EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21st October 2010
EMA/13901/2011
Human Medicines Development and Evaluation

Assessment Report
For
Lucentis
(Ranibizumab)

Procedure No.: EMEA/H/C/000715/II/0020

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Background information on the procedure

1.1. Submission of the dossier

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (EMEA/516566/2009) for the following condition:

- treatment of visual impairment due to diabetic macular oedema

on the granting of a (product-specific) waiver in

- all subsets of the paediatric population in the treatment of visual impairment due to diabetic macular oedema.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on April 2007 (with a follow up advice on January 2008). The Scientific Advice pertained to clinical aspects of the dossier. A pre-submission meeting was also held with the two Rapporteurs and the European Medicines Agency in June 2009. The following main comments were provided:

- *Central advice*
  The exploratory phase II programme is insufficient with respect to i) demonstration of efficacy in target population including the various patient subgroups, ii) recommendations of dose and treatment regimen, iii) study endpoints and duration of treatment and iv) safety assessment in diabetic population. A confirmatory phase III clinical programme is thus requested. In case of a single pivotal confirmatory study, the trial should be in line with the Guideline CPMP/EWP/2330/99. However, in case of very compelling results on visual acuity (not only statistically compelling, but clinically convincing as well), the study RESOLVE might however be considered as the basis for the approvability of the indication.
- *Pre-submission meeting*
  The Rapporteurs acknowledged that the results of the Phase II trial RESOLVE appeared highly interesting and may be considered compelling.

1.2. Scope of the variation and changes to the dossier

Scope of the variation: Extension of indication

Update of the SPC (sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3) to include information on treatment of visual impairment due to diabetic macular oedema (DME). Sections 1, 2, 3 and 4 of the Package Leaflet have been updated accordingly. In addition, Annex IIB was updated. The MAH also took the opportunity to update the contact details of the local representatives in Estonia, Slovenia, Finland, Cyprus and Latvia.

Product presentations affected: See Annex A to the Opinion

Dossier modules/sections affected: Modules 1, 2, 4 & 5.

Product Information affected: Summary of Product Characteristics, Annex II and Package Leaflet (Annex 1 - changes highlighted)

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur were:

Rapporteur: Dr Kristina Dunder

Co-Rapporteur: Dr Gonzalo Calvo Rojas

EMA Product Team Leader: Johan Holmgren

- The application was received by the EMA on 10 December 2009
- The procedure started on 20 December 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2010 (Annex 2). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2010 (Annex 3).
- During the meeting in March 2010 the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the applicant on 18 March 2010 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2010.
- The Rapporteurs circulated the Joint Updated Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 July 2010 (Annex 5).
- During the CHMP meeting on 22 July 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the MAH (Annex 6).
- The applicant submitted the responses to the CHMP list of outstanding issues on 20 August 2010.
- The Rapporteurs circulated the Final Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 October 2010 (Annex 7).
- During the meeting in October the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion on the Lucentis II/20 variation application on 21 October 2010. The MAH provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 October 2010 (Annex 8).

2. Scientific discussion

2.1. Introduction

Problem statement
DME is characterised by swelling of the central part of the retina, the macula, which mediates high-resolution visual acuity (VA). DME is one of the most sight-threatening complications in diabetes mellitus. DME has been estimated to occur in around 10% of the diabetic population, with a prevalence as high as 30% in patients with more than a 25-year history of diabetes.

The natural progression of DME leads to vision loss of two or more lines (≥ 10 letters) of VA within 2 years in approximately 50% of patients (Ferris, et al 1984). The current standard of care in the treatment of DME is laser photocoagulation that has been demonstrated to slow the progression of vision loss. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), a key study within the field of diabetic eye disease, patients with mild to moderate DR (diabetic retinopathy) and DME assigned to early focal laser photocoagulation were half as likely to lose 15 or more letters on the ETDRS visual chart compared to non-treated subjects. In the non-treated population, 8, 16 and 24 % lost ≥ 15 letters after 12, 24 and 36 months, respectively (ETDRS Report No 1, 1985). On average, laser photocoagulation stabilised VA over 3 years, however visual improvement was uncommon (<3%) which leaves 13% or more patients losing 15 or more letters after three years. (ETDRS Reports No 1, 1985; No 2, 1987 and No 9, 1991).

DME arises from breakdown of the blood retinal barrier (BRB), leading to leakage of fluid and plasma constituents in the surrounding retina, resulting in retinal oedema. It is well established through non-clinical as well as clinical data that vascular endothelial growth factor (VEGF) has a major role in the disruption of the BRB. For example, in the study by Vinores et al (1997), a dramatic increase in VEGF staining of the retina from diabetic patients compared to that observed in the normal human retina that contained little or no VEGF, was demonstrated. Elevated VEGF concentrations were also present in the vitreous humour of patients with diabetic retinopathy (Aiello et al., 1994).

Since VEGF appears to be a major endogenous mediator of macular oedema in diabetic retinopathy (DR), pharmacological therapy with ranibizumab to inhibit VEGF aims to address this underlying cause of the pathology. As a consequence, this effect is intended to translate into a reduction in vascular permeability and thus reducing macular oedema and subsequent loss of vision.

About the product
Ranibizumab (Lucentis) is a recombinant humanised IgG1 κ isotype monoclonal antibody fragment (Fab) that selectively binds and neutralises vascular endothelial growth factor (VEGF-A).

Lucentis was approved for the treatment of neovascular (wet) age-related macular degeneration (AMD) in January 2007. The approval was based on demonstrated efficacy in three pivotal clinical studies (MARINA-FVF2598g – 2 year data, ANCHOR-FVF2587g – 1 year data and PIER- FVF 3192g – 1 year data). Post approval, two year data from all pivotal studies confirmed the efficacy of the drug.
In wet AMD, Lucentis, 0.5 mg, is to be administered by intravitreal (IVT) injections with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase where a new injection should be given if the patient experiences a loss of > 5 letters in visual acuity (VA). Two doses, 0.3 and 0.5 mg, of ranibizumab were tested in the pivotal trials, the higher dose was found slightly more effective than the 0.3 mg dose.

In AMD, there was a significant proportion of patients experiencing important adverse events (AE), including intraocular inflammation, increased intraocular pressure (IOP) > 30 mmHg and occasional cases of endophthalmitis. However, these problems were considered to be outweighed by the efficacy of the study drug.

Development program
For the proposed additional indication, there are no changes related to quality. Since the new targeted population is considerably younger than the AMD-population, one reprotoxicity study in monkeys has been conducted.

To support safety and efficacy of Lucentis in the treatment of DME, the MAH have submitted 12-month data from one pivotal phase II clinical study, Study D2201 (RESOLVE). In addition, supportive safety data from diabetic patients from the AMD development programme (Table 1) and information from the published READ-2 study (Nguyen et al, 2009) was included in the dossier. Safety signals from a number of currently ongoing phase III studies are also evaluated, see Table 1.

As a response to the CHMP request for supplementary information, results of the pivotal study D2301 (RESTORE), a 12-months study exploring the efficacy and safety of ranibizumab 0.5 mg, laser photocoagulation or the combination of both in 345 patients with visual impairment due to DME was submitted.

Also in this submission, the selected dose is 0.5 mg ranibizumab in 50 μl, and as in AMD, treatment is to be initiated with monthly injections until VA and the macular oedema (e.g. optical coherence tomography (OCT) measurement) are stabilised for at least three consecutive months. Treatment should be resumed when clinically relevant changes, as measured by VA and/or macular oedema are attributable to activity of DME.

2.2. Quality aspects

Not Applicable

2.3. Non-clinical aspects

IVT administration of 0, 0.125 and 1.0mg/eye of ranibizumab to pregnant Cynomolgus monkeys
The Cynomolgus monkeys were each given bilateral IVT of 0 (vehicle control), 0.125 and 1.0 mg/eye, every 14 days from Day 20 until Day 62 of gestation neither affected prenatal loss, or placental appearance, nor caused embryotoxicity or teratogenicity. This could be expected due to the pharmacological mechanism of action of antibodies directed against VEGF and the importance of angiogenesis in follicle, corpora luteal and embryo-foetal development. The absence of ranibizumab-mediated effects on reproductive parameters might be due the low levels of ranibizumab in the systemic circulation reaching placenta and foetus following administration via the IVT route and/or to a limited transfer of a Fab-fragment across the placenta.

In the 1.0 mg/eye dose group, a more than dose dependent increase in serum C_{max} values was shown. The mean maternal C_{max} values ranged between 131-420 ng/ml (range 51-1,990 ng/ml in individual animals). The more than dose-dependent increase correlated with an increased immunoreactivity to ranibizumab which may have been mediated by a placental transport of ranibizumab to the foetus with anti-ranibizumab antibodies as carriers, however, the results of EFD study suggest that the antibody mediated transport of ranibizumab across the placenta is limited. Only one foetus, from a mother with unusually high maternal ranibizumab concentrations, showed measurable (230 pg/ml) levels of ranibizumab in the cord blood. The minor developmental findings in this male foetus were however within the same range as the controls and raise no concern.

As opposed to the observation in cynomolgus monkeys, anti-ranibizumab antibodies rarely developed in the clinical phase II and III studies performed for the patients with wet AMD and in the few cases where these antibodies were found, they did not seem to cause an increase in (total) serum ranibizumab levels and did not affect the systemic PK profile of ranibizumab. Hence, monkeys seem not to be predictive for humans in this respect.

The CHMP concluded that the information derived from this study is indeed instructive and gives some reassurance. However, the limited pharmacokinetic data from patients with DME indicated that in case of a worst case clinical exposure (mean C_{max} 8.5 ng/ml while a single subject had a C_{max} of 58 ng/ml), the exposure margin to the mean C_{max} values obtained in the monkey study ranged from 0.9 – 7-fold. Thus, there is no safety margin. Since VEGF inhibition has a potential to adversely affect the embryo-foetal development, the lack of a safety margin in case of a worst case clinical exposure warranted further changes to section 4.6 and 5.3 of the SPC. The MAH accepted the CHMP request and updated section 4.6 and 5.3 accordingly (see section 3.7 of this report).

The CHMP considered that the MAH had appropriately justified the lack of an Environmental Risk Assessment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of dose-response and main clinical studies

Table 1 - Clinical studies of ranibizumab in DME indication

Study No.	Study Objectives	No. Treated	Study Duration	Treatment arms	Ranibizumab regimen*
Completed DME studies					
D2201 RESOLVE	Efficacy and safety	151	12 months	• Ranibizumab 0.3 mg and/or 0.6 mg (6 mg/ml) • Ranibizumab 0.5 mg and/or 1.0 mg (10 mg/ml) Sham	prn
D2301 RESTORE **PIVOTAL STUDY**	Efficacy and safety	345	12 months	• Ranibizumab 0.5 mg • Laser • Ranibizumab 0.5 mg + Laser	prn
Supportive safety data in AMD patients with diabetes		**Safety population Ranibizumab (control)**			
A1201 EXTEND I	Safety and efficacy	Diabetic: 9 Non-diabetic: 38	12 months	• Ranibizumab 0.5 mg	monthly
A2302 EXCITE	Safety and efficacy	Diabetic: 10 Non-diabetic: 108	12 months	• Ranibizumab 0.5 mg	quarterly
FVF3689g SAILOR	Safety	- Cohort I Diabetic: 170 Non-diabetic:1039 - Cohort II Diabetic: 267 Non-diabetic:1655	12 months	• Ranibizumab 0.5 mg	prn
FVF2587g ANCHOR	Efficacy and safety	Diabetic:25 (23) Non-diabetic:115(120)	24 months	• Ranibizumab 0.5 mg • Verteporfin	monthly
FVF2598g MARINA	Efficacy and safety	Diabetic: 34 (25) Non-diabetic:205(211)	24 months	• Ranibizumab 0.5 mg • Sham	monthly
FVF3192g PIER	Efficacy and safety	Diabetic: 8 (6) Non-diabetic: 53 (56)	24 months	• Ranibizumab 0.5 mg • Sham	quarterly
Ongoing DME studies		**No treated (planned)**	**Duration (results expected)**		
D2301E1 RESTORE Extension	Long-term safety	(320)	24 months (Q2 2012)	• Ranibizumab 0.5 mg	prn
D2303 REVEAL	Efficacy and safety	(390)	12 months (Q2 2011)	• Ranibizumab 0.5 mg • Laser • Ranibizumab 0.5 mg + Laser	prn
FVF4168g RIDE	Efficacy and safety	382	36mo (Q2 2012)	• Ranibizumab 0.5 mg • Ranibizumab 0.3 mg • Sham	monthly
FVF4170g RISE	Efficacy and safety	377	36mo (Q2 2012)	• Ranibizumab 0.5 mg • Ranibizumab 0.3 mg • Sham	monthly

*prn regimen refers to study specific dosing regimens for individualised treatment.

2.4.2. Pharmacokinetics and Pharmacodynamics

Pharmacodynamics
No specific pharmacodynamic studies have been performed. 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 retinal vessels in DME or choroidal vessels in AMD.

Pharmacokinetics
No data evaluating the systemic exposure in DME patients was initially submitted. The MAH stated that pharmacokinetics studies in these patients were at the time of submission ongoing and data became available in the first half of 2010. Given the IVT route of administration, a limited absorption into the systemic circulation is expected. However, subjects with DME have highly permeable retinal vessels and likely a more viscous vitreous since they are younger and the release from the vitreous may necessarily not be the same in DME patients as in the previously studied AMD-population. In patients with AMD, the predicted C_{max} was 2.4 ng/ml while single C_{max} levels were higher (up to 38 ng/ml) and there were no indications that ranibizumab accumulated in serum over time after monthly IVT treatment of 0.5 mg. In subjects with RVO, the majority of serum concentrations ranged between 0.075 and 2 ng/ml, while some subjects had plasma levels between 4 to 6 ng/ml at 2 months. In view of the fairly low margin to where a systemic pharmacological action cannot be excluded, the CHMP concluded that data evaluating the systemic exposure of ranibizumab in patients with DME had to be submitted.

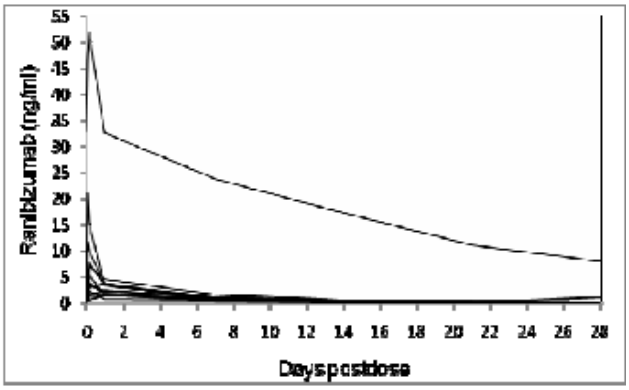
In the response the MAH stated that the PK evaluation as a part of the extension of the RESOLVE study (D2301E1) was still ongoing since all patients that had consented to participate in the study had not yet needed the next ranibizumab dose. Consequently, the MAH was not in position to provide the PK evaluation in DME patients as part of the response to the first request for supplementary information.

Together with the response to the list of outstanding issues, the MAH submitted the data from study RFB002D2301E, i.e. Pharmacokinetics of ranibizumab in patients with diabetic macular edema.

- DME population

As described, data evaluating the systemic exposure in 17 DME-patients from 11 centres was submitted as a sub-study of Study D2301 (Study RFB002D2301E1). Blood samples were obtained over one monthly dose interval before injection (not necessarily the first); 2, 4, and 24 hours post-injection; and once on days 7, 14, 21, and 28 post-injection (136 samples in total). Analyses were made with a validated ELISA with a lower limit of quantification (LLoQ) of 0.075 ng/ml. Non-compartmental PK parameters were derived with WinNonlin (Pharsight Corporation, Mountain View, CA, USA) and included Cmax, Tmax and AUC over a dose interval (AUCtau). Plots of the concentration-time data in DME patients were generated and compared to data from patients with AMD.

Of the 136 samples, 44 (32%) were below LLoQ, generally predose, day 21, and day 28 samples. The remaining 92 concentrations were quantifiable. C_{max} in most of these (78 concentrations) were <5 ng/ml and 14 concentrations were higher (7.0 – 51.8 ng/ml). The highest concentrations were observed at 2 to 4 hours after intravitreal injection and were generally < 5 ng/ml by 24 hours post-injection for the remainder of the dose interval (days 2 to 28). A single subject with a C_{max} of 58.1 ng/ml (15^{th} dose) had pre-dose concentration of 33 ng/ml and an end-of-dose-interval concentration of 7.8 ng/ml on day 28. Two additional subjects had a $C_{max} \geq 10$ ng/ml (11.6 and 21.0 ng/ml). AEs for the three subjects with the highest plasma levels gave no concern, see section 3.6 on clinical safety. For concentration-time profiles and PK parameters, see below.



Patient	Tmax (h)	Cmax (ng/ml)	AUCtau (ng.h/ml)
N	15	15	15
Mean	9	8.5	1219
SD	9	13.0	3103
Min	2	1.3	158
Median	4	3.6	409
Max	24	51.8	12425

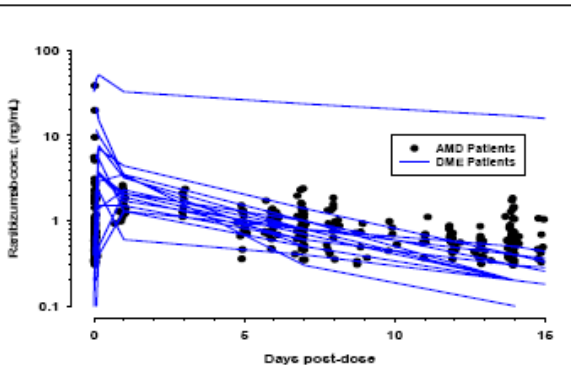
Table 2 Pharmacokinetic parameters. Two subjects had no quantifiable concentrations

Figure 1. Concentration-time profiles in DME patients

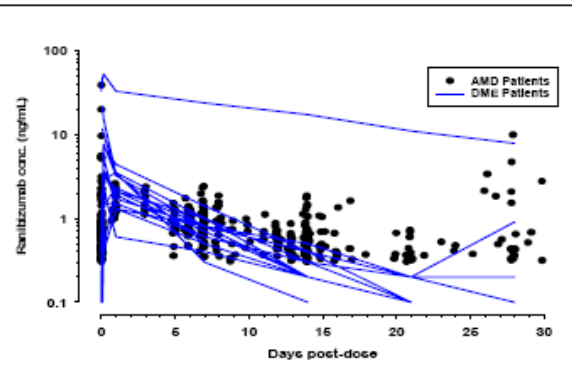
- Comparison between DME- and AMD-patients

In AMD-patients, blood samples were taken at 1 hour post-injection (DME 2 and 4 hours). The highest concentrations in both populations are on day 1 shortly after the IVT injection while serum concentrations were generally < 5 ng/ml 24 hours after the injection (**Figure 2**). There is a trend in the DME concentration data for a faster decline over the dose interval then in AMD patients (**Figure 2**, right).

Figure2. Comparison of concentration profiles in DME and AMD patients



Synoptic view of individual ranibizumab concentration-time profiles in DME patients (*lines*) with an overlay of data from AMD patients (*filled circles*). All patients received 0.5 mg Lucentis intravitreally.



As in left panel plotted over the full 28-day dose interval.

- CHMP conclusion on pharmacokinetics

Ranibizumab inhibited VEGF-induced human umbilical vascular endothelial cell proliferation with IC_{50} levels for the $VEGF_{165}$, $VEGF_{121}$, and $VEGF_{110}$ isoforms in the range of 21 - 57 ng/ml (the highest for the major isoform, $VEGF_{165}$). In view of the few DME-patients characterised (n=17, AMD: 228 subjects with measurable samples), the three subjects with plasma levels in this range represents a significant proportion of the analysed subset of patients. Although the elevations in plasma ranibizumab were transient and seemed to decline faster than in subjects with AMD, the highest plasma level so far has been reported from a DME-patient. In view of the few patients analysed, the analysis is highly uncertain, but may nevertheless indicate that a slightly higher systemic exposure in these patients cannot be excluded. This may represent an increased risk in subjects with DME, especially in cardiovascular high risk patients and in case of pregnancy. However, to best appreciate the risks in the cardiovascular high risk patients, the ongoing studies as well as the post-marketing safety study is considered by the CHMP as the most valuable and no additional PK-data were requested.

2.5. Clinical efficacy

2.5.1. Main studies

Study D2201- RESOLVE

Methods

A single, double-masked 12-months study, Study D2201, evaluating 151 patients (ranibizumab 6 or 10 mg/ml or sham; 1:1:1) was submitted by the MAH.

The study was originally designed as an exploratory study with a flexible design containing interim analyses to increase the probability to provide information for the future development, or to stop the trial early due to futility. Based on the results of the interim analysis, it was decided to have two parts for the analysis of efficacy, a pilot part (Group A – unmasked and evaluated in the interim analysis) and a confirmatory part introducing the new primary efficacy endpoint 'mean average change in visual acuity from baseline from Month 1 to Month 12' (Group B, remained masked). That endpoint was recommended in the CHMP scientific advice. The CHMP identified a few questions regarding methodological issues of the study, but no major issues. On the other hand, considering that a single, pivotal study was submitted, it must be confirmed without doubt that the study is flawless. Therefore, from an efficacy point of view, Group B was regarded as the single pivotal study (n=109), while Group A (n=42) will be regarded as an independent exploratory (and supportive) study. For analysis of safety, the results of the two groups are pooled. The CHMP considered that even though all data remained blinded during the preliminary review before proposing the amendments, a full description of the methodology used for changing the endpoint was to be provided. The MAH therefore provided further justification on why they integrity of the trial was maintained. The CHMP considered the MAH's explanation acceptable.

The study included patients with type I or II diabetes mellitus, with stable HbA1c ($\leq$ 12.0%), focal or diffuse DME with centre involvement (central retinal thickness, CRT $\geq$ 300 μm) and a BCVA score in the study eye between 73 and 39 letters ($\sim$ Snellen equivalent of 20/40 to 20/160). As patients with a significant retinal ischaemia were excluded from the study the CHMP questioned whether the limited study population can be extrapolated to the overall target population. The MAH responded by reiterating that 23 subjects with less central retinal ischaemia were included (in RESOLVE), of these 11 ranibizumab-treated subjects with ischaemia involving an enlarged foveal zone. The mean VA in these 11 subjects increased with 9.7 letters. In the 68 ranibizumab-treated patients with retinal ischaemia at baseline (moderate capillary loss to completely destroyed capillaries in the centre subfield) in RESTORE, there were no indications of an inferior treatment effect in these subjects (mean average change from baseline 6.3 letters, $p<0.0005$) compared to subjects with no retinal ischaemia (mean average change from baseline 5.9-7.2 letters). The CHMP considered that the data from 79 subjects with retinal ischaemia are reassuring and the treatment effect observed in the general population appears to be possible to extrapolate also to this subgroup of patients.

The study also included subjects that were to have a best corrected visual acuity between 73 and 39 letters and if both eyes were affected, the eye with the worse best corrected visual acuity was to be selected. It was not clear to the CHMP why in the inclusion criteria, the lower best corrected visual acuity limit in the untreated, fellow eye was allowed to be even lower (24 letters). The MAH was therefore asked to explain this. The MAH responded by explaining that if both eyes were affected and eligible for enrolment into the study (i.e. each having BCVA between 73 and 39 letters), the worse eye was to be chosen for randomization into the study, unless appropriate justification based on medical reason could be provided by the investigators. However, if the fellow eye was not concomitantly affected by the disease under study, and thus not eligible for study entry, another inclusion criterion was to be fulfilled. Under this inclusion criterion it was ensured that a patient with only one seeing eye is not enrolled in the study, thus the fellow eye BCVA needed to be a minimum 24 letters, in compliance with clinical research ethical requirements. This inclusion criterion explains why BCVA levels in the fellow eye could be lower than 39 letters. The CHMP accepted the MAH's explanation.

The first dose was 0.3 or 0.5 mg ranibizumab. Based on specified Optical coherence tomography criteria (OCT-criteria), the dose could be doubled to 0.6 or 1.0 mg at any time point after the first dose by doubling the injection volume. Dosing was initiated with 3 monthly injections, thereafter a flexible, VA and/or OCT-driven re-treatment approach was taken. In this study, a comparison vs. sham, and not laser treatment was performed. Since the disease course in DME – with and without laser

treatment - is well characterised through the ETDRS, the choice of sham as comparator in a 12 months study is accepted. Rescue laser photocoagulation was permitted.

The primary outcome measure was "the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 12 and the baseline level of BCVA". It was not clear to the CHMP how this had been calculated and the MAH was therefore asked to clarify. The MAH subsequently presented the algorithm for calculation of the primary endpoint. The endpoint as such is not questioned by the CHMP, although, in retrospect, considered conservative due to the continuous increase in VA over time.
Key secondary endpoints were "the change from baseline in BCVA at all post-baseline visits", the responder analysis categorising the "change from baseline in terms of gain or loss of 10 and 15 letters" and "the proportion of subjects with a VA of >73 or less than 39 letters". Additional secondary and exploratory endpoints assessed the central retinal thickness (CRT), severity of diabetic retinopathy (DR) and retinal perfusion.

Results

In this section, focus is on the confirmatory Group B and comparisons between the pooled ranibizumab groups and sham are made since several subjects have received the doubled dose at different time points. Thereafter, the effect/dose-relationship is assessed.

Demographics in the included patient population were essentially comparable across treatment arms. Very few subjects with type I diabetes were included in the study. Considering that vision loss in type I diabetes is predominantly due to proliferative complications of retinopathy, whereas vision loss in type II diabetes is mainly due to DME, it may not be possible to extrapolate the results from type II to type I diabetes. The range of the HbA1c was between 5 and 11, which is rather representative, albeit on the more controlled side, of the overall diabetes population. Importantly, only subjects without significant retinal ischaemia were included in study D2201. Published data indicate that treatment with VEGF-inhibitors may not be of benefit in this population and this needed to be further addressed. Finally, although no differences in outcome were observed between subjects that were naïve to laser photocoagulation vs. those who had previous laser treatment, it is important to further address this issue as patients with DME without visual impairment will be treated with laser and it should be confirmed that this does not affect the outcome of ranibizumab treatment. Bearing in mind the few included subjects, especially those with type I diabetes, the included population appears rather representative of a reasonably controlled diabetic target population without significant retinal ischaemia. With these limitations, it was not clear to the CHMP how the included population can be extrapolated to the overall target population.

In the response the MAH acknowledged that vision loss in type I diabetes is predominantly due to proliferative complications while in type II, mainly due to DME. However, in the RESOLVE study no subjects with Proliferative diabetic retinopathy (PDR) were included and the MAH argued that DME as such should not differ between the subgroups. This was acknowledged by the CHMP despite the limited number of subjects with type I diabetes. There was also evidence of a treatment effect in subjects with Type I diabetes. The CHMP did however request that information on the lack of experience in subjects with proliferative diabetic retinopathy should be added to the SPC, section 4.4 (see section 3.7 of this report).

As a response to the CHMP request for supplementary information, results of study D2301 (RESTORE), a 12-months study exploring the efficacy and safety of ranibizumab 0.5 mg, laser photocoagulation or the combination of both in 345 patients with visual impairment due to DME was submitted.

As for the previously discussed subgroups, with regards to metabolic control of the included patient population, there appears to be no important differences between subgroups. However, RESTORE included subjects with a stricter metabolic control (HbA1c≤ 10%) compared to RESOLVE (HbA1c≤ 12%) and there were no subjects with an HbA1c above 11 % in any of the studies. Consequently, The CHMP requested the MAH to include information on the lack of experience with in uncontrolled disease in section 4.4 of the SPC.

The primary and key secondary endpoints for the confirmatory part (Group B) are shown in Table 3 below.

Table 3 - Primary and key secondary endpoints (Group B). Full analysis set /(FAS) LOCF

		Ranibizumab			
Outcome	**Statistic**	**6 mg/ml**	**10 mg/ml**	**Pooled**	**Sham**
Mean <u>average</u> change from baseline from Month 1 to Month 12, VA (letters).		**N=37**	**N=40**	**N=77**	**N=32**
	Mean (SD)	9.4 (5.8)	6.0 (9.9)	7.6 (8.3)	1.2 (8.4)
Comparison vs. sham	Difference in LS means	8.2	4.8	6.4	
	95% CI for difference	(4.7, 11.6)	(0.4, 9.2)	(3.0, 9.9)	
	p-value[1]	<0.0001	0.0130	0.0002	
Mean BCVA (letters) change from baseline to Month 12					
	Mean (SD)	12.4 (6.8)	9.2 (11.9)	10.7 (9.8)	-0.4 (12.1)
Comparison vs. sham	Difference in LS means	12.8	9.6	11.1	
	95% CI for difference	(8.2, 17.4)	(3.9, 15.2)	(6.7, 15.5)	
	p-value[1]	<0.0001	0.0008	<0.0001	
Gain of ≥ 15 letters					
	n (%) (95% CI)	15 (40.5) (12.4, 49.9)	13 (32.5) (5.4, 40.8)	28 (36.4) (12.2, 41.7)	3 (9.4)
Gain of ≥10 letters	n (%) (95% CI)	27 (73.0) (34.5, 73.9)	21 (52.5) (13.2, 54.3)	48 (62.3) (26.3, 60.9)	6 (18.8)
	Treatment difference, p[1]	<0.0001	0.0039	<0.0001	

[1] CMH test (stratified)

In the confirmatory Group B (FAS with LOCF), there was a mean average improvement from baseline in the two ranibizumab-treated dose groups of 7.6 letters while the difference vs. sham was 6.7 letters, since a slight improvement was observed also in the sham arm. It is not unexpected that subjects being part of a study improve their metabolic control, thus stabilising their VA. The outcome based on the mean average change from baseline is clinically interesting, however not conclusive.

The effect on improvement of VA was rapid and there appears to be a continuous mean improvement in VA over time in the ranibizumab-treated groups. During the 12 months, it is not evident that a plateau has been reached. Therefore, the analysis of VA as an average mean between months 1-12 is highly conservative and the secondary endpoint analysing the "mean change from baseline" at 12 months is considered of equal importance. There was also a meaningful proportion of subjects that reached a good VA (>73 letters), 49 % in the pooled ranibizumab groups vs. 12 % in the sham-treated group (p=0.0002).

Sensitivity analyses of these endpoints supported the outcome of the primary analyses (FAS/LOCF). The outcome in the exploratory Group A was consistent with that of Group B. There appeared to be no major differences in VA outcome between the different subgroups, e.g. type of DME, baseline VA, retinal thickness, HbA1c and duration of DME. However, there were few subjects in many of the subgroups.

In the supportive Group A, 20% vs. 11% gained ≥ 15 letters (P=0.2191), 71 vs. 18 % gained ≥ 10 letters (p= 0.0061) and 0 vs. 18 % lost ≥ 10 and 15 letters in VA in the pooled ranibizumab groups and the sham group, respectively. Although the proportion of patients who gained >10 letters at Month 12 was threefold higher in the pooled ranibizumab group compared to sham, the CHMP requested the MAH to provide an analysis of the 10 letter increase in VA according to baseline VA levels (if the limited sample size allowed this) and a discussion on the clinical relevance of this increase depending on baseline VA.

Based on the MAH's response to this request, the CHMP considered that the results in the RESTORE study support those from the RESOLVE study. Nevertheless the clinical relevance of 10 letters gains was only discussed by the MAH in the context of the proportion of subjects that achieve this outcome. The clinical impact on other relevant clinical parameters, such as quality of life remains only partly supported since NEI-VFQ-25 gives some support, while other quality of life questionnaires do not.

Approximately 70% and 40% of ranibizumab treated subjects gained ≥ 10 and ≥ 15 letters, respectively in VA compared to 20 and 10 % in the sham group (Group B, pooled ranibizumab doses p=0.0002). Few patients treated with ranibizumab lost VA. After 12 months, 50% of ranibizumab-treated patients had a VA over 79 letters (>20/25) vs. 12% in the sham group. These effects are

considered to be of major importance for the patient and must be regarded as compelling according to the CHMP.

Treatment with ranibizumab also had a rapid and substantial effect on reducing the thickness of the oedema (Group B, $p<0.0001$ vs. sham). Overall, the exploratory parameters evaluated tended to show a benefit of ranibizumab over sham (numerically or statistically significant). Among the exploratory parameters, besides being an efficacy measure, the evaluation of loss of retinal capillaries (total areas of non-perfusion) is of importance also for the evaluation of safety since VEGF-inhibition has been hypothesised to negatively affect retinal perfusion. No increase in the areas of non-perfusion was evident during the 12 months treatment period. There appears to be no major differences in VA outcome between the different subgroups, e.g. type of DME, baseline VA, retinal thickness, HbA1c and duration of DME. However, few subjects have been part of the study and it is difficult to draw any definite conclusions. The observation indicated that the duration of DME did not appear to influence the effect of ranibizumab-treatment.

Selection of dose

The mean dose administered was stated by the MAH to be 0.61 mg (Groups A and B combined) and the MAH consequently applied for the 0.5 mg dose with a flexible dosing frequency in line with that recommended for wet AMD. Although it is recognised that all doses appear to have an effect on VA, an optimal (and the most clinically convincing) effect should be aimed for. Further evaluation of the choice of dose was therefore considered as needed by the CHMP.
The MAH therefore presented how the mean 0.6 mg dose was calculated and it was acknowledged that selection bias (different for mainly 0.5 mg – immediate responders and mainly 0.6 mg – non-immediate responders) could be introduced by addressing the two groups separately, and possibly also together. Only the 0.5 mg dose has been studied in RESTORE and the overall magnitude of effect was smaller than in RESOLVE (somewhat worse population and potentially also due to the more frequent dosing in RESOLVE). The comparison of the effect in the subgroup in RESTORE with inclusion/exclusion criteria matching those in RESOLVE (VA up to 73 letters, 78 in RESTORE; CRT > 300 μm – no limit in RESTORE) essentially reproduced the outcome of RESOLVE, although data is limited to the first months of the study due to the later differences in re-treatment criteria.

However, analysing the very few subjects in the RESTORE subgroup with a good baseline VA (>73 letters) with a concomitant limited oedema (< 300 μm), there was no benefit over ranibizumab vs. laser treatment. Until information on whether these subjects will have a potential future benefit of early ranibizumab treatment is available, these subjects should not be treated with IVT ranibizumab. The MAH was therefore requested by the CHMP to include a clear statement on this in the SPC. The MAH agreed and updted the product information accordingly.

Re-treatment criteria are based on either a decrease in VA or an increase in central retinal thickness. However, in the sought indication, an oedema alone is not an indication for treatment. This is an important distinction, since subjects with DME do not necessarily have a visual impairment. An evaluation on the outcome (primary and key secondary endpoints) of subjects that were re-treated due to an increased retinal thickness only vs. those who were re-treated due to visual impairment (with or without oedema) was considered to be needed by the CHMP together with a justification of the proposed re-treatment criteria in relation to the proposed indication "treatment of visual impairment due to DME".

The MAH therefore provided further analysis (although on limited data) which concluded that re-treatment based on an increase in CRT only while VA is stable does not give a significant benefit in terms of increased VA and that re-treatment should be based on decrease in VA and not on a decrease in VA or an increase in the oedema. Further, if an acutely increased CRT is not treated, it does not seem to lead to any short term (4 months perspective) negative effects on VA, however, subjects with a fairly good VA (>73 letters) and a CRT of > 300 μm, may lose VA if untreated. On the other hand, the few subjects with a VA ≥ 73 letters and a limited oedema (<300 μm) did not appear to have a benefit of treatment. The change to re-treat patient only based on loss of VA has been implemented in the SPC, section 4.2 as proposed by the MAH (see section 3.7). Until it has been shown that there is a long-term benefit on a future impairment of VA if treatment is based on an increase in CRT, this change is endorsed by the CHMP.

Study D2301- RESTORE

As a response to the CHMP request for supplementary information, results of the pivotal study D2301 (RESTORE), a 12-months study exploring the efficacy and safety of ranibizumab 0.5 mg, laser photocoagulation or the combination of both in 345 patients with visual impairment due to DME was submitted.

Methods

A randomised, double-masked, 12-months multicenter, laser-controlled Phase III study assessing the efficacy and safety of IVT ranibizumab (0.5 mg) as adjunctive to laser photocoagulation or as mono-therapy (+ sham laser) vs. laser (+sham IVT injection) in patients with visual impairment due to DME (n=345, 1:1:1).

Treatment with IVT ranibizumab or sham was initiated with one injection per month for three consecutive months (Day 1, Month 1 and Month 2) where after monthly administration was continued until vision was stabilised for 2 visits or reached > 84 letters (~20/20 Snellen equivalent). Treatment was re-initiated with monthly injections if there was a decrease in BCVA due to DME progression until the criteria above were fulfilled. These are criteria applicable to clinical practice and differ somewhat from RESOLVE where re-treatment was based on a decrease in VA and/or an increase in CRT. Laser treatment (active or sham) was administered at Day 1, 30 minutes prior to ranibizumab (or sham) and thereafter when needed according to the ETDRS protocol.

The study included a somewhat different patient population compared to RESOLVE, see main differences in inclusion/exclusion criteria in the table below.

Table 4. Main difference in inclusion/exclusion criteria RESOLVE vs. RESTORE

	RESOLVE	RESTORE
Inclusion		
Upper limit of VA (letters)	≤73	≤78
Macular thickness (μm)	≥300	No lower limit
Laser photocoagulation	Could be deferred 3 mo	Eligible for
HbA1c	≤12%	≤10%
Exclusion		
Retinal ischaemia (area μm/location from central macula)	≥500/≤500	No restrictions
Duration of DME	Max 9 months	No restrictions
History of stroke	No restrictions	Excluded

The outcome measures were similar to those in RESOLVE with "the difference between the average level of BCVA (letters) over all monthly post-baseline assessments from Month 1 to Month 12 and the baseline level of BCVA" as the primary endpoint. Key secondary endpoints were "the change from baseline in BCVA at all post-baseline visits", the responder analysis categorising the "change from baseline in terms of gain or loss of 10 and 15 letters (or had a BCVA of 84 letters)", "the proportion of subjects with a VA of >73 or less than 39 letters" and change in CRT. Exploratory analyses included severity of DR, retinal perfusion and quality of life questionnaires (e.g. NEI-VFQ-25).

Results

The conduct of the study was acceptable to the CHMP with relatively few discontinuations (12-13%) that were comparable between groups. The majority of these subjects withdrew consent or discontinued due to AEs.

Baseline characteristics were reasonably similar between treatment arms, but compared to RESOLVE, subjects had an average better baseline VA (+3 letters) and thinner macula (-40μm) and the study included also 68 ranibizumab-treated subjects with central retinal ischaemia. In addition, besides having an active PDR, there were no restrictions on the type or duration of DR which indicate a potential to include a population representative for the target population. Also in this study, there were few ranibizumab-treated subjects with type I diabetes (n=28). Although vision loss in type I diabetes is predominantly due to proliferative complications while in type II, mainly due to DME, no subjects with PDR (proliferative retinopathy) were included and therefore, the DME as such should not differ between the subgroups. There were also no subjects with uncontrolled diabetes, proliferative changes, prior history of TIA and very few ranibizumab-treated subjects with a previous stroke (only in RESOLVE, n= 5). The CHMP requested that this should be reflected in the SPC. The MAH accepted this and updated the product information accordingly (see section 3.7).

Extent of exposure: Subjects received in average 7 injections (ranibizumab or sham). The majority (>95%) received the three initial monthly injections with the remaining 4 during months 3-11. In the subgroups with a CRT < 300 μm fewer injections were given (5.4, 4.7 and 5.9 in the ranibizumab, ranibizumab + laser and laser arms, respectively) compared to those with a CRT of > 400 μm (7.5, 7.9 and 8.0 injections). Compared to RESOLVE, subjects received on average 3 fewer injections in RESTORE.

The mean number of active/sham laser administrations was similar for the groups. After patients received their fist active or sham laser at baseline, during months 3-11, patients received on average ~ 1 active/sham laser administration. Only two subjects appeared to receive additional rescue laser treatment, which is consequently not likely to have affected the overall outcome of the study.

Outcome: The outcome of the primary and key secondary endpoints is shown in **Tables 5-6** and **Figure 3** below.

Table 5 - Primary endpoint. Mean average change from baseline from Month 1 to Month 12, VA (letters). FAS / LOCF

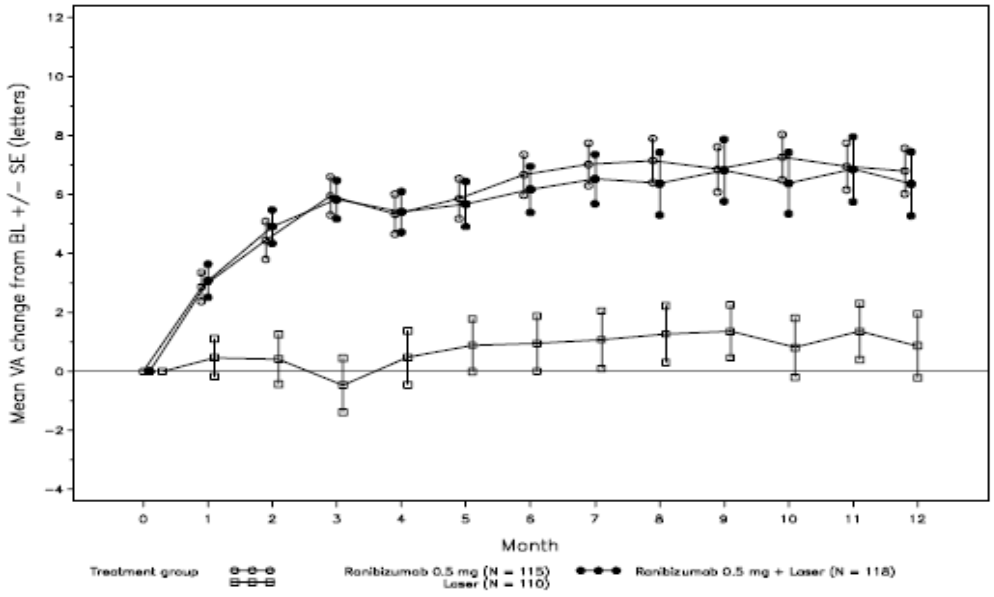
Parameter	Statistic	Ranibizumab 0.5 mg	Ranibizumab 0.5 mg + Laser	Laser
Full analysis set / LOCF[1] (PT Table 14.2-1.3)		**N=115**	**N=118**	**N=110**
	Mean (SD)	6.1 (6.4)	5.9 (7.9)	0.8 (8.6)
	95% CI for mean[2]	(4.9, 7.3)	(4.4, 7.3)	(-0.8, 2.4)
Comparison vs. laser	Difference in LS means[3]	5.3	4.9	
	95% CI for difference[3]	(3.5, 7.3)	(2.8, 7.0)	
	p-value[4]	<0.0001	<0.0001	

[1] LOCF - missing values replaced by the mean of the last observation observed before and the first observation after the missing time-point.
[2] Two-sided 95% confidence intervals (CI) based on t-distribution
[3] Differences in LS means vs. sham and the two-sided 95% CIs estimated from pair wise ANOVA (stratified).
[4] Stratified CMH test (two-sided)

Similar outcomes were observed independent on LOCF-imputation method or population (observed, PP) with p-values consistently below 0.0001. The outcome of the primary endpoint is statistically convincing and clinically interesting, however not compelling. Compared to study D2201 where the mean average change was 7.6 letters, this is somewhat lower.

The treatment effect in ranibizumab-treated groups was rapid and the increase in VA was statistically significant vs. laser from month 1 (see **Figure 3** below). VA appears to stabilise after 6-8 months. As in RESOLVE, the analysis of VA as an average mean between months 1-12 is considered conservative and the secondary endpoint analysing the "mean change from baseline" at 12 months is considered of equal importance.

Figure 3 Visual acuity of the study eye: Mean change from baseline over time, (FAS, LOCF)



BL = baseline; SE = standard error of the mean.

Table 6 Selected secondary endpoints (FAS/LOCF[1]).

Parameter	Statistic	Ranibizumab 0.5 mg	Ranibizumab 0.5 mg + Laser	Laser
		N=115	N=118	N=110
Mean BCVA (letters) change from baseline to month 12				
	Mean (SD)	6.8 (8.2)	6.4 (11.8)	0.9 (11.4)
	95% CI for mean[2]	(5.3, 8.3)	(4.2, 8.5)	(-1.3, 3.0)
Comparison vs. laser	Difference in LS means[3]	5.9	5.5	
	95% CI for difference[3]	(3.3, 8.5)	(2.5, 8.5)	
	p-value[4]	<0.0001	0.0004	
Categorised change in BCVA, change from baseline to Month 12				
	Gain of ≥ 10 letters or BCVA ≥ 84	43 (37.4)	51 (43.2)	17 (15.5)
	p-value[4]	<0.0001	<0.0001	
	Loss of ≥ 10 letters	4 (3.5)	5 (4.2)	14 (12.7)
	Gain of ≥ 15 letters or BCVA ≥ 84	26 (22.6)	27 (22.9)	9 (8.2)
	p-value[4]	0.0032	0.0021	
	Loss of ≥ 15 letters	1 (0.9)	4 (3.4)	9 (8.2)
Proportion of patients with BCVA > 73 letters at Month 12				
Baseline	Proportion (%)	19.8	16.1	15.3
Month 12	Proportion (%)	53.0	44.9	23.6
Comparison vs. laser	Difference in LS means[3]	29.4	21.3	
	95% CI for difference[3]	(17.3, 41.5)	(9.3, 33.3)	
	p-value[4]	<0.0001	0.0002	
Proportion of patients with BCVA <39 letters at Month 12				
Baseline	Proportion (%)	0.9	0.9	1.8
Month 12	Proportion (%)	0.9	3.4	5.5
Comparison vs. laser	Difference in LS means[3]	-4.6	-2.1	
	95% CI for difference[3]	(-9.2, 0.0)	(-7.4, 3.3)	
	p-value[4]	0.0652	0.3742	

n is the number of patients with a value at both baseline and the Month 12 visit.
[1] LOCF with carrying forward the last observed value
[2] Two-sided 95% confidence intervals (CI) based on t-distribution
[3] Differences in LS means vs. sham and the two-sided 95% CIs estimated from pair wise ANOVA (stratified).
[4] Stratified CMH test (two-sided).

As for the primary endpoint, the outcomes were consistent for the secondary endpoints in various sensitivity analyses. Overall, there was no difference between ranibizumab as monotherapy and ranibizumab in combination with laser treatment. Consequently, the data do not give any guidance on when a combination treatment would be needed.

Treatment with ranibizumab also had a rapid and substantial effect in reducing the thickness of the oedema.

In the VFQ-25 questionnaire, the mean change from baseline for the composite score and for subscales related to vision were in favour of ranibizumab and statistically different vs. laser (p varied between 0.0446 – 0.0005). Some improvement was also observed with regards to social functioning (4-5 units), but there was no effect on dependency or driving (p>0.05). The magnitudes of changes in vision related effects were numerically similar to the observed in the AMD-population.

With regards to mean change in VA from baseline, the absolute figures are lower than reported in study D2201 where the mean change from baseline was 10.7 letters. However, subjects in RESTORE had a somewhat better baseline VA (~3 letters) and a less affected retinal thickness compared to RESOLVE. Therefore, the subgroup analyses below are of particular interest. Further, subjects received, on average, 3 fewer injections of ranibizumab in this study compared to RESOLVE which may also have impacted the magnitude of the outcome but has to be weighed against a decreased risk with fewer injections.

There was a clinically significant proportion of subjects that gained ≥10 (~25% more than laser) and ≥15 (~15% more than laser) letters, but as for the mean change in VA, the size of the effect is smaller than in study D2201 (~44 and 27% more than laser). The proportion of subjects that had a VA of >73 letters (mean in ranibizumab groups 49%) is considered to be of clinical significance and comparable to the outcome in RESOLVE (49%). As in RESOLVE, very few subjects had a VA below < 39 letters at month 12.

The MAH also presented an additional analysis on RESTORE-subjects with RESOLVE-like inclusion/exclusion criteria which indicates, although data are limited, that the lower magnitude of effect in the RESOLVE study may have been affected by the better baseline VA/reduced retinal thickness.

Several subgroup analyses on for example, age, DME type, diabetes type, prior laser, presence of central retinal ischaemia, baseline BCVA, baseline CRT, blood pressure, HbA1c, duration of DME and combinations of more than one of these parameters were performed. Although few subjects were included in many of the subgroups and the data should be interpreted with caution, in none of the groups, laser treatment was superior to ranibizumab or the combination of ranibizumab and laser and in most subgroups, the treatment effect of ranibizumab ± laser in terms of mean average change in VA was statistically significant vs. laser.

Subjects with a lower baseline VA (≤60 letters) had a larger benefit than subjects with a better initial VA, while subjects with a baseline VA of >73 letters or those with a thin central retina (<300 μm) had a smaller and non-statistically significant (p>0.05) benefit of ranibizumab. However, no firm conclusion can be made, since there was a "ceiling effect", i.e. a number of subjects with a relatively good baseline VA reached a VA of ≥ 84 letters. Importantly, subjects with retinal ischaemia at baseline had a benefit of ranibizumab (±laser) compared to laser (p<0.0006). Subjects with a VA of > 73 letters and diffuse DME responded poorly in terms of number of letters improvement and the combination with ranibizumab and laser resulted in a deterioration of VA (-1.9 letters). However, few subjects were evaluated and in this subgroup, the loss of VA was even more pronounced in the laser treatment group (-4.7 letters). On the other hand, subjects with a CRT < 300μm together with a baseline VA of > 73 letters did equally well as those treated with laser. Although a very limited number of subjects were included in this subgroup, considering the risks with the IVT injection, the benefit/risk may not be positive for this subset of patients. Until information on whether these subjects will have a potential future benefit of early ranibizumab treatment is available, information on the lack of benefit for these subjects has been included in the SPC (see section 3.7).

Factors like baseline blood pressure, cholesterol, triglycerides and HbA1c did not reveal any relevant differences in outcome. Improvement in VA was observed independent on the type of diabetes (Type I or II), however, borderline significant (p=0.0532 for ranibizumab as monotherapy, p= 0.0352 for the combination), but few subjects were analysed.

Choice of dose, dosing frequency and criteria for re-treatment

The choice of the 0.5 mg dose has been substantiated in the RESOLVE study and is further supported by the study from DRCRnet (see *supportive studies* below).

Data support the treatment and re-treatment criteria, i.e. treatment is to be initiated with monthly dosing and continued until VA is stable (on treatment) for three months, where after monthly monitoring of VA should determine whether re-treatment (based on a decrease in VA) should be resumed. Data does however not give support to a re-treatment based on an increase in CRT only while VA is stable, since such patients do not experience a significant benefit in terms of increased VA. Further, if an acutely increased CRT was not treated, it did not seem to lead to any short term (4 months perspective) negative effects on VA. Since additional analyses suggest that if assessing the response over 2 months, there is a risk of missing a relevant number of patients that gain an increase in VA between month 2 and 3. However, very few subjects with a stable VA seem to have a potential for an even later gain (after 3 months) in VA. Thus, the treatment criteria are in the opinion of the CHMP reasonably described in the SPC, section 4.2. Further, subjects that experience an initial decrease in VA are not necessarily non-responders (as observed in AMD-patients) since those on ranibizumab-treatment experienced a gain in VA with continued treatment, while laser-treated subjects did not. However, since DME is a chronic problem, and anti-VEGF therapy is likely to be required in an ongoing fashion, the MAH will evaluate a more practical regimen when additional information on the persistence of the effect and treatment-free intervals is available from planned and ongoing studies.

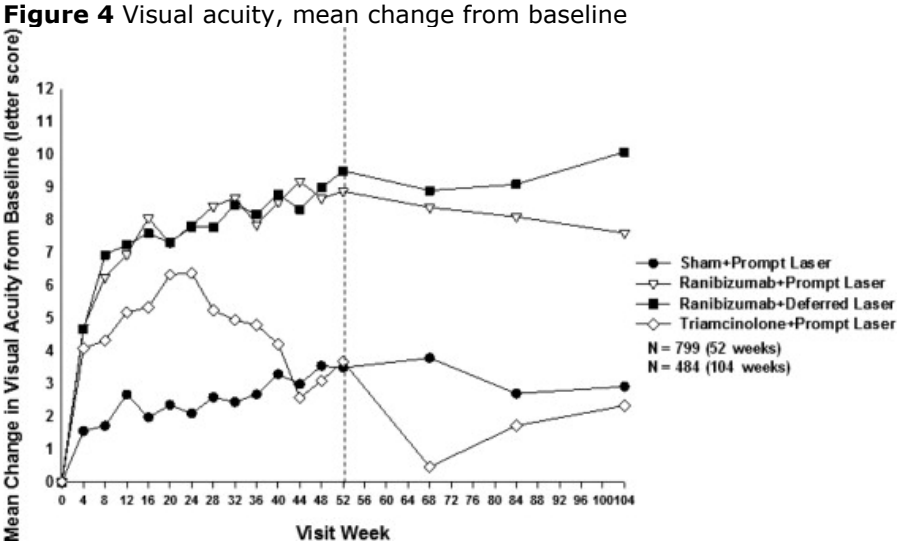
It is not known whether there are patients with specific characteristics that may not respond to treatment and it is not fully clear when treatment should be discontinued. The MAH was therefore requested to commit to collect and analyse data related to specific initial treatment responses (both stability and decline) to identify possible non-responders from all ongoing studies including previously finished studies.

Supportive studies

The published study by Nguyen et al., compared ranibizumab (0.5 mg) with focal/grid laser or the combination of ranibizumab and laser treatment (n=126, 1:1:1). At month 6, the mean gain in BCVA was significantly greater in the ranibizumab group (+7.2 letters, P = 0.01) compared with the laser group (+0.4 letters), and the group combining ranibizumab and laser (+3.8 letters), the latter not statistically different from the other groups. Improvement of ≥15 letter occurred in 8/37 (22%) in the ranibizumab group compared with 0/38 (0%) in the laser group (P = 0.002) and 37/40 (8%) in the combination group. Excess foveal thickness was reduced by 50%, 33%, and 45% in the three groups. The study supports the use of ranibizumab to improve VA in DME, also when comparing to best standard of care, i.e. laser treatment. However, the combination of ranibizumab and laser appeared to reduce the effect of ranibizumab as monotherapy.

A recently published supportive study from DRCRnet (Diabetic Retinopathy Clinical Research Network (2010), Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. Ophthalmology. 2010 Apr 22. [Epub ahead of print]) included a patient population very similar to that included in the submitted studies. After 1 year, there was a 9 letter increase vs. baseline for both groups that received ranibizumab (0.5 mg, n=187 and 188/group) after 8-9 injections and 2-3 laser treatments, while laser (n=293) and triamcinolone (TA)+laser-treated subjects (n=186) had a 3-4 letters increase. Responder data in ranibizumab-treated groups were similar to those obtained in RESOLVE (~30% ≥ 15 letter increase, ~50% ≥ 10 letter increase vs. baseline). The study is of particular interest, since there is a significant proportion (57%) of patients that have been followed for 2-years so far. During the 2nd year, subjects received 2-3 ranibizumab-injections, and ranibizumab + prompt laser had a mean increase in VA of 7 letters while the increase in the ranibizumab + deferred laser arm had a 10 letter increase from baseline (sham+laser +2 letters, TA+laser +1 letter) with maintained responder data, see Figure 4 below.

Figure 4 Visual acuity, mean change from baseline



2.6. Clinical safety

Safety assessments included monitoring and recording all adverse events (AEs), serious adverse events (SAEs), VA, concomitant medications, ophthalmic examinations (slit lamp biomicroscope and indirect ophthalmoscope), IOP, vital signs and laboratory parameters. Risks (potential safety issues) that have been previously identified in the treatment of AMD were also analysed in the RESOLVE and RESTORE data set.

Patient exposure

In RESOLVE and RESTORE (primary safety data set), 335 subjects have been administered ranibizumab (0.3 – 1 mg), whereof the majority on 0.5 mg and 120 subjects have been given the combination with laser photocoagulation. Subjects have been given in average 7-10 injections during 12 months.

Additional supportive safety data:

- AMD subjects with diabetes: 523 ranibizumab-treated diabetic (and 3213 ranibizumab-treated non-diabetic) subjects from controlled and non-controlled AMD trials. The 523 diabetic patients had received, in average 5 injections of 0.5 mg ranibizumab for up to two years.
- SAEs from 4 ongoing, still masked trials in DME (see Table 1).
- 6-month safety data in 84 DME patients treated with ranibizumab and ranibizumab + laser are provided from the published READ-2 study (Nguyen et al.).
- In total, 799 DME patients from the DRCRnet study whereof ~ 200 have been treated with ranibizumab (+ laser) for 2 years has been provided.

The primary safety data set is still rather limited, especially with regards to treatment with the combination of ranibizumab and laser. In this data set demographics and disease characteristics were fairly well balanced at baseline. Including the elderly subjects with AMD and diabetes adds to the information on age-related risk factors in this group. On the other hand, considering that the general DME patient is younger, additional number of years with IVT treatment may be expected. Although of support, in the AMD studies, the mean duration of diabetes was shorter than in the RESOLVE and RESTORE studies and these patients have not been diagnosed with DME and due to their shorter duration of diabetes, the AMD subjects likely have a less advanced disease. The 2-year data from the published study from DRCRnet is of high interest as the reporting of AEs from this study is very detailed.

Adverse events

Ocular Adverse Events

No increased frequency or any new ocular AEs compared to those already listed in the SPC, section 4.8 were identified. AEs were predominantly of mild or moderate severity. The frequency of AEs in RESTORE was markedly lower than in RESOLVE and there were no indications that the combination of ranibizumab and laser resulted in an increased frequency or more serious AEs.

Table 7 - RESOLVE Ocular adverse events by preferred term regardless of relationship to treatment ("All" ≥3.0% in any group) and AEs suspected by the Company as treatment (drug/injection)-related ("Susp") in Dataset A (Study D2201; safety set)

	Ranibizumab						**Sham**	
	6 mg/ml		**10 mg/ml**		**Pooled**			
	N=51		**N=51**		**N=102**		**N=49**	
Preferred term	**All**	**Susp**	**All**	**Susp**	**All**	**Susp**	**All**	**Susp**
Total	38(74.5)	27(52.9)	42(82.4)	34(66.7)	80(78.4)	61(59.8)	28(57.1)	17(34.7)
Conjunctival haemorr.	10(19.6)	10(19.6)	13(25.5)	13(25.5)	23(22.5)	23(22.5)	7 (14.3)	7 (14.3)
IOP increased	6 (11.8)	6 (11.8)	15(29.4)	14(27.5)	21(20.6)	20(19.6)	1 (2.0)	-
Eye pain	9 (17.6)	8 (15.7)	9 (17.6)	8 (15.7)	18(17.6)	16(15.7)	10(20.4)	8(16.3)
Vitreous floaters	1 (2.0)	1 (2.0)	8 (15.7)	7 (13.7)	9 (8.8)	8 (7.8)	0 (0.0)	-
Lacrimation increased	4 (7.8)	2 (3.9)	4 (7.8)	3 (5.9)	8 (7.8)	5 (4.9)	0 (0.0)	-
Visual acuity reduced	1 (2.0)	-	6 (11.8)	-	7 (6.9)	-	5 (10.2)	-
Foreign body sensation	3 (5.9)	3 (5.9)	3 (5.9)	2 (3.9)	6 (5.9)	5 (4.9)	1 (2.0)	1 (2.0)
Corneal disorder	3 (5.9)	-	2 (3.9)		5 (4.9)	-	0 (0.0)	-
Eye pruritus	3 (5.9)	2 (3.9)	2 (3.9)	2 (3.9)	5 (4.9)	4 (3.9)	2 (4.1)	-
Vitreous haemorrhage	1 (2.0)	1 (2.0)	4 (7.8)	2 (3.9)	5 (4.9)	3 (2.9)	0 (0.0)	-
Cataract	2 (3.9)	-	2 (3.9)	-	4 (3.9)	-	1 (2.0)	-
Eye irritation	3 (5.9)	3 (5.9)	1 (2.0)	1 (2.0)	4 (3.9)	4 (3.9)	1 (2.0)	1 (2.0)
Ocular hyperemia	2 (3.9)	1 (2.0)	2 (3.9)	2 (3.9)	4 (3.9)	3 (2.9)	4 (8.2)	4 (8.2)
Retinal disorder	3 (5.9)	-	1 (2.0)	-	4 (3.9)	-	0 (0.0)	-
Vision blurred	2 (3.9)	1 (2.0)	2 (3.9)	2 (3.9)	4 (3.9)	3 (2.9)	2 (4.1)	-
Visual disturbance	3 (5.9)	-	1 (2.0)	-	4 (3.9)	-	1 (2.0)	-
Blepharitis	2 (3.9)	-	1 (2.0)	-	3 (2.9)	-	2 (4.1)	-
Conjunctival hyper.	2 (3.9)	2 (3.9)	1 (2.0)	1 (2.0)	3 (2.9)	3 (2.9)	3 (6.1)	1 (2.0)
Corneal erosion	1 (2.0)	-	2 (3.9)	-	3 (2.9)	-	1 (2.0)	-
Endophthalmitis	1 (2.0)	1 (2.0)	2 (3.9)	2 (3.9)	3 (2.9)	3 (2.9)	0 (0.0)	-
Lenticular opacities	1 (2.0)	-	2 (3.9)	-	3 (2.9)	-	0 (0.0)	-
Retinal exudates	2 (3.9)	-	1 (2.0)	-	3 (2.9)	-	4 (8.2)	-
Retinal haemorrhage	1 (2.0)	-	2 (3.9)	-	3 (2.9)	-	3 (6.1)	-
Vitreous detachment	1 (2.0)	-	2 (3.9)	-	3 (2.9)	-	1 (2.0)	-

Conjunctivitis	1 (2.0)	-	1 (2.0)	-	2 (2.0)	-	4 (8.2)	2 (4.1)
Macular edema	2 (3.9)	-	0 (0.0)	-	2 (2.0)	-	2 (4.1)	-
Eyelid edema	1 (2.0)	-	0 (0.0)	-	1 (1.0)	-	3 (6.1)	3 (6.1)
Retinal aneurysm	1 (2.0)	-	0 (0.0)	-	1 (1.0)	-	2 (4.1)	-
Conjunctivitis allergic	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-	2 (4.1)	-

The majority of the events were regarded as mild to moderate in severity and related to the ocular injection. There were no major differences in AEs when doubling the dose by doubling the injection volume.

Table 8 RESTORE Ocular adverse events by preferred term regardless of relationship to treatment ("All" ≥3.0% in any group) and all AEs suspected by the Company as treatment (drug/injection)-related ("Susp") (Study D2301, Safety set)

	Ranibizumab 0.5 mg N=116 n (%)		**Ranibizumab 0.5 mg + Laser N=118 n (%)**		**Laser N=111 n (%)**	
Preferred term	**All**	**Susp**	**All**	**Susp**	**All**	**Susp**
Total	49 (42.6)	28 (24.3)	51 (42.5)	27 (22.5)	43 (39.1)	20 (18.2)
Eye pain	13 (11.3)	12 (10.4)	10 (8.3)	10 (8.3)	12 (10.9)	11 (10.0)
Conjunctival hyperemia	9 (7.8)	8(7.0)	6 (5.0)	4(3.3)	6 (5.5)	6(5.5)
Conjunctival hemorrhage	8 (7.0)	4(3.5)	10 (8.3)	7(5.8)	0 (0.0)	2(1.8)
Foreign body sensation in eyes	5 (4.3)		8 (6.7)		2 (1.8)	
Diabetic retinal oedema	4 (3.5)		3 (2.5)		4 (3.6)	
Visual impairment	4 (3.5)	3(2.6)	2 (1.7)	2(1.7)	1 (0.9)	0(0.0)
Eye discharge	3 (2.6)	3(2.6)	4 (3.3)	3(2.5)	1 (0.9)	1(0.9)
Cataract	2 (1.7)		6 (5.0)		7 (6.4)	
Conjunctivitis	2 (1.7)		5 (4.2)		3 (2.7)	
Eye pruritus	2 (1.7)		2 (1.7)		5 (4.5)	
Lacrimation increased	2 (1.7)	2(1.7)	4 (3.3)	3(2.5)	1 (0.9)	1(0.9)
Vision blurred	2 (1.7)		3 (2.5)		5 (4.5)	
Diabetic retinopathy	1 (0.9)		6 (5.0)		3 (2.7)	
Visual acuity reduced	0 (0.0)		1 (0.8)		4 (3.6)	
Eye irritation		2(1.7)		0(0.0)		2(1.8)
Eyelid oedema		2(1.7)		3(2.5)		1(0.9)
Vision blurred		2(1.7)		1(0.8)		2(1.8)
Corneal erosion		1(0.9)		1(0.8)		0(0.0)
Eye pruritus		1(0.9)		1(0.8)		2(1.8)
IOP increased		1(0.9)		1(0.8)		0(0.0)
Ocular hyperaemia		1(0.9)		1(0.8)		0(0.0)
Photophobia		1(0.9)		1(0.8)		0(0.0)
Ocular discomfort		0(0.0)		1(0.8)		2(1.8)

In RESOLVE, the increase in Intraocular pressure (IOP) was more frequent in subjects administered 1 mg of ranibizumab. This appeared not to be due to the doubled injection volume and may be due to the higher amount of drug. However, none of the cases were regarded as severe as they consisted mainly of transient increases in conjunction with the IVT injection that can be managed. Nevertheless, the 0.5 mg dose is applied for, and in RESTORE there were very few cases of increased IOP and no such serious event.

In RESOLVE, there was also a higher frequency of corneal disorders or cataracts/ lenticular opacities. They were all non-serious, therefore, only the investigator (judged as not related), not the MAH, assessed the causality. Further, in RESOLVE, only single cases of corneal erosions were reported. Taken the studies together, this is considered by the CHMP to be adequately reflected in the SPC. To note is that the frequency of intraocular inflammation is substantially lower than in the AMD trials.

There appeared to be no new risks in subjects with significant central retinal ischaemia (68 subjects included in RESTORE, 15 with less significant and less central ischaemia in RESOLVE). Ocular AEs from the 6-months READ-2 study revealed no additional risks (no SAEs were reported).

In the study from DRCRnet major AEs (available data up to 2 years, n=484 in total) included 2 cases of endophthalmitis (ranibizumab-treated), retinal vein occlusion (1 each in laser and the two ranibizumab arms, 3 in the triamcinolone arm) and increased IOP (similar in ranibizumab and laser 6-9%, 42% in triamcinolone (TA) arm). Additional AEs reported were similar as previously identified for ranibizumab.

Non-Ocular Adverse Events

In both studies, the most frequently reported non-ocular events were nasopharyngitis and hypertension. The majority of non-ocular AEs were mild to moderate in severity and few were suspected to be related study drug and/or ocular injection. Besides an increased frequency of urinary tract infection in ranibizumab (monotherapy)-treated subjects in RESTORE (3.5%), there were no new AEs. The SPC has been updated accordingly. There were no major changes in HbA1c and blood pressure during the course of the study. However, the CHMP considered that there is potential signal of AEs related to systemic VEGF-inhibition, also in this population, as shown in **Table 9** and **10**. This is considered by the CHMP to be adequately reflected in the updated SPC provided by the MAH (see section 3.7).

Table 9 – RESOLVE Number (%) of patients with adverse events potentially related to systemic VEGF inhibition by category and preferred term (Safety set, Study D2201)

	Ranibizumab			
Preferred Term	**6 mg/ml N = 51 n(%)**	**10 mg/ml N = 51 n(%)**	**Pooled N = 102 n(%)**	**Sham N = 49 n(%)**
Total	5 (9.8)	9 (17.6)	14 (13.7)	6 (12.2)
Arterial thromboembolic events	0 (0.0)	3 (5.9)	3 (2.9)	2 (4.1)
Myocardial infarction	0 (0.0)	1 (2.0)	1 (1.0)	1 (2.0)
Retinal artery occlusion	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)
Transient ischaemic attack	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)
Hypertension	4 (7.8)	5 (9.8)	9 (8.8)	5 (10.2)
Hypertension	3 (5.9)	4 (7.8)	7 (6.9)	4 (8.2)
Blood pressure increased	1 (2.0)	1 (2.0)	2 (2.0)	1 (2.0)
Non-ocular haemorrhage	1 (2.0)	1 (2.0)	2 (2.0)	0 (0.0)
Epistaxis	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)
Haemorrhage	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)

Table 10 RESTORE Number (%) of patients with adverse events potentially related to systemic VEGF inhibition by category and preferred term (Safety set, Study D2301)

	Ranibizumab 0.5 mg N=115 n (%)	**Ranibizumab 0.5 mg + Laser N=120 n (%)**	**Ranibizumab pooled N=235 n (%)**	**Laser N=110 n (%)**
Total	14 (12.2)	7 (5.8)	21 (8.9)	11 (10.0)
Arterial thromboembolic events	6 (5.2)	1 (0.8)	7 (3.0)	1 (0.9)
Angina pectoris	2 (1.7)	0 (0.0)	2 (0.9)	0 (0.0)
Pulmonary embolism	2 (1.7)	0 (0.0)	2 (0.9)	1 (0.9)
Cerebrovascular accident	1 (0.9)	0 (0.0)	1 (0.4)	0 (0.0)
Myocardial infarction	1 (0.9)	1 (0.8)	2 (0.9)	0 (0.0)
Hypertension	9 (7.8)	6 (5.0)	15 (6.4)	9 (8.2)
Non-ocular haemorrhage	1 (0.9)	0 (0.0)	1 (0.4)	1 (0.9)
Epistaxis	1 (0.9)	0 (0.0)	1 (0.4)	1 (0.9)
Proteinuria	1 (0.9)	1 (0.8)	2 (0.9)	0 (0.0)

In the limited PK sub-study, 3 subjects had plasma levels over 10 ng/ml, i.e. a level where systemic VEGF-inhibition may be relevant. The subject with the highest VEGF-levels (52 ng/ml) experienced a mild hypertension 28 days after the last (15^{th}) dose of ranibizumab and 56 days after plasma sampling. The event was regarded as non-related to treatment. No AEs possibly related to VEGF-inhibition were observed in the two remaining subjects.

In the study from DRCRnet (484 subjects, 2-years treatment), the frequency of CV events during the 2 years (defined according to the Antiplatelet Trialists' Collaboration) was lowest in the ranibizumab-treatment arms (5%) vs. 12 and 6 % in the laser and TA arms, respectively.

Serious adverse event/deaths/other significant events

Ocular Serious Adverse Events
Three cases of endophthalmitis were identified in RESOLVE. Although no events of endophthalmitis were observed in RESTORE, considering the still relatively limited safety database in subjects with DME, there is a need for the continued monitoring, since the diabetic population is known to be more susceptible to infections. None of the SAEs in RESTORE were considered related to treatment.

Non-Ocular Serious Adverse Events
In RESOLVE; there were, in total 8 (7.8%) and 5 (10.2%) SAEs in the pooled ranibizumab dose groups and in the sham group, respectively. Events of particular interest included a case of MI (10 mg/ml ranibizumab) and an allergic reaction. In RESTORE, SAEs occurred in 13.9% of the patients in the ranibizumab arm, 8.3% of the patients in the ranibizumab + laser arm, and in 11.8% of the patients in the laser arm and were mainly related to the following System organ classes: cardiac disorders (3.5% of the patients in the ranibizumab arm, 1.7% ranibizumab + laser, 4.5% laser) and infections and infestations (3.5%, 0.8%, and 4.5%, respectively). It is somewhat surprisingly that the frequencies of AEs and SAEs were higher in the ranibizumab treatment arm compared to the combination arm. This may be by chance; however, only 4 subjects experienced SAEs suspected as treatment-related (3 in ranibizumab monotherapy arm, 1 in the combination arm). Events of interest were coronary artery occlusion (n=1), pulmonary embolism (n=2) and arterial thrombosis limb (n=1), but the frequencies are not considered as alarming by the CHMP.

One death (urinary bladder cancer) was reported in RESOLVE study and in RESTORE, seven patients died during the study, two in each ranibizumab treatment arm and three in the laser treatment arm. None of the deaths was considered by the investigator to be related to study treatment, however, in the ranibizumab treatment arms they were due to cardiopulmonary failure, cerebrovascular accident, MI and renal failure and in the laser arm due to cardiac disorder/failure and diabetic foot. For some of the events, a relation with VEGF-inhibition cannot be excluded. On the other hand, this is a population with major cardiovascular co-morbidities for which the issue will be monitored through the RMP and further addressed in the post-marketing study where subjects at risk (including previous cardio/cerebrovascular events, hypertension etc) will be included.

In the ongoing DME studies, so far, the total number of fatal events is similar as in the AMD-studies. In the READ-2 study, there was one death due to cerebral vascular accident. The patient had a history of cardiovascular disease and death occurred six weeks after first injection of ranibizumab. The event was not considered suspected related to study drug. In the DRCRnet study, the frequency of the vascular deaths after 2 years was highest in the laser treatment group (5%) vs. 2 % in the ranibizumab treatment groups.

Adverse event profile compared to the AMD-population with and without diabetes

In the primary data set, an increased frequency of urinary tract infection (RESTORE – ranibizumab monotherapy) and the higher frequency of increased IOP (RESOLVE, 1 mg ranibizumab) and endophthalmitis (RESOLVE only) were observed. The signal regarding increased IOP and endophthalmitis in diabetes patients from RESOLVE was not supported from data in diabetic subjects with AMD, nor is the high frequency of endophthalmitis supported from the ongoing studies (3 events in 1104 patients). Compared to subjects with AMD, in the DME-studies subjects appears to have a lower frequency of intraocular inflammation.

Importantly, ranibizumab-treatment did not appear to increase the incidence of retinal blood flow deterioration in the diabetic AMD subjects or in the subjects with retinal ischaemia included in RESTORE. However, there are still few subjects with significant retinal ischaemia that has been treated. This is further addressed in this report as part of the assessment of the RMP (see section 3.8).

Although there was no difference in diabetic and non-diabetic subjects with regards to non-ocular SAEs the signal with regards to AEs potentially related to VEGF-inhibition is relevant also for subjects with DME.

Safety in special populations

No influence of intrinsic factors (age, gender, blood pressure, HbA1c, duration of diabetes, time since diagnosis of diabetes, time since diagnosis of DME and concomitant insulin medication) was observed. There were no pregnancies during the study and there is no previous experience. The potential of ranibizumab to affect embryo-foetal and/or placental development pregnant cynomolgus monkeys did not reveal any adverse effects. However, the limited pharmacokinetic data from patients with DME indicated that in case of a worst case clinical exposure (mean C_{max} 8.5 ng/ml while a single subject had a C_{max} of 58 ng/ml), the exposure margin to the mean C_{max} values obtained in the monkey study ranged from 0.9 – 7-fold. Thus, there is no safety margin.

There is also no, or very limited, experience of ranibizumab-treatment of diabetic subjects with uncontrolled disease, proliferative DR, history of stroke or TIA. The MAH was therefore requested by the CHMP to address this in the SPC. The MAH subsequently updated section 4.4 of the SPC, which was considered acceptable by the CHMP (see section 3.7).

Immunological events

In RESOLVE, three subjects had positive post baseline immunoreactivity results to ranibizumab. No additional evaluation has been performed in RESTORE. The CHMP considered that there are no important differences between AMD and DME-subjects with regards to immunoreactivity.

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. There is no information available on concomitant intraocular medication in the dossier provided by the MAH. The efficacy and safety of subjects with previous laser treatment as well as concomitant treatment with laser photocoagulation and ranibizumab was similar as in subjects without prior laser treatment and those on ranibizumab as monotherapy although the experience is limited. This was considered by the CHMP to be adequately reflected in the updated SPC submitted by the MAH (see section 3.7).

Discontinuation due to adverse events

In the RESOLVE and RESTORE studies, there were relatively few discontinuations (from the study or from treatment) due to AEs.

Post marketing experience

The post-marketing data is analysed in the most recent Lucentis PSUR (No.6), submitted on 23 September 2009, covering the time period from 1-Jan-2009 to 30-Jun-2009. Based on the assessment of post marketing safety information received during the PSUR 6 period, as well as cumulative data, the positive benefit-risk profile of Lucentis in treating patients with neovascular AMD remains.

2.7. Product Information

Only changes to the SPC of particular importance are discussed in this section of the report. A detailed description of all changes is included as attachment 1 to this report. The included changes are underlined and deletions are shown as ~~strikethrough~~.

Summary of Product Characteristics

Section 4.1

Lucentis is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD) (see section 5.1).
- the treatment of visual impairment due to diabetic macular oedema (DME) (see section 5.1).

Section 4.2

Based on the discussion of the submitted data as described in detail previously in this report the CHMP finally agreed on the following text to be included in section 4.2 of the SPC:

Treatment of visual impairment due to DME
In visual impairment due to DME, the recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml.

Treatment is given monthly and continued until maximum visual acuity is achieved i.e the patient's visual acuity is stable for three consecutive monthly assessments performed while on ranibizumab treatment. Consequently, if there is no improvement in visual acuity over the course of three injections, continued treatment is not recommended.

Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed when monitoring indicates loss of visual acuity due to DME. Monthly injections should then be administered until stable visual acuity is reached again for three consecutive monthly assessments (implying a minimum of two injections). The interval between two doses should not be shorter than 1 month.

Lucentis and laser photocoagulation in DME
There is some experience of Lucentis administered concomitantly with laser photocoagulation (see section 5.1). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

Pending the outcome of the planned and ongoing studies, the MAH should, if warranted, suggest further updates to this section of the SPC. There are no relevant data to specify when treatment should be discontinued in case of an ongoing loss during the "resumed" treatment phase. The CHMP therefore suggested that this is left for the treating physician to decide upon.

Section 4.4

More detailed information on the risk for developing hypersensitivity has been included as follows:

As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis. Since there is a potential for an increased systemic exposure in subjects with DME, an increased risk for developing hypersensitivity in this patient population cannot be excluded. Patients should also be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation.

In addition, two paragraphs on the limitations on the data for the treatment on populations that has not been sufficiently studied (included patients with type I diabetes) have been included as follows:

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, proliferative diabetic retinopathy, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Lucentis in diabetic patients with an HbA1c over 12% and uncontrolled hypertension.

There are no data on safety in the treatment of DME patients with prior history of stroke or transient ischaemic attacks. Since there is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors caution should be exercised when treating such patients (see section 4.8).

Section 4.6

This section has been updated to reflect the data in cynomolgus monkeys. Recommendations have also been included on the time recommended for waiting after the last treatment before conceiving a child (i.e. to wait at least 3 months). In case of a worst case exposure, DME-subject may have a systemic exposure close to the exposure margins in the reprotoxicity study. The CHMP therefore considered that this justifies a more stringent recommendation. The amended wording would be as follows:

Women of childbearing potential/contraception in females
Women of childbearing potential should use effective contraception during treatment.

Pregnancy
For ranibizumab no clinical data on exposed pregnancies are available. Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development (see section 5.3). The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Breast-feeding ~~Lactation~~
It is ~~not~~ unknown whether Lucentis is excreted in human milk. Breast-feeding is not recommended during the use of Lucentis.

Section 4.8

This section has been updated to reflect the safety data accumulated for the DME population (see attachment 1).

Section 5.1

Several paragraphs have been added to this section. The information included is mainly in relation to results from studies in DME with a focus on the confirmatory phase III study (see attachment 1).

2.8. Pharmacovigilance

Detailed description of the Pharmacovigilance system

Not Applicable

Risk Management Plan

Ongoing safety concerns
Initial analysis by the MAH of safety data did not reveal any new important identified and important potential risks apart from the previously identified risks in the AMD-population. However, during CHMP assessment, vitreous haemorrhage was noted as an imported identified risk. Additionally, several areas of missing information concerning treatment with ranibizumab in DME-patients were identified. The list of ongoing safety concerns has been amended. The resulting list is shown below (Table 11).

Table 11 - Ongoing safety concerns

Important identified risks	
	Hypersensitivity reactions
	Retinal pigment epithelial tear
	Endophthalmitis
	Retinal detachment
	Retinal tear
	Traumatic cataract
	Intraocular inflammation
	Intraocular pressure increase
	Vitreous haemorrhage

Important potential risks	
	Hypertension
	Non-ocular haemorrhage
	Proteinuria
	Myocardial infarction (MI)
	Non-MI Arterial thromboembolic events (ATEs)
	Venous thromboembolic events
	Deterioration of retinal blood flow including CRAO
Important missing information	
	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. ROP)
	Long-term safety beyond two years
	Intraocular antibody formation
	Long term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti- VEGF injections (DME only)
	Effects of Lucentis on the deterioration of retinal blood flow including macular ischemia (DME only)
	Systemically unstable patients (DME only)
	Age greater than 75 (DME only)
	Ethnicities other than Caucasian (DME only)

In the updated RMP version 7, ATEs were separated into MI events and non-MI ATEs.

Pharmacovigilance Plan

The long-term extension of the RESTORE study (visual impairment in DME) has been included in the list of planned pharmacovigilance actions concerning all important identified and potential risks and important missing information regarding long-term safety beyond 2 years and intraocular antibody formation. The aim of the study is to evaluate ocular and non-ocular adverse events over an additional two years of ranibizumab treatment following one year of treatment in the core study. In addition, data from the extension study will be combined with the core study data to evaluate ocular and non-ocular adverse events over a cumulative three-year period.

Evaluation of the need for a Risk minimisation plan

The MAH proposed that the risk minimisation measures already in place for the AMD-indication are adequate and no additional measures are planned in relation to the DME-indication.

The MAH considered that the established routine risk minimisation activities for hypersensitivity reactions, retinal pigment epithelial tear, retinal detachment, retinal tear, intraocular inflammation, IOP increase, vitreous haemorrhage, hypertension, non-ocular haemorrhage, proteinuria, MI, non MI-ATEs, VTEs, deterioration of retinal blood flow including CRAO, systemic AEs related to bilateral treatment and overdose, AEs related to off-label use, long-term safety beyond 2 years, intraocular antibody formation, long term effects on the progression of diabetic retinopathy including the potential effect on diabetic retinopathy of stopping periodic anti- VEGF injections (DME only), effects of Lucentis on the deterioration of retinal blood flow including macular ischemia (DME only), systemically unstable patients (DME only) and age greater than 75 (DME only) are sufficient.

For endophthalmitis and traumatic cataract additional risk minimisation activities comprise an educational plan for healthcare professionals and patients.

CHMP discussion and conclusion on the RMP

The CHMP considered the RMP to be in accordance with the Vol. 9A guideline.

The safety population for the sought extension of the indication to include treatment of visual impairment due to DME initially consisted of patients enrolled in the RESOLVE study (CRFB002D2201). In addition, patients with diabetes enrolled in the randomised clinical trials for AMD have been identified and safety data analysed. The diabetic patients in the AMD-trials were older and had a shorter duration of diabetes compared to the patients enrolled in the RESOLVE study. Patients with DR were excluded from the AMD clinical trials. Although the safety populations have different characteristics, important information can be collected from the diabetic-AMD-group. The supportive data from this patient population has been included in an updated RMP (annex 7). Additionally, the RMP has been amended with data from the recently-completed visual impairment due to DME in the RESTORE study. However, there is limited information with regards to treatment of elderly subjects

with DME and subjects that have an unstable disease. In addition, there is a lack of information regarding treatment of other ethnicities than Caucasians. This is now reflected in the RMP and partly in the SPC, except for the limited experience in treatment in subjects >75 years with DME.

Overall, the ocular and non-ocular AE pattern was similar between the DME patients and the AMD population. The CHMP endorsed that ongoing routine and additional risk minimisation measures are extended to include the DME-indication.

The risk of endophthalmitis in the DME patients in the RESOLVE study was 10 times higher than expected from the AMD-studies. Safety data from the pooled diabetic population in the AMD-studies do not indicate an increased risk of endophthalmitis in diabetes patients. In the now available data from the RESTORE study there were no reports of endophthalmitis. The pooled incidence of endophthalmitis for patients with DME in controlled trials after one year is 3/217 (1.4%) on ranibizumab monotherapy, which is comparable to the incidence in AMD (1.6%).

Patients with a history of chronic renal failure or kidney transplant were excluded from the RESOLVE study. Advanced DR often occurs simultaneously with renal microangiopathy and proteinuria. In the study by Hirai 2008 (Am J Ophthalmol 145;700) in patients with clinically significant macular oedema, nephropathy was present in 49% of patients with type 1 diabetes, 21% in type 2 diabetes patients without insulin and 30% in type 2 patients with insulin treatment. There is a potential class-effect of anti-VEGF-drugs inducing proteinuria due to an effect on the renal glomerular capillaries. Results from the RESOLVE and RESTORE studies concerning protein levels in urine have been presented. There is no immediate indication of increased risk of proteinuria in diabetic patients treated with ranibizumab. Proteinuria is included in the RMP as an area of missing information and will be closely monitored and reported in future PSURs.

In contrast to the high levels of VEGF found in the eyes of diabetic patients with retinopathy, low levels of VEGF and its receptors are found in the myocardium, resulting in inadequate collateral formation. These findings suggest that diabetic patients might be more prone to the development of myocardial ischemia if circulating VEGF is blocked. The CHMP considered that this issue is adequately discussed in the updated RMP.

Diabetic retinopathy (DR) is characterised by vascular changes giving rise to progressive reduction of retinal blood flow. Eventually, new blood vessels might be formed within the eye (Proliferative Diabetic Retinopathy - PDR). Vascular changes in peripheral retina can occur simultaneously with DME. Patients with PDR were not enrolled in the RESOLVE study. Results from the RESTORE study indicate that the treatment with ranibizumab does not have a negative impact on the progression of the overall DR over the first treatment year. However, the long-term effect on progression of DR is not known. This was an area of missing information which has now been included in the RMP.

There is the potential of off-label use in patients with DME without visual impairment. The proposed indication and subsequent labelling and summary of educational materials support the use of ranibizumab "in visual impairment due to DME" only. The proposed update of the educational material was endorsed by the CHMP. The MAH has committed to submit this material for review.

From available data, it seems that there are no identified safety concerns if ranibizumab is administered concomitantly with laser or in patients who previously have received laser. However, data are limited and the relation of IVT ranibizumab treatment to conventional focal/grid laser treatment in the long-term remains an area of missing information.

The effect of ranibizumab treatment on the progression of overall diabetic retinopathy and on the development of macular ischemia should be addressed in the ongoing long-term studies (36-month studies RIDE and RISE and the RESTORE 24-month extension study).

User consultation

No full user consultation with target patient groups on the package leaflet has been performed. The MAH did however submit a bridging report making reference to the user test results of the Lucentis wet AMD Package Leaflet carried out in April 2006. The bridging report submitted by the MAH was considered acceptable by the CHMP.

2.9. Benefit-Risk Balance

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 DME or choroidal vessels in AMD. Therefore, available data from the AMD-population adds to the basic understanding of the drug. This is of relevance also for understanding the treatment of DME.

A statistically convincing effect of ranibizumab in the treatment of visual impairment due to DME has been demonstrated in one phase II (RESOLVE) and one phase III study (RESTORE). Sufficient data support the choice of dose, 0.5 mg, the flexible dosing frequency, the re-treatment and stopping criteria that are based on assessment of VA. The effect of ranibizumab was consistently superior to that of sham treatment or laser photocoagulation. The effect of ranibizumab as monotherapy or if combined with laser treatment was similar and consistent across analysis of primary and secondary analyses independent on analysis population.

In the pivotal, RESTORE study, the mean average improvement in VA (+6 letters- similar in both ranibizumab treatment arm, vs. +1 letter in the laser therapy group) as well as the proportion of subjects that gained ≥ 10 (~40%) or ≥15 (23%) letters (16 and 8 % in the laser group) in VA was lower than in RESOLVE (8 letter mean average improvement, vs. no change in the sham group, 62 and 36 % gained ≥ 10 and ≥15 letters vs. 19 and 9% in the sham group).

In ranibizumab-treated eyes, the increase in VA was rapid and continued over 6-12 months, thus the analysis of VA as an average mean over time is highly conservative. Therefore, the key secondary endpoint analysing the "mean change from baseline at 12 months", is considered of equal importance. After 12 months treatment, the mean improvement in VA was 11 letters vs. no change in the sham group (-0.4 letters) in RESOLVE and 7 (similar in both ranibizumab treatment arm) vs. 1 letter in the laser treatment arm in RESTORE.

Subjects with a lower baseline VA had the most benefit from treatment, but due to a potential ceiling effect for subjects with a better baseline VA (some subjects reached ≥84 letters, ~20/20 Snellen equivalents in VA), no overall conclusion can be drawn. Therefore, the lower overall gain in VA in RESTORE may not be surprising since the population in this study had a better baseline VA (+3 letters) and less CRT (-40μm) compared to subjects in RESOLVE. This is supported by additional analysis, although limited, on RESTORE-subjects with RESOLVE-like inclusion/exclusion criteria.

Even though the improvement in VA alone is not significant, the proportion of subjects that gain ≥10 and ≥15 letters/reach the 'ceiling' of 84 letters is considered to be of clinical relevance. The proportion of subjects that had a VA of >73 letters (~50%) or < 39 letters (1-3%) was also clinically significant and comparable to the outcome in RESOLVE. Overall, it is considered that the meaningful benefit of ranibizumab indicated from RESOLVE has been confirmed in the RESTORE study and that this effect is relevant for the majority of patients in the target population.

Many subgroups were of limited size. However, with one exception, subgroup analyses indicate a benefit of ranibizumab (±laser) over laser. The very limited subgroup of subjects with a rather good baseline VA (>73 letters, 20/40 Snellen equivalent) together with a limited DME (<300 μm) had no additional benefit of ranibizumab-treatment. The observations that the duration of DME, previous laser photocoagulation or the presence of significant retinal ischaemia did not appear to influence the effect of ranibizumab-treatment is important, both from the patient's view and from the perspective of clinical practice. Few subjects with type I diabetes were included in the two studies. In type I diabetes, vision loss is predominantly due to proliferative complications while in type II, mainly due to DME. However, in this study no subjects with proliferative retinopathy were included, only subjects with DME and DME as such should not differ between the subgroups. Furthermore, there was evidence of a treatment effect of ranibizumab also in subjects with Type I diabetes.

The presented studies are limited to 12 months and the long-term effects on VA are not known. However, the recently published study from DRCRnet (similar population as in the submitted studies) has 2-year data available from ~200 subjects treated with Lucentis and laser photocoagulation (377 such patients treated for 1 year). During the 2nd year, subjects received 2-3 additional ranibizumab-injections while essentially maintaining the 12-month gain in VA (9 letters).

Overall, from a clinical perspective, the demonstrated effect appears convincing since, even with laser treatment (the only currently available treatment) no significant improvement of VA is to be expected in this population.

Uncertainty in the knowledge about the beneficial effects.

The persistence of the effect of ranibizumab, i.e. treatment-free intervals, of ranibizumab needs to be further explored to evaluate a more practical dosing regimen. Although treatment with ranibizumab has been the first treatment that significantly improves VA over 12 months in subjects with visual impairment due to DME, the long term effects of treatment is not known. A long treatment may be expected since the current target population is 10-15 years younger than the previously studied AMD-population. Although some support is given by the recently published DRCRnet study, additional long-term data is needed. Such data are to be generated in planned and ongoing studies.

Ranibizumab may be used as monotherapy or in combination with laser photocoagulation. However, it is not known if an early, and maybe not lasting, gain in VA due to ranibizumab-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. On the other hand, since there were no additional treatment benefits with the combination, taking the (long term) destructive effects as well as benefits of laser into account, it remains unknown which population that may have a benefit of the combination treatment and how the combination is best used.

Risks

Demonstrated risks
Ranibizumab is given by IVT injections. The risks with such injections are characterised in the previous development programme including patients with AMD also apply to DME. The risks consist 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 are fairly similar for patients with DME and no new adverse events were reported.

With regards to non-ocular AEs, as in the AMD-population, the majority were mild to moderate in severity and few were suspected to study drug and/or ocular injection. The most important adverse events in DME patients were the previously identified AEs potentially related to systemic VEGF-inhibition. Despite a significant co-morbidity associated with diabetes, the incidence of these AEs was low and not higher than reported for AMD-patients, nor were there any new non-ocular AEs besides urinary tract infection. Supportive data from four ongoing studies in DME have, so far, also not indicated any notable differences with regards to severe AEs compared to what is already known.

One death was reported in RESOLVE and 7 in RESTORE. None were considered by the investigator to be related to study treatment. However, for some of the events, a relation to a systemic VEGF-inhibition cannot be excluded. On the other hand, this is a population with major cardiovascular co-morbidities and, in the ongoing DME studies, the frequency of fatal events reported so far is similar to the one in the AMD-studies.

Potential risks
Overall, ranibizumab has been administered to 312 patients with DME (77 subjects in RESOLVE and 235 subjects in RESTORE) which is limited. Of these, 120 have received the combination with laser. Importantly, there appeared to be no additional risks in subjects with significant retinal ischaemia. However, few subjects have been evaluated. There is also no, or limited, information on any potential risks for, amongst others, ATEs if treating subjects with proliferative diabetic retinopathy, uncontrolled disease, previous stroke or TIA. The experience in other ethnicities than Caucasians is also limited.

On the other hand, there is additional support from the ongoing studies, from published studies as well as from patients with AMD and diabetes, although the latter population is likely to have a less severe disease. Even though the high incidence of elevated IOP and endophthalmitis observed in DME patients in RESOLVE was not supported by data from RESTORE or from diabetic patients with AMD, available data cannot conclude on the magnitude of these ocular risks, bearing in mind the possibility of an increased susceptibility towards infections in subjects with advanced disease. A continued monitoring of these risks in the target population is needed. In addition, potential risks regarding progression of

diabetic retinopathy and macular ischaemia are expected to be further addressed in the ongoing as well as planned studies.

Another uncertainty is the long-term risks in the targeted DME population. Including the elderly subjects with AMD and diabetes adds to the information on age-related risk factors in the target population. On the other hand, considering that the general DME patient with the diabetes co-morbidities is younger, additional number of years with IVT treatment may be expected. Further, very few elderly subjects with DME (and potentially more severe vascular disease) have been treated. The potential long-term risks for impairment of VA due to halting or deferring laser photocoagulation are also not known. Although the longer-term data from the study from DRCRnet (2-year data from 484 patients whereof ~200 subjects treated with Lucentis ±laser photocoagulation) support the current safety profile of ranibizumab in the treatment of patients with DME, additional long-term safety data are needed. Such data are to be generated in planned and ongoing studies.

Given the IVT route of administration, a limited absorption into the systemic circulation is expected. Since subjects with DME have more permeable eyes compared to subjects with AMD, there may be an increased systemic exposure. The submitted pharmacokinetic data in this population is limited, but indicate that some subjects may have a slightly higher maximal plasma exposure level than previously reported in AMD-patients. Moreover, a slightly higher systemic exposure in subjects with DME cannot be excluded. Consequently, there may be an increased risk in subjects with DME, especially in cardiovascular high risk patients. The risk in these patients will be further addressed in the post-marketing study where subjects at risk (including previous cardio/cerebrovascular events, hypertension etc) will be enrolled.

In case of pregnancy during treatment with Lucentis, the information derived from the embryo-foetal study in monkeys gives assurance since no foetal adverse effects were observed. However, the exposure margin in this study compared to a worst case clinical exposure is limited (0.9-7-fold). Since VEGF inhibition has a potential to adversely affect the embryo-foetal development, there is a potential risk for adverse effects during pregnancy.

Benefit/Risk Balance

Importance of favourable and unfavourable effects

Treatment with ranibizumab resulted in a clinically convincing and a statistically significant mean improvement of VA in subjects with DME. After 12 months treatment, the difference vs. sham treatment was 11 letters vs. sham injection and 6 letters vs. laser photocoagulation, in the RESOLVE and RESTORE studies, respectively. An important proportion, 40-62% and 23-36 % gained ≥ 10 and ≥15 letters in VA in the two studies. An increase of 15 letters may translate into benefits such as driving and reading.

Treatment is not without risks; however the risks, based on the submitted data, appear comparable to that previously identified in the AMD-population. 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 DME patients seem to be those that are previously identified in patients with AMD, i.e. risks that may be related to systemic VEGF-inhibition.

Benefit-risk balance

The natural progression of DME leads to vision loss of more than ≥ 10 letters of VA within 2 years in approximately 50% of patients. The only treatment and current standard of care is laser photocoagulation as it has been demonstrated to reduce the risk for severe decrease of VA (≥15 letters) with 50 % over 2-3 years. However, there is a substantial group of patients who are unresponsive to laser treatment and for whom no significant improvement in VA is to be expected. In comparison with laser photocoagulation, the risk profile in ranibizumab-treated patients is very different, and the immediate risk is estimated to be higher due to the IVT injection. However, laser photocoagulation is a destructive treatment and there is an important risk of damaging the centre of the macula, creating scotomas, when the leaks to be treated are close to the macula. Moreover, in the long term, repeated photocoagulation may impair peripheral vision since large parts of the retina will eventually be destroyed.

Despite the safety database being limited, Ranibizumab-treatment is the first treatment that has shown to increase VA in subjects with DME. From the submitted data, the magnitude of effect is

considered to outweigh the risks, at least in the majority of subsets of the target population, since the strength of the efficacy data is convincing.

2.9.1. Discussion on the benefit-risk balance

The current data show a benefit of ranibizumab as monotherapy that is considered to outweigh the identified as well as the potential risks.

The subjects in the safety database are sufficient to ensure that there is a 95% probability that a common AE in this population has been detected which is not the case for subjects that are also treated with laser. Thus, the safety database is still rather limited and less than common AEs are not characterised in this population. Although the non-ocular risk profile in diabetic subjects treated with ranibizumab appears reassuring, it cannot be excluded that the diabetes co-morbidity profile may put the target population at a higher risk. In addition, compared to the elderly AMD-population, diabetic patients are considerably younger and may be treated for several years. Even though long-term laser photocoagulations results in retinal scars that may impair vision, the potential complications after repeated long-term intravitreal injections are still not known.

The current standard of care in DME is treatment with laser photocoagulation to reduce the risk for a future, severe loss of vision. In clinical practice, subjects with DME may not have a visual impairment, but are nevertheless treated with laser photocoagulation. Treatment with ranibizumab will therefore introduce a new treatment paradigm, since only subjects with an impaired vision due to DME should be treated. Consequently, the treatment approach would be to treat the oedemas with laser photocoagulation and, when vision becomes impaired, start ranibizumab-treatment. This approach is in agreement with the new DME indication, the proposed re-treatment criteria and supported by the submitted data.

With only limited support for efficacy beyond 12 months, (in the form of 2-year data from a publication), it is not known whether there is a long-term benefit of ranibizumab-treatment (as established with laser) in subjects with oedema only. Therefore, the information to treat only the visual impairment has to reach the physicians. This will be done through using the educational material as specified in section 2.3. Although a large proportion of the retinal specialists are familiar with ranibizumab treatment in AMD, it is possible that a new subset of specialist will be introduced to treatment. As there are major risks if the injection procedure is handled incorrectly, there will be a need for a continuous education of physicians in this field and the educational programme for the AMD-population has been further adapted.

There is also only limited support for the safety of Lucentis beyond 12 months (again in the form of 2-year data from a publication). Although reassuring, the long-term data in this condition is too limited. Together with this arises the concern related to uncertainty if the 12-months gain in VA due to ranibizumab-treatment will result in a loss of the well characterised long-term preservation of vision due to laser treatment if laser is halted or deferred. Consequently, there is a need for long-term data. Such data will be available in 2012. On the other hand, since there were no additional treatment benefits with the combination of ranibizumab and laser, taking the destructive effects as well as the previously characterised benefits of laser into account, it remains unknown whether there is population that may have a benefit of the combination treatment. However, this will be further explored in a planned additional study.

Despite some limitations of the safety database, in view of the supportive data from ongoing and published studies together with the experience from the AMD-population as well as the planned 5-year post marketing observational efficacy and safety study, the above-mentioned uncertainties, including those related to the lack of safety data after long-term treatment, are considered possible to handle with post-authorisation commitments, additional updates of the SPC and the RMP.

2.9.2. Risk management plan

An update to the risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns. The CHMP endorsed that ongoing routine and additional risk minimisation measures in place for the AMD indication are extended to include the DME-indication.

2.10. Recommendation

Based on the CHMP review of data on safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Lucentis in the treatment of visual impairment due to diabetic macular oedema (DME) was favourable and therefore recommended the granting of a positive opinion to the type II application to extend the indication for DME.