



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ranibizumab

Proprietary Product Name: Lucentis

Sponsor: Novartis Pharmaceuticals Australia Pty
Ltd

November 2011

TGA Health Safety
Regulation

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	11 October 2011
<i>Active ingredient(s):</i>	Ranibizumab
<i>Product Name(s):</i>	Lucentis
<i>Sponsor's Name and Address:</i>	Novartis Pharmaceuticals Australia Pty Ltd 54 Waterloo Road North Ryde NSW 2113
<i>Dose form(s):</i>	Injection solution for intraocular injection
<i>Strength(s):</i>	1.8 mg/0.3 mL and 2.3 mg/0.23 mL
<i>Container(s):</i>	Glass vial (colourless type I glass) with chlorobutyl rubber stopper.
<i>Pack size(s):</i>	One pack contains one vial, one filter needle for withdrawal of the vial contents, one needle for intravitreal injection and one syringe for withdrawal of the vial contents and for intravitreal injection.
<i>Approved Therapeutic use:</i>	Lucentis is indicated for: <ul style="list-style-type: none">· the treatment of neovascular (wet) age-related macular degeneration (AMD)· the treatment of visual impairment due to diabetic macular oedema (DME)
<i>Route(s) of administration:</i>	Intraocular (intravitreal)
<i>Dosage:</i>	0.5 mg each month until visual acuity is stable for 3 consecutive months.
<i>ARTG Number (s):</i>	125968, 148325

Product Background

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms, thereby preventing binding of VEGF-A to its receptors.

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and revascularization, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age related macular degeneration and play a role in diabetic macular oedema.

VEGF also plays a part in embryonic and postnatal vasculogenesis and angiogenesis, skeletal muscle regeneration, cardiac remodelling, endochondrial bone formation, the female reproductive cycle and kidney function.

Ranibizumab (Lucentis) is registered for use in exudative ('wet') macular degeneration; this accounts for 10-15% of cases of macular degeneration. Ranibizumab is the

established but not the sole registered treatment for that particular indication. There is an additional anti-VEGF agent (pegaptanib) being marketed for neovascular wet age related macular degeneration (AMD). The current indication for Lucentis is:

Lucentis (ranibizumab) is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD). Lucentis 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month.

This AusPAR describes the evaluation of a submission by Novartis Pharmaceuticals Australia Pty Ltd (the sponsor) to extend the indications to include:

The treatment of visual impairment due to diabetic macular oedema (DME).

According to the sponsor there is no approved anti-VEGF agent for the indication sought in this application. An additional anti-VEGF agent, aflibercept, is in development at Phase II for this indication (it is also an anti-placental growth factor agent).

DME arises from breakdown of the blood retinal barrier (BRB), resulting in accumulation of fluid and macromolecules in the retina. The BRB breakdown is partly mediated by VEGF. An increase in vascular permeability secondary to VEGF has been demonstrated in an *in vivo* model [Aiello et al., 1994].¹ Consistent with this pathological finding, it has been demonstrated through immunohistochemical staining that there is a dramatic increase in VEGF staining of the retina from diabetic patients compared with the normal human retina which contains little or no VEGF [Vinores et al., 1997].² Elevated VEGF concentrations are also present in the vitreous humour of patients with diabetic retinopathy [Aiello et al., 1994]. Since VEGF appears to be a primary endogenous mediator of macular oedema in diabetic retinopathy, the sponsor considers that therapy with ranibizumab to block VEGF directly addresses one of the key pathophysiological pathways in DME. The sponsor argues that this effect translates into a reduction in vascular permeability resulting in a reduction in macular oedema.

Diabetic retinopathy is a common complication of diabetes mellitus and is one of the leading causes of visual loss [Tapp et al., 2003].³ Information from the Australian Diabetes Obesity and Lifestyle study (AusDiab) indicates that in patients with known type 2 diabetes mellitus (T2DM), the prevalence of retinopathy is 21.9% and the prevalence of macular oedema is 3.3% (bilateral in 1.5%) [Tapp et al., 2003]. It has been estimated that approximately half of patients with DME will lose two or more lines (≥ 10 letters) of visual acuity within 2 years if untreated [Ferris and Patz, 1984].⁴

The standard of care for DME for over 20 years has been laser photocoagulation [RCOph, 2011].⁵ Laser photocoagulation has been shown to reduce the risk of moderate vision loss (doubling the visual angle) from clinically significant macular oedema (CSME) by 50%

¹ Aiello LP, Avery RL, Arrigg PG et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. *N Engl J Med* 1994; 331: 1480-7.

² Vinores SA, Youssri AI, Chen YS et al. Upregulation of vascular endothelial growth factor in ischemic and non-ischemic human and experimental retinal disease. *Histol Histopathol* 1997; 12: 99-109.

³ Tapp RJ et al. On Behalf of the AusDiab Study Group. The prevalence of and factors associated with diabetic retinopathy in the Australian population. *Diabetes Care* 2003; 26: 1731-1737.

⁴ Ferris FL, III, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol* 1984; 28 (Suppl May): 452-61.

⁵ Royal College of Ophthalmologists (RCOph, 2011) – Statement to National Institute for Health and Clinical Excellence (NICE) – Single Technology Appraisal of ranibizumab for the treatment of diabetic macular oedema.

[NHMRC, 2008].⁶ CSME was defined in the Early Treatment of Diabetic Retinopathy Study (ETDRS) as any of the following characteristics: thickening of the retina at or within 500 microns of the centre of the macular; hard exudates at or within 500 microns of the centre of the macular if associated with thickening of the adjacent retina (not residual hard exudates remaining after disappearance of retinal thickening); and a zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the centre of the macula [EDTRS Research Group, 1985].⁷

In the ETDRS, DME patients assigned to immediate focal laser photocoagulation were about half as likely to lose 15 or more letters on the ETDRS visual acuity chart at 1, 2 and 3 years than patients assigned to deferral of laser photocoagulation: 5% vs 8%, 1 year; 7% vs 16%, 2 years; and 12% vs 24%, 3 years [EDTRS Research Group, 1985]. Eyes in which macular oedema was not clinically significant at baseline had lower rates of visual loss, especially during the first year of follow up, in both the immediate and deferral of laser photocoagulation groups. Consequently, the presence of absence clinically significant macular oedema was considered to be the most important factor to consider when deciding which patients to treat with laser photocoagulation. However, despite the effectiveness of laser photocoagulation for the treatment of DME it is known that this treatment does not reverse or halt visual loss in all eyes with CSME [RCOph, 2011].⁵ Therefore, there is a recognized need to find other treatments for this condition.

The target population for this requested indication is potentially quite large and will grow as the incidence (and prevalence) of diabetes increases in the Australian population. The prevalence of DME, as identified by the sponsor, in type 1 diabetes ranges from 2.3 to 12%, and for type 2 diabetes from 5.3 to 10%. One study reports that over a 10 year period clinically significant DME will develop in 10% of Americans with known diabetes (Klein 1995).⁸

The current NH&MRC Guidelines for the Management of Diabetic Retinopathy (2008) refer to anti-VEGF drugs under medical therapies for (proliferative) diabetic retinopathy (PDR) as below:⁶

“Anti-Vascular Endothelial Growth Factor (VEGF) drugs, administered by repeat intravitreal injection, offer great promise in managing both PDR (including iris new vessels) and DME.

Their use is accompanied by acceptably low rates of serious adverse ocular effects (less than from IVTA). Repeated applications are needed, and their long term safety is not known.”

The proposed dosing regimen is ranibizumab 0.5 mg by intravitreal (IVT) injection each month until visual acuity is stable for 3 consecutive months. This implies a minimum of two monthly injections. The cycle can be repeated as needed, subsequent to monthly assessments. Concomitant or previous laser therapy is not excluded.

⁶ Australian Diabetes Society for the Department of Health and Ageing. Guidelines for the Management of Diabetic Retinopathy, 2008, National health and Medical Research Council, available at <http://www.nhmrc.gov.au/files/nhmrc/file/publications/synopses/di15.pdf>.

⁷ Early Treatment Diabetic Retinopathy Study Research Group (1985) Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Arch Ophthalmol 1985; 103: 1796-806.

⁸ Klein R, Klein BEK, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy XV : the long-term incidence of macular edema. Ophthalmology 1995; 102: 7-16.

The draft product information (PI) document does not exclude bilateral treatment but does mention that the safety and efficacy of Lucentis therapy administered to both eyes concurrently have not been studied.

This application does not specifically request a changed dosing regimen for the approved indication but the recommendation of monthly injections has also been deleted from the Dosage and Administration section. Other changes to the PI have been requested.

Ranibizumab has been marketed in the US, European Union (EU) and Australia for neovascular wet-AMD for about 5 years. During this time the sponsor reports an estimated 693,500 patient years of exposure.

This application is one of a pair of applications to register extended indications. The other application (2010-03258-3-5) has the proposed indication of "the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)". Approval for this indication was granted in the US in June 2010, and a positive opinion was provided by the Committee for Medicinal Products for Human Use (CHMP) of the EU in March 2011.

Regulatory Status

The product received initial ARTG Registration on 19 February 2007.

At the time of application, similar applications had been made in the European Union (EU), Switzerland, Canada and New Zealand. Approval was obtained in the EU on 6 January 2011 and in Switzerland on 10 May 2011. The indication in both the latter jurisdictions is as follows:

Lucentis is indicated in adults for:

- *the treatment of neovascular (wet) age-related macular degeneration (AMD).*
- *the treatment of visual impairment due to diabetic macular oedema (DME).*
- *the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).*

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

The sponsor submitted a Good Laboratory Practice (GLP) compliant embryofetal development study in cynomolgus monkeys with accompanying toxicokinetic data. This is appropriate as the potential for the drug to adversely affect embryofetal development had not been previously examined in a study specifically conducted with this agent and the new indication (diabetic macular oedema) encompasses a patient group that may include pregnant women.

Pharmacology

Ranibizumab binds to monkey VEGF (vascular endothelial growth factor), which is 99% homologous with human VEGF. Ranibizumab also bound to rabbit VEGF but with lower affinity (at least 40 fold lower). Ranibizumab did not bind to VEGF in rodents.

No nonclinical data specifically addressed the proposed indication of treatment of visual impairment due to diabetic macular oedema. Efficacy for this indication, though, is rationalised based on elevated VEGF being implicated in diabetic macular oedema in the literature and is consistent with the previously submitted *in vitro* and *in vivo* data.

Pharmacokinetics

From the original evaluation, a one compartment model with first order absorption into and first order elimination from the systemic circulation best described the systemic concentration time data of ranibizumab following IVT administration to humans. Elimination of ranibizumab from the systemic circulation appeared to be absorption rate limited. The vitreous elimination half-life was estimated to be about 9 days (d) in humans (3 d in monkeys) and the systemic half-life in humans was about 2 hours (h).

Transfer of immunoglobulin G (IgG) molecules across the human placenta is dependent on Fc receptors on the syncytiotrophoblasts and endothelial cells. As ranibizumab does not contain an Fc region, Fc dependent placental transport would not be expected to occur. The placental transfer of another Fab fragment, abciximab (binds to platelet GPIIb/IIIa), was investigated using an *in vitro* term human placental lobular dual perfusion model (Miller et al, 2003).⁹ Tritiated water, ¹⁴C-inulin and ¹²⁵I-F105 human IgG₁ were all transported across the placenta using this model. However, abciximab was not detectable by solid phase enzyme immunoassay (<3.9 ng/mL) in the fetal circuit during or at the end of perfusion. Immunohistochemistry of the placental tissue demonstrated that a very small amount of abciximab crossed the placenta and this abciximab was bound to fetal platelets in the placental villi capillaries in 4/6 placentae. Thus abciximab did cross the placenta in this model, but the quantity involved was very small.

The only data for placental transfer available for ranibizumab is from the new monkey embryofetal development study, conducted by the IVT route. Unfortunately, this study was not designed to detect fetal ranibizumab concentrations shortly after dosing. The last dose was administered on gestation day (GD) 62 and 38±1 days later, caesarean sections were conducted and fetal blood was collected. All except one fetal serum sample was negative for ranibizumab. With such a time lag between dosing and sample collection, this negative result is not surprising. A comparison between these negative results for fetal serum and maternal serum at the same time point cannot be made, because although maternal blood was collected at necropsy, it was only analysed for anti-ranibizumab antibodies, and not for ranibizumab concentrations. Thus, this study has not adequately investigated the extent that ranibizumab crosses the placenta but it is clear that the drug can cross the placenta, because detectable levels were present in one fetus. The mother of this fetus had high serum levels of both ranibizumab and anti-ranibizumab antibodies. Although it can be speculated that the anti-ranibizumab antibodies assisted placental transport by binding to both ranibizumab and Fc transporters, it is also possible that ranibizumab crossed the placenta in all animals and this was the only fetus that still had detectable levels 38±1 days post-dose.

⁹ Miller RK, Mace K, Polliotti B, DeRita R, Hall W, Treacy G. Marginal transfer of ReoPro™ (abciximab) compared with immunoglobulin G (F105), inulin and water in the perfused human placenta *in vitro*. *Placenta* 2003; 24: 727–738.

Relative exposure

The sponsor undertook a population pharmacokinetic analysis of the human pharmacokinetic data in AMD patients. No human data were available for patients with DME. Animal:human exposure ratios in the monkey embryofetal development study are estimated in Table 1 based on relative serum concentrations, half-life and dosing frequency, with high margins of exposure achieved.

Table 1: Exposure comparison for the monkey embryofetal development study

Parameter	Monkey (pregnant)		Human
Dosing frequency	Every 2 weeks		Every month
Dose (mg/eye)	0.125	1.0	0.5
Serum concentration [Estimated C _{max}] (ng/mL)	16.5 [*]	131 [*]	1.5
Estimated t _{1/2} (days)	3	3	9
C _{max} ·t _{1/2} (ng.days/mL)	49.5	393	13.5
Animal:human exposure ratio [†]	7.3	58	-

–: not applicable; ^{*}: value at GD 35 chosen as this was the lowest of the four 24 h post-dose concentrations recorded; [†]: calculated as $2 \times (C_{max} \cdot t_{1/2})_{animal} / (C_{max} \cdot t_{1/2})_{human}$

C_{max}: maximum plasma concentration

T_{1/2}: half-life

Toxicology

Reproductive toxicity

The cynomolgus monkey is considered to be an appropriate animal model to assess the reproductive toxicity of ranibizumab. The embryofetal development study in monkeys was appropriately designed, although as discussed above (*Pharmacokinetics*) it could have been designed so that it was more informative about placental transfer. No embryofetal development study was conducted in a second species. However, the only suitable second species would have been another primate or the rabbit. Noting this and the affinity of ranibizumab for rabbit VEGF being considerably less than that for monkey and human VEGF, the use of only the cynomolgus monkey is considered acceptable. It should be borne in mind though, that due to the relatively small number of fetuses, primate studies are less well equipped to reveal potential hazards compared to embryofetal development studies conducted in the usual species (rat and rabbit).

IVT ranibizumab treatment up to 1.0 mg/eye/fortnight had no effect on the mother, the placenta or the fetus. Relative exposure at the No Observable Effect Level (NOEL) was estimated to be 58.

Nonclinical Summary and Conclusions

Primary pharmacology data were consistent with efficacy for the new indication but none of the nonclinical studies specifically addressed the treatment of visual impairment due to diabetic macular oedema. Evidence for efficacy relies on clinical data.

Transfer of ranibizumab across the placenta was not well characterised in the monkey embryofetal study due to an extended period between the end of maternal dosing and fetal serum collection. Nevertheless, ranibizumab was detected in the serum of one fetus, demonstrating that fetal transfer is possible.

In the monkey embryofetal development study, at an estimated exposure ratio of up to 58, there were no effects of IVT ranibizumab on the mother, placenta or fetus.

There were no nonclinical objections to the proposed extension of indications.

IV. Clinical Findings

Introduction

The submission included the following clinical information:

- 2 clinical efficacy and safety studies supporting the proposed extension of indication to include the treatment of DME [REVOLVE and RESTORE].
- 4 pharmacokinetic (PK) and PK/pharmacodynamic (PD) studies previously submitted to the TGA.
- 1 population pharmacokinetic report previously submitted to the TGA.
- 4 clinical efficacy and safety studies and/or reports in AMD previously submitted to the TGA [MARINA; PIER; ANCHOR; SAILOR].
- 6 clinical efficacy and safety studies and/or reports in AMD not previously submitted to the TGA [PIER 24 month results; EXCITE; SUSTAIN open label 12 month study; EXTEND open label study with results up to 24 months in Japanese patients with AMD; EXTEND II; and EXTEND III].
- 23 literature references.

Evaluator comment

The submission included two clinical efficacy and safety studies [RESOLVE and RESTORE] supporting the proposed extension of indication. The sponsor identified both of these studies as pivotal. However, it was considered that only RESTORE was pivotal and RESOLVE is supportive (see later discussion).

In addition to the two clinical efficacy and safety studies in DME, the submission also included pharmacokinetic, pharmacodynamic and clinical efficacy and safety studies in patients with AMD. The sponsor stated that these AMD studies were included for information only and were not directly relevant to the DME application. The sponsor also indicated that all the listed PK and PK/PD studies were included in the previous Lucentis AMD submission but not all the listed AMD clinical efficacy and safety studies. The unevaluated clinical efficacy and safety studies included ranibizumab safety data through to 24 months in patients with AMD [PIER and EXTEND] and these safety data have been evaluated in this AusPAR

The submission also included 23 references from the published literature. Of these, 2 were considered to include relevant efficacy and safety data in patients with DME [READ-2 Nguyen et al., 2009, and DRRCR.net, 2010].^{10,11} READ-2 included efficacy and safety data through to 6 months, while DRRCR.net included efficacy and safety data through to 24 months. Both of these studies were evaluated and the efficacy and safety data were considered to be supportive. In addition, 2 year outcome data from READ-2 have recently

¹⁰ Nguyen QD, Shah SM, Heier JS et al. Primary endpoint (six months) results of the Ranibizumab for Edema of the macular in Diabetes (READ-2) study. *Ophthalmology* 2009; 116: 2175-2181.

¹¹ Elman MJ, Aiello LP, Beck RW et al. The Diabetic Retinopathy Clinical Research Network. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology* 2010; 117: 1064-1077.

been published [Nguyen et al., 2010].¹² This study was published after the date of submission. The data from this study were evaluated and were considered to provide supportive efficacy data to 24 months. However, the safety reporting in the study was minimal and, consequently, it was considered not to provide meaningful 24 month safety data.

The submission indicated that there are 4 ongoing clinical efficacy and safety studies involving ranibizumab for the treatment of DME:

RESTORE (Novartis) long term extension study (primarily safety) to 24 months (n=240), ranibizumab 0.5 mg, open label, individualized dosing regimen, expected results Q2 2012;

REVEAL (Novartis) 12 month study (n=390) comparing ranibizumab 0.5 mg vs ranibizumab 0.5 mg + laser vs laser, individualized dosing regimen, report expected Q2 2011;

RIDE (Genentech) 36 month study (n=382) comparing ranibizumab 0.5 mg vs ranibizumab 0.3 mg vs sham monthly injection regimens, results expected Q2, 2012; and

RISE (Genentech) 36 month study (n=377), comparing ranibizumab 0.5 mg vs ranibizumab 0.3 mg vs sham monthly injection regimens; results expected Q2, 2012.

In addition to the original data, the sponsor submitted data provided in response to clinical questions raised during the course of the clinical evaluation. The sponsor's responses to these questions have been included in the relevant sections of this AusPAR.

Pharmacokinetics

The submission included 4 PK and/or PK/PD studies and 1 population-PK report in patients with AMD. These 5 studies have been previously submitted to the TGA for evaluation and the sponsor stated that the studies were included for information only and were not directly relevant to the DME application. These studies have not been re-evaluated.

Pharmacodynamics

No new pharmacodynamic data were included in the submission.

Efficacy

Dose selection

In the absence of formal dose finding studies dose selection was based on the following considerations:

(1) Two ranibizumab dose levels (0.3 mg and 0.5 mg) had been used in the AMD pivotal Phase III studies and had also been safely used in earlier Phase I and Phase I/II AMD studies. Additional escalating doses in the range 0.3 mg to 2.0 mg had also been explored and were found to be well tolerated. The 0.5 mg dose was selected due to a numerical efficacy benefit and no safety concerns compared with the 0.3 mg dose.

(2) The same dose levels tested in patients with AMD were evaluated during the development of the DME indication. In RESOLVE, the starting doses of ranibizumab were 0.3 mg or 0.5 mg. Furthermore, based on observations suggesting that VEGF levels might be considerably higher in the retina and vitreous of patients with DME than in patients with AMD [Aiello et al., 1994], higher doses of ranibizumab were explored in RESOLVE.¹ The study allowed doubling of the initial dose at any time during the study based on the

¹² Nguyen QD, Shah SM, Khwaja AA et al. Two-year outcomes of the Ranibizumab for Edema of the macular in Diabetes (READ-2) study. *Ophthalmology* 2010; 117: 2146-2151.

observed treatment effect on reduction of central retinal thickness (CRT). Based on the preliminary observations from an interim analysis in RESOLVE, followed by discussions with European health authorities and confirmation of the interim observations by the final results in RESOLVE, only the 0.5 mg dose was investigated in the pivotal study [RESTORE].

Evaluator comment

There were no formal ranibizumab dose ranging studies specifically designed for the treatment of DME. The sponsor's approach to dosing was based on the results of the studies in patients with AMD and interim results from RESOLVE in patients with DME.

Proposed indication – diabetic macular oedema (DME) – Data Overview

RESTORE and RESOLVE considered pivotal by the sponsor

The sponsor's covering letter stated that the "efficacy and safety of Lucentis is supported by two controlled double masked pivotal studies: RESTORE (Study D2301) and RESOLVE (Study D2201)". The sponsor's *Clinical Overview* also identified these two studies as being pivotal "for the efficacy and safety claims in the DME patient population". However, while RESTORE was considered by the evaluator to be a pivotal study, RESOLVE was considered to be a supportive study. Both RESTORE and REVOLVE were fully evaluated and the two studies are outlined in Table 2.

Table 2: Summary of controlled trials in DME

Study	Objectives	Patients	Duration	Treatments	Efficacy Endpoints
RESOLVE D2201 Phase II	Ranibizumab, efficacy & safety in patients with DME compared with sham.	Total = 151 Group A = 42 Group B = 109	12 months	R 0.3 mg (dose-doubling permitted PRN). R 0.5 mg (dose-doubling permitted PRN). Sham injection.	Group A: CRT (primary) + BCVA (secondary); interim analysis at month 6. Group B: BCVA (primary) over 12 months + CRT (secondary); confirmatory analysis at month 12.
RESTORE D2301 Phase III	Ranibizumab, efficacy & safety in patients with DME compared with laser.	Total = 345	12 months	R 0.5 mg + Sham Laser. R 0.5 mg + Laser. Sham injection + Laser.	BCVA at 12 months (primary). CRT and other BCVA changes (secondary) at month 12, at interim time points, and over the duration of the study

BCVA = best corrected visual acuity; CRT = central retinal thickness; PRN = according to trial specific treatment criteria; R = ranibizumab; Group A = pilot part; Group B = confirmatory part.

RESOLVE was considered to be a supportive rather than a pivotal study for the following reasons: (i) the unusual design features (that is, initially designed to be an exploratory study but subsequently amended to be confirmatory); (ii) the use of a ranibizumab injection regimen with the option of dose doubling based on central retinal thickness (CRT) response after the initial dose rather than the proposed fixed dose regimen; (iii) the majority of patients received a ranibizumab injection dose greater than the 0.5 mg dose being proposed (68.6% of patients received a dose \geq 0.6 mg, 17.6% received a dose of 0.5 mg and 13.7% received a dose of 0.3 mg; and (iv) the relatively small number of patients in the confirmatory Group B population (n=109).

RESOLVE was a randomized, double masked, multicentre, sham controlled Phase II clinical trial that assessed the efficacy and safety of two ranibizumab dose regimens (0.3 mg and 0.5 mg, with the option of dose doubling) for the treatment of DME. The sponsor stated that RESOLVE was designed with a "flexible/adaptive" approach with two planned interim analyses and the option to increase or decrease the number of analyses based on the observed interim results. The interim analyses were undertaken in order to increase the

probability that the study would provide the relevant information needed for decisions relating to the future development of ranibizumab in DME.

In the original protocol, the first interim analysis was to be undertaken when approximately 36 patients had completed 2 months treatment. However, when the data for this analysis was being compiled it was noted that visual acuity had improved in all three treatment groups. Therefore, a protocol amendment (Protocol Amendment 2) was made to extend the treatment duration with the interim analysis now to be undertaken in approximately 36 patients at 6 months rather than at the originally specified 2 months. The first interim analysis took place after 42 patients had completed the Month 6 visit (0.3 mg [n=14]; 0.5 mg [n=11]; sham [n=17]). All available data from these 42 randomized patients at this time point were then used to evaluate the effect of ranibizumab on reduction of macular oedema and change in visual acuity. In addition, ocular and non-ocular adverse events provided a first assessment of the safety and tolerability of ranibizumab in patients with DME.

Based on the results of the 6 month interim analysis relating to improvements in CRT (originally specified as the primary efficacy endpoint) and BCVA (originally specified as the secondary endpoint) the purpose of RESOLVE was extended (Protocol Amendment 3). This amendment changed the purpose “from a pure exploratory assessment of ranibizumab in DME to a confirmatory approach with a primary objective to demonstrate superiority of ranibizumab therapy compared to sham treatment in the mean change from baseline in BCVA over a 12 month treatment period”. To avoid questions regarding the validity of the confirmatory approach, the protocol amendment stated that the approach was to be based on non-interim patients only (the 109 patients in Group B). The 42 patients included in the interim analysis (Group A) were not included into the confirmatory analysis (Group B), but were to be analysed as supportive data both separately and pooled with Group B.

In summary, the RESOLVE population (n=151) was divided into a pilot group (Group A, n=42) who were analysed in an interim efficacy and safety analysis at 6 months and a confirmatory group (Group B, n=109) who were analysed in a confirmatory efficacy analysis at 12 months. The two groups (Group A+B) were also used to estimate the safety and efficacy (supportive) of ranibizumab compared with sham in the 12 month analysis after all randomized patients had completed the 12 month visit. In the response to the clinical question raised during the clinical evaluation relating to the status of RESOLVE, the sponsor maintained that the study should be considered to be pivotal due to its “randomized, controlled, masked, multicenter design and its conduct according to GMP guidance”. The sponsor also noted that the study population was broadly representative of patients with “mainly controlled” diabetes. Despite the sponsor’s arguments, it was considered that this study should be considered to be supportive rather than pivotal for the reasons discussed above.

READ-2 and DRCCR.NET provide limited supportive data

The sponsor’s *Clinical Overview* identified published data from READ-2 [Nguyen et al., 2009] and DRCCR.net [Elman et al., 2010] which were stated to provide supportive data to the two “pivotal” studies in patients with DME.^{10,11} The two final published papers were provided by the sponsor following a request from the TGA subsequent to the submission and the sponsor then identified the two studies as being supportive as regards efficacy and safety. Both studies were evaluated and were considered to provide only limited support for the submission due to different dosing regimens from that being proposed. The 2 year outcome data from READ-2 have been recently published [Nguyen et al., 2010].¹² The efficacy data from this 2 year outcome study were considered to be supportive and were

considered in this AusPAR but the safety data were not comprehensively reported and cannot be considered to be supportive.

Pivotal efficacy studies - RESTORE [D2301]

Objectives, design, location and design

RESTORE was a Phase III, randomized, double masked, multicentre, efficacy and safety study in patients with visual impairment due to DME treated with one of three regimens for a period of 12 months. The three treatment regimens were: ranibizumab 0.5 mg + sham laser (ranibizumab monotherapy); ranibizumab 0.5 mg + active laser (ranibizumab as adjunctive therapy to laser treatment); sham injection + active laser (laser monotherapy).

The **primary objective** was to demonstrate the superiority of ranibizumab (0.5 mg) monotherapy or adjunctive therapy (to laser treatment) relative to laser monotherapy, as assessed by the mean change from baseline in best corrected visual acuity (BCVA) over a 12 month treatment period.

The **secondary objectives** were:

- to evaluate whether ranibizumab (0.5 mg) as monotherapy or adjunctive therapy to laser treatment was superior to laser treatment:-
 1. in the number of patients with visual acuity above 73 letters; and
 2. in the number of patients with improvement in BCVA.
- to evaluate the time course of BCVA changes on ranibizumab (0.5 mg) monotherapy and adjunctive therapy relative to laser treatment.
- to evaluate the effects of ranibizumab (0.5 mg) monotherapy and adjunctive therapy on central retinal thickness (CRT) and other anatomical changes relative to laser treatment.
- to evaluate the effects of ranibizumab (0.5 mg) monotherapy and adjunctive therapy on patient reported outcomes relative to laser treatment.
- to evaluate the safety of intravitreal (IVT) injections of ranibizumab (0.5 mg) as monotherapy and adjunctive therapy in patients with DME overall and relative to laser treatment.

The **exploratory objectives** were to evaluate pharmacogenetics in patients with DME and to evaluate the effect of ranibizumab (0.5 mg) as monotherapy and adjunctive therapy to laser on the progression of diabetic retinopathy relative to treatment with laser monotherapy.

The study was initiated on 13 May 2008 (first patient visit) and was completed on 27 January 2010. The study report (final content) was dated 7 May 2010. The study was sponsored by Novartis, Switzerland and the principal investigator was located at Westmead Hospital, Sydney, Australia. The study was undertaken in 73 sites in 14 countries: Australia (4), Belgium (2), Canada (7), France (4), Germany (15), Greece (5), Hungary (5), Italy (6), Netherlands (3), New Zealand (1), Spain (6), Switzerland (6), Turkey (6) and the United Kingdom (3).

Investigational plan

The study included an initial screening period lasting 3 to 14 days followed by a treatment period of 12 months (Table 3). It included patients (n=345) aged > 18 years with either Type I or Type II diabetes and with visual impairment due to macular oedema. Only one

eye was selected and treated as the study eye. At Visit 2, patients were randomized using a validated automated system in a 1:1:1 ratio to one of the three treatment groups: ranibizumab 0.5 mg + sham laser (n=115); ranibizumab 0.5 mg + active laser (n=118); and sham injection + active laser (n=110).

Table 3: RESTORE – Overview of study

Screening	Treatment period			
Screening Day -28 (-3) to -4	Baseline Day 1	Initiation phase Day 30 & Day 60	Maintenance	End of study
Month 0	Month 0 Randomization	Month 1 & Month 2 Treatment	Month 3 - 11	Month 12
Visit 1	Visit 2	Visit 3 & Visit 4	Visit 5 - 13	Visit 14

Sham IVT injections and sham laser treatment were used to ensure the study treatment was masked for the patient and the evaluating investigators. BCVA assessors (masked to treatment assignment) performed visual acuity (VA) assessments and provided the results to the investigator. Evaluating investigators (masked to treatment assignment) received the VA result, conducted or supervised all remaining assessments, and provided the treatment decision to the treating investigator. The treating investigator (unmasked to treatment assignment) performed the treatment (injection active/sham or laser active/sham).

Independent review and standardized grading of fundus photography, fluorescein angiography and optical coherence tomography (OCT) images for all patients screened and enrolled in the study were performed at a central reading centre. This centre did not have access to any other patient data.

Patients withdrawn from the study prior to completion of the 12 month treatment phase were asked to return for an early termination evaluation 30±7 days following their last study visit. An Independent Data Monitoring Committee (IDMC) was not used in this study. No interim analyses were performed. Patients completing the 12 month treatment phase were eligible to enrol in a long term extension study [D2301E1].

Evaluator comment

Laser photocoagulation is the current standard of care for patients with DME. However, the study could have been designed to compare ranibizumab with no treatment control (sham injection), with criteria for rescue laser therapy being incorporated into the study design. Nevertheless, active control with laser photocoagulation is considered to be an acceptable design. Randomization procedures were satisfactory and were sufficient to reduce the risk of selection bias. Masking procedures were satisfactory with separation of study functions among BCVA assessors (masked to treatment assignment), evaluating investigators (masked to treatment assignment) and treating investigators (unmasked to treatment assignment). The masking procedures were sufficient to reduce the risk of observer bias. In addition, centralized, independent review and standardized grading of retinal anatomy of patients enrolled in the study also reduced the risk of observer bias. It was considered unusual that an independent DMC was not appointed in this multinational study.

BCVA was assessed by certified assessors at every study visit and VA measurements were taken in a sitting position using ETDRS-like visual acuity testing charts at a testing distance of 4 metres. Colour fundus photography and fluorescein angiography were performed at baseline, Month 6 and Month 12. The images were evaluated to determine the presence and the type of DME, the area of leakage, and severity of diabetic retinopathy (using the ETDRS severity scale). Optical Coherence Tomography (OCT) was performed at

every study visit and the images were reviewed by a central reading centre to ensure standardized evaluation. The National Eye Institute Visual Function questionnaire-25 (NEI-VFQ-25), Time Trade Off (TTO) and EuroQoL (EQ-5D) questionnaires were used to measure health outcomes at specified visits. All study procedures relating to the assessment of efficacy were standard for patients with retinal disease and are well established in ophthalmologic clinical practice and/or clinical research.

Inclusion and exclusion criteria

The inclusion criteria were:

- Male or female patients ≥ 18 years of age who provided signed informed consent.
- Patients with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with glycosylated haemoglobin 1c (HbA1c) not more than 10.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes.
- Patients with visual impairment due to focal or diffuse DME in at least one eye who were eligible for laser treatment in the opinion of the investigator. The study eye must have fulfilled the following criteria at Visit 1 (if both eyes are eligible, the study eye was selected by the investigator):
 - BCVA score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/160).
 - Decrease in vision was due to DME and not due to other causes, in the opinion of the investigator.
- Medication for the management of diabetes must have been stable within 3 months prior to randomization and expected to remain stable during the course of the study.

The **exclusion criteria** were extensive. The main exclusion criteria were:

- Concomitant medications in the study eye which could, in the opinion of the investigator, prevent the improvement of visual acuity on study treatment.
- Active intraocular inflammation (grade trace or above), active infection, history of uveitis, iris neovascularization, evidence of vitreomacular traction or uncontrolled glaucoma in either eye.
- Structural damage within 0.5 disc diameter of the centre of the macular in the study eye likely to preclude improvement in visual acuity following the resolution of macular oedema.
- Ocular disorders in the study eye that may confound interpretation of study results or compromise visual acuity or require medical or surgical intervention during the 12 month study period.
- Active proliferative diabetic retinopathy in the study eye.
- Patients who were monocular or had a BCVA score in the non-study eye (fellow eye) ≤ 24 letters (approximate Snellen equivalent of 20/320) at Visit 1.
- Panretinal laser photocoagulation in the study eye within 6 months prior to the study. Focal/grid laser photocoagulation in the study eye within 3 months prior to study entry
- History of stroke; systolic blood pressure (BP) > 160 mmHg or diastolic BP > 100 mmHg blood pressure

Evaluator comment

The inclusion and exclusion criteria were considered to be satisfactory. There was no restriction with regard to diabetes type (Type 1 or Type 2), type of DME (focal or diffuse), duration of diabetic retinopathy or prior treatment for DME (except for time windows defined to avoid treatment carryover effects). Overall, the study population was considered to be representative of patients with visual impairment due to DME for whom treatment with ranibizumab might be considered. The inclusion criteria did not include CRT (which differs from RESOLVE where a CRT inclusion criterion was required). Patients were included in the study if considered eligible for laser treatment (because active laser treatment [with active or sham injections] was one of the baseline treatments following randomization). This criterion differed from that in RESOLVE which included patients for whom laser treatment could be deferred for 3 months (because baseline treatments following randomization were active or sham injections). The upper limit of BCVA required for inclusion was greater in this study (78 letters) than in RESOLVE (73 letters).

The exclusion criteria were extensive and were aimed at excluding patients with significant concomitant ocular conditions and diseases, including active proliferative diabetic retinopathy in the study eye. The study criteria excluded monocular patients or patients with severe visual impairment in the non-study eye (fellow eye), which is ethically appropriate. No criteria were provided indicating how the study eye was chosen if both were involved, other than the study eye was selected by the investigator (that is, was the better or worse eye chosen for treatment).

Treatment

The study included initiation and maintenance treatment phases. The initiation phase involved treatment with once monthly ranibizumab 0.5 mg IVT injections or sham injections for three consecutive months (Day 1, Month 1 and Month 2). The maintenance phase began at Month 3 and injections were continued once monthly until visual stability was achieved. Treatment was suspended if either one of the two following visual stability criteria were met: in the opinion of the investigator, no (further) BCVA improvement was attributed to treatment with IVT injection at the two last consecutive visits; or BCVA > 84 letters (approximate Snellen equivalent of 20/20) was observed at the two last consecutive visits.

IVT injections were reinitiated following suspension if there was a decrease in BCVA due to DME progression in the opinion of the investigator (based on OCT measurements and/or other anatomical and clinical parameters). The patient was then treated at monthly intervals until stable vision was reached. Reinitiating IVT injections encompassed at least two monthly treatments.

Laser treatment (active or sham) was administered at Day 1 and initial laser photocoagulation could be split into two sessions separated by 4 weeks. Subsequent laser treatments (together with ranibizumab or sham injections) were re-administered in accordance with ETDRS guidelines at intervals no shorter than 3 months from the last treatment if deemed necessary by the evaluating investigator. Patients receiving re-treatment with active or sham laser continued treatment with monthly ranibizumab or sham injections until visual stability had been achieved.

Decisions relating to re-treatment with (sham) laser were independent of decisions to administer (sham) IVT injections and vice versa. The decision of the "evaluating investigator" was followed by the "treating investigator" as much as the randomized treatment assignment allowed. The "treating investigator" was to consider the decision of the "evaluating investigator", but the treatment always followed the randomly assigned treatment and was not switched during the course of the study.

The “evaluating investigator” might, at any time, request that additional “rescue” laser treatment be given in the study eye irrespective of treatment allocation. In this circumstance, the patient discontinued “study treatment” and received laser treatment outside the protocol. However, visits were to continue until the scheduled final end of study visit.

Active/sham laser treatment was always administered before (sham) IVT injections and the minimum interval between the two treatments was 30 minutes. Ranibizumab dose adjustments were not permitted during the study. At the Canadian sites, intraocular pressure measurements were required pre- and 1 hour post-injection but in other countries these measurements were not mandatory.

Laser photocoagulation and standard of care according to the investigator’s practice for DME and other diseases in the fellow eye were permitted at any time. Prohibited treatments in the study included systemic medications known to be toxic to the lens, retina or optic nerve, treatment with glitazones when newly started during the study and panretinal laser photocoagulation in the study eye.

The study included standard procedures relating to patient discontinuation prior to completion. The study also included emergency unmasking procedures to be undertaken when necessary in order to treat the patient. The study drug was discontinued after emergency unmasking. The study drug was also discontinued if the treatment code had been broken inadvertently or for any non-emergency reason.

Evaluator comment

The ranibizumab dose used in this study (0.5 mg) was chosen as it had been shown to be safe and efficacious in patients with DME in an interim analysis of the then ongoing Phase II study [RESOLVE]. The 0.5 mg dose also represented the highest ranibizumab dose whose safety had been evaluated in large scale clinical studies (AMD). While the sponsor stated that ranibizumab dosing essentially followed AMD guidelines, “the duration of the loading phase [in DME] will be individualized in order to maximize the initial treatment effect”.

Primary efficacy variable

The primary efficacy variable in the study eye 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 (using an ETDRS-like chart at 4 metres).

Evaluator comment

The primary efficacy variable was the mean average difference between the BCVA over all monthly post-baseline assessments from Month 1 to Month 12 and the baseline level of BCVA, rather than the mean difference between the BCVA at Month 12 and baseline level. The mean average VA response for the treatments was calculated as the sum of the VAs at each of the 12 monthly visits divided by 12. The chosen endpoint is likely to be less sensitive to monthly variations in treatment effect and uses all the available treatment effect data. It is arguably a more suitable efficacy variable than mean change from baseline to Month 12 when treatment over the study period is not fixed but can vary among treatment groups and among patients within groups. The use of an ETDRS-like chart at 4 metres is a standard method of measuring BCVA in clinical trials studying the effect of treatment on visual acuity.

Secondary and exploratory endpoints efficacy variables

There were numerous secondary efficacy variables assessing various BCVA and CRT endpoints. In addition, the study included exploratory efficacy endpoints relating to the

Early Treatment Diabetic Retinopathy (ETDRS) severity score and the size of the foveal avascular zone in the study eye. In addition, assessment of self reported change in visual function using the National Eye Institute Visual Function questionnaire-25 (NEI-VFQ-25), and health outcomes using Time Trade Off (TTO) and EuroQoL (EQ-5D) questionnaires were performed at specified visits. However, the status of the outcomes assessed by the self-reporting visual function instruments could not be determined in the study report (that is, outcomes were not listed as primary, secondary or exploratory efficacy variables).

Statistical methods

Analysis of the primary efficacy variable

The primary efficacy variable in the study eye 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. Hierarchical statistical hypothesis testing using a Hochberg procedure was undertaken with the aim being to demonstrate superiority of ranibizumab 0.5 mg as adjunctive to laser therapy and/or monotherapy compared with laser monotherapy. Due to the conditional ordering of the first and second steps of hypothesis testing the overall type I error was maintained at a one-sided level of 0.025 or a two-sided level of 0.05. Statistical hypothesis testing of the mean average changes from baseline in BCVA was based on a stratified Cochran-Mantel-Haenszel (CMH) test using the observed values as scores (with a last observation carried forward [LOCF] approach being used for missing observed values). Stratification was based on categories of DME type (focal, diffuse) and categories of baseline BCVA (≤ 60 letters, 61-73 letters, > 73 letters).

The primary analysis was performed on the “full analysis set” (FAS). This set consisted of all patients who received at least one study treatment and had at least one post-baseline BCVA assessment. Following the “intent to treat” (ITT) principle, patients were analysed according to the assigned treatment. No data were excluded from the FAS analyses because of protocol deviations. The FAS included a LOCF approach with missing values being replaced by the mean of the last observation before and the first observation after the missing time point. If missing values occurred without subsequent observed values, the last observed value was carried forward to subsequent scheduled visits. Values from unscheduled visits were included in the imputation. Using this approach, baseline values were only used if at least one post-baseline assessment was available and patients without post-baseline values were excluded from the FAS.

Supportive analyses of the primary efficacy variable were also assessed by parametric statistical methods. The two-sided 95% confidence interval (CI) for the absolute BCVA, for the average changes in BCVA and for the corresponding pairwise difference between treatments, was calculated using the least square means from an analysis of variance (ANOVA) model with treatment, DME type and baseline BCVA as factors. In a sensitivity analysis, the primary analysis was repeated using the “per protocol set” (PPS). Missing data in the PPS were handled in the same way as in the primary analysis. Subgroup analyses of the primary efficacy variable based on the FAS (LOCF) were also assessed using pairwise comparisons.

Analyses of the secondary and exploratory efficacy variables

Analyses of the secondary and exploratory efficacy variables were in the FAS (LOCF), with the assessment before the missing observation being carried forward. No baseline values were carried forward. Values from unscheduled visits were included in the imputation. Supporting analyses were undertaken based on observed data with no imputation of missing data.

General methods

Data were summarized using standard statistical methods. No interim analysis was performed. In general, the following conventions were used throughout the analyses: (i) confidence intervals were two-sided and at a 95% level; and (ii) hypothesis tests were evaluated at a two-sided 0.05/one-sided 0.025 level of significance.

Analysis sets

In addition to the FAS, the study also included randomized, per-protocol and safety sets. The “randomized set” consisted of all randomized patients; patients were considered randomized when they were given a randomization number and were assigned to a treatment group. The “per protocol set” (PPS) consisted of all patients in the FAS who received study treatment as randomized and completed the treatment phase of the trial without clinically significant protocol deviations. The “safety set” consisted of all patients who received at least one study treatment and had at least one post-baseline safety assessment; patients were analysed by actual treatment received.

Evaluator comment

The analysis of the primary efficacy endpoint using the stratified CMH test was considered appropriate. The method stratified the repeat measurements (monthly change from baseline in BCVA) by potential confounders of baseline DME type and baseline BCVA. The use of the LOCF method in which missing values are imputed based on the mean of the before and after values is considered appropriate. The Hochberg procedure was used to account for multiple pairwise comparisons of the primary efficacy endpoint; this is a standard method. No adjustment for multiplicity appears to have been made for the numerous pairwise comparisons of the secondary efficacy variables. Consequently, it was considered that p-values for the secondary efficacy endpoints should be considered to be nominal.

Sample size

A sample size of 105 randomized patients per treatment group was estimated to have more than 90% power to detect a treatment difference of 5 letters in the mean average change in BCVA compared with baseline from Month 1 to Month 12 (for example, 8 letters on ranibizumab vs 3 letters on laser treatment) at a one-sided alpha level of 0.0125, assuming a standard deviation (SD) of 10 letters and an underlying normal distribution for an unstratified Mann-Whitney test. It was assumed that the stratification of the primary analysis had a “tendency” to further increase power. The alpha level of 0.0125 took into account a Bonferroni adjustment for testing two hypotheses in parallel (that is, the superiority of ranibizumab monotherapy relative to laser monotherapy, and the superiority of ranibizumab adjunctive to laser therapy relative to laser monotherapy). The assumed SD of 10 letters was derived from an interim analysis in RESOLVE.

In RESOLVE, an interim analysis suggested that for ranibizumab a responder rate of about 70% could be expected. For the responder definition “improvement in VA at all visits”, it was estimated that 105 patients per treatment group would provide a power of 90% to identify a treatment difference of 70% versus 45% at one-sided alpha 0.0125 based on Fisher’s exact test.

Evaluator comment

Patient numbers in the FAS (LOCF) exceeded 105 in each of the three treatment groups. Consequently, it can be inferred that the power of the study was $\geq 90\%$ to detect the treatment differences based on the assumptions used to calculate the sample size. In the response to clinical questions raised during the clinical evaluation, the sponsor indicated

that the margin of 5 letters was considered to be the lower limit of clinical relevance for the assessment of the effect of ranibizumab treatment compared with laser control. The 5 letter margin was based on ETDRS reports indicating that definitions of VA stabilization include “loss of < 15 letters”, and “maintenance of ± 5 letters”, and DRCR.net 1 year trial results indicating that subjects treated with ranibizumab \pm laser had statistically significant improvements of +6 letters compared with laser alone. Overall, it was considered that an improvement of at least 5 letters with ranibizumab treatment compared with laser treatment is clinically meaningful.

Study patients

Disposition

A total of 459 patients were screened and 345 were randomized. The reasons for the 114 screening failures included unacceptable test results (23.7%), subject withdrew consent (19.3%), patients did not meet diagnostic/severity criteria (18.4%), unacceptable laboratory values (14.9%), unacceptable past medical history/concomitant diagnosis (10.5%), intercurrent medical event (5.3%), unacceptable use of excluded medications/therapies (3.5%), and other (14.9%). Patient disposition in the randomized set are summarised in Table 4.

Table 4: RESTORE – Patient disposition

Disposition/Reason	Ranibizumab 0.5mg N=116 n (%)	Ranibizumab 0.5mg + Laser N=118 n (%)	Laser N=111 n (%)
Completed	102 (87.9)	103 (87.3)	98 (88.3)
Discontinued	14 (12.1)	15 (12.7)	13 (11.7)
Adverse Event(s)	5 (4.3)	3 (2.5)	3 (2.7)
Abnormal laboratory value(s)	1 (0.9)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	1 (0.9)	1 (0.8)	1 (0.9)
Subject withdrew consent	4 (3.4)	7 (5.9)	7 (6.3)
Lost to follow-up	0 (0.0)	1 (0.8)	0 (0.0)
Death	2 (1.7)	2 (1.7)	2 (1.8)
Protocol deviation	1 (0.9)	1 (0.8)	0 (0.0)

Protocol deviations and analysis sets

Overall, 28 patients (24.1%) in the ranibizumab group 0.5 mg, 29 (24.6%) in ranibizumab 0.5 mg + laser group, and 27 (24.3%) in the laser group had at least one major protocol deviation. The analysis sets used in the study are summarised below in Table 5.

Table 5: RESTORE – Analysis sets

Analysis sets	Ranibizumab 0.5mg n (%)	Ranibizumab 0.5mg + Laser n (%)	Laser n (%)
Randomized set	116 (100)	118 (100)	111 (100)
Full analysis set	115 (99.1)	118 (100)	110 (99.1)
Per-protocol set	108 (93.1)	113 (95.8)	98 (88.3)
Safety set	115 (99.1)	120 (101.7)	110 (99.1)

Evaluator comment

The percentage of patients in each treatment group completing treatment was high ($\geq 87\%$). The most common reason for discontinuation in the ranibizumab 0.5 mg group was adverse events (4.3%), which compared with rates of 2.5% in the ranibizumab 0.5 mg + laser group and 2.7% in the laser group. The most common reason for discontinuation in the ranibizumab 0.5 mg + laser and laser groups was withdrawn consent (5.9% and 6.3%, respectively), which compared with a rate of 3.4% in the ranibizumab 0.5 mg group.

Major protocol deviations occurred commonly in the three treatment groups, with similar rates in each of the three groups (24.0% to 25.0%). Individual protocol deviations generally occurred in no more than 3 patients in any of the three treatment groups. In the FAS, 2 randomized patients were excluded from the efficacy analysis due to no post-baseline visual acuity data (1 patient in the ranibizumab 0.5 mg group and 1 patient in the laser group). In the PPS, 26 randomized patients were excluded and there was an imbalance across the three treatment groups (ranibizumab 0.5 mg [n=8, 6.9%]; ranibizumab 0.5 mg + laser [n=5, 4.2%]; and laser [n=13, 11.7%]).

The most common deviations leading to exclusion from the PPS were HbA1c >10.0% at the time of screening (8 patients), and non-completion of the 3 month loading phase (10 patients). Three patients (one in each treatment group) received active ranibizumab and active laser in the study eye at Visit 2 without consideration of randomization and were excluded from the PPS. The patient in the ranibizumab 0.5 mg monotherapy group also recorded a protocol deviation for a dispensing error regarding active/sham laser. In addition, there were 65 patients with protocol deviations leading to data censoring in the PP analysis, 7 of whom were excluded completely from the PP set due to other deviations. Of the 58 patients with censored data, 20 were in the ranibizumab 0.5 mg group, 24 in the ranibizumab 0.5 mg + laser group and 14 in the laser group.

Demographic and other baseline characteristics

The mean age in the three groups ranged from 62.9 to 64.0 years, with the overall range being from 38 to 87 years. There was an imbalance in the age distribution between the three treatment groups with the ranibizumab 0.5 mg group having an approximately twofold higher percentage of patients aged < 55 years than the other two treatment groups. There was also an imbalance in the sex between the three groups, with the percentage of males in the laser group being lower than in the two other groups. Nearly all patients in the three treatment groups were Caucasian (94.0% to 95.5%).

The majority of patients in the three treatment group had type II diabetes mellitus (T2DM) (86.4% to 88.8%). The mean time since first diagnosis of diabetes was similar in the three treatment groups (12.9 to 15.2 years). Overall, diabetes characteristics at baseline were similar in the three treatment groups. Baseline blood pressure readings were similar in the three treatment groups with the mean systolic BP (SBP) ranging from 138.8 to 139.7 mmHg and the mean diastolic BP (DBP) ranging from 78.1 to 78.6 mmHg. The percentage of patients with SBP \geq 140 mmHg ranged from 53.4% to 61.3%, with the laser treatment group having a higher percentage of patients with levels \geq 140 mmHg than the two other treatment groups. The percentage of patients with DBP \geq 90 mmHg ranged from 13.8% to 16.2%, with the laser treatment group having a higher percentage of patients with levels \geq 90 mmHg than the two other treatment groups.

Mean time since first diagnosis of DME in the three treatment groups ranged from 1.6 to 2.0 years, and the overall range was 0 to 20.4 years. Focal DME ranged from 47.7% to 55.2% of patients in the three treatment groups, with the laser treatment group having a lower percentage of patients with focal DME than the two other treatment groups. The mean visual acuity in the three treatment groups ranged from 62.4 to 64.8 letters, and the percentage of patients having VA \leq 60, 61-73, and \geq 73 letters was similar in the three groups. The mean CRT ranged from 412.4 to 426.6 μ m in the three groups, with the mean CRT being greater in the ranibizumab 0.5 mg group than in the two other groups. The mean intraocular pressure (IOP) ranged from 15.2 to 15.5 mmHg in the three treatment groups, and the overall range was 10 to 25 mmHg.

Primary efficacy variable – results

The results for the primary efficacy variable in the study eye of 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 are summarized in Table 6.

Table 6: RESTORE: Primary efficacy results (FAS, LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	115	118	110
	Mean (SD)	64.7 (10.07)	63.4 (9.99)	62.6 (11.01)
	Median	68.0	65.0	65.0
	Min - Max	38.0 - 81.0	38.0 - 79.0	36.0 - 78.0
Average Month 1 to Month 12	n	115	118	110
	Mean (SD)	70.8 (10.53)	69.2 (11.44)	63.4 (12.26)
	Median	73.7	71.5	66.2
	Min - Max	38.6 - 88.7	28.5 - 93.3	32.0 - 84.2
Average change from baseline	n	115	118	110
	Mean (SD)	6.1 (6.43)	5.9 (7.92)	0.8 (8.56)
	Median	6.1	6.0	1.3
	Min - Max	-10.9 - 25.2	-26.7 - 27.6	-37.8 - 26.8
	95% CI for mean (1)	(4.9, 7.3)	(4.4, 7.3)	(-0.8, 2.4)
Comparison vs. Laser	Difference in LS means (2)	5.4	4.9	
	95% CI for difference (2)	(3.5, 7.4)	(2.8, 7.0)	
	p-value (3)	<.0001	<.0001	

n is the number of patients with a value for both baseline and average Month 1 to Month 12. Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).

(1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.

(2) Differences in LS means and the two-sided 95% CIs are estimated from pair-wise ANOVA (stratified) model.

(3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score

Within the FAS, two supportive analyses were performed: (i) an “as documented” approach where the average change from baseline in BCVA was calculated from observed changes only; and (ii) an approach where missing values were imputed using the LOCF method. The results for both of these supportive analyses were consistent with those for the primary efficacy analysis, as was the analysis of the primary efficacy variable in the PP set (results examined but not included).

In the secondary VA efficacy endpoint analysis (FAS/LOCF), the BCVA mean change from baseline at Month 12 was 6.8 letters in the ranibizumab 0.5 mg group, 6.4 letters in the ranibizumab 0.5 mg + laser group and 0.9 letters in the laser group. The estimated treatment difference at Month 12 for ranibizumab 0.5 mg vs laser was 6.2 letters [95% CI: 3.6, 8.7]; $p < 0.0001$), and the estimated treatment difference for ranibizumab 0.5 mg + laser vs laser was 5.4 letters ([95% CI: 2.4, 8.4]; $p = 0.0004$)

In both the ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser treatment groups there was rapid improvement in BCVA of about 6 letters over the first three months following the initial injection. This improvement was then maintained over the remaining 9 months of the study. In contrast, in the laser treatment group an improvement of about 1 letter was maintained over the 12 months of the study.

Evaluator comment

The mean (SD) average increase in BCVA from Month 1 to Month 12 compared with baseline was 6.1 (6.4) letters in the ranibizumab 0.5 mg group, 5.9 (7.9) letters in the ranibizumab 0.5 mg + laser group and 0.8 (8.6) letters in the laser group. The high SD values compared with the mean observed for each of the three groups indicates high inter-subject variability in response within each of the three groups. The difference in the mean average increase in BCVA from Month 1 to Month 12 compared with baseline was 5.4 letters [95% CI: 3.5, 7.4] for the ranibizumab 0.5 mg group vs laser comparison, and 4.9 letters [95% CI: 2.8, 7.0] for the ranibizumab 0.5 mg + laser group vs laser comparison. Both differences were statistically significant ($p < 0.001$, CMH test). There was no statistically significant difference between the ranibizumab 0.5 mg and the ranibizumab 0.5 mg + laser groups as regards the primary efficacy variable: difference in LS means = 0.5 [95%CI: -1.3, 2.3]. The small improvement in BCVA observed in the laser group of 0.8 letters suggests that laser treatment stabilized rather than improved visual acuity. The results for the supportive analyses of the primary efficacy variables were consistent with the results for the primary analysis of the primary efficacy variable.

The subgroup analyses of the primary efficacy endpoint should be considered to be exploratory and hypothesis generating as the analyses were underpowered. However, the following general comments can be made about the comparative results: ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser demonstrated greater improvement in BCVA than laser which was consistent with the primary efficacy analysis; and patients with baseline visual impairment ≤ 73 letters improved to a greater extent with all treatments compared with patients with baseline visual impairment of > 73 letters.

Secondary efficacy analyses

In this section, only the results for key secondary efficacy endpoints are discussed. The changes in VA from baseline to Month 12 categorised by gain of ≥ 10 or with Month 12 BCVA score of ≥ 84 or gain of ≥ 15 letters or with Month 12 BCVA score of ≥ 84 , and loss of ≤ 10 or ≤ 15 letters are descriptively summarised below in Table 7.

Table 7: RESTORE: VA (study eye) mean change from baseline at Month 12 (FAS, LOCF)

Categorized change from baseline	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
N	115	118	110
Gain of ≥ 10 letters [1]	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥ 10 letters	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥ 15 letters [1]	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥ 15 letters	1 (0.9)	4 (3.4)	9 (8.2)

- N is the number of patients with a value at both baseline and the Month 12 visit.

- [1] specified gain, or BCVA of 84 letters or more

The mean CRT at Month 12 decreased from baseline by 118.7 μm in the ranibizumab monotherapy group, 128.3 μm in the ranibizumab adjunctive therapy to laser group and 61.3 μm in the laser monotherapy group in the FAS (LOCF) population: ranibizumab monotherapy vs laser monotherapy LSM = -61.5 [95%CI: -93.8, -29.2], $p=0.0002$, CMH (stratified); ranibizumab adjunctive therapy to laser vs laser monotherapy difference LSM = -70.6 [95%CI: -102.1, -39.0], $p<0.0001$, CMH (stratified). The percentage of patients (FAS, LOCF) with CRT < 275 μm at Month 12 was 49.1% in the ranibizumab monotherapy group, 55.1% in the ranibizumab adjunctive therapy to laser group and 39.1% in the laser monotherapy group; ranibizumab monotherapy vs laser monotherapy difference = 10% [95%CI:-2.9, 23.0], $p=0.0408$, CMH (stratified); and ranibizumab adjunctive therapy to

laser vs laser monotherapy difference = 16.0% [95%CI: 3.2, 28.8], p=0.0075, CMH (stratified).

The NEI VFQ-25 was recorded at baseline, Month 3 and Month 12. The 12 subscales in the VFQ-25 are general health, general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, colour vision and peripheral vision, in addition to an overall composite score. Summary statistics and treatment comparisons for the change from baseline at Month 12 were provided for all subscales. The results for the composite score (which could range from 0 to 100 with higher scores indicating better function) showed that for the ranibizumab monotherapy vs laser monotherapy comparison and the ranibizumab adjunctive therapy to laser vs laser monotherapy comparison, the LSM differences between treatments for change from Month 12 to baseline statistically significantly favoured both ranibizumab treatment groups compared with laser monotherapy: 4.1 [95%CI: 0.8, 7.4] and 4.7 [95%CI: 1.7, 7.8], respectively. Baseline scores for the three treatment groups were similar and ranged from 72.8 to 74.1. Similar results were seen for the NEI FVQ-25 questionnaire for general vision, near activities and distance activities scores with both ranibizumab groups showing statistically significantly greater improvements at Month 12 from baseline than the laser monotherapy group.

Evaluator comment

The analyses of the key secondary efficacy variables support the analysis of the primary efficacy analysis. Improvements in secondary efficacy variables relating to visual acuity, retinal anatomy and self-reported visual function were (nominally) statistically significantly greater in both the ranibizumab 0.5 mg monotherapy and ranibizumab 0.5 mg + laser groups compared with the laser monotherapy group. The observed changes in the key secondary efficacy variables were considered to be clinically significant. The percentage of patients achieving changes from baseline relating to 10 and 15 letters were considered to be the most clinically relevant of the secondary endpoints. In the pivotal AMD studies the primary endpoint was loss of < 15 letters. In a published study of health related quality of life (HRQL) associated with change in visual acuity in patients with diabetic retinopathy, a loss of at least 10 letters on the ETDRS VA chart was associated with substantial declines in HRQL domains such as driving, dependency, role limitations, and mental health [Matza et al., 2008].¹³

The percentage of patients losing ≥ 10 letters at Month 12 compared with baseline was statistically significantly lower in the ranibizumab 0.5 mg monotherapy group (3.5%) compared with the laser monotherapy group (12.7%) (p< 0.0001; CMH stratified) and in the ranibizumab 0.5 mg + laser group (4.2%) compared with the laser monotherapy group (12.7%) (p=0.0001; CMH stratified). Similarly, the percentage of patients losing ≥ 15 letters at Month 12 compared with baseline was statistically significantly lower in the ranibizumab 0.5 mg monotherapy group (0.9%) compared with the laser monotherapy group (8.2%) (p=0.0005; CMH stratified) and in the ranibizumab 0.5 mg + laser group (3.4%) compared with the laser monotherapy group (8.2%) (p=0.0037; CMH stratified).

The percentage of patients gaining ≥ 10 letters (or BCVA of ≥ 84 letters) at Month 12 from baseline was statistically significantly higher in the ranibizumab 0.5 mg monotherapy group (37.4%) compared with the laser monotherapy group (15.5%) (p<0.0001; CMH stratified) and in the ranibizumab 0.5 mg + laser group (43.2%) compared with the laser monotherapy group (15.5%) (p<0.0001; CMH stratified). Similarly, the percentage of patients gaining ≥ 15 letters (or BCVA of ≥ 84 letters) at Month 12 from baseline was

¹³ Matza LS, Rousculp MD, Malley K et al. The longitudinal link between visual acuity and health-related quality of life in patients with diabetic retinopathy. *Health and Quality of Life Outcomes* 2008; 6: 95.

statistically significantly higher in the ranibizumab 0.5 mg monotherapy group (22.6%) compared with the laser monotherapy group (8.2%) ($p=0.0005$; CMH stratified) and in the ranibizumab 0.5 mg + laser group (22.9%) compared with the laser monotherapy group (8.2%) ($p=0.0037$; CMH stratified).

Changes in CRT at 12 months were consistent with the improvement in VA in both the ranibizumab 0.5 mg monotherapy and ranibizumab 0.5 mg + laser groups compared with the laser monotherapy group, as were improvements in self reports of visual function. No 95%CI estimates could be identified for the differences in the pairwise comparisons for changes in VA from baseline based on the number of letters. There was no statistical adjustment for the multiple pairwise comparisons between treatment groups for the secondary efficacy variables. Consequently, all reported p-values should be considered to be nominal for the pairwise comparisons. The sample size calculation included data relating to responder rates defined as “improvement in VA at all visits”, but results for this analysis could not be identified in the submitted data.

Treatment regimen characteristics

The number of injections received by patients in each of the treatment groups (safety set) are summarised below in Table 8. Exposure criteria were generally assessed in the safety set and this set was virtually identical to the FAS, LOCF set. The data showed that the mean number of injections was similar in the three treatment groups, and the median number of injections was identical.

Table 8: RESTORE: Number of injections (safety set)

	Ranibizumab 0.5 mg N=115	Ranibizumab 0.5 mg + Laser N=120	Laser N=110
Total number of injections			
Total	800	816	802
Mean	7.0	6.8	7.3
SD	2.81	2.95	3.22
Median	7.0	7.0	7.0
Min	1	2	1
Max	12	12	12
Distribution of injections – n (%)			
1 – 3	16 (13.9%)	23 (19.2%)	19 (17.3%)
4 – 6	37 (32.2%)	34 (28.3%)	32 (29.1%)
7 – 9	40 (34.8%)	35 (29.2%)	22 (20.0%)
10 – 12	22 (19.1%)	28 (23.3%)	37 (33.6%)

In the Month 3 to Month 11 time period (maintenance period), the mean (SD) number of injections were 4.1 (2.7), 3.8 (2.9) and 4.5 (3.1) in the ranibizumab 0.5 mg group (n=115), ranibizumab 0.5 mg + laser group (n=119) and sham injection + laser group (n=110), respectively. During the Month 3 to Month 11 time period and taking into account patients who prematurely discontinued the study and missed visits, an injection was missed due to disease improvement for 49.2% of the injection visits for patients in the ranibizumab 0.5 mg group, 49.8% of the injection visits for patients in the ranibizumab 0.5 mg + laser group and 40.2% of the injection visits for patients in the sham injection + laser group.

The first time point of stopping treatment due to efficacy (missed injection with reason “as per protocol” or “disease improvement under study”) was Month 3. The percentage of patients stopping treatment for efficacy at this first time point (after the initial 3

injections) was 33.0%, 30.8% and 20.9% in the ranibizumab 0.5 mg group, ranibizumab 0.5 mg + laser group and sham injection + laser group, respectively. Overall, the respective percentage of patients stopping treatment at least once during the study was 85.2% (n=98), 81.7% (n=96) and 68.2% (n=75). Conversely, the respective percentage of patients “never” stopping treatment for efficacy during the study was 14.8% (n=17), 18.3% (n=22) and 31.8% (n=35).

After Month 2 (the third injection), mean (SD) duration of treatment free interval in the FAS was 2.0 (2.7), 2.4 (3.1) and 2.1 (2.9) months in the ranibizumab 0.5 mg group, ranibizumab 0.5 mg + laser group and sham injection + laser group, respectively. After Month 2, the maximum (SD) treatment free interval in the FAS was 3.8 (2.8), 4.1 (3.0) and 3.7 (2.9) months in the ranibizumab 0.5 mg group, ranibizumab 0.5 mg + laser group and sham injection + laser group, respectively. The proportion of patients with a maximum treatment free interval of ≥ 3 months was similar across treatment groups (57.9% to 61.9%).

Within the first treatment free interval starting on or after Month 3, the mean (SD) change in BCVA in the month between the first non-treatment visit and the second non-treatment visit was -1.8 (5.1) [n=93], -1.2 (5.5) [n=99] and -1.2 (0.7) [n=75], in the ranibizumab 0.5 mg, ranibizumab 0.5 mg and laser groups, respectively. The percentage of patients losing ≤ 3 letters in the corresponding treatment groups was 74.2% (n=69), 72.7% (n=72.7) and 89.3% (n=67). The percentage of patients in each of the three treatment groups losing ≤ 15 letters, ≤ 10 letters and ≤ 5 letters ranged from 96.8% to 99.0%, 93.9% to 97.3% and 82.8% to 93.8%, respectively.

Following re-initiation of treatment, the mean (SD) increase in BCVA at the first month visit post-injection, was 3.2 (5.1) letters, 2.1 (5.4) letters and 1.0 (3.7) letters in the ranibizumab 0.5 (n=81), ranibizumab 0.5 mg + laser (n=74) and laser (n=37) groups, respectively.

Evaluator comment

The sponsor's *Clinical Study Report* stated that protocol as needed (PRN) re-treatment regimen after Month 2 of the study (after the third monthly dose) was designed to ensure an individualized treatment regimen for patients based on disease stability outcomes. Overall, the Month 3 to 11 results for mean number of injections received and injections missed due to disease improvement suggest that, on average, patients in the ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser groups were better able to maintain improvement with PRN treatment than patients in the sham injection + laser group. However, the mean and maximum duration of the treatment free interval were both marginally longer in the ranibizumab 0.5 mg + laser group than in the two other treatment groups, with minimal differences being observed for the differences between the ranibizumab 0.5 mg and the sham injection + laser groups.

Other efficacy studies

RESOLVE [D2201]

Objectives, design, locations and dates

RESOLVE was a Phase II, randomized, double masked, multicentre clinical trial designed to assess the safety and efficacy of two dosage regimens of ranibizumab (0.3→0.6 mg [6 mg/mL solution] and 0.5→1.0 mg [10 mg/mL solution]) administered by IVT injection compared with non-treatment (sham injection) control for the treatment of DME with centre involvement. The study was designed as an exploratory study, however, following promising results relating to improvement in visual acuity at the 6 month interim analysis the purpose of the study was changed from exploratory to confirmatory via a protocol

amendment. This resulted in the study being divided into pilot and confirmatory parts, with the respective parts including 42 patients (Group A) and 109 patients (Group B). The reasons for considering this study to be supportive rather than pivotal have been discussed above.

The **primary objective** of the pilot part was to explore whether ranibizumab treatment was superior to non-treatment in reducing macular oedema (CRT) from baseline to Month 6 in patients diagnosed with DME with centre involvement. The **primary objective** of the confirmatory part was to confirm the efficacy of ranibizumab on visual acuity from baseline to Month 12 in patients diagnosed with DME with centre involvement.

The **secondary objectives** in Group A, Group B and Group A+B included additional BCVA outcomes, retinal anatomy outcomes and need for laser photocoagulation, and in Group A+B. ocular and non-ocular adverse events. The study also included **exploratory objectives** to be assessed at selected sites, including visual function encompassing contrast sensitivity and reading performance, patient reported outcome measures, ETDRS Score and the area of retinal capillaries loss.

The first patient was enrolled on 28 October 2005 and the last patient completed on 17 June 2008. The study reported was dated 10 September 2010. The study was sponsored by Novartis, Switzerland, and the principal investigator was located in the University of Bern, Switzerland. The study was undertaken in 30 sites in Europe, Australia (2 sites), New Zealand and Asia. The study has been published [Massin et al., 2010].¹⁴

Investigational plan

Patients entered a screening period lasting up to 28±3 days during which study eligibility was assessed. At Visit 1 (screening visit) OCT images, fluorescein angiograms and stereoscopic fundus photographs were collected and sent to the central reading centre for confirmation of patient eligibility regarding diagnosis of DME. If eligible, patients were then randomized at Visit 2 (Baseline) in a 1:1:1 ratio to one of the three treatment groups.

Prior to each scheduled treatment, patients were required to self-administer a topical antimicrobial agent for 3 days. Patients received an IVT injection of ranibizumab or sham injection monthly over 12 months for a maximum of 12 injections. Ranibizumab dose doubling to 0.6 mg (for patients randomized to 0.3 mg) or 1.0 mg (for patients randomized to 0.5 mg) was permitted after the first injection, if criteria for doubling were met (see below for criteria). Laser photocoagulation was permitted as rescue treatment for the study eye after 3 consecutive monthly injections (see below for rescue criteria).

The first treatment of ranibizumab or sham was performed by the injecting physician on Day 1, and patients returned to the clinical centre within 7 days (Day 8 ± 2 days) for safety assessments and assessments of treatment effect on retinal structure by the evaluating physician. Ranibizumab or sham injection was repeated at monthly intervals, and at each visit patients had a safety evaluation by the evaluating physician prior and post study treatment. The assessments consisted of visual acuity measurements, ophthalmic examinations and evaluation of adverse events and vital signs. An overview of the study design is shown below in Table 9.

¹⁴ Massin P et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE study). *Diabetes Care* 2010; 33: 2399-2405.

Table 9: RESOLVE Study design

Phase	Pre-randomization	Study Drug Treatment														
Period	SCN	BL	PT	Re-treatment Visits												Exit
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Study Day	-28 (-3) to -4	1	8													
Study Month	0	0	0	1	2	3	4	5	6	7	8	9	10	11	12	
Randomization		X														
SCN-screening; BL – baseline; PT – post-treatment																

Evaluator comment

The investigational plan was considered to be satisfactory. It provided for laser photocoagulation rescue treatment in the event of deteriorating disease. Subjects receiving sham injections did not receive IVT injections of “placebo”. This is justifiable as there are ethical concerns relating to the potential risk of infection and/or injury with IVT injections. In sham treatment, the syringe (without the needle) was placed against the conjunctival surface and pressure applied with the aim being to mimic the action of an IVT injection.

Inclusion and exclusion criteria

The key inclusion criteria were:

- Male or female patients >18 years of age who provided signed informed consent.
- Patients with Type 1 or Type 2 diabetes mellitus diagnosed ≥ 24 months prior to screening, with HbA1c not more than 12.0% at Visit 1 and a documented history of stable HbA1c compared with the previous measurement within the last 6 months with a difference of not more than 1.0%.
- Patients with DME with centre involvement in at least one eye, including those with focal or diffuse DME. For this eye, the following three criteria were required at Visit 1:
 - central retinal thickness (CRT) of ≥ 300 μm in the centre subfield, as assessed by OCT and confirmed by the central reading centre;
 - BCVA score between 73 and 39 letters, inclusive, using ETDRS like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/40 to 20/160); and
 - decrease in vision due to foveal thickening from DME and not due to other causes, in the opinion of the investigator.
- BCVA score in the non-study eye (fellow eye) ≥ 24 letters (approximate Snellen equivalent of 20/320) at Visit 1.
- Patients for whom, in the opinion of the investigator, laser photocoagulation in the study eye could be withheld for at least 3 months after randomization.

The **exclusion criteria** were extensive. The study included comprehensive standard provisions relating to patient discontinuation with the addition of adverse events including Stage 3 or 4 macular hole. All efforts were made to contact patients who were lost to follow up. Protocol violations did not result in withdrawal, unless the violations posed a significant risk to patient safety.

Evaluator comment

The inclusion criteria included patients with stable diabetes with DME in whom laser photocoagulation in the study eye could be deferred for at least 3 months after randomization. This raises the issue of whether the data from this study can be extrapolated to patients with more advanced disease requiring prompt laser photocoagulation. Continued observation rather than active treatment might be an option for patients for whom laser photocoagulation can be withheld for at least 3 months. The patients in this study are likely to be on the border of active treatment or continued observation [Massin et al., 2010], and the decision to treat or observe is likely to differ among clinicians.¹⁴ In the opinion of the authors, the results of the study “are relevant to patients in the intermediate stages of the development of DME” [Massin et al., 2010].

Only one eye was selected for study treatment (study eye), although both eyes could potentially satisfy the inclusion and exclusion criteria. If both eyes were eligible, the eye with the worse visual acuity, as assessed at Visit 1, was selected for study treatment unless, the investigator deemed on medical grounds the other eye to be the more appropriate candidate for study treatment.

Treatment

All eligible patients were treated (study eye) with ranibizumab or sham injections over a period of 12 months. Treatments were administered every month (Day1/Month 0 through to Month 11) and patients could receive up to a total of 12 injections. It was specified that repeat ranibizumab/sham dosing should not occur earlier than 14 days after the previous treatment, and that missed doses were not to be replaced.

The initial injection dose was 0.3 mg or 0.5 mg, and the **initial dose could be doubled** from 0.3 mg to 0.6 mg or from 0.5 mg to 1.0 mg if one of the following conditions were met:

- if at the Month 1 visit following the first injection retinal thickness in the study eye remained > 300 µm; or
- if at any monthly visit after Month 1, following injection retinal thickness in the study eye was > 225 µm and reduction in retinal oedema from the previous assessment was < 50 µm.

No further increases in dose after doubling of the initial dose were allowed. If treatment was withheld for more than 45 days for any reason, subsequent injections were restarted with the initial dose.

Study treatment was considered successful and could be discontinued if the evaluating physician assessing VA and OCT scans obtained during the monthly study visits considered at any visit following the third ranibizumab/sham injection the centre of the macula of the study eye to be flat (defined as average retinal thickness in the OCT central subfield ≤ 225 µm) and the BCVA to be ≥ 79 letters (~ Snellen ≥ 20/25). Patients discontinuing study treatment continued to undergo scheduled monthly assessments.

Study treatment was re-initiated if it had been discontinued due to success, if the average macular thickness of the study eye increased by ≥ 50 µm as assessed by the evaluating physician on OCT scans or BCVA of the study eye decreased by ≥ 5 letters and was < 74 letters.

Study treatment was considered futile if after 3 consecutive monthly ranibizumab/sham injections, treatment had not produced at least borderline improvement in the study eye. Borderline improvement was defined as a decrease in average retinal thickening in the study eye of at least 50 µm as assessed by the evaluating physician on OCT scan and

represented at least a 20% reduction in calculated average retinal thickening compared with baseline at the beginning of the 3 month period, or as an increase in BCVA score in the study eye of ≥ 5 letters compared with baseline at the beginning of the 3 month period. However, the physician was not obliged to discontinue study treatment for futility after the third consecutive injection and could continue treatment if desired.

Study treatment was considered “toxic” in cases where treatment was interrupted or discontinued because of adverse events. The dose holding criteria are outlined below in Table 10.

Table 10: RESOLVE: Dose holding criteria

Event	Study Drug Dose-Holding Criteria
Intraocular inflammation	Hold dose if intraocular inflammation is $\geq 1+$. Treatment will be permitted when the intraocular inflammation resolves to Trace levels or less.
Visual acuity loss	Hold dose if there is a treatment-related decrease in best corrected visual acuity of ≥ 30 letters from the baseline assessment. Treatment will be permitted when the change in BCVA improves to a ≤ 10 letters below the visual acuity score measured prior to the last injection value.
Intraocular pressure (IOP)	Hold dose if IOP in the study eye is ≥ 30 mmHg. Treatment will be permitted when IOP has been lowered to < 30 mmHg, either spontaneously or by treatment, as determined by the investigator.
Vitreous hemorrhage	Hold dose if there is a $\geq 2+$ vitreous hemorrhage and a ≥ 30 -letter decrease in visual acuity compared with baseline.
Sensory rhegmatogenous retinal break or detachment	Hold dose if a retinal break or detachment is present. Patients with a Stage 3 or 4 macular hole will be discontinued from treatment for the duration of the study.
Subfoveal hemorrhage	Hold dose if there is a subretinal hemorrhage involving the fovea and the size of the hemorrhage is ≥ 1 disc area in size.
Local or systemic infection	Hold dose if any of the following are present: infectious conjunctivitis, keratitis, scleritis, in either eye, or if the patient is currently receiving treatment for a systemic infection.
Intraocular surgery	Hold dose if intraocular surgery has been performed within the previous 30 days.

Rescue laser photocoagulation treatment for the study eye could be administered after 3 consecutive monthly ranibizumab/sham treatments if the BCVA in the study eye had decreased from baseline by > 10 letters at 2 consecutive visits at least 1 month apart, and the investigator did not consider the macula to be flat ($\leq 225 \mu\text{m}$) as assessed with OCT. Laser photocoagulation was performed according to the standard of care, and could include both focal and grid laser therapy.

Evaluator comment

The ranibizumab treatment regimen differed significantly from that being proposed as dose doubling was allowed following the initial dose based on criteria relating to CRT thickness but not involving VA criteria. There was no discussion on the reason for excluding VA from the dose doubling criteria. It seems unusual that criteria for inclusion in the study included both VA and CRT but dose doubling was determined only by CRT. It is possible that some patients with improved VA might have had their dose doubled based only on CRT criteria. Furthermore, dose doubling is not part of the proposed dosing regimen. The study report indicates that the option to test higher doses of ranibizumab than used in AMD was based on published observations “suggesting that retinal VEGF levels may be considerably higher in the retina and vitreous of patients with DME than in patients with AMD”. The results in the treatment group were analysed based on the strength of solution administered rather than the dose (that is, 6 mg/mL or 10 mg/mL). Consequently, after the first injection the 6 mg/mL group included patients who had been treated with 0.3 or 0.6 mg and the 10 mg/mL group included patients with 0.5 mg or 1.0 mg. As discussed below, this has complicated the interpretation of the data as regards the efficacy of the 0.5 mg dose proposed for approval.

Randomization and blinding methods

Patients were randomized 1:1:1 to one of the three treatment groups. The randomization numbers were generated to insure that treatment assignment was unbiased and concealed from patients and investigator staff. Randomization was stratified by thickness of the retina as assessed by the central reading centre at Visit 1 ($\leq 400 \mu\text{m}$ versus $> 400 \mu\text{m}$). The study was double masked and in order to meet the masking requirements a minimum of two investigators per study site were required. One investigator, masked to treatment assignment, was designated as the evaluating physician and conducted all ocular assessments, including OCT and visual acuity assessments, as well as overall safety assessments. At least one further investigator, unmasked to treatment assignment, was designated as the injecting physician and performed the ranibizumab or sham injections and the immediate safety assessments following the injection. The masked evaluating physician evaluated the OCT images and BCVA scores and decided on the need for treatment, dose doubling and/or the need for laser photocoagulation rescue treatment. Laser photocoagulation treatment could be performed by either the evaluating or injecting physician. Once the designated investigator roles were determined, they could not be switched during the study. Injecting physicians were not permitted to be involved in the conduct of the study in any other manner apart from that specified and were required not to communicate with any other personnel or patients regarding treatment assignment. It was specified that each site should have had no more than five unmasked personnel in order to ensure the integrity masking.

An independent review of fundus photography, fluorescein angiography and OCT images was performed at the central reading centre to provide an objective, masked assessment of patient eligibility, and assessment of retinal thickness, area of retinal oedema and resolution of leakage at selected visits during the study. The review team consisted of graders and ophthalmologists experienced in clinical trials.

Patients, investigator staff, persons performing the assessments, personnel at the central reading centre, and sponsor personnel directly involved directly in the conduct of the study remained masked to the identity of the treatment from the time of randomization until the final database lock. The following methods were used to prevent unmasking: randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone else involved in the study apart from injecting physicians, drug accountability monitor, trial programmer, trial biostatistician, disease area expert and clinical program leader. Unmasking only occurred in the case of protocol specified patient emergency, at the protocol specified time of the interim analysis, and at the conclusion of the study.

Evaluator comment

Overall the randomization and masking methods were considered to be reasonable. However, there was potential for observer bias across the study sites as the OCT images and BCVA scores at all treatment visits at all study sites were not undertaken by the central reading centre. In addition, randomization was stratified only on the basis of retinal thickness and not on the basis of BCVA. It would have been preferable to stratify on the basis of baseline visual acuity as this was more likely to be a clinically relevant confounder than baseline retinal thickness. However, this was subsequently addressed in the 12 month analysis which was stratified by baseline visual acuity (≤ 60 vs > 60 letters) and CRT (≤ 400 vs $> 400 \mu\text{m}$) in the study eye.

Efficacy variables

Primary efficacy variables

The primary efficacy variable 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. VA measurements were performed sitting using ETDRS-like visual acuity testing charts at a testing distance of 4 metres.

Secondary efficacy and exploratory variables

There were numerous secondary and exploratory efficacy variables.

Evaluator comment

The primary and secondary outcomes were considered to be satisfactory. The primary endpoint use in this study was identical to that used in RESTORE. The exploratory efficacy evaluations were considered not to be directly relevant to the efficacy evaluation for the purpose of approving the submission and have not been formally reviewed in this AusPAR.

Statistical methods

Interim analysis

In the original protocol, a first interim analysis was planned at the time when 2 month data on approximately 36 patients were available. However, the sponsor stated that during the blinded review of the data in preparation for the first interim analysis at month 2 it became evident that patients had experienced an improvement in VA. Therefore, to allow for a “thorough” assessment of the hypothesized treatment effect of ranibizumab on VA, the timing of the first interim analysis was changed (Protocol Amendment 2) to include 6 month data on a total of approximately 36 patients (that is, approximately 12 per treatment group). The database lock (DBL) for the 6 month interim analysis occurred on 31 January 2007 and 42 patients were included in the analysis. At the DBL of the interim 6 month analysis, 72% (108 out of 151) of the final study patient population had been randomized into the study. The interim 6 month analysis showed clinically and statistically significant treatment effects not only on the originally specified primary efficacy endpoint of CRT, but also on BCVA ($p < 0.01$ ranibizumab vs sham at Month 6, both comparisons).

Statistical and analytical plans

The purpose of the study was extended in Protocol Amendment 3 from “pure exploratory” to “confirmatory”, with the primary objective being amended to demonstrate the superiority of ranibizumab treatment compared with sham treatment as assessed by the mean change from baseline in BCVA over a 12 month treatment period. The protocol amendment divided the study into two parts: a pilot part (Group A) consisting of the 42 randomized patients who were included in 6 month interim analysis; and a confirmatory part (Group B) consisting of the 109 randomized patients who were not included in the 6 month interim analysis.

Three types of analyses were performed for the 12 month data:

1. an analysis based on the 42 patients in Group A included in the 6 month interim analysis;
2. a confirmatory analysis based on the 109 patients in Group B not included in the 6 month interim analysis; and
3. an analysis which included patients from both parts of the study (Group A+B).

The analyses were performed on the pooled ranibizumab group (0.3 mg + 0.5 mg), the 0.3 mg group and the 0.5 mg group versus the sham injection control group,

Data were summarized with respect to demographic and baseline disease characteristics, and efficacy and safety assessments. Standard summary statistics were used to describe continuous and categorical variables. Estimates of treatment group differences, confidence intervals (CIs) and p-values were presented, where appropriate. In general, CIs were two-sided at a 95% level, and hypothesis tests were evaluated at a two-sided 0.05/one-sided 0.25 level of significance.

Populations for analysis

The following patient populations were used for the 12 Month analyses of Group A, Group B and Group A+B, except the “per protocol set” (PPS) which was used only for analyses of Group B. The “randomized set” consisted of all randomized patients. The “full analysis set” (FAS) consisted of all patients who received at least one study treatment (ranibizumab injection or sham injection) and had at least one post-baseline assessment for BCVA. Following the “intent-to-treat” (ITT) principle, patients were analysed according to the treatment assigned. No data were excluded from the FAS analyses because of protocol deviations. The PPS consisted of all patients in the FAS who received study treatment as randomized and had no clinically significant deviations from the protocol which could potentially affect treatment results. The study also included a “safety set” which consisted of all patients who received at least one study treatment and had at least one post-baseline safety assessment, and patients were analysed according to treatment received.

Primary efficacy analysis

The primary objective of the confirmatory study part (Group B) was to demonstrate superiority of ranibizumab to sham treatment in the mean change from baseline in BCVA over a 12 month treatment period. The primary efficacy variable 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. Multiplicity of pairwise comparisons for the primary efficacy endpoint analysis was handled by a hierarchical Closed Testing Procedure. In the first step of hypothesis testing, the global one-sided hypothesis “Lucentis is superior to sham” was tested at the alpha level of 0.025. The second step of hypotheses testing, the comparisons were tested only if the first step of hypothesis testing was statistically significant. In the second step the two ranibizumab treatment groups (0.3 mg and 0.5 mg) were compared separately against the sham treatment group with a one sided alpha level of 0.025 for each of the comparisons.

Statistical hypothesis testing of the mean average changes from baseline in BCVA was based on a stratified CMH test using the observed values (permutation test) as scores. Based on the interim data, the 12 month analysis was stratified by baseline (study eye) visual acuity (≤ 60 letters vs > 60 letters) and CRT ($\leq 400 \mu\text{m}$ vs $> 400 \mu\text{m}$). Due to the conditional ordering of the first (pooled ranibizumab group vs sham) and second (0.3 mg vs sham and 0.5 mg vs sham) step of hypothesis testing the overall type one error for the study was maintained at a one-sided level of 0.025.

The primary analysis was performed based on the FAS, with missing data imputed using a LOCF method, with missing values occurring between observed values being replaced by the mean of the last observation observed before and the first observation after the missing value. If missing values occurred without a subsequent observed value, the last observed value was carried over to subsequent scheduled visits. Values from unscheduled visits were included. Baseline values were only used for the LOCF approach if at least one post-baseline assessment was available (that is, a patient with a baseline value but

without any post-baseline value was excluded from the FAS). For the primary efficacy variable, additional sensitivity analyses were undertaken using observed data only.

Supportive sensitivity analyses: The primary efficacy variable was also assessed by parametric statistical methods. The two sided 95% CI for the primary efficacy variable and corresponding difference in means between treatments according to pooled ranibizumab group, 0.3 mg and 0.5 mg vs sham was calculated using the least square means from an analysis of variance (ANOVA) model with treatment, baseline visual acuity and baseline central retinal thickness as factors. The primary analysis was also repeated using the PPS for sensitivity.

Supportive subgroup analyses: Subgroup analyses were performed for the primary efficacy variable based on the following criteria (as assessed for the study eye): baseline CRT (≤ 400 vs > 400 μm); DME type (focal vs diffuse); diabetes type (I vs II); prior laser treatment (yes vs no); and baseline BCVA (≤ 60 vs > 60 letters). Patients with missing baseline values used to define the subgroups were excluded from the respective subgroup analyses. Subgroup analyses were performed on the FAS (using LOCF).

Secondary efficacy analysis

The secondary efficacy analyses were performed in the FAS (LOCF) and CMH methods were used to compare differences between treatment groups. The LOCF method carried forward the value occurring immediately before the missing value to all subsequent visits with missing values. No baseline values were carried forward. Values from unscheduled visits were included in the LOCF method. Sensitivity analyses were also undertaken.

Evaluator comment

The statistical methods for analysis of the primary efficacy variable were considered to be satisfactory. The statistical methods use to analyse the secondary efficacy variables were comprehensively described. These methods were also considered to be appropriate. However, the analyses of the secondary (or exploratory) variables appear not to have been adjusted for multiple pairwise comparisons. Consequently, in the absence of statistical adjustment for multiplicity the p values for the secondary efficacy endpoint analyses should be considered to be nominal.

RESOLVE was originally designed as an exploratory Phase II study and interim analyses were specified in the original protocol. In addition, the amendments to the originally proposed interim analysis were specified in a formal protocol amendment (Administrative Amendment # 2). This amendment indicated that study sites, Novartis personnel directly involved in the conduct of the trial, external personnel, investigators and patients were to remain masked to treatment allocation and results until final database lock, with the exceptions being the injecting physicians.

Study sites were subsequently informed about the outcome of the interim analysis through Protocol Amendment 3 at which time point more than 90% of the patients had completed the study. At the time of the 6 month interim analysis, 43 (28%) of the 151 final randomized patients comprising the study population had not been randomized into the study. The sponsor considers that, based on the timing of the interim analysis, the analysis could not have triggered selection bias of the study population after 31 January 2007 (the remaining 43 patients). However, in order to allow for assessment of such bias a number of efficacy endpoints were analysed separately for patients randomized before and after 31 January 2007.

It was considered that the key efficacy data from the study should focus on analysis of the confirmatory population (Group B, n=109). Group B was specifically described in the

study as the confirmatory population. The total population (Group A+B, n=151) should be considered as providing supportive efficacy data.

Sample size

In this study, the total sample size for the confirmatory part was 109 patients, while the pilot part included 42 subjects. The pilot data suggested that treatment with ranibizumab during the first year would result in a mean average increase in BCVA of 8 to 9 letters compared with a mean average decrease in BCVA of about 2 letters for sham treatment. The pilot analyses revealed that the SD for the mean BCVA change was twice as high for the control group compared with the ranibizumab group (11 vs 5.4 letters, respectively).

For the first step of the confirmatory hypothesis testing, the comparison of 72 pooled ranibizumab patients versus 36 sham treated patients, there was a 95% power to detect a treatment difference of 8 letters in the mean average change in BCVA (for example, 8 letters for ranibizumab vs 0 letters for sham) at a one-sided alpha level of 0.025, assuming a SD of 6 letters for ranibizumab and 12 letters for sham, and a normal distribution for an unstratified Mann-Whitney test. For the second step of the confirmatory hypothesis testing there was a 93% power for each of the two comparisons of the 36 patients randomized to each of the 0.3 mg and 0.5 mg ranibizumab groups versus the 36 patients randomized to sham to detect an 8 letter superiority at a one-sided alpha level of 0.025, assuming the same pattern of variability (SD) as above.

Results of the pilot part of the study suggested that for the secondary efficacy variable defined as “critical” by the sponsor of “improvement in VA at all visits Month 1 – Month 12”, an approximately 60% responder rate for ranibizumab treated patients compared with an approximately 20% rate for sham treated patients. With 32 patients per treatment group such a difference could be identified at a one-sided alpha 0.025 with a power of 88% using Fisher’s exact test.

Protocol amendments

The study protocol was amended three times. The key elements of Amendments 2 and 3 relating to the purpose, design, and analysis of the study have been described above. All changes to the protocol were made before database lock and unblinding.

Study patients

Disposition

The number of patients assigned to the three different treatment groups was well balanced in Group A+B (n=151). Patient disposition is summarized in Table 11.

Table 11: RESOLVE: Patient disposition (randomized data set)

Disposition Reason	Ranibizumab 6 mg/ml N=51 n (%)	Ranibizumab 10 mg/ml N=51 n (%)	Ranibizumab Pooled N=102 n (%)	Sham N=49 n (%)
Completed	46 (90.2)	46 (90.2)	92 (90.2)	40 (81.6)
Discontinued	5 (9.8)	5 (9.8)	10 (9.8)	9 (18.4)
Adverse Event(s)	1 (2.0)	1 (2.0)	2 (2.0)	1 (2.0)
Unsatisfactory therapeutic effect	0 (0.0)	1 (2.0)	1 (1.0)	3 (6.1)
Protocol violation	0 (0.0)	1 (2.0)	1 (1.0)	2 (4.1)
Subject withdrew consent	2 (3.9)	2 (3.9)	4 (3.9)	2 (4.1)
Lost to follow-up	1 (2.0)	0 (0.0)	1 (1.0)	1 (2.0)
Death	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)

Evaluator comment

The completion rates in the three groups were satisfactory (90.2% in the pooled ranibizumab group and 81.6% in the sham group). The main difference in disposition between the treatment groups was the higher rate of discontinuations due to unsatisfactory therapeutic effect in the sham group (6.1%) compared with the pooled ranibizumab group (1.0%). However, the absolute number of patients in each of the discontinuation categories for each of the treatment groups was small. Consequently, the clinical significance of the observed differences between treatment groups should be interpreted cautiously.

Data sets analysed

Data sets analysed in Groups B and A+ B are provided below in Tables 12 and 13.

Table 12: RESOLVE: Analysis sets, Group B

	Ranibizumab 6 mg/ml n (%)	Ranibizumab 10 mg/ml n (%)	Ranibizumab Pooled n (%)	Sham n (%)
Randomized set	37 (100.0)	40 (100.0)	77 (100.0)	32 (100.0)
Full analysis set	37 (100.0)	40 (100.0)	77 (100.0)	32 (100.0)
Per-protocol set	35 (94.8)	40 (100.0)	75 (97.4)	32 (100.0)
Safety set	37 (100.0)	40 (100.0)	77 (100.0)	32 (100.0)

Table 13: RESOLVE: Analysis sets, Group A+B

	Ranibizumab 6 mg/ml n (%)	Ranibizumab 10 mg/ml n (%)	Ranibizumab Pooled n (%)	Sham n (%)
Randomized set	51 (100.0)	51 (100.0)	102 (100.0)	49 (100.0)
Full analysis set	51 (100.0)	51 (100.0)	102 (100.0)	49 (100.0)
Safety set	51 (100.0)	51 (100.0)	102 (100.0)	49 (100.0)

In Group A+B (randomized set), protocol deviations occurred in 72.5% (n=74) of patients in the pooled ranibizumab group compared with 79.6% (n=39) of patients in the sham treated group. The most common individual protocol deviation in the ranibizumab group was monthly visits not within 15 to 45 days after last injection (11.8% [n=12] vs 14.3% [n=7]). Other protocol deviations occurring in $\geq 5\%$ (≥ 10 patients) in the pooled ranibizumab group (vs sham) were: laser treatment in study eye (8.8% vs 32.7%); no treatment due to lack of efficacy without fulfilling futility criteria which are assessed in comparison to baseline (7.8% vs 10.2%); and subject missed a monthly visit which was not followed by 3 consecutive completed visits (7.8% vs 6.1%).

Evaluator comment

Protocol deviations were common in the ranibizumab data set in the three treatment groups. However, no deviations resulted in exclusion from the efficacy analyses.

Demographic and other baseline characteristics

In Group A+B, baseline demographic characteristics were similar across the three treatment groups in Group A+B. The mean age of the total number of randomized patients was 63.6 years [range: 32-85]; 84.8% of the population was aged ≥ 55 years; male/female ratio was 53.6/46.4%; and 87.4% were Caucasian. In Group B, the baseline demographic characteristics were consistent with those in Group A+B.

In Group A+B, baseline diabetes characteristics were similar across the three treatment groups. Nearly all patients had T2DM (97.4%); mean duration since diagnosis was about 14.5 years [range: 0.7-46.0 years]; mean HbA1c was 7.5% [range: 5.3-11.1%]; and

approximately 70% had HbA1c levels < 8%. In Group B, the baseline diabetes characteristics were similar to those in Group A+B.

In Group A+B, baseline ocular characteristics of the study eye were similar across the three treatment groups. DME was present in all patients; the mean time from first DME diagnosis was 1.25 years; 47.0% had focal DME, 50.3% had diffuse DME; mean CRT was 453.3 μm ; mean VA was 60.5 letters [range: 37-79 letters]; mean intraocular pressure was 15.6 mmHg [range: 9-26 mmHg]; and 18.5% had received prior laser photocoagulation therapy. In Group B, the baseline ocular characteristics of the study eye in patients were similar to those in Group A+B.

Primary efficacy outcome

The results for the primary efficacy analyses for the mean average change in VA (letters) from baseline from Month 1 to Month 12 in the FAS (LOCF) were consistent in Group B (confirmatory population) and Group A+B (supportive population), and the results are summarized below in Tables 12 and 13, respectively. In both analyses, the results were summarized on the basis of the ranibizumab solution strength. Consequently, the 6 mg/mL solution group included patients treated with both 0.3 mg and 0.6 mg (initial dose 0.3 mg doubled to 0.6 mg), the 10 mg/mL group included patients treated with both 0.5 mg and 1.0 mg (initial dose 0.5 mg doubled to 1.0 mg).

Table 14: RESOLVE: Group B, VA (study eye), mean average change in letters from baseline from Month 1 to Month 12 (FAS, LOCF)

Parameter	Statistic	Ranibizumab 6 mg/ml N=37	Ranibizumab 10 mg/ml N=40	Ranibizumab Pooled N=77	Sham N=32
Baseline	n	37	40	77	32
	Mean (SD)	58.8 (10.74)	63.4 (8.06)	61.2 (9.66)	60.2 (8.52)
	Median	60.0	63.0	63.0	61.0
	Min-Max	37.0-73.0	47.0-79.0	37.0-79.0	42.0-74.0
Average Month 1 to Month 12	Mean (SD)	68.2 (10.85)	69.4 (11.79)	68.8 (11.29)	61.4 (11.52)
	Median	69.3	71.2	70.7	62.4
	Min-Max	42.8-87.9	34.8-88.3	34.8-88.3	32.8-83.1
Average change from baseline	Mean (SD)	9.4 (5.82)	6.0 (9.86)	7.6 (8.29)	1.2 (8.38)
	Median	9.7	7.0	8.2	2.8
	Min-Max	-2.9-24.3	-24.9-21.4	-24.9-24.3	-22.8-14.8
	95% CI for mean (1)	(7.4, 11.3)	(2.9, 9.2)	(5.7, 9.5)	(-1.8, 4.2)
Comparison vs. sham	Difference in LS means (2)	8.1	5.5	6.7	
	95% CI for difference (2)	(4.7, 11.5)	(1.0, 9.9)	(3.2, 10.1)	
	p-value (3)	<0.0001	0.0067	0.0002	

n is the number of patients with a value for both baseline and average Month 1 to Month 12.

Stratified analysis includes baseline visual acuity (≤ 60 , > 60 letters) and baseline central retinal thickness (≤ 400 , $> 400 \mu\text{m}$).

(1) Two-sided 95% confidence intervals (CI) are based on t-distribution.

(2) Differences in LS means and the two-sided 95% CIs are estimated from pairwise ANOVA (stratified) model.

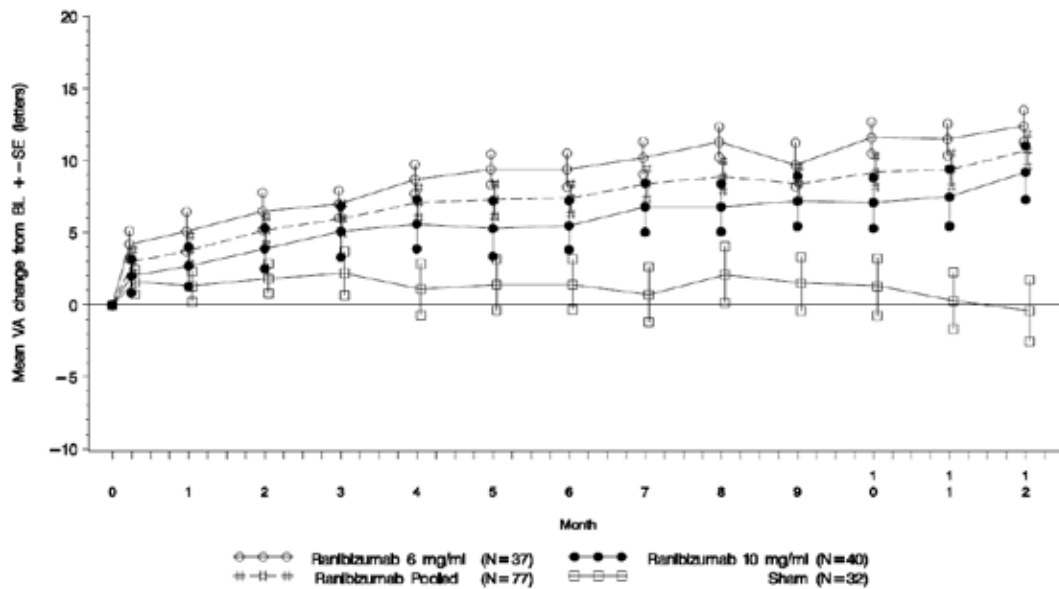
(3) p-values for treatment difference are from the one-sided exact Permutation test (stratified) using the observed values as scores.

Table 15: RESOLVE: Group A+B, VA (study eye), mean average change in letters from baseline from Month 1 to Month 12 (FAS, LOCF)

Parameter	Statistic	Ranibizumab 6 mg/ml N=51	Ranibizumab 10 mg/ml N=51	Ranibizumab Pooled N=102	Sham N=49
Baseline	n	51	51	102	49
	Mean (SD)	59.2 (10.23)	61.2 (9.48)	60.2 (9.86)	61.1 (9.04)
	Median	61.0	61.0	61.0	63.0
	Min-Max	37.0-73.0	39.0-79.0	37.0-79.0	39.0-76.0
Average Month 1 to Month 12	Mean (SD)	68.4 (11.09)	67.5 (12.37)	68.0 (11.70)	61.0 (13.91)
	Median	69.4	70.4	70.3	63.0
	Min-Max	38.9-87.9	34.8-88.3	34.8-88.3	19.9-83.1
Average change from baseline	Mean (SD)	9.2 (5.60)	6.4 (9.21)	7.8 (7.72)	-0.1 (9.77)
	Median	9.5	7.4	8.2	2.8
	Min-Max	-2.9-24.3	-24.9-21.4	-24.9-24.3	-36.1-14.8
	95% CI for mean (1)	(7.7, 10.8)	(3.8, 9.0)	(6.3, 9.3)	(-2.9, 2.7)
Comparison vs. sham	Difference in LS means (2)	9.4	6.7	7.9	
	95% CI for difference (2)	(6.2, 12.6)	(3.0, 10.5)	(5.0, 10.9)	
	p-value (3)	<0.0001	0.0004	<0.0001	

Notes as for Table 14.

In Group B, over the 12 month study period, improvement in VA in the ranibizumab groups compared with sham in the FAS (LOCF) data set were observed as early as 8 days after the first injection and continued to improve over the duration of the study (Figure 1). This pattern was similar in Group A+B.

Figure 1: RESOLVE: Group B (n=109) VA (study eye) mean change from baseline over time for treatment groups (FAS, LOCF)

— First visual acuity value post-baseline was assessed at Day 8.
 — BL = baseline; SE = standard error of the mean.

Evaluator comment

In both Group B and Group A+B, the VA comparisons for both the high and low strength ranibizumab treatment groups vs the sham treatment group statistically significantly

favoured ranibizumab. Based on the sample size calculations, it can be inferred that the sponsor considered the clinically significant difference in BCVA between the ranibizumab and sham treatment groups in patients with DME to be ≥ 8 letters. Based on this criterion, only the 6 mg/mL dose group achieved a clinically meaningful improvement compared with sham in both Group B and Group A+B. There was no dose response relationship between the 6 mg/mL and 10 mg/mL groups as regards improvement in BCVA.

The interpretation of the efficacy results in this study is complicated due to the two strength ranibizumab solution groups each consisting of patients treated with a low or high dose. In Group B, the majority of patients in both ranibizumab groups had their dose doubled during the course of the study. In the 6 mg/mL group, 67.6% of patients (25/37) had their dose doubled from 0.3 mg to 0.6 mg during the study with 68.0% (17/25) of these patients having their dose doubled at Month 1 (at the first opportunity). In the 10 mg/mL group, 72.5% of patients (29/40) had their dose doubled from 0.5 mg to 1.0 mg during the study with 72.4% (21/29) of these patients having their dose doubled at Month 1 (at the first opportunity). Similarly, in Group A+B in the ranibizumab 6 mg/mL group 72.5% of patients (37/51) had their dose doubled from 0.3 mg to 0.6 mg with 64.9% (24/37) of these patients having their dose doubled at 1 Month, and in the ranibizumab 10 mg/mL group 64.7% of patients (33/51) had their dose doubled from 0.5 mg to 1.0 mg with 75.8% (25/33) of these patient having their dose doubled at Month 1.

Over the entire study period, the average dose received was 0.47 mg in the low concentration group (6 mg/mL), 0.76 mg in the high concentration group (10 mg/mL), and 0.62 mg in pooled concentration group. The sponsor stated that the majority of patients in the ranibizumab treated groups (86%) received a dose of 0.5 mg or higher during the study period. Closer inspection of the data shows that 68.6% of patients in the ranibizumab treated groups received a dose of 0.6 mg or higher during the study, 17.6% received a dose of 0.5 mg and 13.7% received a dose of 0.3 mg. Therefore, the majority of patients (68.6%) received doses of ranibizumab higher than 0.5 mg which is the proposed dose. However, given that the results for the 6 mg/mL group are the most relevant as regards improvement in BCVA it can be inferred that the average dose of 0.47 mg per injection in this group is likely to represent the clinically relevant actual dose. Consequently, the efficacy data from the 6 mg/mL group were considered to support the proposed 0.5 mg dose.

The sponsor argued that dose doubling had no significant effect on BCVA and, consequently, the study supports a dose of 0.5 mg without doubling. The sponsor stated that due to the study design there were limitations related to assessing the effect of dose (for example, no randomization to the time point of dose doubling, limited separation of dose doubling effect and possible time effects). Therefore the sponsor provided *post hoc* descriptive subgroup analyses by time point of first dose doubling (that is, patients with first dose doubling at Month 1, Month 2 and after Month 2 versus patients without any dose doubling). The plots of the corresponding time course of VA and CRT were then visually inspected regarding specific responses to dose doubling (for example, for the subgroup with first dose doubling at Month 1 by assessing the change between Month 1 and 2, in comparison to the other monthly changes). The sponsor concluded that, based on this evaluation, no specific changes in the VA time course could be identified, and the identified additional decreases in CRT from Month 2 to Month 3 in patients who had their dose doubled in both the 0.6 mg/mL and 1.0 mg/mL groups at 2 months would be minimal compared with the overall changes in CRT. However, it was considered that little evidentiary weight should be given to these *post hoc* analyses because the study was not designed to test such dose comparisons and was underpowered to detect statistically significant differences in BCVA or CRT between the two doses in the 6 mg/mL and 10 mg/mL strength groups.

Key secondary efficacy outcomes

Key secondary efficacy results for Group B and Group A+B are summarised below in Tables 16 and 17, respectively.

Table 16: RESOLVE: Group B treatment comparisons key secondary efficacy variables (FAS, LOCF)

Variable	Ran 6 mg/mL (n=37)	Ran10 mg/mL (n=40)	Ran Pooled (n=77)	Sham (n=32)
Gain \geq 15 letters [Δ BL to month 12] ¹	40.5% (n=15)	32.5% (n=13)	36.4% (n=28)	9.4% (n=3)
Loss \geq 15 letters [Δ BL to month 12] ¹	0%	7.5% (n=3)	3.9% (n=3)	21.9% (n=7)
Gain \geq 10 letters [Δ BL to month 12] ²	73.0% (n=27)	52.5% (n=21)	62.3% (n=48)	18.8% (n=6)
Loss \geq 10 letters [Δ BL to month 12] ²	0%	12.5% (n=5)	6.5% (n=5)	25.0% (n=8)
CRT μ m mean (SE) [Δ BL to month 12] ³	-206.2 (20.26)	-184.1 (23.09)	-194.7 (15.40)	-73.7 (28.17)
CRT < 225 μ m (%) at month 12 ⁴	35.1% (n=13)	32.5% (n=13)	33.8% (n=26)	12.5% (n=4)

Δ BL = change from baseline.

¹ CMH test, stratified: 6 mg/mL vs sham p < 0.0003; 10 mg/mL vs sham p=0.0057; and pooled vs sham p = 0.0002.

² CMH test, stratified: 6 mg/mL vs sham p < 0.0001; 10 mg/mL vs sham p=0.0039; and pooled vs sham p < 0.0001

³ CMH test, stratified: 6 mg/mL vs sham p < 0.0001; 10 mg/mL vs sham p = 0.0003; pooled vs sham p < 0.0001.

⁴ CMH test, stratified: 6 mg/mL vs sham p=0.0410; 10 mg/mL vs sham p=0.0695; pooled vs sham p=0.0277.

Table 17: RESOLVE: Group A+B treatment comparisons key secondary efficacy variables (FAS, LOCF)

Variable	Ran 6 mg/mL (n=51)	Ran10 mg/mL (n=51)	Ran Pooled (n=102)	Sham (n=49)
Gain \geq 15 letters [Δ BL to month 12] ¹	35.3% (n=18)	29.4% (n=15)	32.4% (n=33)	10.2% (n=5)
Loss \geq 15 letters [Δ BL to month 12] ¹	0%	5.9% (n=3)	2.9% (n=2)	20.4% (n=10)
Gain \geq 10 letters [Δ BL to month 12] ²	72.5% (n=37)	49.0% (n=25)	60.8% (n=62)	18.4% (n=9)
Loss \geq 10 letters [Δ BL to month 12] ²	0%	9.8% (n=5)	4.9% (n=5)	24.5% (n=12)
CRT μ m mean (SE) [Δ BL to month 12] ³	-200.7 (17.11)	-187.6 (20.70)	-194.2 (13.38)	-48.4 (21.92)
CRT < 225 μ m (%) at month 12 ⁴	31.4% (n=16)	39.2% (n=20)	35.3% (n=36)	10.2% (n=5)

Δ BL = change from baseline.

¹ CMH test, stratified: 6 mg/mL vs sham p = 0.0001; 10 mg/mL vs sham p=0.0037; and pooled vs sham p = 0.0001.

² CMH test, stratified: 6 mg/mL vs sham p < 0.0001; 10 mg/mL vs sham p=0.0010; and pooled vs sham p < 0.0001

³ CMH test, stratified: 6 mg/mL vs sham p < 0.0001; 10 mg/mL vs sham p < 0.0001; pooled vs sham p < 0.0001.

⁴ CMH test, stratified: 6 mg/mL vs sham p=0.0108; 10 mg/mL vs sham p=0.0007; pooled vs sham p=0.0011.

Evaluator comment

The proportion of patients in whom VA improved by \geq 15 letters and \geq 10 letters from baseline to Month 12 was significantly higher in the three ranibizumab groups compared with sham in both Group B and Group A+B. Similarly, the proportion of patients in whom VA decreased by \geq 15 letters and \geq 10 letters from baseline to Month 12 was significantly lower in the three ranibizumab groups compared with sham in both Group B and Group A+B. The results for all four VA parameters in both Group B and Group A+B were better in the lower strength group (6 mg/mL) than in the higher strength group (10 mg/mL). Improvements in CRT thickness at 12 months were greater in the three ranibizumab groups compared with sham and improvements were better in the 6 mg/mL group compared with the 10 mg/mL group.

Summary of Clinical Efficacy - exploratory analyses

The sponsor's *Summary of Clinical Efficacy* included *post hoc* efficacy analyses on patients in Group A+B (FAS, observed cases) exploring the proposed dosage regimen interrupting treatment when VA is achieved and re-starting treatment when VA is lost.

In an exploratory analysis, patients were defined as being stable when BCVA changes between the minimum and maximum of the last three visits (including the current visit) were within a range of 3 letters (minimum to maximum \leq 3 letters). Using this definition, 84.3% (86/102) of ranibizumab treated patients had treatment interrupted for stability based on BCVA, with treatment stability being most commonly achieved after the third (14.7%) or fourth (27.5%) injections. The time point of first visit with stability based on visual acuity was highly variable after the Month 2 or 3 visit.

In a further exploratory analysis, the effect of re-treatment (single injection) on VA was examined using a “re-start/re-initiation” criterion of $>$ 3 letters loss of VA. Of the 50 re-start injections, 42% (n=21) met this VA criterion and evaluable data as regards mean change in VA following a single “re-start/re-initiation” was available for 20 of the 21 injections. For these 20 injections, the mean (SD) change in VA from treatment to 1 month post-treatment was 10.0 (5.7) letters, which suggests that re-treatment following loss of stability (VA $>$ 3 letters) resulted in a clinically meaningful improvement following 1 re-treatment injection. In contrast, when the VA “re-start/re-initiation” criterion was \leq 3 letters the mean (SD) improvement in VA following a re-treatment injection (n=18) was -0.6 (4.6) letters at the next visit, which suggests that if VA is stable at the time of the re-treatment injection then further improvement in VA at the following visit is unlikely.

In addition, further exploratory analyses in RESOLVE (and RESTORE) suggest that adding CRT as a re-treatment parameter to VA does not result in a better VA outcome at the first assessment 1 month after the re-treatment injection. Consequently, the sponsor considered that the current level of evidence was not sufficient to support a recommendation for a CRT re-treatment criterion.

Evaluator comment

These exploratory analyses were *post hoc* and involved small patient numbers. Neither RESOLVE nor RESTORE was specifically designed to explore the effect of different re-treatment criteria on subsequent VA. However, the exploratory analyses of the RESOLVE data suggest that the effect on VA at 1 month following a re-start injection can be reasonably predicted by VA alone at the time of the injection.

DRCR.NET [2010]

Objectives

The objective of this published study conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net) was to evaluate IVT 0.5 mg ranibizumab combined with focal/grid laser and 4 mg triamcinolone combined with focal/grid laser compared with focal/grid laser alone for the treatment of diabetic macular oedema (DME).¹¹

Design

The study was a Phase III, randomized, multicentre, clinical trial undertaken at 52 clinical sites in the United States. The study adhered to the principles of the Declaration of Helsinki, complied with appropriate US legislation and was approved by relevant institutional review boards (IRBs). Study participants gave written informed consent. Study oversight was provided by an independent data and safety monitoring committee. The study was conducted under an Investigational New Drug Application from the Food and Drug Administration.

Inclusion and exclusion criteria

Eligible patients were at least 18 years old with T1DM or T2DM. The major eligibility criteria for the study eye included: (1) BCVA letter score of 78 to 24 (approximate Snellen equivalent 20/32–20/320) using the E-ETDRS Visual Acuity Test; (2) definite retinal

thickening due to DME on clinical examination involving the centre of the macula assessed to be the main cause of visual loss; and (3) retinal thickness $\geq 250 \mu\text{m}$ in the central subfield measured by OCT.

Principal exclusion criteria were: (1) treatment for DME within prior 4 months; (2) panretinal photocoagulation within prior 4 months or anticipated need for panretinal photocoagulation within the next 6 months; (3) major ocular surgery within prior 4 months; (4) history of open angle glaucoma or steroid induced IOP elevation that required IOP lowering treatment, and; (5) IOP $\geq 25 \text{ mmHg}$. Patients were excluded if systolic BP was $> 180 \text{ mmHg}$ or diastolic BP was $> 110 \text{ mmHg}$, or if myocardial infarction, other cardiac event requiring hospitalization, cerebrovascular accident, transient ischaemic attack or treatment for acute congestive heart failure had occurred within 4 months before randomization. A patient could have 2 study eyes in the trial only if both were eligible at the time of study entry.

Investigational plan

Study participants with 1 study eye were randomized with equal probability to 1 of 4 treatment groups: (1) sham injection plus prompt focal/grid laser photocoagulation (sham + prompt laser); (2) ranibizumab 0.5 mg IVT injections plus prompt focal/grid laser photocoagulation (ranibizumab + prompt laser); (3) ranibizumab 0.5 mg IVT injection with deferred focal/grid laser photocoagulation (ranibizumab + deferred laser); and (4) triamcinolone 4 mg IVT plus prompt focal/grid laser photocoagulation (triamcinolone + prompt laser). Prompt laser treatment was administered within 3-10 days after the injection and deferred laser treatment was administered ≥ 24 weeks after the injection. For study participants with 2 study eyes, the right eye was assigned randomly with equal probability to 1 of the 4 groups as indicated above. If the right eye was assigned to a treatment group other than the sham + prompt laser group, then the left eye was assigned to the sham + prompt laser group. If the right eye was assigned to the sham + prompt laser group, then the left eye was assigned randomly to 1 of the other 3 groups. Thus, there were more eyes in the sham + prompt laser group than in the other 3 groups.

Follow up was planned for 3 years, with the primary outcome at 1 year. During the first year, follow up visits occurred every 4 weeks (± 1 week). Study participants in the three groups receiving prompt laser were masked to treatment assignment through to the primary outcome visit, but study participants in the ranibizumab + deferred laser group were not masked. After the first year, visits occurred every 4 to 16 weeks depending on the treatment group, disease course, and treatment administered. Study participants were made aware treatment group allocation following the primary outcome visual acuity examination at 1 year, and sham injections were discontinued. Visual acuity examiners and OCT technicians were masked to treatment group assignment before and at the 1-year primary outcome visit.

At baseline and each follow-up visit, BCVA letter score was measured by a certified examiner using an E-ETDRS Visual Acuity Test at 3 metres. OCT scans were obtained at baseline and each follow up visit by a certified operator. All baseline OCT scans, annual follow-up scans with a standard deviation of the centre point $\geq 10.0\%$, and scans from any visits in which the investigator suspected erroneous measurements were sent to the a central reading centre for grading. If the automated thickness measurements were judged by the reading centre to be inaccurate on any submitted image, centre point thickness was measured manually and this value was used to impute a value for the central subfield. Manual grading of the baseline scans resulted in an imputed baseline central subfield value $< 250 \mu\text{m}$ for 60 eyes (7%). Additional testing at baseline and each follow up visit included slit-lamp examination, measurement of IOP and fundus examination after pupil dilation.

Treatment

Ranibizumab 0.5 mg was given every 4 weeks for the first 16 weeks regardless of the visual acuity or central subfield thickness. Therefore, in this regimen all patients received at least 4 initial injections at monthly injections compared with at least 3 injections in the proposed regimen. In DRCR.net, after the fourth injection ranibizumab 0.5 mg could be continued based on a complex re-treatment algorithm.

Efficacy outcomes, statistical methods and sample size

The primary efficacy outcome was the mean change in visual acuity from baseline to 1 year adjusted for baseline visual acuity. The primary analysis consisted of three pairwise comparisons of the mean change in the sham + prompt laser group compared with each of the other three groups. The primary analysis included all randomized eyes and followed ITT principles. Data were included in the 1 year analysis when an examination was performed between 308 and 420 days after randomization. For eyes without 1 year data, the LOCF method was used to impute data for the primary analysis. The study also included a number of sensitivity analyses of the primary efficacy endpoint which were described but the results were not provided. In addition, there were a number of subgroup analyses of the primary efficacy outcome based on prior treatment for DME, baseline visual acuity, baseline OCT measured central subfield thickening, baseline level of diabetic retinopathy determined by grading of fundus photographs, or description of oedema by the treating ophthalmologist as predominantly focal or diffuse. There were a number of secondary VA efficacy outcomes relating to the proportion of letters gained or lost from baseline to Year 1. In addition, there were secondary efficacy outcomes relating to change in retinal thickness from baseline to Year 1.

For all continuous outcomes, treatment group comparisons were made using ANOVA models with generalized estimating equations to account for correlated data from study participants with 2 study eyes. For binary outcomes, proportions were compared between treatment groups using logistic regression models with generalized estimating equations. All analyses included adjustment for baseline visual acuity. In addition, models in which the central subfield thickness was the outcome included baseline central subfield thickness as a covariate, and models with retinal volume as the outcome included both baseline central subfield thickness and retinal volume as covariates. Similar analyses were performed on 2 year results. All p-values were reported as being two-sided.

Sample size was estimated to be 842 eyes (~ 701 study participants assuming 20% of study participants would have 2 study eyes) on the basis of an expected population difference in the letter score of 6.0 and SD of 18, a correlation between baseline and 1 year scores of 0.48, a type 1 error rate of 0.016 (adjusted for multiple comparisons and alpha spending for interim data reviews) and a power of approximately 90%.

Patient population

Between March 2007 and December 2008, 691 study participants (mean age 63±10 years; 44% women) were enrolled, 163 (24%) with 2 study eyes. The mean baseline visual acuity letter score in study eyes was 63±12 (~ 20/63±2.4 lines), and the mean OCT central subfield retinal thickness was 405±134 µm. The 854 study eyes were assigned to either sham+prompt laser (n=293), ranibizumab+prompt laser (n=187), ranibizumab+deferred laser (n=188) or triamcinolone+prompt laser (n=186). The baseline demographic and ocular criteria were reasonably well balanced across the four treatment groups.

Results

The 1 year mean \pm SD increase in the VA letter score from baseline was 9 \pm 11 letters in the ranibizumab+prompt laser group and 3 \pm 13 letters in the sham injection+prompt laser group: difference of 5.8 letters [95%CI: 3.2, 8.5]; $p < 0.001$. In the ranibizumab+deferred laser group the increase was 9 \pm 12 letters and the difference between this group and the sham+prompt laser group was +6.0 letters [95%CI: +3.4, +8.6]; $p < 0.001$. The results for the comparison with triamcinolone have not been discussed in this evaluation as these results were considered not to be relevant to the submission

The results also showed a statistically significantly greater proportion of eyes with a substantial improvement of ≥ 10 letters (50% and 47%) and ≥ 15 letters (30% and 28%), and a lower proportion of eyes with a substantial worsening of ≥ 10 letters (4% and 3%) and ≥ 15 letters (2% and 2%) in the ranibizumab+prompt laser and ranibizumab+deferred laser groups, respectively, compared with the sham+prompt laser group (28% and 15% for ≥ 10 and ≥ 15 letter gain, respectively, and 13% and 8% for ≥ 10 and ≥ 15 letter loss, respectively). Most of the overall improvement in mean visual acuity and proportion of patients with ≥ 10 letter improvement from baseline within the ranibizumab treated groups occurred by the 8 week study visit, with continued improvement through the 1 year primary outcome visit and stabilization thereafter.

Mean \pm SD reductions from baseline in central subfield thickness at 1 year were 102 \pm 151 μ m, 131 \pm 129 μ m and 137 \pm 136 μ m in the sham+prompt laser (n=271), ranibizumab+prompt laser (n=171), and ranibizumab+deferred laser groups (n=175), respectively. The difference between sham+prompt laser and ranibizumab+prompt laser was -55 μ m [95%CI: -78, -32] ($p < 0.001$), and the difference between sham+prompt laser and ranibizumab+deferred laser was -49 μ m [95%CI: -72, -26] ($p < 0.001$).

Subgroup analyses in all treatment groups showed that patients with baseline VA letter scores ≤ 65 (Snellen $\leq 20/50$) had greater VA improvements from baseline at Year 1 than patients with baseline VA letter scores ≥ 66 (Snellen $> 20/50$). In the two ranibizumab + laser groups, patients with baseline central subfield thickness ≥ 400 μ m had greater VA improvements from baseline at 1 year than patients with baseline subfield thickness of < 400 μ m, while no difference in the subgroups was noted in the sham + prompt laser group. None of the other subgroup analyses in the two ranibizumab + laser groups showed notable differences in change in VA from baseline at Year 1.

Evaluator comment

DRCR.net was considered to be a good quality study. However, it provided only limited data directly supporting the submission as it included no ranibizumab 0.5 mg only treatment group. It did include an unmasked ranibizumab 0.5 mg + deferred (≥ 24 week) laser group (n=188). At the 16 week visit (after 1 month after the fourth injection), 47 (25%) of the 187 eyes in the ranibizumab 0.5 mg + prompt laser group and 41 (22%) of the 188 eyes in the ranibizumab 0.5 mg + deferred laser group met "success" criteria (visual acuity letter score ≥ 84 [$\geq 20/20$] or OCT central subfield < 250 μ m) and did not receive an injection at the 16 week visit. In the ranibizumab 0.5 mg + deferred laser group no patients had received laser treatment prior to the 16 week visit. A total of 17 eyes (9%) in the ranibizumab 0.5 mg + prompt laser group and 15 eyes (8%) in the ranibizumab 0.5 mg + deferred laser group met "success" criteria at 16 weeks and did not receive an additional injection before the 1 year primary outcome visit. At the 1 year primary outcome visit, 89 (32%) of the eyes in the sham + prompt laser group, 109 (64%) of the eyes in the ranibizumab 0.5 mg + prompt laser group and 92 (52%) of the eyes in the ranibizumab 0.5 mg + deferred laser group met the "success" criteria. At 1 year, mean (SD) improvement in BCVA from baseline was 9 (12) letters in the ranibizumab 0.5 mg +

deferred laser group (n=188) and 9 (11) letters in the ranibizumab 0.5 mg + prompt laser group (n=187).

Focal/grid laser treatment was not permitted in the ranibizumab 0.5 mg + deferred laser group until the 24 week study visit; from the 24 week study visit and before the 1 year primary outcome visit, 128 (72%) of these study eyes received no focal/ grid laser treatment, 35 (20%) received only 1 focal/grid laser treatment, and 15 (8%) received 2 focal/grid laser treatments. Overall, the efficacy results in ranibizumab 0.5 mg + prompt laser group were similar to those in the ranibizumab 0.5 mg + deferred laser, and both treatments were superior to sham treatment alone. However, in the ranibizumab 0.5 mg + deferred laser group not all eyes avoided the need for focal/grid laser treatment over the 12 month study period, with 28% requiring at least 1 laser treatment between the 24 week visit and the 1 year visit when the re-treatment algorithm was followed. Overall, the study provides evidence that ranibizumab 0.5 mg with prompt or deferred laser is more effective at 1 year than prompt laser alone for the treatment of DME.

READ-2 Study [Nguyen et al., 2009]

Objectives

The objective was to compare the effects of treatment with ranibizumab 0.5 mg, focal/grid laser and ranibizumab 0.5 mg + focal/grid laser on visual acuity and CRT in patients with visual impairment due to DME.¹⁰

Design

The study adhered to the guidelines of the Declaration of Helsinki, and the protocol and consent form were approved either by relevant local IRBs or by the Western IRB. Each subject provided written informed consent. The study was monitored by an independent data and safety monitoring committee. It was conducted at 14 sites in the USA through an investigator initiated IND granted by the FDA. The study was sponsored by the Juvenile Diabetes Research Foundation and Genentech. The trial is also referred to as the Ranibizumab for Edema of the macula in Dibabetes (READ-2) Study.

Inclusion and exclusion criteria

Patients (aged ≥ 18 years) with T1DM or T2DM and DME were eligible if they had reduction in visual acuity between 20/40 and 20/320 and met the following criteria: (1) centre subfield thickness ≥ 250 μm measured by OCT; (2) glycosylated haemoglobin $\geq 6\%$ within 12 months before randomization; (3) no potential contributing causes to reduced visual acuity other than DME; (4) reasonable expectation that scatter laser photocoagulation would not be required for the next 6 months. Patients were excluded if they had received focal/grid laser treatment within 3 months, intraocular injection of steroid within 3 months or intraocular injection of a VEGF antagonist within 2 months. If both eyes were eligible, the eye with the greater centre subfield thickness was the study eye.

Investigational plan

Consenting patients were screened with medical history, physical examination, and measurement of BCVA by an experienced examiner using the ETDRS protocol, a slit-lamp examination, measurement of intraocular pressure, dilated fundoscopic examination, an OCT evaluation, a fluorescein angiogram and laboratory tests on blood and urine. Eligible patients were randomized 1:1:1 to ranibizumab 0.5 mg alone, focal/grid laser alone, or ranibizumab 0.5 mg + focal/grid laser. Patients in the ranibizumab 0.5 mg group received IVT injections at baseline and Months 1, 3 and 5. Patients in the focal/grid laser group received treatment at baseline and again at Month 3 if centre subfield thickness was ≥ 250

µm. Patients in the ranibizumab 0.5 mg + laser group received IVT injections at baseline and Month 3, followed by focal/grid laser 1 week after each injection.

After Month 6, patients were eligible to receive ranibizumab no more than every 2 months or focal/grid laser treatment no more than every 3 months if the re-treatment criterion of centre subfield thickness ≥ 250 µm was met. Safety evaluations, measurement of BCVA, eye examinations and OCT scans were done at all study visits. Fluorescein angiography was performed at baseline and 3 and 6 months. Measurements of glycosylated haemoglobin were done at baseline and 3 and 6 months. Haematology and blood chemistry tests were performed at baseline and 6 months.

A central reading centre served as the coordinating, data management and reading centre. Personnel from the participating sites were certified to perform digital fluorescein angiography and OCT based on standardized protocols. Visual acuity examiners were required to be certified.

Treatment

Ranibizumab 0.5 mg was administered by IVT injection using standard procedures. The fundus was examined after injection to ensure retinal perfusion, and patients were observed for 1 hour or until intraocular pressure returned to normal. Patients were contacted the day after each injection and asked if they had decreased vision, eye pain, unusual redness or any new symptoms.

Focal/grid laser treatment was administered according to the ETDRS protocol with some modifications. Focal treatment was administered to each leaking microaneurysm and grid treatment was placed in areas of thickened retina and areas of non-perfusion between 500 and 3000 µm from the centre of the fovea.

Efficacy outcomes

The primary efficacy outcome was the mean change in BCVA from baseline to Month 6.

The secondary efficacy outcomes included vision related and anatomic outcomes. The vision related secondary efficacy outcomes were mean change in BCVA from baseline to Month 3 and percentage of patients with improvement in visual acuity of ≥ 3 lines and ≥ 2 lines between baseline and Month 6. The anatomic secondary efficacy outcomes were mean change in excess foveal thickness between baseline and Month 6 and the percentage of patients with elimination of 90% or 50% excess foveal thickness. Excess foveal thickness was defined as normal 1 mm centre subfield thickness (212 µm) subtracted from measured centre subfield thickness to give the excess foveal thickness for each patient.

Statistical methods

Change from baseline in ETDRS visual acuity and change from baseline in excess foveal thickness were compared across the 3 groups at Months 3 and 6 using one-way ANOVA with Bonferroni *post hoc* correction for multiplicity. Outcome comparison between different time points within a group was done using a single sample t-test. Secondary anatomic and functional outcomes were compared using a two-sided Fisher exact test. All patients who did not have 6 month visit data, but had any post-treatment data at a time point before Month 6, had the LOCF for analysis of the primary outcome.

Baseline characteristics and disposition of the study groups

Baseline characteristics of the 126 randomized patients are provided below in Table 18. The 3 groups were balanced with respect to age, mean BCVA and Hb1Ac levels. However, there were imbalances among the three treatment groups with respect to gender, race, and mean excess foveal thickness. In particular, mean excess foveal thickness was notably

greater in Group 3 (ranibizumab 0.5 mg + focal/grid laser) compared with both Groups 1 (ranibizumab 0.5 mg) and 2 (focal/grid laser). At baseline, 78 of the 126 patients had hypercholesterolemia that required treatment, and this was balanced among the groups: 26 in Group 1; 29 in group 2; and 23 in group 3. Of the 126 randomized patients, 5 were excluded from the efficacy analysis, 4 discontinued and had LOCF, and 2 missed the 6 month primary endpoint visit and had LOCF.

Table 18: READ-2: Baseline characteristics (randomized patients)

	Group 1: Ranibizumab (n = 42)	Group 2: Laser (n = 42)	Group 3: Ranibizumab (n = 42)
Gender (% women)	69	55	52
Race (% Caucasian)	76	64	69
Age (mean yrs)	62	62	62
Mean BCVA (ETDRS letters read)	24.85	28.35	24.87
Mean BCVA (Snellen equivalent)	20/80	20/80+3	20/80
Mean excess foveal thickness (μm)	198.75	227.67	262.52
Hemoglobin A1C (mean mg/dl)	7.39	7.77	7.59

BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study.

Efficacy outcome results – visual acuity (primary and secondary outcome measures)

At Month 6, the mean change in BVCA from baseline (primary efficacy outcome) was +7.24 letters in the ranibizumab 0.5 mg group, -0.43 in the focal/grid laser group, and +3.80 in group the ranibizumab 0.5 mg + focal/grid laser group. The comparison between the ranibizumab 0.5 mg and the focal/grid laser groups was statistically significant ($p=0.01$, ANOVA) but there was no statistically significant difference between the ranibizumab 0.5 mg and the ranibizumab 0.5 mg + ranibizumab 0.5 mg + focal/grid laser ($p=0.08$). It is not clear from the description of the results how many patients were included in each of the three treatment groups for the 6 month analysis of the primary efficacy endpoint. However, 42 patients were randomized to each of the three treatment groups.

At Month 3, the mean gain in BCVA from baseline (secondary efficacy analysis) was 3.98 letters in the ranibizumab 0.5 mg group and was significantly better than the mean loss of 1.48 letters in the focal/grid laser group ($p = 0.01$) but not significantly different from the mean gain of 1.93 letters in the ranibizumab 0.5 mg + focal/grid laser group 3 ($p=0.22$). No patient numbers could be identified in the report for the three treatment groups.

For patients with available data at 6 months, 22% (8/37) in the ranibizumab 0.5 mg group had an improvement of ≥ 3 or more lines of BCVA compared with 0% (0/38) in the focal/grid laser group ($p=0.002$), with the respective values for improvement of ≥ 2 lines being 46% (17/37) and 5% (2/38) ($p=0.00004$). In the ranibizumab 0.5 mg + laser group, 8% (3/40) of patients had an improvement of ≥ 3 lines and 30% (12/40) had an improvement of ≥ 2 lines. The comparison between ranibizumab 0.5 mg + focal/grid laser and focal/grid laser for improvement by ≥ 2 lines statistically significantly favoured the combination group ($p=0.007$).

Efficacy outcome results – anatomic (secondary outcome measures)

In the ranibizumab 0.5 mg group ($n=37$), there was a reduction in mean excess foveal thickness from 210.0 μm at baseline to 103.7 μm at Month 6, an approximately 50% reduction in macular oedema. In the ranibizumab 0.5 mg + laser group ($n=40$), there was a

reduction in mean excess foveal thickness from 262.5 µm at baseline to 145.3 µm at month, an approximately 45% reduction in macular oedema. In the laser group (n=38), there was a reduction in mean excess foveal thickness as baseline to 227.6 µm at baseline to 144.8 µm at Month 6, an approximately 36% reduction in macular oedema. There were no reported statistical results for the pairwise comparisons.

Evaluator comment

READ-2 was considered to provide limited data supporting the submission. It showed that ranibizumab 0.5 mg alone administered at baseline and Months 1, 3 and 5 resulted in statistically significantly greater reductions in mean BCVA from baseline to Month 6 (primary efficacy outcome) than laser alone given at baseline and Month 3. The treatment regimen in this study for the ranibizumab 0.5 mg alone group was significantly different from that being proposed for approval. The BCVA letter gain from baseline at 6 months was lower in the ranibizumab 0.5 mg + laser group than in the ranibizumab 0.5 mg group. This difference might reflect the lower number of ranibizumab injections given in the combined ranibizumab 0.5 mg + laser group (2 injections) compared with the monotherapy ranibizumab 0.5 mg group (4 injections).

READ-2 was not considered to be methodologically robust. The study report has the following deficiencies: (i) confusing reporting of the number of patients included in the primary efficacy endpoint analysis; (ii) no information on the method of randomization; (iii) no information on masking; (iv) no information on the efficacy populations, in particular no information on whether the efficacy analyses used an ITT approach; (v) no 95% CIs provided for the differences in BCVA or anatomic endpoints between treatments; (vi) no standard deviations provided for mean BCVA and anatomic changes from baseline in the three treatment groups; and (vii) baseline imbalance in mean excess foveal thickness among the three treatment groups.

Analyses performed across studies

No pooled data were provided analysing the results from RESTORE and RESOLVE and no meta-analyses were performed. This is acceptable as the heterogeneity of dose in the 6 mg/mL and 10 mg/mL treatment groups in RESOLVE would preclude satisfactory pooling of results with the 0.5 mg treatment group in RESTORE. In addition, the patient populations in the two studies differed with patients in RESOLVE being enrolled if laser treatment could be deferred for 3 months, while patients in RESTORE were enrolled if laser treatment was indicated at baseline.

Evaluator's conclusions on clinical efficacy

Restore 12 month data

The submission included one high quality pivotal study [RESTORE]. This study showed that the mean (SD) average increase in BCVA from baseline from Month 1 to Month 12 was statistically significantly greater in both the ranibizumab 0.5 mg and the ranibizumab 0.5 mg + laser groups than in the sham injection + laser group (6.1 [6.4], 5.9 [7.9], and 0.8 [0.6] letters, respectively). The large SD values in each of the three treatment groups indicate high intersubject variability as regards the primary efficacy outcome for each of the three treatments.

Data from a pairwise ANOVA (stratified) model showed that the LSM difference between ranibizumab 0.5 mg and sham injection was 5.4 letters [95%CI: 3.5, 7.4]; $p < 0.0001$ (CMH). Similar results were observed for the comparison between ranibizumab 0.5 + laser and sham injection + laser, with the difference being 4.9 letters [95%CI: 2.8, 7.0]; $p < 0.0001$ (CMH).

In the two ranibizumab 0.5 mg treatment groups, improvement in BCVA of about 6 letters was observed at Month 3 following initiation of treatment and this improvement was then maintained through to Month 12. In contrast, an improvement in BCVA of about 1 letter was maintained from about Month 3 through to Month 12 in the sham injection + laser treatment group.

The secondary efficacy endpoint analyses relating to VA, CRT, and self reported improvement in visual function all supported the primary efficacy endpoint analysis. In particular, the proportion of patients gaining ≥ 15 letters (or with BCVA ≥ 84 letters) at endpoint, or gaining ≥ 10 letters (or with BCVA of ≥ 84 letters) at endpoint was statistically significantly greater in the ranibizumab 0.5 mg group (22.6% and 37.4%, respectively) and the ranibizumab 0.5 mg + laser group (22.9% and 43.2%, respectively) than in the sham injection + laser group (8.2% and 15.5%, respectively). Similarly, the proportion of patients losing ≥ 15 or losing ≥ 10 letters was statistically significantly lower in the ranibizumab 0.5 mg group (0.9% and 3.5%, respectively) and the ranibizumab 0.5 mg + laser group (3.4% and 4.2%, respectively), than in the sham injection + laser group (8.2% and 12.7%, respectively). The mean reduction in CRT from baseline to Month 12 was statistically significantly greater in both ranibizumab groups compared with the sham injection + laser group. Self reported improvement in visual function assessed by various NEI FVQ-25 scores statistically significantly favoured both ranibizumab groups compared with the sham injection + laser group.

The subgroup analyses of the primary efficacy endpoint should be considered to be exploratory and hypothesis generating as the analyses were underpowered. Nevertheless, primary BCVA efficacy endpoint analyses were generally similar in the subgroup populations to the corresponding analysis in the total population. However, BCVA in patients with baseline visual impairment ≤ 73 letters improved to a greater extent with all treatments compared with patients with baseline visual impairment > 73 letters, as did BCVA in patients with lower baseline CRT and in patients aged < 65 years compared with patients aged ≥ 65 years. There were no notable differences in outcomes based on gender, DME type (focal or diffuse), duration of DME at baseline, or prior laser treatment.

Overall, RESTORE was considered to provide convincing evidence of the superiority of ranibizumab 0.5 mg compared with laser as regards improving visual acuity, reducing CRT and improving self reported visual function. There were no significant efficacy differences between the ranibizumab 0.5 mg group and the ranibizumab 0.5 mg + laser group during the 12 month study period. There was only a small improvement in BCVA (primary endpoint) with laser treatment (mean average increase from baseline of 0.8 letters) suggesting that in this study laser treatment stabilized rather than improved visual acuity.

Resolve 12 month data

In addition to RESTORE, the submission included one additional study identified by the sponsor as being pivotal [RESOLVE]. However, for the reasons previously discussed, RESOLVE was considered to be supportive rather than pivotal. Nevertheless, this was a good quality study. The study compared ranibizumab administered as 6 mg/mL and 10 mg/mL solution strength injections with sham injections. The initial ranibizumab doses consisted of 0.3 mg (6 mg/mL solution) and 0.5 mg (10 mg/mL solution) with doubling of the initial dose being permitted from Month 1 if criteria relating to changes in retinal thickness were met. Treatment could be discontinued for “success” after the third injection (from Month 3) if the evaluating physician considered that both the CRT and BCVA “stability” criteria had been met.

The primary efficacy endpoint was identical to that for RESTORE and the secondary efficacy endpoints were also similar for the two studies. However, interpretation of the

efficacy data in RESOLVE is complicated by dose doubling allowed in both treatment groups after the first dose.

The key population for confirmatory purposes was considered to be Group B (n=109). In this group, the mean (SD) average BCVA increase from baseline from Month 1 to 12 was 9.4 (5.8), 6.0 (9.9), 7.6 (8.3) and 1.2 (8.3) letters for ranibizumab 6 mg/mL (n=37), ranibizumab 10 mg/mL (n=40), ranibizumab pooled (n=77) and sham injection (n=32) groups, respectively. The LSM difference estimated from a pairwise ANOVA (stratified model) between ranibizumab 6 mg/mL and sham injection was 8.1 letters ([95%CI: 4.7, 11.5], $p < 0.0001$), for the corresponding comparison between ranibizumab 10 mg/mL and sham injection the difference was 5.5 letters ([95%CI: 1.0, 9.9], $p = 0.0067$) and for the corresponding comparison between ranibizumab pooled and sham injection the difference was 6.7 letters ([95%CI: 3.2, 10.1], $p = 0.0002$).

The BCVA difference (Group B) between ranibizumab 6 mg/mL and sham injection was considered to be clinically meaningful as it exceeds 8 letters, which was the treatment difference on which the sample size calculations were based. However, the 6 mg/mL group included patients who had been given 0.3 mg and 0.6 mg doses and 67.6% of patients in Group B (25 out of 37) had their dose doubled from 0.3 mg to 0.6 mg during the study, and 68.0% (17 out of 25) of these patients had their dose doubled at Month 1 (at the first opportunity).

The BCVA difference (Group B) between ranibizumab 10 mg/mL and sham injection of 5.5 letters was considered to be of doubtful clinical significance. Patients in the 10 mg/mL dose group included those who had been administered 0.5 mg and 1.0 mg doses and 72.5% of patients in Group B (29 out of 40) had their dose doubled from 0.5 mg to 1.0 mg during the study, and 72.4% (21 out of 29) had their dose doubled at the Month 1 (at the first opportunity).

In Group B, the increase in BCVA (primary efficacy endpoint) was greater in the 6 mg/mL group compared with the 10 mg/mL group, indicating no dose response relationship. When the two ranibizumab treatment groups were combined, the difference in BCVA (primary efficacy endpoint) between the ranibizumab combined and the sham injection groups was 6.7 letters [95%CI: 3.2, 10.1], $p = 0.0002$. This result suggests that the treatment difference between the combined ranibizumab group and the sham group is of doubtful clinical significance.

The results for the primary efficacy analysis in Group A+B were consistent with those for the corresponding analysis in Group B. However, the differences between the three ranibizumab groups and the sham injection group were greater in Group A+B compared with Group B. The mean average injection doses in the ranibizumab 6 mg/mL, ranibizumab 10 mg/mL, and ranibizumab 10 mg/mL groups were 0.47 mg, 0.76 mg and 0.62 mg respectively.

The key secondary endpoint analyses in Group B were consistent with those for the primary efficacy analysis, with differences between ranibizumab 6 mg/mL and sham being greater than differences between ranibizumab 10 mg/mL and sham and differences between the ranibizumab combined and sham falling between the lower and upper dose groups. The results for all three ranibizumab dose groups were impressive when compared with sham as regards the proportion of patients gaining ≥ 10 or ≥ 15 letters and losing ≥ 10 or ≥ 15 letters, and all differences between the three ranibizumab groups and sham were considered to be clinically meaningful.

DRCR.net [2010] 12 month data

The data from the published study DRCR.net were considered to provide support for the submission. At the Week 16 visit, patients in the ranibizumab 0.5 mg + deferred laser group had received 4 ranibizumab 0.5 mg injections at monthly intervals (0, 1, 2, and 3 months) and no laser treatment. This allowed a comparison to be made at this time point between patients in this group and patients in the ranibizumab 0.5 mg + prompt laser group. However, patients in the ranibizumab 0.5 mg + deferred laser group (n=188) were not masked to treatment allocation. At the 16 week visit, 47 (25%) of the 187 eyes in the ranibizumab 0.5 mg + prompt laser group and 41 (22%) of the 188 eyes in the ranibizumab 0.5 mg + deferred laser group met “success” criteria (visual acuity letter score ≥ 84 [$\geq 20/20$] or OCT central subfield $< 250 \mu\text{m}$) and did not receive an injection at the 16 week visit. This suggests that after 4 injections success criteria were similar for the two treatment groups. In addition, a total of 17 eyes (9%) in the ranibizumab 0.5 mg + prompt laser group and 15 eyes (8%) in the ranibizumab 0.5 mg + deferred laser group met “success” criteria at 16 weeks and did not receive an additional injection before the 1 year primary outcome visit.

At the 1 year primary outcome visit, 89 (32%) of the eyes in the sham + prompt laser group, 109 (64%) of the eyes in the ranibizumab 0.5 mg + prompt laser group and 92 (52%) of the eyes in the ranibizumab + deferred laser group met the success criteria. At 1 year, mean (SD) improvement in BCVA from baseline was 3 (13) in the sham injection + prompt laser group, 9 (11) letters in the ranibizumab 0.5 mg + prompt laser group and 9 (12) letters in the ranibizumab 0.5 mg + deferred laser group. Overall, at the 1 year primary outcome visit the efficacy results for ranibizumab 0.5 mg + prompt laser were similar to those for ranibizumab 0.5 mg + deferred laser and both treatments were superior to laser treatment alone. Of note, in the ranibizumab 0.5 mg + deferred laser group, from the 24 week study visit and before the 1 year primary outcome visit, 128 (72%) of the study eyes received no laser treatment, 35 (20%) received only 1 laser treatment, and 15 (8%) received 2 laser treatments.

The 1 year results provided evidence for the superior efficacy of ranibizumab 0.5 mg with prompt or deferred laser compared with prompt laser alone. However, in the ranibizumab 0.5 mg + deferred laser group not all eyes avoided the need for laser treatment over the 12 month study period with 28% requiring at least 1 laser treatment between the 24 week and the 1 year study visit when the re-treatment algorithm was followed.

READ-2 [Nguyen et al., 2009] 12 month data

The data from READ-2 [Nguyen et al., 2009] were considered to provide only limited support for the submission due to the open label design, the small number of patients and the different dosage regimen from that being proposed.

At Month 6, the mean gain in BCVA was significantly greater in the ranibizumab 0.5 mg group (+7.24 letters, $p=0.01$ [ANOVA]) compared with the laser group (+0.43 letters), while the improvement in the ranibizumab 0.5 mg + laser group (+3.80 letters) was not statistically different from the other two groups. The number of patients in the three treatment groups for the analysis of the primary efficacy endpoint was not entirely clear from the study report but 42 patients had been randomized to each of the three treatment groups.

Of the 37 patients in the ranibizumab 0.5 mg group for whom data were available at 6 months, 8 (22%) had an improvement of ≥ 3 or more lines of BCVA and 17 (46%) had an improvement of ≥ 2 or more lines. In the laser group, none of the 38 patients improved by ≥ 3 or more lines and 2 patients (5%) improved by ≥ 2 more lines, both significantly less than in the ranibizumab group ($p=0.002$ and $p=0.00004$, respectively, Fisher’s exact test).

The dosage regimen used in this study was 4 injections for all patients administered at time points 0, 1 month, 3 months and 5 months. There was no option to discontinue treatment from Month 3 if VA had been stable following the first 3 injections. In addition, laser administered in combination with ranibizumab 0.5 mg appeared to reduce the effect of ranibizumab 0.5 mg alone (+3.61 vs +7.07 letters, respectively).

Long term data

There were no efficacy data in RESTORE or RESOLVE beyond 12 months. However, DRCR.net included efficacy data extending beyond 12 months, as did a recent published study reporting the 2 year outcomes in READ-2 [Nguyen et al., 2010].¹² In *Nguyyen et al., 2010*, in those patients who had remained in the study for 24 months the respective mean improvements in BCVA at 6 months and 24 months were 7.4 and 7.7 letters for ranibizumab 0.5 mg (n=33), 0.5 and 5.1 letters for laser (n=34), and 3.8 and 6.8 letters for ranibizumab 0.5 mg + laser (n=34). These results suggest that mean improvement at 6 months can be maintained through to 24 months in patients treated with ranibizumab 0.5 mg, with or without laser therapy.

The published data from DRCR.net showed that improvement in BCVA from baseline observed at 1 year in the ranibizumab 0.5 mg with prompt or deferred laser groups were maintained through to 2 years. In the ranibizumab 0.5 mg + deferred laser group the BCVA mean (SD) improvement from baseline to 2 years was 10 (15) letters in 112 patients compared with 9 (12) letters at 1 year in 188 patients and the corresponding results for the sham injection + prompt laser group were 2 (16) letters in 163 patients and 3 (13) letters in 293 patients. At 2 years, the comparison between the ranibizumab 0.5 mg + deferred laser and sham injection + prompt laser groups for mean (SD) change in BCVA from baseline (+10 [15] and +2 [16], respectively) was statistically significant (p=0.01).

In DRCR.net, for the 218 study participants (58%) with 2 years of follow up in the ranibizumab groups, the [interquartile range (IQR)] number of ranibizumab injections between the 1 year visit, inclusive, and before the 2 year visit were 2 [0, 4] and 3 [1, 7] in the ranibizumab 0.5 mg + prompt laser group and the ranibizumab 0.5 mg + deferred laser group, respectively, for a total of 11 [7, 14] and 13 [8, 17] injections from baseline to the 2 year visit. Only 32% of participants in the ranibizumab 0.5 mg + prompt laser group, and 21% of participants in the ranibizumab 0.5 mg + deferred laser group had no ranibizumab injections between the 1 and 2 year visits.

Safety

Studies providing evaluable safety data

In this AusPAR, evaluation of safety in patients with DME treated with ranibizumab focuses primarily on the 12 month data (pooled and individual) from RESTORE and RESOLVE, supported by the 24 month data primarily from the published study DRCR.net. In addition, the 24 month safety data from two studies in patients with AMD have also been reviewed [PIER and EXTEND]. The 24 month data from these two AMD studies have not been previously evaluated by the TGA and were stated by the sponsor to have been included in the submission “for information only and not directly relevant to the DME application”.

Patient exposure in the safety sets

The sponsor's *Summary of Clinical Safety (SCS)* included pooled safety data from RESOLVE and RESTORE and safety data from both studies considered individually. In the SCS, the primary data set for analysis of safety was the RESTORE/RESOLVE pooled safety set which included 376 patients of whom 217 had received ranibizumab IVT injections as monotherapy and 159 had received control treatment (Table 19). In the

RESOLVE/RESTORE pooled safety set, the ranibizumab group was created by pooling the two ranibizumab groups from RESOLVE (the 6 mg/mL and the 10 mg/mL treatment groups) and the ranibizumab monotherapy group from RESTORE (the 0.5 mg group) and the control group was created by pooling the sham injection group from RESOLVE and the sham injection + laser group from RESTORE. The data from the ranibizumab 0.5 mg + laser group in RESTORE was not pooled in the RESOLVE/RESTORE safety set.

Table 19: RESTORE/RESOLVE: Pooled safety set number of patients

	Ranibizumab monotherapy	Control
RESOLVE	102 [1]	49 [2]
RESTORE	115 [3]	110 [4]
TOTAL	217	159

[1] Ranibizumab 6 mg/ml and Ranibizumab 10 mg/ml pooled.

[2] Sham injection.

[3] Ranibizumab 0.5 mg injection [+ Sham laser].

[4] Laser [+ Sham injection].

In RESOLVE/RESTORE, the 217 patients in the ranibizumab group received 1,837 injections with a mean (SD) of 8.5 (3.1) injections and median of 9.0 injections [range: 1-12] and the corresponding figures in the 159 patients in the control group were 1,236 injections, mean (SD) 7.8 (3.4) and median 8.0 [range: 1-12]. The median duration of follow up in the ranibizumab and control groups was 364 days [range: 15-492] and 364 days [range: 21-469], respectively.

In RESOLVE, the protocol allowed dose doubling over the 12 month treatment period after the first dose (0.3→0.6 mg and 0.5→1.0 mg). The majority of patients in all three treatment groups were exposed to more than 9 injections (74.5% in the 6 mg/mL group, 72.5% in the 10 mg/mL group and 59.2% in the sham group). The mean number of injections received over the duration of the study was comparable in all three treatment groups (10.2 in the 6 mg/mL group, 10.1 in the 10 mg/mL group and 8.9 in the sham group). The median [range] treatment duration in the 6 mg/mL, 10 mg/mL and sham treatment groups was 330 [41-401], 330 [1-424] and 324 [47-425] days. Dose doubling occurred in 68.6% of ranibizumab treated patients and in 91.8% of sham injection treated patients during the study, with the majority of cases of dose doubling occurring at Month 1 (70.0% ranibizumab vs 77.8% sham). The RESOLVE safety analysis also included examination of data from the pooled ranibizumab group (6 mg/mL + 10 mg/mL groups) which included 102 patients who had received a mean number of 10.2 injections with an average dose per injection of 0.62 mg.

In RESTORE, the majority of patients in all three treatment groups were exposed to more than 7 injections (53.9% in the ranibizumab 0.5 mg group, 52.5% in the ranibizumab 0.5 mg + laser group and 53.6% in the sham + laser group). The mean number of injections received from 0 to 11 months was similar in all three treatment groups (7.0 in the ranibizumab 0.5 mg group, 6.8 in the ranibizumab 0.5 mg + laser group and 7.3 in the sham injection + laser group).

Patient characteristics in the safety sets

In RESOLVE/RESTORE, the baseline demographics of the ranibizumab and control groups were similar. The baseline ocular and DME disease characteristics in the two treatment groups were also similar. The diabetes characteristics of the two treatment groups were also similar with > 90% of patients having T2DM, mean HbA1c ~ 7.3% (~ 70% of patients having mean HbA1c < 8%) and mean time since diagnosis of diabetes about 14 years. Baseline blood pressure characteristics of the two treatment groups were also similar with

mean systolic BP being ~ 139 mmHg and mean diastolic BP being ~ 79 mmHg, with about 60% of patients having a systolic BP \geq 140 mmHg and ~ 20% of patients having a diastolic BP \geq 90 mmHg.

In RESOLVE/RESTORE, more patients in the ranibizumab group had an active ocular history at baseline than in the control group (56.2% vs 44.0%), consisting primarily of the MedDRA System Organ Class (SOC) of *Eye Disorders*.¹⁵ Active cataract at baseline was recorded in a similar proportion of patients in ranibizumab and control groups (19.8% and 14.5%, respectively). A history of glaucoma was present in 8 (3.7%) ranibizumab patients and 3 (1.9%) control patients. A history of blepharitis was reported in 13 (6.0%) versus 7 (4.4%) patients in the ranibizumab and control groups, respectively.

In RESOLVE/RESTORE, all patients had active non-ocular medical histories at the start of study treatment. The most common SOCs with reported active events were *Cardiac Disorders* (16.1% in ranibizumab, 13.2% in control), *Gastrointestinal Disorders* (10.1% in ranibizumab, 11.3% in control), *Musculoskeletal and Connective Tissues Disorders* (16.6% in ranibizumab, 15.7% in control), *Nervous System Disorders* (13.4% in ranibizumab, 11.3% in control) and *Vascular Disorders*, including hypertension as a diabetic comorbidity (77.4% in ranibizumab, 74.8% in control).

In RESTORE, 44.3% (51/115) of patients in the ranibizumab 0.5 mg group had an active ocular medical condition at baseline compared with 37.5% (45/120) in the ranibizumab 0.5 mg + laser group and 39.1% (43/110) in the sham injection + laser group. The majority of reports in the three treatment groups were *Eye Disorders* (43.5% vs 35.8% vs 37.3%, respectively). Of these disorders, diabetic retinopathy was the most commonly reported (21.7% vs 16.7% vs 15.5%, respectively). In RESOLVE, 69.6% (71/102) of patients in the pooled ranibizumab group had an active ocular medical condition at baseline compared with 55.1% (27/49) in the sham injection group. The majority of reports in both the pooled ranibizumab and sham injection groups were *Eye Disorders* (69.6% vs 55.1%, respectively). Of these disorders, the most commonly reported in the pooled ranibizumab and sham injection groups were cataract (31.3% vs 28.6%, respectively).

In RESTORE, 5.8% to 7.3% of patients in each of the three treatment groups had used ocular medications and/or significant ocular therapies in the study eye prior to the start of the study, with the most commonly used medication in the three treatment groups being triamcinolone (1.7% to 3.4%). After the start of study drug treatment, 20.0% to 25.2% of patients in each of the three treatment groups were actively on or started to use ocular medications and/or significant ocular non-drug therapies in the study eye, with the most commonly used medication being Cosopt (dorzolamide hydrochloride/timolol maleate) which was used in 2.6% to 4.5% of patients in the three treatment groups. Non-ocular medications and/or non-ocular significant non-drug therapies prior to the start of the study had been used by 4.3% to 6.7% of patients in each of the three treatment groups. Non-ocular concomitant medications and/or non-ocular significant non-drug therapies after the start of treatment in the study eye were used by nearly all patients in the three treatment groups with the most frequently used medications being insulin, metformin, acetyl salicylic acid and statins. The pattern of concomitant therapies was similar in the three treatment groups.

In RESOLVE, ocular medications and/or significant non-drug therapies in the study eye were reported prior to the start of the study drug in 6.9% of patients in the pooled ranibizumab group and 6.1% in the sham group. After the start of the study drug treatment, 38.2% of patients in the pooled ranibizumab group and 61.2% of patients in the

¹⁵ MedDRA: Medical Dictionary for Regulatory Activities

sham group used ocular concomitant medications and/or significant non-drug therapies in the study eye, with the most commonly used ocular medication in the pooled ranibizumab group being metipranolol hydrochloride. Non-ocular medications and/or significant non-drug therapies prior to the start of the study drug were used by 2.9% of patients in the pooled ranibizumab group and 6.1% of patients in the sham group. After the start of treatment, non-ocular medications and/or non-drug therapies in the study eye were used in all patients with the most common medications being acetyl salicylic acid, metformin, statins and insulin. The pattern of concomitant therapies was similar in the three treatment groups.

Inclusion and exclusion criteria differences - RESOLVE/RESTORE

In RESTORE and RESOLVE, both studies included male and female patients > 18 years of age with either T1DM or T2DM with stable HbA1c levels (< 10%). Inclusion criteria required patients to have visual impairment due to focal or diffuse DME in at least one eye. If both eyes were eligible, then the one with the worse visual acuity was selected for study treatment unless the investigator deemed the other eye the more appropriate candidate based on medical grounds. The differences between the two studies as regards the key ocular inclusion criteria are summarized in Table 20.

Table 20: RESTORE and RESOLVE: Key ocular inclusion criteria differences

D2201 (RESOLVE)	D2301 (RESTORE)
diabetic macular edema for whom laser photocoagulation, in the opinion of the investigator, could be withheld for at least 3 months after randomization	N/A
study eye best-corrected visual acuity (BCVA) score between 73 and 39 letters, inclusively, using ETDRS-like visual acuity charts at 4 meters (approximate Snellen equivalent of 20/40 to 20/160)	study eye best-corrected visual acuity (BCVA) score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity charts at 4 meters (approximate Snellen equivalent of 20/32 to 20/160)
study eye central retinal thickness (CRT) \geq 300 μ m in the center subfield, as confirmed by the central reading center's evaluation of the optical coherence tomography (OCT) scans obtained at Visit 1	N/A

In RESTORE and RESOLVE, key concurrent ocular conditions/ocular history exclusion criteria shared by the two studies were: active intraocular inflammation or infection; active proliferative diabetic retinopathy; vitreomacular traction in the study eye; monocular patients or BCVA in the fellow eye < 24 letters (approximate Snellen equivalent 20/320); uncontrolled glaucoma (intraocular pressure (IOP) > 24 mmHg); or prior panretinal laser photocoagulation within 6 months prior to study entry. Key concurrent systemic conditions/systemic history exclusion criteria shared by the two studies included: chronic use of systemic corticosteroids within 4 months prior to randomization; history of renal failure requiring dialysis or renal transplant; any type of advanced, severe or unstable disease or its treatment that could interfere with primary and/or secondary outcome evaluations, including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk. The key exclusion criteria differences between the two studies are summarized in Table 21.

Table 21: RESTORE and RESOLVE: Key ocular exclusion criteria differences

D2201 (RESOLVE)	D2301 (RESTORE)
area of retinal ischemia $\geq 500\mu\text{m}$ and located $\leq 500\mu\text{m}$ from the center of the macula in the study eye as assessed by fluorescein angiography and confirmed by the Central Reading Center (CRC)	N/A
focal/grid laser photocoagulation in study eye within 6 months prior to study entry	focal/ grid laser photocoagulation in study eye within 3 months prior to study entry
N/A	renal insufficiency with creatinine levels $>2.0\text{mg/dl}$
N/A	history of stroke
change in antihypertensive treatment within 2 months prior to randomization with blood pressure systolic $>160\text{mmHg}$ or diastolic $>100\text{mmHg}$ at baseline or within 1 month prior to randomization	untreated hypertension or change in antihypertensive treatment within 3 months prior to randomization with blood pressure systolic $>160\text{mmHg}$ or diastolic $>100\text{mmHg}$ at baseline

Adverse Events

Common adverse events

Ocular adverse events

RESOLVE/RESTORE pooled safety set

In RESTORE/RESOLVE, ocular AEs were observed more commonly in patients in the ranibizumab group (59.4%) than in patients in the control group (44.7%). The SOCs *Eye Disorders, Investigations and Injury, Poisoning and Procedural Complications* were observed more commonly in the ranibizumab group than in the control group (Table 22). Ocular AEs (preferred term) occurring in $\geq 3\%$ of patients in the ranibizumab group (vs control) were: conjunctival haemorrhage 14.3 % vs 4.4%; eye pain 14.3% vs 13.8%; increased intraocular pressure 10.1% vs 0.6%; conjunctival hyperaemia 5.5% vs 5.7%; foreign body sensation in eye 5.1% vs 1.9%; lacrimation increased 4.6% vs 0.6%; myodesopsia 4.6% vs 0.6%; visual impairment 3.7% vs 1.3%; eye pruritis 3.2% vs 4.4%; and visual acuity reduced 3.2% vs 5.7%.

Table 22: RESTORE/RESOLVE : Ocular AEs (SOC) regardless of study drug relationship (pooled safety set)

SYSTEM ORGAN CLASS	Ranibizumab monotherapy N=217		Control N=159	
	n (%)	95% CI	n (%)	95% CI
Any AE	129(59.4)	(52.6, 66.0)	71(44.7)	(36.8, 52.7)
EYE DISORDERS	110(54.8)	(48.0, 61.6)	60(43.4)	(35.6, 51.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3(1.4)	(0.3, 4.0)	1(0.6)	(0.0, 3.5)
IMMUNE SYSTEM DISORDERS	2(0.9)	(0.1, 3.3)	0(0.0)	(0.0, 2.3)
INFECTIONS AND INFESTATIONS	5(2.3)	(0.8, 5.3)	1(0.6)	(0.0, 3.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9(4.1)	(1.9, 7.7)	2(1.3)	(0.2, 4.5)
INVESTIGATIONS	22(10.1)	(6.5, 14.9)	2(1.3)	(0.2, 4.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1(0.5)	(0.0, 2.5)	0(0.0)	(0.0, 2.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0(0.0)	(0.0, 1.7)	1(0.6)	(0.0, 3.5)
VASCULAR DISORDERS	0(0.0)	(0.0, 1.7)	1(0.6)	(0.0, 3.5)

Primary system organ classes are presented alphabetically.
Multiple occurrences of the same event in a patient were only counted once.
Any AE represents number of patients with at least one corresponding adverse event.
MedDRA V12.1 was used for primary system organ classes.
95% CI is based on Clopper-Pearson exact method.

RESTORE and RESOLVE individual studies

In RESTORE, ocular AEs occurred more commonly in the ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser groups than in the sham injection + laser group (42.6%,

42.5%, and 39.1%, respectively). In the ranibizumab 0.5 mg group, ocular AEs (preferred term) occurring in $\geq 3\%$ of patients (vs ranibizumab 0.5 mg + laser vs sham injection + laser) were: eye pain 11.3% vs 8.3% vs 10.9%; conjunctival hyperaemia 7.8% vs 5.0% vs 5.5%; conjunctival haemorrhage 7.0% vs 8.3% vs 0%; foreign body sensation in eye 4.3% vs 6.7% vs 1.8%; diabetic retinal oedema 3.5% vs 2.5% vs 3.6%; and visual impairment 3.5% vs 1.7% vs 0.9%. The number of patients in this study treated with ranibizumab with AEs defined as "intraocular pressure increased" was small (2 [1.5%] events in 235 patients in the combined ranibizumab groups). This appears to be due to post-injection IOP assessment not being mandatory, except for the 11 Canadian patients. This suggests that reporting raised IOP as an AE was dependent on IOP actually being measured post-injection.

In RESOLVE (Group A + B), ocular AEs occurred more commonly in the pooled ranibizumab group than in the sham injection group (78.4% vs 57.1%, respectively). In the pooled ranibizumab group, ocular AEs (preferred term) occurring with an incidence of $\geq 3\%$ (vs sham injection) were: conjunctival haemorrhage 22.5% vs 14.3%; increased intraocular pressure 20.6% vs 2.0%; eye pain 17.6% vs 20.4%; vitreous floaters 8.8% vs 0%; lacrimation increased 7.8% vs 0%; visual acuity reduced 6.9% vs 10.2%; foreign body sensation in eye 5.9% vs 2.0%; corneal disorder 4.9% vs 0%; eye pruritus 4.9% vs 4.1%; vitreous haemorrhage 4.9% vs 0%; cataract 3.9% vs 2.0%; eye irritation 3.9% vs 2.0%; ocular hyperaemia 3.9% vs 8.2%; retinal disorder 3.9% vs 0%; blurred vision 3.9% vs 4.1%; and visual disturbance 3.9% vs 2.0%.

In RESOLVE (Group A+B), there appeared to be a dose response relationship with patients in the higher strength group (10 mg/mL) who received an average dose of 0.76 mg per injection experiencing more frequent ocular AEs than patients in the lower strength group who received an average dose of 0.47 mg per injection (82.4% vs 74.5%, respectively). AEs occurring in $\geq 3\%$ of patients in the higher strength group (10 mg/mL) and $\geq 2\%$ more frequently than in the lower strength group (6 mg/mL) were: conjunctival haemorrhage 25.5% vs 19.6%; increased intraocular pressure 29.4% vs 11.8%; vitreous floaters 15.7% vs 2.0%; visual acuity reduced 11.8% vs 2.0%; and vitreous haemorrhage 7.8% vs 2.0%.

Severity of ocular AEs

In RESOLVE/RESTORE, the majority of ocular AEs were reported as being of mild severity in both the ranibizumab and control groups. In the ranibizumab group, non-ocular AEs were reported in 129 patients with mild events being reported in 81 (62.8%) of these patients, moderate events in 39 (30.5%) of these patients and severe events in 9 (7.0%) of these patients. In the control group, non-ocular AEs were reported in 71 patients with mild events being reported in 40 (56.3%) of these patients, moderate events in 25 (35.2%) of these patients and severe events in 6 (8.5%) of these patients.

Treatment related ocular AEs

In RESTORE/RESOLVE, ocular AEs suspected of being related to ocular injection or study drug were reported in 89 (41.0%) patients in the ranibizumab group and 37 (23.3%) of patients in the control group (Table 23). In RESTORE/RESOLVE, ocular AEs (preferred term) suspected of being related to ocular injection or study drug and occurring in $\geq 3\%$ of patients in the ranibizumab group (vs control) were: conjunctival haemorrhage 14.3% vs 4.4%; eye pain 12.9% vs 11.9%; increased intraocular pressure 9.7% vs 0%; and conjunctival hyperaemia 5.1% vs 4.4%.

Table 23: RESTORE/RESOLVE: Ocular AEs (SOC) in the study eye suspected of being related to ocular injection of study drug (pooled safety data)

SYSTEM ORGAN CLASS Preferred Term	Ranibizumab monotherapy N=217		Control N=159	
	n (%)	95% CI	n (%)	95% CI
Any AE	89(41.0)	(34.4, 47.9)	37(23.3)	(16.9, 30.6)
EYE DISORDERS	77(35.5)	(29.1, 42.2)	37(23.3)	(16.9, 30.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1(0.5)	(0.0, 2.5)	1(0.6)	(0.0, 3.5)
INFECTIONS AND INFESTATIONS	3(1.4)	(0.3, 4.0)	0(0.0)	(0.0, 2.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6(2.8)	(1.0, 5.9)	0(0.0)	(0.0, 2.3)
INVESTIGATIONS	21(9.7)	(6.1, 14.4)	0(0.0)	(0.0, 2.3)

Primary system organ classes are presented alphabetically.

Multiple occurrences of the same event in a patient were only counted once.

Any AE represents number of patients with at least one corresponding adverse event.

MedDRA V12.1 was used for primary system organ classes.

In RESTORE, ocular AEs suspected of being related to ocular injection or study drug occurred more commonly in the ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser groups than in the sham injection + laser group (24.3%, 22.5% and 18.2%, respectively). Ocular AEs (preferred term) suspected of being related to ocular injection or study drug and occurring in $\geq 3\%$ of patients in the ranibizumab 0.5 mg group (vs ranibizumab 0.5 mg + laser group vs sham injection + laser group) were: eye pain 10.4% vs 8.3% vs 10.0%; conjunctival haemorrhage 7.0% vs 7.5% vs 0%; conjunctival hyperaemia 7.0% vs 3.3% vs 5.5%; and foreign body sensation in the eye 3.5% vs 5.8% vs 1.8%.

In RESOLVE (Group A+B), ocular AEs suspected of being related to ocular injection or study drug occurred in 52.9% of patients in the 6 mg/mL group, 66.7% of patients in the 10 mg/mL group, 59.8% of patients in the pooled ranibizumab group and 34.7% of patients in the sham injection group. Ocular AEs (preferred term) suspected of being related to ocular injection or study drug and occurring in $\geq 3\%$ of patients in the pooled ranibizumab group (vs sham injection) were: conjunctival haemorrhage 22.5% vs 14.3%; raised intraocular pressure 19.6% vs 0%; eye pain 15.7% vs 16.3%; vitreous floaters 7.8% vs 0%; foreign body sensation in the eye 4.9% vs 2.0%; lacrimation increased 4.9% vs 0%; eye irritation 3.9% vs 2.0%; and eye pruritus 3.9% vs 0%. The most notable difference between the ranibizumab 6 mg/mL and 10 mg/mL groups in ocular AEs suspected of being related to study drug and/or intraocular injection was increased intraocular pressure which was reported in 11.8% and 27.5% of patients, respectively. There were no other notable differences between the two ranibizumab groups (6 mg/mL and 10 mg/mL) as regards ocular AEs considered to be related to study drug.

Non-Ocular adverse events

RESOLVE/RESTORE pooled safety set

In RESOLVE/RESTORE, non-ocular AEs occurred with similar frequencies in the ranibizumab and control groups (60.4% and 62.9%, respectively). The SOC *Infections and Infestations* accounted for the most commonly occurring non-ocular AEs in both the ranibizumab and control treatment groups (27.6% vs 26.4%, respectively), followed by *Vascular Disorders* (10.1% and 11.9%, respectively), and *Musculoskeletal and Connective Tissues Disorders* (9.7% and 9.4%, respectively).

Non-ocular AEs (preferred term) occurring in $\geq 2\%$ of patients in the ranibizumab group (vs control) were: nasopharyngitis 9.7% (n=21) vs 10.7% (n=17); hypertension 7.4% (n=16) vs 7.5% (n=12); influenza 5.1% (n=11) vs 4.4% (n=7); bronchitis 3.7% (n=8) vs

2.5% (n=4); back pain 3.2% (n=7) vs 5.0% (n=8); urinary tract infection 2.8% (n=6) vs 1.3% (n=2); anaemia 2.8% (n=6) vs 1.9% (n=3); nausea 2.8% (n=6) vs 4.4% (n=7); hypoglycaemia 2.8% (n=6) vs 2.5% (n=4); gastroenteritis 2.3% (n=5) vs 1.3% (n=2); and cough 2.3% (n=5) vs 3.1% (n=5).

RESTORE and RESOLVE individual studies

In RESTORE, non-ocular AEs occurred more commonly in the ranibizumab 0.5 mg group than in ranibizumab 0.5 mg + laser group (58.3% and 45.8%, respectively). The pattern of non-ocular AEs in the RESTORE safety set was similar to that in the RESTORE/RESOLVE pooled safety set. Non-ocular AEs occurring with a frequency of $\geq 2\%$ in the ranibizumab 0.5 mg group and more commonly than in the ranibizumab 0.5 mg + laser group were: hypertension 7.8% vs 5.0%; influenza 5.2% vs 1.7%; back pain 4.3% vs 2.5%; bronchitis 3.5% vs 2.5%; nausea 3.5% vs 2.5%; urinary tract infection 3.5% vs 0.8%; and headache 2.6% vs 1.7%.

In RESOLVE (Group A+B), non-ocular AEs occurred in a similar proportion of patients in the ranibizumab 6 mg/mL, ranibizumab 10 mg/mL, pooled ranibizumab and sham injection groups (62.7%, 62.7%, 62.7% and 65.3%). There was no notable dose response relationship between the two ranibizumab groups (6 mg/mL and 10 mg/mL). The pattern of non-ocular safety AEs in RESOLVE was consistent with those in RESTORE and in the RESOLVE/RESTORE pooled safety set.

Severity of non-ocular AEs

In RESOLVE/RESTORE, the majority of non-ocular AEs were reported as being mild/moderate in severity in both the ranibizumab and control groups. In the ranibizumab group, non-ocular AEs were reported in 131 patients with mild events being reported in 53 (40.5%), moderate events in 54 (41.2%) and severe events in 24 (18.3%). In the control group, non-ocular AEs were reported in 100 patients with mild events being reported in 47 (47%), moderate events in 35 (35%) and severe events in 18 (18%).

Treatment related non-ocular AEs

In RESOLVE/RESTORE, non-ocular AEs suspected of being related to the study drug and/or intraocular injection were reported in 10.1% (n=22) of patients in the ranibizumab group and 3.1% (n=4) of patients in the control group. Non-ocular AEs (preferred term) suspected of being related to study drug and/or intraocular injection and occurring in $\geq 1\%$ of patients in the ranibizumab group (vs control) were: hypertension 1.8% (n=4) vs 1.9% (n=3); and heart rate irregular 1.4% (n=3) vs 0%.

In RESTORE, non-ocular AEs suspected of being related to the study drug and/or intraocular injection were reported in a greater percentage of patients in the ranibizumab 0.5 mg group (7.8% [n=9]) than in both the ranibizumab 0.5 mg + laser group (2.5% [n=3]) and the sham injection + laser group (1.8% [n=2]). However, most of the non-ocular AEs suspected of being related to the study drug and/or intraocular injection occurring in the ranibizumab 0.5 mg group occurred in 1 patient with the only exception being pulmonary embolism which occurred in 2 patients.

In RESOLVE (Group A+B), non-ocular AEs suspected of being related to the study drug and/or intraocular injection were reported in 11.8% (n=6) of patients in the ranibizumab 6 mg/mL group, 13.7% (n=7) in the ranibizumab 10 mg/mL group, 12.7% (n=13) in the combined ranibizumab group, and 6.1% (n=3) in the sham group. There were no notable differences in the non-ocular AEs profiles between the two ranibizumab groups (6 mg/mL and 10 mg/mL). The pattern of non-ocular AEs suspected of being related to the study drug and/or intraocular injection in RESOLVE was similar to that in RESOLVE/RESTORE.

Adverse events reflecting RMP safety concerns

The Risk Management Plan version 7 (RMP v.7) noted the following important identified risks associated with ranibizumab treatment: hypersensitivity reactions; retinal pigment epithelial tear; endophthalmitis; retinal detachment; retinal tear; traumatic cataract; intraocular inflammation; and increased intraocular pressure. In addition, the RMP noted the following important potential risks associated with ranibizumab treatment: hypertension; non-ocular haemorrhage; proteinuria; myocardial infarction (MI); non-MI arterial thromboembolic events; venous thromboembolic events; and deterioration of retinal blood flow (including central retinal artery occlusion).

The submission included an integrated summary of the pooled safety data from RESOLVE/RESTORE which focused on those AEs in the two studies which reflected the RMP safety concerns associated with ranibizumab treatment. In RESOLVE/RESTORE, the proportion of patients reported as experiencing any AE reflecting RMP safety concerns were similar in the ranibizumab group (81.1% [n=176]) and the control group (81.8% [n=130]). The most commonly occurring non-ocular AE reflecting RMP safety concerns in patients in both groups was hypertension. Hypersensitivity also occurred commonly in both treatment groups, but based on the definition of “hypersensitivity reactions” used in the RMP hypersensitivity AEs relate to a variety of events involving the study eye and/or the fellow eye. The proportion of patients in both treatment groups was similar for all other AEs reflecting RMP safety concerns with the exception of intraocular pressure increase (12.4% for ranibizumab vs 1.9% for control) and endophthalmitis (1.4% for ranibizumab vs 0% for control). The results are summarized in Table 24 and it should be noted that ocular AEs in this table include those occurring in the study eye and/or the fellow eye.

Table 24: RESOLVE/RESTORE: AEs (any) reflecting RMP safety concerns (pooled safety set)

Risk Category	Ranibizumab monotherapy N=217		Control N=159	
	n (%)	95% CI	n (%)	95% CI
Total number of patients with any adverse event	176(81.1)	(75.3, 86.1)	130(81.8)	(74.9, 87.4)
Endophthalmitis	3(1.4)	(0.3, 4.0)	0(0.0)	(0.0, 2.3)
Intraocular inflammation	12(5.5)	(2.9, 9.5)	8(5.0)	(2.2, 9.7)
Traumatic cataract	19(8.8)	(5.4, 13.3)	14(8.8)	(4.9, 14.3)
Intraocular pressure increased	27(12.4)	(8.4, 17.6)	3(1.9)	(0.4, 5.4)
Deterioration of retinal blood flow	12(5.5)	(2.9, 9.5)	12(7.5)	(4.0, 12.8)
Retinal tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Retinal detachment	1(0.5)	(0.0, 2.5)	1(0.6)	(0.0, 3.5)
Retinal pigment epithelial tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Hypersensitivity	19(8.8)	(5.4, 13.3)	13(8.2)	(4.4, 13.6)
Hypertension	19(8.8)	(5.4, 13.3)	15(9.4)	(5.4, 15.1)
Non-ocular hemorrhage	4(1.8)	(0.5, 4.7)	2(1.3)	(0.2, 4.5)
Proteinuria	1(0.5)	(0.0, 2.5)	0(0.0)	(0.0, 2.3)
Myocardial infarction	2(0.9)	(0.1, 3.3)	2(1.3)	(0.2, 4.5)
Other arterial thromboembolic events	5(2.3)	(0.8, 5.3)	3(1.9)	(0.4, 5.4)
Venous thromboembolic events	2(0.9)	(0.1, 3.3)	2(1.3)	(0.2, 4.5)

Multiple occurrences of the same event in a patient were only counted once. MedDRA V12.1 was used for risk description. 95% CI based on Clopper-Pearson exact method.

In RESOLVE/RESTORE, the proportion of patients reported as experiencing an ocular AE in the study eye reflecting RMP safety concerns was higher in the ranibizumab group (59.4% [n=129]) than in the control group (44.7% [n=71]). As in the AE (any) analysis, the most notable difference between two treatment groups was in the higher proportion of patients experiencing increased intraocular pressure in the ranibizumab group (11.1%) than in the control group (1.3%). The other ocular AE of note was the small number of

patients experiencing endophthalmitis in the ranibizumab group (n=3 [1.4%] vs n=0 in the control group). The results are summarized in Table 25.

Table 25: RESOLVE/RESTORE: Ocular AEs in the study eye reflecting RMP safety concerns (pooled safety set)

Risk Category	Ranibizumab monotherapy N=217		Control N=159	
	n (%)	95% CI	n (%)	95% CI
Total number of patients with any study eye adverse event	129(59.4)	(52.8, 66.0)	71(44.7)	(36.8, 52.7)
Endophthalmitis	3(1.4)	(0.3, 4.0)	0(0.0)	(0.0, 2.3)
Intraocular inflammation	8(3.7)	(1.6, 7.1)	8(5.0)	(2.2, 9.7)
Traumatic cataract	12(5.5)	(2.9, 9.5)	12(7.5)	(4.0, 12.8)
Intraocular pressure increased	24(11.1)	(7.2, 16.0)	2(1.3)	(0.2, 4.5)
Deterioration of retinal blood flow	7(3.2)	(1.3, 6.5)	9(5.7)	(2.6, 10.5)
Retinal tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Retinal detachment	0(0.0)	(0.0, 1.7)	1(0.6)	(0.0, 3.5)
Retinal pigment epithelial tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)

Multiple occurrences of the same event in a patient were only counted once. MedDRA V12.1 was used for risk description. 95% CI based on Clopper-Pearson exact method.

Adverse events potentially related to VEGF inhibition

Adverse events (AEs) potentially related to systemic VEGF inhibition reflecting the identified safety concerns in the Risk Management Plan (RMP) (*see Section V*) were categorized as MIs, other arterial thromboembolic events, venous thromboembolic events, hypertension, non-ocular haemorrhage and proteinuria.

In RESTORE, MI, other arterial thromboembolic events, and proteinuria occurred more frequently in patients in at least one of the ranibizumab groups compared with the sham injection + laser group (Table 26).

Table 26: RESTORE: AEs potentially related to systemic VEGF inhibition (safety set)

Risk category	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
	Myocardial infarction	1 (0.9)	2 (1.7)
Other arterial thromboembolic events	4 (3.5)	2 (1.7)	2 (1.8)
Venous thromboembolic events	2 (1.7)	0 (0.0)	2 (1.8)
Hypertension	9 (7.8)	7 (5.8)	10 (9.1)
Non-ocular hemorrhage	2 (1.7)	0 (0.0)	2 (1.8)
Proteinuria	1 (0.9)	1 (0.8)	0 (0.0)

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

In RESOLVE (Group A+B), hypertension and non-ocular haemorrhage were the only two events to occur more frequently in patients in at least one of the ranibizumab 6 mg/mL or 10 mg/mL groups compared with the sham injection group (Table 27).

Table 27: RESOLVE: AEs potentially related to systemic VEGF inhibition (safety set)

Risk category	Ranibizumab 6 mg/ml N = 51 n (%)	Ranibizumab 10 mg/ml N = 51 n (%)	Ranibizumab Pooled N = 102 n (%)	Sham N = 49 n (%)
Myocardial infarction	0 (0.0)	1 (2.0)	1 (1.0)	1 (2.0)
Other arterial thromboembolic events	0 (0.0)	1 (2.0)	1 (1.0)	1 (2.0)
Venous thromboembolic events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	4 (7.8)	6 (11.8)	10 (9.8)	5 (10.2)
Non-ocular hemorrhage	1 (2.0)	1 (2.0)	2 (2.0)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

Adverse events – DRCR.net and READ-2

In DRCR.net, there was no ranibizumab 0.5 mg only group with safety data during the 2 years of follow up. The study report included a list of major ocular AEs and an extensive list of systemic AEs reported during 2 years of follow up reported in the four treatment groups. The most commonly reported major ocular AE during 2 years of follow up in the ranibizumab 0.5 mg + prompt laser group (1883 injections in 187 patients) was increase in IOP \geq 10 mmHg from baseline (9% [16/187] vs 8% [22/293] sham + prompt laser). The incidence of IOP \geq 30 mmHg in the ranibizumab 0.5 mg + prompt laser and sham + prompt laser groups was similar (2% [3/187] vs 3% [8/293], respectively). Overall, the major ocular AEs reported in the ranibizumab 0.5 mg + laser group were not unexpected and were reported at similar frequencies with those in the sham injection + prompt laser group. Examination of the extensive list of systemic AEs reported in DRCR.net during the 2 years of follow up do not give rise to new or unexpected safety signals, with similar event frequencies being reported in the four treatment groups.

The READ-2 study reports included a summary of AEs at the 6 month endpoint [Nguyen et al., 2009] but reported negligible safety data at the 2 year endpoint [Nguyen et al., 2010]. In the 6 month report, there was 1 serious adverse event; a patient in the ranibizumab 0.5 mg + laser group died of a cerebral vascular accident 6 weeks after his first injection of ranibizumab. The patient was stated to have been at high risk for cerebral vascular accident because of pre-existent cardiovascular disease and the event was judged to be unrelated to ranibizumab because of the long period between its occurrence and the prior injection. Ocular adverse events included vitreous haemorrhages in 8 patients (1 [2.4%] patient in the ranibizumab 0.5 mg group, 4 [9.5%] patients in the laser group, and 3 [7.1%] patients in the ranibizumab 0.5 mg + laser group). There were small non-clinically significant changes in blood pressure in the three treatment groups over the 6 month treatment period.

Deaths

In RESOLVE and RESTORE, 7 deaths were recorded during the studies and 1 death was recorded in the 4 week follow up period after the last visit. None of the deaths were considered by the investigators to be related to study treatment. The sponsor commented that 4 of the deaths were related to concomitant cardiac disorder, “which is an expected outcome of cardiovascular comorbidity in patients with diabetes mellitus”.

In RESOLVE, 1 death was reported in a 66 year old Caucasian male in the 6 mg/mL dose group on Day 127 of the double blind period (17 days after the last dose received) due to bladder cancer. This death was not suspected as being related to the study drug.

In RESTORE – (a) 4 deaths were recorded as being due to the SOC of *Cardiac Disorders* (1 x cardiopulmonary failure, 1 x MI, 1x cardiac failure, 1 x cardiac disorder); (b) 1 death was

recorded as being due to SOC *Nervous System Disorders* (cerebrovascular accident); (c) 1 death was recorded as being due to SOC *Renal and Urinary Disorders* (renal failure); (d) 1 death was recorded as being due to unknown cause.

There were no deaths reported in the ongoing study REVEAL and there were 3 deaths in the ongoing RESTORE extension study at the cut-off date of 30 March 2010. The 3 deaths in RESTORE extension were (preferred terms): 1 x cerebrovascular accident; 1 x pulmonary embolism; 1 x acute MI. The acute MI was suspected of being related to study treatment because at the time of reporting the cause of death was not known and it is the policy of the sponsor to assess causality as “suspected” if the cause of death is unknown in such circumstances.

In the ongoing RIDE and RISE studies there were 24 deaths at the cut-off date of 30 March 2010 and 2 of these deaths were suspected to be related to treatment (both deaths due to unexplained or unknown cause). Of these 24 deaths – 10 were identified as being due to *Cardiac Disorders* (5 x cardiac arrest; 2 x cardiac failure congestive; 1 x MI; 1 x coronary artery disease; 1 x intracardiac thrombus); 3 were identified as being due to *General Disorders and Administration Site Conditions* (1 x death, unreported cause, possible MI; 1 x death unknown cause; 1 x death, unexplained); 2 were identified as being due to *Renal and Urinary Disorders* (1 x acute renal failure; 1 x renal failure); 2 were identified as being due to *Vascular Disorders* (1 x hypertension; 1 x aortic aneurysm rupture); 2 were identified as being due to *Infections and Infestations* (1 x pneumonia; 1 x clostridial infection); 1 was identified as being due to *Gastrointestinal Disorders* (large intestine perforation); 1 was identified as being due to *Respiratory, Thoracic and Mediastinal Disorders* (respiratory failure); 1 was identified as being due to *Injury, Poisoning and Procedural Complications* (completed suicide, carbon monoxide intoxication); and 1 was identified as being due to *Nervous System Disorders* (cerebrovascular accident).

There was one death reported in the READ-2 study, and the cause of death “cerebral vascular accident” was not suspected by the investigator to be related to study drug [Nguyen et al., 2009]. In the DRCR.net study, 18 study participants (2.6%) died through to 2 years due to “vascular death” (that is, death from any potential vascular or unknown cause), with the distribution across the treatment groups being 6 (5%) in the sham injection + prompt laser group, 8 (2%) in the two combined ranibizumab 0.5 mg + prompt and deferred laser groups, and 4 (2%) in the triamcinolone + prompt laser group. Unknown cause was reported for 4 of the 6 vascular deaths in the sham injection + laser group, 1 of the 8 vascular deaths in the ranibizumab 0.5 mg + laser group and 1 of the 4 vascular deaths in the triamcinolone + laser group.

Serious adverse events other than death

RESOLVE/RESTORE pooled data

In RESOLVE/RESTORE, ocular serious adverse events (SAEs) (any) in the study eye were reported in 1.8% (n=4) of patients in the ranibizumab group and 1.9% (n=3) of patients in the control group. The ocular SAEs in the ranibizumab group (5 in 4 patients) were endophthalmitis (2), retinal artery occlusion (1), retinal ischaemia (1) and vitreous haemorrhage (1). The ocular SAEs in the control group (4 in 3 patients) were cataract (2), maculopathy (1) and retinal detachment (1).

In RESOLVE/RESTORE, non-ocular SAEs (any) were reported in 17.1% (n=37) of patients in the ranibizumab group and 14.5% (n=23) of patients in the control group. No individual SAE (preferred term) occurred in more than 3 (1.4%) patients in the ranibizumab. The SAEs occurring in ≥ 2 patients in the ranibizumab group (vs control) were: hypoglycaemia [3 (1.4%) vs 1 (0.6%)]; angina pectoris [2 (0.9%) vs 1 (0.6%)]; coronary artery disease [2 (1.4%) vs 1 (0.6%)];

(0.9%) vs 1 (0.6%); MI [2 (0.9%) vs 1 (0.6%)]; pulmonary embolism [2 (0.9%) vs 0%]; fall [2 (0.9%) vs 0%].

RESOLVE and RESTORE individual study data

In RESOLVE, the proportion of patients with SAEs (total) was similar in the ranibizumab 6 mg/mL (17.6% [n=9]), ranibizumab 10 mg/mL (17.6% [n=9]), ranibizumab pooled (17.6% [n=18]) and sham injection (18.4% [n=9]) groups. Ocular SAEs in the study eye occurred more frequently in patients in the ranibizumab 10 mg/mL group (5.9% [n=3]) than in the 6 mg/mL group (2.0% [n=1]) and the sham injection group (2.0% [n=1]). In the ranibizumab 10 mg/mL group, reported ocular SAEs (3 in 3 patients) were endophthalmitis (3), retinal artery occlusion (1) and retinal ischaemia (1); in the ranibizumab 6 mg/mL group reported ocular SAEs (2 in 1 patient) were endophthalmitis (1) and vitreous haemorrhage (1); and in the sham injection group the reported SAE (1 in 1 patient) was retinal detachment (1).

In RESOLVE, non-ocular SAEs occurred more frequently in patients in the sham injection group (16.3% [n=8]) than in the ranibizumab 6 mg/mL, ranibizumab 10 mg/mL and ranibizumab pooled groups (15.7% [n=8], 11.8% [n=6], and 13.7% [n=14], respectively). Non-ocular SAEs were reported less frequently in the ranibizumab 10 mg/mL group than in the ranibizumab 6 mg/mL group. The only non-ocular SAE reported in more than 1 patient in the four treatment groups was hypoglycaemia which was reported in 2 (2.0%) patients in the pooled ranibizumab group.

In RESTORE, SAEs (total) were reported more frequently in patients in the ranibizumab 0.5 mg group (22.6% [n=26]) than in the ranibizumab 0.5 mg + laser and laser groups (16.7% [n=20] and 15.5% [n=17], respectively). Ocular SAEs in the study eye occurred with similar frequencies in patients in the ranibizumab 0.5 mg group + laser group (1.7% [n=2]) and laser group (1.8% [n=2]), while there were no reports of patients experiencing ocular SAEs in the ranibizumab 0.5 mg group. In RESTORE, non-ocular SAEs were reported more frequently in the ranibizumab 0.5 mg group (20.0% [n=23]), than in the ranibizumab 0.5 mg + laser and laser groups (14.2% [n=17] and 13.6% [n=15], respectively).

Discontinuations due to adverse events

In RESOLVE/RESTORE, the incidence of ocular AEs (any) resulting in discontinuation were similar in the ranibizumab and control groups (1.4% [n=3] and 1.9% [n=3], respectively). The most commonly occurring ocular AE resulting in discontinuation in the ranibizumab group (vs control) was endophthalmitis (1.4% [n=3] vs 0%). The only other ocular AE leading to discontinuation in the ranibizumab group (vs control) was retinal ischaemia (0.5% [n=1] vs 0%). The ocular AEs leading to discontinuation in the control group were diabetic retinal oedema, maculopathy, and visual acuity reduced. The frequency of each of these three events in the control group was 0.6% (n=1), and none of these events occurred in the ranibizumab group.

In RESOLVE/RESTORE, the incidence of non-ocular AEs resulting in discontinuation was higher in the ranibizumab group than in the control group (4.1% [n=9] and 3.1% [n=5], respectively). *Nervous System Disorders* (cerebral artery embolism, cerebrovascular accident, hepatic encephalopathy) accounted for 3 (1.4%) discontinuations in the ranibizumab group compared with none in the control group. There was no significant difference in the frequency of discontinuation due to *Cardiac Disorders* between the two treatment groups: ranibizumab 2 (0.9%) patients with 2 events (MI, cardiac disorder) vs control 3 (1.9%) patients with 3 events (MI, cardiac disorder, cardiac failure).

In RESOLVE/RESTORE, AEs (all) reflecting RMP safety concerns occurred with similar frequencies in the ranibizumab and control groups (5.5% [n=12] and 5.0% [n=8], respectively). The results are summarised in Table 28.

Table 28: RESOLVE/RESTORE: AEs (all) RMP safety concerns leading to study drug discontinuation (safety set)

Risk Category	Ranibizumab monotherapy N=217		Control N=159	
	n (%)	95% CI	n (%)	95% CI
Total number of patients with any adverse event leading to study drug discontinuation	12(5.5)	(2.9, 9.5)	8(5.0)	(2.2, 9.7)
Endophthalmitis	3(1.4)	(0.3, 4.0)	0(0.0)	(0.0, 2.3)
Intraocular inflammation	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Traumatic cataract	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Intraocular pressure increased	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Deterioration of retinal blood flow	1(0.5)	(0.0, 2.5)	0(0.0)	(0.0, 2.3)
Retinal tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Retinal detachment	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Retinal pigment epithelial tear	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Hypersensitivity	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Hypertension	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Non-ocular hemorrhage	0(0.0)	(0.0, 1.7)	1(0.6)	(0.0, 3.5)
Proteinuria	0(0.0)	(0.0, 1.7)	0(0.0)	(0.0, 2.3)
Myocardial infarction	1(0.5)	(0.0, 2.5)	1(0.6)	(0.0, 3.5)
Other arterial thromboembolic events	2(0.9)	(0.1, 3.3)	0(0.0)	(0.0, 2.3)
Venous thromboembolic events	1(0.5)	(0.0, 2.5)	0(0.0)	(0.0, 2.3)

Multiple occurrences of the same event in a patient were only counted once. MedDRA V12.1 was used for risk description. 95% CI is based on Clopper-Pearson exact method.

Laboratory tests

Haematology and clinical chemistry

In RESOLVE and RESTORE, all laboratory tests were undertaken by the Central Laboratory. No integrated summary of laboratory test results was provided. A standard range of haematology and serum biochemistry tests were measured during the screening period and at the study exit visit (Month 12 or earlier in the case of discontinuation). No repeated laboratory testing was routinely undertaken over the course of the studies. HbA1c levels were analysed separately. Shift tables using critical values with thresholds representing clinical relevant abnormalities (as defined by the Central Laboratory) were provided in order to compare baseline laboratory evaluation with the most extreme evaluation post-baseline, including all scheduled and unscheduled visits. The critical values were examined and were considered to be clinically acceptable.

In RESOLVE (Group A+B), post-baseline laboratory tests exceeding the critical level in $\geq 2\%$ of patients in the ranibizumab 6 mg/mL, ranibizumab 10 mg/mL and sham injection groups were: raised serum alkaline phosphatase (> 145 U/L) - 2.3% (1/43) in the 6 mg/mL group and 2.3% (1/44) in the 10 mg/mL group compared with 0% in the sham group; blood urea nitrogen (BUN) increased (>17.5 mmol/L) - 2.4% (1/41) in the 6 mg/mL group compared with 0% in the other two groups; increased creatinine (> 168 μ mol/L) - 2.4% (1/41) in the 6 mg/mL group and 2.2% (1/45) in the 10 mg/mL group compared with 0% in the sham group; and raised alanine aminotransferase (ALT) (> 75 U/L) - 2.3% (1/43) in the ranibizumab 6 mg/mL group and 0% in the other two groups. In the sham group, none of the laboratory parameters exceeded critical values post-baseline in $\geq 2\%$ of patients.

In RESTORE, post-baseline laboratory tests exceeding the critical level in patients in the ranibizumab 0.5 mg, ranibizumab 0.5 mg + laser, and sham injection + laser groups are summarised below in Table 29.

Table 29: RESTORE – Laboratory tests critical values post-baseline; safety set

Parameter	Criterion	Ranibizumab 0.5 mg N=115 n/N (%)	Ranibizumab 0.5 mg + Laser N=120 n/N (%)	Laser N=110 n/N (%)
Hematology				
Hemoglobin	< 80 g/L	0/113 (0.0)	0/119 (0.0)	1/105 (0.9)
Biochemistry				
Blood urea nitrogen (BUN)	> 17.5 mmol/L	7/112 (6.3)	2/116 (1.7)	2/105 (1.9)
Creatinine	> 168 mmol/L	4/113 (3.5)	3/115 (2.6)	3/106 (2.8)
Potassium	> 6.3 mmol/L	0/113 (0.0)	1/114 (0.9)	1/106 (0.9)
Glycosylated hemoglobin (HbA1c)	> 12%	0/113 (0.0)	1/119 (0.8)	0/106 (0.0)
AST	> 66 U/L	1/113 (0.9)	1/116 (0.9)	0/106 (0.0)
ALT	> 75 U/L	0/113 (0.0)	1/117 (0.9)	2/106 (1.9)

-n is the number of patients with critical laboratory values at any time post-baseline, and a baseline value that is normal or missing (i.e. critical values in patients with missing baseline values are included).

-N is the number of patients with at least one post-baseline value for the specific laboratory test and a baseline value that is normal or missing. It is used as denominator in calculating the percentages.

Urinalysis

Urinalysis results pre and post-baseline in RESOLVE and RESTORE were examined and gave no rise to concern.

Vital Signs

Blood pressure

In RESOLVE (Group A+B), the mean (SD) change in sitting SBP from baseline to the last post-baseline value in the ranibizumab pooled group (n=101) was +1.7 (16.1) mmHg compared with +2.0 (18.1) mmHg in the sham injection group (n=47), and the corresponding changes in sitting DBP pressure were -1.5 (11.4) mmHg and -3.4 (13.7) mmHg. In RESTORE, the mean (SD) change from baseline to month 12 in the sitting SBP in the three treatment groups ranged from -1.4 (17.3) to -1.8 (14.4) mmHg and the corresponding values for sitting DBP were -0.8 (10.7) to -3.5 (10.8) mmHg.

Other safety parameters

Intraocular pressure

In RESTORE, at Month 12, IOP was increased in the study eye by 0.7 mmHg in the ranibizumab group, 0.6 mmHg in the ranibizumab + laser group, and 0.1 mmHg in the laser group.

Immunoreactivity to ranibizumab

In RESOLVE (Group A+B), in the ranibizumab pooled group, of the 78 patients who were seronegative at baseline, 61 (78.2%) were still seronegative post-baseline, 3 (3.8%) had seroconverted (positive), and data were missing on 14 (17.9%). There were no seropositive patients at baseline in the ranibizumab pooled group. In the sham injection group, of the 36 patients who were seronegative at baseline, 27 (75.0%) were still seronegative post-baseline, 0 had seroconverted (positive), and data were missing on 9

(25.0%). There was 1 patient in the sham injection group who was seropositive at baseline.

Other safety issues

Safety in special populations

AEs reflecting RMP safety concerns (subgroups)

In RESOLVE/RESTORE, AEs reflecting the RMP safety concerns were evaluated in demographic subgroups, baseline characteristics (diabetes and DME disease characteristics, blood pressure levels), time since diagnosis of diabetes and DME, urinalysis values, and concomitant use of insulin.

Gender

The proportion of male and female patients with any AE was similar in both the ranibizumab group (81.3% [n=104] vs 80.9% [n=72], respectively) and the control group (79.3% [n=65] vs 84.4% [n=65], respectively). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, traumatic cataract occurred more frequently in male patients than in female patients (10.2% [n=13] and 6.7% [n=6]), as did hypersensitivity (10.9% and 5.6%) and intraocular inflammation (7.0% [n=9] and 3.4% [n=3]). Applying the same criteria, hypertension occurred more frequently in female patients than in male patients (11.2% [n=10] and 7.0% [n=9]).

Age

The proportion of patients with AEs (any) was higher in patients aged < 65 years than in those aged ≥ 65 years in the ranibizumab group (83.8% [n=98] vs 78.0% [n=78]), while the reverse was observed in the control group (77.5% [n=69] vs 87.1% [n=61]). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, increased intraocular pressure occurred more commonly in patients aged < 65 years than in patients aged ≥ 65 years (15.4% [n=18] vs 9.0% [n=9]), as did hypersensitivity (10.3% [n=12] vs 7.0% [n=7]) and hypertension (10.3% [n=18] vs 9.0% [n=9]). Applying the same criteria, traumatic cataract occurred more commonly in patients aged ≥ 65 years than in patients aged < 65 years (10.0% [n=10] vs 7.7% [n=9]), as did deterioration of retinal blood flow (7.0% [n=7] vs 4.3% [n=5]).

Baseline HbA1c

The proportion of patients with AEs (any) was similar in those with baseline HbA1c $< 8\%$ and in those with baseline HbA1c $\geq 8\%$ in both the ranibizumab group (81.1% [n=129] vs 82.1% [n=46], respectively) and the control group (82.0% [n=91] vs 80.0% [n=36]). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, intraocular inflammation occurred more commonly in patients with baseline HbA1c $< 8\%$ than in patients with baseline HbA1c $\geq 8\%$ (7.5% [n=12] vs 0%), as did hypersensitivity (9.4% [n=15] vs 7.1% [n=4]). Applying the same criteria, traumatic cataract occurred more commonly in patients with baseline HbA1c $\geq 8\%$ than in patients with baseline HbA1c $< 8\%$ (12.5% [n=7] vs 6.9% [n=11]), as did deterioration of retinal blood flow (7.1% [n=4] vs 5.0% [n=8]) and hypertension (12.5% [n=7] vs 7.5% [n=12]).

Baseline blood pressure (BP)

The proportion of patients with AEs (any) in the elevated BP group (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) and in the normal BP group (SBP < 140 mmHg and DBP < 90 mmHg) was similar in both the ranibizumab group (79.9% [n=107] vs 82.5% [n=66], respectively)

and the control group (84.0% [n=84] vs 77.2% [n=44], respectively). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, increased intraocular pressure occurred more commonly in patients with elevated BP than in patients with normal BP (15.7% [n=21] vs 7.5% [n=6]), as did hypertension (11.2% [n=15] vs 5.0% [n=4]), and intraocular inflammation (6.7% [n=9] vs 3.8% [n=3]). Applying the same criteria, deterioration of retinal blood flow occurred more commonly in patients with normal BP than patients with elevated blood pressure (7.5% [n=6] vs 4.5% [n=6]).

Time since diagnosis of DM

The proportion of patients with AEs (any) with time since diagnosis of DM < 10 years and ≤ 10 years was similar in both the ranibizumab group (80.3% [n=53] vs 81.5% [n=123], respectively) and the control group (84.9% [n=45] vs 80.2% [n=85], respectively). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, traumatic cataract occurred more commonly in the < 10 years since diagnosis cohort than in the ≥ 10 years since diagnosis cohort (10.6% [n=7] vs 7.9% [n=12]). Applying the same criteria, deterioration of retinal blood flow occurred more commonly in the ≥ 10 years since diagnosis cohort than in the < 10 years since diagnosis cohort (6.6% [n=10] vs 3.0% [n=2]), as did hypertension (9.9% [n=15] vs 6.1% [n=4]).

Time since diagnosis of DME

The proportion of patients with AEs (any) with time since diagnosis of DME ≤ 3 months was lower than the proportion of patients with AEs (any) with time since diagnosis of DME < 3 to 12 months in both the ranibizumab group (72.4% [n=42] vs 86.5% [n=64]) and the control group (76.1% [n=35] vs 85.7% [n=36]). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, hypertension occurred more commonly in the time since DME diagnosis ≤ 3 month cohort than in the > 3 to 12 month cohort (13.8% [n=8] vs 8.1% [n=6]). Applying the same criteria, traumatic cataract occurred more commonly in the time since DME > 3 to 12 months cohort than in the ≤ 3 month cohort (17.6% [n=13] vs 8.6% [n=5]), as did hypersensitivity (9.5% [n=7] vs 6.9% [n=4]) and deterioration of blood flow (8.1% [n=6] vs 1.7% [n=1]).

Concomitant insulin

The proportion of patients with AEs (any) using concomitant insulin was higher than the proportion of patients with AEs (any) not using concomitant insulin in the ranibizumab group (83.9% [n=120] vs 75.7% [n=56]), but the reverse was observed in the control group (78.7% [n=74] vs 86.2% [n=56]). Of the AEs (any) occurring in the ranibizumab group with an incidence of $\geq 5\%$ in either of the two subgroups with a difference between subgroups of $\geq 2\%$, hypersensitivity occurred more commonly in the concomitant insulin group than in the non-concomitant insulin group (11.2% [n=16] vs 4.1% [n=3]), as did hypertension (9.8% [n=14] vs 6.8% [n=5]).

Baseline retinal ischaemia

The proportion of patients with AEs (any) was lower in those with baseline retinal ischaemia than in those without baseline ischaemia in both the ranibizumab group (79.6% [n=39] vs 86.8% [n=105]) and the control group (78.4% [n=29] vs 81.5% [n=66]).

Baseline creatinine

The proportion of patients with AEs (any) was similar in those with baseline creatinine ≤ 1.2 mg/dL and baseline creatinine > 1.2 mg/dL in both the ranibizumab group (81.2%

[n=147] vs 80.6% [n=29], respectively) and the control group (81.8% [n=112] vs 80.0% [n=16], respectively).

Baseline urine protein

The proportion of patients with AEs (any) was higher in those with low baseline urine protein dipstick test than in those with high baseline urine protein dipstick test (84.5% [n=125] vs 73.8% [n=48]), while the proportions were similar in the control group (82.4% [n=89] vs 84.4% [n=38], respectively).

Baseline ETDRS

The proportion of patients with AEs (any) was similar in those with lower ETDRS scores 10-35 and those with higher ETDRS scores 43 or 47 in both the ranibizumab (81.0% [n=51] vs 83.6% [n=61], respectively) and control groups (83.0% [n=44] vs 83.9% [n=47], respectively). The number of patients in the ETDRS subgroup with scores of 53-85 were too small (n=27) to make meaningful comparisons with the two other EDTRS subgroups with lower scores.

Baseline DM Type

The subgroup comparison of patients with T1DM and T2DM was considered to provide no meaningful information due to the marked imbalance in patient numbers between the two patient populations (n=20 and n=345, respectively).

AEs reflecting VEGF inhibition safety concerns (subgroups)

In RESOLVE/RESTORE, AEs reflecting the VEGF inhibition safety concerns of MI, other arterial thromboembolic events and venous thromboembolic events were analysed in the same subgroups as discussed above. In all subgroups, the absolute number of subjects experiencing these selected AEs was small. Examination of the small differences in the AE profiles in the subgroups suggest that they reflect differences in underlying cardiovascular risk between the cohorts rather than differences in ranibizumab toxicity.

Ocular adverse events in the fellow eye

In RESOLVE/RESTORE, ocular AEs (regardless of study drug relationship) occurred in 32.3% (n=70) of patients in the ranibizumab group and 35.2% (n=56) of patients in the control group. Ocular AEs reported in the fellow eye in the ranibizumab group (vs control) with a frequency of $\geq 2\%$ were: vitreous haemorrhage 4.6% vs 3.8%; cataract 3.2% vs 3.8%; diabetic retinal oedema 2.8% vs 7.5%; visual acuity reduced 2.8% vs 3.8%; intraocular pressure increased 2.3% vs 0.6%; and macular oedema 2.3% vs 0%. There were 3 (1.4%) reports of SAEs in the ranibizumab group (2 vitreous haemorrhage; 1 diabetic retinal oedema) and 2 (1.3%) in the control group (1 vitreous haemorrhage; 1 diabetic retinal oedema). There were no ocular AEs in either treatment group leading to discontinuation of the study drug.

Safety in AMD in 2 year follow up data

PIER

The submitted data included 24 month efficacy and safety data in AMD patients from PIER. PIER is a Phase IIIb, multicentre, randomized, double masked, sham injection controlled study of the efficacy and safety of ranibizumab in subjects with subfoveal choroidal neovascularisation (CNV) with or without classic CNV secondary to age related macular degeneration. The 12 month, but not the 24 month, efficacy and safety data have been previously evaluated by the TGA. The 24 month safety data from this study have been evaluated for the purposes of the current submission and the results are summarised below.

Exposure

During the 2 year treatment period, the mean (SD) number of injections received by patients in the sham before crossover group (n=62), ranibizumab 0.3 mg group (n=59) and ranibizumab 0.5 mg group (n=61) were 8.3 (3.5), 10.3 (2.1) and 10.0 (2.3) respectively. The respective mean (SD) duration of safety observation in the safety evaluable subjects in the three treatment groups was 626 (197) days, 713 (43) days and 690 (108) days. The study included 39 patients who had crossed over from sham to monthly ranibizumab 0.5 mg beginning at 14 months and the mean number of ranibizumab injections received by subjects in this group were 4 and the mean (SD) duration of exposure during the ranibizumab cross-over treatment period was 224 (70) days. In the following summary of the key 2 year safety data the focus is primarily on the sham (n=62) ranibizumab 0.3 mg (n=59) and ranibizumab 0.5 mg (n=61) groups.

Ocular adverse events in the study eye

Total study eye ocular AEs were reported with similar frequencies in the sham (n=62), ranibizumab 0.3 mg (n=59) and ranibizumab 0.5 mg (n=61) groups: 93.5% (n=58), 94.9% (n=59) and 85.2% (n=52), respectively. Study eye ocular AEs reported with a frequency of $\geq 10\%$ of patients in any group during the 2 year treatment period and $\geq 2\%$ in more frequently in either of the ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): conjunctival haemorrhage 29.0% (n=18) vs 50.8% (n=30) vs 52.4% (n=32); intraocular pressure increased 4.8% (n=3) vs 23.7% (n=14) vs 31.1% (n=19); eye pain 12.9% (n=8) vs 18.6% (n=11) vs 18.0% (n=11); eye irritation 4.8% (n=3) vs 13.6% (n=8) vs 13.1% (n=8); vitreous floaters 3.2% (n=2) vs 11.9% (n=7) vs 13.1% (n=8); detachment of retinal pigment epithelium 3.2% (n=2) vs 8.5% (n=5) vs 16.4% (n=10); foreign body sensation in the eye 6.5% (n=4) vs 10.2% (n=6) vs 9.8% (n=6); and macular oedema 6.5% (n=4) vs 10.2% (n=6) vs 3.3% (n=2).

Endophthalmitis in the study eye was not reported in any patient. Intraocular inflammation in the study eye was reported in 2 (3.2%) patients in the sham group (1 vitritis, 1 iridocyclitis, 1 iritis), 3 (5.1%) in the ranibizumab 0.3 mg group (1 vitritis, 1 iridocyclitis, 1 iritis) and 3 (4.9%) in the ranibizumab 0.5 mg group (3 vitritis, 1 iridocyclitis, 1 iritis). Cataract, nuclear cataract or cortical cataract in the study eye were reported in 5 (8.1%) patients in the sham group, 5 (8.5%) in the 0.3 mg group and 11 (18.0%) in the 0.5 mg group. No traumatic cataract (lens damage) was reported in the study eye of any patient during the study. IOP increases in the study eye were reported in 3 (4.8%) patients in the sham group, 14 (23.7%) in the 0.3 mg group and 19 (31.1%) in the 0.5 mg group. Glaucoma in the study eye was reported in 1 patient (1.7%) in the 0.3 mg group and 1 (1.6%) in the 0.5 mg group.

Ocular SAEs in the study eye were reported in 24 patients during the 2 year treatment period and occurred more frequently in the sham group than in the ranibizumab groups: 11 (17.7%) in the sham group, 6 (10.2%) in the 0.3 mg group and 7 (11.5%) in the 0.5 mg group. The most frequently reported SAE occurring with a frequency of $\geq 2\%$ (≥ 2 patients) in any of the three treatment groups (sham vs 0.3 mg vs 0.5 mg) were: macular degeneration 8.1% (n=5) vs 5.1% (n=3) vs 3.3% (n=2); and visual acuity reduced 4.8% (n=3) vs 1.7% (n=1) vs 4.9% (n=3). No SAEs of endophthalmitis, intraocular inflammation (uveitis), traumatic cataract (lens damage), vitreous haemorrhage, rhegmatogenous retinal detachments or retinal tears were reported in the study eye during the 2 year treatment period.

Discontinuations resulting from ocular AEs in the study eye in the 2 years study period occurred more frequently in the sham group (16.1% [n=10]) than in either of the two ranibizumab groups (0% [0/59] and 4.9% [n=3] in the 0.3 mg and 0.5 mg groups,

respectively). Ocular AEs in the 0.5 mg group (vs sham) leading to discontinuation were macular degeneration 3.3% (n=2) vs 6.5% (n=2); retinal haemorrhage 1.6% (n=1) vs 6.5% (n=4); and iridocyclitis 1.6% (n=1) vs 0%.

Ocular adverse events in the fellow eye

More patients in the two ranibizumab groups (69.5% [n=41] and 67.2% [n=41] in the 0.3 mg and 0.5 mg groups, respectively) experienced at least one ocular AE affecting the fellow eye compared with patients in the sham group (61.3% [n=38]). Fellow eye ocular AEs reported with a frequency of $\geq 10\%$ of patients in any group during the 2 year treatment period and $\geq 2\%$ in more frequently in either of the two ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): retinal haemorrhage 16.1% [n=10] vs 11.9% [n=7] vs 26.2% [n=16]; macular degeneration 4.8% [n=3] vs 10.2% [n=6] vs 16.4% [n=10]; and dry eye 6.5% [n=4] vs 10.2% [n=6] vs 3.3% [n=2].

Ocular SAEs in the fellow eye were uncommon during the 2 year treatment period. No ocular SAEs in the fellow eye were reported in patients in the sham group, 2 were reported in one patient in the ranibizumab 0.3 mg group who appears to have been treated with bevacizumab (endophthalmitis and macular degeneration) and 2 were reported in one patient in the 0.5 mg group (choroidal neovascularisation and visual acuity reduced). Ocular AEs in the fellow eye leading to discontinuation during the 2 year study period occurred in 3 (4.8%) patients in the sham group, 3 patients (5.1%) in the 0.3 mg group and 2 patients (3.3%) in the ranibizumab group. AEs leading to discontinuation were (sham vs 0.3 mg vs 0.5 mg): macular degeneration 0% vs 4.4% (n=2) vs 1.6% (n=1); retinal haemorrhage 0% vs 0% vs 1.6% (n=1); and choroidal neovascularisation 4.8% (n=3); 1.7% (n=1); and 1.6% (n=1).

Non-ocular adverse events

Death was reported in 4 patients during the study: 1 in the sham injection before crossover to ranibizumab group (1/62 [1.6%]), 1 in the sham injection after crossover to ranibizumab group (1/39 [2.6%]) and 2 in the ranibizumab 0.3 mg group (2/59 [3.4%]). Each of these deaths occurred during the second year of treatment. There was 1 death due to acute renal failure (sham before crossover group), 1 death due to intracerebral haemorrhage (0.3 mg group) and 2 deaths due to motor vehicle accidents (1 in the sham after crossover group and 1 in the 0.3 mg group).

More patients in the two ranibizumab groups (84.7% [n=50] and 86.9% [n=53] in the 0.3 mg and 0.5 mg groups, respectively) experienced at least one non-ocular AE compared with patients in the sham group (77.4% [n=48]). Non-ocular AEs reported with a frequency of $\geq 7\%$ of patients in any group during the 2 year treatment period and $\geq 2\%$ more frequently in either of the ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): hypertension 11.3% vs 10.2% vs 18.0%; urinary tract infection 8.1% vs 8.5% vs 6.6%; constipation 4.8% vs 11.9% vs 4.9%; arthralgia 1.6% vs 6.8% vs 8.2%; oedema peripheral 4.8% vs 8.5% vs 4.9%; anaemia 0% vs 6.8% vs 8.2%; hypercholesterolaemia 3.2% vs 10.2% vs 3.3%; back pain 3.2% vs 1.7% vs 6.6%; chest pain 3.2% vs 1.7% vs 8.2%; and hypokalaemia 0% vs 0% vs 8.2%.

More patients in the two ranibizumab groups (28.8% [n=17] and 26.2% [n=15] in the 0.3 mg and 0.5 mg groups, respectively) experienced at least one non-ocular SAE compared with patients in the sham group (14.5% [n=9]). Non-ocular SAEs reported in ≥ 2 subjects in any group during the 2 year treatment period and more frequently in either of the ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): atrial fibrillation 3.2% [n=2] vs 0% vs 3.3% [n=2]; cardiac failure congestive 0% vs 1.7% [n=1] vs 3.3% [n=2]; chronic obstructive pulmonary disease 0% vs 5.1% [n=3] vs 0%; coronary artery disease 0% vs 5.1% [n=3] vs 0%; and hip fracture 0% vs 3.4% vs 0%.

AEs potentially related to systemic VEGF inhibition during the 2 year treatment period were reported in 17.7% (n=11) of patients in the sham group, 15.3% (n=9) of patients in the 0.3 mg group and 32.8% (n=20) patients in the 0.5 mg. The total number of patients in the sham vs 0.3 mg vs 0.5 mg group reporting the following relevant AEs were: hypertension [7 (11.3%) vs 6 (10.2%) vs 13 (21.3%)]; arterial thromboembolic events [2 (3.2%) vs 1 (1.7%) vs 2 (3.3%)]; non-ocular haemorrhage [3 (4.8%) vs 4 (6.8%) vs 6 (9.8%)]; and other potentially related events (blood creatinine increased) 0% vs 0% vs 1 (1.6%).

The frequency of Antiplatelet Trialists' Collaboration (APTC) arterial thromboembolic events (vascular deaths, non-fatal MIs, non-fatal ischemic strokes and non-fatal hemorrhagic strokes) during the 2 year study period was low. The numbers of patients experiencing these events were (sham vs 0.3 mg vs 0.5 mg): 1 (1.6%) (non-fatal MI) vs 1 (1.7%) (vascular death) vs 0.

Laboratory abnormalities

Laboratory abnormalities above the upper limit of normal (ULN) during the 2 year treatment period reported in > 2 subjects in any treatment group and more frequently in either of the two ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): basophils present 2.0% (1/51) vs 7.0% (4/57) vs 8.6% (5/58); neutrophils segmented 12.5% (6/48) vs 13.2% (7/53) vs 3.8% (2/53); red blood cells (RBC) 0% vs 3.4% (2/59) vs 0%; prothrombin time 0% vs 1.8% (1/56) vs 3.5% (2/57); lactate dehydrogenase 2.0% (1/50) vs 5.5% (3/55) vs 1.9% (1/53); alkaline phosphatase 6.1% (4/49) vs 0% vs 7.1% (4/56); creatinine 3.9% (2/51) vs 8.9% (5/56) vs 12.5% (7/56); blood urea nitrogen 4.0% (2/50) vs 12.7% (7/55) vs 12.7% (7/55); uric acid 8.5% (11/43) vs 7.4% (4/54) vs 15.4% (8/52); glucose 25.6% (11/43) vs 24.4% (10/41) vs 34.1% (15/44); and urine specific gravity 0% vs 5.3% (3/57) vs 0%.

Laboratory abnormalities below the lower limit of normal during the 2 year treatment period reported in > 2 subjects in any treatment group and more frequently in either of the two ranibizumab groups compared with sham were (sham vs 0.3 mg vs 0.5 mg): haemoglobin 2.1% (1/48) vs 8.5% (5/59) vs 16.0% (8/50); haematocrit 2.1% (1/48) vs 5.1% (3/59) vs 10.7% (6/56); RBC 0% vs 8.5% (5/59) vs 12.7% (7/55); prothrombin time 21.7% (5/23) vs 30.3% (10/33) vs 17.2% (5/29); serum sodium 3.9% (2/51) vs 7.3% (4/55) vs 7.3% (4/55); and glucose 1.9% (1/53) vs 5.3% (3/57) vs 1.7% (1/59).

Evaluator comment

Overall, the ocular AEs in the study eye and the non-ocular AEs in the 2 year safety data in patients with AMD were consistent with the corresponding AEs in the 1 year safety data in patients with DME. However, ocular AEs in the fellow eye occurred more frequently in the two ranibizumab treatment groups than in the sham treatment group in the 2 year safety data in patients with AMD. The greater frequency of laboratory abnormalities below the lower limit of normal for the haemoglobin, haematocrit and RBC were not unexpected as anaemia is a known AE associated with ranibizumab treatment. The other laboratory abnormalities of note were the greater frequencies of abnormalities above the ULN in both ranibizumab groups compared with the sham groups for creatinine, BUN and uric acid.

EXTEND

The submission included an abbreviated Clinical Study Report of the 24 month efficacy and safety results from an open label extension study in Japanese patients with AMD [EXTEND]. This was a Phase I/II open label, multicentre study assessing the safety and efficacy of ranibizumab in Japanese patients with subfoveal CNV secondary to AMD. The study has not been previously evaluated by the TGA.

During the multiple dose phase of this study patients received fixed 11 or 12 monthly injections of ranibizumab 0.3 mg or 0.5 mg. After completion of the multiple dose phase, the protocol of the study was amended to continue as extension phase in which all eligible patients had the option to receive the study drug as individually needed. In the extension phase, ranibizumab was administered as an IVT injection of 0.3 mg or 0.5 mg according to an individualized "as needed" flexible interval regimen. The estimated number of ranibizumab injections per year was 4.19 and 4.27 in the 0.3 mg dose group and the 0.5 mg dose group, respectively. Part A of the study (which appears to have been a pilot phase) initially included 12 patients (6 treated with either 0.3 mg or 0.5 mg) and Part B of the study was the efficacy and safety part of the study and initially included 72 patients (36 treated with either 0.3 mg or 0.5 mg). In the 24 month extension phase, Part A included 9 (3 in the 0.3 mg group and 6 in the 0.5 mg group) and Part B included 61 patients (28 in the 0.3 mg group and 33 in the 0.5 mg group). The focus in the following safety summary is on the patients in Part B, unless otherwise specified.

Ocular AEs in the study eye were reported in 71.4% (n=20) and 54.5% (n=33) of patients in the ranibizumab 0.3 and 0.5 mg groups, respectively. Ocular AEs in the study eye occurring in ≥ 2 patients in least one of the treatment groups (0.3 mg vs 0.5 mg) were: conjunctival haemorrhage 12 (42.9%) vs 11 (33.3%); retinal haemorrhage 8 (28.6%) vs 8 (24.2%); retinal detachment 3 (10.7%) vs 4 (12.1%); conjunctival hyperaemia 2 (7.1%) vs 1 (3.0%); eye pain 2 (7.1%) vs 1 (3.0%); and intraocular pressure increased 2 (7.1%) vs 0%.

There were no deaths during the 24 month study period. Other ocular SAEs in the study eye occurred in 2 (7.1%) patients in the 0.3 mg group (3 events - 1 glaucomatocyclitic crises; 1 retinal detachment; 1 vitreous haemorrhage) and 0 patients in the 0.5 mg group. SAEs in the study eyes were also reported in Part A in 1 (33.3%) patient in the 0.3 mg group (1 macular degeneration) and 0 patients in the 0.5 mg group. The only ocular AEs or SAEs resulting in discontinuation from the study occurred in 2 patients (7.1%) in the 0.3 mg group.

Non-ocular AEs were reported in 67.9% (n=19) and 72.7% (n=24) of patients in the 0.3 and 0.5 mg groups, respectively. Non-ocular AEs in the study eye occurring in ≥ 2 patients in least one of the treatment groups (0.3 mg vs 0.5 mg) were: nasopharyngitis [5 (17.9%) vs 8 (24.2%)]; diabetes mellitus [3 (10.7%) vs 0%]; hypertension [3 (10.7%) vs 1 (3.0%)]; cough [0 vs 2 (6.1%)]; dental caries [1 (3.6%) vs 2 (6.1%)]; and fall [1 (3.6%) vs 2 (6.1%)]. Non-ocular SAEs occurred in 2 (7.1%) patients in the 0.3 mg group (1 cerebral infarction; 1 colon cancer), and 6 (18.2%) patients in the 0.5 mg group (8 events - abscess neck, cerebral infarction, depression, emphysema, gastric cancer, gastric polyp, small cell lung cancer unspecified, spondylytic myelopathy). Non-ocular AEs (preferred terms not identified) resulting in discontinuation from the study occurred in 1 (3.6%) patient in the 0.3 mg group and 2 (6.1%) patients in the ranibizumab 0.5 mg group.

AEs potentially related to systemic VEGF inhibition occurred in 4 (14.3%) patients in the 0.3 mg group (4 events - 3 hypertension; 1 cerebral infarction) and 2 (6.1%) patients in the 0.5 mg group (2 events - hypertension, cerebral infarction). No cases of MI were reported during the 24 months study period.

Laboratory test abnormalities above the ULN post-baseline in $\geq 10\%$ of patient in both of the two treatment groups in Part B (0.3 mg vs 0.5 mg) were: serum alkaline phosphatase 14.3% (n=4) vs 18.2% (n=6); BUN 25.0% (n=7) vs 24.2% (n=8); glucose 21.4% (n=6) vs 27.3% (n=9); and uric acid 14.3% (4/28) vs 15.2% (n=5).

Laboratory test abnormalities below the lower limit of normal post-baseline in $\geq 10\%$ of patients in both treatment groups (0.3 mg vs 0.5 mg) were: haematocrit 17.9% (n=5) vs

15.2% (n=5); haemoglobin 17.9% (n=5) vs 18.2% (n=6); and RBC 25.0% (n=7) vs 12.1% (n=4). None of the laboratory abnormalities were classified as SAEs or resulted in treatment of study discontinuation. These results were not unexpected as anaemia is a known AE associated with ranibizumab treatment.

Evaluator comment

The 24 month AE data from this study in Japanese AMD patients were consistent with the 12 month AE data in primarily Caucasian DME patients. However, in this uncontrolled extension study, 21.4% (6/28) and 27.3% (9/33) of patients in the ranibizumab 0.3 mg and 0.5 mg, respectively, had glucose levels above the ULN at post-baseline during the 24 month study period. In addition, 3 (10.7%) patients in the 0.3 mg were reported as experiencing diabetes mellitus an AE during the 24 month study period. These findings suggest potential glucose dysregulation in patients treated with ranibizumab. However, in the absence of a sham injection control group it is difficult to meaningfully interpret these data. In the response to clinical questions raised during the clinical evaluation, the sponsor stated that none of the 15 > ULN hyperglycaemic laboratory events in the extension phase were reported as AEs, "suggesting that the increases were not considered clinically relevant by the investigator". Furthermore, of the 3 patients with DM, 2 had the disease at study entry and the remaining patient had a blood glucose level above the ULN at screening (before entering the core study). In addition, the sponsor stated that all blood samples were drawn non-fasting. No further action appears indicated relating to the findings of hyperglycaemic laboratory events observed in this study.

Evaluator's overall conclusions on clinical safety

The 12 month safety data from RESOLVE/RESTORE and the 24 month safety data from DRCR.net were consistent with the known safety information for ranibizumab from the AMD studies. It is considered that no new safety signals or concerns have emerged from the safety data in patients with visual impairment due to DME treated with ranibizumab.

The clinical safety of ranibizumab is supported primarily by the 12 month safety data from the RESOLVE/RESTORE pooled safety set which included a total of 217 patients treated with IVT injections of ranibizumab as monotherapy. In the pooled safety set, 217 patients received a total of 1,837 injections with the dose per injection ranging from 0.3 to 1.0 mg and the mean (SD) number of injections being 8.5 (3.1). The median duration of follow up in both RESOLVE and RESTORE was 364 days and ranged from minimum of 15-21 days to a maximum of 469-492 days.

In RESOLVE, a total of 102 patients were treated with ranibizumab, 51 received 6 mg/mL (0.3 – 0.6 mg) with the mean (SD) number of injections being 10.2 (2.5) and 51 received 10 mg/mL (0.5 mg – 1.0 mg) with the mean (SD) number of injections being 10.1 (2.6). In RESTORE, 115 patients were treated with ranibizumab 0.5 mg and the mean (SD) number of injections was 7.0 (2.8).

The only meaningful safety data in patients with DME treated with ranibizumab for more than 12 months comes from DRCR.net. In this study, 375 patients treated with ranibizumab 0.5 mg + laser (prompt or deferred) were followed up for 2 years during which time they received a total of 3,973 injections (mean of 10.6 injections). No new or unexpected safety signals associated with ranibizumab were identified in the 24 month safety data in patients with DME. Similarly, the 24 month safety data from PIER and EXTEND in patients with AMD did not identify new or unexpected safety signals with long term ranibizumab treatment.

In the RESTORE/RESOLVE pooled safety set, ocular AEs (any) in the study eye occurred more commonly in the ranibizumab group (59.4% [129/217]) than in the control group

(44.7% [71/159]). Ocular AEs occurring in $\geq 3\%$ of patients in the study eye in the ranibizumab group (vs control) were: conjunctival haemorrhage 14.3% vs 4.4%; eye pain 14.3% vs 13.8%; increased IOP 10.1% vs 0.6%; conjunctival hyperaemia 5.5% vs 5.7%; foreign body sensation in eye 5.1% vs 1.9%; lacrimation increased 4.6% vs 0.6%; myodesopsia 4.6% vs 0.6%; visual impairment 3.7% vs 1.3%; eye pruritis 3.2% vs 4.4%; and visual acuity reduced 3.2% vs 5.7%. The most marked differences between the two groups were the greater incidence of increased IOP and conjunctival haemorrhage in the ranibizumab group. The majority of ocular AEs in both treatment groups were reported as being mild in severity. In RESOLVE (Group A+B), the incidence of ocular AEs was greater in the higher strength (higher dose) 10 mg/mL dose group (82.4%) than in the lower strength (lower dose) 6 mg/mL dose group (74.5%).

In the RESOLVE/RESTORE pooled safety set, non-ocular (any) AEs occurred with similar frequencies in the ranibizumab and control groups (60.4% and 62.9%, respectively). Non-ocular AEs occurring in $\geq 3\%$ of patients in the ranibizumab group (vs control) were: nasopharyngitis 9.7% vs 10.7%; hypertension 7.4% vs 7.5%; influenza 5.1% vs 4.4%; bronchitis 3.7% vs 2.5%; and back pain 3.2% vs 5.0%. In both treatment groups the majority of non-ocular AEs were reported as being mild/moderate in severity. In RESOLVE (Group A+B), there was no difference in the incidence of non-ocular AEs between the higher strength (higher dose) 10 mg/mL and the lower strength (lower dose) 6 mg/mL dose groups (62.7%, both groups).

In the analysis of AEs reflecting RMP safety concerns in the RESOLVE/RESTORE pooled safety set, the incidence of AEs (any) in patients in the ranibizumab group did not differ from that in the control group (81.1% [n=176] and 81.8% [n=130], respectively). However, the incidence of ocular AEs in the study eye reflecting safety concerns was greater in the ranibizumab group than in the control group (59.4% vs 44.7%, respectively). The most notable AE differences between the two treatment groups in the study eye were intraocular pressure increased (11.1% [n=24] in the ranibizumab group vs 1.3% [n=2] in the control group) and endophthalmitis (1.4% [n=3] in the ranibizumab group vs 0% in the control group). The most frequently occurring non-ocular AE reflecting RMP safety concerns was hypertension which occurred with similar frequencies in both treatment groups (9.8% [n=19] in the ranibizumab group vs 9.4% [n=15] in the control group). MIs reflecting RMP safety concerns occurred in 0.9% (n=2) of patients in the ranibizumab group and 1.3% (n=2) of patients in the control group. In addition, other arterial thromboembolic events, venous thromboembolic events, and non-ocular haemorrhage occurred infrequently in both treatment groups with similar incidences for the two treatment groups.

In RESOLVE, 1 (1.0%) death was reported in combined ranibizumab group (6 mg/mL component) and no deaths were reported in the sham injection. In RESTORE, 6 deaths occurred during the reporting period and 1 death occurred in the 4 week follow up period. Of the 6 deaths in the reporting period, 2 (1.7%) occurred in the ranibizumab 0.5 mg group, 2 (1.7%) in the ranibizumab 0.5 mg + laser group, and 2 (1.8%) in the sham injection + laser group, while the 1 death in the 4 week follow up period occurred in sham injection + laser group. There were 24 deaths reported up to the data cut-off date in the ongoing RIDE and RISE studies. The majority of deaths reported in association with ranibizumab appear to be related to *Cardiac Disorders*. Diabetes mellitus is an independent risk factor for cardiac disease and confounds interpretation of cardiac AEs and deaths due to "cardiac disease" associated with ranibizumab.

In the RESOLVE/RESTORE pooled safety set, ocular SAEs occurred infrequently in patients in both the ranibizumab group (1.8% [n=4]) and the control group (1.9% [n=3]). In ranibizumab treated patients there were 2 SAE reports of endophthalmitis and 1 report

each of retinal artery occlusion, retinal ischaemia and vitreous haemorrhage. In the control group there were 2 SAE reports of cataract and 1 report each of maculopathy and retinal detachment. In the pooled safety set, non-ocular SAEs were reported in 17.1% (n=37) of patients in the ranibizumab group and 14.5% (n=23) of patients in the control group. Non-ocular SAEs occurring in ≥ 2 patients in the ranibizumab group (vs control) were: hypoglycaemia 3 (1.4%) vs 1 (0.6%); angina pectoris 2 (0.9%) vs 1 (0.6%); coronary artery disease 2 (0.9%) vs 1 (0.6%); MI 2 (0.9%) vs 1 (0.6%); pulmonary embolism 2 (0.9%) vs 0%; and fall 2 (0.9%) vs 0%. There was an imbalance between the two treatment groups in SAEs of angina pectoris, coronary artery disease and MI, with the small number of patients experiencing these events being greater in the ranibizumab group than in the control group.

In the RESOLVE/RESTORE pooled safety set, discontinuations due to AEs were reported with similar frequencies in the ranibizumab 5.5% [n=12]) and the control (5.0% [n=8]) group. The main difference between the two groups was the higher frequency of discontinuations due to endophthalmitis in the ranibizumab group (1.4% [n=3]) than in the control group (0%).

In both RESOLVE and in RESTORE, the percentage of patients with post-baseline haematology and biochemical laboratory values exceeding critical levels was small in all treatment groups. Post-baseline urinalysis results for protein (dipsticks) did not give rise to concern, and the AE of proteinuria was reported in only 1 patient in the ranibizumab group in the RESOLVE/RESTORE pooled safety set.

Subgroup analyses of AEs reflecting RMP safety concerns and AEs reflecting VEGF inhibition safety concerns did not identify particular subgroups at increased risk when treated with ranibizumab.

Overall, in the RESOLVE/RESTORE pooled safety set the ocular safety profile in the fellow eye was similar for both the ranibizumab and control groups.

Clinical Summary and Conclusions

Benefit risk assessment and recommendations

Assessment of benefits

Overall, it was considered that the submitted data have satisfactorily established that the treatment of DME with ranibizumab IVT injections results in a clinically meaningful improvement in visual acuity compared with laser therapy alone (the current standard treatment for DME). The pivotal data from RESTORE and the supportive data from RESOLVE were considered to have satisfactorily demonstrated the efficacy of ranibizumab 0.5 mg in patients with DME. In addition, limited data supporting the efficacy of ranibizumab for the proposed indication were provided by the DRCR.net and READ-2 studies. There were no pivotal data supporting the efficacy of ranibizumab 0.5 mg for longer than 12 months. However, the published data from READ-2 suggest that maintenance of improvement observed at 6 months can be maintained through to 12 months in ranibizumab treated patients.

The data from RESTORE indicate that treatment should be initiated with 3 consecutive monthly injections of ranibizumab (0.5 mg) at 0, 1 and 2 months. The data showed that, following the initial 3 ranibizumab injections, most patients required subsequent additional doses in order to maintain the beneficial effects on visual acuity observed after initiation of treatment. Over the 12 month duration of the study, the median [range] number of injections administered was 7.0 [1-12] in the ranibizumab 0.5 mg group, 7.0 [2-12] in the ranibizumab 0.5 mg + laser group [2-12] and 7.0 [1-12] in the sham injection +

laser group. On average, about 4 additional injections were required in the “as needed” maintenance period in each of the three study groups.

In RESTORE, about 85% (98/115) of patients in the pooled ranibizumab group (safety set) had treatment interrupted/stopped due to disease improvement. Treatment was suspended if either of the following two “stability” criteria were met: (1) no further BCVA improvement attributed to treatment over the two last consecutive visits in the opinion of the investigator; or (2) BCVA > 84 letters (approximate Snellen equivalent of 20/20) observed at the two last consecutive visits. Injections were reinitiated if there was a decrease in BCVA due to DME progression in the opinion of the investigator. In this case the patient was treated at monthly intervals until stable vision was reached. Patients achieving stability based on VA criteria did so most commonly at Visit 5 (Month 3) (37.4% [37/99], FAS [observed]). However, the visit at which VA stability was first achieved was highly variable. This suggests that the duration of treatment needed to achieve a satisfactory response in individual patients will be variable and that treatment will need to be “individualized”.

In RESOLVE, ranibizumab was initiated with 3 consecutive monthly injections (0, 1, 2 months) with the initial dose being 0.3 mg (6 mg/mL group) or 0.5 mg (10 mg/mL group). The initial dose could be doubled once during the study if doubling criteria were met at any time from Month 1 through to Month 11. In the pooled ranibizumab group (Group A + B), 109 patients were treated with ranibizumab injections with the mean dose per injection being 0.62 mg. Dose doubling occurred in 68.6% (70/102) of patients in the pooled ranibizumab group (safety set), with the majority of patients whose dose was doubled (70% [49/70]) having their dose doubled at the first opportunity (Month 1). In the safety set, the mean (SD) number of injections in the pooled ranibizumab group (n=102) was 10.2 (2.5) and the median number of injections was 11 [range: 1-12], with the corresponding figures in the sham injection group (n=49) being 8.9 (3.5) and 10.0 [range: 2-12]. The high median number of ranibizumab injections reflects the strict “success” criteria followed in RESOLVE, with both BCVA and CRT criteria being required to interrupt treatment.

In RESTORE, treatment with ranibizumab 0.5 mg (n=115) improved BCVA mean (SD) average change from baseline from Month 1 to Month 12 by 6.1 (6.4) letters compared with 5.9 (7.9) letters in the ranibizumab 0.5 mg + laser group (n=118) and 0.8 (0.9) letters in the sham injection + laser group (n=110). The difference between ranibizumab 0.5 mg and sham injection + laser in the mean average change from baseline from Month 1 to Month 12 was 5.4 letters ([95%CI: 3.5, 7.4], p<0.0001). This difference was considered to be clinically meaningful as well as statistically significant. There was no statistical or clinical significant difference in improvement in BCVA between ranibizumab 0.5 mg and ranibizumab 0.5 mg + laser. In the two ranibizumab 0.5 mg treatment groups, improvement in BCVA of about 6 letters was observed at Month 3 following initiation of treatment and was then maintained through to Month 12. In contrast, in the sham injection + laser treatment group an improvement in BCVA of about 1 letter was maintained through to Month 12.

In RESTORE, the secondary efficacy endpoint analyses of VA, CRT and self reported improvement in visual function all supported the primary efficacy endpoint analysis. In particular, the proportion of patients gaining ≥ 15 letters or BCVA ≥ 84 letter, or gaining ≥ 10 letters or BCVA of ≥ 84 letters was statistically significantly greater in the ranibizumab 0.5 mg group (22.6% and 37.4%) respectively) compared with the sham injection + laser group (8.2% and 15.5%, respectively). Similarly, the proportion of patients losing ≥ 15 letters or losing ≥ 10 letters was statistically significantly lower in the ranibizumab 0.5 mg group (0.9% and 3.5%, respectively) compared with the sham injection + laser group

(8.2% and 12.7%, respectively). The mean reduction in CRT from baseline to Month 12 was statistically significantly greater in the ranibizumab 0.5 mg group compared with the sham injection + laser group. Self reported improvement in visual function assessed by various NEI FVQ-25 scores statistically significantly favoured the ranibizumab 0.5 mg group compared with the sham injection + laser group.

In RESTORE, the subgroup analyses of the primary efficacy endpoint should be considered to be exploratory and hypothesis generating as the analyses were underpowered. The effect of treatment as regards the primary BCVA efficacy endpoint was similar in the subgroup populations to the total population. However, it was noted that patients with baseline visual impairment ≤ 73 letters improved to a greater extent with all treatments compared with patients with baseline visual impairment of > 73 letters, as did patients with lower baseline CRT and patients < 65 years compared with patients aged ≥ 65 years. There were no notable differences in outcomes based on gender, DME type (focal or diffuse), the duration of DME at baseline or prior laser treatment

RESOLVE was considered to provide strong supportive evidence for the efficacy of ranibizumab for the treatment of DME. However, the interpretation of the efficacy data in this study is complicated by the inclusion of patients administered 0.3 mg or 0.6 mg in the 6 mg/mL group and 0.5 or 1.0 mg in the 10 mg/mL group due to dose doubling being allowed after the first month.

In RESOLVE, the key population for confirmatory purposes is considered to be Group B (n=109). In this group, the mean (SD) average BCVA increase from baseline from Month 1 to 12 was 9.4 (5.8), 6.0 (9.9), and 1.2 (8.4) letters in the ranibizumab 6 mg/mL (n=37), ranibizumab 10 mg/mL (n=40) and sham injection (n=32) groups, respectively. The difference in LS means between ranibizumab 6 mg/mL and sham injection was 8.1 letters ([95%CI: 4.7, 11.5], $p < 0.0001$) and between ranibizumab 10 mg/mL and sham injection was 5.5 letters ([95%CI: 1.0, 9.9], $p = 0.0067$). The BCVA difference between ranibizumab 6 mg/mL and sham injection was considered to be clinically meaningful as it exceeded 8 letters, which was the treatment difference on which the sample size calculations were based. In the 6 mg/mL group (Group B), 67.6% (25/37) of patients had their dose doubled from 0.3 mg to 0.6 mg during the study, and 68.0% (17/25) of these patients had their dose doubled at Month 1 (at the first opportunity).

In RESOLVE [Group B], the BCVA difference between ranibizumab 10 mg/mL and sham injection of 5.5 letters is considered to be of doubtful clinical significance. In the 10 mg/mL group (Group B), 72.5% (21/40) of patients had their dose doubled from 0.5 mg to 1.0 mg during the study, and 72.4% (17/21) of these patients had their dose doubled at Month 1 (at the first opportunity). The efficacy results for the 6 mg/mL and 10 mg/mL failed to demonstrate a dose response relationship as regards improvement in BCVA. When the two ranibizumab treatment groups were combined, the difference in BCVA (primary efficacy endpoint) between the combined injection and sham injection groups was 6.7 letters [95%CI: 3.2, 10.1], $p = 0.0002$).

In RESOLVE [Group B], the key secondary endpoint analyses were consistent with the those for the primary efficacy analysis with the differences between ranibizumab 6 mg/mL and sham being greater than those between ranibizumab 10 mg/mL and sham, and the results for the ranibizumab combined group and sham falling between the lower and upper dose groups. The results for all three ranibizumab dose groups were impressive when compared with sham as regards the proportion of patients gaining ≥ 10 or ≥ 15 letters and losing ≥ 10 or ≥ 15 letters, and all differences between the three ranibizumab groups and sham were considered to be clinically meaningful.

The data from the published study DRCR.net were considered to provide limited support for the submission as the study included no ranibizumab 0.5 mg only treatment group. However, the study did include an unmasked ranibizumab 0.5 mg + deferred (≥ 24 week) laser group (n=188). At the Week 16 visit, patients in the ranibizumab 0.5 mg + deferred laser group had received 4 ranibizumab 0.5 mg injections at monthly intervals (0, 1, 2 and 3 months) and no laser treatment. This allowed a comparison to be made at this time point between patients in this group and patients in the ranibizumab 0.5 mg + prompt laser group. At the 16 week visit, 47 (25%) of the 187 eyes in the ranibizumab 0.5 mg + prompt laser group and 41 (22%) of the 188 eyes in the ranibizumab 0.5 mg + deferred laser group met "success" criteria (visual acuity letter score ≥ 84 [$\geq 20/20$] or OCT central subfield $< 250 \mu\text{m}$) and did not receive an injection at the 16 week visit. This suggests that, after 4 injections, success criteria are similar for the two treatment groups. In addition, a total of 17 eyes (9%) in the ranibizumab 0.5 mg + prompt laser group and 15 eyes (8%) in the ranibizumab 0.5 mg + deferred laser group met "success" criteria at 16 weeks and did not receive an additional injection before the 1 year primary outcome visit.

In DRCR.net, at the 1 year primary outcome visit, 89 (32%) of the eyes in the sham + prompt laser group, 109 (64%) of the eyes in the ranibizumab 0.5 mg + prompt laser group and 92 (52%) of the eyes in the ranibizumab + deferred laser group met the success criteria. Mean (SD) improvement in BCVA from baseline was 3 (13) in the sham injection + prompt laser group, 9 (11) letters in the ranibizumab 0.5 mg + prompt laser group and 9 (12) letters in the ranibizumab 0.5 mg + deferred laser group. Overall, the efficacy results at 1 year for ranibizumab 0.5 mg + prompt laser were similar to those for ranibizumab 0.5 mg + deferred laser and both treatments were superior to laser treatment alone. Of note, in the ranibizumab 0.5 mg + deferred laser group, from the 24 week study visit and before the 1 year primary outcome visit, 128 (72%) of the study eyes received no laser treatment, 35 (20%) received only 1 laser treatment, and 15 (8%) received 2 laser treatments.

The data from published study READ-2 [Nguyen et al., 2009] were considered to provide only limited support for the submission due to the open label design, the small number of patients and the different dosage regimen from that being proposed. The study showed that the mean increase in BCVA from baseline to Month 6 (primary efficacy outcome) was statistically significantly greater in the ranibizumab 0.5 mg group (n=42) than in the laser group (n=42): +7.07 vs -0.41 letters, respectively (p = 0.01). Of the 37 patients in the ranibizumab 0.5 mg group for whom data were available at 6 months, 8 (22%) had an improvement of ≥ 3 or more lines of BCVA and 17 (46%) had an improvement of ≥ 2 or more lines. In the laser group, none of the 38 patients improved by ≥ 3 or more lines and 2 patients (5%) improved by ≥ 2 more lines, both significantly less than in the ranibizumab group (p=0.002 and p=0.00004, respectively). In this study, the dosage regimen was 4 injections for all patients administered at time points 0, 1 month, 3 months and 5 months. There was no option to discontinue treatment from Month 3 if VA had been stable following the first 3 injections. In addition, in this study laser administered in combination with ranibizumab 0.5 mg appeared to reduce the effect of ranibizumab 0.5 mg alone (+3.61 vs +7.07 letters, respectively).

There were no efficacy data in RESTORE or RESOLVE beyond 12 months. However, DRCR.net included some efficacy data extending beyond 12 months as did a recent published study reporting the 2 year outcomes from READ-2 [Nguyen et al., 2010]. The READ-2 data showed that in those patients who had remained in the study for 24 months the respective mean improvements at 6 month and 24 months in BCVA were 7.4 and 7.7 letters for ranibizumab 0.5 mg alone (n=33), 0.5 and 5.1 letters for laser alone (n=34), and 3.8 and 6.8 letters for ranibizumab 0.5 mg + laser (n=34). These results suggest that mean improvement at 6 months can be maintained through to 24 months in patients treated with ranibizumab. The published data from DRCR.net showed that improvement in BCVA

observed at 1 year in the ranibizumab 0.5 mg groups with prompt or deferred laser can be maintained through to 2 years. However, the data were of limited relevance to patients treated with ranibizumab 0.5 mg alone.

Assessment of risks

No new safety signals associated with ranibizumab have emerged from the safety data in patients with DME. Therefore, the risks of treatment with ranibizumab for the treatment of DME were consistent with the known risks for the approved indication of treatment of neovascular (wet) age related macular degeneration.

In the RESTORE/RESOLVE pooled safety set, ocular AEs (any) in the study eye occurred more commonly in the ranibizumab group (59.4% [129/217]) than in the control group (44.7% [71/159]). The most marked differences between the two groups were the greater incidence in the ranibizumab group (vs control) of conjunctival haemorrhage (14.3% vs 4.4%) and increased IOP (10.1% vs 0.6%).

In the RESOLVE/RESTORE pooled safety set, non-ocular (any) AEs occurred with similar frequencies in the ranibizumab and control groups (60.4% and 62.9%, respectively). In both treatment groups, the majority of non-ocular AEs were reported as being mild/moderate in severity.

In the RESOLVE/RESTORE pooled safety set, AEs (any) reflecting RMP safety concerns occurred with similar frequencies in the ranibizumab and control groups (81.1% and 81.8%, respectively). However, the incidence of ocular AEs in the study eye reflecting safety concerns was greater in the ranibizumab group than in the control group (59.4% vs 44.7%, respectively). The most notable differences in ocular AEs in the study eye between the two treatment groups were the greater incidence in the ranibizumab group (vs control) of increased intraocular pressure (11.1% vs 1.3%) and endophthalmitis (1.4% vs 0%). Other ocular AEs in the study eye reflecting RMP safety concerns occurred with similar frequencies in the two treatment groups or more commonly in the control group than in the ranibizumab group.

In the RESOLVE/RESTORE pooled safety set, the most frequently occurring non-ocular AE reflecting RMP safety concerns was hypertension which occurred with similar frequencies in the ranibizumab and control groups (9.8% vs 9.4%, respectively). MI occurred uncommonly in both the ranibizumab and control groups (0.9% vs 1.3%, respectively). Other arterial thromboembolic, venous thromboembolic and non-ocular haemorrhage events occurred infrequently in both treatment groups.

In the RESOLVE/RESTORE pooled safety set, ocular SAEs occurred infrequently in both the ranibizumab and control groups (1.8% and 1.9%, respectively). In the ranibizumab group, there were 2 SAE reports of endophthalmitis and 1 report each of retinal artery occlusion, retinal ischaemia and vitreous haemorrhage, while in the control group there were 2 SAE reports of cataract and 1 report each of maculopathy and retinal detachment. Non-ocular SAEs were reported more frequently in the ranibizumab group than in the control group (17.1% and 14.5%, respectively). Non-ocular SAEs occurring in ≥ 2 patients in the ranibizumab group (vs control) were: hypoglycaemia 1.4% vs 0.6%; angina pectoris 0.9% vs 0.6%; coronary artery disease 0.9% vs 0.6%; MI 0.9% vs 0.6%; pulmonary embolism 0.9% vs 0%; and fall 0.9% vs 0%. There was an imbalance between the two treatment groups in SAEs of angina pectoris, coronary artery disease and MI, with the small number of patients experiencing these events being greater in the ranibizumab group than in the control group.

In the RESOLVE/RESTORE pooled safety set, discontinuations due to AEs were reported with similar frequencies in the ranibizumab and control groups (5.5% and 5.0%,

respectively). The main difference between the two groups was the higher frequency of discontinuations due to endophthalmitis in the ranibizumab group than in the control group (1.4% and 0%, respectively).

In RESOLVE, 1 (1.0%) death was reported in combined ranibizumab group (6 mg/mL component) and no deaths were reported in the sham injection group. In RESTORE, 6 deaths occurred during the reporting period and 1 death occurred in the 4-week follow up period. Of the 6 deaths in the reporting period, 2 (1.7%) occurred in the ranibizumab 0.5 mg group, 2 (1.7%) in the ranibizumab 0.5 mg + laser group, and 2 (1.8%) in the sham injection + laser group, while the 1 death in the 4 week follow up period occurred in sham injection + laser group. There were 24 deaths reported up to the data cut-off date in the ongoing RIDE and RISE studies. The majority of deaths reported in association with ranibizumab appear to be related to *Cardiac Disorders*. Diabetes mellitus is an independent risk factor for cardiac disease and confounds interpretation of cardiac AEs and deaths due to “cardiac disease” associated with ranibizumab.

In both RESOLVE and in RESTORE, the percentage of patients with post-baseline haematology and biochemical laboratory values exceeding critical levels was small in all treatment groups. Post-baseline urinalysis results for protein (dipsticks) did not give rise to concern, and the AE of proteinuria was reported in only 1 patient in the ranibizumab group in the RESOLVE/RESTORE pooled safety set. Subgroup analyses of AEs reflecting both RMP and VEGF inhibition safety concerns did not identify particular subgroups at increased risk when treated with ranibizumab.

The 24 month published safety data from DRCR.net in patients with DME treated with ranibizumab do not give rise to new safety concerns. Similarly, the 24 month safety data from PIER and EXTEND in patients with AMD treated with ranibizumab do not give rise to new safety concerns.

Assessment of benefit risk balance

The benefit risk benefit of ranibizumab (Lucentis), given the proposed usage, is favourable.

Final recommendation

It was recommended that ranibizumab (Lucentis) be approved for the treatment of visual impairment due to diabetic macular oedema.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The summary of the Ongoing Safety Concerns as specified by the sponsor are shown in Table 30.

Table 30: Ongoing safety concerns

Important identified risks	<ul style="list-style-type: none"> Hypersensitivity reactions Retinal pigment epithelial tear Endophthalmitis Retinal detachment Retinal tear Traumatic cataract Intraocular inflammation Intraocular pressure increase
Important potential risks	<ul style="list-style-type: none"> Hypertension Non-ocular hemorrhage
	<ul style="list-style-type: none"> Proteinuria Myocardial infarction Non-MI arterial thromboembolic events (ATEs) Venous thromboembolic events Deterioration of retinal blood flow including CRAO
Important missing information	<ul style="list-style-type: none"> 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 pediatric off-label use (e.g. retinopathy of prematurity) Long-term safety beyond two years Intraocular antibody formation

The OPR reviewer noted that the nonclinical evaluator had identified ranibizumab's activity as anti-angiogenic raising concerns about the potential toxicity for the embryo/fetus during pregnancy and the animal study did not allow this concern to be excluded or removed. Furthermore, pregnant or lactating women were excluded from the clinical program investigating DME, and it appears that there is no clinical data available from the wet-AMD program. It has a Pregnancy Category D and the PI directly addresses use in pregnancy with significant information. Use in pregnancy would therefore be considered off-label, and would be captured under missing information for adverse events related to off-label use.

Pharmacovigilance plan

For all ocular safety concerns, routine pharmacovigilance will be supported by the targeted follow up of all serious post-marketing and clinical trial reported adverse events using a questionnaire/checklist.¹⁶ The RMP states that this is to obtain “higher quality information regarding the details of the event and to ensure a standard approach to obtain follow-up information”.

Three ongoing studies are proposed by the sponsor to address all identified and potential risks, both ocular and non-ocular. Brief details of each of these studies are provided below.

1. Cohort study (Epi-COHORT) (wet-AMD) (CRFB002A2401) is a prospective cohort study design in patients with choroidal neovascularisation secondary to age-related macular degeneration. A total of 70 patients included to 29 April 2010 with follow up for 2 years.
2. A long term extension study SECURE (wet-AMD) (CRFB002A2402) which is a Phase IV study exploring the safety of ranibizumab 0.5mg over 24 months in patients completing a prior study of at least 12 months duration. It is a single arm, open label study with 234 patients enrolled.
3. The long term extension of RESTORE study (visual impairment due to DME) which is a Phase IIIb extension study evaluating the safety and persistence of efficacy of ranibizumab 0.5mg prn as symptomatic treatment for visual impairment due to diabetic macular oedema. It is a single arm, open label 24 month extension of Phase III with 390 patients followed for 12 months.

Some of the above studies are also proposed to inform some of the non-ocular missing information safety concerns, specifically:

- Systemic adverse events (bilateral treatment and overdose) – cohort (Epi-COHORT) study
- Long term safety beyond 2 years – SECURE and RESTORE.

The OPR reviewer noted that the protocols of the ongoing studies have not been reviewed as these are already in progress, however the following points were raised in relation to the additional information provided by the studies and therefore the ability to address the safety concerns:

- It was difficult to ascertain the usefulness of the additional information gained from the Epi-COHORT, SECURE and RESTORE studies for two reasons - the populations being studied (wet-AMD and DME) are a different at risk group and therefore generalisability of the results will need to be considered and the patient years of follow up (approx 1540, 693, 1170) may reveal very few adverse event reports given the postmarketing cumulative reporting rates so far are <1/1,000 patient years.
- Long term safety use (beyond 2 years, missing information safety concern) –SECURE and RESTORE extension studies are proposed additional pharmacovigilance activities

¹⁶ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

for this concern. The extension studies involve a total follow up period of 3 years. It was not clear at this time what the overall period of time treatment could be provided for, but given that there is no cure for this progressive condition, it is possible that treatment will be provided off and on for an extended period of time.

It was considered unlikely that the ongoing studies (including the extension) are likely to provide significant further information to assist in clarifying or refining these risks. Therefore, the majority of future information regarding these safety concerns will be gained through routine pharmacovigilance activities, combined with the targeted follow up of serious reports of the ocular adverse events. The main concern regarding this is around long term safety use and the sponsor was requested to provide further information on the adequacy of long term safety from only 3 years worth of follow up data.

The OPR reviewer noted that the use of targeted follow up seems appropriate, in particular to ensure a standard approach to collecting information. However, to determine the contribution and appropriateness of this activity in monitoring and assessing the risks, further information on the details collected as part of the follow up questionnaire or checklist was required. In particular, the monitoring of long term safety (ocular risks) of ranibizumab use beyond 3 years should be addressed, as this will be dependent on this mechanism.

The OPR reviewer agreed that the use of routine pharmacovigilance activities to monitor non-ocular safety risks is considered acceptable at this time, in view of the information that clinical trials have not identified an elevated RR for any of these concerns. However the CIs are wide indicating a low degree of certainty about these estimates and this determination remains dependent on the clinical evaluators report and assessment of the risk.

Risk minimisation activities

The sponsor proposed that routine risk minimisation activities are adequate for safety concerns apart from endophthalmitis and traumatic cataract.¹⁷

The OPR reviewer noted that an elevated relative risk has been identified with both endophthalmitis and traumatic cataract in the clinical study program. In addition postmarketing experience identifies endophthalmitis as having one of the highest cumulative reporting rates (0.31 per 1,000 patient years). The mechanism of action proposed for both these risks is a complication of IVT injection and therefore it was acceptable that additional activities be considered for these two risks.

For the remaining ocular concerns, there is also a potentially elevated relative risk for IOP increase. In their analysis, the sponsor identified that the majority of increased IOP events in DME were from the study (RESOLVE) in which a volume of 100 µL ranibizumab was given to the majority of patients (22 of the 24 reports). In a further study (RESTORE) the indicated dose and volume (0.5 mg in 50 µL) was used in all patients and only 2 reports were received. This reduction in injected volume has appeared to reduce the risk of IOP events.

Another ocular safety concern with a similar cumulative reporting rate to endophthalmitis is intraocular inflammation. This may arise as a complication of IVT injection or in the presence of a history of intraocular infection or inflammation. The additional activities for endophthalmitis and traumatic cataract will also address the risk of intraocular inflammation, as does the information in the PI. For completeness however, it would be

¹⁷ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

appropriate to include this safety concern as being addressed by additional risk minimisation activities.

For the non-ocular safety concerns, the theoretical mechanism of action is related to the systemic effects of anti-VEGF and there is no statistically significant elevated risk at this stage. Postmarketing experience reports a cumulative reporting rate of 0.33 for hypersensitivity reactions and 0.34 for non-MI arterial thromboembolic events, while the remainder are all less than 0.1 per 1,000 patient years. Routine risk minimisation was considered acceptable for these concerns.

The additional risk minimisation activities for endophthalmitis and traumatic cataract are a healthcare professional and patient educational plan. The objectives of these activities are:

- To prevent or minimize the likelihood of IVT injection-related adverse events, and
- To inform and educate physicians and patients on early recognition and management of these events.

The OPR reviewer agreed that the identification of endophthalmitis and traumatic cataract as safety concerns requiring additional risk minimisation activities was acceptable. The professional and patient education plan focuses on IVT injection techniques and minimising these adverse events and also seems to address other safety concerns in the package where appropriate.

However, there was no information on the current or potential use of these educational plans in Australia. While it is agreed that the additional risk minimisation activity is appropriate, it was not possible at this stage to make a recommendation to the Delegate regarding the adequacy of this activity. Further information from the sponsor on the relevance of the plans in Australia, and the practical considerations here, was required to consider the effectiveness and appropriateness of this in Australia.

Pharmacovigilance summary and conclusions

The OPR provided the following recommendations to the Delegate.

It was recommended that the relevant sections of the safety specification of the RMP be modified as recommended by the nonclinical evaluator.

The majority of future information regarding ongoing safety concerns will be gained through routine pharmacovigilance activities, combined with the targeted follow up of serious reports of the ocular adverse events. The adequacy of this in addressing the long term safety use is questioned and the sponsor was requested to provide further information on the adequacy of long term safety from only 3 years worth of follow up data.

A final recommendation on the contribution and appropriateness of targeted follow up of adverse events cannot be made until further information regarding the details collected as part of the follow up questionnaire or checklist, in particular for the monitoring of long term safety (ocular risks) of ranibizumab use beyond 3 years, was provided.

While the fill volume was reduced from 0.3 to 0.23 mL in 2007, the vial still contains enough active agent for around 4 doses (recommended maximum dose is 0.5 mg (0.05 mL)) and therefore the risk for overdose, transmission of infectious agents and adverse events such as increased IOP is still present. To provide a recommendation to the Delegate on this issue, further information on the justification for including approximately 4 doses in a single use vial was requested.

It was recommended that the Delegate consider a statement referring to the lack of long term safety information in the PI.

The proposed use of a healthcare professional and patient educational plan to address the risks of endophthalmitis and traumatic cataract was considered appropriate, however it is not possible to make a recommendation to the Delegate regarding the adequacy of this activity in Australia. Further information from the sponsor on the relevance of the plans in Australia, and the practical considerations here, was required to consider the effectiveness and appropriateness of this in Australia.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The submission included a small amount of new data, that is, a new, GLP compliant embryofetal development study in cynomolgus monkeys, conducted by the clinical route and including toxicokinetic data. Ranibizumab was detected in the serum of one fetus, demonstrating that fetal transfer is possible. In the monkey embryofetal development study, at an estimated exposure ratio of up to 58, there were no effects of IVT ranibizumab on the mother, placenta or fetus.

There was no new nonclinical study that specifically addressed efficacy in the treatment of visual impairment due to diabetic macular oedema. The previously submitted primary pharmacology studies are consistent with efficacy for this new indication.

The sponsor disputed the conclusions concerning ocular inflammation. The evaluator was of the view that the findings of ocular inflammation in monkeys are not consistent solely with a specific immune response to a humanised protein in animals. This is supported by findings of inflammatory responses and the development of anti-ranibizumab antibodies in humans.

Clinical

The evaluator questioned the proposed dosage regimen. In reply, the applicant clarified it. The evaluator reports this to be that:

"The recommended dose of Lucentis is 0.5 mg (0.05 mL) given as a single IVT injection. The interval between two doses should not be shorter than one month. Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than one month."

"Lucentis can be safely administered concomitantly with laser photocoagulation as well as in patients who have received previous laser photocoagulation. When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation."

Phase II studies

The evaluator was of the view that the utility of ranibizumab in diabetic macular oedema is biologically plausible. No new specific pharmacological studies were submitted. Previously submitted pharmacokinetic studies were not re-evaluated.

Studies that contributed efficacy data in DME

The new studies in the data package included two clinical efficacy and safety studies supporting the proposed extension of indication to include the treatment of DME [REVOLVE and RESTORE]. Also submitted were six clinical efficacy and safety studies and/or reports on the currently registered indication that had not previously been submitted to the TGA: PIER 24 month results; EXCITE; SUSTAIN open label 12 month study; EXTEND open label study with results up to 24 months in Japanese patients with AMD; EXTEND II; and EXTEND III.

The new efficacy studies, RESOLVE and RESTORE involved a single eye per subject (Table 2). Each ran for 12 months and was of an acceptable randomised, controlled, double masked design. RESOLVE was a three arm Phase III dose finding study (ranibizumab 0.3 mg or 0.5 mg) against sham injection. RESTORE was a larger three arm study that compared ranibizumab +/- active laser treatment versus sham injection + active laser treatment. That is, it was not a study against sham treatment with the option of laser rescue therapy.

Pivotal trials (efficacy)

The evaluator only considered that one study was pivotal – RESTORE. Most of patients who were enrolled in the study had diabetes mellitus type 2 – from 86.4% to 88.8% in the three treatment arms.

The primary efficacy outcome was to demonstrate the superiority of ranibizumab (0.5 mg) monotherapy or adjunctive therapy (to laser treatment) relative to laser monotherapy, as assessed by the mean change from baseline in BCVA averaged from monthly assessments over the 12 month treatment period. The assessment of visual acuity was done independently of the treating investigator by blinded assessors.

There were six secondary endpoints and the role of pharmacogenetics was explored as well. In regard to the statistical analytical plan, the evaluator noted that (i) the sample size was adequate for the primary and that (ii) no adjustment was made for the numerous pairwise comparisons of the secondary variables. The evaluator considered that an improvement in the BCVA score would be clinically significant if it were ≥ 5 .

The dosing regimen reflected the proposed Dosage and Administration advice in the product information document. Discontinuations and protocol deviations were broadly similar across the three treatment arms of the study high ($\geq 87\%$ in each arm completed the study). As noted by the evaluator: “During the Month 3 to Month 11 time period [the maintenance period] and taking into account patients who prematurely discontinued the study and missed visits, an injection was missed due to disease improvement for 49.2% of the injection visits for patients in the ranibizumab 0.5 mg group, 49.8% of the injection visits for patients in the ranibizumab 0.5 mg + laser group and 40.2% of the injection visits for patients in the sham injection + laser group.”

The primary endpoint results are shown in Table 6. The evaluator noted that: “The mean (SD) average increase in BCVA from Month 1 to Month 12 compared with baseline was 6.1 (6.4) letters in the ranibizumab 0.5 mg group, 5.9 (7.9) letters in the ranibizumab 0.5 mg + laser group and 0.8 (8.6) letters in the laser group. The high SD values compared with the mean observed for each of the three groups indicate high inter-subject variability in

response within each of the three groups.” Most of the gains attributable to ranibizumab occurred in the first few months.

The Delegate noted that if read literally, the patients enrolled could have been poorly controlled and under-treated, “Patients with Type 1 or Type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 10.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes.” In fact, worse control than this was a common amongst deviations from the protocol.

Furthermore, it was noted that the differences between both ranibizumab arms and laser alone were statistically significant and the point estimate for ranibizumab alone was clinically significant as well. Adjunctive use of ranibizumab with laser fell short of clinical significance, perhaps reflecting the destructive effect of laser therapy.

Despite certain concerns about the secondary variables, the evaluator noted that the ranibizumab only treatment arm did better than laser alone with respect to:

- The percentage of patients losing ≥ 10 letters at month 12 compared with baseline; and,
- The percentage of patients gaining ≥ 10 letters (or BCVA of ≥ 84 letters) at month 12 from baseline.

Supportive study

The evaluator considered that the other new study (RESOLVE) was supportive and that it is a Phase II dose finding study. The reasons for this opinion were clearly articulated. The primary endpoint was also shifted from central retinal thickness to BCVA.

The dosing regimen enabled dose doubling from 0.3 mg or 0.5 mg per eye to 0.6 mg or 1.0 mg per eye per month according to these criteria that relate to retinal thickness and not to visual acuity:

“The initial injection dose was 0.3 mg or 0.5 mg, and the initial dose could be doubled from 0.3 mg to 0.6 mg or from 0.5 mg to 1.0 mg if one of the following conditions were met:

- if at the Month 1 visit following the first injection retinal thickness in the study eye remained $> 300 \mu\text{m}$; or
- if at any monthly visit after Month 1, following injection retinal thickness in the study eye was $> 225 \mu\text{m}$ and reduction in retinal oedema from the previous assessment was $< 50 \mu\text{m}$.

No further increases in dose after doubling of the initial dose were allowed. If treatment was withheld for more than 45 days for any reason, subsequent injections were restarted with the initial dose.”

The evaluator reported that: “the majority of patients received a ranibizumab injection dose greater than the 0.5 mg dose being proposed (68.6% of patients received a dose ≥ 0.6 mg, 17.6% received a dose of 0.5 mg and 13.7% received a dose of 0.3 mg”).

The study results were reported not by dose but the strength of the injected solution, that is: “The results in the treatment group were analysed based on the strength of solution administered rather than the dose (6 mg/mL or 10 mg/mL). Consequently, after the first injection the 6 mg/mL group included patients who had been treated with 0.3 or 0.6 mg and the 10 mg/mL group included patients with 0.5 mg or 1.0 mg. As discussed below, this has complicated the interpretation of the data as regards the efficacy of the 0.5 mg dose

proposed for approval". Moreover, there was not complete central adjudication of the BCVA outcomes.

Within the limits of the change to protocol, the primary objective of the confirmatory study part (Group B) was to demonstrate superiority of ranibizumab to sham treatment in the mean change from baseline in BCVA over a 12 month treatment period. Multiple statistical tests were performed in this relatively small study.

The evaluation report includes the tabulation of BCVA results for Group B but it is reported by strength of solution, not the doses given (Table 14).

The limitations of these results were discussed by the evaluator. In regard to actual doses given, dose doubling was very common, meaning that most patients received doses above those used in the later pivotal study, RESTORE:

The evaluator was not convinced that this study could have been used to inform the dose selected for RESTORE: "...it is considered that little evidentiary weight should be given to these *post hoc* analyses because the study was not designed to test such dose comparisons, and is underpowered to detect statistically significant differences in BCVA or CRT between the two doses in the 6 mg/mL and 10 mg/mL strength groups."

The Delegate noted that patients who were enrolled could have poor diabetic control: "Patients with Type 1 or Type 2 diabetes mellitus diagnosed \geq 24 months prior to screening, with HbA1c not more than 12.0% at Visit 1 and a documented history of stable HbA1c compared with the previous measurement within the last 6 months with a difference of not more than 1.0%."

The Delegate presumed that the choice of the strength of the solution that was injected rather than the dose of the active that was given reflects an intention to consider and report local safety and tolerability of a higher vs lower strength solution. However, this was not clear. Of patients treated, the majority in RESOLVE was given a dose higher than that used in RESTORE.

Other information supplied included READ-2 [Nguyen et al., 2009] and DRCR.net – the evaluator considered them to be inadequately reported, particularly with regard to safety.

In regard to READ-2, the evaluator reported: "At Month 6, the mean change in BVCA from baseline (primary efficacy outcome) was +7.24 letters in the ranibizumab 0.5 mg group, -0.43 in the focal/grid laser group, and +3.80 in group the ranibizumab 0.5 mg + focal/grid laser group. The comparison between the ranibizumab 0.5 mg and the focal/grid laser groups was statistically significant ($p=0.01$, ANOVA) but there was no statistically significant difference between the ranibizumab 0.5 mg and the ranibizumab 0.5 mg + ranibizumab 0.5 mg + focal/grid laser ($p=0.08$). It was not clear from the description of the results how many patients were included in each of the three treatment groups for the 6 month analysis of the primary efficacy endpoint. However, 42 patients were randomized to each of the three treatment groups."..

" It showed that ranibizumab 0.5 mg alone administered at baseline and Months 1, 3 and 5 resulted in statistically significantly greater reductions in mean BCVA from baseline to Month 6 (primary efficacy outcome) than laser alone given at baseline and Month 3. The treatment regimen in this study for the ranibizumab 0.5 mg alone group was significantly different from that being proposed for approval."

"The dosage regimen used in this study was 4 injections for all patients administered at time points 0, 1 month, 3 months and 5 months. There was no option to discontinue treatment from Month 3 if VA had been stable following the first 3 injections. In addition,

laser administered in combination with ranibizumab 0.5 mg appeared to reduce the effect of ranibizumab 0.5 mg alone (+3.61 vs +7.07 letters, respectively)."

In regard to the second study, the evaluator commented:

"DRCR.net is considered to be a good quality study. However, it provides only limited data directly supporting the submission as it included no ranibizumab 0.5 mg only treatment group. It did include an unmasked ranibizumab 0.5 mg + deferred (≥ 24 week) laser group (n=188)."

"The 1 year results provided evidence for the superior efficacy of ranibizumab 0.5 mg with prompt or deferred laser compared with prompt laser alone. However, in the ranibizumab 0.5 mg + deferred laser, group not all eyes avoided the need for laser treatment over the 12 month study period with 28% requiring at least 1 laser treatment between the 24 week and the 1 year study visit when the re-treatment algorithm was followed."

It was noted that the data extend to 24 months of treatment.

Safety

The two new studies contribute safety data to 12 months (Table 19). The 217 patients in the ranibizumab group received 1,837 injections on study. The median duration of follow up was 364 days. As previously mentioned, dose doubling was a feature of RESOLVE. In both studies, the patients were well matched across the treatment arms.

In RESTORE/RESOLVE, ocular adverse events were observed more commonly in patients in the ranibizumab group (59.4%) than in patients in the control group (44.7%). A number of these were related to the injection. Adverse events that were identified in the Risk Management Plan were tabulated in the evaluation and no overall trend was noted in respect of ranibizumab versus control but, consistent with the previous observation, some local adverse events were more common in the patients who received ranibizumab. As noted: "In RESOLVE/RESTORE, the incidence of non-ocular AEs resulting in discontinuation was higher in the ranibizumab group than in the control group (4.1% [n=9] and 3.1% [n=5], respectively)."

The evaluator noted that there was slight tendency to dose dependency of local ocular adverse events in RESOLVE. It was of note that there was a trend to higher intraocular pressure after IVT ranibizumab but there was some insensitivity, that is, routine testing was not generally done. "The most marked differences between the two groups were the greater incidence in the ranibizumab group (vs control) of conjunctival haemorrhage (14.3% vs 4.4%) and increased IOP (10.1% vs 0.6%)."

The Delegate noted that the evaluator reported the safety findings in detail but the overall number of serious events was small. No new safety signals emerged from these two studies or from the literature provided.

Other safety data

The sponsor provided 24 month safety data from the previously evaluated study in age related macular degeneration, PIER. No new information of significance was noted in the second twelve month period versus the first. The evaluator commented that there was a higher rate of adverse events in the fellow eye for ranibizumab versus sham but this is of doubtful significance, given the relatively small differences seen amongst fewer than 42 patients per treatment arm.

EXTEND was a newly submitted uncontrolled study in age related macular degeneration. The 24 month safety data were qualitatively similar to other studies in this indication. Some worsening of control of diabetes was noted in the second year.

The evaluator supported registration.

Risk Management Plan

As noted by the evaluator: "A number of ongoing safety concerns have been identified in the RMP, specifically 8 important identified risks (7 ocular), 7 potential risks (1 ocular), and 4 important missing information safety concerns. A pharmacovigilance and risk minimisation plan has been outlined for each of the ongoing safety concerns. In addition to required routine pharmacovigilance activities, it is proposed that 3 ongoing studies will provide additional information on several of these safety concerns until 2012. Additional risk minimisation activities have been proposed for two of the identified risks." However, "It is unlikely that the ongoing studies (including the extension) are likely to provide significant further information to assist in clarifying or refining these risks. Therefore, the majority of future information regarding these safety concerns will be gained through routine pharmacovigilance activities, combined with the targeted follow up of serious reports of the ocular adverse events."

Risk-Benefit Analysis

Delegate considerations

New indication

Efficacy data are limited to 12 months.

Changed dosing advice for currently registered indication

The drug development program has not defined an optimal dose or dosing schedule or duration. It would seem that ranibizumab 0.3 mg is likely to be associated with less likelihood of inflammatory reactions than the 0.5 mg dose but this supposition is not strongly supported by the clinical studies. Doses of ranibizumab above 0.5 mg are not sought due to this tolerability issue. It is not clear whether the tolerability relates to ranibizumab per se but this has not been excluded.

The dosing regimen should mirror that used in RESTORE.

The Delegate indicated that the application is approvable on the basis of biological plausibility, one pivotal study and one supportive study. It is doubtful that RESOLVE should appear in the product information document as it adds little relevant information and may be seen to support dose doubling. Moreover, it was a supportive study only. The Committee's views were sought.

There was no basis for altering the indication of the registered indication, "Lucentis 0.5 mg or 0.3 mg is recommended to be administered by IVT injection once a month."

The Delegate proposed that the extended indication for Lucentis should be approved for *The treatment of visual impairment due to diabetic macular oedema (DME).*

The existing indications should not be modified by removal of the text, "Lucentis 0.5 mg or 0.3 mg is recommended to be administered by intravitreal injection once a month."

The sponsor should be encouraged to undertake clinical trials to investigate longer term response and safety and to undertake further clinical trials on dose ranging and the optimal dosing interval.

Response from sponsor

The sponsor concurred with the Delegate's recommendation and addressed the issues raised above. Each issue has been reproduced in *italics* below.

Phase III studies (pivotal trials (efficacy) - RESTORE

If read literally, the patients enrolled could have been poorly controlled and under-treated, "Patients with Type 1 or type 2 diabetes mellitus (according to ADA or WHO guidelines) with HbA1c not more than 10.0% at screening (Visit 1). Patients should be on diet, exercise, and/or pharmacological treatment for diabetes." In fact, worse control than this was common amongst deviations from the protocol.

The sponsor noted there were 8 patients out of 345 with a baseline value of HbA1c of more than 10%. Therefore, to evaluate this aspect the sponsor used the cut-off point of 8.0% in order to perform further subgroup analyses in the RESTORE study. Ranibizumab as monotherapy or in combination with laser was compared to laser monotherapy. The analyses included the subgroups HbA1C <8.0% and ≥8.0%.

The magnitude of the treatment effect for the primary efficacy endpoint (mean average change in BCVA between Month 1 and Month 12 compared to baseline) did not appear to differ between these subgroups.

These additional subgroup analyses of RESTORE demonstrated the benefits of ranibizumab treatment were consistent in the different metabolic control subgroups. Consequently, the sponsor considered that the effect of treatment is not confounded by this metabolic variable and is applicable in patients with varying systemic control of the disease. However, Novartis identified that healthcare professionals may require additional guidance in this area and therefore proposed the inclusion of additional text in the PI in accordance with the EU Summary of Product Characteristics (SmPC):

The differences between both ranibizumab arms and laser alone were statistically significant and the point estimate for ranibizumab alone was clinically significant as well. Adjunctive use of ranibizumab with laser fell short of clinical significance, perhaps reflecting the destructive effect of laser therapy.

The sponsor concurred that the RESTORE study did not demonstrate additional benefit regarding the efficacy of ranibizumab/laser combination vs ranibizumab monotherapy. However, the ocular and non-ocular safety outcomes in both treatment arms of the study (ranibizumab and ranibizumab/laser) were comparable and therefore additional safety concerns regarding the combined use of ranibizumab/laser could not be identified.

Supportive study - RESOLVE

Patients who were enrolled could have poor diabetic control, "Patients with Type 1 or Type 2 diabetes mellitus diagnosed ≥24 months prior to screening, with HbA1c not more than 12.0% at Visit 1 and a documented history of stable HbA1c compared with the previous measurement within the last 6 months with a difference of not more than 1.0%.

While the inclusion criteria of RESOLVE allowed for an HbA1c up to 12.0%, the average level at baseline in patients enrolled in the study, as well as at month 12 was below 8.0%.

However, to evaluate the influence of the HbA1c levels on the efficacy outcome, further subgroup analyses were conducted in the RESOLVE study. The analyses included the subgroups HbA1c <8.0% and ≥8.0%. The magnitude of the treatment effect for the primary efficacy endpoint (mean average change in BCVA between month 1 and month 12 compared to baseline) did not appear to differ between these subgroups.

The additional subgroup analyses of RESOLVE demonstrated the benefits of ranibizumab treatment were consistent in the two different metabolic control subgroups. Consequently, the sponsor considered that the effect of treatment is not confounded by this metabolic variable and is applicable in patients with varying systemic control of the disease.

Therefore, there is no indication that the observed treatment differences are confounded by changes in risk factors during the course of the study, or because of an imbalance between the groups at baseline. However, consistent with the response given above, the sponsor proposed an update of the PI in accordance with the EU SmPC.

One presumes that the choice of the strength of the solution that was injected rather than the dose of the active that was given reflects an intention to consider and report local safety and tolerability of a higher vs lower strength solution. However, this is not clear. Of patients treated, the majority in RESOLVE was given a dose higher than that used in RESTORE.

The randomisation of patients in this study was based on the ranibizumab concentration, rather than the dose. Thus the analyses were performed according to this randomised treatment allocation. Doubling of the dose to 0.6 mg or 1.0 mg was guided by the observed treatment effect. The efficacy comparisons by actual doses administered in the RESOLVE study are confounded by the patient's initial response to Lucentis treatment. The patients with no dose doubling (patients remaining on 0.3 mg and 0.5 mg), represented the patients with an immediate response to treatment, while the patients with dose doubling (receiving the higher doses of 0.6 mg and 1.0 mg) mainly represented patients with a delayed and less pronounced therapeutic response. A dose response assessment derived from these data would be difficult to interpret and could be misleading. Attempts to assess a possible dose doubling effect were made regarding both efficacy and safety by assessing the time course of BCVA and OCT around the time point of first dose doubling and by looking at the incidence of AEs within 14 days after the injection by volume. These analyses did not reveal an indication for a relevant impact of dose doubling.

New indication: efficacy data are limited to 12 months

The sponsor's clinical development program in DME, including Phase IIIb studies, is ongoing and includes the following:

- RESTORE Extension study D2301E1 follows the patients from RESTORE for an additional 24 months for a total of 36 months on treatment with ranibizumab
- RETAIN study D2304 is a 24 month study evaluating efficacy and safety of ranibizumab treatment administered in alternative treatment regimens

It is doubtful that RESOLVE should appear in the product information document as it adds little relevant information and may be seen to support dose doubling. Moreover, it was a supportive study only. The Committee's views are sought.

The sponsor acknowledged the evaluator's reasons for considering RESOLVE a supportive study, rather than a pivotal study. Contrary to the views of the Delegate, the evaluator did not question the inclusion of RESOLVE in the product information, implying that its inclusion does have clinical utility. Indeed, the clinical evaluator states that "...this is a good quality study. Moreover, the evaluator recommended certain changes to the clinical aspects of the PI, which Novartis accepted and subsequently made in its response to the clinical evaluation report. Detailed descriptions concerning the content of the PI is beyond the scope of this AusPAR

Proposed actions

The sponsor concurred with the Delegate's recommendation to approve the extension of indication "...for the treatment of visual impairment due to diabetic macular oedema (DME)." Furthermore, the submitted application benefit risk evaluation data support the registration of 0.5 mg dose for the treatment of visual impairment due to diabetic macular oedema, with limited data available for the 0.3 mg dose. The 0.5 mg dose is given by administering 50 µL of the 2.3 mg/0.23 mL concentration, while to achieve a 0.5 mg dose

from a 1.8 mg/0.3 mL solution a higher injection volume than 50 µL would need to be administered. There is no supportive data available to support this higher injection volume. Therefore, considering this dose/volume relation, the 2.3 mg/0.23 mL solution is the only feasible concentration in the treatment of patients with visual impairment due to diabetic macular oedema (DME).

The sponsor advised that the approved dosage is outlined in the Dosage and Administration section of the PI. It indicated that this is the section that healthcare professionals would refer to for this information and therefore the inclusion of this information with the indication is not appropriate.

Advisory Committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate that the evidence of safety and efficacy provided in the submission supported a positive risk benefit profile for Lucentis. The committee was of the view that the submission was suitable to be considered for approval. In coming to this opinion the ACPM considered the following matters:

Efficacy

The single, Phase III, pivotal study (RESTORE) submitted demonstrated efficacy compared to sham or laser treatment alone over 12 months. This efficacy was supported by the Phase II study (RESOLVE). However, the committee noted that most of the gains attributable to ranibizumab occurred in the first few months and efficacy appeared to diminish over time.

Safety

The safety profile of the product is well known and while no overall trend was seen in respect of ranibizumab treatment versus control, it was noted that there was slight tendency to dose dependency of local ocular adverse events in the RESOLVE study. No new safety signals emerged from the studies or from the literature provided. However, the trials submitted were too small to reveal rare adverse events. The committee was concerned immune reactions would need monitoring and that any possible association with stroke may be missed by general physicians, unaware of this treatment.

The Committee also recommended amendments to the Product Information (PI) and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

The ACPM considered the sponsor should be encouraged to undertake longer term clinical trials to investigate response and safety and to undertake further clinical trials on dose ranging and the optimal dosing interval.

It was the view of the committee that the sponsor should also be encouraged to market the medication in sterile prefilled syringes that can provide increased patient safety and deliver an accurate dose.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lucentis containing ranibizumab (rbe) 1.8 mg/0.3 mL and 2.3 mg/0.23 mL solution for injection vial, indicated for:

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

Included among the specific conditions of registration was the implementation in Australia of the Lucentis (ranibizumab) Risk Management Plan (RMP), version 9, dated 8 June 2011, and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

LUCENTIS[®]

ranibizumab (rbe)

NAME OF THE MEDICINE

Active ingredient:	Ranibizumab
Chemical name:	Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ 1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ -chain
CAS number:	347396-82-1
Molecular weight:	Approximately 48kDa
Structure:	Ranibizumab is the Fab moiety of a high affinity version of recombinant humanised monoclonal antibody rhuMAb vascular endothelial growth factor (VEGF). It consists of a 214-residue light chain linked by a disulfide bond at its C-terminus to the 231-residue N-terminal segment of the heavy chain. The expected amino acid sequences of the heavy and light chains are shown in Figures 1a and 1b.

Figure 1a The amino acid sequence of the heavy chain of ranibizumab

10	20	30	40	50	60
EVQLVESGGGLVQPGGSLRLSCAASGYDF <u>THYGMNWVRQAPGKGLEWVGWINTYTGPE</u> TY					
70	80	90	100	110	120
<u>AA</u> DFKRRFTFSLDTSKSTAYLQMN <u>SLRAEDTAVYYCAKYP</u> YYYGTSHWYFDVWGQGLVT					
130	140	150	160	170	180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL					
190	200	210	220	230	
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDK <u>THL</u>					

Complementarity-determining regions (CDR) are underlined.

Figure 1b The amino acid sequence of the light chain of Ranibizumab

10 20 30 40 50 60
 DIQLTQSPSSLSASVGDRTITCSASQDISNYLNWYQQKPGKAPKVLIIYFTSSLHSGVPS
 70 80 90 100 110 120
 RFSGSGSGTDFTLTISSLPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
 130 140 150 160 170 180
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
 190 200 210
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Complementarity-determining regions (CDR) are underlined.

DESCRIPTION

Ranibizumab is a humanised monoclonal antibody fragment produced in *Eschericia coli* cells by recombinant DNA technology.

Each vial contains either 1.8 mg of ranibizumab in 0.3 mL solution for intravitreal injection or 2.3 mg of ranibizumab in 0.23 mL solution for intravitreal injection. The solution is sterile, clear, colourless to pale yellow, aqueous and preservative free.

Excipients: Trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections.

PHARMACOLOGY**Pharmacotherapeutic group, ATC**

Antineovascularisation agents, ATC code: S01LA04.

Mechanism of action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF₁₁₀, VEGF₁₂₁ and VEGF₁₆₅), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Pharmacodynamics

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration and the diabetic macular oedema causing visual impairment.

Pharmacokinetics

Absorption:

Following monthly intravitreal administration of Lucentis to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11 to 27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Upon monthly intravitreal administration of Lucentis 0.5 mg/eye, serum ranibizumab C_{max} , attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/mL, and C_{min} is predicted to generally range between 0.07 and 0.49 ng/L.

Distribution and Elimination:

Based on analysis of population pharmacokinetics and disappearance of ranibizumab from serum for patients treated with the 0.5 mg dose, the average vitreous elimination half-life of ranibizumab is approximately 9 days. Serum ranibizumab exposure is predicted to be approximately 90,000-fold lower than vitreal ranibizumab exposure.

Renal impairment: No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with renal impairment. Sixty-eight percent (136 of 200) of patients in a population pharmacokinetic analysis had renal impairment (46.5% mild [50 to 80 mL/min], 20% moderate [30 to 50 mL/min] and 1.5% severe [< 30 mL/min]). Systemic clearance was slightly lower, but this was not clinically significant.

Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with hepatic impairment.

CLINICAL TRIALS

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of Lucentis have been assessed in three randomised, double-masked, sham* - or active-controlled studies in patients with neovascular age-related macular degeneration (AMD). A total of 1,323 patients (879 active and 444 control) was enrolled in these studies.

* *The sham Lucentis injection control procedure involved anaesthetising the eye in a manner identical to a Lucentis intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.*

In study FVF2598g (MARINA), patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) received monthly intravitreal injections of Lucentis 0.3 mg or 0.5 mg or sham injections. A total of 716 patients was enrolled in this study (sham, 238; Lucentis 0.3 mg, 238; Lucentis 0.5 mg, 240). A total of 664 subjects (92.7%) completed month 12 (defined as having a visual acuity score for the study eye at month 12) and a total of 615 subjects (85.9%) completed the 2-year study period. Data are available up to the end of month 24.

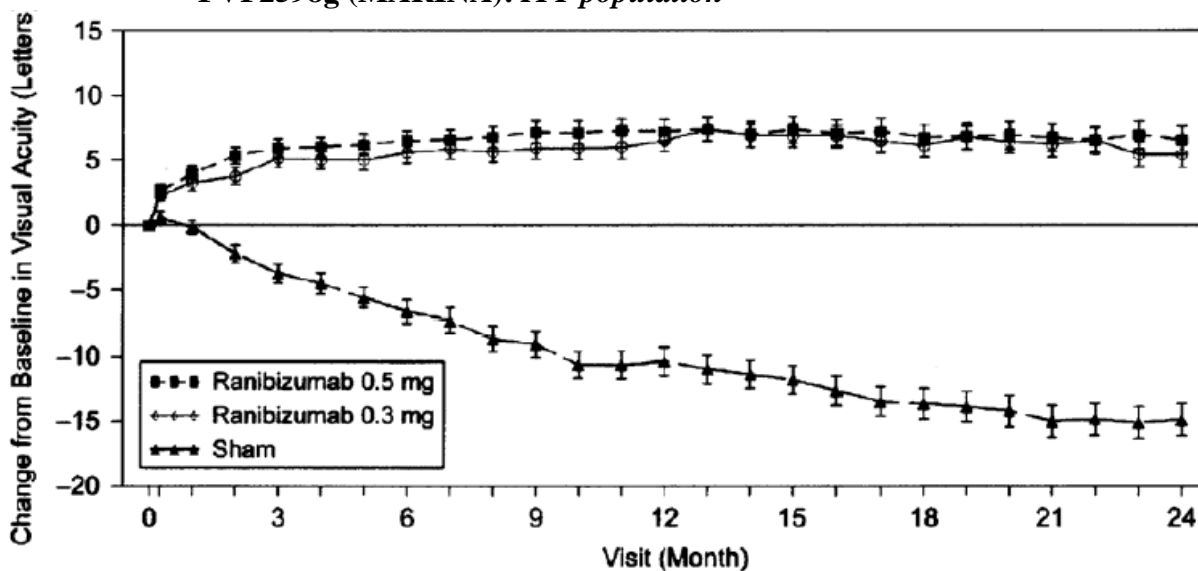
In study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Sham or active verteporfin PDT was given with the initial Lucentis injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients was enrolled in this study (sham, 143; Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140). A total of 386 subjects (91.3%) completed month 12 of the study and 343 subjects (81.1%) completed month 24 of the study. Data are available up to the end of month 24.

In both studies the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared to baseline. Almost all Lucentis-treated patients (approximately 95%) maintained their visual acuity. 34 to 40% of Lucentis-treated patients experienced a clinically significant improvement in vision, defined as gaining 15 or more letters at 12 months. The size of the lesion did not significantly affect the results.

In MARINA, the primary endpoint was fewer than 15 letters loss at 12 months. 148 of 238 randomised to sham injections met this criterion, as did 225 of 238 injected with 0.3 mg, and 227 of 240 injected with 0.5 mg. The difference between sham and injected groups is statistically ($p < 0.0001$) and clinically significant but the difference between the two ranibizumab dose groups is not, as shown in Figure 1.

The visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 24, compared to a gradual deterioration in the sham treatment group, as shown in Figure 1.

Figure 1 Mean change in visual acuity from baseline to month 24 in study FVF2598g (MARINA): ITT population



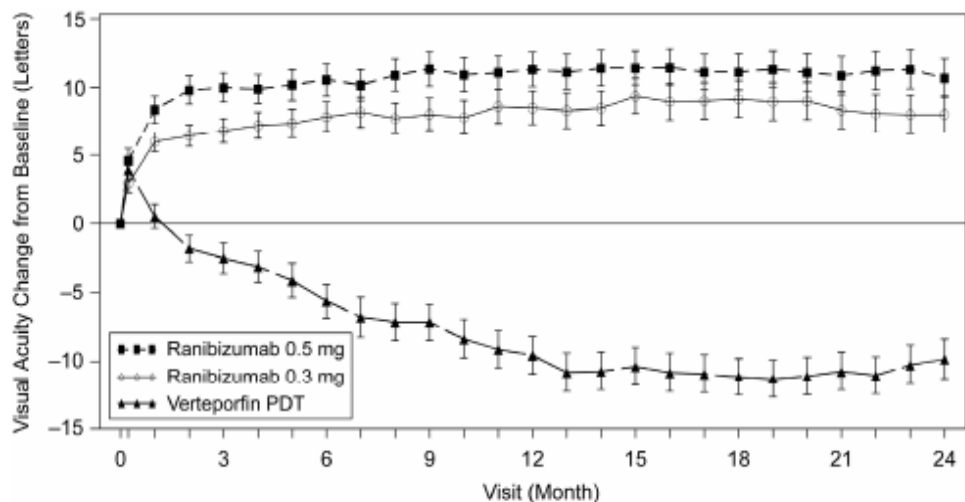
Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.

In ANCHOR, the primary endpoint was fewer than 15 letters loss at 12 months. 92 of 143 randomised to sham injections and verteporfin met this criterion, as did 132 of 140 injected with 0.3 mg ranibizumab, and 134 of 140 injected with 0.5 mg.

The difference between sham and injected groups is statistically ($p < 0.0001$) and clinically significant but the difference between the two doses of ranibizumab is not. The secondary endpoint of a (clinically significant) gain of at least 15 letters was met in 8 of the 143 verteporfin group and in 50 of the 140 0.3 mg group: $z = 37.6$, $p < 0.0001$. 56 of the 140 0.5 mg group met this criterion also, statistically not significantly better than the 0.3 mg group: $z = 0.38$, $p > 0.8$.

The visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 12 compared to a gradual deterioration in the verteporfin treatment group, as shown in Figure 2.

Figure 2 Mean change in visual acuity from baseline to month 24 in study FVF2587g (ANCHOR): ITT population



PDT=photodynamic therapy.

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

Detailed results are shown in the tables below:

Table 1 Outcomes at month 12 and month 24 in study FVF2598g (MARINA)

Outcome measure	Month	Sham (n=238)	Lucentis 0.3 mg (n=238)	Lucentis 0.5 mg (n=240)
Loss of <15 letters in visual acuity n (%) ^a (Maintenance of vision)	Month 12	148 (62.2%)	225 (94.5%)	227 (94.6%)
	Month 24	126 (52.9%)	219 (92.0%)	216 (90.0%)
Gain of ≥ 15 letters in visual acuity n (%) ^a	Month 12	11 (4.6%)	59 (24.8%)	81 (33.8%)
	Month 24	9 (3.8%)	62 (26.1%)	80 (33.3%)
Mean change in visual acuity (letters) (SD) ^a	Month 12	-10.5 (16.6)	+6.5 (12.7)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+5.4 (15.2)	+6.6 (16.5)

^a p<0.01.

Table 2 Outcomes at month 12 and 24 in study FVF2587g (ANCHOR)

Outcome measure	Month	Verteporfin PDT (n=143)	Lucentis 0.3 mg (n=140)	Lucentis 0.5 mg (n=140)
Loss of <15 letters in visual acuity n (%) ^a (Maintenance of vision)	Month 12	92 (64%)	132 (94%)	134 (96%)
	Month 24	94(66%)	126 (90%)	125 (90%)
Gain of ≥15 letters in visual acuity n (%) ^a	Month 12	8 (6%)	50 (36%)	56 (40%)
	Month 24	9(6%)	48 (34%)	57 (41%)
Mean change in visual acuity (letters) (SD) ^a	Month 12	-9.5 (16.4)	+8.5 (14.6)	+11.3 (14.6)
	Month 24	-9.8 (17.6)	+8.1 (16.2)	+10.7 (16.5)

^a p<0.01

Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At month 12, the mean change in the total area of the CNV lesion was 0.1 to 0.3 DA for Lucentis versus 2.3 to 2.6 DA for the control arms.

The use of Lucentis beyond 24 months has not been studied.

In MARINA, at month 12, patients treated with Lucentis reported, on average, a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency, as measured by the NEI VFQ-25, while sham-treated patients reported a decrease in their ability to perform these activities. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +10.4 point increase (0.3 mg: +9.4), while sham-treated patients had a -2.6 point decrease (p< 0.01). On the distance activities scale, Lucentis 0.5 mg-treated patients had a +7.0 point increase (0.3 mg: +6.7), while sham-treated patients had a -5.9 point decrease (p< 0.01). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients experienced +6.8 point increase (0.3 mg: +3.6), while sham-treated patients reported a decrease of -4.7 points (p< 0.01).

This increase from baseline in each of these three VFQ-25 subscales at month 12 was maintained at month 24 for Lucentis-treated patients, while in the sham-injection group the mean change from baseline decreased further from month 12 to month 24 in each of these subscales. Therefore, the treatment benefit of Lucentis over the sham control at month 24 was greater than that at month 12.

In ANCHOR, at month 12, patients treated with Lucentis reported a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency compared to patients receiving verteporfin PDT treatment. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +9.1 point increase (0.3 mg: +6.6), while verteporfin PDT-treated patients had a +3.7 point increase (p< 0.01). On the distance activities scale, Lucentis 0.5 mg-treated patients reported a +9.3

point increase (0.3 mg: +6.4), while verteporfin PDT-treated patients had a +1.7 point increase ($p < 0.01$). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients reported a +8.9 point increase (0.3 mg: +7.6), while verteporfin PDT-treated patients had a -1.4 point decrease ($p < 0.01$). In the verteporfin PDT group, the mean improvement from baseline in the near activities and distance activities subscale scores at month 12 were lost at month 24, while the mean decrease from baseline in the vision-specific dependency subscale score at month 12 was maintained at month 24. These changes between months 12 and 24 within each treatment group resulted in either maintained or greater treatment benefit of ranibizumab over verteporfin PDT compared with month 12, while the treatment benefit of ranibizumab in the vision-specific dependency subscale was smaller at month 24 compared with month 12 (p-values ranging from 0.0023 to 0.0006).

Study FVF3689g (SAILOR) was a Phase IIIb, single-masked, one-year multicentre study in naïve and previously treated subjects with CNV secondary to AMD. The primary study objective was to estimate the incidence of ocular and non-ocular serious adverse events in subjects treated for 12 months. Two thousand three hundred seventy eight patients were randomised in a 1:1 ratio to receive one intravitreal injection of 0.3 mg or 0.5 mg ranibizumab every month for three consecutive months followed by as-needed re-treatment not more often than monthly.

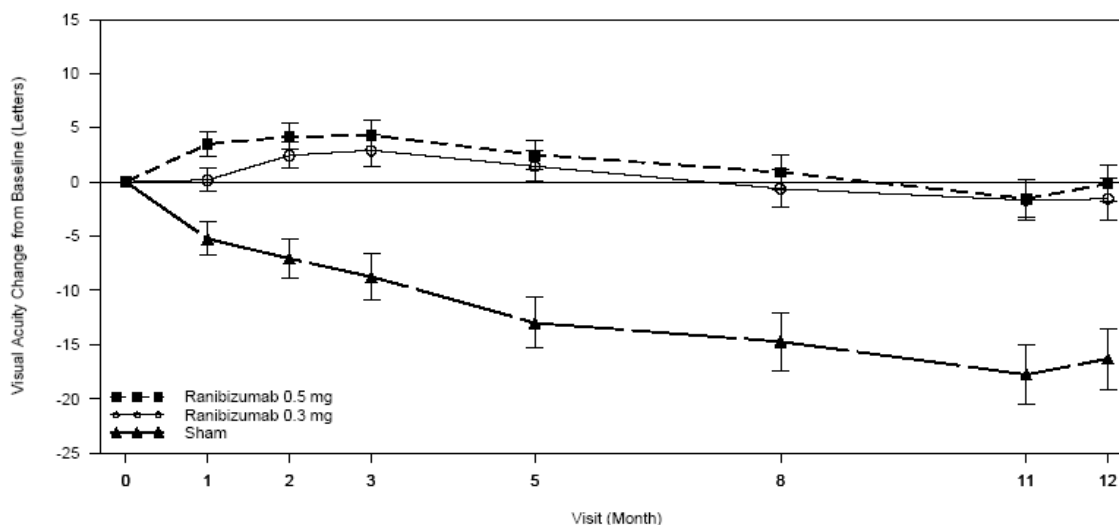
Overall, no imbalances between the two dose groups were observed in the frequency of ocular and non-ocular adverse events. There was a statistically non significant trend towards a higher stroke rate in the 0.5 mg group compared to the 0.3 mg group. The respective 95% CIs for the overall stroke rate were wide (0.3% to 1.3% for the 0.3 mg group vs. 0.7% to 2.0% for the 0.5 mg group). The number of strokes was small in both dose groups, and there is not sufficient evidence to conclude (or rule out) that there is a true difference in stroke rates among the treatment groups. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke and transient ischaemic attack.

Quarterly Dosing after Three Consecutive Monthly Doses: Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of Lucentis in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of month 12. Patients received Lucentis 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months. A total of 184 patients was enrolled in this study (Lucentis 0.3 mg, 60; Lucentis 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with Lucentis in PIER received a mean of 6 total treatments out of possible 6 from day 0 to month 12.

In PIER, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 3). After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with Lucentis **lost the**

initial visual acuity gain, returning to **baseline** at month 12. In PIER, almost all Lucentis-treated patients (90%) maintained their visual acuity at month 12.

Figure 3 Mean change in visual acuity from baseline to month 12 in Study FVF3192g (PIER): ITT population



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

Interpretation of PIER: Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Treatment of Visual Impairment Due to DME

The efficacy and safety of Lucentis have been assessed in two randomized, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular edema. A total of 496 patients (336 active and 160 control) was enrolled in these studies, the majority had type II diabetes, 28 ranibizumab-treated patients had type I diabetes.

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular edema was randomised to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham injection and laser photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments. The treatment was reinitiated when there was a reduction in best corrected visual acuity (BCVA) due to

DME progression. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before injection of ranibizumab, and then as needed based on ETDRS criteria.

Key outcomes are summarised in Tables 3 and 4 and Figures 4 and 5.

Table 3 Primary Efficacy Outcomes at month 12 in study D2301 (RESTORE):
Visual acuity of the study eye (letters): Mean average change from Month 1 to Month 12 compared to baseline (Full analysis set / LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	115	118	110
	Mean (SD)	64.7 (10.07)	63.4 (9.99)	62.6 (11.01)
	Median	68.0	65.0	65.0
	Min - Max	38.0 - 81.0	38.0 - 79.0	36.0 - 78.0
Average Month 1 to Month 12	n	115	118	110
	Mean (SD)	70.8 (10.53)	69.2 (11.44)	63.4 (12.26)
	Median	73.7	71.5	66.2
	Min - Max	38.6 - 88.7	28.5 - 93.3	32.0 - 84.2
Average change from baseline	n	115	118	110
	Mean (SD)	6.1 (6.43)	5.9 (7.92)	0.8 (8.56)
	Median	6.1	6.0	1.3
	Min - Max	-10.9 - 25.2	-26.7 - 27.6	-37.8 - 26.8
	95% CI for mean (1)	(4.9, 7.3)	(4.4, 7.3)	(-0.8, 2.4)
Comparison vs. Laser	Difference in LS means (2)	5.4	4.9	
	95% CI for difference (2)	(3.5, 7.4)	(2.8, 7.0)	
	p-value (3)	<.0001	<.0001	

- n is the number of patients with a value for both baseline and average Month 1 to Month 12.

- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (≤ 60 , 61-73, >73 letters).

- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.

- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.

- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score

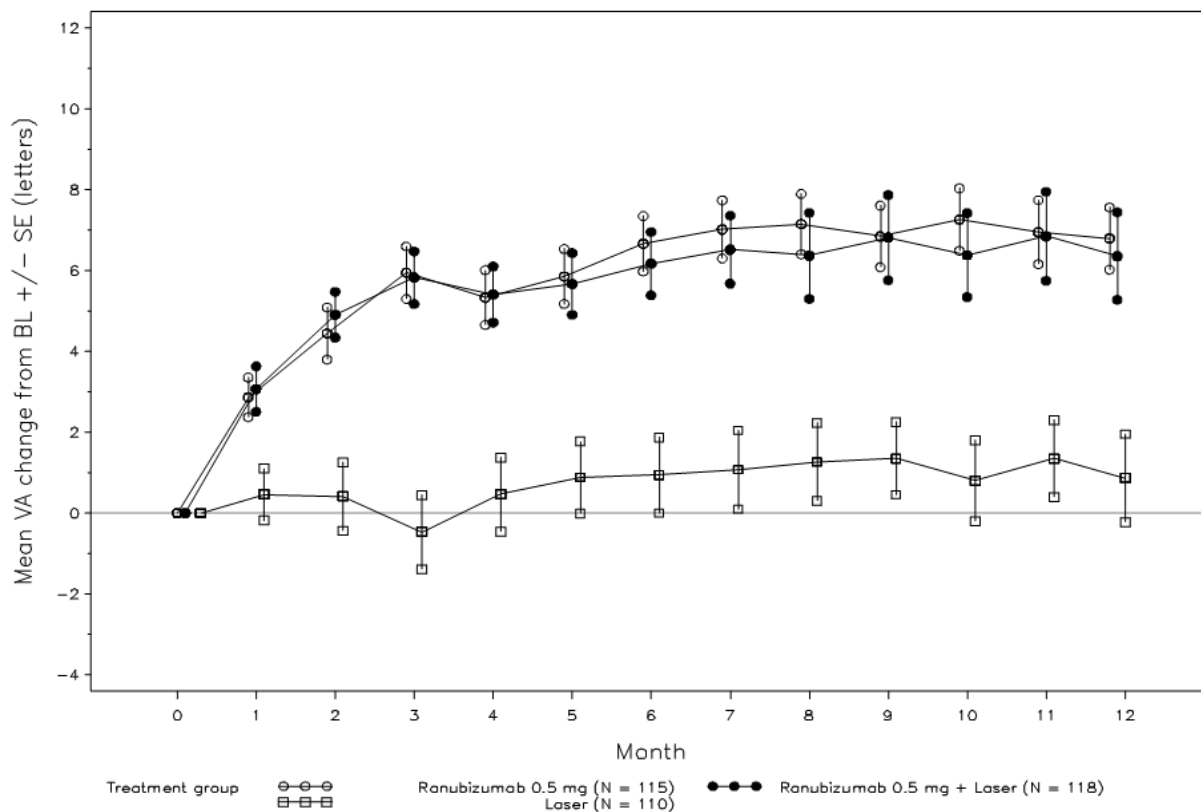
Table 4 Secondary Efficacy Outcomes at month 12 in study D2301 (RESTORE):
Visual acuity of the study eye (letters): Categorized change from baseline at Month 12 (FAS / LOCF)

Categorized change from baseline	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
N	115	118	110
Gain of ≥ 10 letters [1]	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥ 10 letters	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥ 15 letters [1]	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥ 15 letters	1 (0.9)	4 (3.4)	9 (8.2)

- N is the number of patients with a value at both baseline and the Month 12 visit.

- [1] specified gain, or BCVA of 84 letters or more

Figure 4 Mean BCVA change from baseline over time in study D2301 (RESTORE)



In a supportive, partly exploratory study D2201 (RESOLVE), a total of 151 patients with DME with centre involvement in at least one eye, including those with focal or diffuse DME, causing visual impairment were treated with ranibizumab (6 mg/mL, n=51, 10 mg/mL, n=51) or sham (n=49) by monthly intravitreal injections until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection if at the Month 1 visit, retinal thickness in the study eye remained $> 300 \mu\text{m}$; or if at any monthly visit after Month 1, retinal thickness in the study eye was $> 225 \mu\text{m}$ and reduction in retinal oedema from the previous assessment was $< 50 \mu\text{m}$. Laser photocoagulation rescue treatment was allowed from month 3 in both treatment arms .

The average injection doses in the 6 mg/mL group, 10 mg/mL group, and pooled group, were 0.47 mg, 0.76 mg and 0.62 mg, respectively. A total of 86% of patients in the ranibizumab treated groups received doses of 0.5 mg/injection or higher, of which 69% received doses of 0.6 mg/injection or higher.

The study was comprised of two parts: an exploratory part (the first 42 patients analysed at month 6 , and a confirmatory part (the remaining 109 patients analysed at month 12) .

The exploratory analysis revealed no sign of a clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of this study therefore do not support the concept of dose doubling where response to the recommended dose is considered inadequate. Key outcomes from the confirmatory part of the study (2/3 patients) are summarised in Tables 5 and 6 and Figure 5 and 6.

Table 5 Overall Population, VA (study eye), mean average change in letters from baseline from month 1 to month 12; FAS, LOCF of study D2201 (RESOLVE):

Visual acuity of the study eye (letters): Mean average change from baseline from Month 1 to Month 12 (Group A+B; FAS / LOCF)

Parameter	Statistic	Ranibizumab	Ranibizumab	Ranibizumab	Sham
		6 mg/ml N=51	10 mg/ml N=51	Pooled N=102	
Baseline	n	51	51	102	49
	Mean (SD)	59.2 (10.23)	61.2 (9.48)	60.2 (9.86)	61.1 (9.04)
	Median	61.0	61.0	61.0	63.0
	Min-Max	37.0-73.0	39.0-79.0	37.0-79.0	39.0-76.0
Average Month 1 to Month 12	Mean (SD)	68.4 (11.09)	67.5 (12.37)	68.0 (11.70)	61.0 (13.91)
	Median	69.4	70.4	70.3	63.0
	Min-Max	38.9-87.9	34.8-88.3	34.8-88.3	19.9-83.1
Average change from baseline	Mean (SD)	9.2 (5.60)	6.4 (9.21)	7.8 (7.72)	-0.1 (9.77)
	Median	9.5	7.4	8.2	2.8
	Min-Max	-2.9-24.3	-24.9-21.4	-24.9-24.3	-36.1-14.8
	95% CI for mean (1)	(7.7, 10.8)	(3.8, 9.0)	(6.3, 9.3)	(-2.9, 2.7)
	Comparison vs. sham	Difference in LS means (2)	9.4	6.7	7.9
	95% CI for difference (2)	(6.2, 12.6)	(3.0, 10.5)	(5.0, 10.9)	
	p-value (3)	<0.0001	0.0004	<0.0001	

- n is the number of patients with a value for both baseline and average Month 1 to Month 12

- Stratified analysis includes baseline visual acuity (≤ 60 , >60 letters) and baseline central retinal thickness (≤ 400 , >400 μm).

- (1) Two-sided 95% confidence intervals (CI) are based on t-distribution.

- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.

- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Table 6 Overall Population, treatment comparisons key secondary efficacy variables; FAS (LOCF) of study D2201 (RESOLVE)

Variable	Ran 6mg/mL (n=51)	Ran 10mg/mL (n=51)	Ran Pooled (n=102)	Sham (n=49)
Gain \geq 15 letters [Δ BL to month 12] ¹	35.3% (n=18)	29.4% (n=15)	32.4% (n=33)	10.2% (n=5)
Loss \geq 15 letters [Δ BL to month 12] ¹	0%	5.9% (n=3)	2.9% (n=2)	20.4% (n=10)
Gain \geq 10 letters [Δ BL to month 12] ²	72.5% (n=37)	49.0% (n=25)	60.8% (n=62)	18.4% (n=9)
Loss \geq 10 letters [Δ BL to month 12] ²	0%	9.8% (n=5)	4.9% (n=5)	24.5% (n=12)
CRT μ m mean (SE) [Δ BL to month 12] ³	-200.7 (17.11)	-187.6 (20.70)	-194.2 (13.38)	-48.4 (21.92)
CRT < 225 μ m (%) at month 12 ⁴	31.4% (n=16)	39.2% (n=20)	35.3% (n=36)	10.2% (n=5)

Δ BL = change from baseline

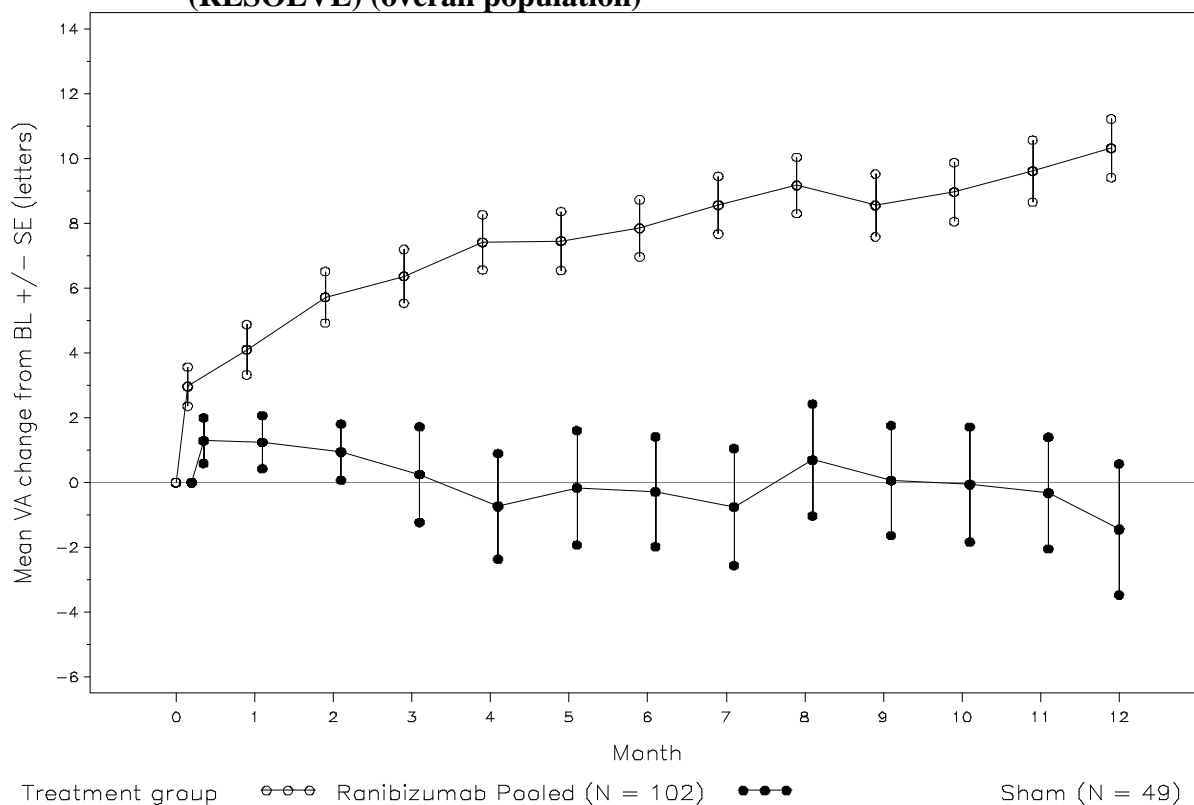
¹CMH test, stratified: 6 mg/mL vs sham p=0.0001; 10 mg/mL vs sham p=0.0037; and pooled p=0.0001

²CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p=0.0010; and pooled p<0.0001

³CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p<0.0001; and pooled p<0.0001

⁴CMH test, stratified: 6 mg/mL vs sham p=0.0108; 10 mg/mL vs sham p=0.0007; and pooled p=0.0011

Figure 5 Mean change in visual acuity from baseline over time in study D2201 (RESOLVE) (overall population)



Patients treated with ranibizumab experienced a continuous reduction in central retina thickness. At month 12, the mean CRT change from baseline was -194 micrometres for ranibizumab versus -48 micrometres for sham control.

Overall, ocular and non-ocular safety findings in DME patients of both studies D2201 and D2301 were comparable with the previously known safety profile observed in wet AMD patients.

INDICATIONS

Lucentis (ranibizumab) is indicated for:

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

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

PRECAUTIONS

Intravitreal injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, iatrogenic traumatic cataract and increased intraocular pressure (see **ADVERSE EFFECTS**). Symptoms of these adverse effects should be explained and the patient should be given a copy of the consumer medicine information document. The patient should be given contact details in the case of adverse effects.

Proper aseptic injection techniques must always be used when administering Lucentis. In addition, patients should be reviewed during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis (see **ADVERSE EFFECTS**). Sustained IOP increases have also been reported but the frequency is unclear. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. Patients should be reviewed for IOP rise pre-injection and 60 minutes post-injection.

The safety and efficacy of Lucentis therapy administered to both eyes concurrently have not been studied (see **DOSAGE AND ADMINISTRATION**).

There is a potential risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF. In the wet AMD Phase III studies, the overall frequency of arterial thromboembolic events was similar between ranibizumab and control. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab

0.3 mg or control, however, the differences were not statistically significant. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack. Therefore, these patients should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and the benefit outweighs the potential risk.

As with all therapeutic proteins, there is a potential for immunogenicity with Lucentis.

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.

Effects on Fertility

No study has been conducted to investigate the effects of ranibizumab on male or female fertility. In animal studies with bevacizumab, a closely related recombinant anti-VEGF monoclonal antibody, a reversible inhibition of ovarian function was observed in rabbits and cynomolgus monkeys following intravenous treatment. This finding is thought to be associated with inhibitory effects of bevacizumab on angiogenesis. The clinical relevance of this finding to Lucentis is unclear.

Use in Pregnancy (Category D)

For ranibizumab, no clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

In pregnant monkeys, intravitreal ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta at doses up to 1 mg/eye/fortnight, yielding systemic exposure levels estimated to be up to 58-times those expected clinically. However, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryofetotoxic. 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.

The absence of ranibizumab-mediated effects on the embryofetal development is plausibly related to the expected inability of the Fab fragment to cross the placenta. Nevertheless, ranibizumab was detected in a fetus coincident with high maternal ranibizumab and anti-ranibizumab antibody serum levels, possibly because the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer.

As the embryofetal development investigations were performed in healthy pregnant animals and disease (e.g. diabetes) may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of child bearing potential in general, and during pregnancy in particular.

Women of Childbearing Potential

Women of childbearing potential should use effective contraception during treatment (see **PRECAUTIONS Use in Pregnancy**).

Use in Lactation

It is not known whether ranibizumab is excreted in human milk. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis.

Children and Adolescents (below 18 years of age)

Safety and efficacy of Lucentis have not been tested in children and adolescents below 18 years of age. Lucentis is therefore not recommended for use in these sub-populations.

Elderly (65 years and above)

No dose adjustment is required in the elderly.

Hepatic Impairment

Lucentis has not been studied in patients with hepatic impairment. However, as systemic exposure is negligible, no special measures are considered necessary in this population.

Renal Impairment:

Dose adjustment is not needed in patients with renal impairment (see **PHARMACOLOGY Pharmacokinetics**).

Carcinogenicity

No carcinogenicity studies were performed with ranibizumab.

Genotoxicity

No genotoxicity studies were performed with ranibizumab.

Interactions with Other Drugs

No formal interaction studies have been performed (see **CLINICAL TRIALS**).

For the adjunctive use of verteporfin and Lucentis in wet AMD, see **CLINICAL TRIALS**.

For the adjunctive use of laser photocoagulation and Lucentis in DME, see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**.

Effects on Ability to Drive and Use Machines

The Lucentis treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see **ADVERSE EFFECTS**). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

ADVERSE EFFECTS

Wet AMD Population

A total of 1,315 patients constituted the safety population in the three phase III studies in wet AMD with 24 months exposure to Lucentis and 440 patients were treated with the 0.5mg dose.

Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see **PRECAUTIONS**). The cumulative 2-year incidence of endophthalmitis (serious and non-serious) in the pooled pivotal trials (i.e. studies FVF2598g(MARINA), FVF2587g (ANCHOR), and FVF3192g (PIER)) was about 1%.

Other serious ocular events observed among Lucentis-treated patients included intraocular inflammation and increased intraocular pressure (see **PRECAUTIONS**).

The adverse events listed below occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with Lucentis 0.5 mg than in those receiving control treatment (sham injection (see definition under **CLINICAL TRIALS**) or verteporfin photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD phase III studies FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER). They were therefore considered potential adverse drug reactions. The safety data described below also include all adverse events suspected to be at least potentially related to the injection procedure or medicinal product in the 440 patients of the combined 0.5 mg treatment groups in wet AMD. The adverse event rates for the 0.3 mg dose were comparable to those for 0.5 mg.

DME Population

The safety of Lucentis was studied in a one-year sham-controlled trial (RESOLVE) and in a one year laser-controlled trial (RESTORE) conducted respectively in 102 and 235 ranibizumab-treated patients with visual impairment due to DME (see **CLINICAL TRIALS**).

The event of urinary tract infection, in the common frequency category, met the criteria for the table above; otherwise ocular and non-ocular events in the RESOLVE and RESTORE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

Tabulated summary of adverse effects from clinical trials

The adverse effects from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse effects are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order

of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS): very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

Table 7 Adverse Effects from Clinical Trials

Infections and Infestations	
<i>Very common</i>	Nasopharyngitis
<i>Common</i>	Influenza, urinary tract infection*
Blood and lymphatic system disorders	
<i>Common</i>	Anaemia
Psychiatric disorders	
<i>Common</i>	Anxiety
Nervous system disorders	
<i>Very common</i>	Headache
<i>Common</i>	Stroke
Eye disorders	
<i>Very common</i>	Intraocular inflammation, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritis.
<i>Common</i>	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia.
<i>Uncommon</i>	Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation.
Respiratory, thoracic and mediastinal disorders	
<i>Common</i>	Cough
Gastrointestinal disorders	
<i>Common</i>	Nausea
Skin and subcutaneous tissue disorders	
<i>Common</i>	Allergic reactions (rash, urticaria, pruritis, erythema)
Musculoskeletal and connective tissue disorders	
<i>Very common</i>	Arthralgia
Investigations	
<i>Very common</i>	Intraocular pressure increase

*Observed only in the DME population

DOSAGE AND ADMINISTRATION

Single-use vial for intravitreal use only. Use of more than one injection from a vial can lead to contamination and subsequent infection.

Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections.

The recommended maximal dose (0.5 mg) should not be exceeded. One eye only should be injected on each occasion and post-injection monitoring is recommended (see **PRECAUTIONS**).

Treatment of Wet AMD

The recommended dose of Lucentis is 0.5 mg (0.05 mL) or 0.3 mg (0.03 mL) given as a single intravitreal injection.

Lucentis is given monthly. The interval between two doses should not be shorter than 1 month. Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Treatment of Visual Impairment due to DME

The recommended dose of Lucentis is 0.5 mg (0.05 mL) given as a single intravitreal injection.

Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments. The interval between two doses should not be shorter than one month.

Lucentis and Laser Photocoagulation in DME

Lucentis has been used concomitantly with laser photocoagulation in clinical trials (see **CLINICAL TRIALS**). 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.

Mode of Administration

As with all medicinal products for parenteral use, Lucentis should be inspected visually for particulate matter and discolouration prior to administration.

The injection procedure should be carried out under aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent), and the availability of sterile paracentesis (if required). The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure (see **CONTRAINDICATIONS**). The periocular skin, eyelid and ocular surface should be disinfected. Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

The patient should be instructed to self-administer antimicrobial drops four times daily for 3 days before and after each injection.

For information on preparation of Lucentis, see **Instructions for Use and Handling**.

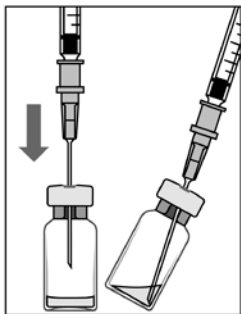
The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The injection volume of 0.05 mL or 0.03 mL is then delivered; the scleral site should be rotated for subsequent injections.

Instructions for Use and Handling

Vials are for single use only.

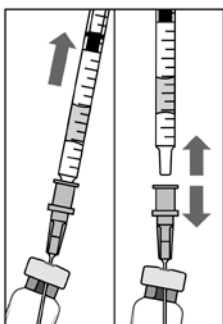
To prepare Lucentis for intravitreal injection, please adhere to the following instructions:

A.



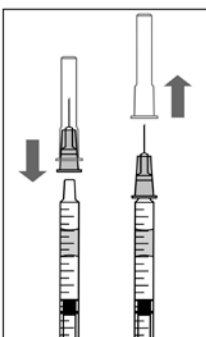
1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.
2. Assemble the 5 µm filter needle (provided) onto the 1 mL syringe (provided) using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.
3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.

B.



4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.

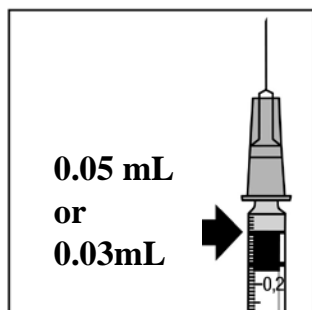
C.



6. Aseptically and firmly assemble the injection needle (provided) onto the syringe.
7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.

Note: Grip at the yellow hub of the injection needle while removing the cap.

D.



8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL or 0.03mL mark on the syringe. The syringe is ready for injection.

Note: Do not wipe the injection needle. Do not pull back on the plunger.

Any unused product or waste material should be disposed of in accordance with local requirements.

Lucentis contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Incompatibilities: In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Storage: Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.

Keep the vial in the outer carton in order to protect from light.

OVERDOSAGE

Cases of accidental overdose have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions most frequently associated with these reported cases were intraocular pressure increased and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION

Lucentis is supplied as 0.23 mL or 0.3 mL solution for injection in glass vials (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial, one filter needle for withdrawal of the vial contents, one needle for intravitreal injection and one syringe for withdrawal of the vial contents and for intravitreal injection. Each 0.23 mL vial contains 2.3 mg and each 0.3mL vial contains 1.8 mg of ranibizumab.

Poisons Schedule: Schedule 4.

SPONSOR

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