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1 PRODUCT NAME

BYOOVIZ™ Ranibizumab 10 mg/mL solution for injection

BYOOVIZ™ is a biosimilar medicine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

One mL contains 10 mg ranibizumab.

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

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.

BYOOVIZ™ is a biosimilar medicine. The prescribing physician should be involved in any decision regarding interchangeability. For further information see:

www.medsafe.govt.nz/profs/RIss/Biosimilars.asp. For more information on biosimilarity of BYOOVIZ™ to Lucentis, see section 5.1, Clinical efficacy and safety.

3 PHARMACEUTICAL FORM

Solution for injection.

BYOOVIZ™ is supplied in a vial.

Sterile, clear, colourless to pale yellow and preservative-free aqueous solution with pH range of 5.5 ±0.3. The osmolality of the solution is 309 ± 69 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BYOOVIZ™ is indicated for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD),
- the treatment of visual impairment due to diabetic macular oedema (DME),
- the treatment of proliferative diabetic retinopathy (PDR),
- the treatment of visual impairment due to choroidal neovascularization (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 (branch RVO or central RVO).

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4.2 Dose and method of administration

Dosage regimen

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

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

The recommended dose for BYOOVIZ™ 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 not be shorter than one month.

The recommended maximal dose (0.5 mg) should not be exceeded. Post-injection monitoring is recommended (see Section 4.4 Special warning 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 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 anatomic parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, BYOOVIZ™ 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, Clinical efficacy and safety).

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 PM, many

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patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see section 5.1, Clinical efficacy and safety).

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, Clinical efficacy and safety). When given on the same day, BYOOVIZ™ should be administered at least 30 minutes after laser photocoagulation. BYOOVIZ™ 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, BYOOVIZ™ should be inspected visually for particulate matter and discoloration prior to administration.

The injection procedure should be carried out under aseptic conditions, which includes 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 for hypersensitivity reactions should be carefully evaluated 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 BYOOVIZ™, see **Instructions for Use and Handling**.

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

Instructions for Use and Handling

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.

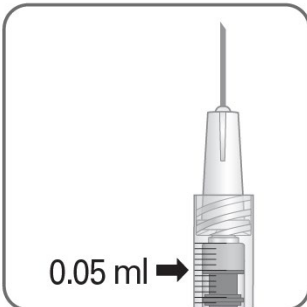
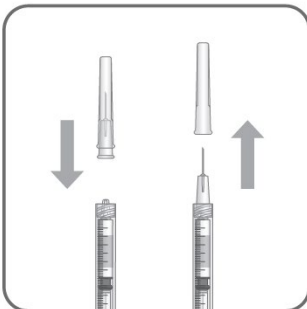
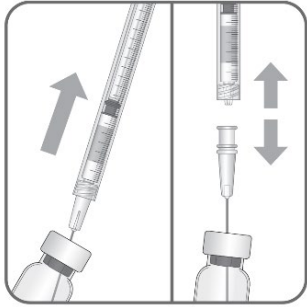
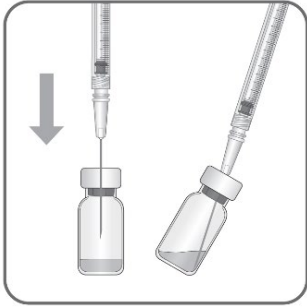
For preparation and intravitreal injection, the following single use medical devices are needed:

- a 5 micrometer filter needle (18G x 1½ inch)
- a 1 mL sterile syringe
- an injection needle (30G x ½ inch)

These medical devices are not supplied in the vial-only BYOOVIZ™ pack that contains only the vial. The 1 mL sterile syringe is not included in the BYOOVIZ™ pack.

To prepare BYOOVIZ™ for intravitreal administration, please adhere to the following instructions:

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1. Before withdrawal, remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).
2. Attach a 5 micrometer filter needle (18 G x 1½) onto the 1 mL syringe using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial.
3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
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.

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.

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

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

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

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.

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

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Special populations

Renal impairment

Dose adjustment is not needed in patients with renal impairment (see section 5.2 Pharmacokinetic properties).

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.

Paediatric patients (below 18 years of age)

Ranibizumab is not recommended for use in children and adolescents due to a lack of 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, Clinical efficacy and safety, Paediatric patients).

Geriatric patients (65 years and above)

No dose adjustment is required in the elderly.

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 and iatrogenic traumatic cataract (see section 4.8 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 monitored during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab (see section 4.8 Undesirable effects). Sustained IOP increases have also been reported. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately. 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 ≥ 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 to with unilateral treatment.

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Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors. 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.

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.

There is limited experience with treatment of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been performed (see section 5.1, Clinical efficacy and safety).

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, Clinical efficacy and safety).

For the adjunctive use of laser photocoagulation and Ranibizumab in DME and BRVO, see section 5.1, Clinical efficacy and safety and see section 4.2 Dose and method of administration.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment.

Pregnancy

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

In pregnant monkeys, intravitreal ranibizumab treatment resulting in maximal systemic exposures 0.9-7-fold a worst case clinical exposure did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, although, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryo-/foetotoxic.

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, a case was

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reported that ranibizumab was detectable in foetus serum as well as in maternal serum with a high concentration. This is possibly due to the anti-ranibizumab antibody containing Fc region be used as 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.

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

Breast-feeding

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 precautionary measure, breast-feeding is not recommended during the use of ranibizumab. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ranibizumab and any potential adverse effects on the breastfed child from ranibizumab.

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.

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 Undesirable effects). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

4.8 Undesirable effects

Summary of the safety profile

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 recommended dose of 0.5 mg.

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).

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The adverse events listed below 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 as defined in Clinical studies, or verteporfin photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD studies. These 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.

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 efficacy and safety).

The event of urinary tract infection, in the common frequency category, met the criteria for the Table 1 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 was studied for up to 24 months in Protocol S, including 191 patients treated with ranibizumab 0.5 mg (see section 5.1, Clinical efficacy and safety). 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). 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

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ranibizumab-treated patients with visual impairment due to CNV (see section 5.1, Clinical efficacy and safety). The safety profile in these patients was consistent with that seen in previous clinical trials with ranibizumab.

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, Clinical efficacy and safety). 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 drug reactions from clinical trials

The adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions 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 III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 1 Adverse drug reactions 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 pruritus.
Common	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate 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

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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
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Allergic reactions (rash, urticaria, pruritus, erythema)
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Investigations	
Very common	Intraocular pressure increased

*observed only in the DME population

A meta-analysis of pooled safety data from completed, randomized, 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 patient years; 20 events in 936 patients) compared to sham/laser treatment (0.27/100 patient years; 2 events in 58 patients); HR 8.07 (95% CI 1.88, 34.74). The relationship to ranibizumab remains unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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 and post-marketing data. Adverse reactions most frequently associated with these reported cases were intraocular pressure increased and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineovascularisation agents, ATC code: S01LA04

5.1 Pharmacodynamic properties

Mechanism of action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human

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vascular endothelial growth factor A (VEGF-A). It binds with high affinity to the VEGF-A isoforms (e.g. VEGF110, VEGF121 and VEGF165), thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2.

Pharmacodynamic effects

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 PM or to the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

Clinical efficacy and safety

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 AMD (FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)). A total of 1,323 patients (879 active and 444 control) were 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 were 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 were 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 anaesthetising 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 Figure 1.

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.

Key outcomes are summarised in Tables 2, 3 and Figure 1.

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Table 2 Outcomes at month 12 and 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 (5) ^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 (%) ^a	Month 12	11 (4.6%)	59 (24.8%)	81 (33.8%)
	Month 24	9 (3.8%)	62 (26.1%)	80 (33.3%)
Mean change in visual acuity (letters) (SD) ^a	Month 12	-10.5 (16.6)	+6.5 (12.7)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+5.4 (15.2)	+6.6 (16.5)

^a $p < 0.01$.

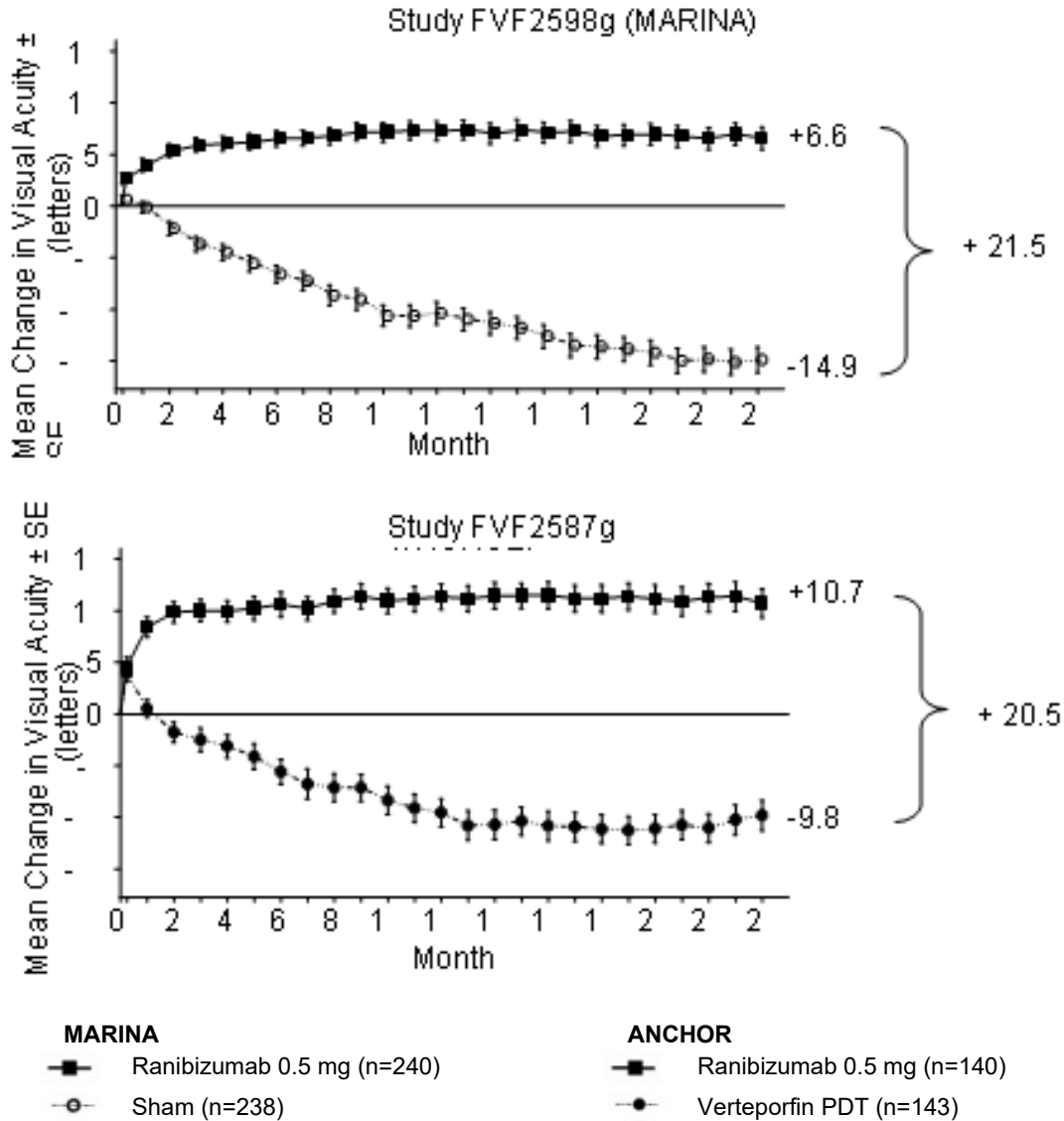
Table 3 Outcomes at month 12 and 24 in study FVF2587g (ANCHOR)

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 (5) ^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 (%) ^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 $p < 0.01$.

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



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

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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 multicenter 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 2,378 patients were randomized 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 ischemic 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 3 consecutive doses, followed by a dose administered

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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 month 12 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, randomized, double-masked, multicenter 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 randomized, 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) were 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 edema was randomised to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation ($n=116$), combined ranibizumab 0.5 mg and laser photocoagulation

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(n=118), or sham injection and laser photocoagulation monotherapy (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments. The treatment was reinitiated when there was a reduction in best corrected visual acuity (BCVA) due to DME progression. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before injection of ranibizumab, and then as needed based on Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.

Key outcomes are summarised in Table 4, 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 0.5 mg + 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)

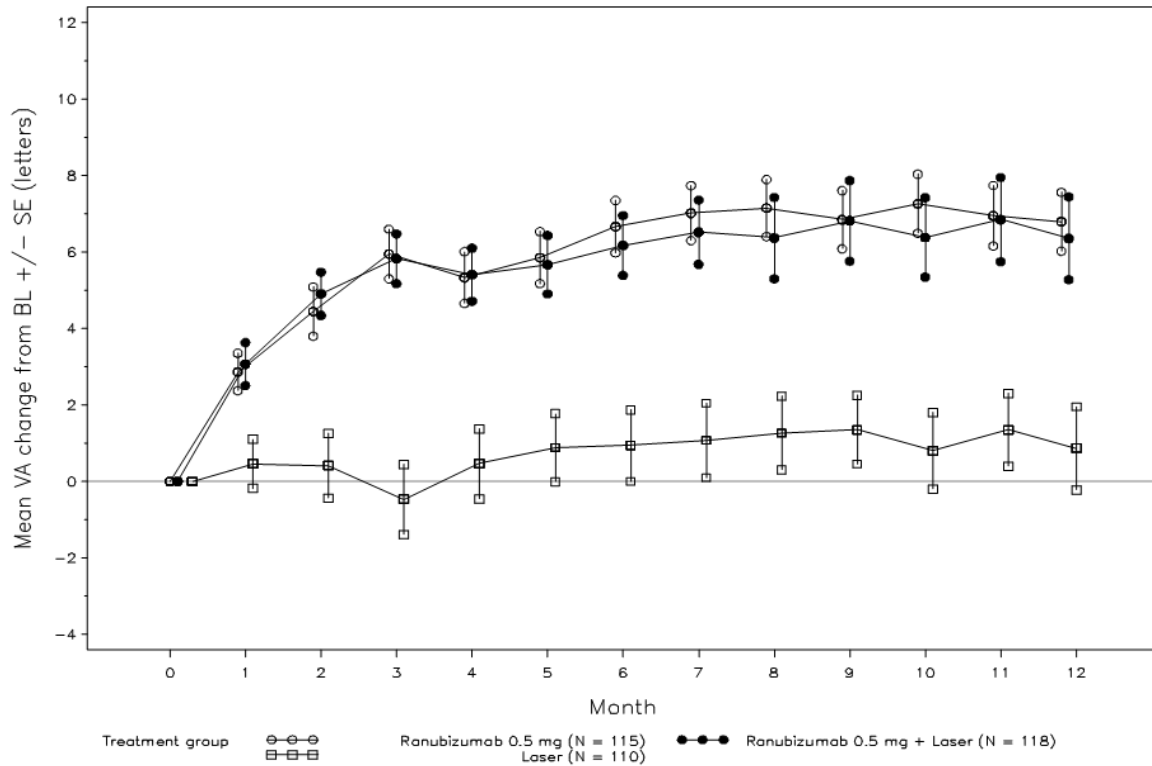
Visual acuity of the study eye (letters): Categorized change from baseline at month 12 (FAS / LOCF)

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)

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- 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)



BL=baseline; SE=standard error of mean

Study D2301E1 (RESTORE Extension)

Study D2301E1 (RESTORE Extension) was an open-label, multi-center, 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 administered monthly 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.

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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 The number of patients with a value both at core 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 $> 300 \mu\text{m}$; or if at any monthly visit after month 1, retinal thickness in the study eye was $> 225 \mu\text{m}$ and reduction in retinal oedema from the previous assessment was $< 50 \mu\text{m}$. Laser photocoagulation rescue treatment was allowed from month 3 in both treatment arms.

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

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

The exploratory analysis revealed no sign of a clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of this study therefore do not support the concept of dose doubling where response to the recommended dose is considered inadequate.

Key outcomes from the confirmatory part of the study (2/3 of the patients) are summarised in Table 7 and Figure 3.

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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 μ m mean (SE) [Δ BL to month 12] ³	-200.7 (17.11)	-187.6 (20.70)	-194.2 (13.38)	-48.4 (21.92)
CRT < 225 μ m (%) at month 12 ⁴	31.4% (n=16)	39.2% (n=20)	35.3% (n=36)	10.2% (n=5)

Δ BL = change from baseline

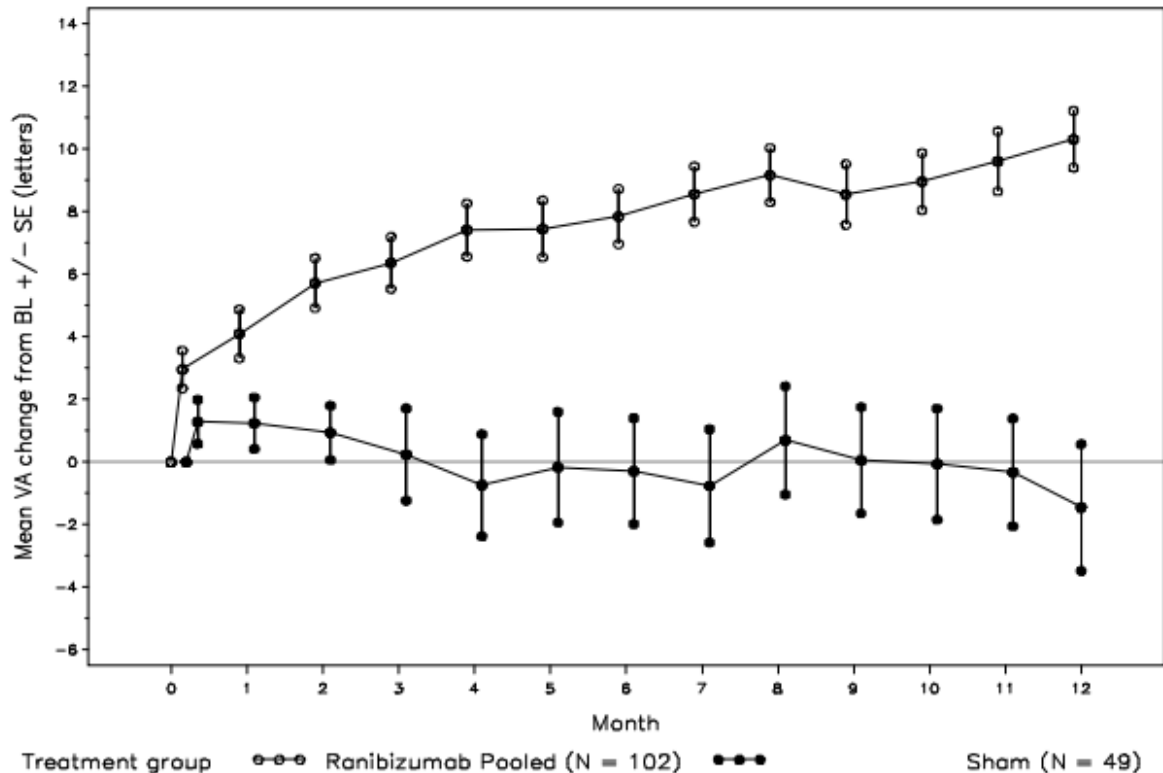
¹CMH test, stratified: 6 mg/mL vs sham p=0.0001; 10 mg/mL vs sham p=0.0037; and pooled p=0.0001

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

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

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

Figure 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 (CRT). At month 12, the mean CRT change from baseline was -194 micrometres for ranibizumab versus -48 micrometres for sham control.

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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 randomized to receive either 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 TE regimen, ranibizumab was administered, at scheduled treatment at intervals of 2-3 months. On 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, and 10.7 (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.

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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 ranibizumab in patients with proliferative diabetic retinopathy (PDR) have been assessed in Protocol S which evaluated 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 multicenter, randomized, active-controlled, parallel-assignment, non-inferiority Phase III study that enrolled 305 patients (394 study eyes) with PDR with or without DME at baseline, and compared ranibizumab 0.5 mg intravitreal injections to standard treatment with PRP. A total of 191 eyes (48.5%) were randomized to ranibizumab 0.5 mg and 203 eyes (51.5%) eyes were randomized 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]).

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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)

Outcome measure compared to baseline	Protocol S		
	Ranibizumab 0.5 mg (N=189)	PRP (N=199)	Difference in proportion (%), CI
≥ 2 -step improvement	79	29	27.4
n (%)	(41.8%)	(14.6%)	(18.9, 35.9)
≥ 3 -step improvement	54	6	25.7
n (%)	(28.6%)	(3.0%)	(18.9, 32.6)
≥ 2 -step worsening	3	23	-9.9
n (%)	(1.6%)	(11.6%)	(-14.7, -5.2)
≥ 3 -step worsening	1	8	-3.4
n (%)	(0.5%)	(4.0%)	(-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 baseline DME (39.9%) and with baseline DME (48.8%).

An analysis of 2-year data from Protocol S demonstrated that 80 (42.3%) eyes in the ranibizumab treated group had ≥ 2 -step improvement in DRSS from baseline compared with 46 (23.1%) eyes in the PRP group. In the ranibizumab treated group, ≥ 2 -step improvement in DRSS from baseline was observed in 24 (58.5%) eyes with baseline DME and 56 (37.8%) 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. 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

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determined by a best corrected visual acuity of 20/40 - or worse - or mean central subfield thickness $\geq 250 \mu\text{m}$ 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.

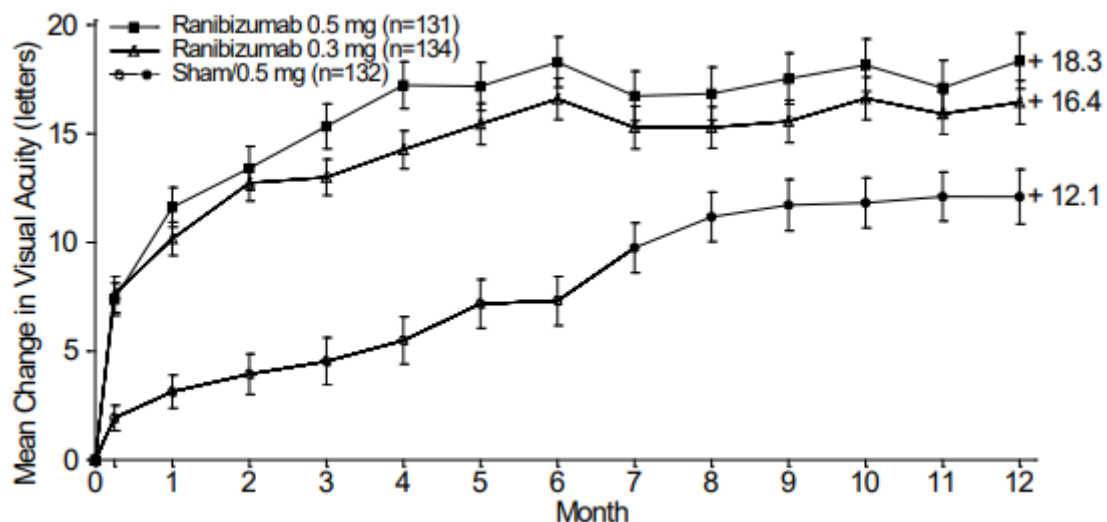
While numerically the better results were seen for 0.5 mg the differences between the two doses of ranibizumab are not clinically significant. Key outcomes from BRAVO and CRUISE are summarised in Tables 10 and 11, and Figures 4 and 5.

Table 10 Outcomes at month 6 and 12 (BRAVO)

Outcome measure	Sham/ranibizumab 0.5 mg (n=132)	Ranibizumab 0.3 mg (n=134)	Ranibizumab 0.5 mg (n=131)
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)



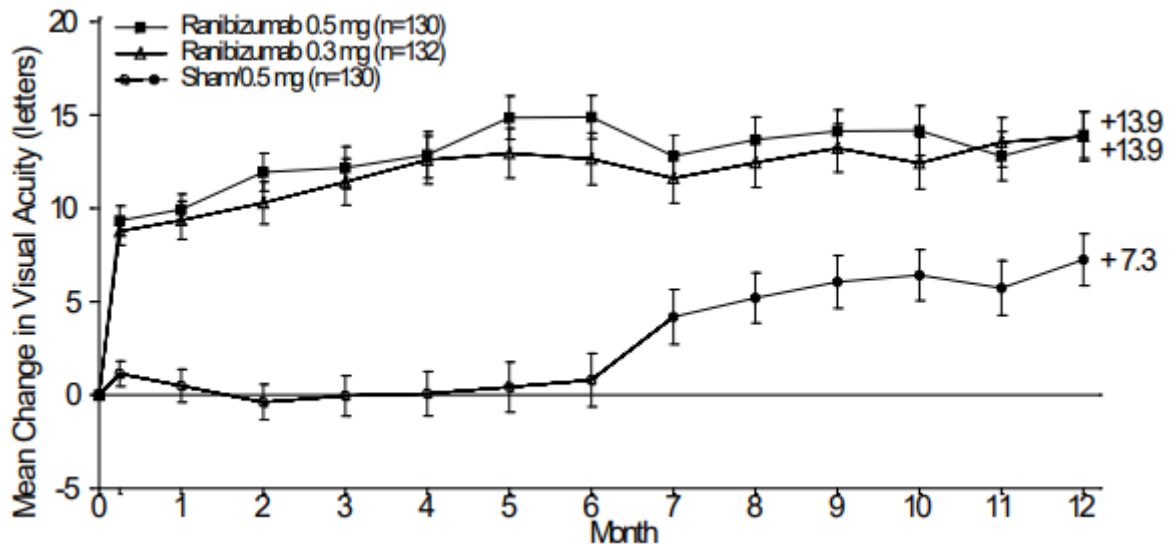
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Table 11 Outcomes at month 6 and 12 (CRUISE)

	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 ^a (letters)	+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.

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

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(angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic chorioretinopathy, and miscellaneous etiology) were pre-defined for analysis. In this study, 178 patients were randomized 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 12 and 13 and Figure 6.

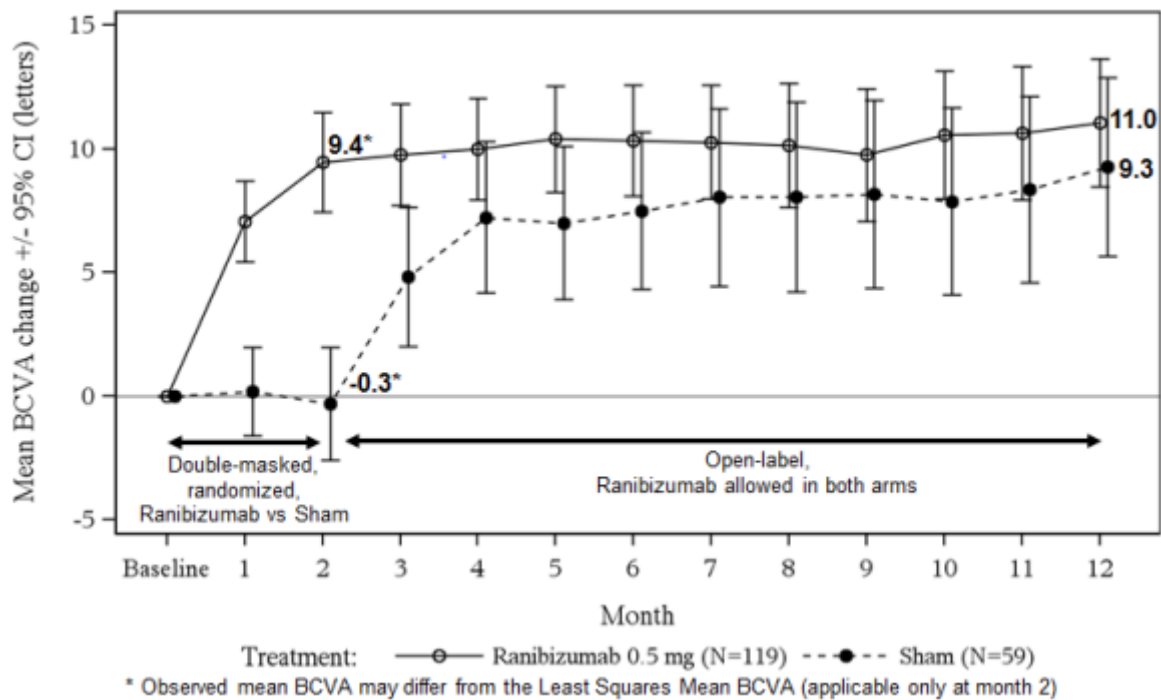
Table 12 Outcomes at month 2 (MINERVA)

	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)



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

Table 13 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, hemorrhage 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 randomized, 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.

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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 study.

Key outcomes from RADIANCE are summarised in Table 14 and Figure 7.

Table 14 Outcomes at month 3 and month 12 (RADIANCE)

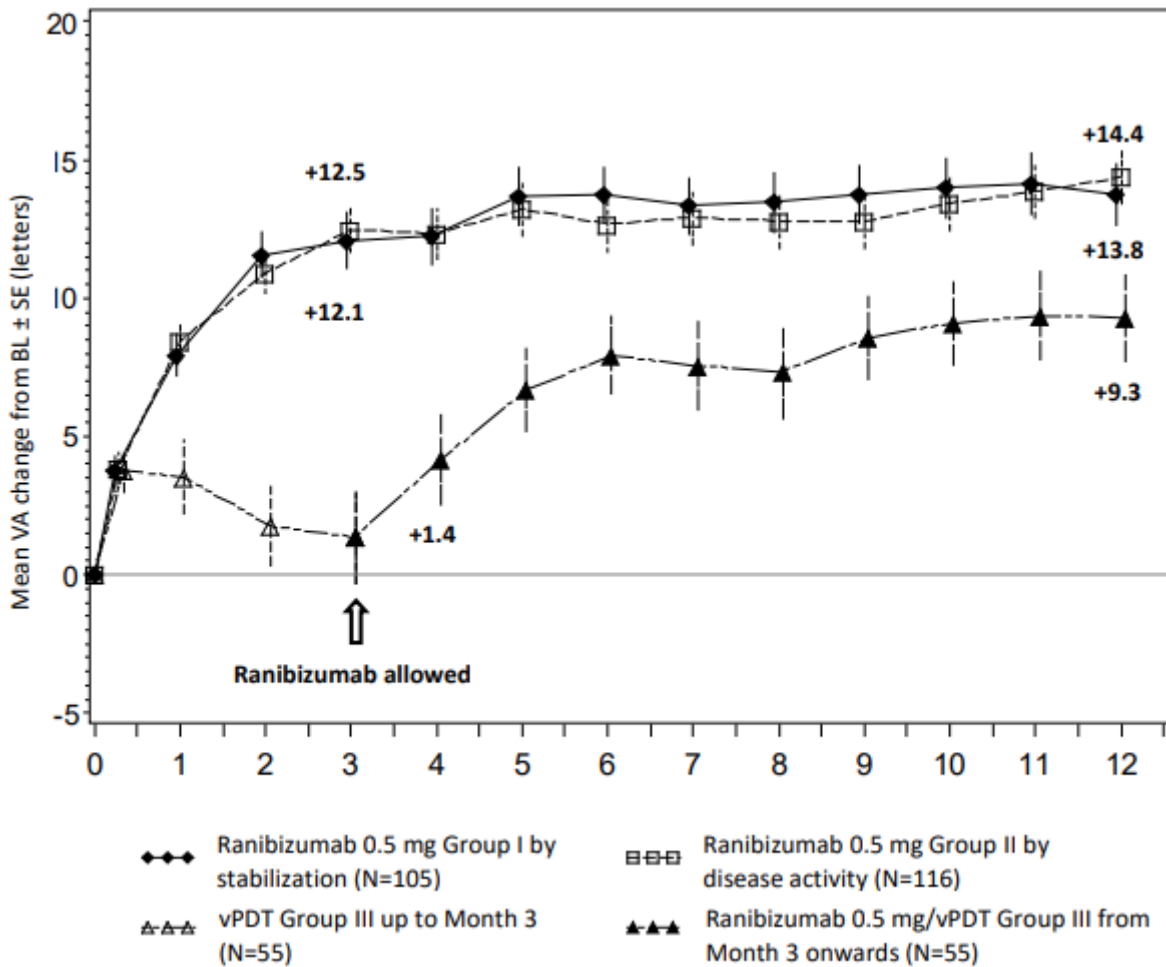
	Group I Ranibizumab 0.5mg “visual acuity stability” (n=105)	Group II Ranibizumab 0.5mg “disease activity” (n=116)	Group III vPDT* (n=55)
Month 3			
Mean average BCVA change from Month 1 to Month 3 compared to baseline ^a (letters)	+10.5	+10.6	+2.2
Proportion of patients who gained			
≥ 10 letters, or 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 randomized 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

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



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

Patients randomized 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 both 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.

Comparability of BYOOVIZ™ to Lucentis

A clinical efficacy and safety study has been conducted in patients with neovascular age-related macular degeneration (AMD) to demonstrate clinical comparability between BYOOVIZ™ and Lucentis (Study SB11-G31-AMD).

Primary efficacy analysis of central subfield thickness (CSFT) was performed for the Per-protocol Set (PPS-CSFT) with the change from baseline in CSFT at Week 4 using an analysis of covariance (ANCOVA) model with the baseline CSFT as a covariate and region (country) and treatment groups as factors. Primary analysis of change from baseline in CSFT at Week 4 in the PPS-CSFT is presented in Table 15. The least squares (LS) mean change from baseline CSFT at Week 4 was -108.40 μm in BYOOVIZ™ treatment group and -100.05 μm in Lucentis treatment group. The equivalence in CSFT for BYOOVIZ™ and Lucentis was declared as the adjusted treatment difference in the CSFT LS mean

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change from baseline between BYOOVIZ™ and Lucentis at Week 4 of $-8.35 \mu\text{m}$ and the 95% CI of the adjusted treatment difference of $[-19.446 \mu\text{m}, 2.747 \mu\text{m}]$ which was completely contained within the pre-defined equivalence margin of $[-36 \mu\text{m}, 36 \mu\text{m}]$.

Table 15: Analysis of Change from Baseline in CSFT at Week 4 (Per-protocol Set for CSFT, Study SB11-G31-AMD)

Timepoint	Treatment	n	LS Mean (SE)	Difference (BYOOVIZ™ – US Lucentis)		
				Mean	(SE)	[95% CI]
Week 4	BYOOVIZ™ (N = 342)	342	-108.40 (4.65)	-8.35	(5.65)	[-19.446, 2.747]
	Lucentis (N = 338)	338	-100.05 (4.64)			

CI = confidence interval; CSFT = central subfield thickness (μm); N = total number of patients; LS = least square; n = total number of patients with available data at Week 4; SE = standard error

Inferential statistics were based on analysis of covariance model with the baseline CSFT as a covariate and region (country) and treatment group as fixed factors.

For the CSFT, therapeutic equivalence is declared if the 2-sided 95% CI of the difference of CSFT LS mean changes from baseline at Week 4 between BYOOVIZ™ and Lucentis lies within the pre-defined equivalence margin of $[-36 \mu\text{m}, 36 \mu\text{m}]$.

Primary efficacy analysis of improvement in best-corrected visual acuity (BCVA) was performed for the Full Analysis Set (FAS) with the change from baseline in BCVA at Week 8 using ANCOVA model with the baseline BCVA as a covariate and region (country) and treatment group as factors. Primary analysis of change from baseline in BCVA at Week 8 between the BYOOVIZ™ and Lucentis treatment groups in the FAS is presented in Table 16. The least squares (LS) mean change from baseline BCVA at Week 8 was 6.18 letters in BYOOVIZ™ treatment group and 6.99 letters in Lucentis treatment group.

The equivalence in BCVA BYOOVIZ™ and Lucentis was declared as the two-sided 90% CI of the difference in terms of BCVA LS mean change from baseline at Week 8 between BYOOVIZ™ and Lucentis $[-1.827 \text{ letters}, 0.219 \text{ letters}]$ which lies within the pre-defined equivalence margin of $[-3 \text{ letters}, 3 \text{ letters}]$.

Table 16: Analysis of Change from Baseline in BCVA at Week 8 (Full Analysis Set, Study SB11-G31-AMD) (Imputation Method: Multiple Imputation – Missing at Random)

Timepoint	Treatment	n	LS Mean (SE)	Difference (BYOOVIZ™ – US Lucentis)		
				Mean	(SE)	[90% CI]
Week 8	BYOOVIZ™ (N = 351)	351	6.18 (0.52)	-0.80	(0.62)	[-1.827, 0.219]
	Lucentis (N = 353)	353	6.99 (0.51)			

BCVA = best corrected visual acuity (ETDRS letter score); CI = confidence interval; ETDRS = early treatment diabetic retinopathy study; LS = least square; MAR = missing-at-random; MI = multiple imputation; N = total number of patients; n = total number of patients with available data at Week 8; SE = standard error

Imputation method: MI-MAR

Inferential statistics were based on analysis of covariance model with the baseline BCVA as a covariate and region (country) and treatment as fixed factors.

For the BCVA, BCVA letter scores at 4 meter and 1 meter were imputed by MI method with the assumption of monotone missing pattern and regression method under the MAR.

Therapeutic equivalence is declared if the two-sided 90% CI of the difference of BCVA LS mean changes from baseline at Week 8 between BYOOVIZ™ and Lucentis lies within the pre-defined equivalence margin of $[-3 \text{ letters}, 3 \text{ letters}]$.

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5.2 Pharmacokinetic properties

Absorption

Following monthly intravitreal administration of ranibizumab to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11 to 27 ng/mL, as assessed in an in vitro cellular proliferation assay). C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Upon monthly intravitreal administration of 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/mL. Serum ranibizumab concentrations in RVO patients were similar to those observed in neovascular AMD patients.

Distribution and elimination

Based on analysis of population pharmacokinetics and 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.

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% percent (136 of 200) of patients in a population pharmacokinetic analysis had renal impairment (46.5% mild [50 to 80 mL/min], 20% moderate [30 to 50 mL/min] and 1.5% severe [<30 mL/min]). 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.

Comparability of BYOOVIZ™ to Lucentis - Pharmacokinetics

A clinical Phase I pharmacokinetic (PK) study was not conducted due to the low systemic exposure of ranibizumab after intravitreal injection.

PK profiles between BYOOVIZ™ and Lucentis were compared in the clinical Phase III Study SB11-G31-AMD in a sub-set of patients with neovascular AMD, and these showed comparable results.

5.3 Preclinical safety data

Bilateral intravitreal administration of ranibizumab to cynomolgus monkeys at doses between 0.25 mg/eye and 2.0 mg/eye once every 2 weeks for up to 26 weeks resulted in dose-dependent ocular effects.

Intraocularly, there were dose-dependent increases in anterior chamber flare and cells with a peak 2 days after injection. The severity of the inflammatory response generally diminished with subsequent injections or during recovery. In the posterior segment, there were vitreal cell infiltration and floaters, which also tended to be dose-dependent and generally persisted to the end of the treatment period. In the 26-week study, the severity of the vitreous inflammation increased with the number of injections. However, evidence of reversibility was observed after recovery. The

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nature and timing of the posterior segment inflammation is suggestive of an immune-mediated antibody response, which may be clinically irrelevant. Cataract formation was observed in some animals after a relatively long period of intense inflammation, suggesting that the lens changes were secondary to severe inflammation. A transient increase in post-dose intraocular pressure was observed following intravitreal injections, irrespective of dose.

Microscopic ocular changes were related to inflammation and did not indicate degenerative processes. Granulomatous inflammatory changes were noted in the optic disc of some eyes. These posterior segment changes diminished, and in some instances resolved, during the recovery period. Following intravitreal administration, no signs of systemic toxicity were detected. Serum and vitreous antibodies to ranibizumab were found in a subset of treated animals.

No carcinogenicity and mutagenicity are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Alpha, alpha-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

Vial

30 months

6.4 Special precautions for storage

Vial

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Prior to usage, the unopened vial may be kept at room temperature not exceeding 30°C for up to 1 month.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Vial + filter needle + injection needle pack

BYOOVIZ™ 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

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contents, one needle for intravitreal injection. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Vial only*

BYOOVIZ™ 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.

* Not all pack types may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Sponsor:

SAMSUNG BIOEPIS NZ LIMITED
TMF Group, Level 11, 41 Shortland Street, Auckland 1010
New Zealand

Distributor:

Biogen NZ Biopharma Limited
Auckland
New Zealand
Telephone: +64 800 852 289

9 DATE OF FIRST APPROVAL

16 March 2023

10 DATE OF REVISION OF THE TEXT

TBD

SUMMARY TABLE OF CHANGES