

ACCENTRIX®

Antineovascularization agents

DESCRIPTION AND COMPOSITION**Pharmaceutical form**

Solution for injection.

Accentrix is supplied in a vial.

Sterile, clear, colorless to pale brownish-yellow and preservative-free aqueous solution.

Active substance

One mL contains 10 mg ranibizumab.

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

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

Excipients

alpha, alpha-trehalose dihydrate, histidine hydrochloride, monohydrate, histidine, polysorbate 20, water for injections.

INDICATIONS

Accentrix is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of proliferative diabetic retinopathy (PDR)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)
- The treatment of visual impairment due to choroidal neovascularization (CNV)

Accentrix is indicated in preterm infants for:

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

DOSAGE REGIMEN AND 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.

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

Posology**Adults**

The recommended dose for Accentrix 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.

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, Accentrix should be discontinued.

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

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 PDR and 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.

The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. Some patients may only need one injection during the first 12 months; others may need more frequent treatment, including a monthly injection. For CNV secondary to pathologic myopia (PM), many patients may only need one or two injections during the first year (see section CLINICAL PHARMACOLOGY).

Ranibizumab and laser photocoagulation in DME and in macular oedema secondary to BRVO

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

Ranibizumab and verteporfin photodynamic therapy in CNV secondary to PM

There is no experience of concomitant administration of ranibizumab and verteporfin.

Preterm infants

The recommended dose for Accentrix in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 ml. In preterm infants treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In total, up to three injections per eye may be administered within six months of treatment initiation if there are signs of disease activity. Most patients (78%) in the 24-week RAINBOW clinical study received one injection per eye. Patients who were treated with 0.2 mg in this

clinical study did not require additional treatment in the subsequent long-term extension study which followed the patients up to five years of age (see section PHARMACODYNAMICS). The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.

Special populations

Hepatic impairment

Ranibizumab has not been studied in patients with hepatic impairment. However, no special considerations are needed in this population.

Renal impairment

Dose adjustment is not needed in patients with renal impairment (see section PHARMACOKINETICS).

Elderly

No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME.

Pediatric population

The safety and efficacy of ranibizumab in children and adolescents below 18 years of age for indications other than retinopathy of prematurity have not been established. Available data in adolescent patients aged 12 to 17 years with visual impairment due to CNV are described in section CLINICAL STUDIES but no recommendation on a posology can be made.

Method of administration

As with all medicinal products for parenteral use, Accentrix 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 CONTRAINDICATIONS). Adequate anesthesia 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 Accentrix, see section 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 center of the globe. The injection volume of 0.05 mL is then delivered; the scleral site should be rotated for subsequent injections.

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.

WARNINGS AND PRECAUTIONS

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 ADVERSE DRUG REACTIONS). Proper aseptic injection techniques must always be used when administering Accentrix. 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.

Intraocular pressure increases

In adults transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of ranibizumab. Sustained IOP increases have also been identified (see section ADVERSE DRUG REACTIONS). Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.

Patients should be informed of the symptoms of these potential adverse reactions and instructed to inform their physician if they develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in their vision, or increased sensitivity to light (see section ADVERSE DRUG REACTIONS).

Bilateral treatment

Limited data on bilateral use of ranibizumab (including same-day administration) do not suggest an increased risk of systemic adverse events compared with unilateral treatment.

Immunogenicity

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).

Withholding Accentrix in adults

The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- a decrease in best-corrected visual acuity (BCVA) of ≥ 30 letters compared with the last assessment of visual acuity;
- an intraocular pressure of ≥ 30 mmHg;
- a retinal break;

- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is $\geq 50\%$, of the total lesion area;
- performed or planned intraocular surgery within the previous or next 28 days.

Retinal pigment epithelial tear

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

Rhegmatogenous retinal detachment or macular holes in adults

Treatment should be discontinued in subjects with rhegmatogenous retinal detachment or stage 3 or 4 macular holes.

Pediatric population

The warnings and precautions for adults also apply to preterm infants with ROP. Long-term safety in preterm infants with ROP has been studied in the RAINBOW extension study up to the age of five years old. The safety profile of ranibizumab 0.2 mg during the extension study was consistent with that observed in the core study at 24 weeks (see section Adverse Drug Reactions).

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 limited experience of treatment with ranibizumab in diabetic patients with an HbA1c over 108 mmol/mol (12%) and no experience in patients with uncontrolled hypertension. This lack of information should be considered by the physician when treating such patients.

There are insufficient data to conclude on the effect of ranibizumab in patients with RVO presenting irreversible ischaemic visual function loss.

In patients with PM, there are limited data on the effect of ranibizumab in patients who have previously undergone unsuccessful verteporfin photodynamic therapy (vPDT) treatment. Also, while a consistent effect was observed in subjects with subfoveal and juxtafoveal lesions, there are insufficient data to conclude on the effect of ranibizumab in PM subjects with extrafoveal lesions.

Systemic effects following intravitreal use

Systemic adverse events including non-ocular haemorrhages and arterial thromboembolic events have been reported following intravitreal injection of VEGF inhibitors.

There are limited data on safety in the treatment of DME, macular oedema due to RVO and CNV secondary to PM patients with prior history of stroke or transient ischaemic attacks. Caution should be exercised when treating such patients (see section ADVERSE DRUG REACTIONS).

Driving and using machines

The Accentrix treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see section ADVERSE DRUG REACTIONS).

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

ADVERSE DRUG REACTIONS

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 for 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 WARNINGS AND PRECAUTIONS).

Other serious ocular events observed among ranibizumab-treated patients included intraocular inflammation and increased intraocular pressure (see section WARNINGS AND PRECAUTIONS).

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 section CLINICAL PHARMACOLOGY/PHARMACODYNAMICS 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 CLINICAL STUDIES). The event of urinary tract infection, in the common frequency category, met the adverse reaction 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 DOSING REGIMEN AND 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 CLINICAL STUDIES). 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 edema secondary to BRVO and CRVO, respectively (see section CLINICAL STUDIES). 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 CLINICAL STUDIES). 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 CLINICAL STUDIES). 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.
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, pruritus, 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, 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) compared to control (0.27/100 patient years). The relationship to ranibizumab remains unknown.

Retinopathy of Prematurity (ROP) population

The safety of Accentrix 0.2 mg was studied in the 6-month clinical trial (RAINBOW), which included 73 ranibizumab-treated preterm infants with ROP (see section CLINICAL STUDIES). Ocular events observed in the RAINBOW trial were consistent with those seen in adults treated with ranibizumab 0.5 mg. In general, the non-ocular events in this trial were consistent with what would be expected for this patient population with multiple comorbidities due to prematurity.

Long-term safety in preterm infants with ROP has been established up to the age of five years in the RAINBOW extension study and showed no new safety signals. The safety profile of ranibizumab 0.2 mg during the RAINBOW extension study was consistent with that observed in the RAINBOW core study at 24 weeks.

INTERACTIONS

No formal interaction studies have been performed.

For the adjunctive use of verteporfin photodynamic therapy (PDT) and ranibizumab in wet AMD, and PM, see section CLINICAL STUDIES.

For the adjunctive use of laser photocoagulation and ranibizumab in DME and BRVO, see section CLINICAL STUDIES and DOSAGE REGIMEN AND ADMINISTRATION.

In clinical studies for the treatment of visual impairment due to DME, the outcome with regard to visual acuity or central retinal subfield thickness (CSFT) in patients treated with ranibizumab was not affected by concomitant treatment with thiazolidinediones.

Pediatric population

No interaction studies have been performed.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Women of childbearing potential/contraception in females

Women of childbearing potential should use effective contraception during treatment.

Pregnancy

For ranibizumab, no clinical data on exposed pregnancies are available.

Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development (see section NON-CLINICAL SAFETY DATA). The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/foetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Breast-feeding

Based on very limited data, ranibizumab may be excreted in human milk at low levels. The effect of ranibizumab on a breast-fed newborn/infant is unknown. As a precautionary measure, breast-feeding is not recommended during the use of ranibizumab.

Fertility

There are no data available on fertility.

OVERDOSAGE

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 increased intraocular pressure 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.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group

Pharmacotherapeutic group: Ophthalmologicals, antineovascularisation agents, ATC code: S01LA04

Mechanism of action (MOA)

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

Pharmacodynamics (PD)

Binding of VEGF A to its receptors leads to endothelial cell proliferation and neovascularization, 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 CNV secondary to pathologic myopia, or to the macular edema causing visual impairment in diabetes and retinal vein occlusion.

Pharmacokinetics (PK)

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 DME and RVO patients were similar to those observed in neovascular AMD patients.

Distribution and elimination

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

Special populations

Pediatric Population (preterm infants with ROP)

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

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) 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.

CLINICAL STUDIES

Treatment of wet AMD

In wet AMD, the clinical safety and efficacy of ranibizumab have been assessed in three randomized, 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) 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).

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

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).

*** The sham ranibizumab injection control procedure involved anesthetizing 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.*

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

Table -2 Outcomes at Month 12 and Month 24 in study FVF2598g (MARINA)

Outcome measure	Month	Sham (n=238)	Ranibizumab 0.5 mg (n=240)
Loss of <15 letters in visual acuity (%) ^a (Maintenance of vision)	Month 12	62%	95%
	Month 24	53%	90%
Gain of ≥15 letters in visual acuity (%) ^a	Month 12	5%	34%
	Month 24	4%	33%
Mean change in visual acuity (letters) (SD) ^a	Month 12	-10.5 (16.6)	+7.2 (14.4)
	Month 24	-14.9 (18.7)	+6.6 (16.5)

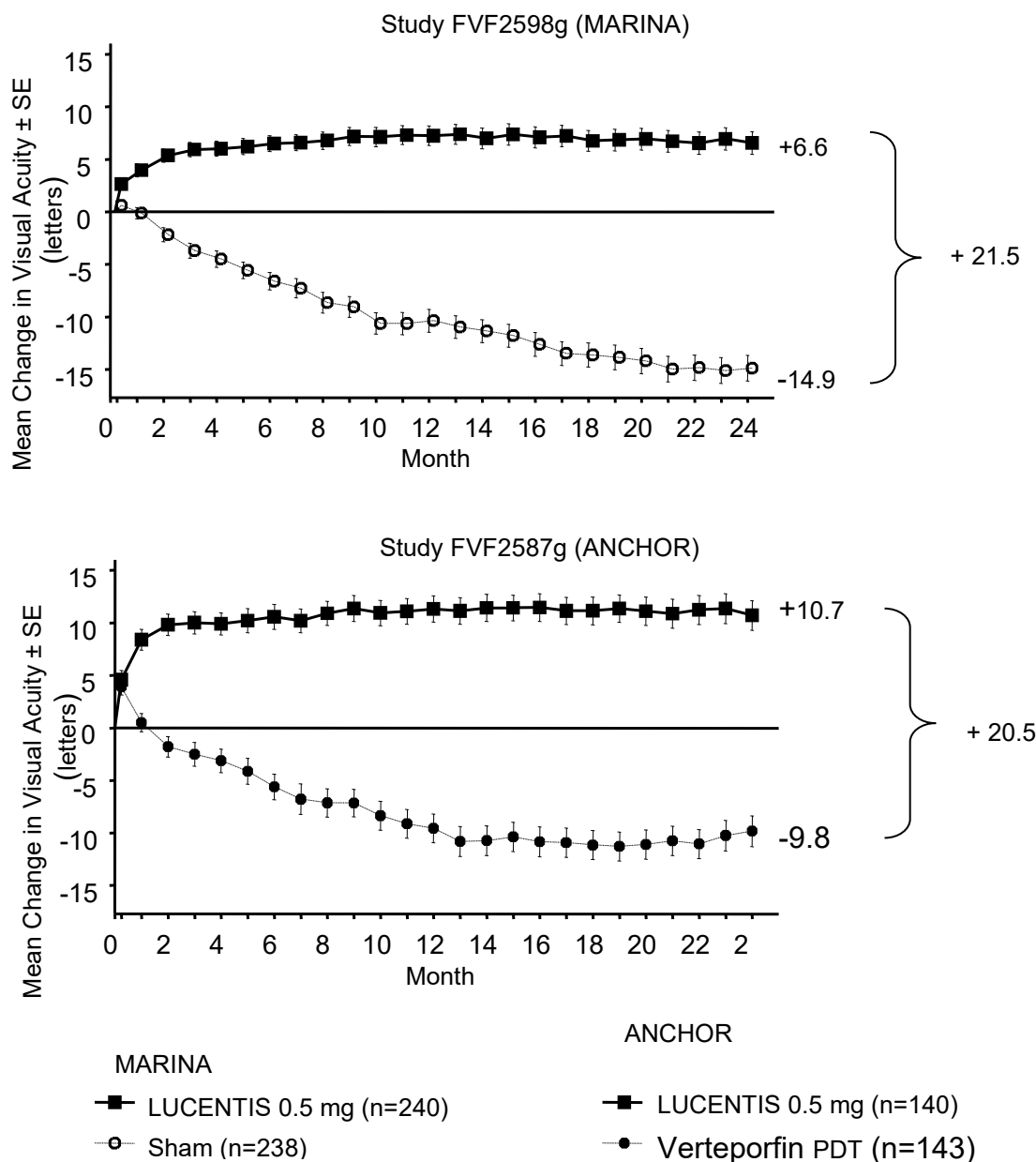
^a p<0.01.

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

Outcome measure	Month	Verteporfin PDT (n=143)	Ranibizumab 0.5 mg (n=140)
Loss of <15 letters in visual acuity (%) ^a (Maintenance of vision)	Month 12	64%	96%
	Month 24	66%	90%
Gain of ≥15 letters in visual acuity (%) ^a	Month 12	6%	40%
	Month 24	6%	41%
Mean change in visual acuity (letters) (SD) ^a	Month 12	-9.5 (16.4)	+11.3 (14.6)
	Month 24	-9.8 (17.6)	+10.7 (16.5)

^a p<0.01

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.

Results from both trials indicated that continued ranibizumab-treatment may be of benefit also in patients who lost ≥ 15 letters of best-corrected visual acuity (BCVA) in the first year of treatment.

In both the MARINA and ANCHOR studies, the improvement in visual acuity seen with ranibizumab 0.5 mg at 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) scores. The differences

between ranibizumab 0.5 mg and the two control groups were assessed with p-values ranging from 0.009 to <0.0001.

Study FVF3192g (PIER)

Study FVF3192g (PIER) was a randomized, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of ranibizumab in 184 patients with neovascular AMD (with or without a classic CNV component). 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 once every 3 months. From Month 14 of the study, sham-treated patients were allowed to cross over to receive ranibizumab and from Month 19, more frequent treatments were possible. Patients treated with ranibizumab in PIER received a mean of 10 treatments during the study. 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 visual acuity, returning to baseline at Month 12. This effect was maintained in most ranibizumab-treated patients (82%) at Month 24. Data from a limited number of subjects that crossed over to receive ranibizumab after more than a year of sham-treatment suggested that early initiation of treatment may be associated with a better preservation of visual acuity.

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, 2378 patients were randomized in a 1:1 ratio to receive one intravitreal injection of 0.3 mg or 0.5 mg ranibizumab every month for three consecutive months followed by 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 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).

The safety profile in these patients was consistent with that seen in previous clinical trials with ranibizumab monotherapy.

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 edema (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)

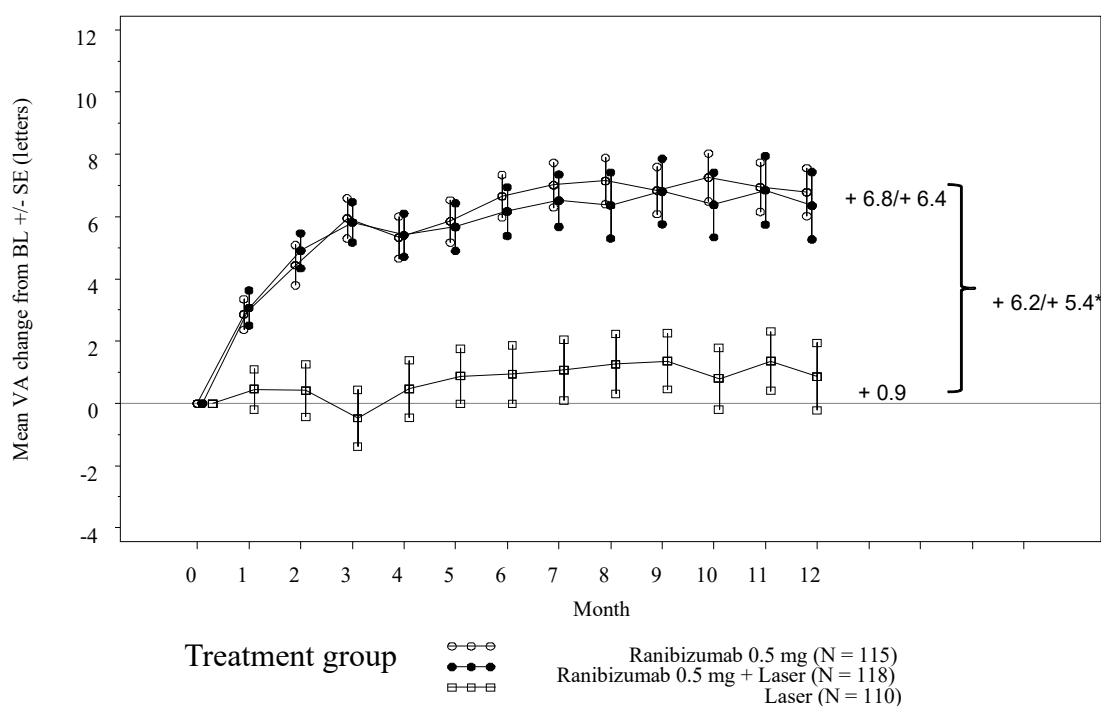
In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular edema were randomized to receive either initial intravitreal injections of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation ($n=116$), combined ranibizumab 0.5 mg and laser photocoagulation ($n=118$), 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 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 summarized in Table 4 and Figure 2.

Table -4 Outcomes at Month 12 in study D2301 (RESTORE)

Outcome measure	Ranibizumab 0.5 mg (n=115)	Ranibizumab 0.5 mg + Laser (n=118)	Laser (n=110)
Mean average change in BCVA from Month 1 to Month 12 compared to baseline (letters) (SD) ^b	+6.1 (6.43)	+5.9 (7.92)	+0.8 (8.56)
Mean change in BCVA at Month 12 compared to baseline (letters) (SD)	+6.8 (8.25) ^b	+6.4 (11.77) ^c	+0.9 (11.44)
Gain of ≥ 10 letters in BCVA (% of patients) at Month 12	37.4 ^d	43.2 ^b	15.5
Gain of ≥ 15 letters in BCVA (% of patients) at Month 12	22.6 ^e	22.9 ^f	8.2

^bp<0.0001, ^cp=0.0004, ^dp=0.0001, ^ep=0.0032, ^fp=0.0021

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 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 in the core study. Of the 74 patients from the core study laser treatment arm, 59 (79%) 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.

Key outcome measures are summarized in Table 5.

Table -5 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 (79%) patients received ranibizumab in the extension study

VFQ-25 scores in patients who were previously treated with ranibizumab PRN in the core study stabilized during the extension phase. Those treated with laser in the core study control group, and then switched to ranibizumab PRN treatment in the extension phase, demonstrated an improvement in VFQ-25 scores.

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)

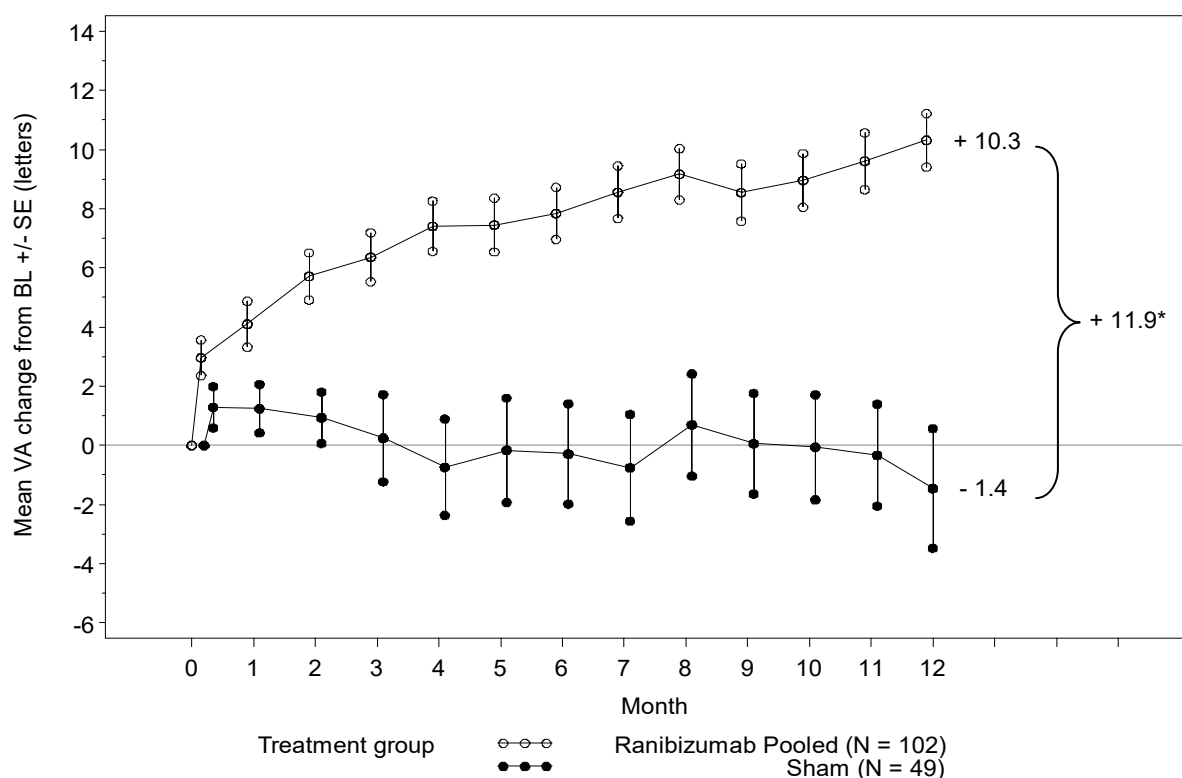
In study D2201 (RESOLVE), a total of 151 patients with macular center involvement causing visual impairment were treated with ranibizumab (6 mg/ml, n=51, 10 mg/ml, n=51) or sham (n=49) by monthly intravitreal injections until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection if the investigator evaluated that response to treatment was not sufficiently achieved. Laser photocoagulation rescue treatment was allowed from Month 3 in both treatment arms. The study was comprised of two parts: an exploratory part (the first 42 patients analyzed at Month 6) and a confirmatory part (the remaining 109 patients analyzed at Month 12).

Key outcomes from the confirmatory part of the study (2/3 of the patients) are summarized in Table 6 and Figure 3.

Table -6 Outcomes at Month 12 in study D2201 (RESOLVE) (overall study population)

Outcome measure	Ranibizumab pooled (n=102)	Sham (n=49)
Mean average change in BCVA from Month 1 to Month 12 compared to baseline (letters) (SD) ^b	+7.8 (7.72)	-0.1 (9.77)
Mean change in BCVA at month 12 compared to baseline (letters) (SD) ^b	+10.3 (9.14)	-1.4 (14.16)
Gain of ≥10 letters in BCVA (% patients) at Month 12 ^b	60.8	18.4
Gain of ≥15 letters in BCVA (% patients) at Month 12 ^g	32.4	10.2
^b p<0.0001, ^g p=0.0043		

Figure -3 Mean change in visual acuity from baseline over time in study D2201 (RESOLVE) (overall population)



BL=baseline; SE= standard error of mean

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

- ranibizumab 0.5 mg with concomitant laser photocoagulation on a treat-and-extend (TE) regimen (n=121),
- 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 then administered, at scheduled treatment at intervals of 2-3 months. On PRN regimen, BCVA was assessed monthly and ranibizumab was 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 the number of scheduled treatment visits required by the TE regimen was 40% lower than the number of monthly visits required by the PRN regimen. With both regimens, more than 70% of patients were able to maintain their BCVA with a visit frequency of ≥ 2 months.

Key outcome measures are summarized in Table 7.

Table -7 Outcomes in study D2304 (RETAIN)

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

^bp<0.0001

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

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

Study D2303 (REVEAL)

The study D2303 (REVEAL), was a 12 month, randomized, 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 edema were randomized 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.

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 (NPDR) 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 NPDR 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 8 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.

DRSS was also assessed in three separate active-controlled phase III DME studies (ranibizumab 0.5 mg PRN vs laser) that included a total of 875 patients, of whom approximately 75% were of Asian origin. In a meta-analysis of these studies, 48.4% of the 315 patients with gradable DRSS scores in the subgroup of patients with moderately severe non-proliferative DR (NPDR) 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 NPDR or better, a ≥ 2 -step DRSS improvement was observed in 1.4% and 0.9% of the ranibizumab and laser groups, respectively.

Treatment of visual impairment due to macular edema 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 edema secondary to RVO have been assessed in the randomized, 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 0.3 mg or 0.5 mg intravitreal ranibizumab or sham** injections. After 6 months, patients in the sham-control arms were crossed over to 0.5 mg ranibizumab. In BRAVO, laser photocoagulation as rescue was allowed in all arms from Month 3.

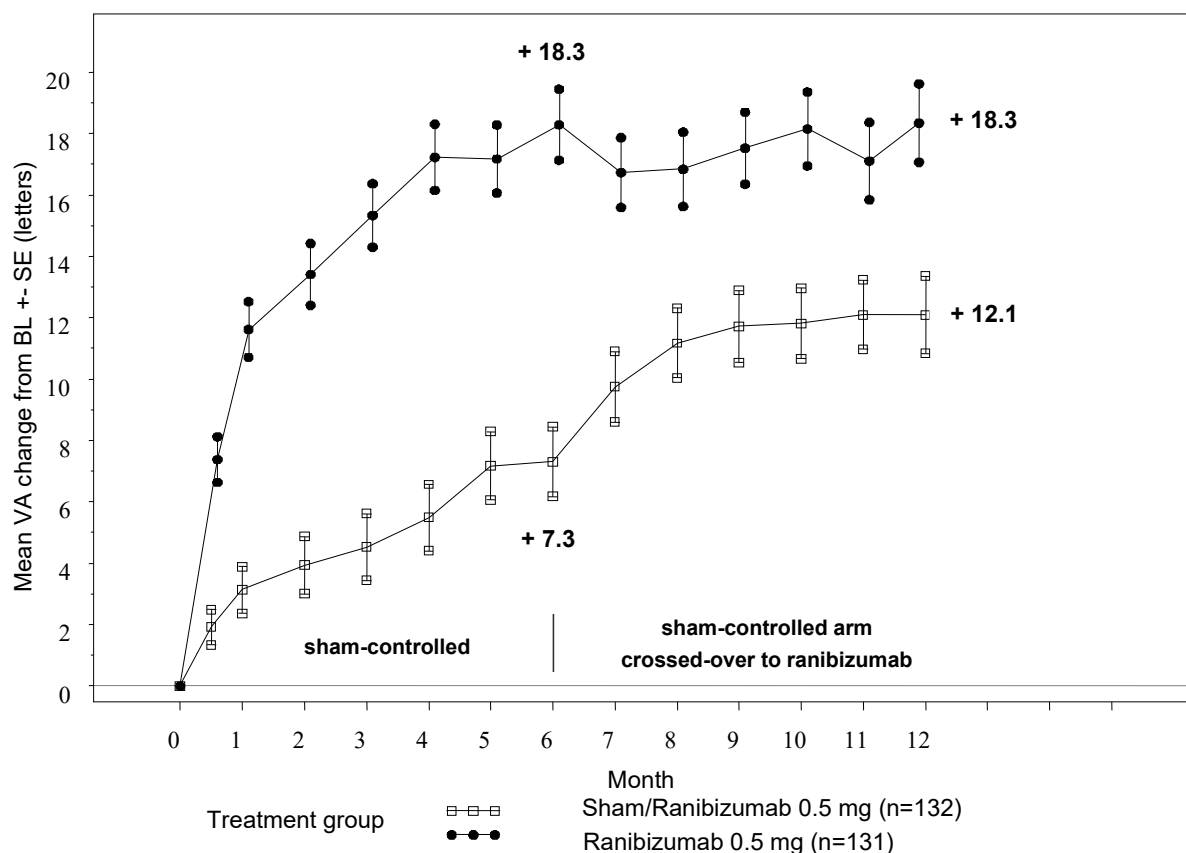
Key outcomes from BRAVO and CRUISE are summarized in Tables 8 and 9, and Figures 4 and 5.

Table 9 Outcomes at Month 6 and 12 (BRAVO)

	Sham/Ranibizumab 0.5 mg (n=132)	Ranibizumab 0.5 mg (n=131)
Mean change in visual acuity from baseline at Month 6 ^b (letters) (primary endpoint)	+7.3	+18.3
Mean change in visual acuity from baseline at Month 12 (letters)	+12.1	+18.3
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 ^b	28.8 %	61.1 %
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12	43.9 %	60.3 %
Proportion of patients receiving laser rescue over 12 months	61.4 %	34.4 %

^b p<0.0001

Figure 4 Mean change from baseline BCVA over time to Month 6 and Month 12 (BRAVO)

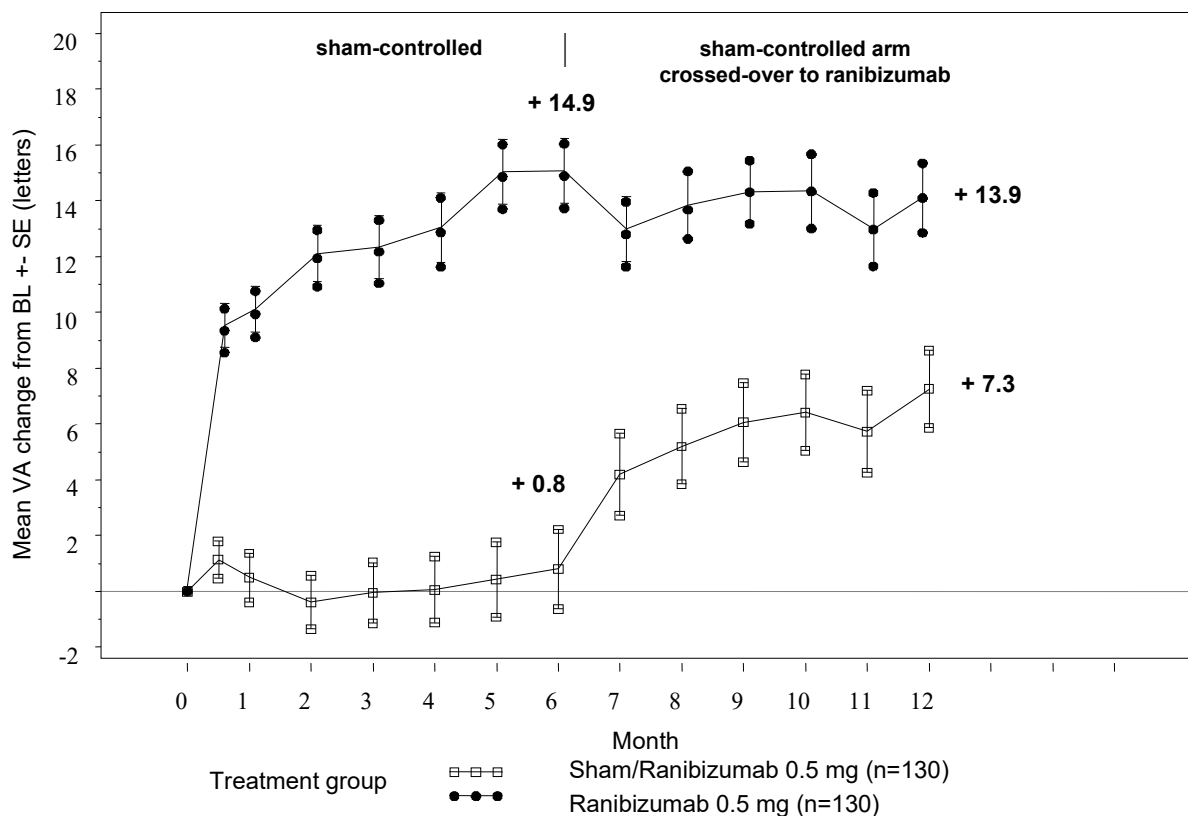


BL=baseline; SE=standard error of mean

Table -10 Outcomes at Month 6 and 12 (CRUISE)

	Sham/Ranibizumab 0.5 mg (n=130)	Ranibizumab 0.5 mg (n=130)
Mean change in visual acuity from baseline at Month 6 ^b (letters)	+0.8	+14.9
Mean change in visual acuity from baseline at Month 12 (letters)	+7.3	+13.9
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 ^b	16.9 %	47.7 %
Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12	33.1 %	50.8 %

^b p<0.0001

Figure -5 Mean change from baseline BCVA over time to Month 6 and Month 12 (CRUISE)

BL=baseline; SE=standard error of mean

In both studies, the improvement of vision was accompanied by a continuous decrease in the macular edema 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.

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, randomized, 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 shown in Table 11 and Figures 6 and 7.

Table -11 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 (10.7)	+14.8 (11.13)	+6.0 (14.27)	+12.0 (13.95)
Mean change in BCVA at Month 24 ^b (letters) (SD)	+15.5 (13.91)	+17.3 (12.61)	+11.6 (16.09)	+12.1 (18.60)
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 (5.81)	11.3 (6.02)	NA	13.1 (6.39)

* 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.

^bp<0.0001 for null hypothesis in CRYSTAL that the mean change at Month 24 from baseline is zero.

Figure -6 BRIGHTER: Mean change in BCVA from baseline over 24 months

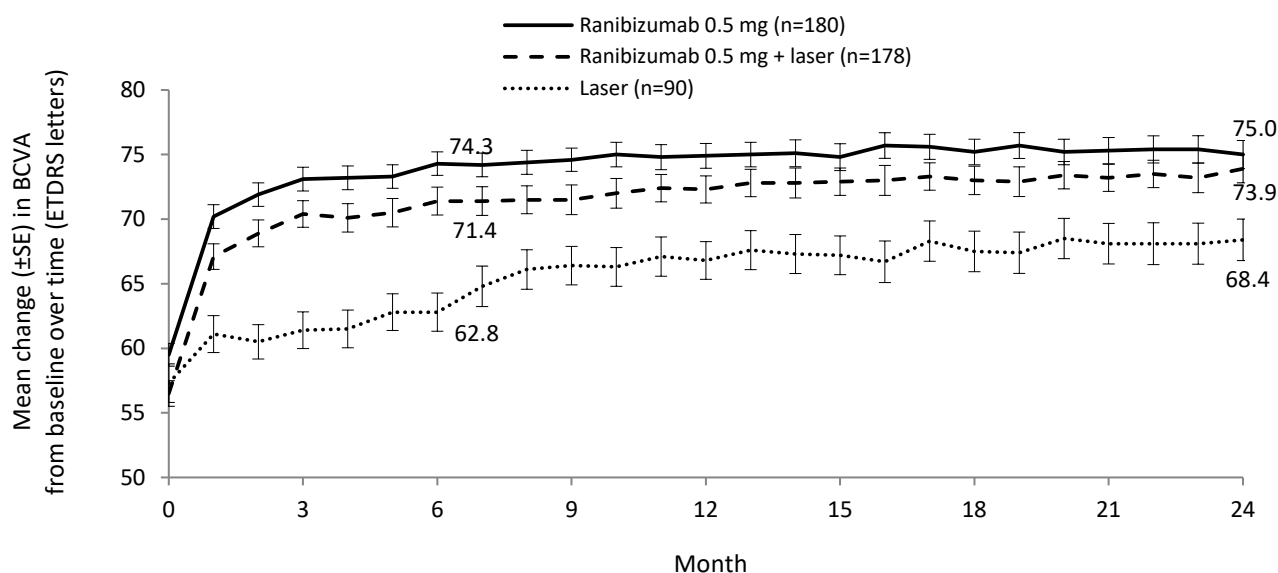
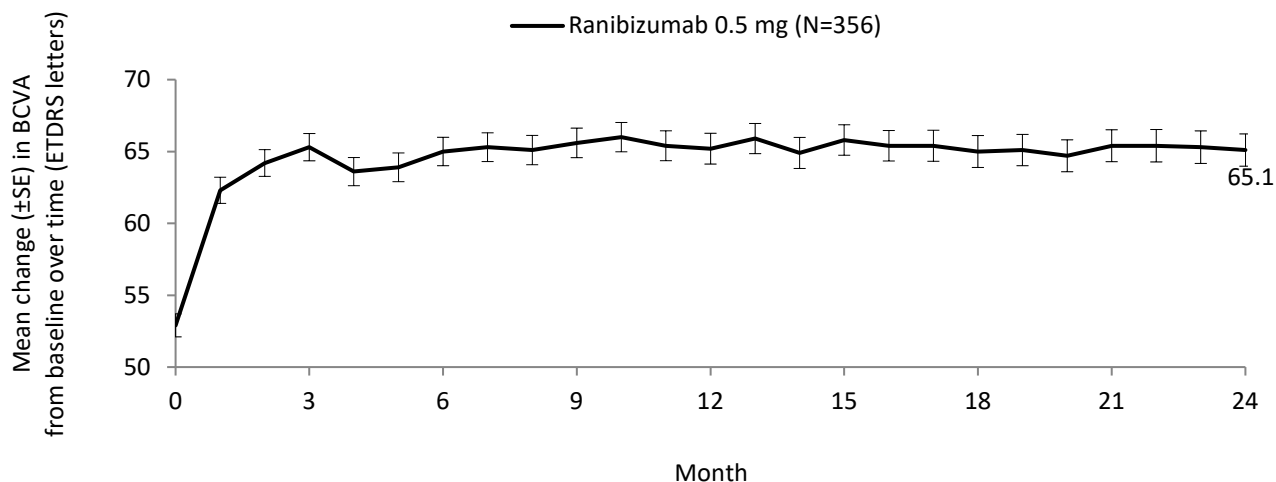


Figure -7 CRYSTAL: Mean change in BCVA from baseline over 24 months

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 beneficial 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 beneficial 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 based on the 12-month data of the randomized, double-masked, sham controlled pivotal study G2301 (MINERVA). 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 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 8.

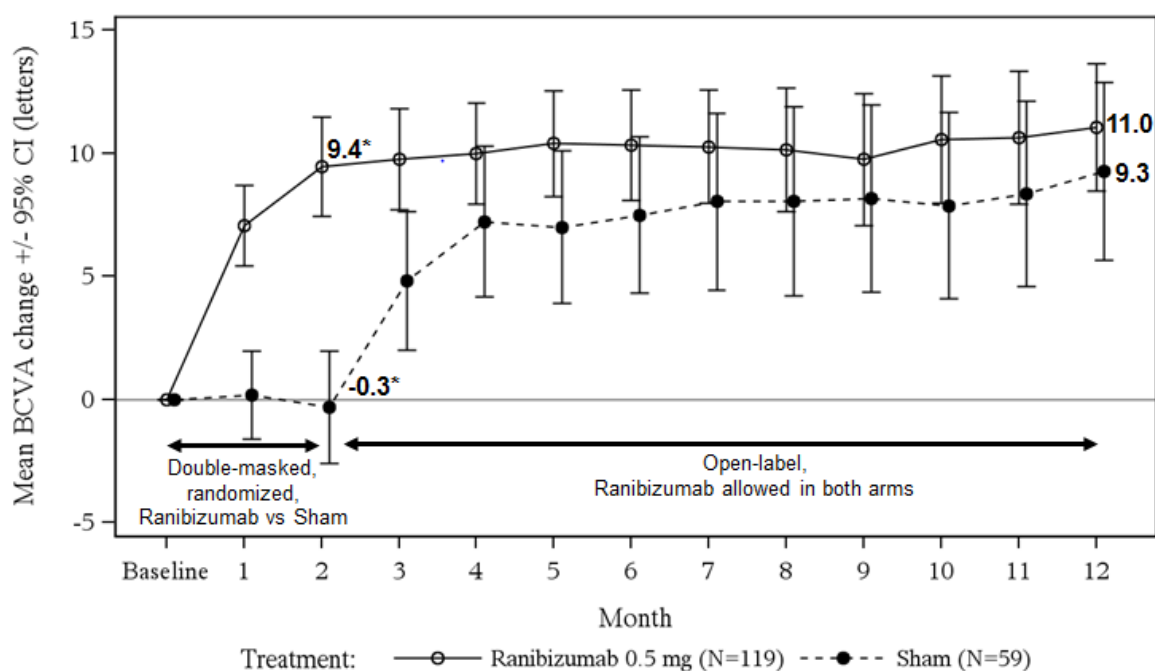
Table -12 Outcomes at Month 2 (MINERVA)

	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 -8 Mean BCVA change from baseline over time to Month 12 (MINERVA)



When comparing ranibizumab versus sham control at Month 2, a consistent treatment effect both overall and across baseline etiology subgroups 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.

A trend in patient-reported benefits, as measured by the NEI VFQ-25 composite score, was observed from baseline to Month 2 for patients receiving ranibizumab treatment versus the sham control group. This trend was maintained to Month 12.

Pediatric 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 DOSAGE REGIMEN AND ADMINISTRATION, Pediatric patients).

Treatment of visual impairment due to CNV secondary to 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 0.5 mg ranibizumab given as intravitreal injection in comparison to verteporfin PDT (vPDT, Visudyne photodynamic therapy).

The 277 patients were randomized to one of the following arms:

- 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 OCT and/or 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 DOSAGE REGIMEN AND 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.

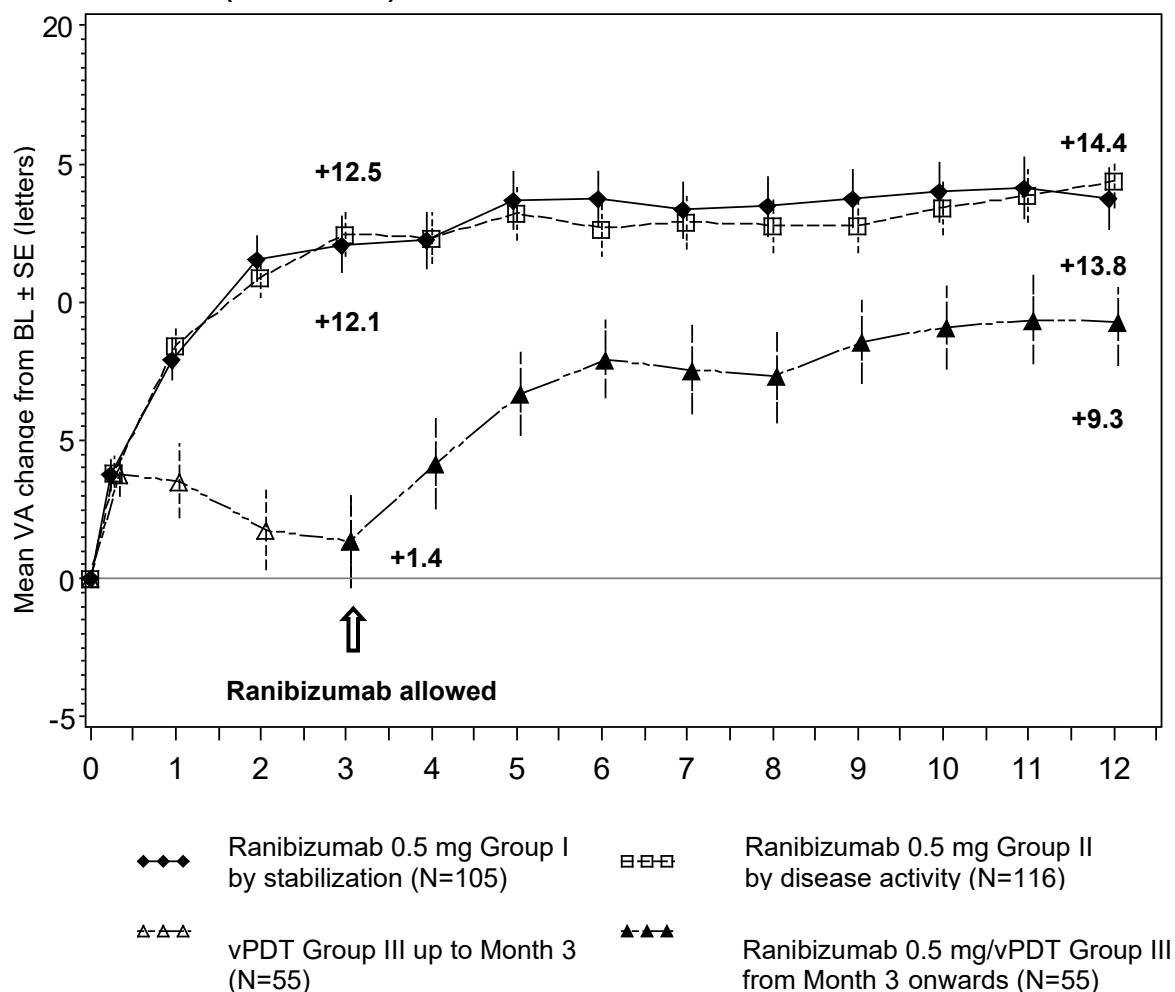
Key outcomes from RADIANCE are summarized in Table 14 and Figure 9.

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 ^h (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)

h: p<0.00001 comparison with vPDT control

Figure -9 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 the ranibizumab treatment arms over vPDT (p-value <0.05) in terms of improvement in the composite score and several subscales (general vision, near activities, mental health and dependency) of the VFQ-25.

Treatment of ROP in preterm infants

Study H2301 (RAINBOW)

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

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

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

Treatment success, as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment, was highest with ranibizumab 0.2 mg (80.0%) compared to laser therapy (66.2%) (see Table 15). The majority of patients treated with ranibizumab 0.2 mg (78.1%) received a single injection per eye.

Table -15 Outcomes at Week 24 (RAINBOW)

Treatment	Treatment Success					
	n/M (%)	95% CI	Comparison	Odds ratio (OR) ^a	95% CI	p-value ^b
Ranibizumab 0.2 mg (N=74)	56/70 (80.0)	(0.6873, 0.8861)	Ranibizumab 0.2 mg vs Laser	2.19	(0.9932, 4.8235)	0.0254
Laser therapy (N=74)	45/68 (66.2)	(0.5368, 0.7721)				

CI= confidence interval, M= total number of patients with non-missing value on primary efficacy outcome (including imputed values), n= number of patients with absence of active ROP and absence of unfavorable structural outcome in both eyes 24 weeks after the first study treatment (including imputed values).
If a patient died or switched study treatment before or at Week 24, then the patient was considered as having active ROP and unfavorable structural outcomes at Week 24
^a odds ratio is calculated by using Cochran-Mantel-Haenszel test with ROP Zone at baseline (Zone I and II; per CRF) as stratum factor.
^b p-value for pairwise comparison is one-sided. For the primary endpoint the pre-specified significance level for the one sided p-value was 0.025.

During the 24 weeks of the study, fewer patients in the ranibizumab 0.2 mg group switched to another treatment modality due to lack of response compared with the laser group (14.9% vs. 24.3%). Unfavourable structural outcomes were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4%) compared with laser therapy (7 patients, 10.1%).

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

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

An ETDRS score in patients who completed the 5th birthday visit was recorded for 83.3% (45/54) and 76.6% (36/47) of patients in the ranibizumab 0.2 mg arm and the laser arm, respectively. The least-squares (LS) mean (SE) was numerically higher in the ranibizumab 0.2 mg arm (66.8 [1.95]) compared to the laser arm (62.1 [2.18]) with a difference in LS mean ETDRS score of 4.7 (95% CI: -1.1, 10.5). The categorised visual acuity outcomes in the better-seeing eye at the patients' 5th birthday is presented in Table 16.

Table 16 Visual acuity outcomes in the better-seeing eye¹ at the patients' 5th

birthday visit

Visual acuity category	Ranibizumab 0.2 mg N=61 n (%)	Laser N=54 n (%)
≥1 to ≤34 letters	1 (1.6)	2 (3.7)
≥35 to ≤70 letters	24 (39.3)	23 (42.6)
≥71 letters	20 (32.8)	11 (20.4)

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

NON-CLINICAL 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 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 or mutagenicity data are available.

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 embryo-foetal development is plausibly related mainly to the inability of the Fab fragment to cross the placenta. Nevertheless, a case was described with high maternal ranibizumab serum levels and presence of ranibizumab in foetal serum, suggesting that the anti-ranibizumab antibody acted as (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling

its placental transfer. As the embryo-foetal development investigations were performed in healthy pregnant animals and disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment, the study should be interpreted with caution.

Pharmaceutical information

INCOMPATIBILITIES

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

STORAGE

See folding box.

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.

Accentrix should not be used after the date marked “EXP” on the pack.

Accentrix must be kept out of the sight and reach of children.

PACK SIZE

Vial with filter needle

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

INSTRUCTIONS FOR USE AND HANDLING

Vials are for single use only (see section DOSAGE REGIMEN AND ADMINISTRATION). After injection any unused product must be discarded.

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 discolored, cloudy, or contains particulates.

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

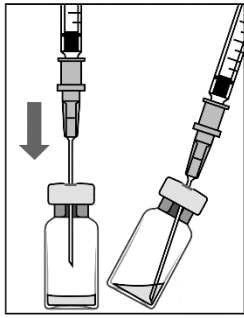
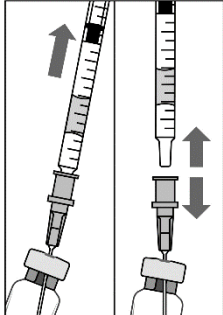
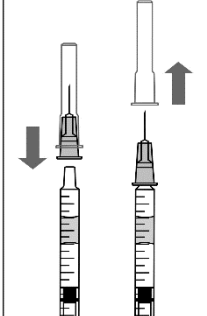
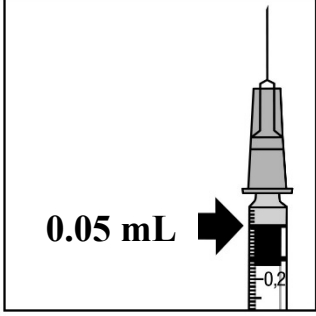
- a 5 micrometer filter needle (18G)
- a 1 mL sterile syringe
- an injection needle (30G x 1/2 inch)

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

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

To prepare Accentrix for intravitreal administration, 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 micrometer filter needle (18G) to a 1 mL syringe using aseptic technique. Push the blunt filter needle into the center 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 1/2 inch) to the syringe. 7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe. Note: Grip at the yellow hub of the injection needle while removing the cap.
D. 	8. Carefully expel the air from the syringe and adjust the dose to the 0.05 mL 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.

Product Registration Holder:

Novartis Corporation (M) Sdn. Bhd.
Level 18, Imazium,
No. 8, Jalan SS21/37, Damansara Uptown,
47400 Petaling Jaya, Selangor.

Malaysian Package Leaflet

Information issued: January 2023 corr May 23

Date of revision: January 2024

® = registered trademark

Novartis Pharma AG, Basel, Switzerland