substance goes through the systemic circulation, systemic effects of VEGF Trap-eye on the circulation cannot be excluded, and appropriate monitoring is foreseen in the RMP.

The number of cerebrovascular events was higher in the VEGF Trap-Eye groups (35) compared with ranibizumab (2 cases) in the elderly, especially in the sub-group ≥ 85 years (20 vs 1 case), during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events in the VEGF Trap-Eye groups vs ranibizumab: 53 vs 12 (27 vs 3 in the sub-group ≥ 85 years). One death due to CVA in the 0.5Q4 group and one death due to ischemic stroke in the 2Q8 group were considered as treatment related.

Among severe non-ocular TEAEs, TIA (transient ischemic attack) was observed in 10 patients treated with VEGF Trap-eye, while no cases occurred in comparator group. The majority of these subjects had pre-existing risk factors for cardiovascular disease. No subject had a positive anti-drug antibody status. Since subjects were randomised to treatment, it is reasonable to assume that there would be an equal prevalence of risk factors in those assigned to ranibizumab.

Arterial thromboembolic events are listed as an important potential risk in the RMP and covered in sections 4.4 and 4.8 of the SmPC. The higher proportion of TIAs and cerebrovascular events reported within the pooled data is of concern and will be carefully considered within further assessments of ATEs during routine pharmacovigilance procedures and PSURs.

No specific studies have been provided in renal and hepatic insufficiency; nor specific interaction studies have been performed.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of aflibercept appears to be similar to the already marketed comparator drug, ranibizumab. No dose related effect was observed.

Concerns were raised on potential role of aflibercept on the arterial thromboembolic events, cerebrovascular events and TIAs. As routine pharmacovigilance, these events will be subject to m monitoring and safety evaluation in each PSUR. A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for ATEs.

The CHMP has also requested additional pharmacovigilance activities in the form of a non-interventional study to assess the safety and real-life treatment practice with aflibercept.

Further long term data are expected at the conclusion of extension study VGFT-OD-0910.

Educational material for physicians and patients to allow correct use of the product will be prepared. The Applicant has submitted a detailed outline in the RMP, but a study protocol should be designed to assess the knowledge and understanding of the key messages by physicians and patients, and submitted to the CHMP before study initiation (see Pharmacovigilance section).

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan (version 7)

The applicant submitted a risk management plan, which included a risk minimisation plan.

SUMMARY OF THE RISK MANAGEMENT PLAN

Safety Concern	**Proposed pharmaco-vigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Important identified risks		
Endophthalmitis	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for an intraocular infection (see Annex 9).	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Serious adverse reactions related to the injection procedure included endophthalmitis. Uncommon: endophthalmitis Labeling (Special warnings and precautions for use, section 4.4): Intravitreal injections, including those with Eylea®, have been associated with endophthalmitis (see section 4.8 Undesirable effects). Proper aseptic injection techniques must always be used when administering Eylea®. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay and these should be managed appropriately. Labeling (Method of administration): ***Method of administration*** Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface) have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Transient intraocular pressure increase	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8) Serious adverse reactions related to

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with Eylea and included endophthalmitis, traumatic cataract and transient increased intraocular pressure IOP increase labeled as ADR (frequency category: common) Labeling (Special warnings and precautions for use, section 4.4): ***Increase in intraocular pressure*** Increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including those with Eylea® (see section 4.8). Special precaution is needed in patients with poorly controlled glaucoma (do not inject Eylea® while the intraocular pressure is ≥ 30 mmHg). In all cases both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Conjunctival hemorrhage	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: very common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Eye pain	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: very common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		injection procedure video, patient information audio-CD and patient information booklet)
Vitreous detachment	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Vitreous floaters	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Retinal pigment epithelium tears	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Undesirable effects, section 4.8) Labeled as ADR (frequency category: common) Labeling (Special warnings and precautions for use, section 4.4): ***Retinal pigment epithelial tears*** Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD, include a large and/or high pigment epithelial retinal detachment. When initiating Eylea® therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears. Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		information audio-CD and patient information booklet)
Important potential risks		
Hypersensitivity and immunogenicity	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labelling (Special warnings and precautions for use, section 4.4): ***Immunogenicity*** As this is a therapeutic protein, there is a potential for immunogenicity with Eylea® (see section 4.8). Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g. pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.
Traumatic cataract	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR.	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with Eylea® and included endophthalmitis, traumatic cataract and transient increased intraocular pressure (see section 4.4). Cataract labeled as ADR (frequency category: common) Additional risk minimization: Educational program (Physician information pack including prescriber guide, intravitreal injection procedure video, patient information audio-CD and patient information booklet)
Arterial thromboembolic events (ATEs) including non-MI ATEs (cerebrovascular events and TIAs) and cardiovascular ischemic events	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR. A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for ATEs (see Annex 9). Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with	Routine risk minimization: Labeling (Undesirable effects, section 4.8): Arterial thromboembolic events (ATEs) are adverse events potentially related to systemic VEGF inhibition. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. ATEs, as defined by Antiplatelet Trialists' Collaboration (APTC) criteria, include nonfatal myocardial infarction, nonfatal stroke, or

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	aflibercept in patients with wet age-related macular degeneration (AMD))	vascular death (including deaths of unknown cause). The incidence in the phase 3 wet AMD studies (VIEW1 and VIEW2) during the 96 weeks study duration was 3.3% (60 out of 1,824) in the combined group of patients treated with Eylea® compared with 3.2% (19 out of 595) in patients treated with ranibizumab (see section 5.1). Labeling (Special warnings and precautions for use, section 4.4): There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors (see section 4.8).
Venous thromboembolic events	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Hypertension	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR A targeted questionnaire will be used to follow-up on any post-marketing or study reports suspicious for hypertension (see Annex 9).	Routine risk minimization: No activities currently planned.
Proteinuria	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Bleeding due to altered wound angiogenesis	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Medication error	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Off label use	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Embryo-fetotoxicity	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Pregnancy and lactation): ***Pregnancy:*** There are no data on the use of aflibercept in pregnant women.

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Studies in animals have shown embryo-fetal toxicity after high systemic exposure (see section 5.3). Although the systemic exposure after ocular administration is very low, Eylea® is not recommended during pregnancy unless the potential benefit outweighs the potential risk to the fetus.
Retinal hemorrhage	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: No activities currently planned.
Important missing information		
Use of Eylea® in patients with uncontrolled glaucoma	Routine pharmacovigilance: Ongoing monitoring and safety evaluation in each PSUR	Routine risk minimization: Labeling (Special warnings and precautions for use, section 4.4): Special precaution is needed in patients with poorly controlled glaucoma
Concomitant use of different anti-VEGF therapies and other therapies for wet AMD	Routine pharmacovigilance: Ongoing monitoring, safety evaluation in each PSUR, provide safety results of ongoing clinical studies Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD))	Routine risk minimization: No activities currently planned.
Long term safety beyond 2 years	Routine pharmacovigilance: Ongoing monitoring, safety evaluation in each PSUR, safety results of ongoing clinical studies Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD)) Safety data from the extension	Routine risk minimization: No activities currently planned

Safety Concern	Proposed pharmaco-vigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	study VGFT-OD-0910	
Posology utilized in marketed use	Routine pharmacovigilance: Ongoing monitoring Additional pharmacovigilance: Registry/PASS for Eylea® use in clinical practice (A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD)) Additional activity: Post authorization efficacy study: clinical trial to compare the proactive dosing regimen with injection every 2 months with a reactive regimen based on visual and anatomic outcomes.	Routine risk minimization: No activities currently planned.

The Applicant reconsidered its position and now agrees to conduct a post-authorisation safety study to assess the risk of arterial thromboembolic and cerebrovascular events including TIAs. A full study protocol should be submitted to the CHMP before study initiation.

To answer to the remaining issue regarding the optimal dosing frequency, the Applicant should commit to submit a post-authorisation randomised study with primary objective to compare the proactive 8-weekly injections to a reactive regimen based on visual and anatomic outcomes.

The Applicant has agreed to provide educational material for physicians and patients and has submitted a detailed outline of the requested educational materials in Annex 8 with the revised RMP.

Moreover, the final cross-sectional observational study protocol to assess the knowledge and understanding of physicians and patients of the key messages in the educational material should be provided to the CHMP before study initiation.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity(ies) in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
A non-interventional study to assess the safety and real-life treatment practice with aflibercept in patients with wet age-related macular degeneration (AMD). (Included in RMP- Final study protocol: February 2013)	Final study report 31 December 2018
Long-term safety extension study VGFT-OD-0910 (Included in RMP)	Final study report: April 2015
A post-authorisation safety study to evaluate physician and patient knowledge	Final study

Description	Due date
of information on safety and safe use for Eylea in Europe. (Included in RMP - Final study protocol Feb 2013)	report 31 December 2014

The following additional risk minimisation activities were required:

All ophthalmological clinics where EYLEA is expected to be used are provided with a physician information pack containing physician information which includes the Summary of Product Characteristics, an intravitreal injection procedure video and -pictogram as well as patient information packs. The patient information packs include the patient information leaflet, a patient information booklet and an audio-CD. The key safety messages of the educational materials are outlined in chapter 4, conditions or restrictions with regard to the safe and effective use of the medicinal product.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Neovascular age-related macular degeneration is a chronic, progressive, degenerative condition affecting the eye, which, left untreated, results in moderate to severe visual loss. Potential benefits of therapies in this area are prevention of progression of vision loss, and improvement of reduced vision.

Anti-angiogenic therapy with the vascular endothelial growth factor inhibitor ranibizumab is currently the treatment of choice for neovascular AMD. Monthly injections of ranibizumab have been shown to prevent moderate vision loss in over 90% of patients, and improve vision by an average of at least 7 letters after 1 year of treatment, with over 30% of patients gaining at least 15 letters of vision.

The sought indication of "treatment of neovascular (wet) age-related macular degeneration (AMD) for adults" implies a disease modifying effect, in that inhibition of VEGF reduces neovascularisation and vessel leakage, and is accompanied by an improvement in clinical signs and symptoms (macular thickness and vision). This is not a first-in-class product and the development program has been designed to demonstrate non-inferiority against an existing VEGF inhibitor. As such the clinical trials were designed to provide long-term (2-year) data.

The development plan of the anti-VEGF treatment Eylea is satisfactory and in agreement with the historical development of other treatments for Wet AMD. As Ranibizumab (Lucentis) is currently the gold standard therapy for patients suffering from wet AMD, it was selected as comparator in the pivotal non-inferiority studies.

A total of 1217 and 1098 patients were respectively randomized in two pivotal studies, VIEW 1 and VIEW 2. The choice of the primary criteria was discussed and agreed through scientific advices. All criteria or methods used for assessment are well validated for the pathology.

The primary endpoint, i.e. proportion of subjects maintaining vision at Week 52, was met for all VEGF Trap-Eye treatment regimens and established the non-inferiority of VEGF Trap-Eye to ranibizumab (at a pre-specified 10% margin). The statistical test sequence showed confirmatory results with narrow confidence intervals (i.e. ≤ 3.1% and ≤ 2.6 %, in VIEW 1 and in VIEW 2, respectively). These intervals were well below the more stringent non-inferiority margin of 7% which was recommended by the Scientific Advice in 2007 specifically for the pooled analysis, with respect to the more modest difference with placebo observed for pegaptanib (i.e. 14%).

Data from the two pivotal studies show that injections of VEGF Trap-Eye every 8 weeks (initiated with three monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) at Year 1. Results for the secondary endpoints show further benefits and support the comparable efficacy of the two therapies; subjects gained an average of 8 letters of vision, with 31% gaining at least 15 letters; choroidal neovascularisation area decreased by an average of 4 mm^2, and visual function questionnaire test scores improved by an average of 5 points. These benefits were evident across all subgroups and regions.

The analysis of the change from baseline in ETDRS letter score in the 2Q4 group vs RQ4 group was the first ordered comparison for testing superiority. Results, in study VIEW 1, showed superiority of VEGF Trap 2Q4 regimen over ranibizumab (p=0.0054) however, no superiority was found in Study VIEW 2. Therefore no superiority of Eylea over ranibizumab could be demonstrated. The 2Q8 regimen was chosen as it reduces the number of injections.

The two year results show that the efficacy is maintained over the second year of treatment despite a slight drop in vision (1-2 letters of ETDRS Chart) and stagnation or slight decrease in improvements of the morphologic criteria based on OCT examinations.

Two Year data from the two pivotal studies show that capped-PRN injections of VEGF Trap-Eye given 8-weekly at entry in Year 1 (2Q8) were non-inferior to capped-PRN injections of ranibizumab, with respectively, 92.4% vs 91.6% of patients maintaining vision at Year 2. Results for the secondary endpoints show that meaningful benefits were also maintained and support the comparable efficacy of the two therapies.

Uncertainty in the knowledge about the beneficial effects.

The non inferiority over ranibizumab monthly administered was demonstrated by 1-year for all fixed proposed dosages and regimens, i.e. 0.5Q4, 2Q4 and 2Q8, and these results have been further confirmed at two years. But, as no fixed regimen was maintained as comparator in the second year, uncertainties remain whether the proposed fixed 2Q8 regimen offers the best long-term benefit. Provision of further long term data at the conclusion of study VGFT-OD-0910 should help to elucidate this point.

The results of Year 2 of the studies failed in appropriately providing guidance to clinicians in the optimal dosing regimen required to maintain initial improvement in vision. Indeed, it is presently not totally clarified whether a rigid dosing schedule with a maximum dosing interval of 8 weeks or retreatment on a capped-PRN basis, are required to maintain the optimal efficacy of VEGF Trap-Eye beyond Year 1. The results submitted for the second year using reactive dosing (PRN), instead of proactive dosing in Year 1, suggest that a part of patients may benefit from less or more frequent dosing than the 2Q8 dosings. This is of importance, since the main benefit of this product over the existing standard of care would be the reduced frequency of injections required to produce a

similar effect. Therefore, the CHMP recommended that this point be further investigated through a post-marketing study.

Risks

Unfavourable effects

The safety database for VEGF Trap-Eye has not highlighted any major safety concerns. Several of the commonly reported adverse events are associated with the injection procedure and may be considered non-serious or easily manageable (conjunctival haemorrhage, eye pain, transient rise in intraocular pressure). Rates of more serious events such as endophthalmitis were low, and there does not appear to be any significant risk of intraocular inflammation.

The risk of clinically significant decrease in visual acuity appeared to be slightly higher in the VEGF Trap-Eye groups than in the ranibizumab control group.

The most common ocular adverse reactions (in at least 5% of patients treated with Eylea) were conjunctival haemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters and increased intraocular pressure.

In addition, cases of endophtalmitis have been associated with intravitreal injections of aflibercept as well as retinal detachment, retinal haemorrhage and retinal tear.

As with all therapeutic proteins, there is a potential for immunogenicity with aflibercept. The number of positive anti-drug antibodies (ADA) was similar between the treatment groups in the pivotal studies.

Hypertension was a very common non-ocular adverse event. Hypersensitivity as well as Arterial thromboembolic events (ATEs) were commonly reported. One case of transient ischemic attack (TIA) was considered to be related to study drug. TEAEs of myocardial infarction, congestive cardiac failure were reported in low rate. These events will specifically be monitored post-marketing.

Uncertainty in the knowledge about the unfavourable effects

Aflibercept is a recombinant protein consisting of portions of human VEGF receptors, and acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, leading to endothelial cell proliferation and neovascularization. With regards to the fact that almost 20% of drug substance goes through the systemic circulation and given the potential role of VEGF in the systemic adverse events, systemic effects of VEGF Trap-eye cannot be excluded. Adverse reactions related to this inhibition: *hypertension, arterial thromboembolic events, haemorrhage* have been reported during the safety review of study data. It has been postulated that a link exists between use of intravitreal VEGF inhibitors and an increased risk of arterial thromboembolic events.

The global rate of arterial thromboembolic events was higher in VEGF Trap-eye groups (3.2%) compared to 1.8% in ranibizumab group. The number of cerebrovascular events was significantly higher in the VEGF Trap-Eye groups compared with ranibizumab, especially in the sub-group ≥ 85 years, during the first year of treatment. Two-year data showed also the increased number of cerebrovascular events and TIAs in the VEGF Trap-Eye groups vs ranibizumab. Two deaths (CVA, ischemic stroke) were considered as treatment related. The applicant agreed to conduct a non-interventional postmarketing study addressing the risk of ATEs, CVAs, and TIAs.

Balance

Importance of favourable and unfavourable effects

Data from the two pivotal studies demonstrate that injections of VEGF Trap-Eye every 8 weeks (initiated three early monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) and established the non-inferiority of VEGF Trap-Eye to ranibizumab (at a pre-specified 10% margin).

Results for the secondary endpoints show further benefits and support the comparable efficacy of the two therapies. These benefits were evident across all subgroups and regions.

The results of Year 2 of the studies failed in appropriately elucidating the optimal dosing regimen required to maintain initial improvement in vision. This is the subject of a post-authorisation measure.

The safety database for VEGF Trap-Eye has not evidenced any unexpected or major safety concerns. Several of the commonly reported adverse events are associated with the injection procedure and may be considered non-serious or easily manageable (conjunctival haemorrhage, eye pain, transient rise in intraocular pressure). Rates of more serious events such as endophthalmitis were low, and there does not appear to be any significant risk of intraocular inflammation.

The applicant agreed to conduct a non-interventional postmarketing study to elucidate the risk of ATEs, CVAs, and TIAs.

Benefit-risk balance

Discussion on the benefit-risk assessment

The two pivotal studies demonstrated that injections of VEGF Trap-Eye every 8 weeks (initiated with three monthly injections) were non-inferior to monthly injections of ranibizumab, with 95% of patients maintaining vision (ie, losing <15 letters) at Year 1. Results for the secondary endpoints support the comparable efficacy of the two therapies.

Results, in study VIEW 1, showed superiority of VEGF Trap 2Q4 regimen over ranibizumab (p=0.0054) however, no superiority was found in Study VIEW 2. Therefore no superiority for the 2Q8 regimen over ranizumab was demonstrated.

The CHMP would like to further elucidate the optimal dosing to be used beyond one year of treatment, as uncertainties remain. A post-marketing study will be performed by the Applicant. (Please refer to efficacy conclusions).

No major or unexpected safety concerns arise from the safety database for VEGF Trap-Eye.

Further elucidation on long term safety and the risk of arterial thromboembolic events, including cerebrovascular events and TIAs, will be provided by post-marketing studies.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Eylea in the

treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1)

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 7 of the Risk Management Plan presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).
In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where EYLEA is marketed, at launch and after launch all ophthalmological clinics where EYLEA is expected to be used are provided with a physician information pack containing the following elements:

- Physician information
- Intravitreal injection procedure video
- Intravitreal injection procedure pictogram
- Patient information packs

The physician information should contain the following key elements:

- The Summary of Product Characteristics
- Sterile techniques, including periocular and ocular disinfection to minimise the risk of infection
- Use of antibiotics
- Use of povidone iodine or equivalent
- Techniques for the intravitreal injection

- Patient monitoring after intravitreal injection
- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- Management of intravitreal injection related adverse events

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

- Patient information leaflet
- How to prepare for EYLEA treatment
- What are the steps following treatment with EYLEA
- Key signs and symptoms of serious adverse events including endophthalmitis, increased intraocular pressure, conjunctival hemorrhage, eye pain, vitreous detachment, vitreous floaters, retinal pigment epithelium tear and traumatic cataract
- When to seek urgent attention from their health care provider

Obligation to complete post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
To perform a post-authorisation randomised study with the primary objective of comparing the standard regime of injections every 8 weeks with a reactive regimen based on visual and anatomic outcomes, based on a CHMP approved protocol.	Final study report submission: 31 December 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Aflibercept is qualified as a new active substance.