26 June 2014
EMA/430291/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Eylea

International non-proprietary name: AFLIBERCEPT

Procedure No. EMEA/H/C/002392/II/0009

Note

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

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List of abbreviations

Laser	Laser treatment with sham IVT
0.5Q4	0.5 mg VEGF Trap every 4 weeks
2Q4	2mg VEGF Trap administered every 4 weeks, with sham laser
2Q8	2 mg VEGF Trap administered every 8 weeks after receiving 5 initial monthly doses
2PRN	2 mg VEGF Trap as needed
ADA	Anti-drug antibodies
ADR	Adverse drug reaction
AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
AUC	Area under the concentration-time curve
BCVA	Best corrected visual acuity
BLQ	Below the limit of quantitation
BMI	Body mass index
CI	Confidence interval
c_{max}	Maximum plasma concentration
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Score
ELISA	Enzyme-linked immunosorbent assay
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EQ-5D	Euro QOL-5 dimensions questionnaire
FAS	Full analysis set
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
Ig	Immunoglobulin

IOP	Intraocular pressure
IVT	Intravitreal
LLOQ	Lower limit of quantitation
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NAb	Neutralising antibody
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire-25
OCT	Optical coherence tomography
PD	Pharmacodynamics
PK	Pharmacokinetics
PlGF-2	Placental growth factor-2
PPS	Per protocol set
PRN	As needed
PT	MedDRA preferred term
RMP	Risk Management Plan
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SOC	MedDRA system organ class
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum plasma concentration
TEAE	Treatment emergent adverse event
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 7 November 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Eylea	AFLIBERCEPT	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH proposed the update of SmPC section 4.1 to add a new indication for the treatment of visual impairment in adult patients with diabetic macular oedema. Consequential updates were proposed for SmPC sections 4.2, 4.4, 4.8, 5.1 and 5.2. SmPC section 4.8 was furthermore updated to introduce a joint summary of the safety profile across all indications. The Package Leaflet was updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request(s) for consideration

Additional data protection / marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 21 February 2008 and 24 June 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

CHMP Rapporteur: Pierre Demolis

CHMP Co-Rapporteur: Robert Hemmings

PRAC Rapporteur: Isabelle Robine

Submission date:	7 November 2013
Start of procedure:	22 November 2013
Rapporteur's preliminary assessment report circulated on:	16 January 2014
CoRapporteur's preliminary assessment report circulated on:	13 January 2014
PRAC RMP advice and assessment overview adopted by PRAC :	5 February 2014
Joint Rapporteur's updated assessment report circulated on:	14 February 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 February 2014
MAH's responses submitted to the CHMP on:	19 March 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	22 April 2014
PRAC Rapporteur's preliminary assessment report:	22 April 2014
PRAC RMP advice and assessment overview adopted by PRAC :	8 May 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	
Rapporteur's assessment report on the MAH's responses circulated on:	5 June 2014
PRAC RMP advice and assessment overview adopted by PRAC :	13 June 2014
Rapporteur's updated assessment report on the MAH's responses circulated on:	20 June 2014
CHMP opinion:	26 June 2014

2. Scientific discussion

2.1. Introduction

Eylea contains the active substance aflibercept (also referred to as VEGF Trap), which is a recombinant fusion protein consisting of ligand binding regions within the extracellular domains of the human VEGF

receptor (VEGFR) linked to the Fc domain of human immunoglobulin IgG1. More specifically, aflibercept comprises immunoglobulin domain 2 from VEGFR1 fused to Ig domain 3 from VEGFR2, which in turn is fused to the constant region of a human IgG1.

Aflibercept binds multiple isoforms of VEGF-A and placental growth factor-2 (PlGF-2) which are members of the VEGF family of angiogenic factors that act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells, producing pathological neovascularization, excessive vascular permeability, and vascular inflammation.

Eylea has been approved in the European Union (EU) under the centralised procedure by Commission Decision on 22 November 2012 for the treatment of adult patients with neovascular (wet) age-related macular degeneration (AMD). The indication was later extended by Commission Decision on 26 August 2013 to include treatment of visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) in adults.

Eylea is a solution for injection available in vials or pre-filled syringes. The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitrers given intravitreally (IVT).

With this application, the MAH sought the addition of a new indication for adults *"for the treatment of diabetic macular oedema (DME)".* In support of this application, the MAH submitted results from the clinical development program including a Phase 2 study (DA VINCI) and two similarly designed phase 3 studies (VISTA and VIVID).

Diabetic macular oedema (DME) is one of the major causes of visual impairment in patients with diabetic retinopathy (DR). DR is a complication of diabetes resulting from damage to the blood vessels of the retina in the back of the eye. The risk of related visual loss in people with diabetes is up to 25 times higher than in the population not affected by diabetes. Vision loss may become irreversible when anatomic structures are impaired due to macula oedema chronicity. DME is often bilateral and therefore, may affect greatly the quality of life of active subjects.

About 10 % of diabetic patients are affected by DME. The control of diabetes-associated metabolic abnormalities (i.e., hyperglycaemia, hyperlipidaemia, and hypertension) is of importance in preserving visual function since these conditions have been identified as major risk factors for both the development and progression of DR and DME.

In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser photocoagulation as the standard of care for DME and laser became for years the mainstay of DME treatment. At the time of this report, other therapeutic options for the management of DME included surgery, steroids, and anti-VEGF agents.

Several proinflammatory cytokines including VEGF have been shown to be extensively involved in the development and progression of DME. VEGF promotes neovascularization and microvascular leakage, which are thought to contribute to vision loss. Consequently, antagonising the VEGF-mediated pathological vascular hyperpermeability in the retina may help stabilising vision but also maintaining and improving vision.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

In line with the Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00 corr 1), since aflibercept is a protein and unlikely to result in a significant risk to the environment, Eylea is exempted from an environmental risk assessment.

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (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.

- Tabular overview of clinical studies

Study Number Section Reference	Study	Study Design and Parameters	Treatment Route, Dose	Subjects with DME
Phase 1				
VGFT-OD-0307 Module 5.3.3.2 Section 2.2.1	Phase 1 exploratory study of safety, tolerability and biological activity	R, DM, PC, RD	IV: 0.3 mg/kg 1 mg/kg 3 mg/kg placebo (normal saline)	9 subjects 6 0 0 3
VGFT-OD-0512 (CLEAR-IT DME 1) Module 5.3.3.2 Section 2.3.1	Phase 1 exploratory study of safety, tolerability, and biological effect	OL, sd	IVT: 4 mg	5 subjects
Phase 2				
VGFT-OD-0706.i (DA VINCI) VGFT-OD-0706.f (DA VINCI) Module 5.3.5.4 Section 2.3.2	Phase 2, multi-center study of efficacy, safety, and tolerability	R, DM, AC,	VEGF Trap-Eye IVT with sham laser: 0.5Q4 2Q4 2Q8 (after 3 initial monthly doses) 2 mg as needed (after 3 initial monthly doses) (2PRN) Laser with sham injection every 4 weeks.	VEGF Trap-Eye: 175 subjects treated 0.5Q4: 44 subjects 2Q4: 44 subjects 2Q8: 42 subjects 2PRN: 45 subjects Laser: 44 subjects treated
VGFT-OD-0706.PK Module 5.3.3.2 Section 2.3.3	PK sub-study of VGFT-OD-0706 (DA VINCI)	OL, PK, sd	VEGF Trap-Eye IVT: 2 mg	 8 subjects Subjects had previously received VEGF Trap-Eye as part of study VGFT-OD-0706 (DA VINCI)
Phase 3				
VIVID DME (91745) Module 5.3.5.1 Section 2.3.4	Phase 3, multi-center study of efficacy, safety, and tolerability Results of the primary analysis at week 52 for this ongoing study	R, DM, AC	VEGF Trap-Eye IVT with sham laser: 2Q4 2Q8 (after 5 initial monthly doses) Laser with sham injection every 4 weeks.	VEGF Trap-Eye: 271 subjects (SAF) 2Q4: 136 subjects 2Q4: 135 subjects Laser: 133 subjects (SAF) Laser group subjects with additional anti-VEGF treatment for study eye: 32 subjects. fellow eye: 32 subjects. FAS: 403 SAF: 404
VISTA DME (VGFT-OD-1009) Module 5.3.5.1 Section 2.3.5	Phase 3, multi-center study of efficacy, safety, and tolerability Results of the primary analysis at week 52 for this ongoing study	R, DM, AC	VEGF Trap-Eye IVT with sham laser: 2Q4 2Q8 (after 5 initial monthly doses) Laser with sham injection every 4 weeks.	VEGF Trap-Eye: 307 subjects (SAF) 2Q4: 155 subjects 2Q8: 152 subjects Laser: 154 subjects (SAF) Laser group subjects with additional anti-VEGF treatment for study eye: 48 subjects fellow eye: 91 subjects FAS: 459 SAF: 461

Note: For the phase 3 studies, subjects in the laser group that met the criteria could have received additional VEGF Trap-Eye treatment after week 24 (VISTA DME section 6.1.1.2; VIVID DME section 6.1.1.2) and subjects in all treatment groups could have received anti-VEGF treatment in the fellow eye (VISTA DME section 6.1.1.4; VIVID DME section 6.1.1.4).

2Q4 = 2 mg VEGF Trap-Eye every 4 weeks; 2Q8 = 2 mg VEGF Trap-Eye every 8 weeks after 3 or 5 initial monthly doses; AC = Active controlled, DM = Double-masked, DME = diabetic macular edema; IVT = Intravitreal; Laser = macular laser coagulation; Open-label = OL; PC = Placebo controlled; PK = Pharmacokinetics; RD = Repeat dose; R = Randomized; sd = Single-dose; VEGF = Vascular endothelial growth factor.

2.3.2. Pharmacokinetics

The development of aflibercept (VEGF Trap) for the treatment of DME occurred concurrently with the clinical development programs for the treatment of neovascular AMD and CRVO. The pharmacokinetics (PK) and pharmacodynamics (PD) observed after VEGF Trap IVT administration in subjects with AMD and CRVO were discussed in previous applications.

The PK characterisation in support of this application relied partly on the data already submitted and assessed for the already approved indications as well as on additional data collected specifically in the target patients (DME patients). Considering the nature of the product and its intended use, PK data based on the measurement of plasma levels was only relevant with regards to the systemic tolerability

of the product. In order to bridge the data for systemic tolerability already collected in AMD and CRVO patients, the systemic exposure in these latter groups of patients was compared to that observed in DME patients.

Two phase 1 studies were conducted in subjects with DME receiving VEGF Trap (VGFT-OD-0307 and VGFT-OD-0512):

- Study VGFT-OD-0307

This was a double-blind, randomised, dose-escalating study evaluating safety, tolerability and bio-effect after intravenous (IV) administration of VEGF Trap in subjects with DME. Subjects were planned to receive 4 IV infusions of VEGF Trap, once every 2 weeks (day 1, day 15, day 29, and day 43), at dose levels of 0.3 mg/kg, 1 mg/kg, or 3 mg/kg, or placebo. However, dosing was stopped before the planned sequential dose escalation when dose-limiting toxicities (grade 2 proteinuria in a single subject and grade 4 treatment-related malignant hypertension in a single subject) were observed in another phase 1 dose-escalation study in subjects with AMD (VGFT-OD-0305). The dose limiting toxicities observed in study VGFT-OD-0305 occurred at the 3 mg/kg IV dose.

Therefore, only the lowest dose (0.3 mg/kg) of study drug was investigated. Nine subjects were randomised and treated (3 placebo, 6 VEGF Trap 0.3 mg/kg). Concentrations of free and bound VEGF Trap were determined at selected time intervals following dose administration (screening, day 1[pre-dose], day 8, day 15, day 29, day 43, day 57, day 71, day 85, and day 133 [3 months post-last dose]).

- Study VGFT-OD-0512

This was an open-label, proof-of-concept study evaluating safety, tolerability and bio-effect of VEGF Trap IVT administration in subjects with DME. Five (5) subjects with DME were enrolled. Subjects received a single IVT injection of 4 mg VEGF Trap into the study eye. During the first 6 weeks after the injection, vital signs as well as ocular and systemic adverse events(AEs) were recorded. Blood samples for analysis of free and bound VEGF Trap concentrations in plasma were collected at screening, day 1 (pre-dose), day 3, day 8, day 15, day 29, day 43 and day 155 following the single IVT administration.

A phase 2 study was conducted in subjects with DME receiving IVT injections of VEGF Trap:

- Study VGFT-OD-0706 – DA VINCI

This study was a double-masked, prospective, randomised, multiple-dose study evaluating the efficacy, safety and tolerability of different IVT dosing regimens of VEGF Trap in DME patients (see section 2.4.1. for details).

PK data was obtained in a sub-study, which employed a dense sampling schedule for PK analysis in 8 subjects with DME who had previous exposure to VEGF Trap in VGFT-OD-0706. Plasma samples were collected on day 1 (at 0 hours [pre dose], 4 hours post-dose, and 8 hours post-dose), day 2, day 3, day 4, day 5, day 8, day 15, and day 29. The PK parameters for free and adjusted bound VEGF Trap were estimated using non-compartmental methods.

PK data was furthermore collected in one of the Phase 3 studies:

- Study 91745 - VIVID

VIVID was a randomised, active-controlled, double-masked, multi-centre international clinical study to assess the potential benefit of VEGF Trap treatment administered IVT compared with the standard of care laser photocoagulation treatment, over 148 weeks in subjects with DME secondary to diabetes mellitus. Data up to the primary endpoint at week 52 were provided in support of this application. A

total of 404 subjects were randomized 1:1:1 to one of 3 treatment groups, 2 different dosing regimens of 2 mg VEGF Trap (with sham laser), 2Q4 or 2Q8 (following 5 initial monthly doses), or laser photocoagulation treatment (with sham injections).

PK data were collected utilising a sparse sampling schedule. Plasma samples for the measurement of free and adjusted bound VEGF Trap concentrations were collected at week 0 (day 1 before study drug administration/baseline and 1 to 4 hours after the first study drug administration), day 2 to day 4, week 24 (before study drug administration) and week 52 (before study drug administration).

Methods

The same analytical methods as in previous applications for AMD and CRVO were used.

Concentrations of free and bound VEGF Trap in plasma were measured using validated enzyme-linked immunosorbent assays (ELISA). The assay for bound VEGF Trap was calibrated using the VEGF: VEGF Trap standards, and results were reported for bound VEGF Trap as weight per volume (µg/mL or ng/mL) of the VEGF:VEGF Trap complex. To determine the amount of bound VEGF Trap (referred to as adjusted bound VEGF Trap), the concentration of the complex must be adjusted by a factor of 0.717 to account for the VEGF present in the bound complex. The lower limit of quantitation (LLOQ) for the free and adjusted bound assays is 0.0156 µg/mL and 0.0315 µg/mL, respectively.

Dense VEGF Trap plasma concentration-time data were used to calculate PK parameters by non-compartmental analysis for these studies. Sparse VEGF Trap plasma concentration data were used to compare concentrations of free and adjusted bound VEGF Trap in the DME subject population and to assess these concentrations in a number of sub-groups. Graphical assessments of individual and mean plasma concentration versus time data were evaluated, and summary statistics of the derived parameters were generated.

In each of the clinical studies, mean VEGF Trap concentrations in plasma were calculated from all the individual subject results. For the calculation of the arithmetic means, those individual concentrations that were below the limit of quantitation (BLQ) were assigned a value of 0 µg/mL.

Results

Study VGFT-OD-0307:

Following administration of 0.3 mg/kg VEGF Trap IV, free VEGF Trap was quantifiable in plasma in 2 of the 6 subjects, 2 weeks after the first dose. Free VEGF Trap concentrations were quantifiable in plasma in 5 of the 6 subjects, 2 weeks after the last dose, but no longer 28 days after the last dose (study day 71). Plasma concentrations of bound VEGF Trap were quantifiable in all subjects after the initial drug administration (day 1) up through day 85 of the study (42 days following the last dose). At the last scheduled sampling time point (day 133, i.e. 90 days following the last dose), concentrations of bound VEGF Trap were still quantifiable in 3 of the 6 subjects. At no time were the levels of free VEGF Trap in excess of bound VEGF Trap, nor was there a plateauing of the systemic bound VEGF Trap concentrations.

The concentrations of both free and adjusted bound VEGF Trap in plasma were higher (approximately 200% and 116%, respectively) at day 8 in study VGFT-OD-0307 (subjects with DME) compared to study VGFT-OD-0305 (subjects with AMD).

At no time were the levels of free VEGF Trap in excess of bound VEGF Trap, nor was there a plateauing of the systemic bound VEGF Trap concentrations. Taken together, these data suggest that in this study, there was no evidence for saturation of VEGF binding.

VGFT-OD-0512

Free VEGF Trap plasma concentrations following a single IVT dose of 4 mg VEGF Trap into the study eye were below LLOQ at baseline, as well as at the day 15 and later visits. Free VEGF Trap was detectable in plasma only at the day 3 and day 8 sampling times. Maximum detected concentration of VEGF Trap was 0.092 mg/L and 0.036 mg/L on day 3 and day 8, respectively, and the mean concentrations were 0.050 mg/L and 0.027 mg/L, respectively.

All plasma concentrations of bound VEGF Trap that were collected before the first dose (screening and day 1), at a follow-up visit (day 155), and at the early termination visit (1 sample, day 82) were BLQ. Measurable concentrations of bound VEGF Trap in plasma were observed between day 3 and day 43. The adjusted bound VEGF Trap concentrations in plasma were generally low. The concentration-versus-time profile of bound VEGF Trap concentrations did not suggest that PK saturation was achieved.

None of the 5 subjects had detectable anti-VEGF Trap antibodies.

VGFT-OD-0706

Following a 2 mg IVT administration, the systemic exposure to free VEGF Trap was low. Complete concentration-time profiles were not obtained for most subjects because of the low systemic concentrations of free VEGF Trap. Each subject had a varying number of samples with concentrations of free VEGF Trap below the LLOQ, and only a total of 35% of the post-dose samples were above the LLOQ and quantifiable. Despite using a dense sampling scheme, only a limited number of detectable concentrations of free VEGF Trap were observed, and thus an elimination half-life ($t_{1/2}$) for free VEGF Trap could not be accurately determined. However, by visual inspection of the mean data, the concentration-time profile of free VEGF Trap could be described by an initial absorption phase followed by a single elimination phase.

The maximum plasma concentration (c_{max}) of free VEGF Trap observed among individual subjects ranged from 0 µg/mL to 0.0760 µg/mL, with a mean of 0.0320 µg/mL and a median of 0.0340 µg/mL. The variability in exposure between subjects was large, presumably because concentrations of free VEGF Trap were close to or below the LLOQ for the analytical assay.

The median time to peak systemic concentrations of free VEGF Trap occurred approximately 14 hours to 15 hours following IVT administration (median t_{max} = 0.625 days). The area under the concentration-time curve (AUC) from time zero to the last validated measurable plasma concentration (AUC_{last}) ranged from 0 to 0.165 day•µg/mL (median of 0.0767 day•µg/mL). For those subjects with detectible concentrations of free VEGF Trap, the duration of exposure was short, with a median time to LLOQ of 3.6 days (ranging from 0.974 days to 7.03 days [actual times]).

The systemic exposure to adjusted bound VEGF Trap was low. In 7 out of 8 subjects, pre-dose concentrations of adjusted VEGF Trap:VEGF complex were below the LLOQ of the assay. A baseline concentration of adjusted VEGF Trap:VEGF complex (0.106 µg/mL) was observed in one subject, who was last treated with VEGF Trap 29 days (as part of VGFT-OD-0706 [DA VINCI]) prior to enrolment in this PK sub-study. For one subject, all post-dose concentrations of adjusted VEGF Trap:VEGF complex were found to be below the LLOQ. Of the remaining 7 subjects, concentrations of adjusted VEGF Trap:VEGF complex were low with a highest observed concentration of 0.182 µg/mL and a total of 54% of the post-dose samples above the LLOQ.

The mean concentration–time profiles observed were described by an initial increase in adjusted bound VEGF Trap concentrations to a plateau. The c_{max} of adjusted bound VEGF Trap observed among individual subjects ranged from 0 µg/mL to 0.182 µg/mL, with a mean of 0.085 µg/mL and a median of

0.0825 µg/mL. Median time to c_{max} (t_{max}) was 13.9 days. Following t_{max}, there is a plateauing of adjusted bound VEGF Trap concentration which extended until the end of sampling (day 28, nominal time), for which an average last observed concentration (C_{last}) of 0.0748 µg/mL was determined. AUC_{last} ranged from 0 day•µg/mL to 4.61 day•µg/mL (median of 1.88 day•µg/mL).

Seven subjects tested negative for ADA in samples collected at hour 0 and at day 29. One subject tested positive in the ADA assay in samples collected at hour 0 and at day 29.

The calculated PK parameters (c_{max}, t_{max} and AUC) are provided for comparison between the DME, AMD, and CRVO subject populations in the table below.

Table 1 - Summary of PK Parameters for Free and Adjusted Bound VEGF Trap in Subjects with DME (VGFT-OD-0706.PK), AMD (VGFT-OD-0702.PK), or CRVO (GALILEO [14130])

			Free VEGF Trap					
			Arithmetic[a] Mean[b]		Geometric[c] Mean		Median	
Study	N	IVT Dose (mg)	C_{max} µg/mL (CV%) (range)	AUC_{0-last}[d] µg•day/mL (CV%) (range)	C_{max} µg/mL (CV%) (range)	AUC_{0-last} µg•day/mL (CV%) (range)	t_{max} day (range)	t_{last} day (range)
VGFT-OD-0706.PK DME	6-8	2	0.0320 (79.7) (0-0.0760)	0.0733 (85.0) (0-0.165)	ND	ND	0.625 (0.326-2.06)	3.55 (0.974-7.03)
VGFT-OD-0702.PK AMD	6	2	0.0193 (118) (0-0.0540)	0.119 (159) (0-0.474)	ND	ND	0.964 (0.253-3.07)	7.03 (1.95-14.1)
GALILEO (14130)[e] CRVO	7	2	0.049 (39.25) (0.024-0.081)	0.133 (51.25) (0.071-0.227)	0.046 (42.5) (0.024-0.081)	0.119 (54.3) (0.071-0.227)	0.95 (0.33-3.0)	4.01 (2.95-6.95)
			Adjusted Bound VEGF Trap					
VGFT-OD-0706.PK DME	7-8	2	0.0850 (59.3) (0-0.182)	1.96 (65.1) (0-4.61)	ND	ND	13.9 (7.04-28.0)	28.0 (27.9-28.1)
VGFT-OD-0702.PK AMD	6	2	0.186 (40.3) (0.100-0.286)	4.43 (42.3) (2.12-6.71)	ND	ND	14.5 (14.0-28.0)	28.0 (28.0-29.0)
GALILEO (14130)[e] CRVO	8	2	0.0862 (25.61) (0.0427-0.108)	1.82 (30.0) (0.700-2.34)	0.083 (31.46) (0.043-0.108)	1.72 (41.59) (0.700-2.34)	14.0 (7-14)	28.5 (23.9-31.0)

AUC_{0-last} = area under the concentration-time curve from time zero to the last validated measurable plasma concentration, BLQ = Below the limit of quantitation; C_{max} = maximal observed concentration, CV = coefficient of variation, IVT = Intravitreal; LLOQ = Lower limit of quantitation; t_{last} = time of last concentration; N=number; ND = not determined; t_{max} = time of maximal concentration.

In the DME subject population, as also observed in the AMD and CRVO subject populations, the concentration of free VEGF Trap was very low. Mean c_{max} values were only 2-times, 1.2-times and 3-times higher than the LLOQ in DME, AMD and CRVO patients, respectively.

VIVID

After IVT administration of 2 mg VEGF Trap (2Q4 and 2Q8), the systemic exposure to free VEGF Trap was low. Concentrations of free VEGF Trap in plasma after repeated VEGF Trap administrations were quantifiable in only a minority of samples evaluated. The majority of the detectable concentrations

were close to LLOQ (LLOQ = 0.0156 µg/mL) and did not exceed the LLOQ by more than about 4-fold. In general, free VEGF Trap concentrations were less than 0.065 µg/mL. Observed maximum concentrations of free VEGF Trap in the plasma were reached after 2 days to 4 days, and declined to BLQ in almost all subjects thereafter. Repeated administration of VEGF Trap 2Q4 or 2Q8 did not result in any accumulation of the VEGF Trap in plasma.

Concentrations of adjusted bound VEGF Trap were detectable in plasma between 2 to 4 days after IVT administration of VEGF Trap. The maximum mean concentrations of adjusted bound VEGF Trap were observed at week 24, i.e. 4 weeks after the sixth administration of the 2Q4 dosing regimen and at week 52, i.e. 4 weeks (half the dosing interval) after the ninth administration of the 2Q8 dosing regimen. The maximum mean concentrations were approximately 0.150 µg/mL and 0.100 µg/mL, after 2Q4 and 2Q8 administration, respectively. At each time, the mean free VEGF Trap concentrations had already declined to BLQ.

Exploratory sub-group analyses in VIVID revealed no relevant differences in free and adjusted bound VEGF Trap plasma concentrations with respect to age, race, body mass index (BMI), renal impairment (as specified by medical history and creatinine clearance), medical history of hepatic impairment, or haemoglobin A1c (HbA1c). Comparison of ethnicity and geographical region (Japan versus non-Japan) did not reveal any relevant differences with respect to free VEGF Trap plasma concentration.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

As in the AMD and CRVO programs, the DME clinical pharmacology program furthermore evaluated PD parameters that differentiated between the local ocular and systemic effects of VEGF Trap after IVT administration in subjects with DME. The ocular PD effect (resolution of macular oedema) was assessed by measurement of central retinal thickness (CRT) using optical coherence tomography (OCT). Systemic PD effects were assessed using measurement of blood pressure as a surrogate marker. Finally, the immunogenic potential of VEGF Trap in DME patients was investigated.

See section 2.3.2. and 2.4. for details on the study design of the clinical studies. A summary of the PD and immunogenicity data collected in the studies is provided below.

- Study VGFT-OD-0307 (phase 1 study, IV administration)

Pharmacodynamic information gathered in this study included macular volume and blood pressure measurements. Furthermore, the last administration of study drug was followed by a 6-week observation period for retinal thickness and development of anti-drug antibodies (ADA). Subjects were followed up to 1 year after the last dose of study drug for safety assessment.

- Study VGFT-OD-0512 (phase 1 study, single IVT administration)

Blood samples for analysis of ADA in serum were collected before study drug administration at screening, day 43, and day 155. Pharmacodynamic information including retinal thickness and blood pressure measurements was obtained.

- Study VGFT-OD-0706 – DA VINCI (phase 2 study)

PD data were obtained with regards to CRT and blood pressure measurements. Serum samples for ADA analysis were collected on day 1 (pre dose) and on day 29.

- VIVID and VISTA

While PK data were only collected in the VIVID study, PD and immunogenicity information was gathered in both phase 3 trials. See section 2.4.2. for details on the design and methodologies for both studies.

With respect to PD, the effect of a 2 mg dose of VEGF Trap administered IVT on CRT and blood pressure was explored. Serum samples for detection of ADA were collected during the first year of the studies at week 0 (before study drug administration) and week 52 (before study drug administration). Samples that were tested positive for ADA were further evaluated for neutralising antibody (NAb) activity. Drug concentration and ADA analyses were performed using the safety analysis set.

Methods

See section 2.4. for a summary of the methods for collection of PD data.

In all clinical studies conducted, serum samples were collected for the analysis of ADAs. Two validated ADA assays were utilised to analyse samples. These were an original ELISA-based ADA assay that was used in the early phase 1 and phase 2 studies for the AMD and DME clinical development programs, and a bridging immunoassay that was used for the phase 3 studies in the AMD, CRVO, and DME clinical development programs. The sensitivity of the original ELISA assay was approximately 240 ng/mL and the sensitivity of the bridging immunoassay was approximately 5.4 ng/mL; about 40-fold more sensitive than the original ELISA.

ADA positive samples were considered to reflect pre-treatment immunoreactivity if a subject was tested positive at baseline and the titer did not increase substantially in subsequent samples. A treatment-emergent response if the ADA test was negative at screening, but post-dose sample(s) were tested positive or in case of a positive screen sample and titer increases in post-dose sample(s) at least 4-fold.

The NAb assay was a validated, competitive, ligand-binding assay used to analyse samples from the phase 3 studies in the AMD, CRVO, and DME clinical development programs. This assay incorporated a VEGF ELISA as an indirect method to determine the presence of NAbs that prevent the binding of VEGF to VEGF Trap. Results were reported as either positive or negative.

Results

PD parameters

PD results for studies VGFT-OD-0706 and VIVID are discussed in section 2.4.

Study VGFT-OD-0307

In this study, the mean and median results for blood pressure measurements varied relative to baseline values, with no obvious trends relating to treatment or treatment duration in subjects receiving VEGF Trap versus placebo. Interpretation of ocular PD measurements was limited by the small total number of subjects studied (N=9) and the fact that 2 out of 3 subjects who received placebo withdrew prematurely from the study. A slight reduction in mean macular volume from baseline to day 57 was seen in the study eye of subjects in the VEGF Trap treatment group. The mean reductions were greater in magnitude at some time points during the study than variations in values determined prior to VEGF Trap administration that occurred between screening and baseline visits. OCT measurements were inconclusive. There was no clear effect of VEGF Trap on foveal thickness.

VGFT-OD-0512

At visits on day 3 through day 43, excess retinal thickness of the study eye was less than the baseline measurements for all subjects (with individual changes ranging from -4 µm to -235 µm, and median changes of -58 µm to -84 µm). At most visits, the changes in mean excess retinal thickness relative to baseline were statistically significant by Student's t test.

At visits from day 3 through day 29, systolic blood pressure was generally lower than baseline, with median changes from baseline ranging from -14 mm Hg to -20 mm Hg. Median changes from baseline in diastolic blood pressure on day 3 through day 29 ranged -2 mm Hg to -6 mm Hg. Blood pressure values on day 43 were similar to baseline values.

Immunogenicity

Results from the bridging ADA assay used to evaluate samples from 864 subjects in the VISTA and VIVID studies are shown in the table below.

Table 2 - Number of Subjects with Anti-VEGF Trap Antibodies by Treatment Group in VISTA and VIVID

Anti-VEGF Trap Antibodies	VEGF Trap 2Q4	VEGF Trap 2Q8	Laser
VISTA DME	**(N = 155)**	**(N = 152)**	**(N = 154)**
Negative	145 (93.5%)	149 (98.0%)	152 (98.7%)
Positive in the assay	10 (6.5%)	3 (2.0%)	2 (1.3%)
Pre-treatment immunoreactivity[a]	7 (4.5%)	2 (1.3%)	1 (0.6%)
Treatment-emergent[b]	3 (1.9%)	1 (0.7%)	1 (0.6%)
Neutralizing Antibodies	1 (0.6%)	1 (0.7%)	0 (0%)
VIVID DME	**(N = 136)**	**(N = 135)**	**(N = 132)**
Negative	136 (100%)	133 (98.5%)	130 (98.5%)
Positive in the assay	0 (0%)	2 (1.5%)	2 (1.5%)
Pre-treatment immunoreactivity[a]	0 (0%)	1 (0.7%)	1 (0.8%)
Treatment-emergent [b]	0 (0%)	1 (0.7%)	1 (0.8%)
Neutralizing Antibodies	0 (0%)	0 (0%)	0 (0%)
VISTA DME/VIVID DME COMBINED	**(N = 291)**	**(N = 287)**	**(N = 286)**
Negative	281 (96.6%)	282 (98.3%)	282 (98.6%)
Positive in the assay	10 (3.4%)	5 (1.7%)	4 (1.4%)
Pre-treatment immunoreactivity[a]	7 (2.4%)	3 (1.0%)	2 (0.7%)
Treatment-emergent[b]	3 (1.0%)	2 (0.7%)	2 (0.7%)
Neutralizing Antibodies	1 (0.3%)	1 (0.4%)	0 (0%)

NOTE: Results from the SAF are presented.

ADA = Anti-drug antibody, N = Number, q4w = drug administered every 4 weeks.

[a] Subject was positive in the ADA assay at baseline and titer did not increase substantially in subsequent samples

[b] Treatment-Emergent Criteria: 1) If the screen sample is negative and post-dose sample(s) is confirmed positive or 2) If the screen sample is positive with a titer and the post-dose sample(s) is positive with a minimum 4-fold increase in titer.

In VISTA and VIVID, samples from 461 and 403 subjects, respectively, were collected at screening or pre-dose day 1 (baseline), and at week 52, or at early termination, and evaluated for ADA. A total of 15 and 4 subjects, respectively, that participated in these studies were tested ADA positive. Of these 19 subjects, 4 were in the laser group that did not receive VEGF Trap. Subjects in the laser group could have been eligible to receive anti-VEGF therapy as additional treatment in the study or fellow eye. Two of these subjects received anti-VEGF therapy (ranibizumab and VEGF Trap, respectively). The majority (10 subjects) of the 15 subjects in the VEGF Trap groups that were positive in the ADA assay did not exhibit a treatment-emergent response, and for none of these subjects neutralising activity was demonstrated. These positive responses in the ADA assay were most likely due to high serum

background levels in the assay or pre-existing immunoreactivity, and not an immune response to VEGF Trap. This is supported by the relatively low titer levels observed, the majority of which were near 30, the minimum for the ADA assay.

Only 7 subjects administered VEGF Trap demonstrated a treatment-emergent positive response in the ADA assay and 2 of these 7 subjects were in the laser group. Most titers in the post-baseline samples were generally minimal or low (titers ranged from 30 to 480). Two subjects with treatment-emergent positive responses in the ADA assay demonstrated neutralising activity at week 52, one in the 2Q4 group and one in the 2Q8 group.

None of the positive responses in the ADA assay appeared to have any impact on safety parameters assessed. None of the subjects with a treatment-emergent positive ADA response or a NAb response experienced any AEs consistent with a potential immune response, such as intraocular inflammation.

The incidence of pre-treatment immunoreactivity to VEGF Trap was approximately 1% to 2% across treatment groups, including the laser treatment group. The incidence of treatment-emergent immunoreactivity to VEGF Trap was approximately 1% across treatment groups, including the laser treatment group. There were no apparent differences in safety between subjects with or without ADA.

In the phase 3 AMD and CRVO clinical studies, the incidence of pre-treatment immunoreactivity to VEGF Trap was 1% to 3% across treatment groups. After dosing with VEGF Trap for 52 weeks, antibodies to VEGF Trap were detected in a similar percentage range of subjects. There were no differences in efficacy or safety between subjects with or without ADA.

2.3.4. Discussion on clinical pharmacology

The development of Eylea for use in DME occurred concurrently with the AMD and CRVO development program. However, additional investigation of the PK, PD and immunogenicity of Eylea specifically in the DME population was needed, given the unique features of this disease and the population affected by it, including the widespread and chronic disruption of the blood-retinal barrier in diabetes, the potential need for long term therapy, and the comorbid status of the diabetic patient population.

PK data were available from a range of studies, including dense PK sampling in a subset of 8 patients in the Phase 2 study DA VINCI. The peak and total systemic exposure to both free and adjusted bound Eylea in DME patients was comparable to that observed in AMD and CRVO patients. Small differences observed in the mean concentration-time data, appeared to reflect the high variability, the few numbers of subjects with detectable concentrations of free VEGF Trap in each study, and the low concentrations measured.

When comparing data from phase 1 IV-dosing studies conducted in DME and AMD patients, both free and adjusted bound VEGF Trap plasma concentrations were found to be higher (approximately 200% and 116%, respectively) in subjects with DME compared to subjects with AMD. This difference was attributed to the higher weight of DME subjects (115.5 kg mean body weight compared to 71.6 kg for AMD patients), which resulted in a higher total dose (0.3 mg/kg) of VEGF Trap administered. In addition, weight is a known covariate affecting systemic exposure of VEGF Trap.

There were no signs of PK saturation. No accumulation of VEGF Trap in plasma was observed after repeated IVT administration.

A subgroup analysis in VIVID did not reveal any effect of age, race, BMI, renal impairment, hepatic impairment, HbA1c, ethnicity or geographical region on systemic exposure. However, the sample sizes were small and associated with a high variability. Furthermore, a high number of concentration values were BLQ.

Overall, no specific PK concerns arose for the DME population. Relevant PK information has been included in the SmPC in relation to the DME population.

In regard to the potential immunogenicity in the DME population, VEGF Trap demonstrated very low immunoreactivity in the VISTA and VIVID studies. Only 7 subjects exhibited a positive response in the ADA assay subsequent to dosing. The antibody titers were generally low, and only 2 subjects developed antibodies with neutralising activity, neither of whom displayed an exacerbated safety profile, which was reassuring. The results were comparable to those from the AMD and CRVO development programs, and did not give rise to concerns.

2.3.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology program presented in support of this application was considered acceptable. The PK profile and immunogenicity of VEGF Trap in DME patients appear to be comparable to that observed in AMD and CRVO patients.

2.4. Clinical efficacy

Data supporting the clinical efficacy of VEGF Trap in the treatment of DME were primarily derived from two phase 3 studies: Study VGFT-OD-1009 (VISTA) and Study 91745 (VIVID). Both studies were on-going at the time of submission of this application.

In addition, the MAH presented result from a phase 2 study VGFT-OD-0706 (DA VINCI) in support of the dosing regimen.

Due to historical timing, laser therapy, which has been the standard DME therapy for years, was the reference treatment in all three studies.

2.4.1. Dose response study

DA VINCI was a phase 2, double-masked, randomised, dose-ranging study conducted in 39 sites in 3 countries (United States, Canada, and Austria) to explore the appropriate dose and dosing schedule for VEGF Trap in the treatment of DME.

The primary objective of the study was to explore the effect of various doses and dose intervals of IVT-administered VEGF Trap on BCVA in patients with DME.

A secondary objective of this study was to assess the dose-related effects of IVT-administered VEGF Trap on central retinal thickness (CRT) by optical coherence tomography (OCT) in patients with DME.

The primary endpoint in the study was change in BCVA from baseline to week 24.

The secondary endpoints were the change in BCVA from baseline to week 52, the proportion of patients who gained at least 15 ETDRS letters in BCVA from baseline at weeks 24 and 52, the change from baseline in CRT at weeks 24 and 52 as assessed by OCT, and the number of focal laser treatments.

In order to be eligible for recruitment, patients had to be adults ≥ 18 years with type 1 or 2 diabetes mellitus with clinically significant DME with central involvement (defined as OCT CRT ≥250 µm) and best corrected visual acuity (BCVA) of 20/40 to 20/320 (letter score of 73 to 24) in the study eye. Major exclusion criteria were previous vitrectomy, recent pan retinal photocoagulation, macular laser, intraocular steroids or anti-VEGF, and proliferative diabetic retinopathy.

Subjects were randomized in a 1:1:1:1:1 ratio to 1 of 5 treatment groups:

- 0.5 VEGF Trap IVT every 4 weeks (0.5Q4);
- 2 mg VEGF Trap IVT every 4 weeks (2Q4),
- 2 mg VEGF Trap IVT every 8 weeks (2Q8) [following monthly injections for the first 3 months],
- 2 mg as needed (2PRN) according to VEGF Trap re-treatment criteria [following monthly injections for the first 3 months];
- laser photocoagulation [focal laser using modified ETDRS technique], at week 1 and once every 16 weeks according to laser re-treatment criteria (laser).

Patients received an injection (active or sham) at every visit, and laser (active or sham) at week 1 (visit 3) and 1 week after study visits at which patient met the laser re-treatment criteria.

The PRN VEGF Trap re-treatment criteria were as follows (any 1 of the criteria was required):

- An increase in retinal thickness >50 µm in the central subfield on OCT compared to the lowest previous measurement;
- New or persistent cystic retinal changes or sub-retinal fluid on OCT or persistent diffuse oedema ≥250 µm in the central subfield on OCT;
- Loss of ≥5 letters from the best previous measurement in conjunction with any increase in retinal thickness in the central subfield on OCT;
- In the absence of retinal oedema in the central subfield, there was an increase in visual acuity (VA) between the current and most recent visit of ≥5 letters.

Laser re-treatment criteria (any 1 of the criteria was required):

- Thickening of the retina at or within 500 microns of the centre of the macula
- Hard exudates at or within 500 microns of the centre of the macula, if associated with thickening of adjacent retina
- A zone or zones of retinal thickening 1 disc area or larger, any part of which was within 1 disc diameter of the centre of the macula.

Eligible patients were enrolled and randomised on day 1 (visit 2), and received treatment (active/sham) at each study visit every 4 weeks, until week 52. After the 1-year treatment period, subjects were to be followed for safety in a 6-month, off-drug, follow-up phase (week 52 to week 76). However, the follow-up period was curtailed and the last visit for this study occurred in September 2010 before all subjects had reached the end of the off-drug follow-up period at week 76.

Results

A total of 221 patients were enrolled and randomised, of whom 219 were treated: 44 patients with laser and 175 patients with VEGF Trap (44 patients with 0.5Q4, 44 patients with 2Q4, 42 patients with 2Q8, and 45 patients with 2PRN). The majority of patients (80%) completed the study to the end of the treatment period (week 52).

The majority of patients in each group were male (52%-64%). Most patients (86%-93%) were white; the mean age ranged from 61 to 64 years, with an overall range of 29 to 87 years. With the exception of ethnicity, no marked differences in demographic characteristics among the treatment groups were observed. A higher proportion of patients in the 0.5Q4, 2Q4, and 2PRN treatment groups (30%-36%) were Hispanic or Latino compared to the patients in the laser and 2q8 groups (12%-18%).

Type 2 diabetes mellitus (89%-98% in each treatment group) with a Diabetic Retinopathy Severity Score (DRSS) which was moderate or severe in intensity (76% to 93% in each treatment group) were the most commonly reported baseline disease. The mean Early Treatment Diabetic Retinopathy Study (ETDRS) letter scores and mean CRT ranged from 57.6 to 59.6 letters and 426.1 to 456.6 µm, respectively. HbA1C and intraocular pressure (IOP) were comparable at baseline.

- Extent of exposure to VEGF Trap in the first 48 weeks of treatment

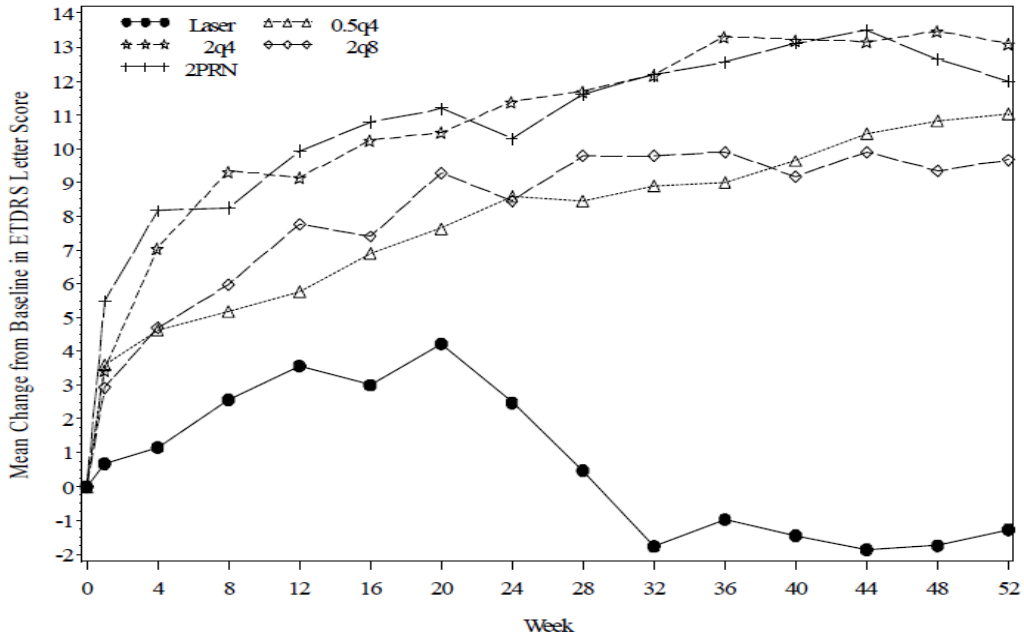
Table 3. Exposure to VEGF Trap in the First 48 Weeks of Treatment

	Laser (N=44)	0.5q4 (N=44)	2q4 (N=44)	2q8 (N=42)	2PRN (N=45)
	Number of patients with VEGF Trap-Eye Injections				
Total number of injections[1]					
Mean (SD)	0.0 (0.00)	11.7 (2.49)	10.8 (2.87)	7.2 (1.74)	7.4 (3.19)
Median	0.0	13.0	12.0	8.0	7.0
(Min:Max)	(0:0)	(2:13)	(1:13)	(1:8)	(1:13)
	Total Amount of VEGF Trap-Eye (mg)				
Total amount (mg)					
Mean (SD)	0.00 (0.00)	5.90 (1.27)	21.64 (5.74)	14.38 (3.48)	14.81 (6.33)
Median	0.00	6.50	24.00	16.00	14.00
(Min:Max)	(0.0:0.0)	(1.0:7.5)	(2.0:26.0)	(2.0:16.0)	(2.0:26.0)

- Primary efficacy endpoint: Change in BCVA from baseline to Week 24

Improvements in mean BCVA from baseline to week 24 were greater in all VEGF Trap groups (8.5 letters to 11.4 letters) compared to the laser group (2.5 letters). All comparisons of mean changes between each VEGF Trap group and the laser group were statistically significant (p ≤0.0085).

Figure 1 - Mean Change from Baseline in ETDRS Letters by Visit



- Secondary efficacy endpoints:

Change in BCVA from baseline to Week 52

Subjects in the VEGF Trap groups showed greater improvement in the mean change in BCVA to week 52 from baseline compared to the laser group. At week 52, the mean change from baseline in the

VEGF Trap groups were 9.7 to 13.1 letters, compared to the mean change from baseline in the laser group which was -1.3 letters. The difference was statistically significant for all VEGF Trap groups.

Subjects with gains in ETDRS letter score of at least 15 letters

Table 4. Patients with Gains of ≥15 and ≥10 Letters at Weeks 24 and 52

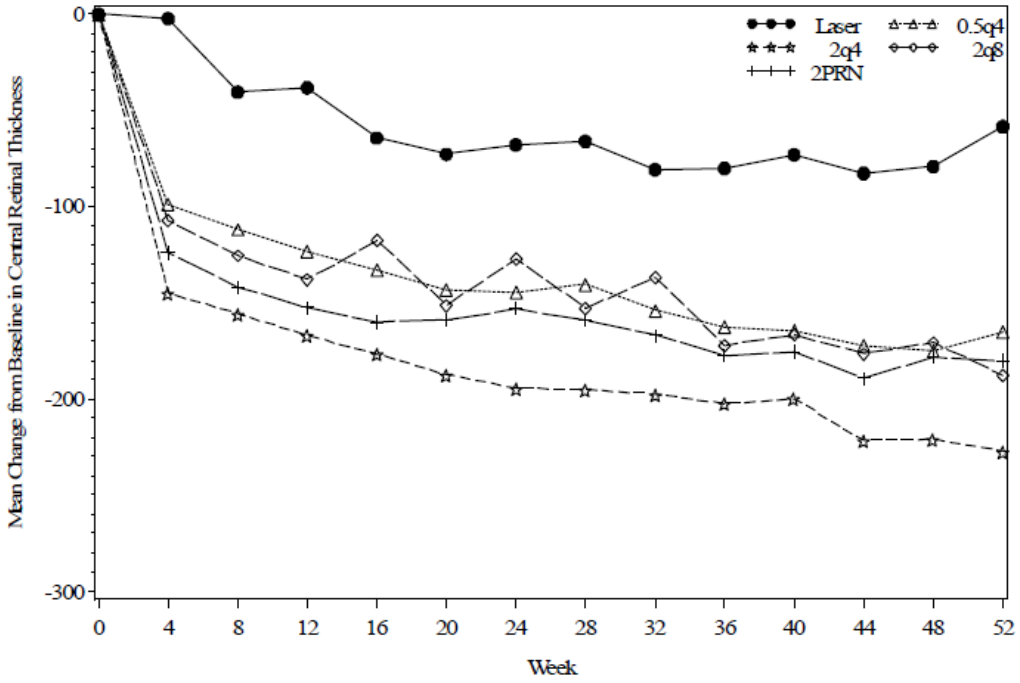
	Laser (N=44) n (%)	0.5q4 (N=44) n (%)	2q4 (N=44) n (%)	2q8 (N=42) n (%)	2PRN (N=45) n (%)
Week 24					
Gain of ≥15 letters	9 (20.5)	15 (34.1)	14 (31.8)	7 (16.7)	12 (26.7)
Gain of ≥10 letters	14 (31.8)	22 (50.0)	28 (63.6)	18 (42.9)	26 (57.8)
Week 52					
Gain of ≥15 letters	5 (11.4)	18 (40.9)	20 (45.5)	10 (23.8)	19 (42.2)
Gain of ≥10 letters	13 (29.5)	25 (56.8)	31 (70.5)	19 (45.2)	28 (62.2)

Change in central retinal thickness (CRT)

From baseline to week 24 the VEGF Trap groups showed greater mean reductions in CRT from baseline (-127.3 µm to -194.5 µm) compared to the laser group (-67.9 µm). The differences were statistically significant. The effects were maintained through week 52.

After completion of the 3 initial monthly doses for the 2Q8 regimen, a rapid onset of small fluctuations in the improvement in CRT was observed that generally decreased over time, ranging from 35 µm to 5 µm. These fluctuations were greater than those seen in the AMD studies.

Figure 2. Change from baseline in central retinal thickness (µm) by visit to Week52 in DA VINCI



Number of Focal Laser Treatments

In the first 20 weeks of treatment, most patients in the laser group received 2 laser treatments, the maximum number allowed.

Starting at week 24, patients in the VEGF Trap groups were allowed to receive laser rescue treatment. At week 48, the mean number of focal laser treatment was <1 for all VEGF Trap groups and 2.5 for patients in the laser group.

Additional analyses not identified as secondary endpoints

- Patients with Loss of ETDRS Letter Score

Only a small number of patients mainly in the laser group and VEGF Trap group applying the lowest dose (0.5Q4) experienced a loss of 10 letters or more in the ETDRS letter score by weeks 24 and 52.

- Change in BCVA from Baseline to Week 76

Not all patients reached week 76; therefore, fewer patients were included in the analysis. In addition, all patients were allowed to receive other treatment for DME during this off-drug follow-up period. The mean change from baseline in BCVA at week 76 was higher in all VEGF Trap treatment groups (5.8 letters to 12.0 letters) compared to laser (3.0 letters).

2.4.1.1. Discussion

In this Phase 2 dose-ranging study, 4 dose levels/regimens of Eylea were compared against focal laser. Laser was permitted no more frequently than once every 16 weeks. In practice laser is usually administered at minimum intervals of 12 weeks. This was reflected in the phase 3 studies. Despite this anomaly, the methodology of this study was considered acceptable.

The results of this study show a rapid increase in BCVA for all active treatment groups over the first 4-6 months, with a declining rate of increase over the subsequent 6 months. The functional endpoints were mirrored by reductions in central retinal thickness. The DA VINCI study was not designed to distinguish among treatment groups and from the data obtained, there was little difference evident between the active treatments in terms of efficacy. The following observations could be made:

- The different doses (0.5 mg or 2 mg) and dosing regimens (given every 4 weeks, every 8 weeks or on a PRN basis, with the latter two following an initial loading regime of 3 monthly dose) were each superior to laser treatment and resulted in statistically significant increases in visual acuity and reductions in OCT measured retinal thickness at week 24. The onset of the treatment effects was observed in all active arms as early as week 1 for BCVA and week 4 for CRT. These effects were relatively well maintained up to week 52.
- The results of the treatment groups where patients received 2 mg VEGF-Trap at more intensive dosing frequencies over a 24 weeks period achieved numerically greater improvements than in the 0.5 VEGF-Trap group.
- Subjects in the 2Q8 group showed numerically less improvement in CRT and in BCVA from baseline compared to the subjects in the 2Q4 group.

Based on these results, the MAH decided that the dose to advance into the phase 3 DME program was 2 mg, and the selected dose regimens were every 4 weeks and every 8 weeks after 5 initial monthly doses.

The rationale for the dose selection of 2 mg VEGF Trap was mainly based on the safety and efficacy results achieved in the phase 2 AMD study VGFT-OD-0508 (CLEAR-IT). Furthermore, the MAH referred to the scientific literature which suggested that intraocular VEGF levels may be higher in DME patients compared to those in AMD or CRVO patients (Campochiaro 2009). The vitreous level of VEGF has also been correlated with the severity of diabetic retinopathy (Funatsu 2003). The MAH also pointed out

that a greater proportion of patients lost vision from baseline at week 52 in the 0.5 mg treatment group as opposed to the 2Q4 group receiving 2mg VEGF Trap. While the CHMP considered that there was little evidence for the inferiority of the 0.5 mg dose compared to the 2 mg dose, the decision to take 2 mg forward into phase 3 rather than 0.5 mg was accepted.

However, the CHMP considered the decision not to investigate the PRN regimen in phase 3 as contentious. It was agreed that a similar number of injections was administered to the 2Q8 and 2PRN groups, that the visual acuity and anatomic outcomes were similar between the two groups, and that it might generally be preferable to treat a disease proactively than prevent its worsening. However, the treatment period was relatively short, and DME is a chronic condition, with a waxing and waning course. It would therefore have been valuable to investigate a PRN dosing regime in phase 3 to gain information about the possible effects of a reduced injection frequency later on in the treatment course.

Furthermore, in order to take into account the fluctuations in CRT observed in the 2Q8 group upon start of the bi-monthly treatment schedule, the applicant changed the phase 3 VISTA and VIVID protocols to try to improve efficacy in the 2Q8 group. The original protocol stated that the subjects in the 2Q8 group were to receive monthly 3 doses at the first 3 visits (baseline, week 4, and week 8) before starting the 2Q8 schedule. This was revised by the addition of another dose at week 12 and hence changing the number of initial monthly doses for subjects in the 2Q8 group to a total of 5 injections. This change was considered acceptable by the CHMP, albeit more or less arbitrary.

Finally, the CHMP noted that BCVA was relatively well-maintained during the 6 month off-drug follow-up period. However, patients were allowed to receive other DME treatments during this time. The MAH clarified that less than a fifth of the subjects, for whom data were available at week 76, received additional treatments, mainly anti-VEGF agents and laser. The treatments were distributed evenly across the groups. Therefore, patients were able to maintain improvements in vision following one year of treatment with Eylea despite the limited use of further treatment in this period. This has a bearing on the issue of possible cessation of treatment (see also discussion on clinical efficacy in section 2.4.3.).

2.4.2. Main studies

The two pivotal phase 3 studies in support of this application, VISTA and VIVID, have nearly identical overall study designs and are described together unless otherwise indicated.

For both studies, data up to 1 year has been provided in the initial application with the period covered being 26 May 2011 (first subject's first dose) to 22 January 2013 (last subject's last visit for the primary endpoint) for Year 1 of VISTA, and 9 May 2011 to 03 June 2013 for VIVID. The next data cuts are for year 2 and 3 results (through week 148), respectively. Upon request of the CHMP, the MAH provided a summary of 2 Year data for the VISTA study, while 2 Year data for VIVID were not yet available at the time of this report.

The primary analysis tested superiority of VEGF Trap compared to laser since laser was the standard of care at the time of initiation of the studies and is still used as primary therapy in many regions of the world.

Efficacy and safety variables were assessed for each study individually and in an integrated analysis of the pooled 12-month data from the two Phase-3 studies.

Study VGFT-OD-1009 (VISTA) and study 91745 (VIVID)

Methods

Study participants

In VISTA approximately 402 subjects were planned to be randomised with a target of approximately 134 subjects randomized in each treatment group. In VIVID, approximately 375 subjects were planned to be randomised with a target of approximately 125 subjects in each treatment group.

The target study population in both studies were men and women 18 years and older with DME, involving the centre of the macula, secondary to diabetes mellitus.

The main inclusion criteria were:

- Adults ≥18 years with type 1 or 2 diabetes mellitus;
- Diagnosis of DME secondary to diabetes mellitus involving the centre of the macula (central subfield on OCT) in the study eye;
- Decrease in vision determined to be primarily the result of DME in the study eye;
- BCVA ETDRS letter score of 73 to 24 (20/40 to 20/320) in the study eye;
- Retinal thickness as assessed by OCT of ≥300 µm in the study eye (**VIVID only**).

The main exclusion criteria were:

- History of vitreoretinal surgery in the study eye (**VIVID: and/or including scleral buckling in the study eye**);
- Laser photocoagulation (panretinal or macular) in the study eye within 90 days of day 1 (**VISTA only**);
- Subject unlikely to benefit from additional macular laser photocoagulation (**VIVID:** More than 2 previous macular laser treatments in the study eye or, in the opinion of the investigator, the subject had no potential to benefit from laser treatments (eg, if too many laser treatments were applied in the past);
- Previous use of intraocular or periocular corticosteroids in the study eye within 120 days of day 1;
- Previous treatment with anti-angiogenic drugs in the study eye within 90 days of day 1;
- Active proliferative DR in the study eye;
- History of idiopathic or autoimmune uveitis in the study eye;
- Cataract surgery in the study eye or aphakia within 90 days of day 1;
- Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that is thought to affect central vision;
- Other ocular infectious or non-infectious diseases or impairments including structural damage of the macular that could confound the interpretation of the study results;
- Uncontrolled diabetes mellitus in the opinion of the investigator [**VIVID: as defined by hemoglobin (HbA1c >12%)**].

Treatments

Participants in both studies received either VEGF Trap, delivered IVT at a dosage of 2 mg and 2 different regimens, or laser treatment as follows:

- 2 mg VEGF Trap every 4 weeks (2Q4);
- 2 mg VEGF Trap every 8 weeks (2Q8) and sham injection at alternating visits, after 5 initial monthly injections (day 1, week 4, week 8, week 12, and week 16);
- Laser therapy using the modified ETDRS protocol (with sham injection) at day 1 and at visits at which patients met any of the criteria for laser re-treatment (but no more often than every 12 weeks). From month 6 onwards laser patients were eligible for VEGF Trap treatment (5 monthly injections followed by 2Q8 regime to the study end) if they met the additional treatment criteria. During Year 3 laser patients were eligible for VEGF-Trap PRN treatment if they met any of the VEGF Trap re-treatment criteria.

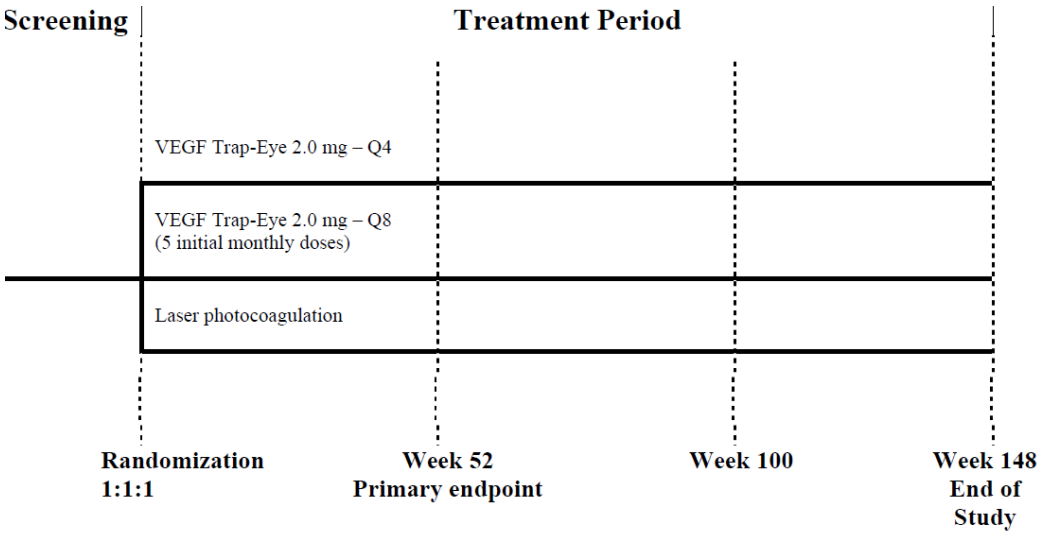


Figure 3 - Study flow diagram for VISTA and VIVID

Subjects had a screening visit (day -21 to day 0), were randomised (day 1) and received active or sham treatment at the baseline visit (day 1) and at study visits every 4 weeks from week 4 to week 144 (to maintain masking). Both active treatment groups also received sham laser therapy at baseline and at every visit starting at week 12, at which subjects met any of the criteria for laser re-treatment.

Starting at week 24 (month 6), active laser therapy could be given to patients in the VEGF Trap groups when subjects met the criteria for additional treatment.

Laser re-treatment criteria were the same as in Phase 2 (see 2.4.1.).

The additional VEGF Trap treatment criteria (from month 6 onwards) were as follows:

- Loss at any single visit of ≥ 15 letters from the best previous visual acuity (VA) score due to DME and the patient's current VA score is not better than the baseline score, or

- Loss at 2 consecutive visits at least 7 days apart (second visit may be an unscheduled visit) of ≥10 letters from the best previous VA score due to DME and the patient's current VA score is not better than the baseline score.

Objectives

Both studies were designed to demonstrate superiority of IVT-administered VEGF Trap compared to laser treatment, which was the standard of care at the time of initiation of the clinical development program, in improving best corrected visual acuity (BCVA) in subjects with DME.

Secondary objectives were to evaluate the safety of IVT-administered VEGF Trap in subjects with DME, including specific PK in VIVID Study and antibody data in VIVID and VISTA studies.

Outcomes/endpoints

All primary and secondary endpoints for both studies were set at Week 52 (i.e. 12 months).

Primary Efficacy Variable:

The primary endpoint was the change by BCVA in ETDRS letter score (assessed using the ETDRS protocol at 4 meters by certified and masked visual acuity examiners to ensure consistent measurement of BCVA) from baseline to week 52 (visit 15).

Secondary Efficacy Variables:

The secondary endpoints were:

- Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 52;
- Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 52;
- The proportion of subjects who achieved a ≥2-step improvement on the ETDRS Diabetic Retinopathy Severity Score (DRSS) from baseline to week 52;
- Change in central retinal thickness (CRT) from baseline to week 52, as assessed by OCT (assessed by reading centre certified and masked OCT technicians; OCT images controlled by the masked readers of independent reading centre and electronically archived at the study sites as part of the source documentation);
- NEI VFQ-25 near activities subscale change from baseline to week 52;
- NEI VFQ-25 distance activities subscale change from baseline to week 52.

Additional Efficacy Variables:

The following additional endpoints were analysed at week 52:

- Proportion of subjects who gained ≥0 and ≥5 ETDRS letters from baseline;
- Proportion of subjects who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline;
- Time to first gain of ≥15 ETDRS letters from baseline;
- Time to first confirmed gain of ≥15 ETDRS letters from baseline;

- Proportion of subjects with a ≥2- or ≥3-step worsening, or a ≥3-step improvement from baseline in the DRSS score as assessed on fundus photography;
- Change from baseline in the NEI VFQ-25 total score and subscales over time.

Quality of Life was assessed based on the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25). In addition, in VIVID, health-related quality of life was assessed using the Euro QOL-5 dimensions questionnaire (EQ-5D) was used, albeit EQ-5D score was not one of the efficacy variables.

Sample size

The sample size calculation is based on the primary endpoint. Assuming a normal distribution for the primary endpoint, a true difference in the mean change in BCVA between the treatment arms (VEGF Trap versus laser) of 7 letters can be expected with a standard deviation for each VEGF Trap arm of 10 letters and laser of 16 letters. A sample size of 92 patients per arm will provide 90% power for rejecting the null hypothesis using a 2-sided t-test at the 2.5% (5%/2) significance level (using Bonferroni adjustment for the 2 comparisons on the primary efficacy endpoint). Allowing for a drop-out rate of around 25% or 30%, approximately 125 or 134 patients per arm will be required depending of the study. This results in a total of approximately 375 or 402 patients for 3 groups.

Randomisation

Eligible subjects were randomised using a ratio of 1:1:1 (2Q4, 2Q8, and laser) via interactive voice response system/ interactive web response system following stratification. Within each stratum, subjects were randomised to 1 of 3 treatment groups according to a predetermined central randomisation scheme.

In the VISTA study, randomisation was stratified by history of myocardial infarction and/or cerebrovascular accident (yes vs. no). In contrast, in VIVID, subjects were stratified by geographic region (Europe/Australia vs. Japan).

Only 1 eye (the study eye) received randomised treatment. If DME were present, the fellow eye could also receive anti-VEGF treatment.

Blinding (masking)

To enable masking of the study, all patients received either active or sham injection and laser (active or sham, if criteria were met) at each scheduled study visit to the end of the study.

A masked physician was assigned to assess adverse events (AEs), perform the masked assessment of efficacy, assess re-treatment criteria, and assess additional treatment criteria.

A separate unmasked (unblinded) physician administered the study drug injection, sham injection, laser/sham photocoagulation, laser re-treatment, and additional treatment. The unmasked physician or designee (eg, pharmacist) did not have any role in the study beyond the receipt, tracking, preparation, destruction, administration of study drug, and safety assessment during the observation period following study drug administration.

Statistical methods

The populations for analysis were defined as follows:

- *The full analysis set (FAS)* includes all randomised patients who receive any study drug and have a baseline and at least 1 post-baseline assessment of BCVA. Patients were analysed

according to the treatment assigned at baseline (as randomised). All efficacy endpoints were analysed using the FAS and the FAS was used for primary analysis (statistical evaluation of superiority).

- *The per protocol set (PPS)* includes all patients in the FAS that did not have any major protocol violations. The final determination on the exclusion of patients from the PPS was made during a validity review meeting on the masked data prior to database lock. Analysis of the PPS is performed according to the treatment the patient actually received (as treated). The primary endpoint was also evaluated on the PPS.
- *The safety analysis set (SAF)* includes all patients who received any study medication. Treatment compliance/administration, all clinical safety and tolerability assessments were analysed using the SAF. Patients were summarised according to the treatment actually received (as treated). The safety analysis was performed on the observed safety data, regardless of additional treatment administered to patients during the study.

Efficacy data were analysed as randomised following the intent-to-treat principle with last observation carried forward on the FAS. The efficacy analysis on the FAS is considered to be the primary one (statistical evaluation of superiority).

Descriptive statistics for continuous variables included the mean, standard deviation, minimum, median, and maximum. Categorical variables were frequency and percentage.

All statistical analysis were performed using Statistical Analysis Software (SAS), version 9.1 or higher.

Analysis of data from the two phase 3 studies was determined based on 2 statistical analysis plans (SAPs) for each study: a global SAP and a US SAP (that was agreed upon with the US FDA). In both SAPs, the primary variables are the same; however, the designation, timing, and hierarchical test sequence for the secondary variables differs between the 2 SAPs. For the hierarchy defined in the US SAP, the only secondary variable at week 52 is the proportion of subjects who gained ≥15 ETDRS letters from baseline. All other secondary variables in the hierarchy defined in the US SAP are analysed in an exploratory manner at week 52. The integrated analysis follows the same approach.

The primary analysis was a multiple-comparison of change in BCVA from baseline to Week 52 comparing both active treatment arms with laser. For the VIVID primary analysis, an analysis of covariance (ANCOVA) model was used with baseline BCVA measurement as a covariate, and treatment group and geographic region (Europe/Australia, Japan) as fixed factors. For VISTA an ANCOVA model with treatment as the main effect, history of myocardial infarction and/or cerebrovascular accident as a fixed effect, and baseline BCVA measurement as the covariate was used. In order to control the nominal family-wise type I error rate of 5%, the Bonferroni multiple comparison test was used to adjust the comparisons between study treatments and control, i.e. each VEGF Trap group versus laser group comparison was tested independently at the 2-sided significance level of 2.5%.

For the primary efficacy analysis, measurements obtained after the initiation of additional treatment were censored. Missing or censored values were imputed using the last non-censored value (last observation carried forward [LOCF]). Baseline values were not carried forward.

Several pre-specified sensitivity analyses were performed to assess the robustness of statistical results and address the impact of missing data due to drop-outs or receipt of additional treatment. All sensitivity analyses were analysed on the FAS. The sensitivity analyses used for the primary efficacy variable were: observed case analysis, including data after additional treatment, repeated measurements model, multiple imputation analysis.

A logistic regression was performed as secondary statistical method of evaluation for the primary endpoint.

A testing hierarchy was defined in the global SAP for secondary criteria. This was to be applied for the respective active arm if the primary efficacy endpoint had shown superiority at the 2.5% level in FAS. While p values were reported for all comparisons, a superiority claim could be made for a given endpoint between the respective VEGF Trap group and the laser group only if all preceding endpoint comparisons in the hierarchy (including the primary endpoint) were shown to be statistically significant at a 2.5% 2-sided significance level.

A series of subgroups analyses based on demographics, disease characteristics, and medical history were explored: Gender; Age: <55 years; ≥55 to <65 years; ≥65 to <75 years; ≥75 years; Race: White versus Asian (VIVID) or Black or African American, Other (VISTA) ; Ethnicity: Hispanic or Latino (no/yes); vivid : Geographic region: Japan, Europe/Australia; Glycosylated hemoglobin (HbA1c): ≤ 8%, > 8%)

Subgroups for efficacy analyses only were: Baseline VA category: <40 letters (20/160), ≥40 to <55 letters (≥20/160 to 20/80); ≥55 to <65 letters (≥20/80 to 20/50); ≥65 letters (≥20/50).

Subgroups for safety analyses only were: Medical history of hypertension, of cerebrovascular disease (eg, cerebrovascular accident [CVA]/stroke), of ischemic heart disease (eg, MI); Renal impairment; Hepatic impairment.

Results

Recruitment

In VISTA, a total of 687 subjects were screened. Of these, a total of 466 subjects were randomised and 461 subjects received treatment, while 5 subjects were randomised but were not treated. Of these 5 subjects, 3 did not meet inclusion criteria and were inadvertently randomised, and 2 withdrew consent.

In VIVID, a total of 604 subjects were screened, of which 406 were randomised as follows: 135 subjects in the laser group, 136 subjects in the 2Q4 group, and 135 subjects in the 2Q8 group. Most of the subjects who were not randomized were screening failures. Two randomised subjects (both in the laser group) discontinued before receiving treatment due to protocol deviations.

Conduct of the study

The VISTA study was conducted in 54 study centres in the United States of America. The original protocol, dated 21 March 2011, was amended three times.

The VIVID study was conducted in 73 centres in Japan, European countries, and Australia. The original protocol was dated 20 October 2010 and was amended twice.

Baseline data

Baseline demographics and disease characteristics in the study eye are summarised in Table 5 and Table 6. The demographics of subjects in both studies were comparable, and balanced with the exception of race, ethnicity, and baseline BMI. In VISTA, a higher proportion of black subjects (11.1% in VISTA versus 0.5% for VIVID) and Hispanic subjects (16.6% in VISTA versus 3.2% for VIVID) were enrolled in the study, and a higher proportion of Asians were enrolled in VIVID (19.6% versus 2.2% for

VISTA DME). Body mass index (BMI) and mean baseline weight were slightly higher in VISTA (29.2% of patients with BMI over >35 kg/m²; mean body weight of 90 kg) as compared to VIVID (9.9% of patients with BMI over >35 kg/m²; mean body weight of 80 kg).

With regards to geographic region (data collected only in VIVID), the majority of subjects in VIVID were non-Japanese (327/403, 81.1%). Regarding the stratification factors in VISTA, 13% of the patients had a history of myocardial infarction and 7% of cerebrovascular accident.

Table 5 – Baseline demographics of the VISTA and VIVID studies

	VISTA Total (N=459)	VIVID Total (N=403)
Sex; n (%)		
Male	250 (54.5%)	249 (61.8%)
Female	209 (45.5%)	154 (38.2%)
Age (years)		
Mean (SD)	62.2 (9.80)	63.6 (8.3)
Min : Max	23 : 87	32 : 84
Age (years) by category (year) n (%)		
< 55	81 (17.6%)	47 (11.7%)
≥ 55 – < 65	178 (38.8%)	165 (40.9%)
≥ 65 – < 75	159 (34.6%)	155 (38.5%)
≥ 75	41 (8.9%)	36 (8.9%)
Race; n (%)		
White	384 (83.7%)	321 (79.7%)
Black	51 (11.1%)	2 (0.5%)
Asian	10 (2.2%)	79 (19.6%)
American Indian or Alaska native	2 (0.4%)	-
Native Hawaiian or other pacific islander	4 (0.9%)	-
Not reported	8 (1.7%)	-
Multiple		1 (0.2%[a])
Ethnicity; n (%)		
Not Hispanic or Latino	383 (83.4%)	387 (96.0%)
Hispanic/Latino	76 (16.6%)	13 (3.2%)
Not reported		3 (0.7%)
BL BMI (kg/m²), n (%)		401
≤30 kg/m²	198 (43.1%)	268 (66.5%)
>30 to ≤35 kg/m²	126 (27.5%)	93 (23.1%)
>35 kg/m²	134 (29.2%)	40 (9.9%)
Geographic region; n		
Non Japanese	0	327
Japan	0	76
Smoking history; n (%)		
Never	263 (57.3%)	224 (55.6%)
Former	149 (32.5%)	146 (36.2%)
Current	47 (10.2%)	33 (8.2%)

Note: The percentage is based on the number of Full Analysis Set (FAS) subjects in each treatment group as denominator.

[a] The subject with "multiple" races is not included in the race subgroup analyses.

BL = Baseline; BMI = body mass index; FAS = Full Analysis Set; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects; SD = standard deviation; VTE 2Q4 = VTE administered as 2 mg every 4 weeks; VTE 2Q8 = 2 mg VTE every 4 weeks until week 16 and every 8 weeks, thereafter.

Table 6 – Baseline disease characteristics of the study eye for VISTA and VIVID

	VISTA Total (N=459)	VIVID Total (N = 403)
BL BCVA (letters)		
Mean (SD)	59.3 (10.85)	60.1 (10.9)
Min : Max	24 : 73	25 : 80
BL BCVA by Category (letters), n (%)		
<40	36 (7.8%)	31 (7.7%)
≥40 - <55	85 (18.5%)	69 (17.1%)
≥55 - <65	161 (35.1%)	125 (30.9%)
≥65	177 (38.6%)	179 (44.3%)
BL IOP (mmHg)		
n	459	403
Mean (SD)	15.1 (3.33)	15.9 (2.63)
Min : Max	6 : 24	10 : 23
BL DRSS,[1] n (%)		
10	9 (2.0%)	NA
20	11 (2.4%)	1 (0.2%)
35	21 (4.6%)	3 (0.7%)
43	161 (35.1%)	95 (23.6%)
47	84 (18.3%)	69 (17.1%)
53	134 (29.2%)	121 (30.0%)
61	4 (0.9%)	5 (1.2%)
65	19 (4.1%)	3 (0.7%)
71	6 (1.3%)	NA
75	1 (0.2%)	NA
90 (cannot grade)	8 (1.7%)	106 (26.3%)
Missing	1	-
BL CRT by OCT (µm)		
n	459	403
Mean (SD)	482.6 (154.15)	520.0 (148.3)
Min : Max	231 : 1179	283 : 1183
BL NEI VFQ-25 Total Score		
n	459	402
Mean (SD)	69.6 (18.36)	75.3 (16.66)
Min : Max	17 : 99	20.9 : 100.0
BL NEI VFQ-25 Near Activities Subscale		
n	458	402
Mean (SD)	58.3 (23.31)	65.4 (23.08)
Min : Max	0 : 100	0 : 100
BL NEI VFQ-25 Distance Activities Subscale		
n	459	402
Mean (SD)	65.3 (23.07)	73.8 (22.24)
Min : Max	0 : 100	0 : 100
BL NEI VFQ-25 Vision Dependency Subscale		
n	458	NA
Mean (SD)	71.7 (29.59)	NA
Min : Max	0 : 100	NA

Note: The percentage is based on the number of Full Analysis Set (FAS) subjects in each treatment group as denominator.

[1] levels 10, 14, 15, 20, 35, 43; None (mild to moderate nonproliferative diabetic retinopathy)
levels 47 and 53; Moderately severe/severe nonproliferative diabetic retinopathy
levels 61, 65, 71, 75, 81, and 85; Mild/moderate/high-risk/ advanced proliferative diabetic retinopathy
Cannot grade cases appear as level 90 in the database.

BCVA = Best Corrected Visual Acuity; BL = Baseline, CRT = central retinal thickness; DRSS = Diabetic Retinopathy Severity Scale; IOP = intraocular pressure; Max = maximum; Min = minimum; N = total number of subjects; n = number of subjects; NA = Not available; NEI VFQ-25 = National Eye Institute Visual Functioning Questionnaire-25; OCT = optical coherence tomography; SD = standard deviation; VTE 2Q4 = VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks; VTE 2Q8 = 2 mg VTE every 4 weeks until week 16 and every 8 weeks, thereafter .

Baseline disease characteristics were generally balanced among the treatment groups of both studies.

In the FAS of VISTA, the total mean baseline BCVA letter score in the study eye was 59.3 and was similar among the treatment groups. However, in the 2Q4 group a smaller proportion of subjects had a BCVA ≥55 to <65 letters compared to the laser and 2Q8 groups (31.8% versus 33.1% and 40.4%). The mean baseline HbA1C was 7.8%. A smaller proportion of patients in the laser group had a baseline HbA1c >8% compared to the 2Q4 and 2Q8 groups (29.2% vs. 37.0% and 37.7%). The mean duration of diabetes mellitus was 17.1 years and most subjects had type 2 diabetes (92.2%) and had received prior treatment for DME in the study eye (317/459, 69.1%).

In the FAS of the VIVID study, the total mean baseline BCVA letter score in the study eye was 60.1 and was similar among the treatment groups. Most subjects (30.0%) had an ETDRS DRSS score of level 53 (moderately severe/severe non-proliferative diabetic retinopathy). The mean CRT was 520.0 µm with a higher mean CRT observed in the laser group compared to the 2Q4 and 2Q8 groups (540.3 µm versus 501.9 µm and 518.4 µm, respectively). The mean IOP was 15.9 mm Hg and similar among treatment groups. The mean baseline HbA1c was 7.7%. The mean duration of diabetes mellitus was 14.3 years. With regards to HbA1c, the proportion of subjects with HbA1c > 8% at baseline was slightly higher in the 2Q4 group (40.4% compared to 32.6% in the 2Q8 group and 31.8% in the laser group).

Overall, baseline disease characteristics could be considered balanced between both phase 3 studies, with the exception of CRT, which was 482.6 µm in the VISTA study and 520 µm in the VIVID study. This may be the result of the CRT inclusion criterion in the VIVID study (≥300 µm) which was not present in VISTA.

Numeric differences were also reported for the NEI VFQ25 “near and distance” activities (about 7 points difference between VISTA and VIVID (higher values).

In both studies and in both VEGF Trap groups, the majority of subjects had a baseline ETDRS score ≥ 55 letters. A diabetic retinopathy severity score (DRSS) of 43, 47 or 53 was observed in 77% of patients at baseline. A quarter of the patients could not be graded in VIVID study (compared to only 1.7% in VISTA study), which the MAH explained to be due to different validated methods used for grading DRSS by the reading centres for VIVID and VISTA. Therefore the DRSS improvement could not be measured in these patients. Furthermore, a total of 92% of subjects in VISTA had type 2 diabetes mellitus. In VIVID, post-hoc review of the medical history allowed confirmation of type 2 diabetes in 44.7% of the patients. However, assignment of the diabetes type was not possible for the majority of the recruited patients (51.1%).

In VISTA, 69.1% had received prior treatment for DME, including anti-VEGF (42.9%), IVT steroids (23.5%), and laser (52.9%). For VIVID, only data on prior treatment with anti-VEGF agents (8.9%) were provided. In VIVID 80% had received prior treatment for DME, including anti-VEGF (9%), IVT steroids (6%), and laser (65%). The total proportion of subjects in each study with a history of both pan retinal photocoagulation and macular laser was 78% in VISTA and 71% in VIVID.

A total of 29% of subjects in VISTA were pseudophakic, compared with 15% in VIVID.

Overall, for both VISTA and VIVID studies, the ocular and non-ocular medical and surgical history findings were as expected for subjects with DME.

Baseline disease characteristics for the PPS were similar to those of the FAS.

Numbers analysed

Only 3 patients in total were excluded from the FAS due to not having any data post-baseline (see Table 7).

Table 7 – Sample size and analysis sets for VISTA, VIVID and the integrated analysis (all enrolled subjects)

Study Identifier	Number of Subjects Enrolled	Treatment group	Randomized	SAF	FAS	PPS
Integrated	1291	Total	872	865	862	774
		Laser	291	287	286	248
		VTE 2Q4	292	291	290	263
		VTE 2Q8	289	287	286	263
		VTE Combined	581	578	576	526
VISTA DME (1009)	687	Total	466	461	459	430
		Laser	156	154	154	145
		VTE 2Q4	156	155	154	144
		VTE 2Q8	154	152	151	141
		VTE Combined	310	307	305	285
VIVID DME (91745)	604	Total	406	404	403	344
		Laser	135	133	132	103
		VTE 2Q4	136	136	136	119
		VTE 2Q8	135	135	135	122
		VTE Combined	271	271	271	241

Note: VTE 2Q4 - VTE administered as 2 mg every 4 weeks; VTE 2Q8 - VTE administered as 2 mg every 8 weeks after receiving 5 initial monthly doses of VTE; Laser - laser therapy at baseline and when re-treatment criteria are met.
FAS = Full Analysis Set; PPS = Per Protocol Set; SAF = Safety Analysis Set

The proportion of subjects completing week 52 in the VISTA study (93.3%) was slightly higher than in VIVID (88.7%) (see Table 8).

Table 8 – Disposition of all randomised subjects in VISTA and VIVID

	VISTA Total (N=466)	VIVID Total (N=406)
Received Study Medication, n (%)	461 (98.9%)	404 (99.5%)
Randomized but not Treated	5 (1.1%)	2 (0.5%)
Completed Week 52, n (%)	435 (93.3%)	360 (88.7%)
Primary Reason for Premature Discontinuation from the Study during 52-week Period, n (%)		
Adverse event	5 (1.1%)	17 (4.2%)
Death	3 (0.6%)	4 (0.9%)[3]
Lack of efficacy (as assessed by the investigator)	NA	1 (0.2%)
Withdrawal by subject[2]	14 (3.0%)	12 (3.0%)
Protocol deviation	NA	3 (0.7%)
Lost to follow up	5 (1.1%)	5 (1.2%)
Physician decision	NA	2 (0.5%)
Therapeutic procedure required	NA	1 (0.2%)
Other[1]	4 (0.9%)	NA

Note: The percentage is based on the number of randomized subjects in each treatment group as denominator.
[1] Refer to Module 5.3.5.1 VISTA DME Listing 14.01.01/2 and Listing 14.01.01/3 for details.
[2] "Withdrawal of consent" was considered to be "withdrawal of consent by subject" according to the eCRF.
[3] One additional death (MI) occurred in year 2 in the 2Q8 group in VIVID DME (77 days after the last and 406 days after the first study treatment) but due to data conventions, it was included in the clinical database for year 1. In the source tables this will not be changed, but will be displayed according to data convention rules.
NA = not applicable

In the integrated analysis, 77 (8.8%) subjects discontinued before week 52. The proportion of subjects who discontinued was somewhat higher in the laser group (10.7%) versus the VEGF Trap groups (7.2% and 8.7% for the VEGF Trap 2Q4 and VEGF Trap 2Q8 groups, respectively), which was mainly due to an imbalance in the discontinuations in the VIVID study. The most common reasons for discontinuation in the laser group were AEs and withdrawal of consent (3.8% for both). The most common reason for discontinuation in the VEGF Trap groups was withdrawal of consent (2.6%).

More than 90% of subjects were at least 75% compliant with their injections during the first 52 weeks.

Outcomes and estimation

Primary efficacy endpoint

For both individual studies as well as in the integrated analysis a statistically significant and clinically meaningful improvement in BCVA after 52 weeks was seen in both VEGF trap groups (2Q4 and 2Q8) compared to the laser group (see Table 9 and Figure 4).

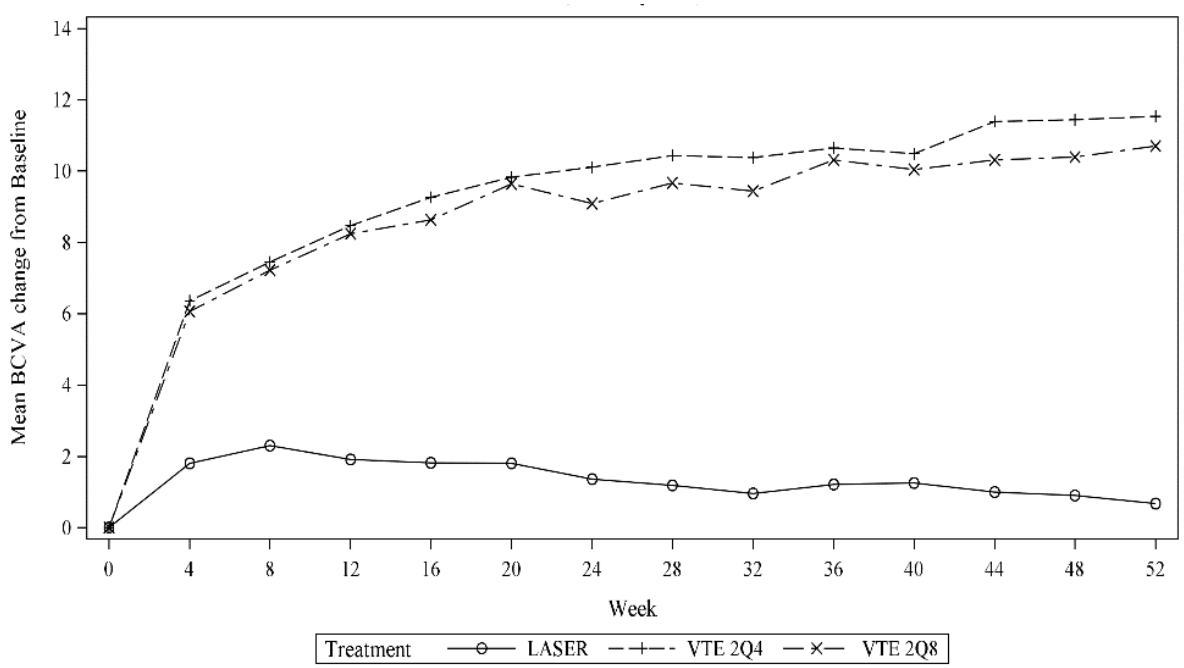
Table 9 – Change in BCVA from baseline to Week 52 (LOCF, integrated FAS)

Study	Treatment Group	Baseline Means (SD)	Mean Change (SD)	LS mean Change (SE)	Num. of Subjects	Contrast	p-Value[2]	Estimate for Contrast &97.5% CI (LS mean)[2]
VISTA DME	VTE 2Q4 (N=154)	58.9 (10.77)	12.5 (9.54)	12.3 (0.76)	154	VTE 2Q4 vs. Laser	<0.0001	12.19 (9.35, 15.04)
	VTE 2Q8 (N=151)	59.4 (10.89)	10.7 (8.21)	10.6 (0.69)	151	VTE 2Q8 vs. Laser	<0.0001	10.45 (7.73, 13.17)
	Laser (N=154)	59.7 (10.95)	0.2 (12.53)	0.1 (1.03)	154			
VIVID DME	VTE 2Q4 (N=136)	60.8 (10.74)	10.5 (9.55)	10.2 (0.89)	136	VTE 2Q4 vs. Laser	<0.0001	9.25 (6.49, 12.02)
	VTE 2Q8 (N=135)	58.8 (11.23)	10.7 (9.32)	10.0 (0.85)	135	VTE 2Q8 vs. Laser	<0.0001	9.05 (6.35, 11.76)
	Laser (N=132)	60.8 (10.61)	1.2 (10.65)	0.9 (1.00)	132			
Integrated	VTE 2Q4 (N=290)	59.8 (10.78)	11.5 (9.58)	11.5 (0.55)	290	VTE 2Q4 vs. Laser	<0.0001	10.78 (8.79, 12.77)
	VTE 2Q8 (N=286)	59.1 (11.03)	10.7 (8.74)	10.6 (0.50)	286	VTE 2Q8 vs. Laser	<0.0001	9.85 (7.92, 11.77)
	Laser (N=286)	60.2 (10.79)	0.7 (11.69)	0.8 (0.70)	286			

[1] LOCF last observation carried forward censoring measurements after additional treatment was given..

[2] The CI with p-value for integrated study is based on treatment difference (VTE group vs. Laser) of the LS mean change using ANCOVA model with baseline measurement as covariate and the treatment and Study as fixed factors.

CI = confidence interval; DME = diabetic macular edema; FAS = Full Analysis Set; LS = least squares; SE = standard error; VTE 2Q4 = VEGF Trap-Eye (VTE) administered as 2 mg every 4 weeks; VTE 2Q8 = 2 mg VTE every 4 weeks until week 16 and every 8 weeks, thereafter.



LOCF - last observation carried forward censoring measurements after additional treatment was given.

Figure 4 - Mean change in BCVA from baseline to Week 52 (LOCF, Integrated FAS)

Results in the PPS yielded consistency with the analyses conducted in the FAS.

Sensitivity analyses performed on the change in BCVA from baseline to week 52 displayed similar results than those in the FAS and PPS using LOCF. Similar results were also displayed for PPS.

Secondary efficacy endpoints

Six secondary variables were explored:

- Proportion of subjects (%) who gained ≥10 ETDRS letters from baseline to week 52;
- Proportion of subjects (%) who gained ≥15 ETDRS letters from baseline to week 52;
- Proportion of subjects (%) who achieved a ≥2-step improvement on the DRSS from baseline to week 52;
- Change in CRT from baseline to week 52, as assessed by OCT;
- NEI VFQ-25 near activities subscale change from baseline to week 52;
- NEI VFQ-25 distance activities subscale change from baseline to week 52.

The results by study are displayed in Table 10.

Table 10 - Secondary efficacy variables – Results from baseline to Week 52 in VISTA DME and VIVID DME

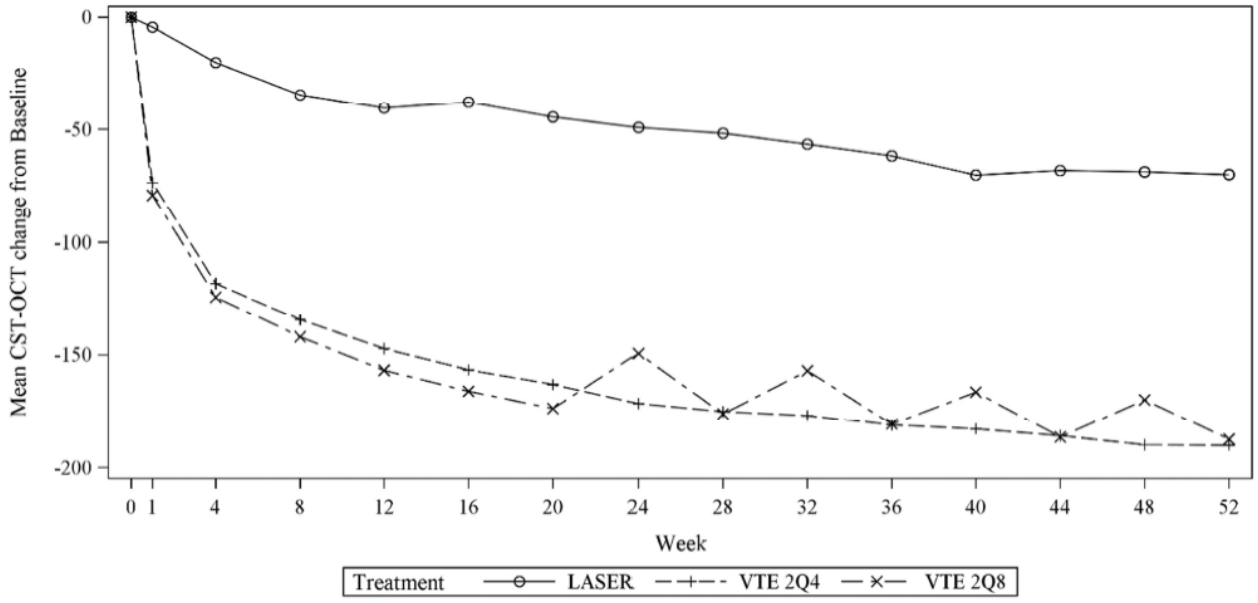
Variable	VISTA DME			VIVID DME		
	VTE 2Q4	VTE 2Q8	Laser	VTE 2Q4	VTE 2Q8	Laser
Subjects gaining ≥10 letters						
n	154	151	154	136	135	132
Number (%) gaining ≥10 letters	100 (64.9)	88 (58.3)	30 (19.5)	74 (54.4)	72 (53.3)	34 (25.8)
Adjusted difference vs. Laser[2]	45.9	38.8	NA	28.7	27.5	NA
(97.5% confidence interval)[2]	(34.7, 57.0)	(27.2, 50.3)	NA	(15.8, 41.6)	(14.6, 40.5)	NA
p value	<0.0001	<0.0001	NA	<0.0001	<0.0001	NA
Subjects gaining ≥15 letters[3]						
n	154	151	154	136	135	132
Number (%) gaining ≥15 letters	64 (41.6)	47 (31.1)	12 (7.8)	44 (32.4)	45 (33.3)	12 (9.1)
Adjusted difference vs. Laser[2]	34.2	23.3	NA	23.3	24.2	NA
(97.5% confidence interval)[2]	(24.1, 44.4)	(13.5, 33.1)	NA	(12.6, 33.9)	(13.5, 34.9)	NA
p value	<0.0001	<0.0001	NA	<0.0001	<0.0001	NA
Subjects with ≥2-step improvement in ETDRS	DRSS					
n	154	151	154	136	135	132
Number (%) with ≥2-step improvement[4]	52/154 (33.8)	44/151 (29.1)	22/154 (14.3)	27/81 (33.3)	23/83 (27.7)	6/80 (7.5)
Adjusted difference vs. Laser[2]	19.7	14.9	NA	25.8	19.3	NA
(97.5% confidence interval)[2]	(9.0, 30.4)	(4.4, 25.4)	NA	(12.2, 39.4)	(6.6, 32.1)	NA
p value	<0.0001	0.0017	NA	<0.0001	0.0010	NA
Change in CRT (by OCT)						
n	154	151	154	136	135	132
Mean change in µm in CRT (SE)	-185.9 (150.68)	-183.1 (153.50)	-73.3 (176.72)	-195.0 (146.59)	-192.4 (149.89)	-66.2 (138.99)
LS mean change in µm in CRT (SE)	-184.1 (6.57)	-186.8 (6.90)	-73.3 (12.09)	-210.1 (7.45)	-196.0 (9.64)	-53.1 (14.14)
Estimate for contrast vs. Laser	-110.78	-113.47	NA	-156.98	-142.82	NA
(97.5% confidence interval)	(-141.34, -80.22)	(-144.19, -82.75)	NA	(-190.89, -123.07)	(-179.31, -106.33)	NA
p value	<0.0001	<0.0001	NA	<0.0001	<0.0001	NA
Change in NEI VFQ-25 near activities score						
n	154	151	154	136	135	132
n Evaluable	146	146	151	128	134	120
Mean change in near activities score (SE)	9.0 (20.60)	9.4 (18.50)	5.4 (20.44)	5.7 (18.93)	5.3 (19.06)	3.5 (16.77)
LS mean change in near activities score (SE)	8.9 (1.58)	8.1 (1.44)	3.7 (1.55)	5.2 (1.55)	1.6 (1.64)	2.8 (1.52)
Estimate for contrast vs. Laser	5.19	4.36	NA	2.41	-1.21	NA
(97.5% confidence interval)	**(0.33, 10.04)**	**(-0.21, 8.93)**	**NA**	**(-2.01, 6.82)**	**(-5.79, 3.37)**	**NA**
p value	0.0168	0.0323	NA	0.2208	0.5537	NA
Change in NEI VFQ-25 distance activities score						
n	154	151	154	136	135	132
n Evaluable	146	147	151	128	134	120
Mean change in distance activities score (SE)	8.6 (20.99)	7.3 (19.32)	6.7 (19.85)	0.9 (16.49)	5.3 (18.47)	2.3 (15.92)
LS mean change in distance activities score (SE)	7.7 (1.57)	6.5 (1.48)	4.9 (1.44)	-0.5 (1.38)	0.3 (1.57)	0.7 (1.46)
Estimate for contrast vs. Laser	2.86	1.65	NA	-1.19	-0.37	NA
(97.5% confidence interval)	(-1.82, 7.54)	(-2.83, 6.13)	NA	(-5.29, 2.91)	(-4.79, 4.05)	NA
p value	0.1702	0.4067	NA	0.5138	0.8498	NA

1 LOCF last observation carried forward censoring measurements after additional treatment was given.
2 Difference with CI is calculated using Mantel-Haenszel weighting scheme.
3 This is the only secondary endpoint defined for the US SAP.
4 Denominator is number of evaluable subjects.

With the exception of the NEI VFQ-25 score results, both VEGF-Trap treatment groups showed statistically significant superiority compared to laser for all secondary endpoints.

For the NEI VFQ-25 scores, numerical improvements were seen in nearly all of the active treatment groups. Statistical superiority compared to laser was only reached for near activities in the 2Q4 group of the VISTA study, while no improvement in the distance activities scores for 2Q8 in VIVID was seen.

With regards to CRT, fluctuations were observed in the mean change from baseline in CRT once 2Q8 administration began (see Figure 5).



LOCF - last observation carried forward censoring measurements after additional treatment was given.

Figure 5 - Mean change in Central Retinal Thickness from baseline to Week 52 (LOCF, Integrated FAS)

Results in the PPS yielded consistency with the analyses conducted in the FAS.

Additional endpoints

At week 52, the 2Q4 and 2Q8 groups in both studies showed greater proportion of subjects who experienced a gain of ≥ 0 and ≥ 5 ETDRS letters compared to the laser group.

At week 52, the 2Q4 and 2Q8 groups in both studies showed a smaller proportion of subjects who lost ≥ 5, ≥ 10, and ≥ 15 ETDRS letters compared to the laser group.

Time and confirmed time to first gain of ≥15 ETDRS letters:

- Less than 25% of the subjects in the laser group gained ≥15 letters over 52 weeks.
- In VISTA, the median time to first gain of ≥15 ETDRS letters was 265 days in the 2Q4 group and 364 days in the 2Q8 group. At the 25% quartile, these were 84 and 140 days in the 2Q4 and 2Q8 group, respectively. In VIVID, a gain of ≥15 letters was achieved by 25% of subjects at week 20.0 in the 2Q4 and 2Q8 groups, respectively.
- In VISTA, a confirmed gain of ≥15 letters was achieved by 25% of subjects at day 139 in the 2Q4 group and at day 196 in the 2Q8 group. The difference between the 2Q4 and 2Q8 groups was seen before week 16 when both groups received monthly doses. In VIVID, a confirmed gain of ≥ 15 letters was achieved by 25% of subjects at week 35.9 in the 2Q4 group and at week 31 in the 2Q8 group.

In VISTA, at week 52, mean increases in NEI VFQ-25 total score of 4.8, 8.5, and 6.8 points were observed in the laser, 2Q4, and 2Q8 groups, respectively. In VIVID, change in mean NEI VFQ-25 total score at week 52 compared with laser were minimal and less <1.50 point.

In both studies, in general, fewer subjects in the 2Q4 and 2Q8 groups had ≥2 or ≥3 level worsening over the 52-week study period and more had ≥3 level improvement in ETDRS DRSS compared to subjects in the laser group.

Worsening on the DRSS ≥2-step:

- VISTA: 22 [14.3%] subjects in the laser group, 11 [7.1%] subjects in the 2Q4 group, and 7 [4.6%] subjects in the 2Q8 group;
- VIVID: 7 [8.8%] subjects in the laser group, 1 [1.2%] subjects in the 2Q4 group, and 2 [2.4%] subjects in the 2Q8 group.

Worsening on the DRSS ≥3-step:

- VISTA: 7 [4.5%] subjects in the laser group, 4 [2.6%] subjects in the 2Q4 group, and 4 [2.6%] subjects in the 2Q8 group, respectively);
- VIVID: 1 [1.2%] subject in both the 2Q4 and the 2Q8 group versus 2 [2.5%] in the laser group.

Improvement on the DRSS by ≥3-steps:

- VISTA: 8 [5.2%] subjects in the laser group, 26 [16.9%] subjects in the 2Q4 group, and 19 [12.6%] subjects in the 2Q8 group.
- VIVID: 0 [0.0%] subjects in the laser group, 3 [3.7%] subjects in the 2Q4 group, and 2 [2.4%] subjects in the 2Q8 group).

VISTA Year 2 results

A summary of the key efficacy variables at week 100 (Year 2) for the VISTA study is provided below. Overall, these results confirmed a persistence of effect over time.

- Change in BCVA

At Week 100, the mean changes from baseline for the two VEGF Trap treatment arms were 11.5 (2Q4) and 11.1 (2Q8). Statistically significant differences to laser were maintained through Week 100. A plateau seemed to be reached at the transition from the first year of treatment into the second year with the gain in visual acuity stabilising on a level significantly and approximately 2 lines better than laser, while no further gains are observed during the second year.

- Gain of ≥ 10 or 15 ETDRS letters from baseline

Compared to Week 52, the gain in ETDRS letters from baseline appeared to slightly decline at Week 100 in the two VEGF Trap treatment arms, while increased improvements were observed for the laser group. Nevertheless, mean differences remained statically and clinically significant in support of VEGF Trap.

- ≥ 2-step improvement in ETDRS DRSS

Compared to Week 52, the difference in ≥ 2-step improvement in ETDRS DRSS at Week 100 for both VEGF Trap groups compared to laser increased and was 21.7 and 21.5% for the 2Q4 and 2Q8 group, respectively.

- Central retinal thickness (CRT)

Between Week 52 and Week 100 improvements in CRT appear very limited (to around -5 µm for VTE groups and -10 µm for laser). As observed from the beginning of the 2Q8 posology (from Week 20 onwards), the curve of improvements in CRT continued to fluctuate between two injections.

- Changes in NEI VFQ-25

With regards to the near activities score, at Week 100, throughout the entire observation period, mean changes for both VEGF Trap groups were higher than the changes in the laser group; p-values for differences to laser were 0.0529 (2Q4) and 0.0218 (2Q8).

With regards to the distance activities score, at Week 100, mean changes for both VEGF Trap groups were higher than the changes in the laser group; the difference between 2Q4 and laser was nominally statistically significant p = 0.0072 but not for the difference between 2Q8 and laser (p = 0.0072).

Ancillary analyses

Overall, subgroup analyses were qualitatively consistent with those in the overall population for both pivotal phase 3 studies.

In addition to the NEI-VFQ-25 score, quality of life was explored in VIVID based on changes in the Euro QOL-5 dimensions questionnaire (EQ-5D) score. Only minimal changes from baseline were observed. No results for EQ-5D were available from the VISTA study.

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).

Table 11 - Summary of Efficacy for VISTA

Title: A Double-Masked, Randomized, Active-Controlled, Phase 3 Study of the Efficacy and Safety of Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema		
Study identifier	VGFT-OD-1009 (VISTA)	
Design	Multicentre, randomized, double-masked, active-controlled, phase 3 study	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	52 weeks (1 year) not applicable total study duration: 148 weeks (3 years)
Hypothesis	Superiority of VEGF Trap in two dosing regimens over laser treatment	
Treatment groups	2Q4	2 mg VEGF Trap administered IVT every 4 weeks, 156 patients randomised.
	2Q8	2 mg VEGF Trap administered IVT every 8 weeks and sham injection at alternating visits, after 5 initial monthly injections, 154 patients randomised.
	Laser	Laser therapy using the modified ETDRS protocol (with sham injection) at day 1 and at visits at which patients met any of the criteria for laser re-treatment (but no more often than every 12 weeks), 156 patients randomised.

Endpoints and definitions	Primary endpoint	BCVA change	Change by BCVA in ETDRS letter score (assessed using the ETDRS protocol at 4 meters by certified and masked visual acuity examiners to ensure consistent measurement of BCVA) from baseline to week 52.		
	Secondary endpoint (1)	% gain ≥10 ETDRS letters	Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 52		
	Secondary endpoint (2)	% gain ≥15 ETDRS letters	Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 52		
	Secondary endpoint (3)	% improvement ≥2-step ETDRS DRSS	Proportion of subjects who achieved a ≥2-step improvement on the ETDRS Diabetic Retinopathy Severity Score (DRSS) from baseline to week 52.		
	Secondary endpoint (4)	CRT change	Change in central retinal thickness (CRT) from baseline to week 52, as assessed by OCT		
	Secondary endpoint (5)	NEI VFQ-25 near activities score	NEI VFQ-25 near activities subscale change from baseline to week 52		
	Secondary endpoint (6)	NEI VFQ-25 distance activities score	NEI VFQ-25 distance activities subscale change from baseline to week 52		
Database lock	52 weeks, 100 weeks, and 148 weeks				
Results and analysis					
Analysis description	**Primary analysis**				
Analysis population and time point description	Intent to treat 52 weeks				
Descriptive statistics and estimate variability	Treatment group	2Q4	2Q8	Laser	
	Number of subjects	**154**	**151**	**154**	
	BCVA change (mean)	12.5	10.7	0.2	
	SD	9.54	8.21	12.53	
	% gain ≥10 ETDRS letters	64.9	58.3	19.5	
	% gain ≥15 ETDRS letters	41.6	31.1	7.8	
	% improvement ≥2-step ETDRS DRSS	33.8	29.1	14.3	
	CRT change (mean in µm)	-185.9	-183.1	-73.3	
	SE	150.68	153.50	176.72	
	NEI VFQ-25 near activities score (mean change)	9.0	9.4	5.4	

	SE	20.60	18.50	20.44
	NEI VFQ-25 distance activities score (mean change)	8.6	7.3	6.7
	SE	20.99	19.32	19.85
Effect estimate per comparison	Primary endpoint: BCVA change	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in BCVA change (LS mean)		(1) 12.19 (2) 10.45
		97.5% CI		(1) 9.35; 15.04 (2) 7.73; 13.17
		P-value		<0.0001
	Secondary endpoint (1): % gain ≥10 ETDRS letters	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain		(1) 45.9 (2) 38.8
		97.5% CI		(1) 34.7; 57.0 (2) 27.2; 50.3
		P-value		<0.0001
	Secondary endpoint (2): % gain ≥15 ETDRS letters	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain		(1) 34.2 (2) 23.3
		97.5% CI		(1) 24.1; 44.4 (2) 13.5; 33.1
		P-value		<0.0001
	Secondary endpoint (3): % improvement ≥2-step ETDRS DRSS	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain		(1) 19.7 (2) 14.9
		97.5% CI		(1) 9.0; 30.4 (2) 4.4; 25.4
		P-value		<0.0001
	Secondary endpoint (4): CRT change	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in CRT change (LS mean)		(1) -110.78 (2) -113.47
		97.5% CI		(1) -141.34; -80.22 (2) -144.19; -82.75
		P-value		<0.0001
	Secondary endpoint (5): NEI VFQ-25 near activities score	Comparison groups		(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in score change (LS mean)		(1) 5.19 (2) 4.36
		97.5% CI		(1) 0.33; 10.04 (2) -0.21; 8.93

		P-value	(1) 0.0168 (2) 0.0323
	Secondary endpoint (6): NEI VFQ-25 distance activities score	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in score change (LS mean)	(1) 2.86 (2) 1.65
		97.5% CI	(1) -1.82; 7.54 (2) -2.83; 6.13
		P-value	(1) 0.1702 (2) 0.4067
Notes	n/a		
Analysis description	**See section 2.4.2 (Methods)**		

Table 12 - Summary of Efficacy for VIVID

Title: A randomized, double masked, active controlled, phase 3 study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema			
Study identifier	91745 (VIVID)		
Design	Multicentre, randomized, double-masked, active-controlled, phase 3 study		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		52 weeks (1 year) not applicable total study duration: 148 weeks (3 years)
Hypothesis	Superiority of VEGF Trap in two dosing regimens over laser treatment		
Treatment groups	2Q4		2 mg VEGF Trap administered IVT every 4 weeks, 136 patients randomised.
	2Q8		2 mg VEGF Trap administered IVT every 8 weeks and sham injection at alternating visits, after 5 initial monthly injections, 135 patients randomised.
	Laser		Laser therapy using the modified ETDRS protocol (with sham injection) at day 1 and at visits at which patients met any of the criteria for laser re-treatment (but no more often than every 12 weeks), 135 patients randomised.
Endpoints and definitions	Primary endpoint	BCVA change	Change by BCVA in ETDRS letter score (assessed using the ETDRS protocol at 4 meters by certified and masked visual acuity examiners to ensure consistent measurement of BCVA) from baseline to week 52.
	Secondary endpoint (1)	% gain ≥10 ETDRS letters	Proportion of subjects who gained ≥10 ETDRS letters from baseline to week 52
	Secondary endpoint (2)	% gain ≥15 ETDRS letters	Proportion of subjects who gained ≥15 ETDRS letters from baseline to week 52

	Secondary endpoint (3)	% improvement ≥2-step ETDRS DRSS	Proportion of subjects who achieved a ≥2-step improvement on the ETDRS Diabetic Retinopathy Severity Score (DRSS) from baseline to week 52.
	Secondary endpoint (4)	CRT change	Change in central retinal thickness (CRT) from baseline to week 52, as assessed by OCT
	Secondary endpoint (5)	NEI VFQ-25 near activities score	NEI VFQ-25 near activities subscale change from baseline to week 52
	Secondary endpoint (6)	NEI VFQ-25 distance activities score	NEI VFQ-25 distance activities subscale change from baseline to week 52
Database lock	52 weeks, 100 weeks, and 148 weeks		

Results and analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	Intent to treat 52 weeks			
Descriptive statistics and estimate variability	Treatment group	2Q4	2Q8	Laser
	Number of subjects	**136**	**135**	**132**
	BCVA change (mean)	10.5	10.7	1.2
	SD	9.55	9.32	10.65
	% gain ≥10 ETDRS letters	54.4	53.3	25.8
	% gain ≥15 ETDRS letters	32.4	33.3	9.1
	% improvement ≥2-step ETDRS DRSS	33.3	27.7	7.5
	CRT change (mean in µm)	-195.0	-192.4	-66.2
	SE	146.59	149.89	138.99
	NEI VFQ-25 near activities score (mean change)	5.7	5.3	3.5
	SE	18.93	19.6	16.77
	NEI VFQ-25 distance activities score (mean change)	0.9	5.3	2.3
	SE	16.49	18.47	15.92
Effect estimate per comparison	Primary endpoint: BCVA change	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser	
		Difference in BCVA change (LS mean)	(1) 9.25 (2) 9.05	

		97.5% CI	(1) 6.49; 12.02 (2) 6.35; 11.76
		P-value	<0.0001
	Secondary endpoint (1): % gain ≥10 ETDRS letters	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain	(1) 28.7 (2) 27.5
		97.5% CI	(1) 15.8; 41.6 (2) 14.6; 40.5
		P-value	<0.0001
	Secondary endpoint (2): % gain ≥15 ETDRS letters	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain	(1) 23.3 (2) 24.2
		97.5% CI	(1) 12.6; 33.9 (2) 13.5; 34.9
		P-value	<0.0001
	Secondary endpoint (3): % improvement ≥2-step ETDRS DRSS	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in % gain	(1) 25.8 (2) 19.3
		97.5% CI	(1) 12.2; 39.4 (2) 6.6; 32.1
		P-value	<0.0001
	Secondary endpoint (4): CRT change	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in CRT change (LS mean)	(1) -156.98 (2) -142.82
		97.5% CI	(1) -190.89; -123.07 (2) -179.31; -106.33
		P-value	<0.0001
	Secondary endpoint (5): NEI VFQ-25 near activities score	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in score change (LS mean)	(1) 2.41 (2) -1.21
		97.5% CI	(1) -2.01; 6.82 (2) -5.79; 3.37
		P-value	(1) 0.2208 (2) 0.5537
	Secondary endpoint (6): NEI VFQ-25 distance activities score	Comparison groups	(1) 2Q4 versus laser (2) 2Q8 versus laser
		Difference in score change (LS mean)	(1) -1.19 (2) -0.37
		97.5% CI	(1) -5.29; 2.91 (2) -4.79; 4.05
		P-value	(1) 0.5138 (2) 0.8498

Notes	n/a
Analysis description	**See section 2.4.2 (Methods)**

Analysis performed across trials (pooled analyses)

Results from the integrated analysis of VISTA and VIVID are presented above, as relevant.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of Eylea in the treatment of DME was assessed in two randomised, multicentre, double-masked, active-controlled phase 3 studies (VISTA and VIVID) conducted in patients with clinically significant DME. Supportive data were available from one phase 2 dose ranging study (DA VINCI, see section 2.4.1.).

A total of 862 subjects were randomised and treated in the phase 3 studies and were evaluable for efficacy. Of those, 576 were randomised to the Eylea treatment groups, whereby 290 patients received 2 mg VEGF Trap every 4 weeks (2Q4), 286 received 2 mg VEGF Trap every 8 weeks following 5 initial monthly injections (2Q8), and 286 were treated with laser photocoagulation.

Generally, the design and conduct of the two studies was considered acceptable.

Differences regarding inclusion and exclusion criteria were limited between the two studies. However, patient population profiles in terms of baseline demographics and characteristics of disease did not completely match across studies. Differences included the BMI, which was higher in VISTA, CRT values (higher in VIVID), lack of DRSS grading in a quarter of the patients in VIVID (compared to 1.7% in VISTA), higher NEI VFQ-25 scores in VIVID and higher number of pseudophakic patients in VISTA.

A total of 92% of subjects in VISTA had type 2 diabetes. In VIVID, a post-hoc review identified 45% of the patients to suffer from type 2 diabetes, but the diabetes type could not be determined for 51% of the patients. From this information, it appeared that only few subjects with type 1 diabetes were included in the phase 3 trials and the limited experience was reflected in the SmPC.

Furthermore, among the total number of subjects enrolled across both studies, only 8 subjects (0.9%) had a baseline HbA1c > 12% (all subjects from VISTA). The limited experience in these subjects has been included in the SmPC.

A larger percentage of subjects in VISTA received prior anti-VEGF treatment (43%) compared to VIVID (9%). As there were no apparent differences in the mean changes in BCVA and CRT at week 52 between treatment naïve subjects and subjects who had received prior anti-VEGF treatment, this didn't appear to be a major issue. Finally, differences between the studies were also noted when looking at any kind of prior DME treatment (69% in VISTA and 80% in VIVID).

Taken together, the differences in the baseline characteristics suggested that subjects in VISTA may have had DME of a more refractory nature, particularly since the proportion of subjects who had received prior anti-VEGF treatment was 4 times higher in VISTA compared to VIVID.

The CHMP also noted that subjects with significant macular ischaemia were excluded from the studies. However, in a small study by Chang et al 2008, anti-VEGF-treatment with bevacizumab was shown to reduce visual acuity in DME patients with macular ischaemia. The CHMP consequently questioned

whether VEGF Trap will be effective in ischaemic patients and whether this subgroup have a higher risk for an impaired vision if treated with VEGF Trap. To clarify the point, the MAH provided an analysis comparing ischemic and non ischemic groups of patients with macula ischemia involving fovea in VIVID where macular ischemia was systematically assessed by the reading centre (not in VISTA). This analysis did not seem to reproduce the vision decrease observed by Chung et al 2008 for ischemic patients. However, the CHMP considered that visual acuity reduced in DME patients with macular ischaemia should be monitored in future PSURs.

The primary and all secondary endpoints for both studies was set at 1 Year. This duration was considered too short to establish long term efficacy. However, summary results for Year 2 in VISTA were submitted during the review of the application (see also discussion below) and additional data were to be collected over the total 3 years duration of the studies.

The choice of efficacy variables was considered acceptable by the CHMP.

Efficacy data and additional analyses

With the initial application, the MAH submitted 1 Year data for both phase 3 studies. Upon request by the CHMP, the MAH also provided a summary of the key efficacy outcomes at Year 2 for the VISTA study. Data for VIVID beyond 1 Year were not yet available at the time of this report.

Results from the two phase 3 studies showed clinically and statically relevant superiority of Eylea treatment over laser photocoagulation with regards to the primary endpoint, with a difference in mean BCVA gain of 9-12 letters in the two VEGF Trap groups compared to laser, as well as in all visual acuity and anatomic secondary endpoints at Week 52 (Year 1).

The difference between the VEGF Trap groups and the laser group with regards to responders with ≥ 15 ETDRS letters gain (i.e. 3 lines on the vision chart) was about 30-20%. Improvements in CRT were also significantly in favour of VEGF Trap and were seen as early as Week 1. Superiority of VEGF Trap compared to laser was also observed with regards to ≥2-step improvement in DRSS. However, supportive literature for the relevance of the DRSS endpoint to the primary indication (DME) and of the relevance of the effect size has not been provided. In addition, for a quarter of the patients in VIVID the DRSS status was not gradable.

Results for the quality of life endpoints based on NEI VFQ-25 scores were neither statistically compelling (except for the near activities score in the 2Q4 group in the VISTA study) nor consistent across the two studies. It therefore appeared that the benefits of Eylea in terms of gain in vision and particularly with regards to the gain in visual acuity of 15 or more letters on the ETDRS chart was not well translated in a useful improvement for the management of current daily activities. However, the MAH explained that vision-related quality of life always considers visual function of both eyes, with more weight on the better-seeing eye than on the worse-seeing eye. Since in both pivotal trials, the study eye was defined as the worse-seeing eye and fellow-eye treatment according to standard of care was allowed, the outcomes may be biased and a strict correlation between visual function on the study eye is not necessarily expected. Furthermore, the NEI-VFQ-25 is known to have a high variability and the sample size might not have been sufficient to detect a difference at the statistical significance level. Since the overall health state of patients is not affected by ophthalmologic treatment, it can also be expected that despite a significant and meaningful gain in visual acuity in the study eye, these changes do not necessarily translate into respective benefits in health status. These explanations were considered acceptable by the CHMP.

The effect of Eylea was consistent across primary analysis and secondary analyses in the FAS and the PPS. Overall, a similar trend was seen in sensitivity analyses. A consistent effect was also achieved in

predefined subgroups although some subgroups were too small to allow firm conclusions. Furthermore, results from the integrated analysis were consistent with the outcome of the individual studies.

No clear advantages were seen for the 2Q4 regimen when compared to the 2Q8 regimen. Therefore, the selection of the 2Q8 regimen with 5 initial monthly injections was considered acceptable by the CHMP from an efficacy perspective at least for the start of treatment. However, due to the limited available data beyond one year of treatment, uncertainties remained regarding the long-term management of DME with VEGF Trap which was considered to not have been fully explored.

Efficacy data from Year 2 in VISTA confirmed maintenance of efficacy beyond Year 1. A plateau is reached in terms of the degree of improvement in visual acuity and CRT after 12 months. A continued regime of injections every 8 weeks was sufficient to maintain these improvements. Further support for maintenance of the effect may be given by previous experience with ranibizumab through the extension phase of the RESTORE study as well as RISE and RIDE studies (Ophthalmology, 2012) and Diabetic Retinopathy Clinical Research Network study (Ophthalmology, 2011). DA VINCI results also suggested that improvements in vision achieved in the first year of treatment may persist after treatment has ceased, as reflected in a relatively well-maintained BCVA gain during the 6 month off-drug follow-up period of the study and despite only limited use of further treatment in this period. This however would support an extended treatment interval.

Therefore, the CHMP considered that it was reasonable to allow a gradually extending interval between treatments after the initial year of therapy, as approved for the AMD indication. However, the benefits of an extended treatment interval versus a fixed dosing regimen in the long-term treatment of DME remain unproven as this was not investigated in the pivotal phase 3 trials. Therefore, the CHMP requested that the posology for long-term treatment should be further investigated in a post-marketing study with a view to comparing different treatment regimens (2Q8, PRN and treat-and-extend) after the first year of treatment, thereby exploring different common practices in the management of DME as well as criteria for possibly ceasing treatment if no longer required.

Furthermore, in the initial posology proposal by the MAH, no rules for treatment cessation in non-responders were defined. To assess the potential for stopping therapy in non-responders, the MAH presented an analysis of outcome over 12 months in three potential groups of non-responders, defined by change from baseline in BCVA after 3 months. However, the number of subjects in the two most meaningful groups (those losing or not gaining vision) was too small to allow any firm conclusions. Still, in order to avoid unnecessary treatment of patients not benefitting from continued therapy, it was recommended to discontinue Eylea if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment. This was agreed by the CHMP.

2.4.4. Conclusions on the clinical efficacy

Taken together, data from the two pivotal phase 3 studies, VISTA and VIVID, supported efficacy of Eylea given every 2 months following 5 initial monthly applications in the treatment of DME. A clinically relevant beneficial effect was shown over 1 year of treatment for relevant visual acuity and morphological outcomes. Efficacy was furthermore supported by the phase 2 trial DA VINICI and 2 year data from the VISTA trial, demonstrating maintenance of efficacy beyond the first year of treatment. Nevertheless, long-term efficacy data from the 2 pivotal trials VISTA and VIVID should be provided, once available, including full reports on the 2 year data as well as the final study reports covering the full treatment period of 3 years.

The CHMP considered furthermore the following measure necessary to address issues related to long-term efficacy:

Interventional post-authorisation efficacy study in patients with diabetic macular oedema with the primary objective of comparing, after the first initial year of Eylea treatment, the standard regime of injections every 8 weeks with alternative treatment regimes, i.e. extended treatment intervals based on visual and anatomic outcomes (PRN and treat-and-extend).

This measure was considered necessary due to concerns about the optimal long term treatment strategy in light of the lack of comparative data for the fixed and flexible dosing regimens. Furthermore, the CHMP considered that the benefits of Eylea as demonstrated in clinical trials based on fixed dosing regimens was impacted by differences in common clinical practices, whereby more flexible regimens are used in the treatment of DME.

2.5. Clinical safety

2.5.1. Introduction

Assessment of the clinical safety of VEGF Trap in subjects with DME was mainly based on 52 week safety data derived from the two pivotal phase 3 studies VISTA and VIVID. These studies included a total of 872 randomised subjects. Both studies had a similar design (see section 2.4.2. for details on the study methodology) and employed three treatment arms VEGF Trap 2Q4, VEGF Trap 2Q8 and laser. No safety data from these studies beyond the first year of treatment was available at the time of this report.

Supportive safety data were provided from 219 subjects with DME treated in the phase 2 DA VINCI study.

The clinical safety of VEGF Trap for the treatment of DME was also supported by the available clinical safety database for AMD and CRVO.

For data on immunogenicity, see section 2.3.3.

Patient exposure

- VIVID AND VISTA: Integrated analysis

In VIVID and VISTA studies, a total of 865 subjects constituted the safety analysis set (please refer to Table 7 summarising the sample size and analysis sets for details).

Approximately 90% of subjects in all the groups completed 52 weeks of treatment.

The majority of subjects received the planned treatment for the study eye, which represent 13 injections in the 2Q4 group and 9 injections in the 2Q8 group. The median (mean) number of injections was 13 (12.0) in the 2Q4 group and 9 (8.5) in the 2Q8 group. The median duration of treatment was 52 weeks.

Subjects could receive additional treatment in the study eye (VEGF Trap for laser subjects and laser for VEGF Trap subjects) at each visit starting with week 24 if the criteria for additional treatment were met. More subjects in the laser arm received additional treatment (27.9%) than in the VEGF Trap arms (3.4% in 2Q4 and 4.2% in 2Q8).

Bilateral treatment

Subjects with bilateral disease could receive anti-VEGF treatment in the fellow eye (for DME) in both VIVID and VISTA. In both studies, subjects received ranibizumab and infrequently, bevacizumab. In

VISTA, subjects could also receive, and primarily did receive, VEGF Trap (only one subject received bevacizumab). In VIVID, subjects could not receive VEGF Trap.

In VISTA, a total of 91 subjects in the laser group, 91 subjects in the 2Q4 group, and 107 subjects in the 2Q8 group received anti-VEGF injections (VEGF Trap or ranibizumab [if VEGF Trap was not available due to logistical reasons]) in the fellow eye over the course of the study. In VIVID, a total of 32 subjects in the laser group, 36 subjects in the 2Q4 group, and 34 subjects in the 2Q8 group received anti-VEGF injections (ranibizumab or bevacizumab; licensed treatment preferred) in the fellow eye over the course of the study.

The percentage of subjects receiving fellow eye treatment during the study across all treatment groups was similar (42.9% - 49.1%). In the subjects who received fellow eye injections, the median number of fellow eye injections across all treatment groups was 4, and the mean number of fellow eye injections across all treatment groups was 4.3 – 4.5.

- DA VINCI

In the DA VINCI study, a total of 219 subjects received any treatment in either of the 5 study arms: VEGF Trap 0.5Q4; VEGF Trap 2Q4; VEGF Trap2Q8; VEGF Trap 2PRN; laser (see section 2.4.1. for details on the study design and sample sizes).

The total mean exposure to VEGF Trap in terms of number of injections was 11.7, 10.8, 7.2, and 7.4 in the 0.5Q4, 2Q4, 2Q8 and 2PRN treatment groups, respectively.

Adverse events

Overall adverse events

- VIVID AND VISTA: Integrated analysis

See Table 13 for an overview of the integrated analysis of adverse events in VISTA and VIVID.

Almost all subjects (89.7% to 89.9% of subjects in each treatment group) experienced at least 1 treatment emergent adverse event (TEAE) during the first year of the study. Overall, the incidences of ocular and non-ocular TEAEs were similar among treatment groups (see also below).

When compared to the VEGF Trap combined group, more subjects in the laser group reported ocular TEAEs in the study eye that were of greater than mild severity. The severities of non-ocular TEAEs were similarly distributed across the treatment groups.

With regards to serious adverse events (SAEs), a notable difference between the groups was a greater frequency of study eye SAEs in the laser group than in the VTE combined group (4.2% vs. 1.7%).

The incidences of TEAEs leading to discontinuation, study drug-related TEAEs, treatment emergent SAEs, and deaths were generally low.

Table 13 - Treatment emergent adverse events overview by treatment groups (Integrated analysis)

(Integrated Safety Analysis Set)	Laser (N=287)	VTE 2Q4 (N=291)	VTE 2Q8 (N=287)	VTE Combined[a] (N=578)
Number (%%) of subjects with any TEAE	**258 (89.9%)**	**261 (89.7%)**	**258 (89.9%)**	**519 (89.8%)**
Any **ocular** TEAE	204 (71.1%)	201 (69.1%)	202 (70.4%)	403 (69.7%)
Study eye	**185 (64.5%)**	**172 (59.1%)**	**167 (58.2%)**	**339 (58.7%)**
Fellow eye	145 (50.5%)	154 (52.9%)	147 (51.2%)	301 (52.1%)
Any **non-ocular** TEAE	**213 (74.2%)**	**217 (74.6%)**	**217 (75.6%)**	**434 (75.1%)**
Any **drug related** TEAE	**8 (2.8%)**	**24 (8.2%)**	**14 (4.9%)**	**38 (6.6%)**
Any drug-related **ocular** TEAE	4 (1.4%)	22 (7.6%)	9 (3.1%)	31 (5.4%)
Study eye	3 1.0%)	21 (7.2%)	8 (2.8%)	29 (5.0%)
Fellow eye	1 (0.3%)	3 (1.0%)	4 (1.4%)	7 (1.2%)
Any drug-related **non-ocular** TEAE	4 (1.4%)	4 (1.4%)	6 (2.1%)	10 (1.7%)
Any **injection related** TEAE	**82 (28.6%)**	**128 (44.0%)**	**114 (39.7%)**	**242 (41.9%)**
Any injection related ocular TEAE	82 (28.6%)	127 (43.6%)	114 (39.7%)	241 (41.7%)
Study eye	76 (26.5%)	125 (43.0%)	112 (39.0%)	237 (41.0%)
Fellow eye	28 (9.8%)	37 (12.7%)	28 (9.8%)	65 (11.2%)
Any injection related **non-ocular** TEAE	0	5 (1.7%)	1 (0.3%)	6 (1.0%)
Any **laser related** TEAE	**17 (5.9%)**	**9 (3.1%)**	**12 (4.2%)**	**21 (3.6%)**
Any laser related **ocular** TEAE	17 (5.9%)	8 (2.7%)	12 (4.2%)	20 (3.5%)
Study eye	16 (5.6%)	6 (2.1%)	10 (3.5%)	16 (2.8%)
Fellow eye	2 (0.7%)	2 (0.7%)	2 (0.7%)	4 (0.7%)
Any laser related **non-ocular** TEAE	0	2 (0.7%)	0	2 (0.3%)
Maximum **intensity** for any **ocular** TEAE	204 (71.1%)	201 (69.1%)	202 (70.4%)	403 (69.7%)
Study eye	185 (64.5%)	172 (59.1%)	167 (58.2%)	339 (58.7%)
Mild	114 (39.7%)	126 (43.3%)	117 (40.8%)	243 (42.0%)
Moderate	63 (22.0%)	39 (13.4%)	46 (16.0%)	85 (14.7%)
Severe	**8 (2.8%)**	**7 (2.4%)**	**4 (1.4%)**	**11 (1.9%)**
Fellow eye	145 (50.5%)	154 (52.9%)	147 (51.2%)	301 (52.1%)
Mild	101 (35.2%)	91 (31.3%)	85 (29.6%)	176 (30.4%)
Moderate	38 (13.2%)	56 (19.2%)	59 (20.6%)	115 (19.9%)
Severe	6 (2.1%)	7 (2.4%)	3 (1.0%)	10 (1.7%)
Maximum intensity for any **non-ocular** TEAE	213 (74.2%)	217 (74.6%)	217 (75.6%)	434 (75.1%)
Missing	0	0	1 (0.3%)	1 (0.2%)
Mild	70 (24.4%)	77 (26.5%)	92 (32.1%)	169 (29.2%)
Moderate	101 (35.2%)	92 (31.6%)	90 (31.4%)	182 (31.5%)
Severe	**42 (14.6%)**	**48 (16.5%)**	**34 (11.8%)**	**82 (14.2%)**
Any treatment emergent **SAE**	**78 (27.2%)**	**76 (26.1%)**	**72 (25.1%)**	**148 (25.6%)**
Any **ocular** treatment emergent SAE	15 (5.2%)	14 (4.8%)	9 (3.1%)	23 (4.0%)
Study eye	**12 (4.2%)**	**5 (1.7%)**	**5 (1.7%)**	**10 (1.7%)**
Fellow eye	5 (1.7%)	10 (3.4%)	5 (1.7%)	15 (2.6%)
Any **non-ocular** treatment emergent SAE	**65 (22.6%)**	**67 (23.0%)**	**64 (22.3%)**	**131 (22.7%)**
Any **drug related** treatment emergent **SAE**	**1 (0.3%)**	**1 (0.3%)**	**2 (0.7%)**	**3 (0.5%)**
Any drug-related ocular TE SAE	0	0	1 (0.3%)	1 (0.2%)
Study eye	0	0	1 (0.3%)	1 (0.2%)
Fellow eye	0	0	1 (0.3%)	1 (0.2%)
Any drug-related **non-ocular** TE SAE	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.3%)
Any **injection related** TE **SAE**	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Any injection related **ocular** TE SAE	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Study eye	0	1 (0.3%)	2 (0.7%)	3 (0.5%)
Fellow eye	0	0	0	0
Any injection related **non-ocular** TE SAE	0	0	0	0
Any **laser related** TE SAE	2 (0.7%)	0	0	0
Any laser related ocular TE SAE	2 (0.7%)	0	0	0
Study eye	2 (0.7%)	0	0	0
Fellow eye	0	0	0	0
Any laser related non-ocular TE SAE	0	0	0	0
Any TEAEs leading to **discontinuation from the study drug**	8 (2.8%)	4 (1.4%)	2 (0.7%)	6 (1.0%)
Any **Death** due to TEAE	2 (0.7%)	2 (0.7%)	4 (1.4%)	6 (1.0%)
Any treatment emergent **APTC-classified events**	8 (2.8%)	9 (3.1%)	10 (3.5%)	19 (3.3%)

a Sum of the columns VTE 2Q4 and VTE 2Q8 through week 52

2Q4: 2 mg VEGF Trap every 4 weeks; 2Q8: 2 mg VEGF Trap every 4 weeks until week 16 and every 8 weeks, thereafter; AE: adverse event; N: total number of subjects; TEAE: treatment-emergent adverse event; TE = treatment-emergent

In general, the pattern of TEAEs was similar between the pivotal studies. However, VISTA had a higher overall incidence of TEAEs (86.6% versus 92.6%), a higher incidence of non-ocular TEAEs (67.1% versus 81.6%), and a higher incidence of treatment emergent SAEs (19.1% versus 32.3%), and more severe TEAEs compared with VIVID. However, the incidence of study drug-related TEAEs were lower in VISTA compared with VIVID (1.5% versus 9.7%).

- DA VINCI

Ocular and non-ocular TEAEs were reported by the majority of subjects in all treatment groups.

The incidences of ocular and non-ocular TEAEs were similar among treatment groups. However, the incidence of serious ocular TEAEs in the study eye occurred at a higher frequency in the laser group (5/44 subjects [11%]) compared to the combined VEGF Trap groups (5/175 subjects [3%]), but the overall frequency was low.

The frequencies of severe non-ocular TEAEs in any VEGF Trap group (VEGF Trap combined, 17.7%) were higher overall than in the laser group (11.4%), but only 2 were considered to be drug-related.

There were few deaths and TEAEs leading to discontinuations, and they occurred at similar frequencies across the treatment groups.

Ocular adverse events

- VIVID AND VISTA: Integrated analysis
    - Study eye treatment

The MAH presented a tabular overview of ocular TEAEs in the study eye occurring in ≥1% of subjects of any treatment group. The number of subjects experiencing at least 1 ocular TEAE in the study eye was higher in the laser group (64.5%) compared to the VEGF Trap 2Q4 group and 2Q8 groups (VEGF Trap combined 58.7%). Some adverse events were more frequent in the laser group compared to the combined VEGF Trap group, which could be related to the progression of diabetic retinopathy: “cystoid macular oedema” (3.5% versus 1.2%), “diabetic retinal oedema” (2.8% versus 0.7%), “diabetic retinopathy” (2.8% versus 0.3%), “macular oedema” (2.1% versus 0.3%), “retinal haemorrhage” (7.3% versus 3.6%), “retinal neovascularisation” (4.5% versus 0.9%), “visual impairment” (2.4% versus 0.9%), “vitreous haemorrhage” (3.8% versus 0.4%) and “visual acuity tests abnormal” (8% versus 2.6%).

Some adverse events were more frequent in the VGEF Trap groups compared to laser and could be related to the injection: “conjunctival haemorrhage” (28% versus 17.4%), “eye pain” (9%vs 6.3%), “ocular hypertension” (2.2% versus 0%) and “increased intraocular pressure” (5% versus 3.5%). Of note, the fact that both VEGF Trap and sham injection procedures required sub-conjunctival anaesthetic injection can explain that these events were also reported in the laser group. Injection-related TEAE were more frequent in the 2Q4 group as could be expected since the number of injections was higher and AEs related to the progression of diabetic retinopathy were almost similar.

Three other adverse effects were more frequent in VEGF groups compared to laser: “increased lacrimation” (3.1% versus 1.7%), “vitreous floaters” (5.9% versus 3.1%) and “punctate keratitis” (2.9% versus 1%).

For the VEGF Trap treatment groups, the most common ocular TEAEs in the study eye were conjunctival haemorrhage (28.0%) and eye pain (9.0%). For the laser treatment group, the most common ocular TEAEs in the study eye were conjunctival haemorrhage (17.4%) and retinal haemorrhage (7.3%).

There were few events consistent with significant ocular inflammation or potential infection: iridocyclitis in 2 subjects, one in the 2Q4 group (0.3%) and one in the 2Q8 group (0.3%); uveitis in 1 subject in 2Q4 group (0.3%), and no reports of endophthalmitis.

The overall incidence of severe ocular TEAEs in the study eye was low and similar in the laser treatment group (2.8%) and the VEGF Trap 2Q4 treatment group (2.4%), but lower in the VEGF Trap 2Q8 treatment group (1.4%).

The overall incidence of study drug-related TEAEs was highest in the VEGF Trap 2Q4 group (8.2%) and lowest in the laser group (2.8%); the incidence in the VEGF Trap 2Q8 group was 4.9%. The most frequently reported study drug related ocular TEAEs in the study eye were intraocular pressure (IOP) increased, ocular hyperemia, and conjunctival haemorrhage.

- Fellow eye treatment

The number of subjects experiencing at least 1 ocular TEAE in the fellow eye was consistent across all treatment groups (50.5% to 52.9%). For all 3 treatment groups, the most common ocular TEAEs (≥0%) in the fellow eye were conjunctival haemorrhage (laser, 10.5%; 2Q4, 11.0%; 2Q8, 9.4%) and diabetic retinal oedema (laser, 7.7%; 2Q4, 11.3%; 2Q8, 8.4%).

- DA VINCI

Overall, the proportion of subjects reporting ocular TEAEs in the study eye was similar across all treatment groups. Most subjects reported events which were mild or moderate in intensity, as determined by the investigator. The 3 most commonly occurring TEAEs in the combined VEGF Trap groups were associated with the injection procedure (conjunctival haemorrhage, eye pain, and increased IOP) and occurred at a higher frequency in the combined VEGF Trap groups compared to the laser group. The rate of these events across the VEGF treatment groups was also consistent with the number of injections administered. According to the MAH, no AE trends were observed relative to dose or to frequency of injection. Indeed, when quadrupling the dose, no major difference in the AE profile was observe except for “eye irritation” (0% in laser group, 2.3% in 0.5Q4 group and 4.5% and 4.8% respectively in 2Q4 and 2Q8 groups). Similarly, there was no major difference in terms of AEs related to diabetic retinopathy progression between 2Q4 and 2Q8 groups.

A total of 6 subjects (3%) in the VEGF Trap groups reported ocular TEAEs in the study eye which were judged by the investigator to be related to study drug. With the exception of eye pain and cataract, which were reported in 2 subjects, all other study drug-related ocular AEs in the study eye were reported in single subjects (ocular hyperaemia, vision blurred, vitreal cells, and citreous floaters).

<u>Non-Ocular adverse events</u>

- VIVID AND VISTA: Integrated analysis

The number of subjects experiencing at least 1 non-ocular TEAE was balanced between treatment groups.

In 6 system organ classes (SOC), a slightly higher incidence of non-ocular TEAEs was observed in the VEGF Trap combined groups than in the laser group: “Blood and lymphatic system disorders” (6.2% in VEGF Trap groups and 4.9% in laser group), “Cardiac disorders” (10.9% in the VEGF Trap groups and 9.4% in laser group), “Immune system disorders” (3.6% versus 1.7% in laser group) “Infections and infestations” (37% versus 34.8% in laser group), “Respiratory disorders”(11.4% in laser group versus 10.1%) and “ Neoplasms benign, malignant and unspecified” (4.7% versus 2. 4%). A difference in incidence was also observed for the preferred term (PT) “oedema peripheral”, and “glycosylated

haemoglobin increased" for which a higher incidence of non-ocular TEAEs in the combined VEGF Trap groups was observed compared to laser.

The number of subjects with events in the SOCs cardiac disorders, immune system disorders, infections and infestations, respiratory, thoracic and mediastinal disorders was slightly higher in the VEGF Trap 2Q4 group compared to the laser and the 2Q8 group.

The number of subjects with events in the SOC neoplasms benign, malignant and unspecified (including cysts and polyps) is slightly higher in the 2Q4 group and the 2Q8 groups compared to the laser group.

The number of subjects with events in the SOC investigations, musculoskeletal and connective tissue disorders, renal and urinary disorders, skin and subcutaneous tissue disorders is slightly higher in the laser group compared to the 2Q4 and the 2Q8 group.

For all 3 treatment groups, the most common non-ocular TEAEs were hypertension and nasopharyngitis and were balanced between treatment groups.

Anaemia occurred at a higher incidence in subjects in the VEGF Trap groups compared to subjects in the laser group (VEGF Trap combined 4.8% versus laser 2.4%). In contrast to this, in the SOC "Investigations" the incidence of "haemoglobin < 115g/L (M) or 95 g/L (F)" was higher in the laser group (9% versus 5.2%). According to the MAH, an analysis of laboratory values for haemoglobin at week 24 and week 52 did not indicate an increased risk for decrease of haemoglobin values for the VEGF Trap groups.

Finally, in most of the SOCs, the VEGF Trap 2Q4 group has a slightly higher incidence of events compared to 2Q8, especially in the SOC "Cardiac disorders". Within this SOC the single most frequently reported TEAE in the VEGF Trap groups was "cardiac failure congestive", which was reported by 15 subjects (2.6%) in the VEGF Trap combined group versus 1 subject (0.3%) in the laser group. Most of the cases were observed in the VISTA study and only one was observed in VIVID.

Other non-ocular TEAEs occurring at a slightly higher incidence in subjects in the VEGF Trap groups compared to subjects in the laser group included peripheral oedema (4.5% versus 2.8%); and pneumonia (2.6% versus 1.4%). Events which occurred more frequently in the laser group included hyperglycaemia (0.9% versus 3.8%), blood creatine phosphokinase increased (0.9% versus 3.1%), and hypercholesterolaemia (1.2% versus 3.1%). With regards to hyperglycaemia, it is noteworthy that the incidence of the term "blood glucose increased" in the SOC "Investigations" was higher in the VEGF Trap combined groups compared to laser (2.5% versus 1.7%).

In general, the pattern of TEAEs was similar between the pivotal studies; however, the incidences of reported TEAEs were different. VISTA had a higher overall incidence of TEAEs, and a higher incidence for every SOC compared to VIVID.

Study drug related non-ocular TEAEs occurred at a low incidence. No PT was reported by more than 2 subjects in any treatment group.

- DA VINCI

Treatment-emergent AEs in the SOCs of Investigations, Metabolism and Nutrition Disorders, Gastrointestinal Disorders and Cardiac Disorders occurred at a higher frequency in the combined VEGF Trap groups compared to the laser group.

The difference in the SOC Investigations was primarily due to blood glucose increased, urine protein/creatinine ratio increased and glycosylated haemoglobin increased. For Metabolism and

Nutrition Disorders, the difference was primarily due to hypercholesterolaemia and conditions affecting glycaemic control (hyperglycaemia, diabetes mellitus). By preferred term, The difference in the SOC Gastrointestinal Disorders was primarily due to nausea, diarrhoea, and constipation. Finally, more patients in the combined VEGF Trap groups had an event in the Cardiac Disorders SOC, primarily due to cardiac failure congestive and coronary artery disease. Of note, a higher proportion of subjects in the VEGF Trap groups had a medical history of cardiac disorders prior to entering the study (33% to 48%) compared to the laser group (18%).

A higher incidence for the VEGF Trap groups compared to laser was also reported for the PT terms "anaemia", "blood glucose increased" and "glycosylated haemoglobin increased".

Serious adverse event / deaths / other significant events

Deaths

- VIVID AND VISTA: Integrated analysis

A total of 8 deaths were reported in the integrated analysis as of week 52: 5 deaths in the VIVID study, and 3 deaths in the VISTA study.

In VIVID, the 5 deaths concerned 1 subject in the laser group (acute myocardial infarction) and 4 patients in the VEGF Trap 2Q8 group (hypertensive heart disease, lung neoplasm, B-cell lymphoma, cardiac failure)

In VISTA, the 3 deaths concerned 1 subject in the laser group (sudden cardiac death) and 2 subjects in the VEGF Trap 2Q4 group (myocardial infarction and death [etiology unknown])

One of the deaths, hypertensive heart disease in a 64-year old Asian male in the VEGF Trap 2Q8 group, was judged by the investigator to be related to study drug.

Finally, 10 other fatal cases were reported in the second year of VISTA study including 6 of cardiovascular origin.

- DA VINCI

A total of 7 deaths were reported during the study, 6/175 subjects in the VEGF Trap groups (1 subject in the 0.5Q4 group with multi organ failure, 3 subjects in the 2Q4 group with cerebral infarction, non-small cell lung cancer, and sudden death, respectively, and 2 subjects in the 2Q8 group with renal failure and acute coronary syndrome, respectively) and 1/44 subject in the laser group (cardiac arrest).

According to the MAH, none of the events that led to death in these subjects were judged by the investigator to be related to study drug or to the study procedure.

Serious ocular adverse events

- VIVID and VISTA: Integrated analysis

A total of 10 ocular adverse events were reported as serious in DME studies, including only one drug-related SAE: IOP increased in 2Q8 group.

The laser treatment group had the highest incidence of serious ocular TEAEs.

The most frequently reported serious ocular TEAE in the study eye was vitreous haemorrhage (1.4% in the laser group versus 0.5% in VEGF Trap combined group). There were no reports of endophtalmitis.

- DA VINCI

Overall, serious ocular TEAEs in the study eye were reported by few subjects but at a higher frequency in the laser group compared to the combined VEGF Trap groups (5 subjects versus 3 subjects). In the laser group, 3 subjects reported events which were both serious and severe while only 1 subject in the 2Q4 group reported an event that was severe and serious. According to the MAH, there were overall no apparent trends relative to dose or frequency of injections. Two endophtalmitis cases were reported.

Serious non-ocular adverse events

- VIVID AND VISTA: Integrated analysis

Overall, 133 serious non-ocular cases were reported. The most reported events were “cardiac failure congestive” (1.9% in the VEGF Trap combined groups versus 0.3% in the laser group), “anaemia” (2.1% in the VEGF Trap combined groups versus 0.3% in the laser group), “cellulitis” (1.7% in the VEGF Trap combined groups versus 0.7% in laser group) and “renal failure acute” (1.9% in the VEGF Trap combined groups versus 1.7% in the laser group).

There were slightly more subjects with serious TEAEs reported for the VEGF Trap combined group compared to laser for the SOC “blood and lymphatic system disorders” and the SOC “neoplasm, benign, malignant and unspecified (including cysts and polyps)”.

There were slightly more subjects with serious TEAEs reported for the laser group compared to the VEGF Trap combined group for the SOC “gastrointestinal disorders”, the SOC “musculoskeletal and connective tissue disorders”.

Two AEs were assessed as drug-related: ischaemic stroke in the VEGF Trap 2Q4 group and hypertensive heart disease in the VEGF Trap 2Q8 group.

- DA VINCI

According to the MAH, the proportion of subjects reporting serious non-ocular TEAEs was comparable across the treatment groups. Compared to the laser group, the VEGF Trap combined group had a higher incidence (by ≥1%) of congestive cardiac failure and cellulitis.

A total of 9 AE were assessed as drug-related and occurred in 2 VEGF Trap subjects: 1 subject with 3 events (acute myocardial infarction, pleural effusion, and respiratory failure) and 1 subject with 6 events (nausea, vomiting, asthenia, blood pressure increased, dizziness, and hyperhidrosis).

Arterial thromboembolic events (ATEs)

ATEs are AEs potentially related to systemic VEGF inhibition and there is a theoretical risk of ATEs following IVT use of VEGF inhibitors. Arterial thromboembolic events, as defined by the APTC criteria (Antiplatelet Trialists’ Collaboration), include non-fatal myocardial infarction, non-fatal stroke, or vascular death (including deaths of unknown cause).

- VIVID AND VISTA: Integrated analysis

The overall incidence of subjects with treatment-emergent APTC events was similar among treatment groups in the integrated analysis. Non-fatal myocardial infarction was more frequent in the laser group, while non-fatal stroke was more frequent in the VEGF Trap combined group. Vascular death was reported with similar frequency in all 3 treatment groups.

- DA VINCI

Events were balanced among the 5 treatment groups. According to the MAH, there was no pattern indicating a higher risk in subjects receiving VEGF Trap.

Laboratory findings

Chemistry

At week 52, in subjects with no pre-defined laboratory assessment of abnormal at baseline who also had a valid laboratory value at week 52, the incidence of predefined laboratory abnormalities was generally balanced among the treatment groups. An exception was hyperglycaemia (glucose ≥11.1 mmol/L [unfasted]), which was observed less frequently in the laser (13.1%) group than in the VEGF Trap 2Q4 (20.2%) and 2Q8 (23.0%) groups. This abnormality was more frequent in VISTA compared to VIVID.

Hyperglycaemia was also observed in the DA VINCI study, where 19 subjects (11%) in VEGF Trap groups reported blood glucose increased compared to 1 subject (2%) in the laser group.

Haematology

At week 52, in subjects with no pre-defined laboratory assessment of abnormal at baseline who also had a valid laboratory value at week 52, the incidence of predefined laboratory abnormalities was generally balanced between the treatment groups. An exception was haemoglobin levels ⩽115 g/L and ⩽95 g/L, which was observed most frequently in the laser (9.0%) group. A similar trend was seen for haematocrit ⩽0.37v/v (male), ⩽0.32v/v (female).

In the DA VINCI study, the highest incidence of decreased haemoglobin and decrease haematocrit was in the VEGF Trap 2Q4 group.

Urinalysis

According to the MAH, no trends towards an increase or decrease in mean values over time were seen for the urinalysis parameter 'specific gravity'. For total protein/creatinine ratio, the mean change from baseline was greater for the VEGF Trap combined group than for the laser group (25.37 mG/mMOL vs. 7.28 mG/mMOL, respectively) but the median differences from baseline were similar (1.00 mg/mMOL vs. -0.50 mG/mMOL, respectively).

Vital signs

According to the MAH, mean systolic and diastolic blood pressure were similar among treatment groups in the integrated analysis at baseline and varied relative to the baseline values in all treatment groups throughout the study, with no obvious trends over time relative to treatment or dose.

Safety in special populations

Sub-group analyses were conducted to evaluate the effects of the following demographic and disease variables on safety: Gender; Baseline Age (<55 years, ≥55 years to <65 years, and ≥65 years to <75 years, ≥75 years); Race (white, Asian and Black/African American); Ethnicity (hipanic and Latino); Geographic region (Japan, Europe & Australia, United States); HbA1c (>8% and ≤8%); Medical history of hypertension, cerebrovascular disease, ischemic heart disease, renal and hepatic impairment.

Overall, according to the MAH, the results of the subgroup analyses for ocular TEAEs in the study eye and non-ocular TEAEs were similar to those seen in the total study population. An extract of the results in relevant subgroups is provided below.

Gender: The most notable difference between genders occurred in the cardiac disorders SOC, where men in both VTE groups had a higher frequency of serious TEAEs than women. Importantly the frequency of these events in the laser group was also higher for men than women.

Baseline age: Overall, according to the MAH, compared to the younger subgroup, the older subgroup did not have a higher incidence of ocular TEAEs, non-ocular AEs or ocular serious TEAEs. However, the older subgroup had a higher incidence of non-ocular serious TEAES and a higher incidence of APTC events.

HbA1c (>8% and ≤8%): Approximately 35% of subjects had a HbA1c above 8%. Concerning non-ocular AE, incidence of glycosylated haemoglobin increased and hypertension were higher in the HbA1c >8% group.

Medical history of hypertension: Approximately 80% of subjects had a medical history of hypertension. Compared to subjects without a medical history of hypertension, the subjects with a medical history of hypertension did not demonstrate greater incidences of overall TEAEs, ocular TEAEs, non-ocular TEAEs, or ocular serious TEAES.

Medical history of cerebrovascular disease: Over 88% of the subjects in the integrated analysis did not have a medical history of cerebrovascular disease (e.g. cerebrovascular accident/ stroke). Compared to the subjects without a medical history of cerebrovascular disease, the subjects with such history had in general a similar incidence across treatment groups of overall TEAEs and ocular TEAEs. However, the incidence of severe non-ocular TEAEs was higher in the VEGF Trap groups than in the laser group in subjects with a medical history of cerebrovascular events.

Medical history of ischaemic heart disease: Approximately 22% of subjects had a medical history of ischemic heart disease. Compared to subjects without a medical history of ischemic heart disease, the subjects with a medical history of ischemic heart disease had similar incidences of overall TEAEs and ocular TEAEs. Incidences were generally balanced across all treatment groups. However, subjects with a medical history of ischemic heart disease, regardless of treatment group, demonstrated a higher incidence of non-ocular TEAEs, overall serious TEAEs (primarily driven by a higher incidence of non-ocular serious TEAEs), and APTC events; the difference was particularly notable for the cardiac SOC.

Medical history of renal impairment: Approximately 57% of subjects had normal renal status, and 30 % had mild renal impairment. According to the MAH, there were no notable differences in TEAE profile between subgroups with normal renal function and mild renal impairment.

Medical history of hepatic impairment: Over 95% of the subjects in integrated analysis did not have a medical history of hepatic impairment. According to the MAH, the subgroup that did have a medical history of hepatic impairment was small and therefore a comparison of subgroups would have very limited utility.

- Bilateral treatment

The MAH analysed subjects based on bilateral anti-VEGF treatment. An increase of non-ocular AEs was observed in patients with fellow eye injections compared to patients without fellow eye injections (80.6% versus 70.3%). A difference was especially observed in the SOC “Nervous system disorders” (10.3% versus 14.9%) and “Vascular disorders” (15.2% versus 26.7%).

To further explore any potential dose response of anti-VEGF treatment on the safety profile, subjects in the laser group in VIVID and VISTA, respectively, who received fellow eye treatment (injected unilaterally) were compared by the MAH to subjects in the 2Q4 and 2Q8 groups combined, who also received fellow eye injections (injected bilaterally). The results for subjects in the laser groups with fellow-eye injections were similar to those for subjects in the VEGF Trap groups with fellow-eye injections.

- Pregnancy, Lactation and Fertility

No new data on the use of VEGF Trap in pregnant or lactating women was provided. Studies in animals have shown reproductive toxicity after systemic administration.

- Overdose/Drug Abuse/Withdrawal and rebound

No cases of overdose, drug abuse or withdrawal and rebound were reported in the DME clinical trials.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with VEGF Trap, which was considered acceptable by the CHMP.

Subjects participating in the DME clinical development program of VEGF Trap received treatment for a variety of diseases common to this study population including their underlying disease, diabetes; and also hypertension, hypercholesterolemia, and cardiovascular disease.

Discontinuation due to adverse events

The incidence of TEAEs resulting in discontinuation of study drug was low in the integrated analysis of VISTA and VIVID. Over the full 52 weeks of the studies, approximately 1% of the VEGF Trap subjects discontinued the studies for a TEAE; 1.4% of subjects from the 2Q4 group and 0.7% from the 2Q8 group. Overall there were more discontinuations due to ocular TEAEs in the laser group than in the VEGF Trap combined group while non-ocular TEAEs were more similarly distributed across the treatment groups.

Post marketing experience

VEGF Trap has been commercially available in the United States since November 2011 and in the EU since November 2012, as well as in a number of other countries as of 2012.

A total of 1761 spontaneous ADRs have been reported starting on the date of product availability in countries where Eylea has been commercially available through to 31 August 2013. Based upon the most recent publicly available sales information (by 2nd Quarter of 2013) the number of vials sold worldwide was estimated to be 996,742. Each vial sold is considered to represent a single drug administration.

Of the 1761 spontaneous ADRs, 1444 were medically confirmed reports by health care providers (HCPs) and 317 were reported by non-HCPs (e.g., patients or family members). Of the 1444 HCP-reported ADRs, 866 were serious.

2.5.2. Discussion on clinical safety

The clinical safety analysis was based on data pooled from the two pivotal phase 3 studies (VISTA and VIVID) during treatment year 1. Supportive safety data were available for 219 subjects with DME treated in the phase 2 DA VINCI study. Overall, data from 578 patients receiving IVT VEGF Trap was available from DME studies. This limited size did not allow detection of rare events. However, overall the extent of the available safety database was considered sufficient to support this application, considering that the clinical safety of VEGF Trap was further enriched by the available data for previously authorised indications, AMD and CRVO.

Limited information was available beyond 1 year of treatment. The CHMP considered that long-term data would be useful to more accurately assess the safety profile of VEGF Trap in DME. To this end, the CHMP considered that the submission of long-term data from the 2 pivotal trials VISTA and VIVID, including full reports on the 2 year data as well as the final study reports covering the full treatment period of 3 years, as already recommended to support long-term efficacy of Eylea (see section 2.4.3. and 2.4.4.) would be sufficient.

The overall incidence of ocular and non-ocular effects in the pooled phase 3 studies seemed to be similar between laser and VEGF Trap groups. However, since 27.9% of subjects in the laser group received additional treatment in the study eye, comparison of AE occurrence between laser and VEGF Trap combined groups, especially for systemic adverse events was considered by the CHMP to be of limited value and should be interpreted with caution.

Overall, 6 deaths were reported in the VEGF Trap groups and 2 patients (not receiving additional VEGF Trap treatment) died in the laser group. Three of the 6 cases in VEGF Trap groups had a cardiac origin. In two cases, despite of cardiovascular medical history, which is a confounding factor, causal role of VEGF Trap could not be excluded. Upon request by the CHMP, the MAH performed a comparison of mortality rates in AMD, CRVO and DME. This analysis did not initially identify any significant difference (1.51%, 0% and 1.08%, respectively), but the comparison was performed based on different periods (1 year data for DME and 2 year data for AMD). Year 2 VISTA results revealed additional 10 fatal cases including 6 cases of cardiovascular origin, resulting in a higher mortality rate (1.38%) compared to the combined year 1 data. The CHMP recommended that additional long-term data, in particular year 2 data from VIVID, were provided post-approval to further investigate this issue.

Bilateral treatment of VEGF Trap was received by some patients in VISTA. An increase of non-ocular AEs, in particular with regards to nervous system disorders and vascular disorders was observed in patients with fellow eye injections compared to patients without fellow eye injections (80.6% versus 70.3%). Therefore, following a request by CHMP, bilateral treatment was added as a subcategory of the missing information 'Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO and DME' in the risk management plan (RMP) in order to closely monitor this concern. In the future analysis in PSURs, the MAH should focus on cardiovascular risks and calculate odds ratios.

Ocular TEAEs in the study eye were generally consistent with the expected adverse consequences of the injection procedure in the VEGF Trap groups (IOP increased, conjunctival haemorrhage, eye pain) or with disease progression in the laser group (macular oedema, diabetic retinopathy, retinal haemorrhage). Injection-related AEs were more frequent in the 2Q4 group as expected since the number of injections was higher. No case of endophthalmitis was reported in the two Phase 3 studies and two cases were reported in the Phase 2 DA VINCI study. As diabetic patients are more at risk for developing infections, the CHMP considered that this AE should be closely monitored in this population. Finally, punctuate keratitis occurred more frequently in VEGF Trap groups than in the laser group and was added as an ADR to SmPC section 4.8. Except for punctuate keratitis, no new ocular AE emerged and no increase in frequency of the already listed ADRs was identified except for cataract cortical (from uncommon to common) and uveitis (from rare to uncommon).

For most of the SOCs, non-ocular TEAEs were similar between the treatment groups. The most common TEAEs in both treatment groups were nasopharyngitis and hypertension, which were adverse events previously reported with the AMD and CRVO applications.

In VISTA, there was a higher incidence of non-ocular TEAEs than in VIVID. The CHMP considered that the difference could be explained by the fact that the 2 populations were different in terms of baseline

characteristics. The VISTA population had more cardiovascular risk factors (hypertension and ischaemic heart disease) and more subjects have an unbalanced glycaemic control.

Regarding cardiac disorders, cardiac failure congestive was reported by 15 subjects (2.6%) in the VEGF Trap combined group of the VISTA and VIVID studies versus 1 subject (0.3%) in the laser group. Most of the cases were observed in the VISTA study and only one was observed in VIVID, which may be due to the fact that more subjects in VISTA had an unbalanced glycaemic control than in VIVID. A higher incidence of this event in the VEGF Trap treatment groups was also observed in the DA VINCI study. As diabetic patients are at risk for developing congestive cardiac failure, this adverse event was of concern. However, two year data from VISTA did not show a major difference between laser (6.5%) and VEGF Trap combined groups (6.8%). The CHMP recommended that these data should be completed by year 2 data from the VIVID study, once available.

Two different analyses of patients with medical history of ischemic heart disease and cerebrovascular accident have been provided by the MAH which show a difference in the incidence of serious non-ocular TEAE compared to patient without such medical history. In the group of subjects with a history of ischemic heart disease, the higher incidence is mostly driven by cardiac disorder events and especially by events of cardiac failure congestive which is not surprising as diabetes mellitus and medical history of myocardial infarction are both related risk factors. With regards to cerebrovascular accident, no firm conclusions could be drawn as the number of patients with such medical history was limited. Nevertheless, the CHMP considered that the safety profile in these patients should be closely monitored in future PSURs. In addition, SmPC section 4.4 was updated to reflect the limited experience in the treatment of patients with a history of stroke or transient ischaemic attacks or myocardial infarction.

Concerning arterial thromboembolic events (ATE), no major difference was observed between VEGF Trap and laser groups. However, non-fatal strokes appeared to be slightly more frequently reported in VEGF Trap groups. Furthermore, 11 new ATE events were reported in the second year of the VISTA study (3 non-fatal MI, 5 non-fatal strokes and 4 vascular deaths). Overall, the interpretability and relevance of these results are limited due to the low number of events. Long-term data were considered to be needed in order to more accurately assess ATE occurrence. As the DME population has major cardiovascular co-morbidities which put them at a greater risk for developing ATE, ATE events were included in the RMP and will be closely monitored in the next PSUR.

Finally, discrepancies between the reporting rates of the PTs ‘anaemia’ versus ‘haemoglobin < 115g/L (M) or 95 g/L (F)’ and ‘hyperglycaemia’ versus ‘blood glucose increased’ were noted. The MAH suggested that these apparent discrepancies arose from the fact that AEs were transferred into PT terms as per MedDRA coding rules as reported verbatim by the investigators. However, investigators are likely to have preferences for how to report a certain adverse events. Therefore, grouping of PTs most likely referring to a similar medical condition, was considered adequate and no safety issue arose when such grouping was done.

2.5.3. Conclusions on clinical safety

In conclusion, the safety profile of VEGF Trap in DME appeared to be similar to the known profile in AMD and CRVO. Overall, the extent of the available safety database supporting this application was considered acceptable, however, it was noted that the size was too limited to detect rare adverse events. Moreover, the safety analysis was mainly based on 1 year data and long term data were considered necessary to complement the safety evaluation post-authorisation. Data from the 2 pivotal trials VISTA and VIVID, including full reports on the 2 year data as well as the final study reports covering the full treatment period of 3 years, were considered by the CHMP to be sufficient to address this concern.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged. However, in future PSURs, the occurrence of arterial thromboembolic events as well as the safety profile in patients with medical history of ischemic heart disease and cerebrovascular accident should be closely monitored.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 16.0, the PRAC considers by consensus that the risk management system for aflibercept (Eylea) in the treatment of

- Neovascular (wet) age-related macular degeneration (AMD) in adults
- Visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO)

and the proposed indication of

- Diabetic macular oedema (DME) in adults

was acceptable. Some deficiencies were noted, which should be addressed with the next RMP update.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Summary of safety concerns	
Important identified risks	• Endophthalmitis (likely infectious origin) • Intraocular inflammation • Transient intraocular pressure increase • Retinal pigment epithelial tears • Retinal tear / detachment • Cataract (especially of traumatic origin) • Hypersensitivity and immunogenicity
Important potential risks	• Arterial thromboembolic events including non-MI ATEs and cardiovascular ischemic events • Venous thromboembolic events • Hypertension • Proteinuria • Non-ocular hemorrhage • Medication error • Off-label use • Embryo-fetotoxicity • Retinal hemorrhage

Missing information	• Use of Eylea® in patients with uncontrolled glaucoma • Concomitant use of different anti-VEGF therapies and other therapies for wet AMD, CRVO, and DME. Concomitant use includes bilateral treatment with anti-VEGFs. • Long term safety beyond 2 years • Posology utilized in marketed use

Pharmacovigilance plan

Table of on-going and planned additional Pharmacovigilance studies / activities in the Pharmacovigilance plan (category 1-3)

Study / activity type, title and category (1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
A Study to Evaluate Physician and Patient Knowledge of Safety and Safe Use Information for Eylea® in Europe: An Observational Post Authorization Safety Study (PASS) **Category 3**	To evaluate: • The level of physicians' knowledge and understanding of key safety information contained in the prescriber guide and the IVT injection procedure video. • The level of patients' knowledge and understanding of the key safety information booklet and audio CD.	• Endophthalmitis • Transient intraocular pressure increase • Retinal pigment epithelium tears • Cataract • Embryo-fetotoxicity • Medication error • Off-label use	Study is planned, final protocol to EMA in Q1/2014. First patient in expected in Q1/2015	Submission of final protocol: Q1/2014. Study report planned to be available Q1/2016 (estimated)
Study 15971 (LIBRA): Long-term Investigation and risk-Benefit analysis of the Real-life utilization of Aflibercept in macular disease. **Category 3**	The primary objective is to identify important potential risks of intravitreal aflibercept when used in patients with wet AMD and CRVO in clinical practice use and under real-life conditions, with special focus on ATEs. Secondary objectives include • evaluation of safety aspects of	• Adverse events, serious or non-serious, related or not related, ocular or non-ocular will be assessed. This includes arterial thromboembolic events (including non-MI ATEs and cardiovascular ischemic events). • Concomitant use of different anti-VEGF therapies and other	Study is planned, final protocol in Q4 2013, first patient to be enrolled in Q2 2014	Final study protocol: Q4 2013. FPFV: Q2 2014 Interim study reports every 12 months; Final study report: Q2-3 2020

Study / activity type, title and category (1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	concomitant use of other anti-VEGF therapies and other therapies for wet AMD and CRVO; • evaluation of drug utilization of aflibercept in real-life clinical settings; • evaluation of how disease activity is monitored including frequency and results; • evaluation of reasons for treatment and re-treatment decisions and optionally: • evaluation of Quality of Life in countries where approved by responsible IECs / IRBs (Please note that current design considerations focus on the inclusion of any subjects exposed to Eylea, the implementation of a reference arm, and the extension of the follow-up period to 6 months).	therapies for wet AMD ,CRVO, and DME • Long term safety beyond 2 years.		

Study / activity type, title and category (1-3)*	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Study VEGF-OD-0910: An Open-label, long-term, safety and tolerability extension Study of intravitreal VEGF Trap-Eye in neovascular age-related macular degeneration. (Extension study in the US for patients previously enrolled in VIEW 1) **Category 3**	• To assess the long-term safety and tolerability of VEGF Trap-Eye in patients with neovascular Age-Related Macular Degeneration (AMD).	• Long-term safety beyond 2 years.	Completed (data base lock in Oct 2013)	Study report planned to be available in end of Q1 2014
Review safety outcomes of Study BAY 86-5321/16598: An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg Eylea administered by IVT injections using two different treatment regimens to patients with wAMD.	• Safety and tolerability.	• Posology and its utilization in marketed use (evaluation of the possibility to extend treatment beyond 2Q8 without impact on efficacy).	Planned (pending EMA feedback and approval)	Submission of final CSR on 31-DEC-2017

*: Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures).

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Endophthalmitis (likely infectious origin)	(**Proposed) text in SmPC:** - Section 4.3 Contraindications: ... Active or suspected ocular or periocular infection. Active severe intraocular inflammation.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	- Section 4.8 Undesirable effects: Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2,600 intravitreal injections with Eylea and included cataract, retinal detachment, vitreous detachment, endophthalmitis, and intraocular pressure increased (see section 4.4). Uncommon (Table 1): endophthalmitis - Section 4.4 Special warnings and precautions for use: Endophthalmitis: 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. - Section 4.2 Posology and 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. .... Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay.	
Intraocular inflammation	(**Proposed) text in SmPC:** - Section 4.3 Contraindications: ... Active or suspected ocular or periocular infection. Active severe intraocular inflammation. - Section 4.8 Undesirable effects: Table 1: Listed as rare ADRs: Vitritis, hypopyon Listed as uncommon ADRs: Iritis, Uveitis, Iridocyclitis, Anterior chamber flare - Section 4.4 Special warnings and precautions for use:	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	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. - Section 4.2 Posology and 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.	
Transient intraocular pressure increase	(**Proposed) text in SmPC:** - Section 4.8 Undesirable effects: 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. IOP increase labeled as ADR (frequency category: common). - Section 4.4 Special warnings and precautions for use: ***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.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Retinal pigment epithelium tears	(**Proposed) text in SmPC:** - Section 4.8 Undesirable effects: Labeled as ADR (frequency category: common). - Section 4.4 Special warnings and precautions for use: ***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	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	detachment. When initiating Eylea® therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.	
Retinal tear / detachment	(**Proposed) text in SmPC:** - Section 4. Possible side effects: Both retinal tear and retinal detachment labeled as ADR (frequency category: uncommon): **Uncommon side effects (may affect up to 1 in 100 people):** ... - decreased sharpness of vision (retinal detachment, retinal tear) - Section 4.4. Special warnings and precautions for use: Other: As with other intravitreal anti-VEGF treatments for AMD, CRVO, and DME the following also applies: ... • Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes Populations with limited data There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy. Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients. Section 4.8 Undesirable effects: ... Serious adverse reactions related to the injection procedure have occurred in less than 1 in 2,400 intravitreal injections with Eylea® and included traumatic cataract, cataract, retinal detachment, vitreous detachment, endophthalmitis, and intraocular pressure increased.	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.
Cataract (especially of traumatic origin)	(**Proposed) text in SmPC:** - Section 4.8 Undesirable effects: 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).	Educational program in order to raise patients' and physicians' awareness on identified and potential risks.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Medication error	(**Proposed) text in SmPC:** - Section 4.2 Posology and methods of administration: The pre-filled syringe contains more than the recommended dose of 2 mg. The extractable volume of the syringe (90 microlitres) is not to be used in total. The excess volume should be expelled before injecting. Injecting the entire volume of prefilled syringe could result in overdose. To expel the air bubble along with excess medicinal product, slowly depress the plunger to align the cylindrical base of the dome plunger with the black dosing line on the syringe (equivalent to 50 microlitres i.e. 2 mg aflibercept). - Section 4.9 Overdose: In clinical trials doses of up to 4 mg in monthly intervals have been used and isolated cases of overdoses with 8 mg occurred. Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdose intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.	Educational program in order to raise physicians' awareness on identified and potential risks.
Off-label use	Provision of SmPC, in which the correct and approved use of Eylea® is detailed.	Educational program in order to raise patients' and physicians' awareness concerning the correct use of Eylea®.
Embryo-fetotoxicity	(**Proposed) text in SmPC:** Section 4.4: Special warnings and precautions for use: ***Other*** Eylea should not be used in pregnancy unless the potential benefit outweighs the potential risk and women of childbearing potential have to use effective contraception during treatment and at least 3 months after the last intravitreal injection of aflibercept (see Section 4.6). Section 4.6: Fertility, pregnancy and lactation: ***Women of childbearing potential*** Women of childbearing potential have to use effective contraception during treatment and at least 3 months after the last intravitreal injection of aflibercept (see section 4.4). ***Pregnancy*** There are no data on the use of aflibercept in pregnant women. Studies in animals have shown embryo-foetal toxicities (see section 5.3). Although the systemic exposure after ocular administration is very low, Eylea® should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.	Educational program in order to raise patients' and physicians' awareness on potential risks and need for contraception.
Hypersensitivity and	(**Proposed) text in SmPC:**	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
immunogenicity	- Section 4.8 Undesirable effects: As with all therapeutic proteins, there is a potential for immunogenicity with Eylea®. Section 4.4 Special warnings and precautions for use: ***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.	
Arterial thromboembolic events (ATEs) including non-MI ATEs and cardiovascular ischemic events	(**Proposed) text in SmPC:** - Section 4.8 Undesirable effects: 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 vascular death (including deaths of unknown cause). The incidence in the phase III 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). The incidence of ATEs in the CRVO studies (GALILEO and COPERNICUS) during the 76/100 weeks study duration was 0.6% (2 out of 317) in patients treated with at least one dose of Eylea compared to 1.4% (2 out of 142) in the group of patients receiving only sham treatment. The incidence of APTC ATEs in the DME studies (VISTA^{DME} and VIVID^{DME}) during the 52 weeks study duration was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group (see section Pharmacodynamic properties / "Clinical efficacy" for further details on the treatment options for the EYLEA and control groups). Section 4.4 Special warnings and precautions for use: ***Systemic effects*** Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors, and there is a theoretical risk that these may relate to VEGF inhibition.	None
Use of Eylea® in patients with	(**Proposed) text in SmPC:** Section 4.4: Special warnings and	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
uncontrolled glaucoma	precautions for use: Special precaution is needed in patients with poorly controlled glaucoma.	
Venous thromboembolic events	None	None
Hypertension	None	None
Proteinuria	None	None
Non-ocular hemorrhage	None	None
Retinal hemorrhage	None	None
Concomitant use of different anti-VEGF therapies and other therapies for wet AMD/ CRVO/DME	None	None
Long-term safety beyond 2 years	None	None
Posology utilized in marketed use.	None	None

The CHMP endorsed this advice with changes to reflect in part IV of the RMP (version 16.1) the post-authorisation efficacy study imposed as a condition to the marketing authorisation.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. The changes in SmPC sections 4.1, 4.2 and 4.4 are shown below (additions highlighted in bold, deletions shown as strike-through). For all other changes, see full product information.

- SmPC section 4.1

Eylea is indicated for adults for the treatment of

  - neovascular (wet) age-related macular degeneration (AMD) (see section 5.1),
  - visual impairment due to macular oedema secondary to central retinal vein occlusion (CRVO) (see section 5.1),
  - **visual impairment due to diabetic macular oedema (DME) (see section 5.1).**

- SmPC section 4.2

Diabetic Macular Oedema

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

Eylea treatment is initiated with one injection per month for five 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. The schedule for monitoring should be determined by the treating physician.

If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued.

Special populations

(…)

Elderly population

No special considerations are needed. **There is limited experience in patients older than 75 years with DME.**

Paediatric population

Safety and efficacy have not been established in children and adolescents. There is no relevant use of Eylea in the paediatric population in the indications wet AMD ~~and~~**,** CRVO **and DME**.

- SmPC section 4.4

Systemic effects

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors and there is a theoretical risk that these may relate to VEGF inhibition. **There are limited data on safety in the treatment of patients with CRVO or DME with a history of stroke or transient ischaemic attacks or myocardial infarction within the last 6 months. Caution should be exercised when treating such patients.**

Other

As with other intravitreal anti-VEGF treatments for AMD ~~and~~**,** CRVO **and DME** the following also applies:

- The safety and efficacy of Eylea therapy administered to both eyes concurrently have not been systematically studied **(see section 5.1)**.
- (…)
- ~~There is limited clinical data with Eylea in patients with diabetic retinopathy.~~

Populations with limited data

There is only limited experience in the treatment of subjects with DME due to type I diabetes or in diabetic patients with an HbA1c over 12% or with proliferative diabetic retinopathy.

Eylea has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Eylea in diabetic patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Eylea 40 mg/ml solution for injection in a vial (as submitted and endorsed with the previous extension of indication application for CRVO). The bridging report submitted by the applicant has been found acceptable.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of France.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Efficacy of VEGF Trap in DME was supported by two phase 3 controlled studies (VISTA and VIVID), each comparing 2 different dosing regimens of VEGF Trap [2mg every 4 weeks (2Q4) and 2mg every 8 weeks after initial 5 monthly doses (2Q8)] against laser photocoagulation. In addition, supportive data were obtained from a phase 2 study (DA VINCI). The phase 3 studies were designed to primarily demonstrate superiority of VEGF Trap over laser photocoagulation with regard to vision and morphological outcomes after 52 weeks (1 year) of treatment. Overall, the CHMP considered that the study design was acceptable including a study population representative of a clinically significant macular oedema state with a reasonable chance of oedema improvement. Laser was considered an adequate control as it was the current standard of care at the time of the DME clinical development program.

In both phase 3 studies, Eylea was superior to laser treatment in the improvement of best-corrected visual acuity (BCVA) assessed by the ETDRS chart in subjects at week 52 compared to baseline. The mean difference (least squares) between the two VEGF treatment groups and laser in the integrated analysis of both studies was 9.9 letters and 10.8 letters for 2Q8 and 2Q4, respectively, which was statistically significant and a clinically relevant gain in vision. Sensitivity analyses confirmed the robustness of the statistical results of the primary analysis. The superiority of treatment with VEGF Trap was further supported by all visual and anatomic secondary outcomes including categorical gains of ≥15 letters in BCVA, which were reported in 31.1% to 41.6% of subjects in the VEF Trap 2Q4 and 2Q8 groups, respectively, compared to 8.4% in the laser group across both studies. This improvement in visual acuity represents a doubling of visual angle which is considered perceptible by patients. Patients treated with VEGF Trap also had a greater reduction in central retinal thickness of about -130µm compared to laser.

Indirect comparison of historical data showed a similar range of improvements for ranibizumab.

Both treatment regimens tested were efficacious, however, since both the 2Q4 and 2Q8 groups had very similar outcomes at year 1 and since the 2Q8 dosing regimen achieved these improvements with fewer median injections (9 injections) compared to 13 injections for the 2Q4 group, the 2Q8 regime was considered by the CHMP to be the most appropriate regime at least for the first year of treatment.

Subgroup analyses in the defined efficacy subgroups (age, gender, race, baseline HbA1c, baseline BCVA, and prior anti-VEGF therapy) generally supported the results in the overall populations.

Finally, both year 2 data from VISTA and data from the 6 month off-drug follow-up period in DA VINCI confirmed maintenance of the beneficial treatment effects beyond year 1. A continued regimen of injections every 8 weeks (2Q8) was sufficient to maintain the improvements in vision achieved during study year 1 in VISTA throughout year 2.

Uncertainty in the knowledge about the beneficial effects

For historical reasons, the clinical development program of Eylea in DME did not employ ranibizumab as direct comparator, since Lucentis had not been approved for use in DME at the time when the program started. Therefore, no definitive conclusion on potential differences between the two anti-VEGF inhibitors could be drawn from the available data.

Only few patients recruited in the clinical trials had type I diabetes mellitus and only 8 patients had a baseline HbA1c > 12%. The limited experience in these patient groups have been reflected in section 4.4 of the SmPC.

Limited information was available on the benefit of treatment in patients with macular ischemia. Reports in the scientific literature had suggested that anti-VEGF-treatment may reduce visual acuity in these patients. However, no such trend was observed from the limited available data from VIVID. Nevertheless, the CHMP requested that events of reduced visual acuity in DME patients with macular ischaemia should be monitored in future PSURs.

Patients recruited in the two phase 3 studies, VISTA and VIVID, differed in some baseline characteristics. The differences in baseline disease characteristics suggested that subjects in VISTA may have had DME of a more refractory nature, particularly since the proportion of subjects who had received prior anti-VEGF treatment was 4 times higher in VISTA. Despite these differences, and while the magnitudes of the effects varied, generally consistent treatment effects were observed across the studies, suggesting that Eylea will be effective across the range of patients requiring treatment. Section 5.1 of the SmPC has been amended to reflect relevant differences between the two studies.

Supportive literature for the relevance of the DRSS endpoint to the indication of DME and of the relevance of the effect size have not been provided. In addition, for a quarter of the patients in VIVID the DRSS status was not gradable. Furthermore, results for the quality of life endpoints did not show a clear benefit of VEGF Tap treatment over laser. However, the outcome of the NEI-VFQ-25 score is based on visual acuity in both eyes, has a high variability and takes into account the overall health state of patients, which might explain why the clinical benefits did not appear to translate in a useful improvement of the management of current daily activities.

As treatment benefits were mainly supported by 1 year data, uncertainties remained regarding the long-term management of DME with Eylea which had not been fully explored. The available data from VISTA and DA VINCI beyond year 1 provided some assurance on the persistence of the beneficial treatment effect. However, at the time of this report only a summary of the key efficacy results at year 2 in VISTA were available in addition to data from the 6 month off-drug follow-up period of DA VINCI. Therefore, the CHMP recommended submission of the full 2-year reports as well as the final clinical study reports of both studies, once available.

Furthermore, both phase 3 trials only studied fixed dosing regimens and no information could be derived from the available data on the required duration of treatment or stopping criteria. Nevertheless, the vision gain achieved during year 1 in the DA VINCI study was relatively well maintained during the 6 month off-drug follow-up period whereas only a fifth of the patients received additional treatments in form of mainly anti-VEGF agents and laser. Therefore and in light of the published data for ranibizumab, a treat-and-extend approach based on visual and anatomic outcomes was considered more suitable for the maintenance therapy of DME with Eylea after the first year. However, the CHMP was of the opinion that it was essential to collect additional comparative data for the 2Q8 regimen and other alternative dosing regimens (PRN and treat-and extend) commonly used in clinical practices in the management of DME in order to confirm the benefits of the selected treatment regime in the long-term management of DME. Such data should be collected in a post-authorisation efficacy study following the first initial year of Eylea treatment also exploring criteria for ceasing

treatment if no longer required. It was considered that a suitable study design would be a randomised non-inferiority study of a duration of at least 2 years (following the first treatment year) and interim study results should be provided after the first study year.

Finally with regards to non-responders, analyses of the efficacy outcomes in three potential groups of non-responders, defined by change from baseline in BCVA, were inconclusive due to the low number of subjects, in particular with regards to the two most meaningful groups (those losing or not gaining vision). Still, in order to avoid unnecessary treatment of patients not benefitting from continued therapy, the CHMP agreed to recommend discontinuation of Eylea if visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment.

Risks

The safety analysis was mainly based on the integrated data of one year data from VISTA and VIVID with 578 DME patients exposed to Eylea treatment. Safety data for DME patients were furthermore supplemented by supportive data from DA VINCI.

Overall, the safety profile of Eyea in DME appeared to be consistent with the known profile in the already approved indications AMD and CRVO. A similar overall incidence of ocular and non-ocular effects was observed when comparing Eylea with laser photocoagulation.

The most common ocular adverse reactions reported were conjunctival haemorrhage, increased intraocular pressure and eye pain, which were related to the injection procedure. Punctuate keratitis occurred more frequently in VEGF Trap treatment groups and has been added to section 4.8 of the SmPC. Except for this adverse event, no other new ocular adverse events emerged and regarding listed effects, no increase in frequency was identified except for cataract cortical (from uncommon to common) and uveitis (from rare to uncommon). Overall, intravitreal injections of VEGF Trap were well tolerated, irrespective of the frequency of injection.

The most common non-ocular treatment-emergent adverse events were nasopharyngitis and hypertension, which had already been reported in AMD and CRVO studies.

Pharmacokinetic and pharmacodynamic data, including immunogenicity data, showed a low systemic exposure and a low immunogenicity in DME patients consistent with what has been observed in previous clinical programs with AMD and CRVO patients.

Uncertainty in the knowledge about the unfavourable effects

The size of the clinical DME safety database was limited precluding detection of rare adverse events. Moreover, the safety review was mainly based on exposure data of one year of treatment. Long-term safety data, i.e. data beyond the first year of Eylea treatment, were limited and only available for VISTA at the time of this report. Therefore, the safety evaluation needs to be completed by a critical discussion about additional events observed in 2 year and 3 year periods, when the related results are submitted for review by CHMP.

A comparison of the mortality rates after VEGF Trap treatment in AMD, CRVO and DME indications was performed to further explore a potential higher risk of deaths in patients treated for DME with anti-VEGF treatment. However, complete 2 year safety data for VIVID were considered necessary to confidently refute an increased risk.

Moreover, non-fatal strokes seemed to be slightly more frequently reported in VEGF Trap treatment groups compared to laser. Due to low number of patients, no firm conclusions could be drawn. As the DME population has major cardiovascular co-morbidities which put them at a greater risk for developing arterial thromboembolic events, these events were included in the RMP and should be closely monitored in the next PSUR.

Finally, the adverse event of congestive heart failure was more frequently reported in VEGF Trap groups in year 1 of in the clinical trials. As diabetic patients are at risk for developing congestive cardiac failure, this adverse event was of concern. However, 2 year data from VISTA did not support a signal of cardiac failure congestive as hardly any difference was observed during this period. Nevertheless, the CHMP was of the opinion that data needed to be completed by full 2 and 3 year data from the pivotal trials.

Benefit-risk balance

Importance of favourable and unfavourable effects

No new safety concerns were identified for Eylea other than punctuate keratitis when administered to patients with DME, whereas a significant superiority in term of efficacy over laser photocoagulation has been demonstrated at week 52 in both on-going pivotal studies.

Improvement in vision and anatomical outcome measures were consistent and statistically significant as well as clinically relevant. In particular, in addition to the primary efficacy analysis, responder analysis in patients gaining ≥15 letters in visual acuity provided convincing evidence of a relevant treatment effect. The treatment effect was further confirmed in sensitivity and subgroup analyses, which suggested that Eylea is effective across the range of patients requiring treatment.

Limited data beyond treatment year 1 provided some evidence of maintenance of efficacy.

The safety profile of Eyea in DME was generally consistent with the known profile in the already approved indications AMD and CRVO. Uncertainties remained with regards to the risk of arterial thromboembolic events and congestive heart failure in the population of DME patients due to the limited availability of long-term safety data and taking into account that diabetes patients have major cardiovascular co-morbidities and are at risk of developing thromboembolic complications.

Benefit-risk balance

Overall, the CHMP considered that the benefits of Eylea in the treatment of DME in adult patients outweighed the treatment related risks in both dosing regimens tested.

Based on the lower number of injections and consequently lower risk of injection related adverse events, the 2Q8 regime was considered the most appropriate regime for the first year of treatment. Thereafter, it was considered more suitable to gradually extend the treatment interval in responders based on visual and anatomic outcomes.

Discussion on the benefit-risk balance

While a positive benefit-risk profile of Eylea in the treatment of DME was shown for the first treatment year, long-term data were limited and additional data should be provided post-approval to confirm maintenance of efficacy and complement the safety database. To this end, the CHMP recommended that full 2-year and 3-year results of VIVID and VISTA should be submitted for review by CHMP. Furthermore, the CHMP was of the opinion that it was essential to collect additional comparative data

for the 2Q8 regimen and other alternative dosing regimens commonly used in clinical practices in the management of DME in order to confirm the benefits of the selected treatment regime in the long-term management of DME. To this end, the CHMP requested a randomised post-marketing study with the primary objective of testing non-inferiority of the 2Q8 regimen with other alternative dosing regimens (PRN and treat-and-extend). The study should also aim at identifying criteria for ceasing treatment if no longer required and should be started as soon as possible.

In conclusion, the CHMP considered the following measures necessary to address issues related to long-term efficacy:

The MAH should perform an interventional post-authorisation efficacy study in patients with diabetic macular oedema with the primary objective of comparing, after the first initial year of Eylea treatment, the standard regime of injections every 8 weeks with alternative treatment regimens, i.e. extended treatment intervals based on visual and anatomic outcomes (PRN and treat-and-extend). The protocol should be submitted for review within 2 months following approval of this application. Interim and final study data should be provided for review. Adequate non-inferiority margins should be applied.

4. Recommendations

The application for approval of Eylea in the treatment of visual impairment due to diabetic macular oedema is approvable since all concerns have all been resolved.

Final Outcome

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

Variation requested		**Type**
C.1.6 a)	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to add a new indication for the treatment of visual impairment due to diabetic macular oedema. As a consequence, updates of sections 4.2, 4.4, 4.8, 5.1 and 5.2 in order to add dosing recommendation for DME patients, update the safety information and provide a summary of relevant clinical data in DME. SmPC section 4.8 was furthermore updated to introduce a joint summary of the safety profile across all indications. Finally, Annex II was updated to reflect the revised conditions with regard to the safe and effective use. Minor editorial changes and corrections were made as well. The Package Leaflet was updated accordingly.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet for France.

The variation proposed amendments to the SmPC, Annex II and Package Leaflet.

This CHMP recommendation is subject to the following new condition:

Interventional post-authorisation efficacy study in patients with diabetic macular oedema with the primary objective of comparing, after the first initial year of Eylea treatment, the standard regime of injections every 8 weeks with alternative treatment regimens, i.e. extended treatment intervals based on visual and anatomic outcomes (PRN and treat-and-extend).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

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 of the new indication diabetic macular oedema (DME) and periodically thereafter, all ophthalmological clinics where Eylea is expected to be used are provided with an updated 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
- Who should be treated with Eylea
- 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
- The need to expel excess volume of the pre-filled syringe before injecting Eylea to avoid overdose
- Patient monitoring after intravitreal injection

- Key signs and symptoms of intravitreal injection related adverse events including endophthalmitis, increased intraocular pressure, retinal pigment epithelium tear and cataract
- Management of intravitreal injection related adverse events
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

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
- Who should be treated with Eylea
- 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, retinal pigment epithelium tear and cataract
- When to seek urgent attention from their health care provider
- Female patients of childbearing potential have to use effective contraception and pregnant women should not use Eylea

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below 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
To perform an interventional post-authorisation efficay study in patients with diabetic macular oedema with the primary objective of comparing, after the first initial year of Eylea treatment, the standard regime of injections every 8 weeks with alternative treatment regimens, i.e. extended treatment intervals based on visual and anatomic outcomes (PRN and treat-and-extend).	Final study report submission: November 2019

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and does not consider, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to add a new indication for the treatment of visual impairment due to diabetic macular oedema. As a consequence, updates of sections 4.2, 4.4, 4.8, 5.1 and 5.2 in order to add dosing recommendation for DME patients, update the safety information and provide a summary of relevant clinical data in DME. SmPC section 4.8 was furthermore updated to introduce a joint summary of the safety profile across all indications.

Summary

Upon review of the data of two phase 3 clinical trials as well as one supportive phase 2 study investigating the safety and efficacy of Eylea in the treatment of visual impairment due to diabetic macular oedema, the CHMP considered that Eylea had been shown to improve vision and reduce macular oedema in a relevant patient population in a significant and clinically meaningful manner. The safety profile remained largely unchanged and the benefit-risk balance was considered favourable.