17 March 2011

EMA/392690/2011

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lucentis

ranibizumab

Procedure No.: EMEA/H/C/000715/II/0022

Note

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

1. Scope of the variation and changes to the dossier

Scope of the variation:	Update of Summary of Product Characteristics, Annex II and Package Leaflet Extension of indications: update of the SPC (sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2) to include information on treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO). Sections 1, 3 and 4 of the information for user of the Package Leaflet have been updated accordingly, as well as the information for healthcare professional. In addition, Annex IIB was updated with amended conditions for the Marketing Authorisation and the new version identifier for the RMP.
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	I, II and V
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	14 October 2010
Start of procedure:	24 October 2010
Rapporteur's assessment report circulated on:	17 December 2010
Co-Rapporteur's assessment report circulated on:	20 December 2010
Rapporteur's updated assessment report circulated on:	14 January 2011
Request for supplementary information and extension of timetable adopted by the CHMP on :	20 January 2011
MAH's responses submitted to the CHMP on:	11 February 2011
Rapporteur's assessment report on the MAH's responses circulated on:	11 March 2011
CHMP opinion:	17 March 2011

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
AMD	age-related macular degeneration
APPT	activated partial thromboplastin time
ATE	arterial thromboembolic event
BCVA	best corrected visual acuity
BRVO	branch retinal vein occlusion
BVOS	Collaborative Branch Vein Occlusion Study
CFT	central foveal thickness
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CVA	cerebrovascular accident
DME	diabetic macular oedema
HRVO	hemiretinal vein occlusion
IOP	intraocular pressure
ITT	intent-to-treat
IVT	intravitreal
LOCF	last-observation-carried-forward
MI	myocardial infarction
OCT	optical coherence tomography
PK	pharmacokinetics
PRN	as needed
RVO	retinal vein occlusion
SAE	serious adverse events
TIA	transient ischaemic attack
VA	visual acuity
VEGF	vascular endothelial growth factor

3. Executive summary

3.1. Scope of the variation

This is a type II variation to extend the indication of Lucentis to include the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

3.2. Problem statement

Retinal vein occlusion (RVO) is the second leading cause of blindness for patients with retinal vascular disease, following diabetic retinopathy. There are two main types of RVO, depending on the site of the vein occlusion: branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). In addition, when the occlusion is located in one of the 2 branches after the division of the central vein the occlusion is classified as a hemiretinal vein occlusion (HRVO). This form is often regarded a subset of BRVO and grouped with BRVO in this report. All type lead to permeability disorders of the retina caused by the blockage of the branch retinal vein or central retinal vein. The incidence of RVO in the US in 2007 was estimated to be 180,000, with 144,000 patients diagnosed with BRVO and 36,000 diagnosed with CRVO (Klein, et al 2008). For the EU, estimates are not available, but the incidence of RVO is expected to be similar to that in the US.

The most common presenting symptom of RVO is an abrupt, painless decrease of central visual acuity (VA) which varies in severity in BRVO and CRVO. Less frequently, patients may present with a history of transient vision loss, lasting a few seconds to minutes, with complete recovery of vision. These symptoms may recur over several days to weeks, followed by a decrease in vision that can last beyond 1 year in some patients.

Untreated eyes with CRVO generally have poor VA (less than 20/40) which declines further over time. In a meta-analysis of studies that investigated the natural history of CRVO, the pooled mean decrease in VA from baseline to 6 months was approximately 10 letters for eyes with non-ischemic CRVO and 15 letters for eyes with ischemic CRVO (McIntosh, et al 2010). By contrast, studies on the natural history of BRVO indicate that untreated eyes (no laser) show improvement rather than worsening over time. However, improvement beyond a VA of 20/40 was uncommon in these studies (Rogers, et al 2010).

The current standard of care for the treatment of BRVO is laser therapy. Laser therapy can provide long-term vision stabilisation, but in some patients, also vision improvement with time. The recovery is lengthy since laser does not yield short-term vision benefits and a significant number of patients still lose vision. In addition to the delayed onset of effect, laser destroys retinal vessels and causes scar tissue. However, laser therapy has not been demonstrated to have a beneficial effect on VA in subjects with CRVO, even though laser is used to treat secondary neovascular complication of both subsets of RVO.

Presently, the only pharmacologically approved treatment (approved for both types of RVO) in the EU is Ozurdex, a sustained-release intravitreal implant containing dexamethasone. Lucentis has been approved to treat RVO in the US.

The use of ranibizumab in the treatment of patients with RVO is supported by its mechanism of action of neutralising the biologic activity of VEGF, which results in the reduction of vascular permeability and macular oedema, hallmarks of RVO. This mechanism is supported by evidence from animal studies and clinical data from the ranibizumab wet age-related macular degeneration (AMD) and visual impairment in diabetic macular oedema (DME) programs.

3.3. About the product

Ranibizumab is a recombinant humanised IgG1 κ isotype monoclonal antibody fragment (Fab) that selectively binds and neutralises VEGF-A.

Lucentis, 0.5 mg was approved for the treatment of neovascular (wet) AMD in January 2007 and for the treatment of visual impairment due to DME in January 2011.

3.4. Development programme/Compliance with CHMP Guidance/Scientific Advice

Development programme

For the proposed additional indication, there are no changes related to quality and no new preclinical studies have been submitted.

The MAH has submitted 12-month data from two phase III clinical studies, one in BRVO (FVF4165g, BRAVO) and one in CRVO (FVF4166g, CRUISE). After the first six months (primary efficacy evaluation) with monthly administration of 0.3 mg, 0.5 mg ranibizumab or sham, dosing with ranibizumab was continued with treatment on as needed basis for the following 6 months, during which previously sham-treated subjects could also receive ranibizumab. Both studies included pharmacokinetic blood sampling to quantify ranibizumab concentrations in serum and screening for immunogenicity in the form of antibodies to ranibizumab. An extension study (HORIZON) with up to 24 months treatment is ongoing (clinical phase finalised) to further address efficacy and safety of the treatment. From this study, narratives describing serious adverse events (SAEs) known to have occurred up to 30 June 2010 have been provided.

Compliance with CHMP guidance/Scientific Advice
One central (including follow up) scientific advice (April 2007, EMEA/H/SA/445/2/2007/II; January 2008, EMEA/H/SA/445/2/FU/1/2007/II; Feb 2008, EMEA/H/SA/445/2/FU/1/2007/II) has been given. A pre-submission meeting was held in February 2010. The following main comments were provided:

- *Central advice*
  One central scientific advice (EMEA/CHMP/SAWP/593356/2008) was given in 2008. The following main comments were provided:
  - A single study of adequate duration in each form of RVO may be acceptable to allow an adequate evaluation of efficacy and safety.
  - The justification for the choice of evaluation of the primary endpoint at 6 months and subsequent submission is not acceptable and 12 month masked data vs. standard care was recommended for both trials.
  - The design of the CRVO study was largely agreed on, although comparative 12-months data were desired.
  - In the BRVO study, the scale and impact of laser rescue should be addressed.
  - Assessment of neovascular complications should be included.
  - If one trial was negative, a submission in the other RVO type would still be possible, but will then be regarded as a single pivotal trial.
- *Pre-submission meeting*
  A pre-submission meeting was held in February 2010. Efficacy data from both trials were acknowledged as promising and very interesting. CRVO represents a more "straight forward" case since, at the time of the meeting, there was currently no treatment available and no improvement in these patients was expected. Therefore, even 6 months efficacy data would be acceptable for a variation submission in CRVO. In BRVO, data need to reflect a convincing and consistent magnitude of the effect compared to spontaneous improvement and laser treatment.

The main deviation from the CHMP scientific advice is that the studies are not sham-controlled after 6 months, however, the studies are still to be regarded as controlled (randomised population maintained) and blinding has been maintained.

3.5. General comments on compliance with GMP, GLP, GCP

The MAH states that the clinical trials performed outside EU meet the ethical requirements of Directive 2001/20/EC. A need for a GCP-inspection has not been identified.

3.6. Type of application and other comments on the submitted dossier

This is a type II variation, extension of the indication.

Paediatric studies
The Paediatric Committee have granted a product-specific waiver (EMEA-000527-PIP01-08) for all subsets of the paediatric population in the treatment of visual impairment associated with RVO.

According to the Guideline on Summary of Product Characteristics, if the European Medicines Agency has waived a paediatric development, this information should be given under the section 5.1. The CHMP therefore requested that the MAH updated the SPC to include the applicable wording, as follows:

"The European Medicines Agency has waived the obligation to submit the results of studies with Lucentis in all subsets of the paediatric population in neovascular AMD, visual impairment due to diabetic macular oedema and visual impairment due to macular oedema secondary to retinal vein occlusion. (see section 4.2 for information on paediatric use)."

4. Scientific Overview and discussion

4.1. Quality aspects

Not Applicable

4.2. Non clinical aspects

No Environmental Risk Assessment (ERA) was submitted. This is justified by the MAH with the protein nature of ranibizumab after application to the patient's eye by injection is completely metabolised and adsorbed in the body. Any medicinal product that reaches water streams via eventual spills during application or after disposal of unused drug is expected to be very rapidly degraded and mineralised to CO_2 by microbial activity.

The CHMP considered that the MAH had appropriately justified the lack of an ERA. The lack of additional non-clinical data is acceptable in view of the data submitted with the previous applications. Ranibizumab is not likely to pose a risk to the environment.

4.3. Clinical aspects

4.3.1. Clinical pharmacology

The mechanism of action of ranibizumab is to decrease permeability of leaking blood vessels. This basic mechanism of action is valid independent on whether targeting choroidal vessels in AMD or retinal vessels in RVO. No dedicated clinical pharmacology profiling studies were conducted in patients with RVO. However, pharmacokinetic (PK) and pharmacodynamic data for ranibizumab were collected in the 2 pivotal RVO clinical studies, FVF4165g and FVF4166g. For details on the study designs see Clinical efficacy below.

Pharmacokinetics

The previous assay to measure ranibizumab in serum was based on an electrochemiluminescense assay (sensitivity of 300 pg/mL). Genentech has now developed an alternative method, a sandwich ELISA with a colorimetric detection system to quantify ranibizumab in human serum (concentrations < 0.075 ng/mL less than reportable for human serum samples). Since there is no cross-validation with the previous analysis used for the AMD data, the comparison of PK data in AMD and RVO patients will be confounded by this fact. However, the ELISA method appears to perform well and with acceptable accuracy and precisions.

To assess whether the systemic exposure in RVO was similar to that in AMD patients, the serum concentration obtained in AMD and RVO patients were compared graphically. Serum sample was collected from all patients in studies FVF4165g and 4166g before the first dose, 7 days after the third dose in month 2, at the end of the 6-month treatment period, and at the end of the observational period in month 12. In both trials, the majority of ranibizumab-treated patients had measurable serum ranibizumab concentrations at time points up to 14 days postdose. At the end of the dose interval (30 days after the previous dose administered), serum concentrations of ranibizumab were below the assay quantification limit for the majority of patients. In both studies there were isolated concentrations >5 ng/mL.

The RVO patients appear to obtain systemic exposure of ranibizumab in the same magnitude as AMD patients, possibly the variability is higher in the RVO data although below the in vitro determined IC50 for inhibition of biologic activity of VEGF-A.

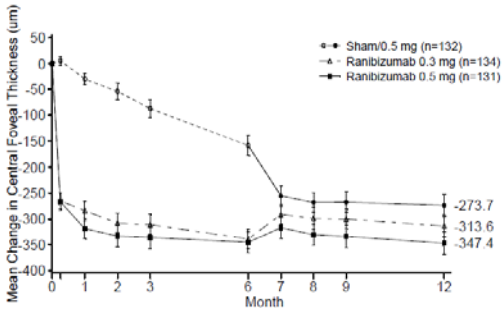
In addition, the previously developed population PK model was used to simulate serum concentrations for the RVO patients and these were compared with the observed concentrations (a total of 441 patients with 843 quantifiable ranibizumab concentrations).

The final population PK model for RVO and AMD indicate similar parameter estimates for the two data sets, but it is noted that the effect of creatinine clearance is numerically higher in the RVO patients. Although a somewhat higher exposure cannot be excluded in such subjects, no concerns are raised, a dose adjustment is not required.

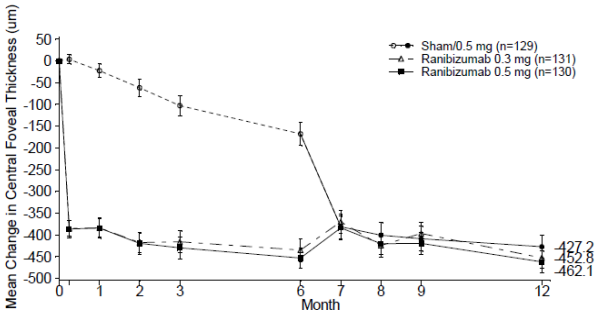
Pharmacodynamics

Pharmacodynamic response data in the form of central foveal thickness (CFT) was assessed using optical coherence tomography (OCT). With retreatment based on the protocol-specified criteria, the proportion of patients with CFT ≤ 250µm in the 0.3-mg and 0.5-mg ranibizumab groups at month 6 was generally maintained through month 12 in both studies. Upon initiation of ranibizumab treatment in the sham/0.5- mg group, the proportion of patients with CFT ≤ 250µm at month 12 was higher than at month 6, see figures below.

Figure 1 Mean change from baseline in CFT



Study FVF4165g BRVO



Study FVF4166g CRVO

Conclusions on clinical pharmacology

The pharmacodynamic assessment of ranibizumab in the treatment of RVO has been made through anatomic outcomes (ranibizumab effect on macular oedema measuring the CFT) and show that ranibizumab reduces retinal thickness over time. The RVO patients appear to obtain systemic exposure of ranibizumab in the same magnitude as AMD patients, possibly the variability is higher in subjects with RVO. Although a somewhat higher exposure cannot be excluded in such subjects, no concerns are raised and a dose adjustment is not considered required and also difficult to make. The CHMP considered that adequate information is given in the updated section 5.2 of the SPC adopted with this Opinion.

4.3.2. Clinical efficacy

A summary of the studies submitted to support the efficacy and safety of ranibizumab in the treatment of visual impairment due to RVO is given in Table 2 below.

Table 2 Clinical studies of ranibizumab in RVO indication

Study No.	Study Objectives	No. Treated	Study Duration	Treatment Arms	Ranibizumab regimen
Completed					
FVF4165g BRAVO[a]	Efficacy and safety	395 (264 ranibizumab)	12 months (6 months double-blind treatment)[b]	Ranibizumab 0.3 mg or 0.5 mg, Sham[c]	Once monthly (6-month treatment) PRN (6-month observation)
FVF4166g CRUISE	Efficacy and safety	390 (261 ranibizumab)	12 months (6 months double-blind treatment)[b]	Ranibizumab 0.3 mg or 0.5 mg, Sham[c]	Once monthly (6-month treatment) PRN (6-month observation)
Ongoing[d]					
FVF3426g HORIZON Cohort 2	Safety and efficacy	608 ranibizumab	Up to 24 months (uncontrolled)	Ranibizumab 0.5 mg	PRN

[a] Patients in Study FVF4165g could receive treatment with laser starting at Month 3.
[b] Six scheduled monthly injections from Day 0 to the Month 5 visit.
[c] Patients who were randomly assigned to treatment with sham for the 6-month double-blind treatment period received ranibizumab 0.5 mg on an as-needed basis during the second 6 months of the study (observation period).
[d] Clinically completed (ie, the final visit for the last patient was completed) on 27 July 2010.
PRN = as needed

Study FVF3426g (HORIZON) is an uncontrolled, Phase 3, open-label extension study performed by Genentech that includes a cohort of patients (Cohort 2) with RVO who have completed Study FVF4165g or Study FVF4166g. Data from this ongoing study are not included in this submission.

The CHMP considered that the efficacy and safety outcome of FVF3426g (HORIZON) should be submitted to support the long-term efficacy and safety of ranibizumab-treatment in RVO.

Main clinical studies – Studies FVF4165g (BRVO) and FVF4166g (CRVO)

Studies FVF4165g (BRVO) and FVF4166g (CRVO) have a similar design and the methodology description below refers to both studies unless otherwise indicated.

Methodology

Studies FVF4165g (BRVO) and FVF4166g (CRVO) were Phase 3, randomised, multicenter, double-masked, sham injection–controlled, 3-arm studies with the primary efficacy endpoint evaluated at Month 6. The study consisted of a 28-day screening period, a 6-month sham-controlled treatment period, and a 6-month observation period with treatment on an as needed basis.

Study FVF4165g (BRVO) also included subjects with HRVO, see inclusion criteria.

Except for the subtypes of RVO, the studies had nearly identical inclusion and exclusion criteria, but Study FVF4165g (BRVO) allowed for the concomitant treatment with laser photocoagulation in all treatment groups if deemed necessary, beginning at the Month 3 visit.

Subjects were randomised (1:1:1) in a masked fashion to receive monthly sham treatment (needleless syringe pressed towards the conjunctiva), 0.3 or 0.5 mg of ranibizumab by intravitreal (IVT) injections during the first 6 months of the study. During the 6-month observation period, subjects were

evaluated monthly to determine the need for retreatment with ranibizumab. All subjects could receive active treatment during this period (see Treatment below).

- **Study Participants**

Study FVF4165g (BRVO) was conducted at 93 sites and Study FVF4166g was conducted at 95 sites, all in the US.

Main inclusion criteria:
Subjects ≥ 18 years, sexually active women of childbearing potential had to use of an appropriate form of contraception.

Ocular (study eye)

- Foveal centre–involved macular oedema secondary to RVO according to the below definitions. Subjects were screened at the time of diagnosis of but no longer than 12 months after diagnosis.

  BRVO: Retinal haemorrhage or other Biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated venous system (or previously dilated venous system) in one quadrant or less of the retina drained by the affected vein. The presence of a BRVO was assessed on fluorescein angiography.
  HRVO: As above but a dilated venous system (or previously dilated) in more than one quadrant and up to three quadrants.
  CRVO: As above but a dilated venous system (or previously dilated) in three quadrants or more of the retina drained by the affected vein
- BCVA using ETDRS charts of 20/40 to 20/400 (BRVO) or 20/40 to 20/320 (CRVO) (Snellen equivalent)
- Mean central subfield thickness ≥ 250 µm (OCT)

Main exclusion criteria

General

- History of cerebral vascular accident or myocardial infarction (MI) within 3 months
- Systemic anti-VEGF therapy within 6 months
- Active malignancies associated with increased systemic VEGF levels
- Uncontrolled hypertension (>180 mmHg/>110 mmHg).
- Pregnancy or lactation

Ocular (study eye)

- Prior episode of RVO
- Brisk afferent pupillary defect, history of radial optic neurotomy or sheathotomy
- History or presence of AMD (dry or wet form)
- History of any ocular anti-VEGF treatment or intraocular corticosteroids within 3 months
- History of laser photocoagulation for macular oedema within 4 months. In case of prior grid laser the current area of leakage must have extended into the fovea (i.e., prior laser treatment was inadequate) and there was no evidence of laser damage to the fovea.
- History of panretinal scatter photocoagulation or sector laser photocoagulation within 3 months or anticipated within the next 4 months
- History of pars plana vitrectomy, previous filtration surgery, or other intraocular surgery within 2 months or anticipated within the next 7 months
- History of herpetic ocular infection, ocular toxoplasmosis, current ocular/extraocular infection
- History of rhegmatogenous retinal detachment, idiopathic central serous chorioretinopathy
- Other causes/conditions (e.g., vitreomacular traction, epiretinal membrane, ocular inflammatory disease, neovascular glaucoma, Irvine–Gass syndrome, or prior macula-off rhegmatogenous retinal detachment) thought to contribute to or affect macular oedema or alter/contribute to reduced VA, including an eye that would not benefit from resolution of macular oedema
- IOP ≥ 30 mmHg (could be re-screened after initiation of glaucoma treatment)
- Pseudoexfoliation, aphakia
- Evidence upon examination of any diabetic retinopathy, defined as eyes of diabetic patients with more than one microaneurysm outside the area of the vein occlusion (inclusive of both eyes)
- Relevant ocular disease that may have been associated with increased intraocular VEGF levels (namely, uveitis, neovascular glaucoma, neovascular AMD, diabetic retinopathy, diabetic maculopathy, or ocular ischemic syndrome)

- Improvement of > 10 letters on BCVA between screening and Day 0

Although both studies were performed in the US the CHMP did not consider the extrapolation of these data to an EU population with regards to intrinsic factors a concern. Extrinsic factors, e.g. potential differences in clinical practice are also not considered likely to have a meaningful impact on the efficacy outcome in view of the internationally recognised treatment recommendations of RVO. Exclusion of subjects with a pronounced afferent pupillary defect may indicate that subjects with major ischaemic RVO are excluded, but subjects with some degree of ischaemia were included in the study (see further baseline data). Overall, ocular exclusion criteria are considered of relevance not to hamper the evaluation of efficacy. However, diabetes is a major risk factor for RVO, several diabetic patients were included in these studies and it is likely that such subjects have significant diabetic retinopathy, or has been through, or are in a need for laser photocoagulation. The MAH is therefore requested to comment on these exclusion criteria with regards to the possibility to extrapolate the treatment to a relevant diabetic target population with RVO. In addition, the lack of experience of treatment in subjects with prior episodes of RVO should be addressed in the SPC.

The last exclusion criterion, improvements of > 10 letters from screening to treatment (28 days) is considered important by the CHMP, since especially in BRVO, a spontaneous improvement is not uncommon. In BRVO (where VA may further improve with laser treatment over 2-3 years), but also in CRVO, the long-term effects of treatment need to be further addressed by the MAH. Therefore, the ongoing phase IIIb extension study (HORIZON, study FVF3426g, up to 2 years) including patients are those who completed the 12 months treatment and follow-up of the phase III studies is acknowledged. Since the clinical phase of the study was finalised in July, 2010, the study report should be submitted. In addition, the 5-year observational, multicenter cohort Luminous study (protocol CRFB002A2406) will be conducted to further study and describe the long-term effectiveness, treatment patterns, safety, and HRQoL associated with ranibizumab treatment for any approved indication. The MAH is requested to confirm that subjects with BRVO and CRVO will be included in this study.

- **Treatments**

Table 3 Study Scheme, Studies FVF4165g and FVF4166g

Month	0	1	2	3	4	5	6	7	8	9	10	11	12
	Treatment Period						Observation Period						
Sham	**x**	**x**	**x**	**x / L**	**x**	**x**	X	X	X	X/L	X	X	
0.3-mg ranibizumab	**X**	**X**	**X**	**X / L**	**X**	**X**	X	X	X	X/L	X	X	
0.5-mg ranibizumab	**X**	**X**	**X**	**X / L**	**X**	**X**	X	X	X	X/L	X	X	
							1°EP						

x = sham injection; **X** = 0.3 mg or 0.5 mg IVT ranibizumab; L = laser (if indicated, study FVF4165g only); X = ranibizumab injection (if indicated); 1°EP = primary endpoint.

- *Months 0 to 5:* Subjects had their first treatment (ranibizumab or sham) on Day 0 and were treated with monthly injections months 0 to 5 (six injections) where after flexible dosing was initiated according to the below criteria. Concomitant laser rescue treatment (according to the below) was allowed in all treatment arms from the month 3 visit in study FVF4165g (BRVO), but not in Study FVF4166g (CRVO). Eyes with HRVO were treated the same as eyes with BRVO.

- *Months 6 to 12:* During the 6-month observation period, subjects were evaluated monthly to determine the need for re-treatment. If qualified for retreatment, subjects randomised to 0.3-mg ranibizumab received the 0.3-mg dose, while subjects randomised to sham or 0.5-mg received 0.5-mg ranibizumab.

- *Criteria for re-treatment (months 6-11):* Subject's BCVA ≤20/40 (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, or subject has mean central subfield thickness ≥ 250 µm on OCT.

- *Criteria for laser rescue* (based on those established by the Branch Vein Occlusion Study (BVOS), 1984): BCVA is ≤ 20/40 or a mean central subfield thickness ≥ 250 µm on OCT.

  Compared with the visit 3 months prior to the current visit, subject has BCVA gain < 5 letters or a decrease < 50 µm in mean central subfield thickness. If not meeting the rescue criteria at Month 3 the subject was to be reassessed at the Month 4 visit and again at the Month 5 visit, if applicable and similarly for the Month 9, 10 and 11 visits.

- *Concomitant treatment:* Subjects continued to receive all medications and standard treatment administered for their other conditions at the discretion of their physician except for those detailed in the exclusion criteria. In addition, concurrent oral and injectable corticosteroids were not allowed.

The CHMP considered that in BRVO, a laser-controlled study, or a study allowing laser rescue from start would have been preferred. By deferring laser treatment in the sham group, some subjects may have not received the best standard of care. The MAH justified this design as it will account for possible spontaneous improvement before allowing laser treatment. The inclusion of a laser photocoagulation therapy and the 3-month waiting period for patients with BRVO is consistent with the outcome of the BVOS study (1984) which concluded that there was no basis for recommending early treatment. This is also consistent with current clinical practice where laser may be deferred for up to 6 months.

However, the inclusion criteria allowed an oedema due to BRVO of 12 months duration and ranibizumab has a 3 month treatment advantage ahead of laser. The consequences of this study design are further discussed in the Subgroup analysis part of this report.

- **Objectives**

Primary:

- To evaluate the efficacy of IVT injections of ranibizumab administered monthly for 6 months in the improvement of VA as measured by the mean change in best corrected visual acuity (BCVA) at 6 months compared with baseline
- To evaluate the safety and tolerability of IVT injections of ranibizumab administered monthly for 6 months, followed by a 6-month observation period with protocol-specified retreatment criteria

Secondary:

- To evaluate the efficacy of IVT injections of ranibizumab administered monthly for 6 months with respect to other VA outcomes, anatomic outcomes, and patient-reported visual function outcomes
- To evaluate the pharmacokinetics of ranibizumab in subjects with BRVO

- **Outcomes/endpoints**

Primary Efficacy Outcome Measure:

- The mean change from baseline in BCVA score at 6 months (4 meter distance).

Secondary efficacy variables up to Month 6:

- Proportion of subjects who gained ≥ 15 letters at 6 months compared with baseline
- Proportion of subjects who lost < 15 letters at 6 months compared with baseline
- Mean change from baseline in BCVA score over time
- Proportion of subjects with a CFT of ≤ 250 µm (OCT), at 6 months
- Mean absolute change from baseline in CFT (OCT), over time up to 6 months
- Mean change from baseline in the NEI VFQ-25 near and distance activities subscale over time up to 6 months

Secondary efficacy variables up to Month 12 were identical to those above but assessment was performed up to month 12.

The CHMP considered that the outcome measures are relevant. However, especially in BRVO, it would have been desired to have a sham-controlled study up to 12 months with a key efficacy outcome measure evaluating the effect on VA at that time point.

- **Sample size**

BRVO: The sample size of 390 subjects (130 subjects per treatment group) provides 90% power in the ITT analysis to detect a statistically significant difference between one or both ranibizumab groups and the control group in the mean change from baseline in BCVA score at 6 months, assuming a change of + 12, + 10, and + 2 letters (BRVO) for the 0.5-mg, 0.3-mg and sham-treated subjects, respectively assuming an SD of 20 letters in the ranibizumab groups and 28 letters in the sham group.

CRVO: As above, but assuming a change of + 8, + 6, and −2 letters for the 0.5-mg, 0.3-mg, and sham-treated subjects, respectively.

In BRVO, it has been estimated that one third to three quarters gain 2 or more lines of VA without intervention. Thus, the calculation based on a +2 letter mean increase in VA is considered optimistic by the CHMP.

- **Statistical methods**

Analysis population:

- Intent-to-treat (ITT) population: all randomised subjects.
- Per-protocol (PP) population: subjects sufficiently protocol-compliant, e.g., non-missing baseline and month 6 BCVA, not missed ≥ 3 treatments unless protocol-specified ditto.
- Safety-evaluable population: subjects who received at least one injection of study drug (ranibizumab or sham)

Missing data

Imputation of missing values to be performed using the last-observation-carried-forward (LOCF) method for the primary and secondary efficacy endpoints.

Statistical analyses:

Primary analyses will be based on the ITT set.

Subgroup analyses

Subgroup analyses to be performed for the primary efficacy endpoint and key secondary efficacy endpoints. These will be based on age (< 65 years, ≥ 65 years), sex (male, female), race (White, non-White), BCVA score in the study eye (≤ 34, 35 to 54, ≥ 55 letters), foveal thickness as assessed on OCT in the study eye (< 450 µm, ≥ 450 µm), and any prior therapies for RVO in the study eye (yes, no)

The choice of statistical methods raises no concern to the CHMP and the hierarchical testing for secondary endpoints is considered stringent. Since analyses include both of mean change from baseline and responder analyses, the planned sensitivity analyses appear adequate. Only descriptive statistics has been planned for during the 6 months follow up phase. In view of the lack of a sham-controlled design of the extension part of the study, this is reasonable. Additional subgroup analyses have been performed as recommended in the CHMP scientific advice, see further Subgroup analyses discussion below.

Results

Table 4 Subject Disposition and Primary Reason for Discontinuation, studies FVF4165g (BRVO) and 4166g (CRVO)

	Study FVF4165g			**Study FVF4166g**		
Status		**Ranibizumab**			**Ranibizumab**	
	Sham n=132	**0.3 mg n=134**	**0.5 mg n=131**	**Sham n=130**	**0.3 mg n=132**	**0.5 mg n=130**
	n (%)					
Received study drug	131 (99.2)	134 (100)	130 (99.2)	129 (99.2)	132 (100)	129 (99.2)
Completed through Month 6	123 (93.2)	128 (95.5)	125 (95.4)	115 (88.5)	129 (97.7)	119 (91.5)
Completed through Mo 12	114 (86.4)	119 (88.8)	123 (93.9)	109 (83.8)	126 (95.5)	114 (87.7)

Table 5 Analysis set

	Study FVF4165g			Study FVF4166g		
Analysis Population	**Sham**	**Ranibizumab**		**Sham**	**Ranibizumab**	
	n=132	**0.3 mg n=134**	**0.5 mg n=131**	**n=130**	**0.3 mg n=132**	**0.5 mg n=130**
Randomized subjects (ITT)	132 (100%)	134 (100%)	131 (100%)	130 (100%)	132 (100%)	130 (100%)
Per-protocol subjects	109 (82.6%)	111 (82.8%)	106 (80.9%)	104 (80.0%)	118 (89.4%)	102 (78.5%)
Safety-evaluable subjects	131 (99.2%)	134 (100%)	130 (99.2%)	129 (99.2%)	132 (100%)	129 (99.2%)

Few subjects discontinued treatment/study, the majority due to subject's or physician's decision and the figures raise no concerns to the CHMP. Somewhat more subjects discontinued were found in the sham treatment arms in both studies. Similar reasons for discontinuations in the treatment as in the

extension phase suggest that the switch to as-needed treatment did not alter the pattern of discontinuations.

In study FVF4165g (BRVO) a total of 397 subjects were randomised into the study with 1-23 subjects per site (total 93 sites). N study FVF4166g (CRVO) 392 subjects were randomised into the study with 1-14 subjects per site (total 95 sites).

The majority of subjects were white (> 80%). In the studies taken together, 38 subjects whereof 30 ranibizumab-treated were ≥ 85 years. For a detailed description of the baseline characteristics see table 6 below.

Table 6 Baseline demographic, diagnostic and visual acuity characteristics

	Study FVF4165g			Study FVF4166g		
	Sham	Ranibizumab		Sham	Ranibizumab	
	(n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	(n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
Age (yr)						
Mean (SD)	65.2 (12.7)	66.6 (11.2)	67.5 (11.8)	65.4 (13.1)	69.7 (11.6)	67.6 (12.4)
Range	26–89	43–90	41–91	20–91	38–90	40–91
Sex, n (%)						
Male	74 (56.1%)	67 (50.0%)	71 (54.2%)	72 (55.4%)	71 (53.8%)	80 (61.5%)
Female	58 (43.9%)	67 (50.0%)	60 (45.8%)	58 (44.6%)	61 (46.2%)	50 (38.5%)
Months since diagnosis of RVO Mean (SD) Range	3.7 (3.7) 0.0–16.0	3.6 (4.1) 0.0–35.0	3.3 (3.1) 0.0–13.0	2.9 (2.9) 0.0–14.0	3.6 (3.2) 0.0–12.0	3.3 (3.7) 0.0–27.0
Visual acuity						
Number of letters (0–100) Mean (SD) Range	54.7 (12.2) 16–73	56.0 (12.1) 25–73	53.0 (12.5) 22–79	49.2 (14.7) 16–71	47.4 (14.8) 9–72	48.1 (14.6) 21–73
Distribution letters, n (%)						
≤ 34	9 (6.8%)	9 (6.7%)	13 (9.9%)	26 (20.0%)	33 (25.0%)	30 (23.1%)
35–54	50 (37.9%)	48 (35.8%)	49 (37.4%)	49 (37.7%)	46 (34.8%)	50 (38.5%)
≥ 55	73 (55.3%)	77 (57.5%)	69 (52.7%)	55 (42.3%)	53 (40.2%)	50 (38.5%)
~ Snellen equivalent Median	20/80	20/63–20/80	20/80	20/100	20/100	20/100
Distribution, n (%)						
≤20/200	14 (10.6%)	14 (10.4%)	21 (16.0%)	35 (26.9%)	41 (31.1%)	39 (30.0%)
>20/200 <20/40	99 (75.0%)	99 (73.9%)	95 (72.5%)	83 (63.8%)	82 (62.1%)	84 (64.6%)
≥20/40	19 (14.4%)	21 (15.7%)	15 (11.5%)	12 (9.2%)	9 (6.8%)	7 (5.4%)

The CHMP concluded that VA was fairly balanced at baseline. In subjects with BRVO, slightly more subjects had a lower baseline VA in the 0.5 mg ranibizumab treatment group, while in subjects with CRVO somewhat more sham-treated subjects had a better baseline VA. As expected, subjects with CRVO had on average, a worse VA.

Baseline characteristics of the study eye as assessed by fundus photography and fluorescence angiography were essentially comparable across the treatment groups, with the following exceptions: Somewhat more BRVO-treated subjects in the ranibizumab-treatment groups had a larger retinal involvement of the occlusion; More CRVO-subjects in the 0.5 mg ranibizumab group had contralateral vessel formation; in BRVO-subjects, baseline CFT was smaller in the sham group although the average central subfield thickness and macular volume were similar across the 3 treatment groups.

Demographics and ocular characteristics were essentially balanced at baseline and the included patient population is considered by the CHMP to be fairly representative for the target population. The few differences are not considered to be in favour of the ranibizumab treatment groups. However, the vast majority of RVOs appeared non-ischaemic as defined by BVOS 1986 and CVOS, 1993 (BRVO < 5 disc

areas, CRVO <10 disc areas). This is considered to be a limitation of the targeted population and the MAH is requested to address this in the SPC and RMP.

During the 12 months, 115 and 110 subjects received sham and 0.5 mg ranibizumab, in studies 4165 and 4166, respectively. The majority of the previously sham-treated subjects (77-79%) received their first ranibizumab-injection month 6. Of the sham-treated subjects, 17 (13%, study 4165) and 20 (15%, study 4166) received no injections during the follow up phase. The majority of subjects received the 6 monthly injections, and 3-4 additional injections during the following 6 months. Most previously sham-treated subjects (>85%) received 0.5 mg ranibizumab during the follow up phase. Upon crossing over to active treatment in the sham arm, the extent of laser treatment was similar between treatment arms, with somewhat more subjects on 0.3 mg ranibizumab needing rescue. Overall, the extent of laser rescue in ranibizumab-treatment groups was markedly lower compared to sham and thus considered reassuring by the CHMP.

Primary endpoint

Table 7 Primary efficacy endpoint: Mean Change from Baseline in Visual Acuity at Month 6, ITT, LOCF

	Study FVF4165g			Study FVF4166g		
	Sham	Ranibizumab		Sham	Ranibizumab	
	(n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	(n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
Primary analysis: Number of letters change from baseline/ITT, LOCF						
Mean (SD)	7.3 (13.0)	16.6 (11.0)	18.3 (13.2)	0.8 (16.2)	12.7 (15.9)	14.9 (13.2)
95% CI for mean [a]	(5.1, 9.5)	(14.7, 18.5)	(16.0,20.6)	(−2.0, 3.6)	(9.9, 15.4)	(12.6, 17.2)
Difference in LS means (vs. sham) [b]		9.4	10.6		11.5	13.8
95% CI for difference [b]		(6.6, 12.2)	(7.6, 13.6)		(7.7, 15.3)	(10.3, 17.4)
p-value (vs. sham) [b]		< 0.0001	< 0.0001		< 0.0001	< 0.0001
Sensitivity analysis: Number of letters change from baseline/PP, Observed data						
	n=109	n=111	n=106	n=104	n=118	n=102
Mean (SD)	8.1 (12.8)	17.0 (10.6)	19.7 (12.4)	2.4 (15.7)	12.6 (16.1)	15.1 (13.4)
95% CI for mean [a]	(5.6, 10.5)	(15.0, 19.0)	(17.3,22.1)	(−0.7, 5.4)	(9.7, 15.5)	(12.5, 17.8)
Difference in LS means (vs. sham) [b]		9.0	11.7		10.2	12.7
95% CI for difference [b]		(5.8,12.1)	(8.3,15.1)		(6.0,14.4)	(8.7,16.8)
p-value (vs. sham) [b]		< 0.0001	< 0.0001		< 0.0001	< 0.0001

a Derived from the t-distributions.
b Based on pairwise ANOVA models adjusted for baseline VA (≤ 34, 35−54, ≥ 55 letters).

The CHMP considered that a convincing outcome in both subsets of RVO has been demonstrated, both with regards to effect size and statistical significance. In view of the natural poor prognosis in CRVO, the outcome in this subset of RVO is even to be considered compelling. These data are supported by analysis of the PP population.

However, in BRVO, although almost three times more sham-treated subjects received rescue laser during the first 6 months, these subjects were deferred rescue during the first three months of the study. In addition, by allowing cross-over of sham-patients to active treatment after 6-months, the impact of a spontaneous improvement in BRVO on the magnitude of effect of ranibizumab cannot be fully assessed. Thus, the results for the treatment groups include the outcome of the spontaneous resolution of the oedema as well as the effect of the delayed laser. This is further discussed in the section Subgroup analyses below.

Secondary endpoints

In conclusion the CHMP considered that all VA-related secondary outcome measures confirmed a robust and convincing effect of ranibizumab. An important proportion of subjects gained ≥ 15 letters at month 6. For ranibizumab 0.5 mg > 60% and almost 50% of subjects with BRVO and CRVO gained ≥15 letters while the corresponding figures in the sham groups were ~ 30 and 17%. The robustness of data was confirmed with sensitivity analyses imputing missing data as failures. These proportions were maintained with continued ranibizumab-treatment during the following 6 months where an improvement was observed in subjects that crossed over to receive sham. However, the overall

magnitude of improvement in the group that crossed over to ranibizumab-treatment remained smaller compared to subjects that received ranibizumab from study start and the 95% CI indicate a sustained effect of ranibizumab also compared with these subjects. Since the majority of subjects received active treatment during this phase, this may indicate that treatment should not be withheld, or that the in average 4 injections administered during this time period were not sufficient for an optimal response.

The outcomes of anatomical parameters, i.e. changes in CFT were consistent with those based on VA. Also near and distance activities were significantly in favour of ranibizumab treatment, with a clinically relevant, although not impressing effect size. Taken together, a convincing effect of ranibizumab has been demonstrated in subjects with both subsets of RVO. However, the impact of weaknesses of the BRVO-study (3-months deferral of laser and short sham-controlled phase) are further addressed in the Subgroup analysis section below.

Selected exploratory endpoints

Table 8 Endpoints associated with neovascular complications of RVO

	Study FVF4165g			**Study FVF4166g**		
	Sham / 0.5 mg	**Ranibizumab**		**Sham / 0.5 mg**	**Ranibizumab**	
	(n = 132)	**0.3 mg** (n = 134)	**0.5 mg** (n = 131)	(n = 130)	**0.3 mg** (n = 132)	**0.5 mg** (n = 130)
Iris neovascularisation any post-baseline visit						
Baseline	1 (0.8%)	4 (3.0)	0 (0.0%)	0 (0.0%)	2 (1.5%)	2 (1.5%)
Up to Month 6						
n (%)	3 (2.3%)	0 (0.0%)	1 (0.8%)	9 (6.9%)	3 (2.3%)	3 (2.3%)
Difference (vs. sham)		−2.3%	−1.5%		−4.7%	−4.6%
95% CI for difference		(−6.8, 0.5)	(−5.9, 2.3)		(-10.8, 0.5)	(-10.8, 0.6)
p-value (vs. sham)		0.1208	0.6221		0.0832	0.1366
Up to Month 12						
n (%)	3 (2.3%)	2 (1.5%)	2 (1.5%)	9 (6.9%)	4 (3.0%)	7 (5.4%)
Difference (vs. sham)		−0.8%	−0.7%		−3.9%	−1.5%
95% CI for difference		(−5.3, 3.5)	(−5.2, 3.6)		(-10.1, 1.7)	(−8.0, 4.8)
Rubeosis in anterior chamber angle any post-baseline visit						
Baseline	NA	NA	NA	0 (0.0%)	2 (1.5%)	3 (2.3%)
Up to Month 6				n=103	n=104	n=104
n (%)				10 (9.7%)	2 (1.9%)	(0.0%)
Difference (vs. sham)					−7.8%	−9.7%
95% CI for difference					(-15.4,-1.7)	(-17.0,-5.1)
p-value (vs. sham)					0.0176	0.0007
Up to Month 12				n=103	n=106	n=104
n (%)				10 (9.7%)	2 (1.9%)	2 (1.9%)
Difference (vs. sham)					−7.8%	−7.8%
95% CI for difference					(-15.4,-1.7)	(-15.4,-1.6)
Rubeosis at pupillary margin any post-baseline visit						
Baseline	NA	NA	NA	0 (0.0%)	2 (1.5%)	3 (2.3%)
Up to Month 6	NA	NA	NA	n=101	n=103	n=105
n (%)				10 (9.9%)	7 (6.8%)	7 (6.7%)
Difference (vs. sham)					−3.1%	−3.2%
95% CI for difference					(-11.5, 5.2)	(-11.5, 5.1)
p-value (vs. sham)					0.4579	0.4545
Up to Month 12	NA	NA	NA	n=101	n=103	n=105
n (%)				11 (10.9%)	9 (8.7%)	9 (8.6%)
Difference (vs. sham)					−2.2%	−2.3%
95% CI for difference					(-11.0, 6.7)	(-11.1, 6.5)
Scatter photocoagulation						
Baseline	NA	NA	NA	6 (4.6%)	1 (0.8%)	0 (0.0%)
Up to Month 6	NA	NA	NA			
n (%)				6 (4.6%)	1 (0.8%)	(0.0%)
Difference (vs. sham)					−3.9%	−4.6%
95% CI for difference					(-9.4, 0.1)	(-10.0,-

	Study FVF4165g			Study FVF4166g		
	Sham / 0.5 mg	Ranibizumab		Sham / 0.5 mg	Ranibizumab	
	(n = 132)	0.3 mg (n = 134)	0.5 mg (n = 131)	(n = 130)	0.3 mg (n = 132)	0.5 mg (n = 130)
						1.5)
p-value (vs. sham)					0.0652	0.0295
Up to Month 12	NA	NA	NA			
n (%)				7 (5.4%)	1 (0.8%)	3 (2.3%)
Difference (vs. sham)					−4.6%	−3.1%
95% CI for difference					(-10.1,-0.5)	(−8.9, 1.9)

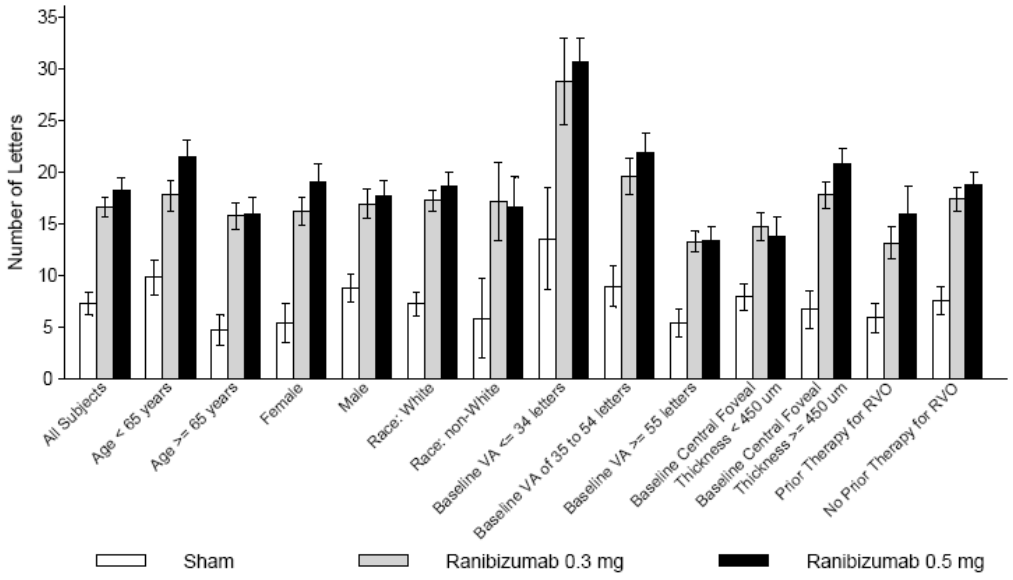
NA- not applicable

The incidence of iris neovascularisation was numerically smaller (few subjects in total) in ranibizumab-treated subjects. However, at 12 months, an increased incidence was observed in ranibizumab-treated subjects and the CHMP therefore requested the MAH to address the limited experience of treating subjects with iris neovascularisation in the SPC, section 4.4. Rubeosis in the anterior chamber angle is further considered by the CHMP to be a serious complication to CRVO that untreated almost always leads to increased IOP and secondary glaucoma. Although few subjects developed this complication, the indication that, overall, ranibizumab seemed to reduce the neovascular complications is of clear interest. Since some of these complications develop over time, the CHMP requested that the MAH should include analyses of these in the extension study (HORIZON), in LUMINOUS.

Subgroup analyses

Study FVF4165g (BRVO): Subgroup analyses for the primary endpoint (mean VA change from baseline) and proportion of subjects that gained ≥ 15 letters by age, gender, race, baseline VA, baseline CFT and presence of prior therapy indicated a consistent treatment effect in all subgroups, see figure 3 below.

Figure 3 Study FVF4165g Subgroup Analyses Mean Change from Baseline in VA, Month 6 (ITT)

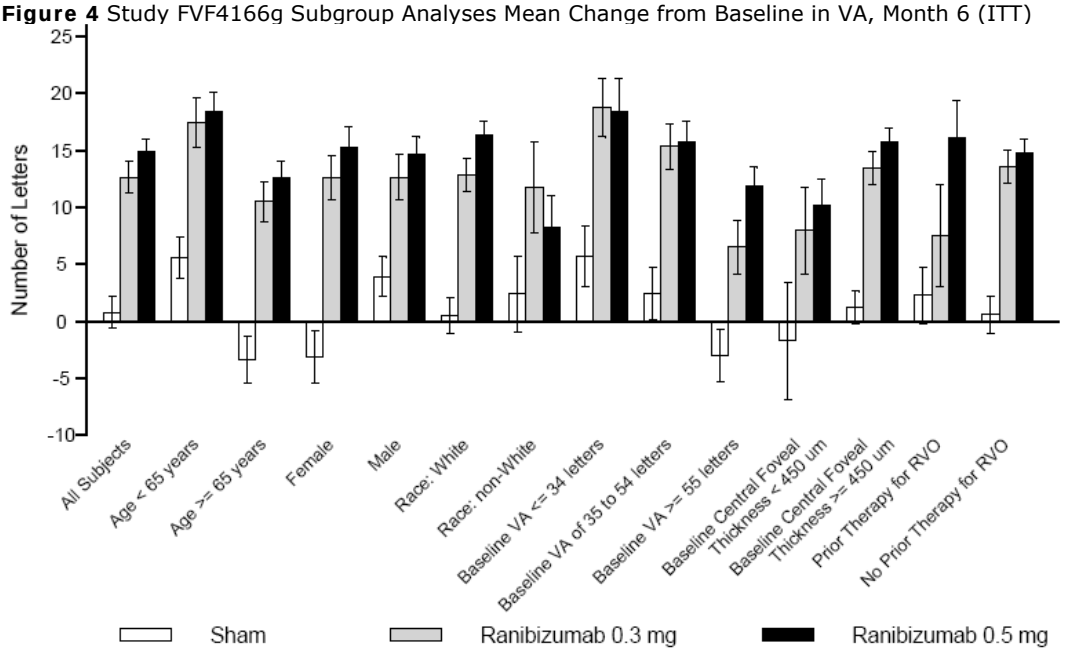


RVO=retinal vein occlusion; VA=visual acuity.
Note: The last-observation-carried-forward method was used to impute missing data. Vertical bars are ±1 standard error of the mean.

As in other analyses, the 12-month data were consistent with the 6-month data with an improvement in the previously sham-treated subjects.

Study FVF4166g (CRVO): As in subjects with BRVO, the treatment effect was consistent over subgroups, see figure 4 below.

Figure 4 Study FVF4166g Subgroup Analyses Mean Change from Baseline in VA, Month 6 (ITT)



RVO = retinal vein occlusion; VA = visual acuity.
Notes: The last-observation-carried-forward method was used to impute missing data.
Vertical bars are ± 1 standard error of the mean.

Additional post hoc subgroup analyses by blood pressure (≥140/≥90 vs. <140/<90), baseline retinal ischaemia (yes/no), history of cataract surgery, time since diagnosis of RVO (≤3 months, 3-12 months, ≥12 months) showed a consistent treatment effect in favour of ranibizumab in all subgroups.

The effect of ranibizumab was consistent in all subgroups. The majority of subjects had a RVO-duration of less than 3 months (BRVO 65%, CRVO 69%). This subgroup analysis indicated a convincing effect of ranibizumab in subjects with BRVO (9-11 letters over sham). Although very small subgroups, it is reassuring to the committee that subjects with a long duration of RVO as well as subjects with retinal ischaemia seemed to have benefit of treatment. However, it is not clear to the CHMP whether the ischaemia, in the total 34 subjects, was classified according to the criteria set up by BVOS (>5 disc areas) and CVOS (>10 disc areas). The MAH was further requested to present key efficacy data comparing the subgroup with HRVO with those with BRVO. Besides further evaluating retinal ischaemia in the ongoing studies, the benefit of treatment in subjects with a long-standing oedema (>12 months) should also be addressed in these studies.

Study FVF4165g (BRVO) *Impact of spontaneous resolution of the oedema and delayed laser*

In the CHMP advice, the following main concerns with regards to the current study design were given:

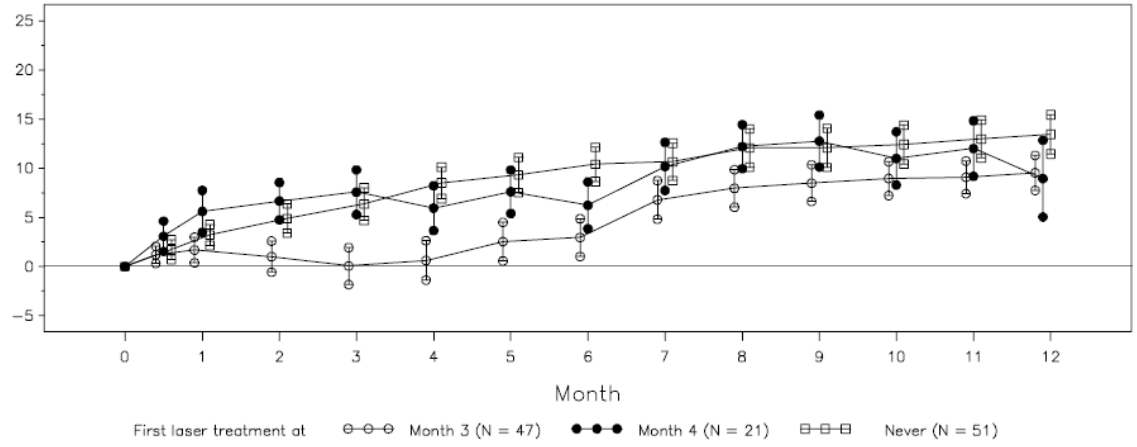
- Spontaneous improvement has been reported between 6 and 12 months and efficacy data that are not sham-controlled between 6 and 12 months will not be easily interpretable.
- The selection of a sham arm with deferred (3 months) laser rescue means that the test agent has a 3 month advance start on any active treatment.
- Laser treatment seems not to improve VA in the short term, rather after 2-3 years and 6 months data could be seen as not providing clear evidence of a sustained advantage of IVT therapy over standard care in the long term.

The MAH consequently made further subgroup analyses to assess a potential laser effect and the effect of spontaneous improvements in BCVA.

- *Subgroup analysis of patients by first laser treatment and spontaneous improvement of VA (BRVO patients)*

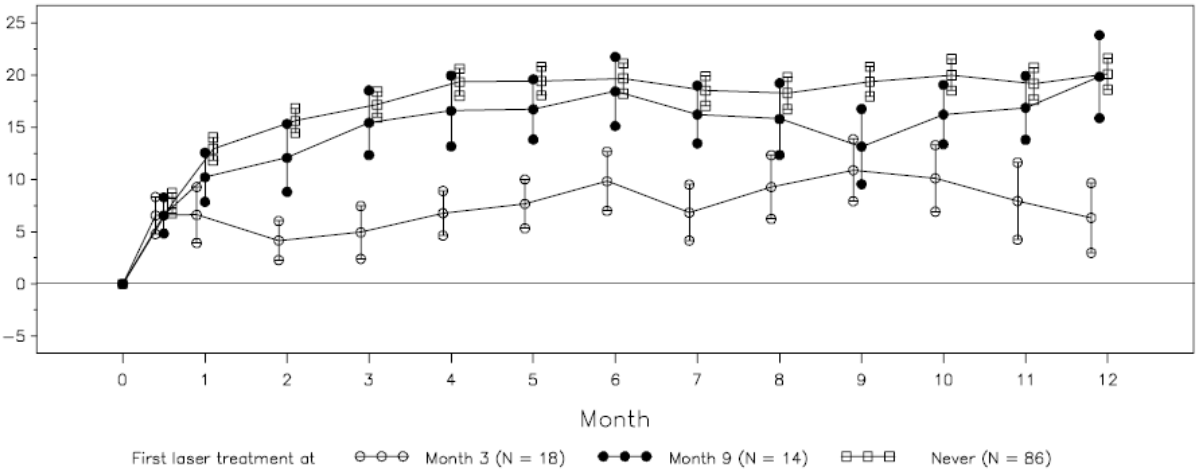
This 3-month laser deferral period was included to account for a spontaneous VA improvement that could occur in sham patients. Subgroups of patients were defined by the visit at which the first laser treatment was administered (including a subgroup with no laser), and within each subgroup the changes from Baseline in BCVA (see figures 5 and 6) and CFT up to Month 12 and the number of treatments (including the proportion receiving ranibizumab/sham injections by visit) were analysed.

Figure 5 BRAVO, sensitivity analysis: VA by time of first laser rescue treatment. Mean change from baseline, sham-sham/0.5 mg ranibizumab (ITT/LOCF)



– ∗: With correction of data errors in three laser application dates (for subjects 10214, 16702 and 18302, year was changed from 2009 to 2008).
– First visual acuity post−baseline was assessed at Day 7.
– BL = baseline; SE = standard error of the mean.
– Results are only presented if more than 10 subjects received laser treatment at the specific visit.

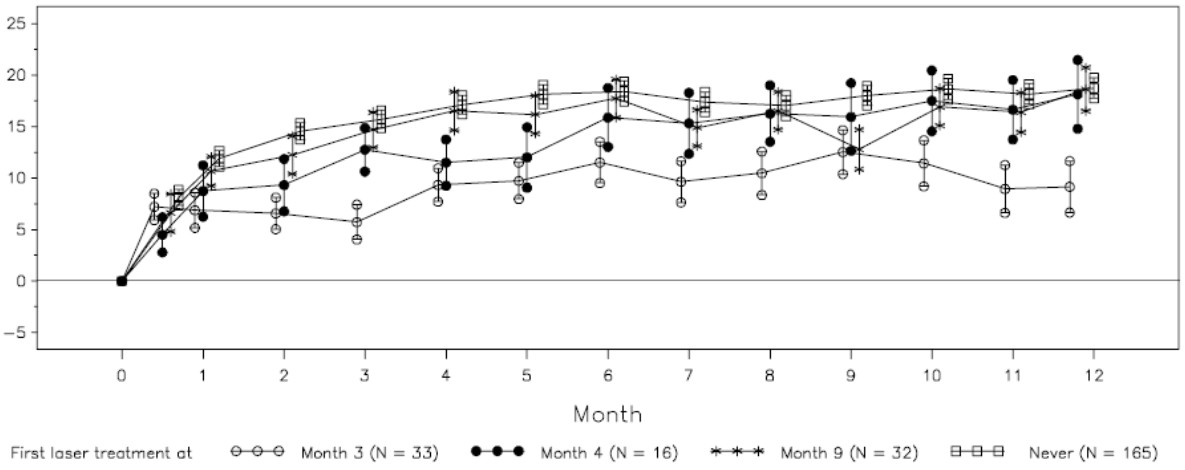
Figure 6 BRAVO, sensitivity analysis: VA by time of first laser rescue treatment. Mean change from baseline – 0.5 mg ranibizumab (ITT/LOCF)



During the entire 12-month study period, 61.4% of the patients (n = 81) in the sham/ranibizumab 0.5 mg group received at least one laser treatment, compared with 41.0% of the patients in the ranibizumab 0.3 group (n = 55) and 34.6% in the ranibizumab 0.5 mg group (n = 45).

Of the 100 patients who received laser photocoagulation treatment in the combined ranibizumab groups, 33 had their first laser treatment at Month 3, 16 at Month 4, 6 at Month 5, and 32 at Month 9. All 4 groups showed, on average, an improvement in VA from Baseline before receiving their first laser treatment. At Month 3, the mean change in BCVA from Baseline ranged from +5 letters in the Month 3 laser group to +15 letters in the Month 9 laser group. All 4 groups showed a mean increase in BCVA following the combination of laser photocoagulation and ranibizumab injection. This increase, which was generally smaller than the increase from Baseline on the preceding ranibizumab monotherapy was sustained through the end of the study.

Figure 7 BRAVO, sensitivity analysis: VA by time of first laser rescue treatment. Mean change from baseline – pooled 0.3 and 0.5 mg ranibizumab (ITT/LOCF)



– *: With correction of data errors in three laser application dates (for subjects 10214, 16702 and 18302, year was changed from 2009 to 2008).
– First visual acuity post−baseline was assessed at Day 7.
– BL = baseline; SE = standard error of the mean.
– Results are only presented if more than 10 subjects received laser treatment at the specific visit.

Because laser treatment was always given in combination with ranibizumab injections, the relative contribution of laser to the subsequent changes in VA cannot be evaluated based on these data.

The results for the sham control group include the outcome of the spontaneous resolution of the oedema as well as the effect of the delayed laser. The superiority of ranibizumab to sham treatment, therefore, implies that the therapeutic effect of the drug in general and its rapid onset in particular cannot be explained by spontaneous improvement of VA. Even "responders" to sham treatment in Study FVF4165g (i.e. 51 sham-treated patients who never required laser treatment during the study) had, on average, a gain in mean BCVA at Month 3 (approximately 6 letters) which was markedly smaller than the mean improvement of approximately 15 letters seen in the entire 0.5 mg group at Month 3.

In response to the MAH's subgroup analyses, the CHMP considered that the MAH's main deviation from the CHMP advice was that the study has not been sham-controlled over 12 months. On the other hand, masking was maintained and so was the controlled design of the study (the originally randomised groups are still compared to each others). Since the sham-controlled design of the study was not maintained, the exact magnitude of effect of ranibizumab cannot be assessed. As detailed below, it is clear that there is an additive effect of ranibizumab. A subgroup analysis by the visit at which the first laser treatment (month 3, 4, 9 and never) was administered has been presented. This subgroup analysis is driven by the outcome (patients in need of laser did worse) and a perspective of efficacy, no conclusions on whether the combination of ranibizumab and rescue laser would be better or worse can be drawn. From a safety point of view (see below), no new concerns were identified with the combination.

All ranibizumab-treated groups showed, on average, an improvement in VA before receiving their first laser treatment; for those who received laser at month 3, the average gain in VA was 5-7 letters (fairly stable over the 12 months) while those who received no or later laser rescue did better (up to ~15 letters increase in VA). The observation that "sham responders" (51 subjects who never required laser) had, on average, an ~ 6 letter gain in mean BCVA at Month 3 compared to the mean ~15 letter gain seen in the corresponding non-laser 0.5 mg group at Month 3 and that the effect of ranibizumab was sustained also at 6 (ranibizumab +18-19 letters, sham +10 letters) and 12 months (ranibizumab +18-19 letters, sham/0.5 mg +~13 letters) supports a clinically relevant treatment effect of ranibizumab.

Still, the study design hampers a conclusion on the magnitude of contribution of the effect of ranibizumab compared to the spontaneous improvement of VA and the effect of laser treatment. In the recent SCORE study (Arch Ophthalmol, 2009), 29% of laser-treated BRVO-subjects gained ≥15 letters of VA after 12 months. This is very similar to the 6 months data in the sham group (29%) in the current study and to be compared with the ~60% of 0.5 mg ranibizumab-treated subjects that gained

≥ 15 letters of VA (month 6 and 12). Taken together, it is clear that ranibizumab has an additional treatment effect also in BRVO and the above subgroup analyses as well as published data indicate that this effect size is of clinical relevance.

Although ranibizumab had a 3 month advance start over laser, deferral of laser for 3-6 months is according to clinical practice and an effect of laser on VA is expected to be seen after a number of years. Since the majority of subjects (65%) had duration of BRVO of less than 3 months, it is reassuring that the subgroup analysis of subjects that will not be treated with laser in clinical practice (i.e. < 3 months duration of BRVO) demonstrated a convincing effect of ranibizumab (9-11 letters over sham). Thus, the rapid improvement of VA in BRVO is acknowledged and of value for the patient. In this study, subjects that improved ≥ 10 letters in VA from screening to study start (28 days) were excluded. Consequently, as with laser, treatment with Lucentis may be deferred for some time, taking the risks with the injection in relation to the possibility for a spontaneous improvement into account.

In conclusion, despite limitations of study FVF4165g, the CHMP considered that a clinically relevant effect of ranibizumab in subjects with BRVO has been sufficiently demonstrated. However, the submitted study does not address whether there is a sustained advantage of ranibizumab therapy over standard care in the long term. In view of the shown effect of ranibizumab, it is difficult to require new laser-controlled studies and long-term effects will have to be addressed in the extension study (HORIZON) as well as in the registry study (LUMINOUS).

Selection of dose and dosing frequency

In this submission the MAH proposed a posology that is essentially identical with the posology previously agreed upon for the treatment of DME. If supported by data, to facilitate the use in clinical practice, a harmonised posology is in general supported by the CHMP.

Based on the MAH's rationale for the posology the CHMP considered that the 0.5 mg dose was frequently numerically in favour over the lower dose and the choice of the 0.5 mg dose is subsequently endorsed. As in previously approved indications, the effect of treatment has mainly been based on changes in VA and 64% (BRVO) and (73%) of re-treatments were based on VA. Thus it is consistent also for RVO to base re-treatment criteria on VA.

The recommendation regarding a treatment interruption after 3 consecutive monthly injections with a stable VA is endorsed, since a fourth consecutive injection gave no additional meaningful improvement in VA in stable subjects. Also the re-treatment recommendations are substantiated with analysis of subjects that re-started treatment after an interruption. However, the MAH has not discussed when to stop treatment due to lack of effect. During the 12 months, a decrease in VA could already occur within 1 month after treatment cessation and presently, monthly monitoring would be required to achieve an optimal treatment response. As in DME, the MAH was requested to commit to further analyse the long-term efficacy of Lucentis with help of the ongoing studies (HORIZON, LUMINOUS) to conclude on whether monthly monitoring and repeat injections are needed long term or if it is possible to withdraw treatment or to reduce treatment intervals, in one or both subsets of RVO, with time. If warranted, the outcome of the studies should be used to suggest new treatment recommendations.

Overall, the proposed posology is considered reasonable by the CHMP and very similar to that in DME, however, the MAH was requested to elaborate on the criteria for when to discontinue treatment due to a lack of effect. Also, as detailed in the assessment of the subgroup analyses above, it is not clear whether ranibizumab-treatment should be deferred for patients with BRVO for one, two or three months to allow for a spontaneous resolution of the event.

Discussion on clinical efficacy

Two single pivotal trials investigated the effect of ranibizumab on the visual impairment due to macular oedema secondary to RVO, one in BRVO and the other in CRVO. Patients from these trials continued for up to 2 additional years (mean additional 1.2 years) in the extension study HORIZON and preliminary data from the extension has been submitted (final study report to be submitted to the CHMP when available).

Six months after being treated on a monthly basis BRVO, and CRVO patients on ranibizumab significantly improved the VA with respect to those following a sham procedure. The main effect appears to be achieved as soon as by week 1 and remains basically stable or improves during the rest of the period. Reassuring results were obtained when the benefit was measured as clinically relevant improvement in VA (perceived as such by patients), anatomical or functional parameters.

During the extension part of the study, in subjects with BRVO, the effects on VA were essentially maintained. The treatment group that initially received sham-injections remained stable during the extension phase with a very similar 24 months outcome compared to those that received ranibizumab from study start. These figures may thus indicate that it is not necessary to initiate treatment immediately. However, the rapid improvement in VA upon treatment initiation is recognised as a benefit for the patient. Since some reports indicate that HRVO differs from BRVO with regards to pathogenesis, clinical features and prognosis, it is reassuring that the VA outcome from the 50 subjects presented with HRVO confirms the effect of ranibizumab also in this subset of patients.

In subjects with CRVO, VA appeared to stabilise from month 15, the time point for the first quarterly visit of HORIZON. The 3-4 letter drop in VA between month 12 and 15 observed in both subsets of patients thus indicate that some subjects needed re-treatment. Overall, subjects that were previously sham-treated did not gain as much VA as those who were treated with ranibizumab from study start ending up with a difference of almost 10 letters. Taken together, the long-term outcome indicates that the effect on VA is maintained over 2 years also in patients with CRVO.

In both subsets of patients, also the initial decrease in CFT remained at fairly stable levels throughout the 24 months independent on when treatment was initiated.

Although neovascular complications developed during the follow up period, they were relatively few. Since the majority of patients had no retinal ischaemia, a limited extent of neovascular complications would be expected. However, the MAH has committed to further address the effect of ranibizumab on the development of neovascular complications in the planned phase 24-months IIIb studies E2401 (CRVO) and E2402 (BRVO). Even though an improvement in VA was indicated also in subjects with retinal ischaemia and the rate of retinal ischaemia raised no new concerns during the extension study, few such subjects were included in the studies, and there is insufficient information to conclude on whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab. Information on the limited experience in these subjects is now given in the SPC. However, information not to treat patients with signs of functional loss due to ischaemia is also warranted. In addition, it is considered of high importance that the MAH make further efforts to characterise the benefits and risks of ranibizumab-treatment in the RVO population with ischaemic disease and the commitment made by the MAH to include such analyses in the planned studies are acknowledged by the CHMP.

Whereas in patients suffering CRVO the effect of ranibizumab has been convincingly established, the potential benefit of ranibizumab in BRVO patients cannot be so easily isolated (in an additional or even synergic way) from that of the concomitant laser therapy that a group of patients received along the study. Additionally, the spontaneous improvement in early stages could also contribute to the observed response given that patients recently diagnosed were preferentially included in the studies. On the other hand, masking was maintained over the 12 months and so was the controlled design of the study (the originally randomised groups were still compared to each others) and as detailed below, it is clear that there is an additive effect of ranibizumab. However, the study design does not allow assessing the exact magnitude of effect of ranibizumab over laser/spontaneous improvement.

The effect of Lucentis was consistent over various subgroups, including the group of RVO patients with diabetes which is of importance since diabetes is a major risk factor for RVO.

During the extension period, subjects received in average 3 additional injections but the variability was large (range 0-11). The MAH has presented subgroup analysis that showed that in BRVO, approximately 40% of subjects remained with a stable VA without any additional injections during the follow up period, while 36% needed ≥3 injections. Also in CRVO, there was a proportion of patients that remained stable without further treatment, although this proportion was lower (20%) and the majority of these patients (55%) needed ≥ 3 additional injections. The analyses of the 2-year data confirm the large variability in both subsets of RVO and also that there is a potential to withdraw treatment in some patients. Thus an individualised treatment regimen appears reasonable. The MAH has committed to further address whether there is a potential to adapt the monitoring frequency to individual needs by assessing the predictive value of observed responses to treatment and for

treatment interruption in the upcoming studies E2401 and E2402 as well as in the registry study LUMINOUS. This approach is endorsed by the CHMP.

In subjects with BRVO, laser treatment is usually withheld for a number of months to allow time for a spontaneous resolution of the oedema and the MAH has further elaborated on when to initiate ranibizumab-treatment in these subjects. Despite that subjects who improved spontaneously between screening and study initiation were not to be enrolled, 17/20 of these subjects were actually included in the study. In this subset (mean duration of the disease 2-3 months, range 0-11), a favour of ranibizumab was indicated (5 letters over sham from baseline to month 3). This favour may be biased since the mean duration of the RVO was shorter in ranibizumab-treated subjects. However, also the initial sham-controlled analyses clearly indicate that there was a rapid improvement in VA upon initiation of treatment with ranibizumab and a statistically significant difference vs. sham (5-6 letters) was observed from day 7 ($p < 0.0001$) while at month 6, in subjects with a short duration of BRVO (and a potential for a rapid spontaneous improvement in VA) indicated an ~10 letter increase in mean VA in ranibizumab-treated subjects over those who were treated with sham. On the other hand, the long-term HORIZON outcome indicates that the initially sham-treated subjects appeared to catch up with those who received ranibizumab from study start. The data thus suggest that there is no need to initiate treatment immediately and even if treatment is delayed with 6 months, the average long-term outcome in VA appears not negatively affected. The option to withhold treatment and "wait and see" should thus be weighed against the potential for a rapid improvement in VA in case of an early treatment initiation. Taken together, an approach to leave the decision whether to initiate treatment immediately or whether to "wait and see" up to the discretion of the physician is supported. As a basis for such decision-making, the SPC, section 5.1 has been amended.

The MAH has also further elaborated on the criteria when to stop treatment to avoid unnecessary injections and argues that the proposed posology is based on study treatment and monitoring as well as data. The post-hoc analyses indicate that no further gain in VA is seen when patients were treated after having reached stability. The MAH also emphasises the high variability between patients to reach stability and underscores the importance of an individualised duration of the initial monthly treatment regimen. Finally, the MAH proposed to add a recommendation to section 4.2 of the SPC that clearly states that continued treatment is not recommended if there is no improvement in VA over the course of the first three injections. This statement is in line with the recommendations for DME and endorsed. However, the posologies for DME and RVO are now identical and have been merged in the SPC adopted with this Opinion, as requested by the CHMP.

Conclusions on clinical efficacy

The benefit of Lucentis in the treatment of BRVO and CRVO has been demonstrated. Additional data to complement the knowledge on this efficacy will be available once the upcoming studies (E2401 and E2402 and 'LUMINOUS') are completed. The MAH has committed to generate the additional data. This is endorsed by the CHMP.

4.3.3. Clinical safety

Safety assessments included the incidence and severity of ocular adverse events, incidence and severity of non-ocular adverse events, changes and abnormalities in clinical laboratory parameters and ocular safety assessments (e.g., IOP and slitlamp), incidence of positive serum antibodies to ranibizumab and changes in vital signs.

Patient exposure
A total of 525 subjects with BRVO or CRVO have been administered ranibizumab (0.3 – 0.5 mg, including those crossing over from sham to active treatment from month 6). Subjects have been given in average 9 injections during 12 months. In addition, the ongoing, uncontrolled Study FVF3426g (HORIZON) (up to 2 year extension of pivotal studies) that was clinically completed in July 2010, but not submitted with this application includes longer term data on 680 subjects treated with 0.5 mg ranibizumab. Information on deaths and other SAEs known to have occurred in this extension up to and including 30 June 2010 was provided.

The CHMP considered that the overall experience of IVT Lucentis in ocular disease has become large, with exposures of ranibizumab in 3736 and 337 patients with AMD and DME, respectively. For HORIZON, only safety line listings of SAEs have been submitted. The CHMP therefore requested that the study report and an updated summary of clinical safety should be submitted when available.

Adverse events

Ocular Adverse Events

The most frequently reported ocular events in the ranibizumab groups were conjunctival haemorrhage and retinal exudates, see table 9 below. For ranibizumab-treated patients, 38.3% and 32.4% of patients in the 0.3 mg and 0.5 groups, respectively, experienced an ocular AE that was suspected by the investigator to be related to study drug or injection procedure compared with 27.3% of sham-treated patients, see table below.

Table 9 Ocular adverse events in the study eye suspected to be related to study drug or to study drug injection procedure – Studies FVF4165g and FVF4166g pooled (safety set)

	6-month treatment			12-month study		
		Ranibizumab		Ranibizumab		
	Sham n=260	0.3 mg n=266	0.5 mg n=259	0.3 mg n=266	0.5 mg n=259	Pooled n=525
Any related adverse event	71 (27.3)	102 (38.3)	84 (32.4)	118 (44.4)	92 (35.5)	210 (40.0)
Conjunctival haemorrhage	50 (19.2)	70 (26.3)	57 (22.0)	80 (30.1)	61 (23.6)	141 (26.9)
Eye pain	19 (7.3)	29 (10.9)	35 (13.5)	32 (12.0)	37 (14.3)	69 (13.1)
Eye irritation	5 (1.9)	9 (3.4)	9 (3.5)	11 (4.1)	11 (4.2)	22 (4.2)
IOP increased	4 (1.5)	13 (4.9)	9 (3.5)	18 (6.8)	15 (5.8)	33 (6.3)
Foreign body sensation	9 (3.5)	4 (1.5)	8 (3.1)	5 (1.9)	9 (3.5)	14 (2.7)
Myodesopsia	0	16 (6.0)	6 (2.3)	18 (6.8)	7 (2.7)	25 (4.8)
Ocular discomfort	5 (1.9)	2 (0.8)	6 (2.3)	4 (1.5)	7 (2.7)	11 (2.1)
Ocular hyperaemia	2 (0.8)	7 (2.6)	6 (2.3)	8 (3.0)	7 (2.7)	15 (2.9)
Punctate keratitis	2 (0.8)	4 (1.5)	4 (1.5)	5 (1.9)	5 (1.9)	10 (1.9)
Lacrimation increased	4 (1.5)	6 (2.3)	4 (1.5)	8 (3.0)	5 (1.9)	13 (2.5)
Vision blurred	1 (0.4)	2 (0.8)	4 (1.5)	2 (0.8)	5 (1.9)	7 (1.3)
Visual impairment	0	1 (0.4)	2 (0.8)	1 (0.4)	3 (1.2)	4 (0.8)
Cataract	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Vitreous haemorrhage	2 (0.8)	2 (0.8)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Vitreous detachment	0	0	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)
Conjunctival oedema	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)
Conjunctivitis	0	0	1 (0.4)			
Corneal erosion	0	0	1 (0.4)			
Keratopathy	0	0	1 (0.4)			
Iritis	0	0	1 (0.4)			
Eyelid oedema	2 (0.8)	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Eye haemorrhage	0	0	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)
Retinal disorder	0	0	1 (0.4)			
Eye discharge	2 (0.8)	3 (1.1)	1 (0.4)	3 (1.1)	1 (0.4)	4 (0.8)
Photophobia	0	2 (0.8)	1 (0.4)	2 (0.8)	1 (0.4)	3 (0.6)
Maculopathy	0	0	1 (0.4)			
Diplopia	0	0	1 (0.4)			
Metamorphopsia	0	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.4)
Drug hypersensitivity	0	0	1 (0.4)	0	2 (0.8)	2 (0.4)
Endophthalmitis	0	0	1 (0.4)			
Corneal abrasion	3 (1.2)	2 (0.8)	1 (0.4)	6 (2.3)	1 (0.4)	7 (1.3)
Hyperesthesia	0	0	1 (0.4)			
Blindness transient	0	2 (0.8)	0	2 (0.8)	0	2 (0.4)
Vitreous opacities	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Conjunctival hyperaemia	0	2 (0.8)	0	4 (1.5)	0	4 (0.8)
Corneal oedema	0	1 (0.4)	0			
Keratitis	0	1 (0.4)	0	1 (0.4)	1 (0.4)	2 (0.4)
Dry eye	1 (0.4)	0	0			
Erythema of eyelid	1 (0.4)	0	0			
Eyelid pain	2 (0.8)	0	0			
Eyelid pruritus	0	1 (0.4)	0	4 (1.5)	0	4 (0.8)
Eye pruritis	1 (0.4)	4 (1.5)	0			
Abnormal sensation in eye	0	1 (0.4)	0			
Retinal detachment	0	1 (0.4)	0			
Retinal tear	0	1 (0.4)	0			
Photopsia	1 (0.4)	1 (0.4)	0			
Injection site haemorrhage	0	1 (0.4)	0			
Injection site irritation	1 (0.4)	0	0			
Injection site pain	0	1 (0.4)	0	2 (0.8)	1 (0.4)	3 (0.6)
Corneal scar	0	1 (0.4)	0			
Procedural pain	0	1 (0.4)	0			
Cataract nuclear				1 (0.4)	1 (0.4)	2 (0.4)
Anterior chamber disorder				0	1 (0.4)	1 (0.2)

The AEs retinal exudates, retinal/ocular vascular disorders, maculopathy and retinal depigmentation were not considered (by the investigator) as related to treatment and may be expected as

manifestations of the disease. However, they appeared more frequently in ranibizumab-treated subjects and have been explained by the MAH to be due to grouping of various related terms each only seen in occasional subjects. Ocular AEs considered related to the injection procedures rather than to ranibizumab included haemorrhages, vitreous deposits, transient blindness, conjunctival hyperaemia, corneal (punctate) keratitis/erosions, pain and endophthalmitis.

HORIZON

During the extension study, ocular AEs were largely comparable with those previously reported although the incidence of retinal depigmentation or pigmentation, increased IOP and cystoid macular oedema increased with time.

Non-Ocular Adverse Events

The most frequently experienced non-ocular AE reported overall during the treatment period was hypertension followed by nasopharyngitis. The pattern was similar during the entire study. All non-ocular AEs (1.5% of patients) that were considered by the investigator to be related to study drug or injection procedure were experienced by single patients, see Table 10 below.

Table 10 Non-ocular adverse events in the study eye suspected to be related to study drug or to study drug injection procedure– Studies FVF4165g and FVF4166g pooled (safety set)

	6-month treatment			12-month study		
		Ranibizumab		Ranibizumab		
	Sham n=260	0.3 mg n=266	0.5 mg n=259	0.3 mg n=266	0.5 mg n=259	Pooled n=525
Any related adverse event	3 (1.2%)	2 (0.8%)	4 (1.5%)	4 (1.5)	4 (1.5)	8 (1.5)
Myocardial infarction	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Sinustitis	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Cerebral hemorrhage	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Thalamus hemorrhage	1 (0.4)	0	0			
Headache	2 (0.8)	0	0			
Dizziness	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Presyncope	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Anxiety	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Hypertension	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
APPT shortened				1 (0.4)	0	1 (0.2)
IOP increased				1 (0.4)	0	1 (0.2)
Blood ALP increased				1 (0.4)	0	1 (0.2)
Crystal urine present				1 (0.4)	0	1 (0.2)
Basophil count increased				1 (0.4)	0	1 (0.2)

During HORIZON, the overall non-ocular AEs, the safety profile remained consistent and there were no new non-ocular safety concerns in the long term RVO safety set.

Serious adverse events and deaths

Serious Ocular Adverse Events

The occurrence of ocular SAEs was uncommon and no treatment differences were observed regarding the frequencies of SAEs in the active groups versus the sham group or between the 2 dose groups. Most SAEs were experienced by a single patient only.

Table 11 Ocular serious adverse events Studies FVF4165g and FVF4166g pooled (safety set)

	6-month treatment			12-month study		
		Ranibizumab		Ranibizumab		
	Sham n=260	0.3 mg n=266	0.5 mg n=259	0.3 mg n=266	0.5 mg n=259	Pooled n=525
Any serious adverse event	8 (3.1)	7 (2.6)	4 (1.5)	11 (4.1)	10 (3.9)	21 (4.0)
Blindness unilateral	0	0	1 (0.4)			
Corneal abrasion	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Corneal edema	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Endophthalmitis	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Foreign body in eye				0	1 (0.4)	1 (0.2)
Iris neovascularization	0	0	1 (0.4)			
Macular ischemia	1 (0.4)	0	0	1 (0.4)	0	1 (0.2)
Macular edema	3 (1.2)	2 (0.8)	0	4 (1.5)	3 (1.2)	7 (1.3)
Macular hole				0	1 (0.4)	1 (0.2)
Retinal artery occlusion	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal artery embolism				1 (0.4)	0	1 (0.2)
Retinal detachment	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal ischemia	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal neovascularization	1 (0.4)	0	0			
Retinal tear	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal vascular disorder	0	1 (0.4)	0	1 (0.4)	0	1 (0.2)
Retinal vascular occlusion	0	0	1 (0.4)	0	1 (0.4)	1 (0.2)
Retinal vein occlusion	2 (0.8)	0	1 (0.4)	1 (0.4)	3 (1.2)	4 (0.8)
Vitreous hemorrhage	1 (0.4)	0	0			
Visual acuity reduced				0	1 (0.4)	1 (0.2)

During the observation period, of patients in the sham/0.5 mg group treated with ranibizumab, 5 patients experienced an ocular SAE in the study eye (1 patient each with diabetic retinal oedema, retinal tear, vitreous haemorrhage, cataract, maculopathy, and VA reduced).

HORIZON

The most common ocular SAE was macular oedema, which is an indication for the treatment, and may reflect suboptimal monitoring and re-treatment. However, a potential relevant AE cannot be discarded. Ocular SAEs for subjects enrolled in HORIZON are summarised in table 12 below.

Table 12 Ocular SAEs in the study eye for the combined BRAVO, CRUISE, HORIZON - Subjects enrolled in HORIZON

		Ranibizumab
		0.3 mg/0.5 mg N = 413
Primary system organ class	**Preferred term**	**n (%)**
Any primary system organ class	Total	31 (7.5)
Eye disorders	Total	26 (6.3)
	macular oedema	11 (2.7)
	visual acuity reduced	5 (1.2)
	retinal vein occlusion	3 (0.7)
	macular ischaemia	2 (0.5)
	optic ischaemic neuropathy	2 (0.5)
	amaurosis fugax	1 (0.2)
	cataract	1 (0.2)
	cystoid macular oedema	1 (0.2)
	retinal ischaemia	1 (0.2)
	visual acuity reduced transiently	1 (0.2)
	vitreous haemorrhage	1 (0.2)
Infections and infestations	Total	1 (0.2)
	endophthalmitis	1 (0.2)
Injury, poisoning and procedural complications	Total	2 (0.5)
	corneal abrasion	1 (0.2)

	foreign body in eye	1 (0.2)
Investigations	Total	3 (0.7)
	intraocular pressure increased	3 (0.7)

Serious Non-Ocular Adverse Events
The occurrence of non-ocular SAEs was uncommon and no treatment differences were observed regarding the frequencies of SAEs in the active groups versus the sham group or between the 2 dose groups. Most SAEs were experienced by single patients only.

Of patients in the sham/0.5 mg group treated with ranibizumab, 15 patients experienced a non-ocular SAE during the observation period. Events included 1 patient each with, for example, chest pain, coronary artery disease, hypertension and MI. The CHMP concluded that there were few non-ocular SAEs and the SAE profile raises no new concerns.

Deaths
A total of 7 patients died in the studies involving patients with RVO. Except for 1 death from cerebral haemorrhage, none of the deaths (respiratory failure, pneumonia, unknown, gastric cancer, cardiac failure congestive, cardiac failure congestive plus sepsis) was suspected by the investigator to be related to study treatment. This event and other notable cases are summarised below.

- During the 6-month treatment period a 78-year-old white male patient (Patient 11009, ranibizumab 0.5 mg) in Study FVF4165g experienced a cerebral haemorrhage on Study Day 169, 18 days after his sixth treatment with study drug (6 February 2009), and died 8 days later on Study Day 177. The medical history of this patient included a haemorrhagic stroke, an intracranial haemorrhage (February 2007 and May 2007, respectively). The cerebral haemorrhage that resulted in the death of the patient was thought likely to be the result of amyloid angiopathy and hypertension. The investigator considered the cerebral haemorrhage to be related to study drug. Other suspected causes for the event included concurrent illnesses. The CHMP considered that the assessment by the investigator's (i.e. assigning the event of cerebral haemorrhage as treatment-related) appeared reasonable. On the other hand, this patient had 2 cerebrovascular accidents before entering the study and would be at high risk of experiencing a new such event.

Two deaths occurred during the extension study (HORIZON): cardiac failure congestive and cardiac failure congestive and sepsis. Both events were not suspected to be related to ranibizumab by the investigator:

- An 84-year-old white male patient (Patient 14404, 0.5 mg ranibizumab) experienced cardiac failure congestive on 31 Dec 2009 in Study FVF3426g (HORIZON) and died as a result on 04 May 2010. The event was not suspected to be related to ranibizumab by the investigator. The last dose of ranibizumab was on 05 Aug 2009. No relevant medical history was reported.

- A 60-year-old white male patient (Patient 35602, 0.5 mg ranibizumab) experienced cardiac failure congestive and sepsis on 24 Nov 2009 in Study FVF3426g (HORIZON) and died the same day due to these AEs. The event was not suspected to be related to ranibizumab by the investigator. The last dose of ranibizumab was on 13 Oct 2009. Relevant medical history included congestive cardiac failure, hypertension, arrhythmia, and gout.

Targeted Adverse Events

This included the analysis of previously identified risks (current safety concerns for Lucentis as defined in wet AMD and DME patients) in the RVO population. The outcome was very similar during the entire 12-months study period. No new safety concerns were identified in this population. There are also no indications that the incidence of AEs is increased in this population compared to subjects with AMD and DME. Nevertheless, information in section 4.4 and 4.8 of the SPC regarding risks with systemic VEGF-inhibition is certainly relevant also for this group of high-risk patients. Thus, the CHMP considered that the addition agreed upon in variation II/20 (DME-indication) should be included also for subjects with RVO. The MAH submitted updated product information documents, as requested.

With regards to retinal ischaemia, even though potentially related to the disease, there was a decrease in the percentage of patients with "no ischemia" from baseline to month 24 which is of concern. During the sham-controlled phase of the study (6-months), more sham-treated patients with no ischaemia at baseline developed retinal ischaemia (6.6% vs. 2.3% for ranibizumab-treated) and during the 12

months, there was a tendency towards an increased number of patients with ischaemia of varying severity compared to baseline (3.4%). At month 24, 6 % of BRVO- and 12 % and CRVO-patients that were non-ischaemic at baseline developed ischaemia.
There were no concerns with regards to the incidence of AEs that may be related to a systemic VEGF-inhibition, e.g. arterial thromboembolic events (ATEs), haemorrhages, hypertension and no new concerns were raised during the extension period.

During the 6- and 12- month treatment periods, the mean changes from Baseline in pre-dose Intraocular pressure (IOP) at each visit were negligible for all treatment groups. Few patients had a pre-dose IOP increase of ≥10 mmHg compared with Baseline: Month 6, 0.9% - sham (2 of 232), 1.2% - 0.3 mg (3 of 250), and 1.7% - 0.5 mg group (4 of 234); Month 12, 4 patients (1.6%) - 0.3 mg group and 5 patients (2.1%) - 0.5 mg group. The CHMP acknowledged that the majority of events of increased IOP were post-injection and transient and manageable.

The number of patients with iris neovascularisation of study eye at baseline was low in both studies. At 6 months, the incidence of iris neovascularisation in the pooled studies was higher in the sham group than in the active ranibizumab groups. The incidences were 4.6% in the sham group compared with 1.1% and 1.6% of patients in the 0.3 and 0.5 mg groups, respectively (slitlamp examination) and 4.6% in the sham group compared with 0.8% and 0.4% in the 0.3 and 0.5 mg groups, respectively (AE reporting). The CHMP considered that iris neovascularisation with subsequent neovascular complications is an event to be targeted in subjects with RVO. Data are reassuring although few subjects presented with this complication and consistent with the mode of action of ranibizumab. It is therefore considered that iris neovascularisation and secondary glaucoma are to be monitored in the PSURs.

Immunological events
Serum samples for evaluation of antibodies to ranibizumab were obtained at Screening, Month 6 (prior to study drug administration), and at Month 12 or the early termination visit. Few subjects tested positive for antibodies, notably several in the sham group and at baseline, possibly because of pre-existing anti-Fab antibodies. At all three assessment occasions the percentages remained below 5%. Changes in VA from baseline to month 12 for these patients were consistent with those in the full study populations, and no clinically relevant differences in adverse events (AEs) between patients with and without a positive antibody response were identified. There was, in summary, no indication that positive antibody tests had a negative effect on VA or was associated with a worse AE profile.

Safety related to drug-drug interactions and other interactions
No specific drug interaction studies were performed. As systemic exposure of ranibizumab is expected to be very low, the potential for drug interactions is considered low. Subgroup analyses on the concomitant use of anticoagulant drugs and ranibizumab indicated no concerns as defined as RMP safety concerns, however, few patients (8%) used anticoagulant drugs during the study. AEs (occurred within 14 days of injection) with and without concomitant laser treatment (within 30 days before the injection) were evaluated (Study FVF4165g). The number of injections that occurred in presence of laser was low, there appeared to be no major effects of concomitant laser treatment on incidence of AEs defined as RMP safety concerns. However, an overall slightly increased incidence of intraocular inflammation and deterioration of retinal blood flow was indicated both in sham and ranibizumab-treated groups when laser was administered.

The CHMP considered that laser photocoagulation as such also induces side effects; however, concomitant ranibizumab treatment did not appear to increase the incidence and severity of these. The proposed wording of the SPC, section 4.2 (according to the wording agreed upon for DME) is endorsed by the committee. The extent of laser rescue has been adequately included in a table in section 5.1 of the SPC.

Discontinuation due to AEs
Both studies had good patient retention, with a total of 739 patients (~95%) completing the studies through Month 6 and 92% of patients completing the overall study, the majority of discontinuations due to subject's or physician's decision. Overall, few subjects discontinued treatment or study due to AEs. During the 6-month treatment period, 6 patients had a ranibizumab or sham injection treatment held according to protocol-specified criteria: 2 patients were in the sham group (VA loss, IOP increased), 3 were in the 0.3 mg group (VA loss, sensory rhegmatogenous retinal break or detachment, intraocular surgery) and 1 was in the 0.5 mg group (intraocular surgery).

Post marketing experience
Lucentis was approved for the treatment of RVO in the US on 22 June 2010. No post-marketing data regarding use of Lucentis in patients with RVO were available to include in this SCS because of the cut off date for PSUR 7 (30 Jun 2010). Lucentis is currently registered in 85 countries for the indication of neovascular (wet) AMD.

Table 13 Exposures as reported in PSURs no 1-7:

	PSUR 1	PSUR 2	PSUR 3	PSUR 4	PSUR 5	PSUR 6	PSUR 7	Total
Europe		9,400	24,700	35,000	43,300	52,600	134,300	299,300
US	31,600[#]	37,100#	34,900	37,300	40,700	43,700	108,100	333,300
Rest of world **(ROW)**	2,100	2,600	7,100	9,300	13,400	20,300	63,700	118500
Total	33,700#	49,100#	66,700	81,600	97,400	116,600	306,100	751,100

Cumulatively, the safety database contains 3419 spontaneous reports, including 1958 reports from health care professionals.

4.3.4. Discussion on clinical safety

The clinical condition for which an indication is being sought differs to the currently authorised indications for Lucentis, i.e. AMD and DME, as the latter are chronic and progressive conditions. These conditions share however similarities with the sought indication from a demographic viewpoint and the proposed regimen has been tested in previous studies, so that the safety database from the authorised indications can be considered supportive and was taken as a reference for this application.

Overall, the safety database for the RVO indication is reassuring. Most of the ocular AEs observed in this RVO population are related to the injection procedure. Frequencies are in line, or even lower, to those registered for the currently authorised conditions. No new significant ocular related AEs have been observed. Most AEs were of mild severity. The most frequently AEs reported were: conjunctival haemorrhage, eye pain, increased IOP, maculopathy, myodesopsia, ocular hyperemia, ocular vascular disorder, retinal depigmentation, retinal exudates, and retinal vascular disorder.

During the extension study (i.e. in subjects exposed to ranibizumab for a mean total of 2.2 years) ocular AEs were largely comparable with those previously reported. Although the incidence of retinal depigmentation or pigmentation and (cystoid) macular oedema increased with time, they were likely manifestations associated with the disease. With respect to the increased incidence of macular oedema observed during this extension, the MAH has justified it as related to suboptimal monitoring and/or treatment. These differences have also been observed when macular oedema was reported as serious event and a potential relevant AE could not be discarded. The two planned 2-year studies (E2401 and E2402) can address this potential issue.

The CHMP expressed their concern over the potential effect of ranibizumab on retinal ischaemia. During the sham-controlled phase of the study (6-months), more untreated patients developed retinal ischaemia, while during the 12 months, there was a tendency towards an increased number of patients with ischaemia of varying severity compared to baseline. At month 24, 6 % of BRVO- and 12 % and CRVO-patients that were non-ischaemic at baseline developed ischaemia. However, development of retinal ischaemia is part of the disease, e.g. there are reports that in subjects with CRVO, 8 to 34 % of non-ischaemic subjects convert to an ischaemic state over a number of years and the rate of conversion presented appears not to be alarming. Still, it is remains unknown whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab and the currently available data only give limited assurance. The limited experience in treating subjects with retinal ischaemia is addressed in the SPC. Additionally, given that the risks with the injection are likely to be larger than a potential benefit in case of signs of functional loss, a statement not to treat subjects with irreversible visual function loss due to ischaemia has also been added to section 4.4 of the SPC. The MAH has also committed to further address this concern in the upcoming studies and in LUMINOUS, as well as to monitor this as detailed in the RMP.

There were occasional subjects experiencing a second event of RVO although the incidence was not remarkable compared to published rates. As for retinal ischaemia, it is not known whether anti-VEGF therapy may increase the risk for recurrences of RVO. This potential risk is, however, covered in the RMP (RVO is included in the search strategy to detect reduced blood flow). However, this issue should also be addressed in future studies.

With regards to non-ocular AEs, as in the previously studied populations, the majority in this fairly representative population was mild to moderate in severity and few were suspected to study drug and/or ocular injection. Although no indications of an increased risk in this population, the major concern relates to the previously identified AEs potentially related to systemic VEGF-inhibition, a risk relevant also for this group of patients. There are no new concerns with regards to immunogenicity in this group of patients. During the extension period, the safety profile remained consistent. An increased number of subjects experienced cardiac heart failure congestive and TIA (SAEs) compared to the first treatment year. However, in view of the significant co-morbidities (confirmed by disease history, see previous assessment report), the figures (including those regarding ATEs) are not considered alarming and are continuously monitored and the safety specification has been updated. There are no new concerns with regards to immunogenicity in this group of patients.

Future long-term safety data (up to 4 year) in these conditions will be collected as part of the observational LUMINOUS study and in the two planned 2-year phase IIIb studies.

4.3.5. Conclusions on clinical safety

The overall safety profile of ranibizumab in the treatment of macular oedema secondary to retinal vein occlusion is considered favourable by the CHMP.

4.3.6. Pharmacovigilance system

Not applicable

4.3.7. Risk Management plan

The most relevant updates to the safety specifications of the ranibizumab Risk Management Plan (RMP) from the previous fully implemented version RMP 7.2 and the interim RMPs produced in response to EMA requests are summarised below.

1.2.1. Exposure: Clinical trial

The safety-evaluable population included 525 patients treated with either ranibizumab 0.3 mg or 0.5 mg and 260 patients treated with sham injections. During the 6-month treatment period with a monthly dosing regimen, 2999 ranibizumab injections and 1436 sham injections were administered. The mean number of injections per patient from Day 0 to Month 5 (of 6 scheduled injections) was 5.5 for the sham group, 5.8 for the 0.3 mg group, and 5.7 for the 0.5 mg group.

During the entire 12-month study with a monthly dosing regimen for the first 6 months and as-needed injections for the second 6 months, a total of 4660 ranibizumab injections were administered. The mean number of injections received from Day 0 to Month 12 per patient was 8.9; 9.1 for the 0.3 mg group and 8.7 for the 0.5 mg group.

The safety population is limited but safety findings are supported by previous clinical trials in AMD and DME.

1.2 Limitations of the human safety database

This section was updated to include RVO studies. The lack of experience in patients with prior episode(s) of RVO has been addressed in the SPC.

1.3. Populations not studied in the pre-authorization phase

This section was updated to include information concerning populations not studied pre-authorization of the proposed indication treatment of macular edema secondary to RVO. As in previous indications patients below 18 years, pregnant/lactating women etc. were not included in the trials. Patients with a history of CVA or MI within the previous three months were not included. The issue is addressed in the SPC. The majority of patients enrolled in pivotal studies were white. Eight percent were black. There is limited experience in patients of other ethnic origin.

1.4 Post-authorisation experience

Projected post-authorisation usage data in visual impairment secondary to RVO is updated.

1.5 Adverse events

1.5.1 Newly identified safety issues

With regards to the indication treatment of visual impairment in DME, the RMP was amended by adding vitreous haemorrhage as an identified risk. Important missing information for patients with DME including long-term effects on the progression of diabetic retinopathy, effects of Lucentis on the deterioration of retinal blood flow, systemically unstable patients, age greater than 75 years and ethnicities other than Caucasian. The extension of the RESTORE study is aimed at collecting additional data on this risk/missing information.

Data from BRAVO and CRUISE do not suggest any difference in safety concerns for patients with RVO. The identified and potential risks and missing information described apply to all indications.

The following safety concerns require further evaluation for AMD (and by extension, RVO):

Important identified risks

- Hypersensitivity reactions
- Retinal pigment epithelial tear
- Endophthalmitis
- Retinal detachment
- Retinal tear
- Traumatic cataract
- Intraocular inflammation
- Intraocular pressure increase
- Vitreous hemorrhage

Important potential risks

- Hypertension
- Non-ocular hemorrhage
- Proteinuria
- Myocardial infarction
- Non-MI arterial thromboembolic events
- Venous thromboembolic events
- Deterioration of retinal blood flow (including central retinal artery occlusion CRAO)

Important missing information for both wet AMD and visual impairment in DME

- Systemic adverse events related to bilateral treatment and overdose
- Adverse events related to off-label use, including potential local and systemic adverse events related to paediatric off-label use (e.g. retinopathy of prematurity)
- Long-term safety beyond two years
- Intraocular antibody formation
- Important missing information for visual impairment in DME

- Long term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections
- Effects of Lucentis on the deterioration of retinal blood flow including macular ischemia
- Systemically unstable patients
- Age greater than 75
- Ethnicities other than Caucasian

Section 1.5.2.1 Details of important identified and potential risks was updated to include data from BRAVO and CRUISE studies. Pooled data from BRAVO and CRUISE studies (ranibizumab 0.5 mg) were used for calculation of incidence rates and relative risks. Data from HORIZON cohort 2 was included in the updated RMP.

Overall, there was no indication of increased risks in the RVO target population. The number of MI and non-MI ATEs reports is low but with a tendency towards an increased risk for MI and non-MI ATEs is of concern. There were 41 reports of deterioration of retinal blood flow in the ranibizumab treated patients and 47 reports in the control group at 6 months, rendering a relative risk of 0.88 (95% CI 0.60, 1.28), which was higher compared to the AMD and DME populations. The figures should be interpreted with caution due to possible confounding by indication (vein occlusion).

1.7 Epidemiology of the indication and important adverse events

1.7.1 Indication

This section was updated to include RVO epidemiology data. Review of published data was performed. The prevalence of RVO in the general population was estimated between 0.3% and 2.1% depending on the study design and population assessed.

Co-morbidity in the target population for RVO is discussed concerning cataract, glaucoma, hypertension, diabetes, MI, stroke, hyperlipidemia, depression and anxiety. These topics are the same as discussed in relation to the approved indications. In the updated RMP coagulapathy is also discussed. Review of the literature demonstrates that prior glaucoma is associated with an increased risk of CRVO. Increase in IOP has been observed in patients treated with Lucentis, both short-term transient increases in IOP related to injection procedure and increase in baseline IOP following long-term treatment.

Pharmacovigilance Plan
Section 2.2 Safety concerns and planned pharmacovigilance actions was updated and the long-term observational study CRFB002A206 (LUMINOUS) was added to all risk. Additionally, detailed action plans (section 2.3) for long term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections, effects of Lucentis on the deterioration of retinal blood flow including macular ischemia, systemically unstable patients, age greater than 75 and ethnicities other than Caucasian have been added. In sections 2.4 and 2.6 long-term observational study CRFB002A206 (LUMINOUS) and study CRFB002D2303 (REVEAL) have been added. These changes do not refer to the RVO indication.

Evaluation of the need for a Risk Minimisation plan
Section 3.1 was amended with planned actions for vitreous haemorrhage, long-term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections, effects on deterioration of retinal blood flow including macular ischemia, systemically unstable patients, age greater than 75, and ethnicities other than Caucasian. These changes do not refer to the new proposed indication treatment of macular oedema in RVO. Section 3.6 Potential for off-label paediatric use was adequately updated. The risk minimisation plan for Endophthalmitis and Traumatic cataract was updated concerning the educational material. The educational material has been updated with information regarding the new proposed indications in DME and RVO. In the health care professional educational material a self-questionnaire is included focusing on knowledge of IVT injection procedure technique, potential injection related side effects and monitoring and management of potential complications.

Risk Minimisation plan
The educational materials for health care professionals and patients have been updated with information regarding the new proposed indication. In the health care professional educational material

a self-questionnaire is included focusing on knowledge of IVT injection procedure technique, potential injection related side effects and monitoring and management of potential complications. The self-questionnaire is considered optional by the MAH and there are no plans for evaluation of the effectiveness of this material. At present, it is considered unlikely that there would be a large number of clinicians treating RVO who have not previously received the educational materials. However, in due time there will be new physicians entering the field of medical retina and the patients still need to be informed. A slight revision of the Conditions for Marketing Authorisation was therefore carried out (see Annex II). Follow-up of efficiency of the educational material is no longer required. The material will be available for distribution to patients and relevant physicians. Follow-up of efficiency of the educational material is no longer required. The HCP self-assessment questionnaire (RMP v 8.0 Annex 8) is considered optional and has therefore been removed from the educational materials referred to in Annex 8 of the RMP.

Table 5.1 Summary of activities for each safety concern has been amended with Long-term observational study CRFB002A2406 (LUMINOUS) for each previously included identified risk, important potential risk and each important missing information item, except for overdose. Safety activities for vitreous hemorrhage, long term effects on the progression of diabetic retinopathy (including the potential effect on diabetic retinopathy of stopping periodic anti-VEGF injections), effects of Lucentis on the deterioration of retinal blood flow including macular ischemia, systemically unstable patients, age greater than 75, and ethnicities other than Caucasian. Additionally, table 5-2 Summary of activities and milestones has been amended with information on long-term observational study CRFB002A2406 (LUMINOUS) and CRFB002D2303 (REVEAL). These changes do not refer to the new proposed indication treatment of macular oedema in RVO.

The issue of potential risk of glaucoma following long-term treatment with Lucentis is discussed by the MAH. In the pooled data for BRAVO and CRUISE for specific glaucoma terms the rates for sham were 6/260 or 2.3% and for 0.5 mg ranibizumab 2/259 or 0.8%, which does not suggest a signal for this event. To assess long-term data in RVO the MAH proposes to further analyse the RMP risk of "Increased IOP" in the planned RVO studies CRFB002E2401 and CRFB002E2402 as well as in the LUMINOUS trial. Additionally, in response to assessment of PSUR 7 including response to the EPITT signal 11801, the MAH proposed the inclusion of a warning in section 4.4 concerning transient as well as sustained increases of IOP and that both IOP and perfusion of the optic nerve head must be monitored and managed appropriately. Since this information is considered especially relevant for the now targeted population, the change is endorsed by the CHMP, to be implemented with this application. Since there is no specific way to distinguish "transient IOP increased" from "sustained IOP increase" it was agreed to amend the list of important potential risks with "glaucoma". Relevant sections of the RMP have been amended accordingly. The measures to assess potential long-term risk of glaucoma have been added to the RMP.

In addition to the above, Annex 8 has been revised to reflect the current situation (post-launch of the AMD- indication) with the new indications, and now includes relevant additional safety concerns.

ORPHAN MEDICINAL PRODUCTS

Not applicable.

4.3.8. Benefit/Risk Assessment

Benefits

Demonstrated benefits

The mechanism of action of ranibizumab is to decrease permeability of leaking blood vessels. This mechanism of action is valid independent on whether targeting retinal vessels in RVO, DME or the choroidal vessels in AMD. Therefore, available data from the AMD- and DME-populations adds to the basic understanding of the drug. This is of relevance also for understanding the treatment of RVO.

BRVO

A convincing outcome has been demonstrated, both with regards to effect size and statistical significance. After 6 months treatment, subjects with BRVO treated with 0.5 mg ranibizumab gained in average 18 letters in VA compared to 7 letters for sham-treated subjects (primary endpoint, $p<0.0001$). After the first 6 months of the study, previously sham-treated subjects received 0.5 mg ranibizumab for an additional 6 months (masking maintained), while subjects previously treated with 0.3 or 0.5 mg ranibizumab continued on their originally assigned treatment. At month 12, previously sham-treated subjects had gained 12 letters (95% CI 9.6, 14.6) vs. 18 letters in the 0.5 mg ranibizumab-treatment group (95% CI 15.8, 20.9). At month 6, also a substantial proportion of ranibizumab-treated (0.5 mg) subjects gained $\geq$ 15 letters in VA; 61 % vs. 29 % in the sham group ($p<0.0001$). The outcomes of the key analyses were supported by sensitivity analyses. As for the primary endpoint, the switch to active therapy during the 2nd part of the study increased the proportion of responders in the previous sham-group, but the numerical advantage for subjects that had received ranibizumab during the whole study remained. The 0.3 mg dose of ranibizumab was also highly effective, but numerically inferior to the higher dose in the VA-based analyses. Other secondary and exploratory endpoints (based on VA or anatomical measures) were consistently in favour of ranibizumab-treatment.

During the extension part of the study, the effects on VA were essentially maintained or increased slightly. At 24 months, the VA outcome in the treatment group that initially received sham-injections was very similar to the outcome in patients that received ranibizumab from study start. These figures may thus indicate that it is not necessary to initiate treatment immediately. However, the rapid improvement in VA upon treatment initiation (5-6 letters over sham after 1 week, $p< 0.0001$) is recognised as a benefit for the patient.

However, the design of the BRVO study has limitations and deviates from recommendations given in the CHMP-advice. Although positive effects on vision after laser photocoagulation are not expected in the short term, laser photocoagulation has been shown to be of long-term benefit for subjects with BRVO. Since subjects in the sham arm were deferred (3 months) laser rescue, the test agent has consequently a 3-month advance start over laser. Further, in BRVO, spontaneous improvement in VA is not uncommon and subjects may continue to improve during the first year. Thus, the 6-months sham-controlled phase of the study limits the possibility to assess the impact of a spontaneous improvement in BRVO vs. the magnitude of (contribution of) effect of ranibizumab, this since the results for the treatment groups include besides the outcome of the spontaneous resolution of the oedema also effects of delayed laser. On the other hand, masking was maintained over the 12 months and so was the controlled design of the study (the originally randomised groups were still compared to each others) and as detailed below, it is clear that there is an additive effect of ranibizumab and that this effect is rapid and substantial. However, the study design does not allow assessing the exact magnitude of effect of ranibizumab.

In subgroup analyses, by visit at which the first laser treatment (month 3, 4, 9 and never) was administered, all ranibizumab-treated groups showed, on average, an improvement in VA before receiving their first laser treatment. Even though this subgroup analysis is driven by the outcome (subjects who did worse received laser treatment), the observation that sham-treated subjects that did not require laser had, on average, an ~ 6 letter gain in mean BCVA at Month 3 compared to the mean ~15 letter gain seen in the corresponding non-laser 0.5 mg group at Month 3 supports a relevant

treatment effect of ranibizumab. Additionally, the extent of the need for laser rescue (almost three-fold more in the sham-group compared to ranibizumab) is supportive of a treatment effect of ranibizumab.

Additionally, in the recent SCORE study (Arch Ophthalmol, 2009), 29% of laser-treated BRVO-subjects gained ≥15 letters of VA after 12 months. This is very similar to the 6 months data in the sham group (29%) in the current study and to be compared with the ~60% of 0.5 mg ranibizumab-treated subjects that gained ≥ 15 letters of VA (month 6 and 12). Taken together, it is clear that ranibizumab has an additional treatment effect also in BRVO and the subgroup analyses as well as published data indicate that this effect size is of clinical relevance.

Although ranibizumab had a 3-month advance start over laser, deferral of laser for 3-6 months is according to clinical practice and an effect of laser on VA is expected to be seen after a number of years. Since the majority of subjects (65%) had a duration of BRVO of less than 3 months, it is reassuring that the subgroup analysis of subjects that will not be treated with laser in clinical practice (i.e. < 3 months duration of BRVO) demonstrated a convincing effect of ranibizumab (9-11 letters over sham).

Overall, the effect of ranibizumab has been demonstrated also taking the spontaneous improvement and the 3-month deferral of laser into account. Thus, the lack of data evaluating the exact magnitude of the additive effect of ranibizumab is of minor concern.

CRVO

The design of this study also deviates from the CHMP advice since the sham-controlled period was not maintained over 12 months. As for BRVO, the masked and controlled design of the study was maintained (the originally randomised groups are still compared to each others) and the presented study is considered acceptable since no overall spontaneous improvement will be expected in this group of patients. In CRVO, ranibizumab-treated subjects (0.5 mg) gained in average 15 letters vs. 1 letter in the sham group ($p<0.0001$). As in the BRVO-study, after the first 6 months of the study, sham-treated subjects received active treatment. At month 12, previously sham-treated subjects had gained 7 letters (95% CI 4.5, 10.0) vs. 14 letters in the 0.5 mg ranibizumab-treatment group (95% CI 11.5, 16.4). Also in CRVO, a substantial proportion of ranibizumab-treated (0.5 mg) subjects gained ≥ 15 letters in VA; 48 % vs. 17 % in the sham group ($p<0.0001$). The outcomes of the key analyses were supported by sensitivity analyses and the secondary and exploratory endpoints were consistently in favour of ranibizumab-treatment. Overall, the outcome in subjects with CRVO is considered impressive. The effect was also maintained during the extension study with a slight drop in VA between month 12-15 (time for the first scheduled visit), where after VA remained stable. At 24 months, subjects that were previously sham-treated did not gain as much VA as those who were treated with ranibizumab from study start ending up with a difference of almost 10 letters in mean VA.

BRVO and CRVO

With preliminary data from the extension study, it has been confirmed that the treatment effect is maintained, at least over one additional year.

Neovascular iris complications, especially in CRVO, are serious and if left untreated, they almost always lead to increased IOP and secondary glaucoma. Importantly, the incidence of iris neovascularisation was numerically smaller (few subjects in total) in ranibizumab-treated subjects compared to those who were sham-treated during the first 6 sham-controlled months of the core studies. However, at 12 months, a slightly increased incidence was observed and even though few subjects developed these complications during the extension study and the MAH has committed to further address neovascular complications in the planned studies E2401 and E2402 as well as in the LUMINOUS study.

The treatment effect was consistent over subgroups, including the group of RVO patients with diabetes which is of importance since diabetes is a major risk factor for RVO. The majority of subjects had a duration of RVO of less than 3 months (BRVO 65%, CRVO 69%). However, a treatment effect was shown also in subjects with a longer duration of RVO. Although very small subgroups, it is also reassuring that subjects with retinal ischaemia seemed to have benefit of treatment, however, the limited experience in these subjects is now addressed in the SPC, section 4.4 and will be further investigated in upcoming studies.

During the extension period, subjects received in average 3 additional injections but the variability was large (range 0-11). Further, in BRVO, approximately 40% of subjects remained with a stable VA without any additional injections while the corresponding figures in CRVO were 20%. Thus, the

analyses of the, in total, 2-year data confirm the large variability in both subsets of RVO and also that there is a potential to withdraw treatment in some patients. The MAH intends to further address whether there is a potential to adapt the monitoring frequency to individual needs by assessing the predictive value of observed responses to treatment and for treatment interruption in the upcoming studies E2401 and E2402 (as well as in LUMINOUS). If appropriate, the outcome of the studies could be used to suggest new treatment recommendations. This approach was endorsed by the CHMP.

Uncertainty in the knowledge about the beneficial effects

Although it is considered that a clinically relevant effect of ranibizumab in subjects with BRVO has been sufficiently demonstrated, the submitted data does not address whether there is a sustained advantage of ranibizumab therapy over standard care in the long-term.

Even though data are reassuring, very few subjects with retinal ischaemia and a long duration (>12 months) of RVO were included in the studies, and some uncertainties with regards to the benefit in these groups remain. In the preliminary data from the extension study HORIZON, the rate of retinal ischaemia raised no new concerns. However, whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab remains unknown, and the currently available data only give limited assurance. Information on the limited experience in these subjects is now given in the SPC. However, information not to treat patients with signs of functional loss due to ischaemia is also warranted. In addition, it is considered of high importance that the MAH will make efforts to characterise the benefits of ranibizumab-treatment in the RVO population with ischaemic disease and the planned studies are acknowledged.

Risks

Demonstrated risks
Ranibizumab is given by IVT injections. The risks with such injections are characterised from the previous development programme including patients with AMD and DME and consists mainly of increased IOP that is, in most cases, non-serious, transient and can be managed. In addition, there are risks for intraocular inflammation, damage to intraocular tissues including increased risks for retinal tears and detachment as well as potentially sight-threatening endophthalmitis. Overall, the submitted studies indicate that the risks appear similar for patients with RVO and there were no significant new safety signals. Concomitant laser rescue and ranibizumab treatment did not appear to increase the incidence and severity of adverse events. Additionally, during the extension study (i.e. in subjects exposed to ranibizumab for a mean total of 2.2 years) ocular AEs were largely comparable with those previously reported. Although the incidence of retinal depigmentation or pigmentation and cystoid macular oedema increased with time, they were likely to be manifestations associated with the disease.

With regards to non-ocular AEs, as in the previously studied populations, the majority in this fairly representative population was mild to moderate in severity and few were suspected to study drug and/or ocular injection. An increased number of subjects experienced cardiac heart failure congestive and TIA (SAEs) compared to the first treatment year. However, in view of the significant co-morbidities (confirmed by disease history), the figures (including those regarding ATEs) are not considered alarming and are continuously monitored. The current information in section 4.4 and 4.8 of the SPC regarding risks with systemic VEGF-inhibition is relevant also for this group of patients.

The safety data set in RVO consists in total of 525 subjects treated with ranibizumab for up to one year and 413 subjects that have been treated in total for a mean of 2.2 years. Of these, 269 subjects have been treated for $\geq$ 2 years (occasional subjects up to 3 years). However the overall experience of IVT Lucentis in ocular disease has become quite large with exposures of ranibizumab in 3736 and 337 patients with AMD and DME, respectively and additional safety data will be generated in the registry study LUMINOUS as well as in the upcoming phase IIIb studies (studies E2401, E2402).

Uncertainty in the knowledge about the unfavourable effects

A remaining concern is the potential effect of ranibizumab on retinal ischemia. During the sham-controlled phase of the study (6-months), more untreated patients developed retinal ischaemia, while

during the 12 months, there was a tendency towards an increased number of patients with ischaemia of varying severity compared to baseline. At month 24, 6 % of BRVO- and 12 % and CRVO-patients that were non-ischaemic at baseline developed ischaemia. However, development of retinal ischaemia is part of the disease, e.g. there are reports that in subjects with CRVO, 8 to 34 % of non-ischaemic subjects convert to an ischaemic state over a number of years and the rate of conversion presented appears not to be alarming. Still, it remains unknown whether and to what extent retinal ischaemia and subsequent effects on vision are affected by ranibizumab and the currently available data only give limited assurance. The MAH has committed to further address this concern in the upcoming phase IIIb studies and in LUMINOUS as well as to follow this as detailed in the RMP.

There were occasional subjects experiencing a second event of RVO. As for retinal ischaemia, it is not known whether anti-VEGF therapy may increase the risk for recurrences of RVO even though the rate of recurrences was not alarming compared with the published rates. Although included in the RMP (covered by search terms), this should be further addressed in future studies.

With respect to the increased incidence of macular oedema observed during the extension period, the MAH has justified it as related to suboptimal monitoring and/or treatment. These differences have also been observed when macular oedema was reported as serious events. However, a potential relevant adverse event cannot be discarded. The post-approval planned studies should thus also address this potential issue.

The RVO is also a population with a high prevalence of glaucoma and IOP may be more closely monitored in ranibizumab-treated subjects with RVO. The MAH-proposed amendment of the SPC section 4.4 to include not only transient increases of IOP, but also to address that such sustained increases are considered of high relevance for the various Lucentis patient populations. The CHMP considered this to be acceptable.

Balance

Importance of favourable and unfavourable effects

Treatment with ranibizumab resulted in a clinically convincing and a statistically significant improvement of VA in subjects with RVO. However, the outcome of the non sham-controlled 6-months phase of the BRVO-study includes the outcome of the spontaneous resolution of the oedema as well as the effect of the delayed laser rescue. Although the exact effect size of ranibizumab cannot be concluded on, the subgroup analyses as well as published data support a clinically relevant magnitude of effect of ranibizumab that cannot be explained by a spontaneous improvement or the deferred rescue laser. The rapid onset of improvement of VA in ranibizumab-treated subjects with BRVO is also acknowledged and of value for the patient. In view of the poor prognosis in CRVO, the outcome in this subset of RVO considered compelling.

Treatment is not without risks; however the risks appear comparable to that previously identified in the AMD- and DME-populations. Besides risks for the manageable increase in IOP and injection-related damage to intraocular tissues, rare, but important and potentially sight threatening risks are those associated with retinal detachment and endophthalmitis. The most important potential, although not frequent, non-ocular risks in RVO-patients that already have major cardiovascular risk factors are those that are previously identified, i.e. risks that may be related to systemic VEGF-inhibition.

Benefit-risk balance

The natural progression of BRVO is very variable. Published data indicate that if untreated, one third to three quarters of patients may improve their VA over 2-3 years, but a limited proportion of subjects gain ≥ 10 letters of VA (<20% year1 to <40% year 3) a significant proportion (>20%) of subjects end up with a poor VA (<20/200) after 3 years. If treated with laser, there are no major short-term benefits with regards to an improved vision (proportion with a ≥10 letter gain year 1 ~35%), however, over 3 years, 65% gain ≥ 10 letters in VA although ≥ 10 % of subjects have a VA ≤20/200 (BVOS, 1984). The current study presented a ≥ 15 letter gain in 61 % of patients after 6 months and 4% with a VA≤20/200 at 12 months. Although the long-term effects of ranibizumab-treatment are not characterised, the rapid improvement (that was sustained over 12 months) in VA is considered to be of high importance. In comparison with laser photocoagulation, the risk profile in ranibizumab-treated

patients appears very different, and the immediate risk is estimated to be higher due to the IVT injection. However, laser photocoagulation destroys retinal vessels and causes scar tissue.

In CRVO, few patients gain significant VA, and with time severe vision loss is often developed. Laser treatment has not been shown to improve VA in CRVO, but during the last decade, a number of treatments have been investigated. Such treatments include vitrectomy and radial optic neurotomy (i.e. surgical procedures are associated with variable outcomes and not without major risks). With Lucentis, ocular drug-related AEs have been reasonably characterised, are manageable, but the potential risks regarding systemic effects of VEGF-inhibition remain. Also in CRVO, the effect of Lucentis on VA was maintained during the second year of treatment.

Recently, Ozurdex (dexamethasone implant) was approved to treat both subsets of RVO. Although no comparative data are available, 20-45% of subjects treated with Ozurdex increased their VA with ≥ 15 letters with no major differences between patients with BRVO and CRVO (EPAR).

The proposed posology for Lucentis in RVO is identical with that agreed upon for the treatment of DME (reason why the two posologies have been merged in the SPC) and supported since clear criteria when treatment is no longer recommended has been outlined in section 4.2 of the SPC. In addition, while in subjects with BRVO, laser treatment is usually withheld for a number of months to allow time for a spontaneous resolution of the oedema, the MAH further elaborated on when to initiate ranibizumab-treatment in these subjects. The MAH presented data that support an additional treatment effect of ranibizumab over sham also in subjects with a very short duration of BRVO, i.e. in subjects that also recovered significantly (≥10 letters between screening and study start) prior to treatment initiation. On the other hand, the (in total) 24 month HORIZON outcome indicate that subjects that were initially sham-treated appeared to catch up with those who received ranibizumab from study start. The data thus suggest that there is no need to initiate treatment immediately and even if treatment is delayed with 6 months, the average long-term outcome in VA is not negatively affected. However, it is clear that the time to improvement in VA is significantly more rapid in case of an early initiation of treatment. Overall, an approach to leave the decision whether to initiate treatment immediately or whether to "wait and see" up to the discretion of the physician is supported. As a basis for such decision-making, section 5.1 of the SPC has been amended.

Overall, the rapid and substantial improvement in VA, taking the reassuring safety profile into account, is considered to outweigh the risk whether there is a sustained advantage of ranibizumab therapy over standard care in the long term in BRVO. In CRVO, the benefits of treatment also outweigh the risks.

Collection of further data

The MAH will further evaluate the efficacy and safety of ranibizumab treatment in patients with visual impairment due to macular oedema secondary to RVO in the LUMINOUS study and in two additional, 24-month, Phase IIIb post-approval studies (CRFB002E2401 in CRVO and CRFB002E2402 in BRVO). These two studies are proposed to start Q4 2011.

In LUMINOUS, the safety reports will include all AEs, including the neovascularisation AEs. Interim reports will be submitted with PSURs, final evaluation within 9 months after end of the study.

In both Phase IIIb studies (E2401 and E2402) the MAH committed to the following:

- Efficacy evaluation of patients with or without retinal ischemia will include efficacy analyses in patient subgroups with different baseline ocular characteristics, including the presence or absence of retinal ischemia

- Safety evaluation of the retinal ischemia progression over time as well as adverse events in patients with or without presence of ischemia

- Safety evaluation of the neovascular complications based on the incidence rates of adverse events of ocular neovascularisation (cornea, iris, choroidal, retinal) - Patients with visual impairment due to macular oedema secondary to RVO will be included without limits of time since diagnosis of RVO

- In the second year, the study design will allow skipping a visit based on the VA stability criterion to evaluate the less frequent monitoring and further evaluate the rate of treatment withdrawal long term

Study E2402 will further evaluate the added benefit of laser standard of care treatment in patients with BRVO. Both E2401 and E2402 protocols will be submitted within 1 month after approval.

The strategy for studies E2401 and E2402 is endorsed. In addition, the MAH may consider differentiating between ischaemic and non-ischaemic subtypes of RVO while applying additional the methodologies, e.g. some of those used by Hayreh and co-workers (2011). The MAH may also consider not excluding subjects with DR (including DME) and RVO in the upcoming studies E2401 and E2402 as well as preparing for analysis of those in the LUMINOUS study.

See section 5 of this report for a tabulated summary of the commitments made by the MAH.

4.4. Product Information

Summary of Product Characteristics (SPC)

Attachment 1 to the CHMP Assessment report included a 'track changes' version of the adopted SPC detailing all the changes.

Labelling

Not applicable

Package Leaflet (PL)

The CHMP reviewed the submitted Results of consultation with target patient groups for the Lucentis Patient Information Leaflet, dated 29 July 2010. The MAH proposed a bridging to a user test carried out on the product Lucentis with indication wet age-related macular degeneration (AMD). The user test of the Lucentis wet AMD leaflet, performed in February/April 2006, was assessed and accepted by the CHMP. The MAH explained that the 'parent' (AMD indication) and the 'daughter' PL (DME + RVO indication) are almost identical in terms of design and layout, and are covering the same key safety messages. The only major differences are the different posology wording and the wording in the Healthcare Professional section due to the additional RVO indication. Because of their inherent similarities, reference to the successful outcome of the user test of the Lucentis 'parent PL' was acceptable to the CHMP and no separate user test for the Lucentis 'daughter PL' was considered to be required.

5. Conclusion

Based on the CHMP review of the data on efficacy and safety, the CHMP considers that the overall B/R of Lucentis in the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion is positive and the variation application EMEA/H/C/715/II/22 for the proposed change to extend the indication to include treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO), is approvable.

On 17 March 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.