AUSTRALIAN PRODUCT INFORMATION

RANIVIZ (RANIBIZUMAB) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Ranibizumab (rbe).

Raniviz is a biosimilar medicine to Lucentis. The evidence for comparability supports the use of Raniviz for the listed indications.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Raniviz is supplied in a vial.

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

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

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

3 PHARMACEUTICAL FORM

Solution for injection

The solution is sterile, clear, colourless to pale yellow, aqueous and preservative free.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Raniviz (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,
- 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).

Not recommended for use in preterm infants.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage regimen

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

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

The recommended dose for Raniviz 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).

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, Raniviz 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).

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

Ranibizumab has been used concomitantly with laser photocoagulation in clinical studies (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). When given on the same day, Raniviz should be administered at least 30 minutes after laser photocoagulation. Raniviz can be administered in patients who have received previous laser photocoagulation.

Ranibizumab and Visudyne photodynamic therapy in CNV secondary to PM

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

Method of Administration

As with all medicinal products for parenteral use, Raniviz 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 Raniviz, 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 center of the globe. The injection volume of 0.05 mL is then delivered; the scleral site should be rotated for subsequent injections.

Instructions for Use and Handling

Raniviz contains no antimicrobial agent and is for single use in one patient only. After injection, any residue should be discarded. (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). The vial is sterile.

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.

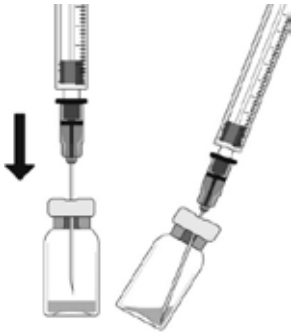
For preparation and intravitreal injection, the following single-use medical devices are needed:

- 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 with Raniviz.

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

A.

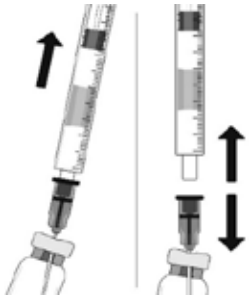


1. Before withdrawal, remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

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.

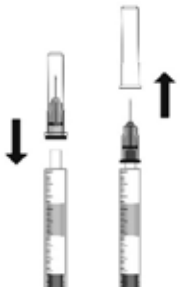
B.



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).

   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.

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 ranibizumab, 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 ranibizumab. 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 ranibizumab (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 ranibizumab (including same day administration) do not suggest an increase of systemic adverse effects compared 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 ranibizumab treatment is appropriate and the benefit outweighs the potential risk.

Immunogenicity

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

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

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.

Patient populations with limited data

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Ranibizumab 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 Ranibizumab 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

Ranibizumab 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 ranibizumab in children and adolescents 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).

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 ranibizumab was not affected by concomitant treatment with thiazolidinediones (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials).

For the adjunctive use of laser photocoagulation and ranibizumab 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 ranibizumab 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 embryofetotoxic. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

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

As the embryofetal development investigations were performed in healthy pregnant animals and disease (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 Raniviz. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Raniviz and any potential adverse effects on the breastfed child from ranibizumab.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The ranibizumab 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 ranibizumab 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 ranibizumab-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 ranibizumab 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 ranibizumab. The adverse event rates for the 0.3 mg dose were comparable to those for 0.5 mg.

DME population

The safety of ranibizumab 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 below; 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 ranibizumab 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 ranibizumab.

RVO population

The safety of ranibizumab 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 ranibizumab 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 ranibizumab.

Pathologic Myopia (PM) population

The safety of ranibizumab 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.

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 ranibizumab remain in accord with the findings observed in clinical trial setting.

Comparative Safety of Raniviz with Lucentis®

The comparative safety of Raniviz and Lucentis® was investigated in FYB201-C2015-01-P3, a multinational phase III study, in which 477 patients with subfoveal neovascular age-related macular degeneration (nAMD) received a once-monthly administration of either Raniviz (238 patients) or Lucentis® (239 patients) via intravitreal (IVT) injection over a period of 48 weeks.

In general, Raniviz was well tolerated and showed a similar safety profile compared to the comparator drug Lucentis®.

The number and percentage of patients experiencing Treatment-Emergent Adverse Events (TEAEs) or specific subcategories of TEAEs were balanced between both treatment groups throughout the study and no clinically relevant differences were observed. At least 1 TEAE was recorded in 154 patients (64.7%; 154/238 patients experiencing a total of 509 TEAEs) in the Raniviz treatment group and in 167 patients (69.9%; 167/239 patients experiencing a total of 597 TEAEs) in the Lucentis® treatment group. Most TEAEs were mild or moderate; severe TEAEs were reported in 11 patients (4.6%) treated with Raniviz and in 22 patients (9.2%) treated with Lucentis®.

Three patients died during the study; 2 patients in the Raniviz treatment group (Preferred Term [PT]: Chronic obstructive pulmonary disease and Cardiopulmonary failure) and 1 patient (PT: Respiratory failure) in the Lucentis® treatment group. The Investigators judged these fatal SAEs as not related to study drug or to the IVT procedure.

TEAEs suspected to be related to study medication were recorded in 20 patients (8.4%) treated with Raniviz and in 25 patients (10.5 %) treated with Lucentis®.

A total of 435 local TEAEs occurring in the study eye were recorded in 183 patients (Raniviz: 221 local TEAEs in 86 patients; Lucentis®: 214 local TEAEs in 97 patients).

Seventy-five serious TEAEs (SAEs) were recorded in 51 patients (Raniviz: 19 patients; Lucentis®: 32 patients), including 5 local SAEs recorded in the study eye (Raniviz: 2 patients with PTs Endophthalmitis and Iridocyclitis; Lucentis®: 3 patients with PTs Endophthalmitis in 2 patients, and Cataract in 1 patient). The local SAEs were determined to be related to study drug or to the IVT procedure or to both. All patients recovered from the local SAEs.

No new signals were detected in the study. There were no clinically meaningful differences between treatments in terms of incidence or type of Treatment-Emergent SAEs.

Any TEAEs that occurred in ≥2% of all patients who received Raniviz or Lucentis® are outlined in Table 2 below.

Table 2 Overall incidence of Treatment-Emergent Adverse Events Occurring in ≥2% of subjects in Phase III Study Safety Analysis Set (Study FYB201-C2015-01-P3)

MedDRA System Organ Class	Raniviz (N = 238)		Lucentis (N = 239)		Total (N = 477)	
Preferred Term	n	%	n	%	n	%
Any	154	64.7%	167	69.9%	321	67.3%
Eye disorders						
Overall	100	42.0%	100	41.8%	200	41.9%
Neovascular age-related macular degeneration	19	8.0%	22	9.2%	41	8.6%
Conjunctival haemorrhage	14	5.9%	19	7.9%	33	6.9%
Punctate keratitis	8	3.4%	12	5.0%	20	4.2%
Visual acuity reduced	6	2.5%	11	4.6%	17	3.6%
Eye pain	9	3.8%	6	2.5%	15	3.1%
Cataract	1	0.4%	11	4.6%	12	2.5%
Lacrimation increased	9	3.8%	2	0.8%	11	2.3%
Choroidal neovascularisation	6	2.5%	4	1.7%	10	2.1%
Conjunctival hyperaemia	4	1.7%	6	2.5%	10	2.1%
Retinal haemorrhage	7	2.9%	3	1.3%	10	2.1%
Vitreous detachment	6	2.5%	4	1.7%	10	2.1%
Infections and infestations						
Overall	55	23.1%	57	23.8%	112	23.5%
Nasopharyngitis	12	5.0%	16	6.7%	28	5.9%
Bronchitis	9	3.8%	5	2.1%	14	2.9%
Upper respiratory tract infection	8	3.4%	6	2.5%	14	2.9%
Conjunctivitis	9	3.8%	2	0.8%	11	2.3%
Investigations						
Overall	32	13.4%	39	16.3%	71	14.9%
Intraocular pressure increased	11	4.6%	12	5.0%	23	4.8%
C-reactive protein increased	10	4.2%	5	2.1%	15	3.1%
Musculoskeletal and connective tissue disorders						
Overall	17	7.1%	29	12.1%	46	9.6%
Back pain	5	2.1%	8	3.3%	13	2.7%
Nervous system disorders						
Overall	10	4.2%	26	10.9%	36	7.5%
Headache	4	1.7%	9	3.8%	13	2.7%
Gastrointestinal disorders						
Overall	13	5.5%	22	9.2%	35	7.3%
Vascular disorders						
Overall	10	4.2%	23	9.6%	33	6.9%
Hypertension	3	1.3%	14	5.9%	17	3.6%
Injury, poisoning and procedural complications	13	5.5%	18	7.5%	31	6.5%
General disorders and administration site conditions	17	7.1%	13	5.4%	30	6.3%

MedDRA System Organ Class Preferred Term	Raniviz (N = 238) n	 %	Lucentis (N = 239) n	 %	Total (N = 477) n	 %
Respiratory, thoracic and mediastinal disorders						
Overall	15	6.3%	9	3.8%	24	5.0%
Cough	5	2.1%	5	2.1%	10	2.1%
Cardiac disorders	8	3.4%	10	4.2%	18	3.8%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	6	2.5%	7	2.9%	13	2.7%
Blood and lymphatic system disorders	8	3.4%	4	1.7%	12	2.5%
Renal and urinary disorders	5	2.1%	6	2.5%	11	2.3%
Skin and subcutaneous tissue disorders	6	2.5%	4	1.7%	10	2.1%

N = total number of patients, n = number of patients with at least one AE of specified AE type

The most commonly affected SOCs in both treatment groups in at least 2.0% of patients in the SAF were Eye disorders (see below for more details), Infections and infestations (Nasopharyngitis, Bronchitis, Upper respiratory tract infection, Conjunctivitis), Investigations (Intraocular pressure increased, and C-reactive protein increased) and Musculoskeletal and connective tissue disorders (Back pain). There were no clinically relevant differences between both treatment groups.

SOC Eye disorders

At least 1 TEAE within this SOC was observed for 100 patients (42.0%) in the Raniviz treatment group and also for 100 patients (41.8%) in the Lucentis® treatment group. The most commonly affected PTs were nAMD (observed for 19 patients (8.0%) in the Raniviz treatment group and for 22 patients (9.2%) in the Lucentis® treatment group), Conjunctival haemorrhage (observed for 14 patients (5.9%) in the Raniviz treatment group and for 19 patients (7.9%) in the Lucentis® treatment group), and Punctate keratitis (observed for 8 patients (3.4%) in the Raniviz treatment group and for 12 patients (5.0%) in the Lucentis® treatment group).

Comparative Safety of Raniviz and Lucentis® IVT Injection Site Reactions and Immunogenicity

TEAEs related to the IVT injection procedure were most frequently recorded in SOC Eye disorders (97 patients; 20.3%). The number and percentage of patients for whom TEAEs related to the IVT injection procedure were reported was balanced between both treatment groups and no clinically relevant differences were observed.

Immunogenicity has been analysed at months 1, 3, 6, and 12 for the whole study population. The immunogenicity profile of Raniviz and Lucentis® was comparable: The number of patients with positive ADAs in blood serum was low. A total of 28 patients [Raniviz and Lucentis® 14 patients each] had at least one confirmed positive ADA assessment after the first administration of study treatment. ADA titres determined for patients with confirmed positive ADAs were balanced between the two treatment groups. No nAbs were detected up to Week 24; one positive nAb sample was detected up to Week 48 (Raniviz treatment group).

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 ranibizumab) 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) ranibizumab 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 VEGFR1 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

Clinical Trials with Lucentis®

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of ranibizumab 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 ranibizumab 0.3 mg or 0.5 mg or sham injections. A total of 716 patients was enrolled in this study (sham, 238; ranibizumab 0.3 mg, 238; ranibizumab 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.

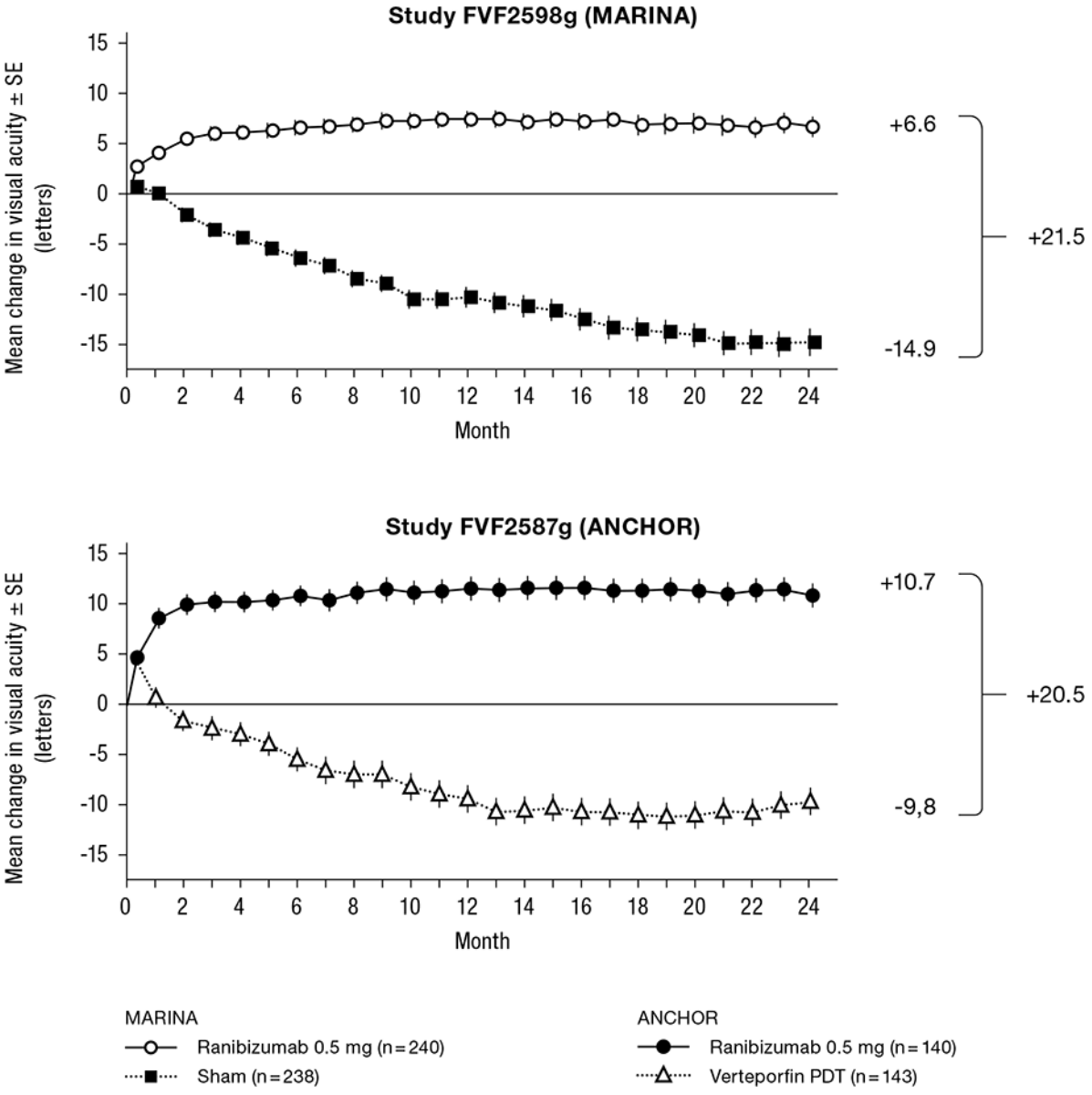
In the 24-month study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of ranibizumab 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of ranibizumab 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Verteporfin (or sham) PDT was given with the initial ranibizumab (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 (ranibizumab 0.3 mg, 140; ranibizumab 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 ranibizumab injection control procedure involved anesthetising the eye in a manner identical to a ranibizumab 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 3 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA)

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

[a] p<0.01.

Table 4 Outcomes at Month 12 and 24 in study FVF2587g (ANCHOR)

Outcome measure	Month	Verteporfin PDT (n=143)	Ranibizumab 0.3 mg (n=140)	Ranibizumab 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 ranibizumab 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 ranibizumab versus 2.3 to 2.6 DA for the control arms.

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

In MARINA, at month 12, patients treated with ranibizumab 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 ranibizumab 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, ranibizumab 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, ranibizumab 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 ranibizumab-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 ranibizumab over the sham control at month 24 was greater than that at month 12.

In ANCHOR, at month 12, patients treated with ranibizumab 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 ranibizumab 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, ranibizumab 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, ranibizumab 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 nonocular 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

ranibizumab in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of month 12. Patients received ranibizumab 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 (ranibizumab 0.3 mg, 60; ranibizumab 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with ranibizumab 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 ranibizumab lost the initial visual acuity gain, returning to baseline at month 12. In PIER, almost all ranibizumab-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 ranibizumab 0.5 mg monotherapy vs. ranibizumab 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 ranibizumab injections, plus sham or active vPDT given with the first ranibizumab injection only. Following treatment initiation, ranibizumab monotherapy and ranibizumab 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 ranibizumab administered with vPDT was superior to ranibizumab 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 ranibizumab with vPDT received on average 2.3 ranibizumab injections less than patients administered ranibizumab monotherapy (5.1 vs. 7.4 injections).

Superiority of ranibizumab with vPDT compared to ranibizumab 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 ranibizumab with vPDT received on average 4.2 ranibizumab injections less than patients administered ranibizumab monotherapy (8.1 vs. 12.3 injections).

Treatment of Visual Impairment Due to DME

The efficacy and safety of ranibizumab 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 5 and 6 and Figure 2.

Table 5 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 (2)	Difference in LS means	5.4	4.9	
(2)	95% CI for difference	(3.5, 7.4)	(2.8, 7.0)	
	p-value (3)	< .0001	< .0001	

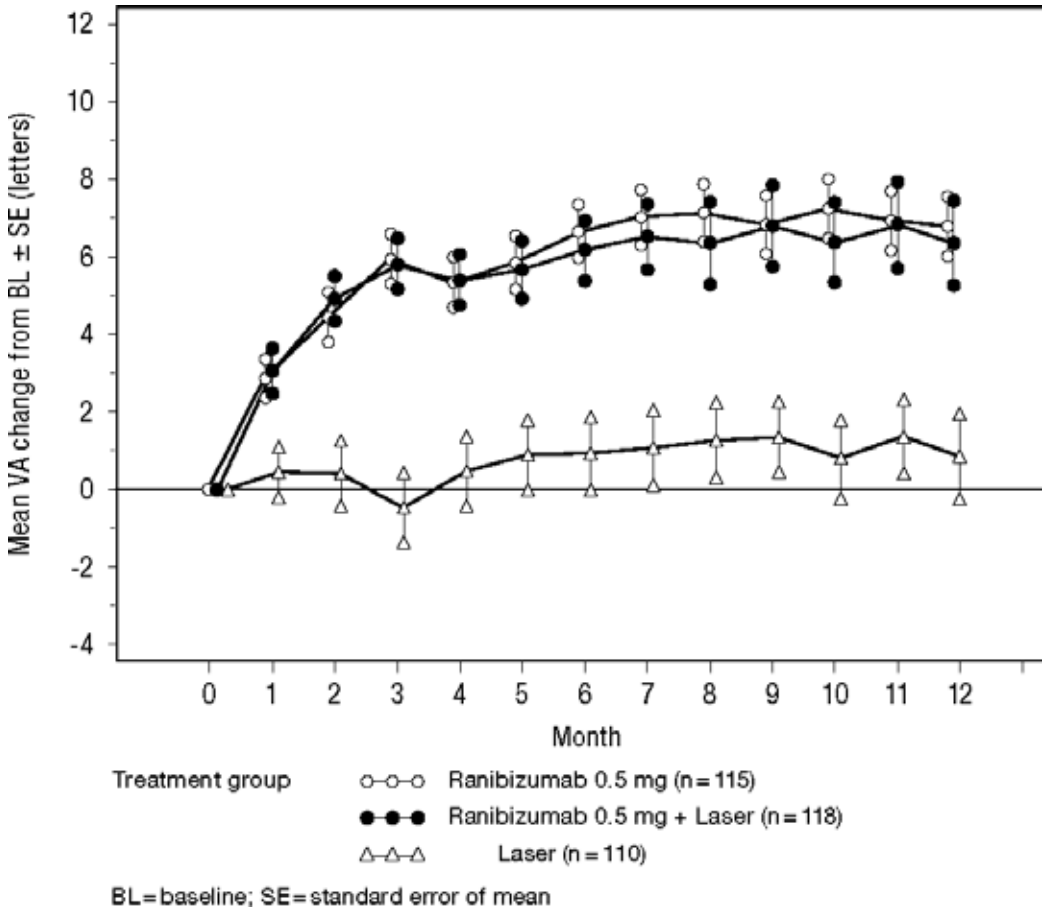
− n is the number of patients with a value for both baseline and average Month 1 to Month 12.
− Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
− Two-sided 95% confidence intervals (CI) are based on the t-distribution.
− Differences 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 6 Secondary Efficacy Outcomes at Month 12 in study D2301 (RESTORE) Visual acuity of the study eye (letters): Categorized change from baseline at Month 12 (FAS / LOCF)

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

− N is the number of patients with a value at both baseline and the Month 12 visit.
− [1] specified gain, or BCVA of 84 letters or more.

Figure 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 7.

Table 7 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 ranibizumab 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 8 and Figure 3.

Table 8 Overall Population, treatment comparisons key secondary efficacy variables; FAS (LOCF) of study D2201 (RESOLVE)

Variable	Ran 6mg/mL6 (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

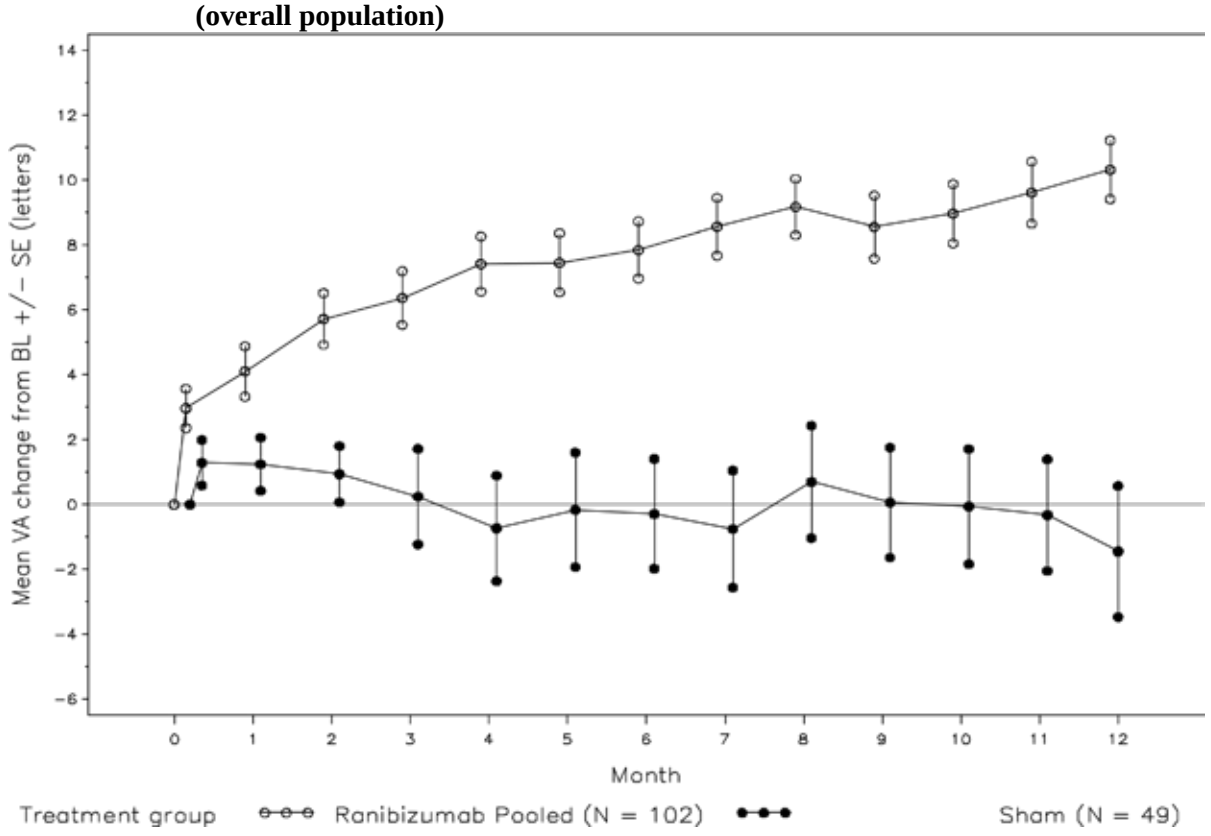
[1]CMH test, stratified: 6 mg/mL vs sham p=0.0001; 10 mg/mL vs sham p=0.0037; and pooled p=0.0001

[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 9.

Table 9 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 ranibizumab 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 10 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 ranibizumab 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 ranibizumab are not clinically significant. Key outcomes from BRAVO and CRUISE are summarised in Tables 11 and 12 and Figures 4 and 5.

Table 11 Outcomes at Month 6 and 12 (BRAVO)

	Sham/ Ranibizumab 0.5 mg (n=130)	**Ranibizumab 0.3 mg (n=134)**	**Ranibizumab 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)

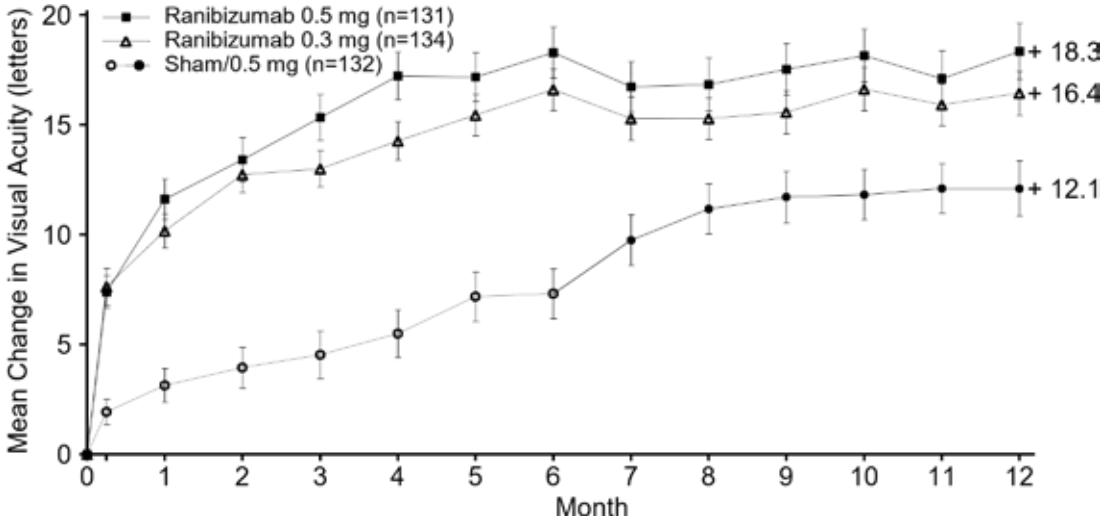
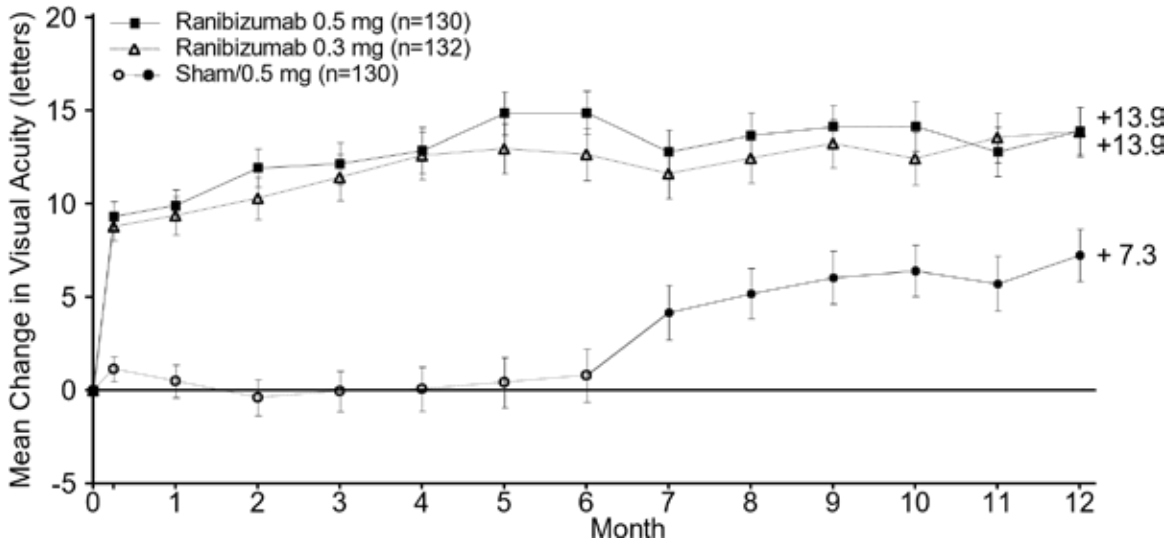


Table 12 Outcomes at Month 6 and 12 (CRUISE)

	Sham/ Ranibizumab 0.5 mg (n=130)	**Ranibizumab 0.3 mg (n=132)**	**Ranibizumab 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 ranibizumab 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 ranibizumab 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 ranibizumab 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 13.

Table 13 Outcomes at Month 6 (BRIGHTER) and Month 24 (BRIGHTER and CRYSTAL)

	BRIGHTER			**CRYSTAL**
	Ranibizumab 0.5 mg N=180	**Ranibizumab 0.5 mg + Laser N=178**	**Laser* N=90**	**Ranibizumab 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: ranibizumab 0.5 mg vs Laser and ranibizumab 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 ranibizumab safety profile.

Treatment of visual impairment due to CNV

Study G2301 (MINERVA)

The clinical safety and efficacy of ranibizumab 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 14 and 15 and Figure 6.

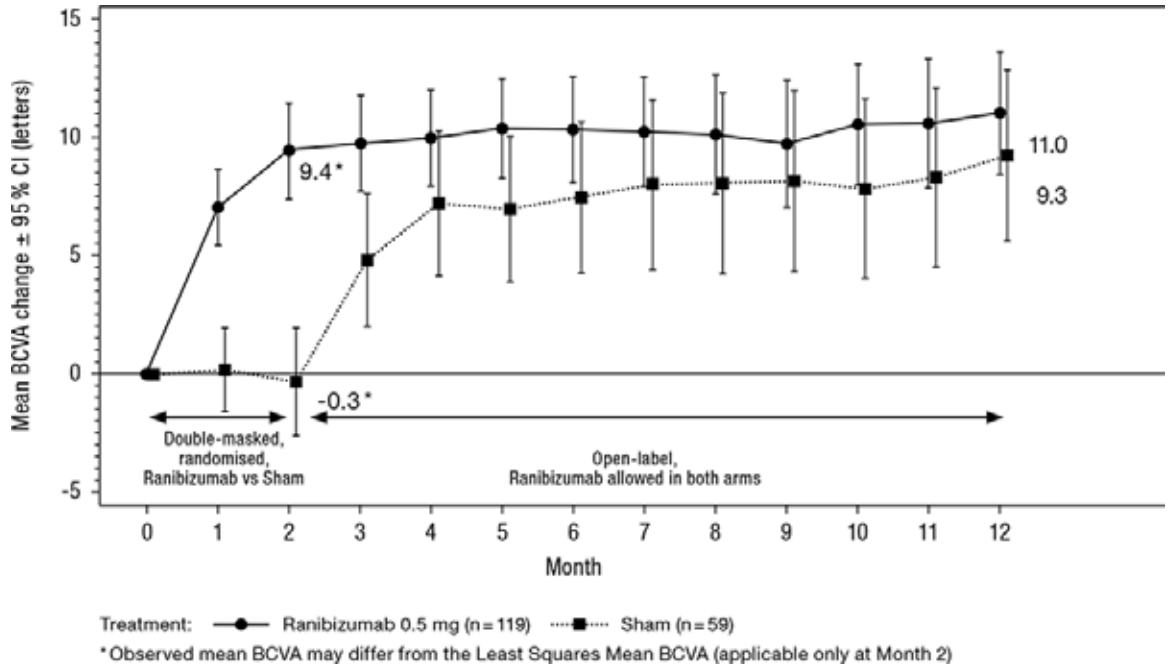
Table 14 Outcomes at Month 2 (MINERVA)

	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 15 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 12month 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 ranibizumab 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 16 and Figure 7.

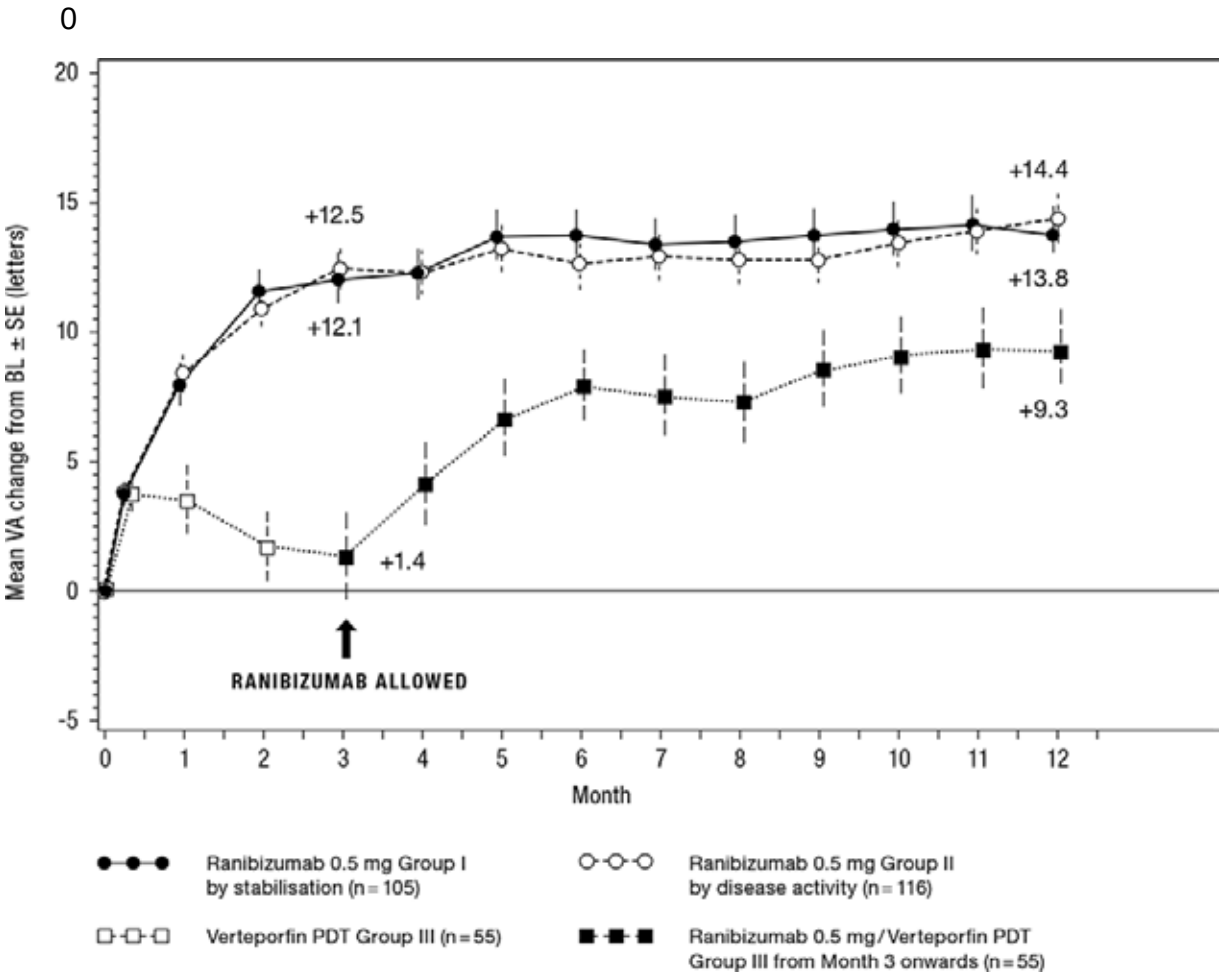
Table 16 Outcomes at Month 3 and Month 12 (RADIANCE)

	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.

Comparative Efficacy of Raniviz and Lucentis®

Study FYB201-C2015-01-P3 consisted of 477 patients with a mean age 75.5 years suffering from newly diagnosed, angiographically documented, subfoveal nAMD. The objective of this study was to compare the efficacy, safety /tolerability and immunogenicity of Raniviz and Lucentis® up to and including 48 weeks of treatment. Patients were randomised in a 1:1 ratio to receive either Raniviz 0.5 mg (n=238) or Lucentis® 0.5 mg (n=239) once-monthly via IVT injection.

The primary endpoint of the study was the change from baseline in Best Corrected Visual Acuity (BCVA) by Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 2 months (8 weeks) of treatment. The hypothesis of biosimilarity of Raniviz and Lucentis was tested with a two-sided equivalence test, with an equivalence margin in BCVA of 3 ETDRS letters. To declare the equivalence

between the treatment groups, the 95% confidence interval (CI) for the treatment difference between Raniviz and Lucentis treatment groups should be contained within the pre-defined equivalence margin of [-3.5; 3.5] ETDRS letters.

Secondary objectives were to evaluate efficacy using relevant functional and morphological efficacy endpoints other than BCVA at Weeks 8, and to evaluate safety /tolerability, and immunogenicity of Raniviz compared to Lucentis®.

A total number of 429 subjects with BCVA assessments at baseline and at Week 8 were evaluated (Raniviz, N=215; Lucentis®, N=214). Equivalence of Raniviz and Lucentis® was demonstrated. The median change from baseline BCVA at Week 8 reached 5.0 ETDRS letters for Raniviz and 6.0 ETDRS letters for Lucentis®. The mean difference between both treatments was -0.7 ETDRS letters with a 95% CI of [-2.3; 0.9] ETDRS letters, which was completely contained within the predefined equivalence margin.

Comparability of Raniviz to Lucentis® was demonstrated for all functional (BCVA over time and up to the end of the observation period) and morphological assessment parameters (retinal oedema and thickening, vascular leakage). Results were consistent over the entire observation period. Improvement of macula function demonstrated after 8 weeks was maintained until the end of the observation period at Week 48.

In conclusion, both IVT treatments improved functional and morphological signs of nAMD with no clinically remarkably or statistically significant differences between all efficacy variables, showing similar results for Raniviz and Lucentis®. The primary efficacy endpoint and all secondary efficacy endpoints demonstrate biosimilarity of Raniviz with Lucentis®.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following monthly intravitreal administration of ranibizumab 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 ranibizumab 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 (C_{max}) 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 halflife of ranibizumab is approximately 9 days. Serum ranibizumab exposure is predicted to be approximately 90,000-fold lower than vitreal ranibizumab exposure.

Renal impairment

No formal studies have been conducted to examine the pharmacokinetics of ranibizumab 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 ranibizumab 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

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 vial in the carton may be kept at room temperature (25°C) for up to 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Raniviz 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. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

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
```

Complementarity-determining regions (CDR) are underlined.

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

```
          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
```

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

Actor Pharmaceuticals Pty Ltd

ABN 69 151 192 602

Level 3, 17 Randle Street

Surry Hills, NSW 2010

Telephone: 1800 322 690

Website: https://actorpharma.com.au/

9 DATE OF FIRST APPROVAL

10 DATE OF REVISION