▼ Use of this medicinal product in paediatric ROP patients is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – LUCENTIS®

(RANIBIZUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ranibizumab (rbe)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lucentis is supplied in a vial or a pre-filled syringe.

Vial

Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution for intravitreal injection.

Pre-filled syringe

Each pre-filled syringe contains 1.65 mg of ranibizumab in 0.165mL solution.

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

May contain potential allergens: traces of milk and residue of tetracycline (antibiotic) from the manufacturing process.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

Vial**:** The solution is sterile, clear, colourless to pale brownish-yellow, aqueous and preservative free.

Pre-filled syringe**:** The solution is sterile, clear, colourless to pale brownish-yellow, aqueous and preservative free.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Lucentis (ranibizumab) 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),
- treatment of proliferative diabetic retinopathy (PDR),
- the treatment of visual impairment due to choroidal neovascularisation (CNV),
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM),
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

Lucentis is indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

Single-use vial for adults and preterm infants or single-use pre-filled syringe (adults only) for intravitreal use only. Use of more than one injection from a vial can lead to product contamination and subsequent ocular infection.

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

Adults

The recommended dose for Lucentis in adults is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should be at least four weeks.

The recommended maximal dose (0.5 mg) should not be exceeded. Post-injection monitoring is recommended (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Preterm infants

For preterm infants, both 0.2 mg and 0.1 mg doses of Lucentis have demonstrated efficacy (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). The recommended dose for Lucentis in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 mL. Alternatively, a dose of 0.1 mg corresponding to 0.01 mL can be given.

Treatment should be initiated and monitored by paediatric ophthalmologists experienced in the treatment of ROP. Treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the clinical study received one injection per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.

General target population

Treatment of wet AMD, DME, PDR, macular oedema secondary to RVO, CNV or CNV secondary to PM.

Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR, and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

Treatment has been described with either fixed (e.g. monthly) or variable dosing regimens. Variable dosage regimens include 'pro re nata' (PRN) where patients are seen at regular intervals and the lesion is treated when it is active, and 'treat-and-extend' where the interval may be extended as described below.

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

There was no sign of clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of clinical studies do not support the concept of dose doubling where response to the recommended dose is considered inadequate (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. In the treatment of visual impairment due to CNV secondary to Pathologic Myopia (PM), many patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

Lucentis and laser photocoagulation in DME and Branch RVO (BRVO)

Lucentis has been used concomitantly with laser photocoagulation in clinical studies (see Section 5.1 PHARMACODYNAMIC PROPERTIES, 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.

Lucentis and Visudyne photodynamic therapy in CNV secondary to PM

There is no experience in using Lucentis in combination with Visudyne.

Method 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). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure (see Section 4.3 CONTRAINDICATIONS). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

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

In adults, 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 is then delivered; the scleral site should be rotated for subsequent injections.

In preterm infants, the injection needle should be inserted 1.0 to 2.0 mm posterior to the limbus with the needle pointing towards the optic nerve. The injection volume is then delivered (0.02 mL for the 0.2 mg dose, or 0.01 mL for the 0.1 mg dose).

Instructions for Use and Handling

Vial (adults and pre-term infants)

Vials are for single use only (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The vial is sterile. After injection any unused product must be discarded.

Do not use the vial if the packaging is damaged. The sterility of the vial cannot be guaranteed unless the packaging seal remains intact. Do not use the vial if the solution is discoloured, cloudy, or contains particulates.

For preparation and intravitreal injection, the following single-use medical devices are needed:

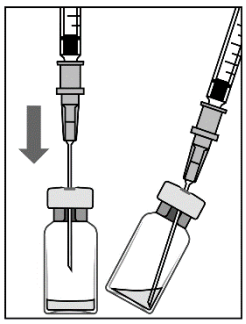
- a 5 micrometre filter needle (18G)
- a 1 mL sterile syringe
- an injection needle (30G x 1/2 inch)

These medical devices are not supplied in the Lucentis pack that contains only the vial.

The 1 mL sterile syringe and the injection needle are not supplied in the Lucentis pack that contains the vial and the filter needle.

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

A.

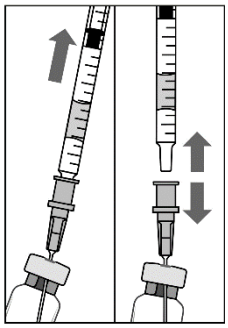


1. Before withdrawal, remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

2. Attach a 5 µm filter needle (18G) to a 1 mL syringe using an 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.

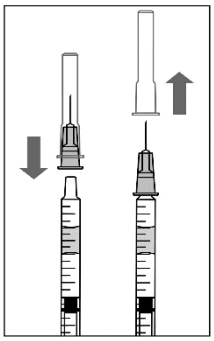
B.



4. Ensure that the plunger rod is drawn back sufficiently 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.

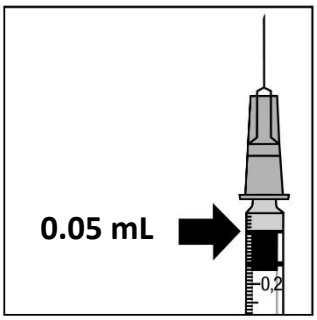


6. Aseptically and firmly attach an injection needle (30G x ½ inch) onto the syringe.

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 appropriate mark on the syringe. The syringe is ready for injection. The dose for adults is 0.05 mL (corresponding to 0.5 mg).
   The dose for preterm infants is 0.02 ml (corresponding to 0.2 mg), or 0.01 mL (corresponding to 0.1 mg).

Note**:** Do not wipe the injection needle. Do not pull back on the plunger.

After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

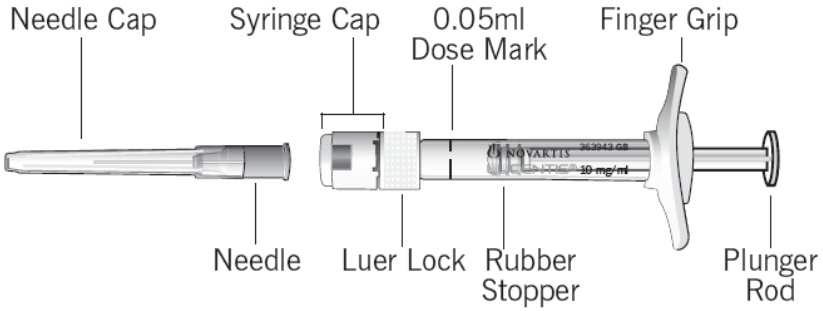
Pre-filled syringe (adults only)

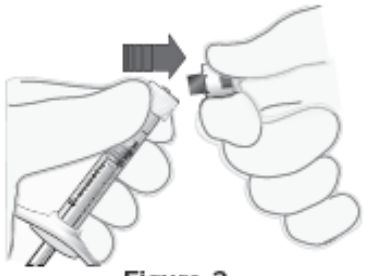
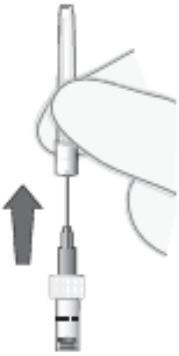
The pre-filled syringe is for single use only (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

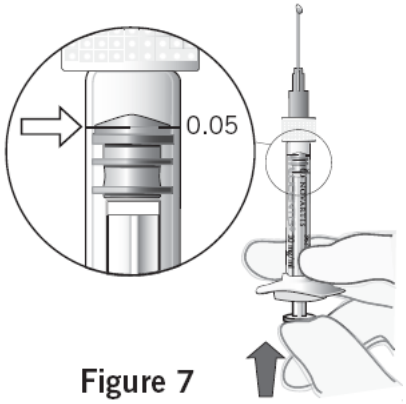
The pre-filled syringe is sterile. Do not use the pre-filled syringe if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discoloured, cloudy, or contains particulates.

For the intravitreal injection, a 30G x 1/2 inch injection needle should be used.

To prepare Lucentis for intravitreal administration, please adhere to the instructions for use:

Heading	Instructions	Diagram/Image
	Read all the instructions carefully before using the pre-filled syringe. The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions. **Note: The dose must be set to 0.05 mL**	
Pre-filled syringe description	 **Figure 1**	
Prepare	1. Make sure that your pack contains: • a sterile pre-filled syringe in a sealed tray. 2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe.	
Check syringe	3. Check that: • the syringe cap is not detached from the Luer Lock. • the syringe is not damaged. • the drug solution looks clear, colourless to pale brownish-yellow and does not contain any particulates. 4. If any of the above is not true, discard the pre-filled syringe and use a new one.	

Heading	Instructions	Diagram/Image
Remove syringe cap	5. Snap off (do not turn or twist) the syringe cap (see Figure 2). 6. Dispose of the syringe cap (see Figure 3).	 Figure 2  Figure 3
Attach needle	7. Attach a 30G x 1/2 inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer Lock (see Figure 4). 8. Carefully remove the needle cap by pulling it straight off (see Figure 5). **Note: Do not wipe the needle at any time.**	 Figure 4  Figure 5
Dislodge air bubbles	9. Hold the syringe upright. 10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).	 Figure 6

Heading	Instructions	Diagram/Image
Set dose	11. Hold the syringe at eye level and carefully push the plunger until the edge below the dome of the rubber stopper is aligned with the dose mark (see Figure 7). • This will expel the air and the excess solution and set the dose to 0.05 mL. Note: the plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.	 Figure 7
Inject	The injection procedure should be carried out under aseptic conditions. 12. The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. 13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL. 14. A different scleral site should be used for subsequent injections. 15. After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.	

Lucentis contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Intravitreal injection-related reactions

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 Section 4.8 ADVERSE EFFECTS, UNDESIRABLE 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.

In adults, transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis (see Section 4.8 ADVERSE EFFECTS, UNDESIRABLE 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 therefore be monitored and managed appropriately. Patients should be reviewed for IOP rise pre-injection and 60 minutes post-injection. The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of an intraocular pressure of ≥30 mmHg.

Bilateral treatment

Limited data on bilateral use of Lucentis (including same day administration) do not suggest an increase of systemic adverse effects compared to with unilateral treatment.

Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events following intravitreal use of inhibitors of VEGF. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). 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.

Immunogenicity

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

Concomitant use of other anti-VEGF (vascular endothelial growth factor)

Lucentis should not be administered concurrently with other anti-VEGF medicinal products (systemic or ocular).

Withholding Lucentis treatment in adults

In the following cases the dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment:

- Decrease in best corrected visual acuity (BCVA) of ≥30 letters compared with the last assessment of visual acuity;
- Retinal break;
- Subretinal haemorrhage involving the centre of the fovea, or if the size of the haemorrhage is ≥50% of the total lesion area;
- Performed or planned intraocular surgery within the previous or following 28 days.

Retinal pigment epithelial tear

Risk factors associated with the development of a retinal pigment epithelial tear after anti-VEGF therapy for wet AMD and potentially also other forms of CNV, include a large and/or high pigment epithelial retinal detachment. When initiating ranibizumab therapy, caution should be used in patients with these risk factors for retinal pigment epithelial tears.

Retinal vasculitis and/or retinal occlusive vasculitis

Retinal vasculitis and/or retinal occlusive vasculitis have been reported with the use of Lucentis in the post-marketing setting. Discontinue treatment with Lucentis in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Patient populations with limited data

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, 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.

Use in renal impairment

Dose adjustment is not needed in patients with renal impairment (see Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in 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.

Use in the elderly

Elderly (65 years and above)

No dose adjustment is required in the elderly.

Paediatric use

Children and Adolescents (below 18 years of age)

The use of Lucentis in children and adolescents for indications other than retinopathy of prematurity has not been established and is, therefore, not recommended due to insufficient data on safety and efficacy in these sub-populations. Limited data on adolescent patients aged 12 to 17 years with visual impairment due to CNV is available (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials - Paediatric patients).

For use in preterm infants with retinopathy of prematurity (ROP) please see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials - Treatment of ROP in preterm infants. The warnings and precautions for adults also apply to preterm infants with ROP. Long-term safety in preterm infants with ROP has been studied in the RAINBOW extension study up to the age of five years old. See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), Retinopathy of Prematurity (ROP) population.

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal interaction studies have been performed (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

In clinical trials for treatment of visual impairment due to DME, the outcome with regards to visual acuity or central retinal thickness in patients treated with Lucentis was not affected by concomitant treatment with thiazolidinediones (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and 4.2 DOSE AND METHOD OF ADMINISTRATION.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 – 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 embryo-foetotoxic. 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 embryo-foetal development is plausibly related to the expected inability of the Fab fragment to cross the placenta. Nevertheless, ranibizumab was detected in a foetus 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 embryo-foetal development investigations were performed in healthy pregnant animals and disease (such as 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.

Use in lactation

Based on limited data, ranibizumab is present in human milk and may suppress VEGF levels. The effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion are unknown. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lucentis and any potential adverse effects on the breastfed child from ranibizumab.

4.7 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 Section 4.8 ADVERSE EFFECTS, UNDESIRABLE EFFECTS). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Wet AMD Population

A total of 1,315 patients constituted the safety population in the three controlled phase III studies in wet AMD (FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)) 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The adverse events listed in Table 1 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 Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials) or verteporfin

photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD phase III studies. 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 wAMD patients treated with 0.5 mg Lucentis. 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 Section 5.1 PHARMACODYNAMIC PROPERTIES, 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.

Post-Registration Study in DME population

An analysis of 24-month data from two Phase III studies in DME, RIDE and RISE, is available. Both studies are randomised, sham-controlled studies of monthly intravitreal ranibizumab injections (0.5 mg or 0.3 mg) for a total of 36 months in patients with clinically significant macular oedema with centre involvement secondary to diabetes mellitus (type 1 or type 2). The patients are treated using a fixed dosing regimen which requires monthly injections as opposed to the approved individualised dosing regimen (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). A total of 500 patients were exposed to ranibizumab treatment in the pooled studies (250 patients in each pooled ranibizumab 0.3mg and 0.5mg arm as well as the sham arm.

The pooled safety analysis showed a numerically higher, but not statistically significant, number of deaths and cerebrovascular events in the 0.5mg group as compared to the 0.3mg or sham groups. The stroke rate at 2 years was 3.2% (8/250) with ranibizumab 0.5mg, 1.2% (3/250) with ranibizumab 0.3mg, and 1.6% (4/250) with sham. Fatalities in the first 2 years occurred in 4.4% (11/250) of patients treated with ranibizumab 0.5mg, in 2.8% (7/250) treated with ranibizumab 0.3mg, and in 1.2% (3/250) of control patients.

PDR population

The safety of Lucentis in patients with PDR was studied for up to 24 months in Protocol S, including 191 patients treated with ranibizumab 0.5 mg (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Ocular and non-ocular events observed were consistent with what would be expected in a diabetic patient population with DR or have been reported with a frequency and severity similar to those seen in previous clinical trials with Lucentis.

RVO population

The safety of Lucentis was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular oedema secondary to BRVO and CRVO, respectively (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Ocular and non-ocular events in the BRAVO and CRUISE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

CNV population

The safety of Lucentis was studied in a 12-month clinical trial (MINERVA), which included 171 ranibizumab-treated patients with visual impairment due to CNV (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). The safety profile in these patients was consistent with that seen in previous clinical trials with Lucentis.

Pathologic Myopia (PM) population

The safety of Lucentis was studied in the 12-month clinical trial (RADIANCE), which included 224 ranibizumab-treated patients with visual impairment due to CNV secondary to PM (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Ocular and non-ocular events in this trial were reported with a frequency and severity similar to those seen in the wet-AMD trials.

Patients with PM have an increased risk for retinal detachment and retinal tear. No case of 'retinal detachment' was reported in the pivotal clinical trial (RADIANCE) in PM and three events coded as 'retinal tear' were reported. This incidence (1.3%) is higher than that seen in other approved indications for ranibizumab (0 to 1.1% in wet AMD, 0 to 0.8% in DME and in RVO) and consistent with the reporting rate for retinal tear described in Table 1.

Retinopathy of Prematurity (ROP) population

The safety of Lucentis 0.2 mg and 0.1 mg was studied in the 6-month clinical trial H2301 (RAINBOW), which included 73 and 76 preterm infants with ROP treated with ranibizumab 0.2 mg and 0.1 mg, respectively (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). Ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2 mg were retinal haemorrhage and conjunctival haemorrhage, while those for ranibizumab 0.1 mg were retinal haemorrhage, conjunctival haemorrhage, conjunctivitis, vitreous haemorrhage and eye haemorrhage. Non-ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2 mg were nasopharyngitis, anaemia, cough, urinary tract infection and allergic reactions, while those for ranibizumab 0.1 mg were anaemia, nasopharyngitis, urinary tract infection and cough. Adverse reactions established for adult indications are considered applicable to preterm infants with ROP, though not all were observed in the RAINBOW trial.

In the extension study H2301E1 (RAINBOW extension), adverse events were analysed over a single observation period between approximately 6-months and the patient's 5th birthday. 180 patients were enrolled, including 61 and 65 patients who initially received ranibizumab 0.2 mg and 0.1 mg, respectively, in the core study H2301. 156 patients completed the 5th birthday visit. For both ranibizumab doses, no clinically significant differences were found between the overall proportions of patients with ocular and non-ocular adverse events among those who initially received ranibizumab compared to those who initially received laser.

Potential systemic suppression of VEGF cannot be excluded following intravitreal administration of ranibizumab in premature infants. In the extension study, adverse events were medically reviewed to identify events of neurodevelopmental impairment, as well as more broadly events that may be considered related to overall developmental impairment associated with CNS disorders. Adverse events retrieve by this review were reported in 31.1%, 18.5% and 25.9% of patients who initially received ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser, respectively. Available data does not allow for the definitive assessment of whether a causal association exits between ranibizumab exposure and neurodevelopmental impairment. Data on long term respiratory, renal and hepatic outcomes is limited.

Interpretation of safety data from H2301E1 is limited by loss to follow-up, and that some patients switched treatment modality during the core study H2301 after receiving the initial treatment.

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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000).

Table 1 Adverse Effects from Clinical Trials

Infections and Infestations	
Very common	Nasopharyngitis
Common	Influenza, urinary tract infection*
Blood and lymphatic system disorders	
Common	Anaemia
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very common	Headache
Common	Stroke
Eye disorders	
Very common	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.
Common	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.
Uncommon	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	
Common	Cough
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	

Common	Allergic reactions (rash, urticaria, pruritis, erythema)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Investigations	
Very common	Intraocular pressure increase

*Observed only in the DME population

A meta-analysis of pooled safety data from completed, randomised, double masked global studies showed a higher incidence rate of non-serious, non-ocular wound infection/inflammation in DME patients treated with ranibizumab 0.5 mg (1.85/100 PY; 20 events in 936 patients) compared to sham/laser treatment (0.27/100 PY; 2 events in 58 patients); HR 8.07 (95% CI 1.88, 34.74). The relationship to ranibizumab remains unknown.

Post-marketing experience

The post-marketing safety profile of Lucentis remain in accord with the findings observed in clinical trial setting.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Cases of accidental overdose (injection of volumes greater than the recommended 0.05 mL Lucentis) 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, transient blindness, reduced visual acuity, corneal oedema, corneal pain, and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

In clinical trials doses up to 2 mg of ranibizumab in an injection volume of 0.05 mL to 0.10 mL have been administered to patients with wet AMD and DME. The type and frequency of ocular and systemic adverse events were consistent with those reported for the 0.5 mg (in 0.05 mL) Lucentis dose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC

Antineovascularisation agents, ATC code: S01LA04.

5.1 PHARMACODYNAMIC PROPERTIES

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. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, to the development of choroidal neovascularisation (CNV), including CNV secondary to pathologic myopia or to the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

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) (FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)). A total of 1,323 patients (879 active and 444 control) was enrolled in these studies.

Study FVF2598g (MARINA) and study FVF2587g (ANCHOR)

In the 24-month 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.

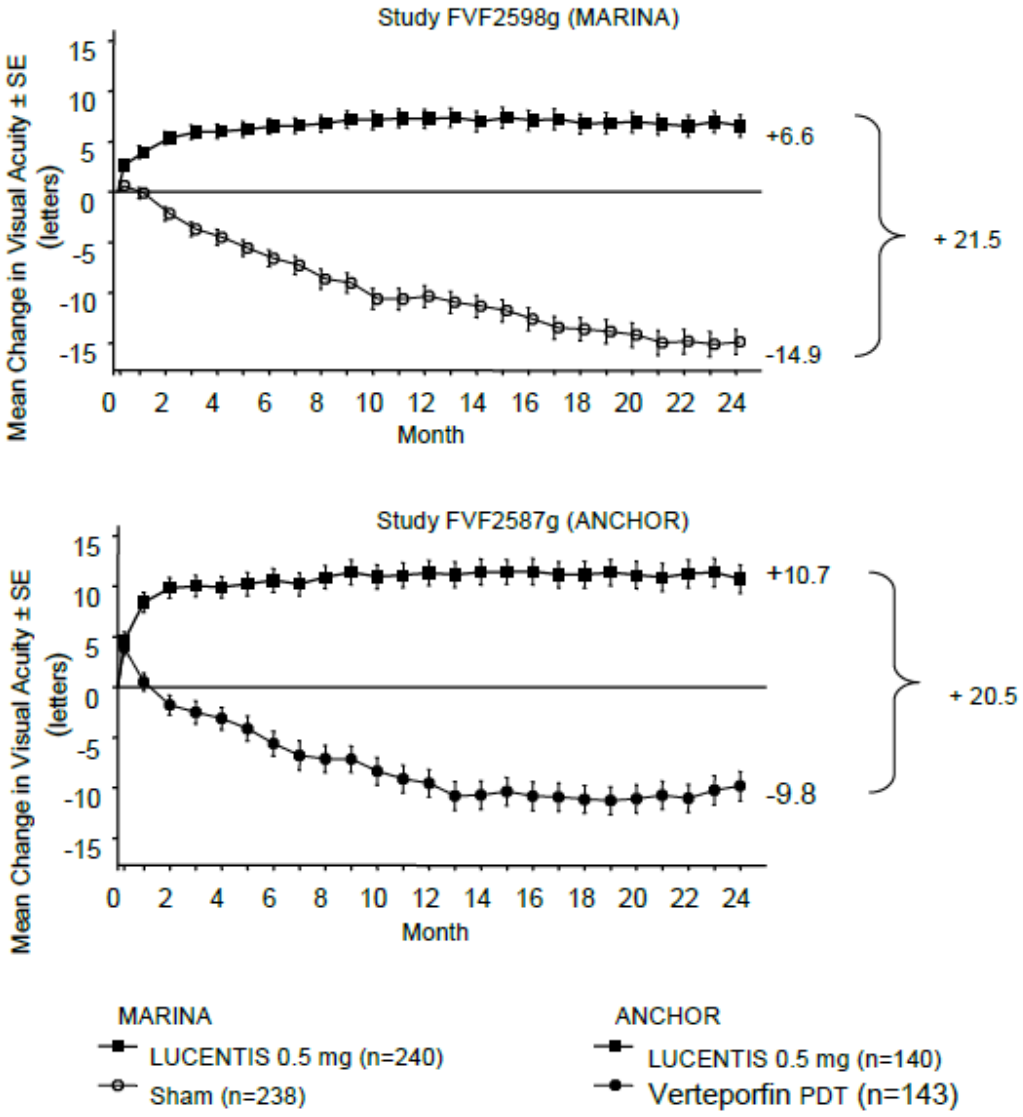
In the 24-month study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Verteporfin (or sham) PDT was given with the initial Lucentis (or sham) 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 (Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140; Verteporfin PDT, 143). A total of 386 subjects (91.3%) completed month 12 of the study and 343 subjects (81.1%) completed month 24 of the study.

*** The sham Lucentis injection control procedure involved anesthetising 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 MARINA, 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 Figure1.

In ANCHOR, 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 1.

Figure 1 **Mean change in visual acuity from baseline to Month 24 in study FVF2598g (MARINA) and study FVF2587g (ANCHOR): ITT population**



Detailed results are shown in the tables below:

Table 2 **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]	Month 12	148 (62.2%)	225 (94.5%)	227 (94.6%)
(Maintenance of vision)	Month 24	126 (52.9%)	219 (92.0%)	216 (90.0%)
	Month 12	11 (4.6%)	59 (24.8%)	81 (33.8%)

Gain of ≥15 letters in visual acuity n (%)[a]	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 3 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 Lucentis 0.5 mg 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 Lucentis 0.5 mg 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)

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. Overall, 2378 patients were randomised in a 1:1 ratio to receive one intravitreal injection of ranibizumab 0.3 mg or 0.5 mg every month for three consecutive months followed by re-treatment as needed 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.

Study FVF3192g (PIER)

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. 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.

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.

Study A2412 (EVEREST II)

Study A2412 (EVEREST II) is a two-year, randomised , double-masked, multi-centre study designed to evaluate the efficacy and safety of Lucentis 0.5 mg monotherapy vs. Lucentis 0.5 mg in combination with verteporfin photodynamic therapy (vPDT) in 322 Asian patients with symptomatic macular polypoidal choroidal vasculopathy (PCV), a subtype of wet AMD. Patients in both study arms initiated treatment with three monthly Lucentis injections, plus sham or active vPDT given with the first Lucentis injection only. Following treatment initiation, Lucentis monotherapy and Lucentis administered with vPDT were given pro re nata (PRN) based on ocular clinical assessments, including imaging techniques (e.g. OCT, FA, ICGA). Primary results at month 12 demonstrated that Lucentis administered with vPDT was superior to Lucentis monotherapy with respect to the BCVA change from baseline (8.3 letters versus 5.1 letters, p=0.013) and complete polyp regression (69.3% versus 34.7%, p<0.001). Patients administered Lucentis with vPDT received on average 2.3 Lucentis injections less than patients administered Lucentis monotherapy (5.1 vs. 7.4 injections).

Superiority of Lucentis with vPDT compared to Lucentis monotherapy was confirmed at month 24 with respect to BCVA change from baseline (9.6 letters vs. 5.5 letters, p=0.005) and complete polyp regression (56.6% versus 26.7%, p<0.0001). Patients administered Lucentis with vPDT received on average 4.2 Lucentis injections less than patients administered Lucentis monotherapy (8.1 vs. 12.3 injections).

Treatment of Visual Impairment Due to DME

The efficacy and safety of Lucentis have been assessed in two randomised, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular oedema (Study D2301 (RESTORE) and D2201 (RESOLVE)). A total of 496 patients (336 active and 160 control) was enrolled in these studies, the majority had type II diabetes, 28 patients treated with ranibizumab had type I diabetes.

Study D2301 (RESTORE)

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular oedema 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 the injection of ranibizumab, and then as needed based on Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.

Key outcomes are summarised in Tables 4 and 5 and Figure 2.

Table 4 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	

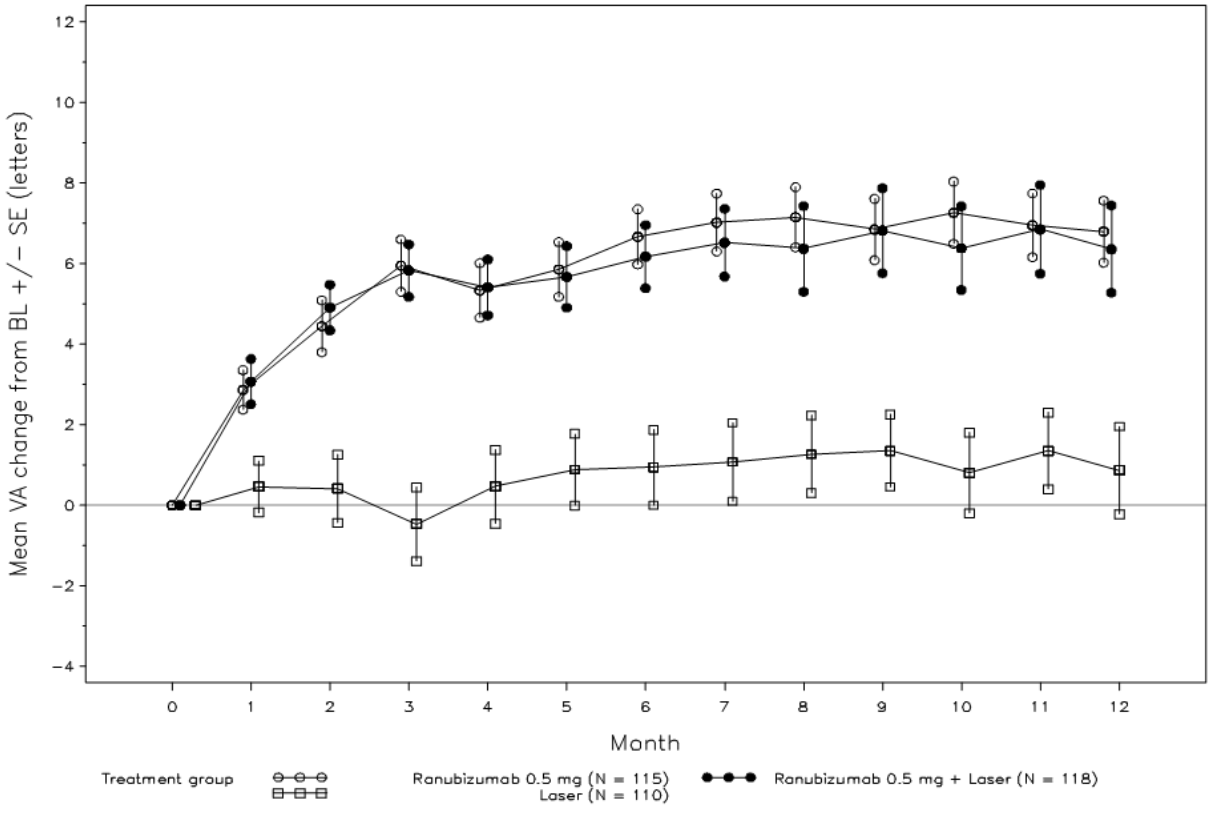
- n is the number of patients with a value for both baseline and average Month 1 to Month 12.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score.

Table 5 **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 0.5 mg + 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 2 **Mean BCVA change from baseline over time in study D2301 (RESTORE)**



Study D2301E1 (RESTORE Extension)

Study D2301E1 (RESTORE Extension) was an open-label, multi-centre, 24-month extension study. 240 patients who had completed the 12-month core study entered the extension study and were treated with ranibizumab 0.5 mg pro re nata (PRN) in the same eye that was selected as the study eye in the core study. Treatment was re-initiated at monthly intervals upon a decrease in BCVA due to DME and

continued until stable BCVA was reached. In addition, laser treatment was administered, if deemed necessary by the investigator, and based on ETDRS guidelines.

On average, 6.4 ranibizumab injections were administered per patient in the 24-month extension period in patients who were treated with ranibizumab, with or without laser treatment, in study D2301. Of the 74 patients from the core study laser treatment arm, 59 (80%) patients received ranibizumab at some point during the extension phase. On average, these 59 patients received 8.1 ranibizumab injections per patient over the 24 months of the extension study. The proportions of patients who did not require any ranibizumab treatment during the extension phase were 19%, 25% and 20% in the prior ranibizumab, prior ranibizumab + laser, and prior laser group, respectively.

Secondary outcome measures are summarized in Table 6.

Table 6 Outcomes at Month 36 in study D2301E1 (RESTORE Extension)

Outcome measure compared to core baseline	**Prior ranibizumab 0.5 mg n=83**	**Prior ranibizumab 0.5 mg + Laser n=83**	**Prior laser n=74***
Mean change in BCVA from baseline in the core study at Month 36 (SD)	8.0 (10.09)	6.7 (9.59)	6.0 (9.35)
Gain of ≥10 letters from core baseline or BCVA ≥84 (%) at Month 36	39 (47.0)	37 (44.6)	31 (41.9)
Gain of ≥15 letters from core baseline or BCVA ≥84 (%) at Month 36	23 (27.7)	25 (30.1)	16 (21.6)

n is the number of patients with a value both at D2301 (RESTORE) baseline (Month 0) and at the Month 36 visit.
* Of the 74 patients with prior laser treatment, 59 (80%) patients received ranibizumab in the extension study.

The long-term safety profile of ranibizumab observed in this 24-month extension study is consistent with the known Lucentis safety profile.

Study D2201 (RESOLVE)

In a supportive, partly exploratory study D2201 (RESOLVE), a total of 151 patients with macular 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 µm; or if at any monthly visit after month 1, retinal thickness in the study eye was > 225 µm and reduction in retinal oedema from the previous assessment was < 50 µm. 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 months 6), and a confirmatory part (the remaining 109 patients analysed at months 12).

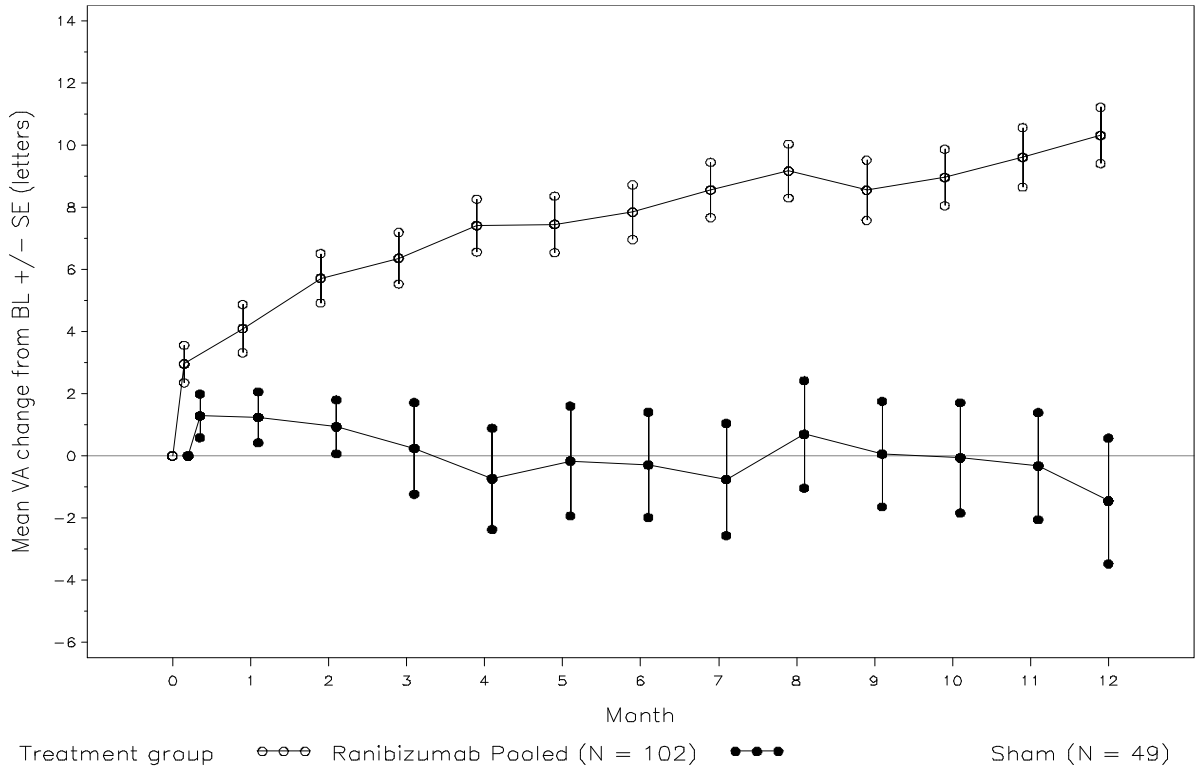
The exploratory analysis revealed no sign of a clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of this study therefore do not support the concept of dose doubling where response to the recommended dose is considered inadequate. Key outcomes from the confirmatory part of the study (2/3 patients) are summarised in Tables 7 and Figure 3.

Table 7 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 ≥ 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 ≥ 15 letters [Δ BL to month 12] [1]	0%	5.9% (n=3)	2.9% (n=2)	20.4% (n=10)
Gain ≥ 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 ≥ 10 letters [Δ BL to month 12] [2]	0%	9.8% (n=5)	4.9% (n=5)	24.5% (n=12)
CRT μm 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 μm (%) 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 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 p<0.0001
[3]CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p<0.0001; and pooled p<0.0001
[4]CMH test, stratified: 6 mg/mL vs sham p=0.0108; 10 mg/mL vs sham p=0.0007; and pooled p=0.0011

Figure 3 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.

Study D2303 (REVEAL)

The study D2303 (REVEAL) was a 12 month, randomised, double-masked Phase IIIb trial conducted in Asian patients. Similar to the RESTORE 12 month core study in trial design and inclusion/exclusion criteria, 390 patients with visual impairment due to macular oedema were randomised to receive either ranibizumab 0.5 mg injection as monotherapy and sham laser photocoagulation (n=133), ranibizumab 0.5 mg injection and laser photocoagulation (n=129), or sham injection and laser photocoagulation (n=128). Mean change in visual acuity at month 12 compared to baseline were +6.6 letters in the ranibizumab monotherapy group, +6.4 letters in the ranibizumab plus laser group and +1.8 letters in the laser group. Overall, the efficacy and safety results of the REVEAL study in Asian DME patients are consistent with those of the RESTORE study in Caucasian DME patients.

Study D2304 (RETAIN)

In the phase IIIb study D2304 (RETAIN), 372 patients with visual impairment due to DME were randomised to receive intravitreal injection of either:

- ranibizumab 0.5 mg with concomitant laser photocoagulation on a 'treat-and-extend' (TE) regimen (n=121), or
- ranibizumab 0.5 mg monotherapy on a TE regimen (n=128), or
- ranibizumab 0.5 mg monotherapy on a pro re nata (PRN) regimen (n=123).

In all groups, treatment with ranibizumab was initiated with monthly intravitreal injections and continued until BCVA was stable for at least three consecutive monthly assessments. Laser photocoagulation was administered at baseline on the same day as the first ranibizumab injection and then as needed based on ETDRS criteria. On the 'treat-and-extend' (TE) regimen, ranibizumab was then administered, at scheduled treatment, at intervals of 2-3 months. On the PRN regimen, BCVA was assessed monthly and ranibizumab was then administered during the same visit, if needed. In all groups, monthly treatment was re-initiated upon a decrease in BCVA due to DME progression and continued until stable BCVA was reached again. The duration of the study was 24 months.

In the RETAIN study, after 3 initial monthly treatment visits, the number of scheduled treatment visits required by the TE regimen was 13 compared to the 20 monthly visits required by the PRN regimen. Over 24 months the mean (median) number of injections was 12.4 (12.0) in TE ranibizumab + laser, 12.8 (12.0) in TE ranibizumab alone, and10.7 (10.0) for the PRN ranibizumab treatment groups. The addition of laser was not associated with a reduced mean number of ranibizumab injections in the TE regimen. On average, patients in both TE groups maintained BCVA over 24 months of treatment. In the TE groups, over 70% of patients had a visit frequency of ≥ 2 months.

Key outcome measures are summarised in Table 8.

Table 8 Outcomes in study D2304 (RETAIN)

Outcome measure compared to baseline	**TE Ranibizumab 0.5 mg + Laser n=117**	**TE Ranibizumab 0.5 mg alone n=125**	**PRN Ranibizumab 0.5 mg n=117**
Mean average change in BCVA from Month 1 to Month 12 (SD)[b]	5.9 (5.5)[a]	6.1 (5.7)[a]	6.2 (6.0)
Mean average change in BCVA from Month 1 to Month 24 (SD)[c]	6.8 (6.0)	6.6 (7.1)	7.0 (6.4)
Mean change in BCVA at Month 24 (SD)[c]	8.3 (8.1)	6.5 (10.9)	8.1 (8.5)
Gain of ≥10 letters or BCVA ≥84 (%) at Month 24[c]	43.6	40.8	45.3
Gain of ≥15 letters or BCVA ≥84 (%) at Month 24[c]	25.6	28.0	30.8

[a] $p<0.0001$ for assessment of non-inferiority to PRN.
[b] difference in BCVA over month 1 to month12 was a primary efficacy variable.
[c] outcomes up to 24 months were secondary efficacy variables.

There was no difference in the BCVA or CRT outcomes of patients in RETAIN study who received or did not receive concomitant thiazolidinediones.

In DME studies, the improvement in BCVA was accompanied by a reduction over time in mean CRT in all the treatment groups.

Diabetic retinopathy severity score (DRSS) was assessed in three of the clinical trials described above. Of the 875 patients of whom approximately 75% were of Asian origin. In a meta-analysis of these studies 48.8% of the 315 patients with gradable DRSS scores in the subgroup of patients with moderately severe non-proliferative DR (NDPR) or worse at baseline experienced a ≥2 step improvement in the DRSS at month 12 when treated with ranibizumab (n=192) vs 14.6% of patients treated with laser (n=123). The estimated difference between ranibizumab and laser was 29.9% (95% CI: [20.0, 39.7]. In the 405 DRSS gradable patients with moderate NDPR or better, a ≥2 step DRSS improvement was observed in 1.4% and 0.9% of the ranibizumab and laser groups respectively.

Treatment of PDR

The clinical safety and efficacy of Lucentis in patients with PDR have been assessed in Protocol S which evaluated the treatment with ranibizumab 0.5 mg intravitreal injections compared with panretinal photocoagulation (PRP). The primary endpoint was the mean visual acuity change at year 2. Additionally, change in diabetic retinopathy (DR) severity was assessed based on fundus photographs using the DR severity score (DRSS).

Protocol S was a multicentre, randomised, active-controlled, parallel-assignment, non- inferiority phase III study in which 305 patients (394 study eyes) with PDR with or without DME at baseline were enrolled. The study compared ranibizumab 0.5 mg intravitreal injections to standard treatment with PRP. A total of 191 eyes (48.5%) were randomised to ranibizumab 0.5 mg and 203 eyes (51.5%) eyes were randomised to PRP. A total of 88 eyes (22.3%) had baseline DME: 42 (22.0%) and 46 (22.7%) eyes in the ranibizumab and PRP groups, respectively.

In this study, the baseline visual acuity was 75.0 letters in the ranibizumab group and 75.2 letters in the PRP group, the mean visual acuity change at year 2 was +2.7 letters in the ranibizumab group compared to -0.7 letters in the PRP group. The difference in least square means was 3.5 letters (95% CI: [0.2 to 6.7]).

At year 1, 41.8% of eyes experienced a ≥2-step improvement in the DRSS when treated with ranibizumab (n=189) compared to 14.6% of eyes treated with PRP (n=199). The estimated difference between ranibizumab and laser was 27.4% (95% CI: [18.9, 35.9]).

Table 9 DRSS improvement or worsening of ≥2 or ≥3 steps at year 1 in protocol s (LOCF method)

Categorised change from baseline	Protocol S		
	Ranibizumab 0.5 mg (N=189)	PRP (N=199)	Difference in proportion (%), CI
≥2-step improvement			
n (%)	79 (41.8%)	29 (14.6%)	27.4 (18.9, 35.9)
≥3-step improvement			
n (%)	54 (28.6%)	6 (3.0%)	25.7 (18.9, 32.6)
≥2-step worsening			
n (%)	3 (1.6%)	23 (11.6%)	-9.9 (-14.7, -5.2)
≥3-step worsening			
n (%)	1 (0.5%)	8 (4.0%)	-3.4 (-6.3, -0.5)
DRSS = diabetic retinopathy severity score, n = number of patients who satisfied the condition at the visit, N = total number of study eyes.			

At year 1 in the ranibizumab-treated group in Protocol S, ≥2-step improvement in DRSS was consistent in eyes without DME (39.9%) and with baseline DME (48.8%).

An analysis of year 2 data from Protocol S demonstrated that 42.3% (n=80) of eyes in the ranibizumab-treated group had ≥2-step improvement in DRSS from baseline compared with 23.1% (n=46) of eyes in the PRP group. In the ranibizumab-treated group, ≥2-step improvement in DRSS from baseline was observed in 58.5% (n=24) of eyes with baseline DME and 37.8% (n=56) of eyes without DME.

Treatment of visual impairment due to macular oedema secondary to RVO

Study FVF4165g (BRAVO) and study FVF4166g (CRUISE)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects received either ranibizumab 0.3 mg or 0.5 mg intravitreal or sham** injections. Patients were initially treated monthly for 6 months. Neither study compared a flexible versus fixed dosing regimen. Thereafter, treatment was given as needed following pre-specified re-treatment criteria. After 6 months, patients in the sham-control arms were crossed over to ranibizumab 0.5 mg. In BRAVO, laser photocoagulation as rescue was allowed in all arms from month 3.

Laser therapy was not used as a comparative treatment. During the first six months, laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group.

In the first six months, ranibizumab was given monthly. In the second six month period, all patients were given only ranibizumab as needed i.e. were given only active treatment as required (0.5mg monthly if previously on sham treatment) and at monthly intervals as necessary, the latter determined by a best corrected visual acuity of 20/40 - or worse - or mean central subfield thickness ≥ 250 μm on optical coherence tomography.

Out of the 525 patients who received active treatment in the first 6 months, 501 patients entered into the observation period, with 87.2% (n=437) of them receiving at least one injection. Overall, patients received from 0 to 6 injections, with the lowest percentage of patients (10%) receiving 1 injection and the highest percentage of patients (20.8%) receiving 6 injections. The average number of injections was 3.3.

While numerically the better results were seen for 0.5 mg the differences between the two doses of Lucentis are not clinically significant. Key outcomes from BRAVO and CRUISE are summarised in Tables 10 and 11 and Figures 4 and 5.

Table 10 Outcomes at Month 6 and 12 (BRAVO)

	Sham/Lucentis 0.5 mg (n=130)	**Lucentis 0.3 mg (n=134)**	**Lucentis 0.5 mg (n=130)**
Mean change in visual acuity from baseline at Month 6[a] (letters) (primary endpoint)	+7.3	+16.6	+18.3
Mean change in visual acuity from baseline at Month 12 (letters)	+12.1	+16.4	+18.3
Proportion of patients gained ≧15 letters in BCVA from baseline at Month 6[a]	28.8 %	55.2%	61.1 %
Proportion of patients gained ≧15 letters in BCVA from baseline at Month 12	43.9 %	56.0%	60.3 %
Proportion of patients receiving laser rescue over 12 months	61.4 %	41.0%	34.4 %

[a] $p<0.0001$

Figure 4 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (BRAVO)

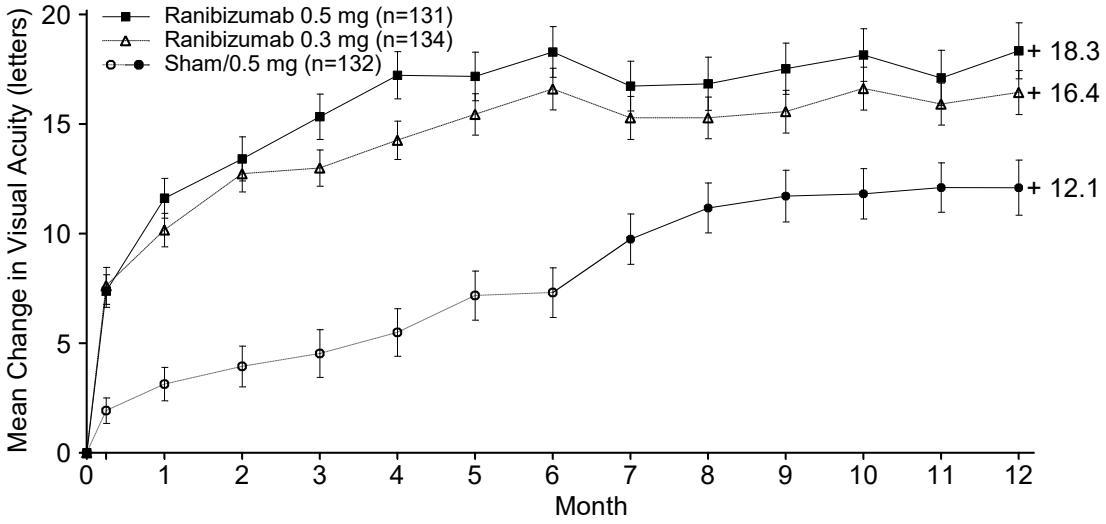
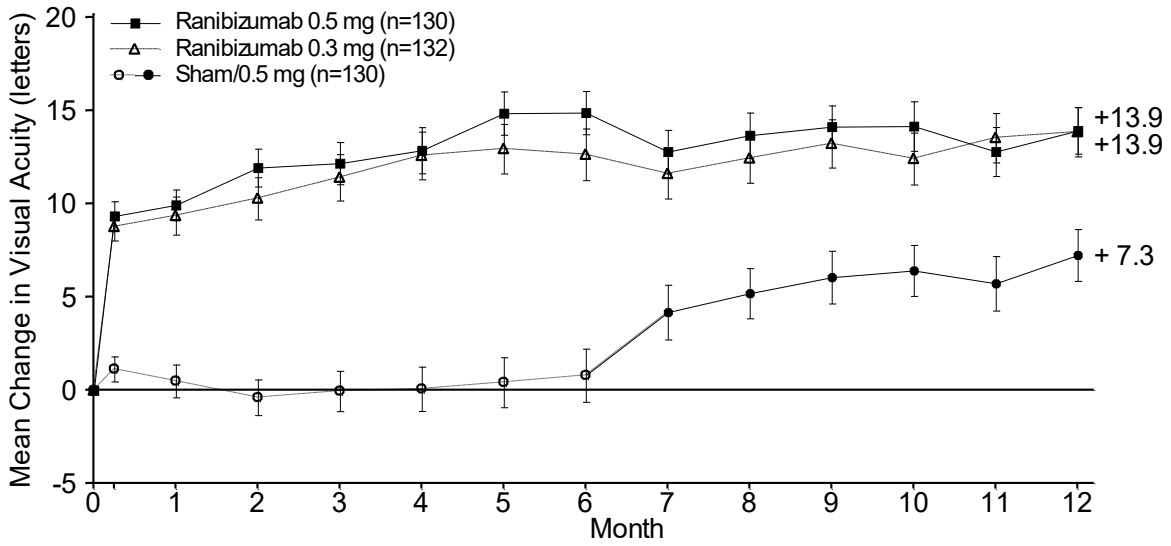


Table 11 Outcomes at Month 6 and 12 (CRUISE)

	Sham/Lucentis 0.5 mg (n=130)	**Lucentis 0.3 mg (n=132)**	**Lucentis 0.5 mg (n=130)**
Mean change in visual acuity from baseline at Month 6 (letters)[a]	+0.8	+12.7	+14.9
Mean change in visual acuity from baseline at Month 12 (letters)	+7.3	+13.9	+13.9
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 [a]	16.9 %	46.2%	47.7 %
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12	33.1 %	47.0%	50.8 %

[a] $p<0.0001$

Figure 5 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (CRUISE)



In both studies, the improvement of vision was accompanied by a continuous decrease in the macular oedema as measured by central retinal thickness.

The improvement in visual acuity seen with ranibizumab treatment at 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) sub-scales related to near and distance activity, a pre-specified secondary efficacy endpoint. The difference between Lucentis 0.5 mg and the control group was assessed at month 6 with p-values of 0.02 to 0.0002.

Efficacy and safety of Lucentis for treatment of visual impairment due to macular oedema secondary to RVO has not been evaluated beyond 12 months.

Study E2401 (CRYSTAL) and Study E2402 (BRIGHTER)

The long term (24 month) clinical safety and efficacy of Lucentis in patients with visual impairment due to macular edema secondary to RVO were assessed in the BRIGHTER and CRYSTAL studies, which recruited subjects with BRVO (n=455) and CRVO (n=357), respectively. In both studies, subjects received a 0.5 mg ranibizumab PRN dosing regimen driven by individualized stabilization criteria. BRIGHTER was a 3-arm, randomised, active-controlled study that compared 0.5 mg ranibizumab given as monotherapy or in combination with adjunctive laser photocoagulation, to laser photocoagulation alone. After 6 months, subjects in the laser monotherapy arm could receive 0.5 mg ranibizumab. CRYSTAL was a single-arm study with 0.5 mg ranibizumab monotherapy.

Key outcome measures from BRIGHTER and CRYSTAL are summarised in Table 12.

Table 12 Outcomes at Month 6 (BRIGHTER) and Month 24 (BRIGHTER and CRYSTAL)

	BRIGHTER			CRYSTAL
	Lucentis 0.5 mg N=180	**Lucentis 0.5 mg + Laser N=178**	**Laser* N=90**	**Lucentis 0.5 mg (N=356)**
Mean change in BCVA at Month 6[b] (letters) (SD)	+14.8	+14.8	+6.0	+12.0
Mean change in BCVA at Month 24[b] (letters) (SD)	+15.5	+17.3	+11.6	+12.1
Proportion of patients gained ≥15 letters in BCVA at Month 24	52.8 %	59.6 %	43.3 %	49.2 %
Mean number of injections (SD) (Months 0-23)	11.4	11.3	NA	13.1

* Starting at Month 6 treatment with ranibizumab 0.5 mg was allowed (24 patients were treated with laser only).

[b]:p<0.0001 for both comparisons in BRIGHTER at Month 6: Lucentis 0.5 mg vs Laser and Lucentis 0.5 mg + Laser vs Laser.

[b]p<0.0001 for null hypothesis in CRYSTAL that the mean change at Month 24 from baseline is zero.

In BRIGHTER, 0.5 mg ranibizumab with adjunctive laser therapy demonstrated non-inferiority to ranibizumab monotherapy from baseline to Month 24 as assessed by the mean average change in BCVA. There was no difference between the two groups in the number of ranibizumab injections administered over this period.

In both studies, a rapid and significant decrease from baseline in central retinal subfield thickness was observed at Month 1. This effect was maintained up to Month 24.

The effect of ranibizumab treatment was similar irrespective of the presence of retinal ischemia. In BRIGHTER, patients with retinal ischemia present (N=87) or absent (N=35) and treated with ranibizumab monotherapy had a mean change from baseline of +15.4 and +12.9 letters respectively, at Month 24. In CRYSTAL, patients with retinal ischemia present (N=107) or absent (N=109), treated with ranibizumab monotherapy had a mean change from baseline of +11.1 and +12.9 letters, respectively.

The effect in terms of visual improvement was observed in all patients treated with 0.5 mg ranibizumab monotherapy regardless of their disease duration in both BRIGHTER and CRYSTAL. In patients with <3 months disease duration an increase in visual acuity of 13.3 and 10.0 letters was seen at Month 1; and 17.7 and 13.2 letters at Month 24 in BRIGHTER and CRYSTAL, respectively. Treatment initiation at the time of diagnosis should be considered.

The long term safety profile of ranibizumab observed in these 24-month studies is consistent with the known Lucentis safety profile.

Treatment of visual impairment due to CNV

Study G2301 (MINERVA)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV secondary to etiologies other than nAMD and PM have been assessed in the pivotal study G2301 (MINERVA), which was randomised, double-masked, sham controlled for 2 months, followed by an open label extension of 10 months. Due to the multiple baseline etiologies involved, five subgroups (angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic chorioretinopathy, and miscellaneous etiology) were pre-defined for analysis. In this study, 178 patients were randomised in a 2:1 ratio to one of the following arms:

- ranibizumab 0.5 mg at baseline followed by an individualized dosing regimen driven by disease activity.
- sham injection at baseline followed by an individualized treatment regimen driven by disease activity.

Starting at month 2, all patients received open-label treatment with ranibizumab as needed. The primary endpoint was assessed by the best corrected visual acuity (BCVA) change from baseline to month 2.

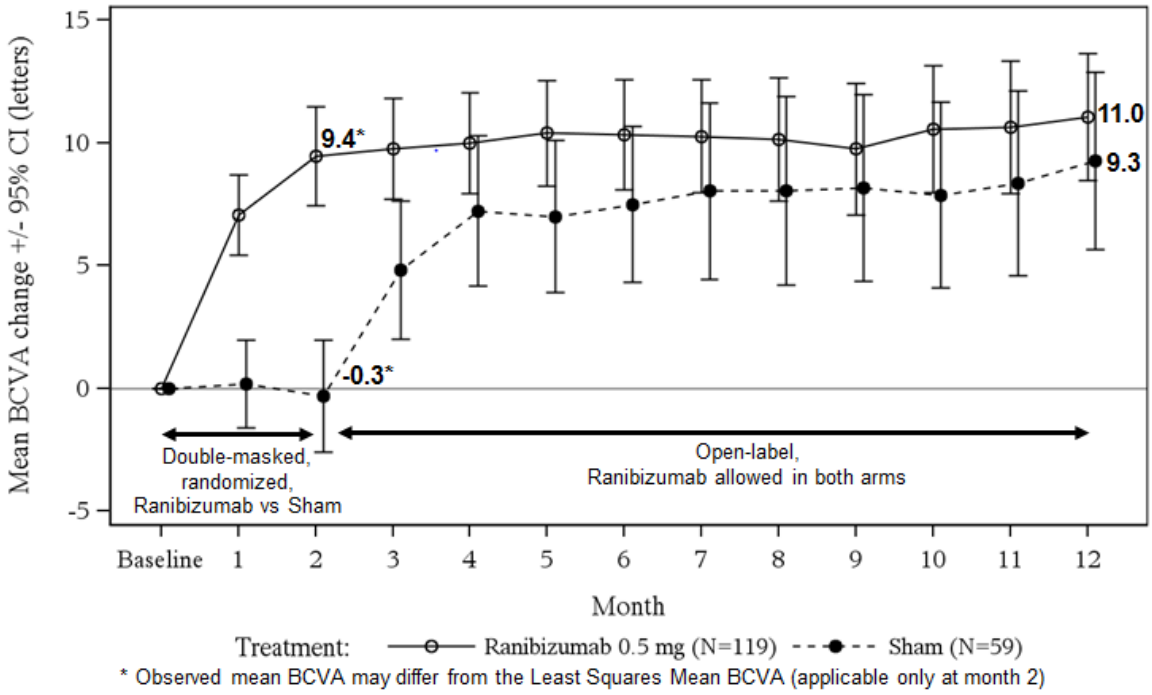
Key outcomes from MINERVA are summarized in Tables 13 and 14 and Figure 6.

Table 13 Outcomes at Month 2 (MINERVA)

	Ranibizumab 0.5 mg (n=119)	**Sham (n=59)**
Mean BCVA change from baseline to Month 2 (letters) (Least Squares Mean) [a]	+9.5	-0.4
Proportion of patients who gained ≥10 letters from baseline or reached 84 letters at Month 2	42.4%	14.0%
Proportion of patients not losing >10 letters from baseline at Month 2	99.2%	91.2%
Reduction in CSFT from baseline to Month 2 (Least Squares Mean) [a]	77 µm	-9.8 µm

CSFT=central subfield thickness.
[a] One sided $p<0.001$ comparison with sham control.

Figure 6 **Mean BCVA change from baseline over time to Month 12 (MINERVA)**



When comparing ranibizumab versus sham control at Month 2, a statistically significant treatment effect for patients in ranibizumab arm was observed.

Table 14 **Overall treatment effect and treatment effect across baseline etiology subgroups for primary variable at Month 2 (MINERVA)**

Overall and per baseline etiology	**Treatment effect over sham (letters)**	**Patient numbers (n) (treatment + sham)**
Overall	9.9	175*
Angioid streaks	14.6	27
Post-inflammatory retinochoroidopathy	6.5	27
Central serous chorioretinopathy	5.0	23
Idiopathic chorioretinopathy	11.4	62
Miscellaneous etiologies[a]	10.6	36

[a] comprises CNV etiologies which do not fall under the other subgroups.
* number of patients with data available in the analysis.

The improvement of vision was accompanied by a reduction in central subfield thickness over the 12-month period.

The mean number of ranibizumab injections given in the study eye over 12 months was 5.8 in the ranibizumab arm versus 5.4 in those patients in the sham with ranibizumab group. In the sham arm, 7 out of 59 patients did not receive any treatment with ranibizumab in the study eye during the 12-month period.

Paediatric patients

Five adolescent patients aged 12 to 17 years with visual impairment secondary to CNV received open-label treatment with ranibizumab 0.5 mg at baseline followed by an individualized treatment regimen based on evidence of disease activity (e.g. VA impairment, intra/sub-retinal fluid, haemorrhage or leakage). BCVA change from baseline to month 12 improved in all five patients, ranging from +5 to +38 letters (mean of 16.6 letters). The improvement of vision was accompanied by a stabilization or reduction in central subfield thickness over the 12-month period. The mean number of ranibizumab injections given in the study eye over 12 months was three (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Paediatric use).

Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to Pathologic myopia (PM)

Study F2301 (RADIANCE)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV in PM have been assessed based on the 12-month data of the randomised, double-masked, controlled pivotal study F2301 (RADIANCE) which was designed to evaluate two different dosing regimens of ranibizumab 0.5 mg given as intravitreal injection in comparison to verteporfin PDT (vPDT, Visudyne photodynamic therapy).

Patients with retinal detachment, cataract, pre-retinal membrane of the macula, history of panretinal or focal/grid laser photocoagulation with involvement of the macular area, history of intraocular treatment with any anti-VEGF or vPDT, history of intra-ocular surgery or treatment with corticosteroids in preceding 3 months were excluded from the trial.

A total of 277 eligible patients participated in the trial. The mean (SD) age of all randomised patients was 55.5 (13.94) years. At baseline, the mean (SD) BCVA was 55.4 (13.11) letters. The mean (SD) axial length was 29.07 (1.892) mm and the mean refraction-sphere was -12 diopters (range -6 to ~-30) at baseline. A total of 68.6% patients had subfoveal, 23.8% patients had juxtafoveal and 4.0% patients had extrafoveal lesions. The patients were randomised to the following three treatment groups:

- Group I (ranibizumab 0.5mg, dosing regimen driven by "stability" criteria defined as no change in BCVA compared to two preceding monthly evaluations)
- Group II (ranibizumab 0.5mg, dosing regimen driven by "disease activity" criteria defined as vision impairment attributable to intra-or-subretinal fluid or active leakage due to the CNV lesion as assessed by Optical Coherence Tomography (OCT) and/or Fluorescein Tomography (FA))
- Group III (vPDT - patients were allowed to receive ranibizumab treatment as of month 3).

Over the 12 months of the study patients received on average 4.6 injections (range 1-11) in Group I and 3.5 injections (range 1-12) in Group II. In Group II (in which patients received the recommended treatment regimen based on disease activity, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections and 14.7% required 6 to 12 injections over the 12-month study period. In Group II, 62.9% of patients did not require injections in the second 6 months of the study.

Key outcomes from RADIANCE are summarised in Table 15 and Figure 7.

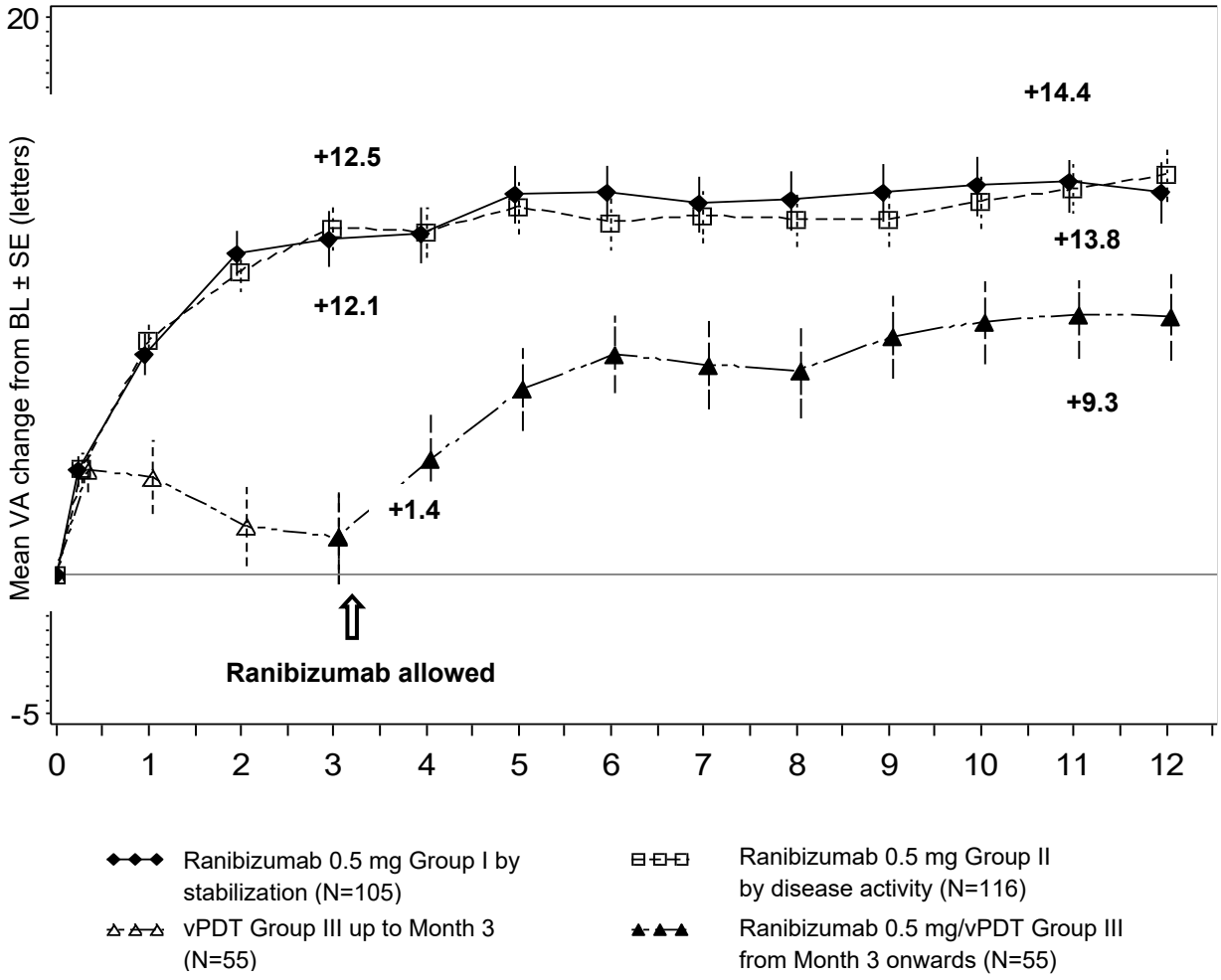
Table 15 Outcomes at Month 3 and Month 12 (RADIANCE)

	Group I Ranibizumab 0.5mg `visual acuity stability` (n=105)	**Group II Ranibizumab 0.5mg `disease activity` (n=116)**	**Group III vPDT* (n=55)**
Month 3			
Mean average BCVA change from Month 1 to Month 3 compared to baseline[a] (letters)	+10.5	+10.6	+2.2
Proportion of patients who gained ≥ 10 letters, or reached ≥ 84 letters in BCVA	61.9 %	65.5 %	27.3 %
≥ 15 letters, or reached ≥ 84 letters in BCVA	38.1 %	43.1 %	14.5 %
Month 12			
Number of injections up to Month 12:			
Mean	4.6	3.5	N/A
Median	4.0	2.0	N/A
Mean average BCVA change from Month 1 to Month 12 compared to baseline (letters)	+12.8	+12.5	N/A
Proportion of patients who gained ≥ 10 letters, or reached ≥ 84 letters in BCVA	69.5 %	69.0 %	N/A
≥ 15 letters, or reached ≥ 84 letters in BCVA	53.3 %	51.7 %	N/A

* Comparative control up to month 3. Patients randomised to vPDT were allowed to receive ranibizumab treatment as of month 3 (in Group III, 38 patients received ranibizumab from month 3 onwards).

a: $p<0.00001$ comparison with vPDT control.

Figure 7 Mean change from Baseline BCVA over time up to Month 12 (RADIANCE)



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

Patients randomised to vPDT were allowed to receive ranibizumab from month 3 onwards.

The improvement of vision was accompanied by a reduction in central retinal thickness.

Patient-reported benefits were observed with the ranibizumab treatment arms over vPDT (p-value <0.05) in terms of improvement in the composite score and several subscales (general vision, near activities, mental health and dependency) of the VFQ-25.

Treatment of ROP in pre-term infants

Study H2301 (RAINBOW)

The clinical safety and efficacy of Lucentis for the treatment of ROP in preterm infants have been assessed based on the 6-month data of the randomised, open-label, 3-arm, parallel group, superiority study H2301 (RAINBOW), which was designed to evaluate ranibizumab 0.2 mg and 0.1 mg given as intravitreal injections in comparison to laser therapy. Eligible patients had to have one of the following retinal findings in each eye:

- Zone I, stage 1+, 2+, 3 or 3+ disease, or
- Zone II, stage 3+ disease, or
- Aggressive posterior (AP)-ROP

In this study, 225 patients were randomised in a 1:1:1 ratio to receive intravitreal ranibizumab 0.2 mg (n=74), 0.1 mg (n=77), or laser therapy (n=74).

Treatment success, as measured by the absence of active ROP and absence of unfavourable structural outcomes in both eyes 24 weeks after the first study treatment, was highest with ranibizumab 0.2 mg (80.0%) compared to laser therapy (66.2%); odds ratio 2.19 (95% confidence interval (CI) [0.9932, 4.8235]). The primary endpoint did not reach statistical significance (see Table 16). The majority of patients treated with ranibizumab 0.2 mg (78.1%) or ranibizumab 0.1 mg (77.6%) did not require re-treatment with ranibizumab.

Table 16 Outcomes at Week 24 (RAINBOW)

	Treatment Success					
Treatment	n/M (%)	95% CI	Comparison	Odds ratio (OR)[a]	95% CI	p-value [b]
Ranibizumab 0.2 mg (N=74)	56/70 (80.0)	(0.6873, 0.8861)	Ranibizumab 0.2 mg vs Laser	2.19	(0.9932, 4.8235)	0.0254
Ranibizumab 0.1 mg (N=77)	57/76 (75.0)	(0.6374, 0.8423)	Ranibizumab 0.1 mg vs Laser	1.57	(0.7604, 3.2587)	0.1118*
Laser therapy (N=74)	45/68 (66.2)	(0.5368, 0.7721)				

CI= confidence interval, M= total number of patients with non-missing value on primary efficacy outcome (including imputed values), n= number of patients with absence of active ROP and absence of unfavourable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values).
If a patient died or switched study treatment before or at Week 24, then the patient was considered as having active ROP and unfavourable structural outcomes at Week 24

[a] Odds ratio is calculated by using Cochran-Mantel-Haenszel test with ROP Zone at baseline (Zone I and II; per CRF) as stratum factor.

[b] p-value for pairwise comparison is one-sided. For the primary endpoint the pre-specified significance level for the one sided p-value was 0.025.

*p-value for pairwise comparison is one-sided without adjusting for multiplicity.

During the 24 weeks of the study, fewer patients in the ranibizumab 0.2 mg and 0.1mg group switched to another treatment modality due to lack of response compared with the laser group (14.9% and 16.9% vs. 24.3%). Unfavourable structural outcomes were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4%) and 0.1mg (5 patients, 6.7%) compared with laser therapy (7 patients, 10.1%). The recurrence of ROP (as measured by the need for any post-baseline intervention at or before 24 weeks) was 31.1%, 31.2% and 18.9% in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively. At week 40, these percentages were 31.1%, 33.8% and 20.4% in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively.

Study H2301E1 (RAINBOW Extension)

The long-term efficacy and safety of ranibizumab 0.2 mg and 0.1 mg for the treatment of ROP in preterm infants have been assessed in study H2301E1 (RAINBOW extension), an extension study of study H2301 (RAINBOW), following patients to their 5th birthday.

The primary objective was to evaluate visual function at the patient's 5th birthday visit by assessing visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) with Lea symbols optotypes in the better-seeing eye (the eye with the higher ETDRS score).

Of the 225 patients initially randomised in the H2301 core study, 180 were enrolled into the H2301E1 extension study. 124 patients had visual acuity data from the 5th birthday visit available for analysis.

Visual acuity data from the patients' 5th birthday visit is descriptive in nature and limited by the number of patients with no available data.

Table 17 Visual acuity outcomes in the better seeing eye[1] at the patient's 5th birthday visit (RAINBOW Extension)

Treatment[2]	**Ranibizumab 0.2 mg**	**Ranibizumab 0.1 mg**	**Laser**
Number of subjects enrolled in extension study[3]	61	65	54
Number of subjects contributing to analysis	45	43	36
Mean ETDRS score[3] (SE)	66.8 (1.8)	64.6 (2.0)	62.1 (2.4)
Visual acuity category – n (%[4])			
≥1 to ≤34 letters	1 (1.6)	3 (4.6)	2 (3.7)
≥35 to ≤70 letters	24 (39.3)	25 (38.5)	23 (42.6)
≥71 letters	20 (32.8)	15 (23.1)	11 (20.4)
Not available	16 (26.2)	22 (33.8)	18 (33.3)

[1] The better-seeing eye is the eye with a higher ETDRS letter score at the 5th birthday visit. If both eyes have the same ETDRS letter score, then the right eye is assigned as the better-seeing eye.

[2] Initial study treatment received at baseline in the core study H2301

[3] ETDRS letter score measured using Lea Symbols charts at an initial test distance of 3 metres. Visual acuity was tested using the child's current refractive index, e.g. child wearing their prescription glasses/ contact lenses as applicable. Mean scores were calculated from the 45, 43 and 36 patients with available data in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser arms, respectively.

[4] Percentage out of subjects enrolled in extension study

ETDRS: Early Treatment Diabetic Retinopathy Study; SE: Standard Error

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following monthly intravitreal administration of Lucentis to patients with neovascular AMD, serum concentrations of ranibizumab were generally low. 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. Maximum levels (Cmax) were 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). Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Distribution and Elimination

Neovascular AMD

Based on analysis of population pharmacokinetics and the disappearance of ranibizumab from serum for patients with neovascular AMD 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.

Paediatric population (preterm infants with ROP)

Following intravitreal administration of Lucentis to preterm infants with ROP at a dose of 0.1 mg or 0.2 mg per eye, serum ranibizumab concentrations were higher than those observed in neovascular AMD adult patients receiving 0.5 mg in one eye. Based on a population pharmacokinetic analysis, the differences in C_{max} and AUC_{inf} were approximately 8-fold and 5-fold higher for 0.1 mg dose, and 16-fold and 12-fold higher for 0.2 mg dose, respectively. The apparent systemic half-life was approximately 6 days. In this analysis, there was no relationship determined between systemic ranibizumab concentrations and systemic VEGF concentrations. The clinical significance of these results is uncertain.

Renal impairment

No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (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]). In RVO patients, 48.2% (253 of 525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies were performed with ranibizumab.

Carcinogenicity

No carcinogenicity studies were performed with ranibizumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Vial

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.

Prior to usage, the unopened tray may be kept at room temperature (25°C) for up to 24 hours.

Pre-filled syringe pack

Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.

Keep the pre-filled syringe in its sealed tray in the carton in order to protect from light. Prior to usage, the unopened tray may be kept at room temperature (25°C) for up to 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Vial pack*

Lucentis is supplied as 0.23 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 vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Vial and filter needle pack

0.23 mL Lucentis solution for injection in a glass vial (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial and one filter needle for withdrawal of the vial content.

Vial only*

Lucentis is supplied as 0.23 mL solution for injection in glass vials (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial.

Pre-filled syringe pack

Lucentis is supplied as 0.165 mL sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap and a Luer Lock adapter. The pre-filled syringe has a plunger rod and a finger grip, and is packed in a sealed tray. One pack contains one pre-filled syringe. Each pre-filled syringe contains 1.65 mg of ranibizumab in 0.165mL solution.

*Not all presentations may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Active ingredient: Ranibizumab

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 8a and 8b.

Figure 8a The amino acid sequence of the heavy chain of ranibizumab

```
          10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY
          70        80        90       100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT
         130       140       150       160       170       180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
         190       200       210       220       230
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
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Complementarity-determining regions (CDR) are underlined.

Figure 8b The amino acid sequence of the light chain of ranibizumab

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          10        20        30        40        50        60
DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
          70        80        90       100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
         130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
         190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
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Complementarity-determining regions (CDR) are underlined.

Chemical name: Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ-chain

Molecular weight: Approximately 48kDa

CAS number

347396-82-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
Level 25, Victoria Cross Tower
155 Miller Street
North Sydney NSW 2060
Telephone 1 800 671 203
Web site: www.novartis.com.au

9 DATE OF FIRST APPROVAL

27 February 2007

10 DATE OF REVISION

17 November 2026

® = Registered trademark

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address update

Internal document code: luc171126i based on CDS dated 31-Jan-2023