Lucentis®

Antineovascularization agents

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Solution for injection.

Lucentis is supplied in a vial.

Sterile, clear, colorless to pale 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

Lucentis is indicated in adult for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD)
- the treatment of visual impairment due to diabetic macular edema (DME)
- the treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR)
- the treatment of visual impairment due to macular edema secondary to retinal vein occlusion (branch RVO or central RVO)
- the treatment of visual impairment due to choroidal neovascularization (CNV)
- the treatment of visual impairment due to choroidal neovascularization (CNV) secondary to pathologic myopia (PM)

Lucentis® is indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) (see section CLINICAL STUDIES)

DOSAGE REGIMEN AND ADMINISTRATION

Dosage Regimen

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

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

The recommended dose for Lucentis in adults is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 mL. The interval between two doses injected into the same eye should not be shorter than one month.

The recommended dose for Lucentis in preterm infants is 0.2 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.02 mL. Treatment of ROP is initiated with a single dose and can be given bilaterally on the same day. Further treatment may be administered if there are signs of disease activity. The interval between two doses injected into the same eye should not be shorter than one month.

General target population

Treatment of wet AMD, DME, moderately severe to severe NPDR or PDR, macular edema secondary to RVO, CNV or CNV secondary to PM

Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity.
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.

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, for example, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by two weeks at a time for wet AMD and central RVO (CRVO), or by one month at a time for DME and branch RVO (BRVO). 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. In the treatment of visual impairment due to CNV secondary to PM, many patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see section CLINICAL STUDIES).

Lucentis and laser photocoagulation in DME and branch RVO:

Lucentis has been used concomitantly with laser photocoagulation in clinical studies (see section CLINICAL STUDIES). When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation. Lucentis can be administered in patients who have received previous laser photocoagulation.

Treatment of ROP in preterm infants

Treatment in preterm infants is initiated with a single injection. Further treatment may be administered if there are signs of disease activity.

Special populations

Renal impairment

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

Hepatic impairment

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

Pediatric patients (below 18 years)

Lucentis is not recommended for use in children and adolescents due to insufficient data on safety and efficacy in these sub-populations. Limited data on adolescent patients aged 12 to 17 years with visual impairment due to CNV is available (see section CLINICAL STUDIES, Pediatric patients).

Geriatric patients (65 years or above)

No dose adjustment is required in the elderly.

Method of administration

As with all medicinal products for parenteral use, Lucentis 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 Lucentis, see section INSTRUCTIONS FOR USE AND HANDLING.

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

In preterm infants, the injection needle should be inserted 1.0 to 2.0 mm posterior to the limbus with the needle pointing towards the optic nerve. The injection volume of 0.02 mL is then delivered.

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

Intravitreal injection-related reactions

Intravitreal injections, including those with Lucentis, 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 Lucentis. 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.

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

Arterial thromboembolic events

There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF (vascular endothelial growth factor) inhibitors. In the wet AMD Phase III studies, the overall frequency of arterial thromboembolic events was similar between ranibizumab and control. A numerically higher stroke rate was observed in patients treated with ranibizumab 0.5 mg compared to ranibizumab 0.3 mg or control, however, the differences were not statistically significant. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke or transient ischemic attack. Therefore, these patients should be carefully evaluated by their physicians as to whether Lucentis treatment is appropriate and whether the benefit outweighs the potential risk.

Immunogenicity

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

Bilateral treatment

Available data do not suggest an increased risk of systemic adverse events with bilateral treatment.

Patient populations with limited data

Lucentis has not been studied in patients with active systemic infections or in patients with concurrent eye conditions such as retinal detachment or macular hole.

Driving and using machines

The Lucentis 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 Lucentis 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 Lucentis-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 Lucentis 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 Lucentis.

DME population

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

DR population

The safety of Lucentis was studied for up to 24 -months in Protocol S and the clinical trials RESTORE, REVEAL, and REFINE, including 395 ranibizumab-treated patients with moderately severe to severe NPDR or PDR (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 Lucentis

RVO population

The safety of Lucentis was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular 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 Lucentis 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 Lucentis.

PM population

The safety of Lucentis was studied in the 12-month clinical trial (RADIANCE), which included 224 ranibizumab-treated patients with visual impairment due to CNV secondary to PM (see section 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.

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

Table 1 Adverse 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 Lucentis 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.

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

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

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

For ranibizumab no clinical data on exposed pregnancies are available.

A study in cynomolgus monkeys does not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/fetal development (see Animal 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-/fetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus. 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.

Animal Data

In pregnant monkeys, IVT administration ranibizumab did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta. However due to restrictions dictated by the IVT route of administration, the doses used in this study did not reach maternal toxicity but achieved a multiple (up to 100-fold) with respect to human systemic exposure.

The absence of ranibizumab-mediated effects on embryo-fetal development is plausibly related to the inability of the antigen-binding fragment (Fab) to cross the placenta due to the absence of an Fc region. Nevertheless, a case was described with high maternal ranibizumab serum levels and presence of ranibizumab in fetal serum, suggesting that the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer. The embryo-fetal development investigations were performed in healthy pregnant animals and disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment.

Lactation

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

Females and males of reproductive potential

Contraception

Females of reproductive potential should use effective contraception during treatment with ranibizumab.

Infertility

There is no fertility data available.

OVERDOSAGE

Cases of accidental overdose (injection of volumes greater than the recommended 0.05 mL Lucentis) have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions most frequently associated with these reported cases were 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) Lucentis dose.

Clinical pharmacology

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. $VEGF_{110}$, $VEGF_{121}$ and $VEGF_{165}$), 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, including 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 Lucentis to patients with neovascular AMD, serum concentrations of ranibizumab were generally low, with maximum levels (C_{max}) generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11 to 27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Upon monthly intravitreal administration of Lucentis 0.5 mg/eye, serum ranibizumab C_{max}, attained approximately 1 day after dosing, is predicted to generally range between 0.79 and 2.90 ng/mL, and C_{min} is predicted to generally range between 0.07 and 0.49 ng/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 Lucentis 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 Lucentis 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 Lucentis in patients with hepatic impairment.

CLINICAL STUDIES

Treatment of wet AMD

In wet AMD, the clinical safety and efficacy of Lucentis 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 Lucentis 0.3 mg or 0.5 mg or sham injections. A total of 716 patients were enrolled in this study (sham, 238; Lucentis 0.3 mg, 238; Lucentis 0.5 mg, 240).

In the 24-month study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham PDT; 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Verteporfin (or sham) PDT was given with the initial Lucentis (or sham) injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients were enrolled in this study (Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140, verteporfin PDT, 143).

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

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)	Lucentis 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)

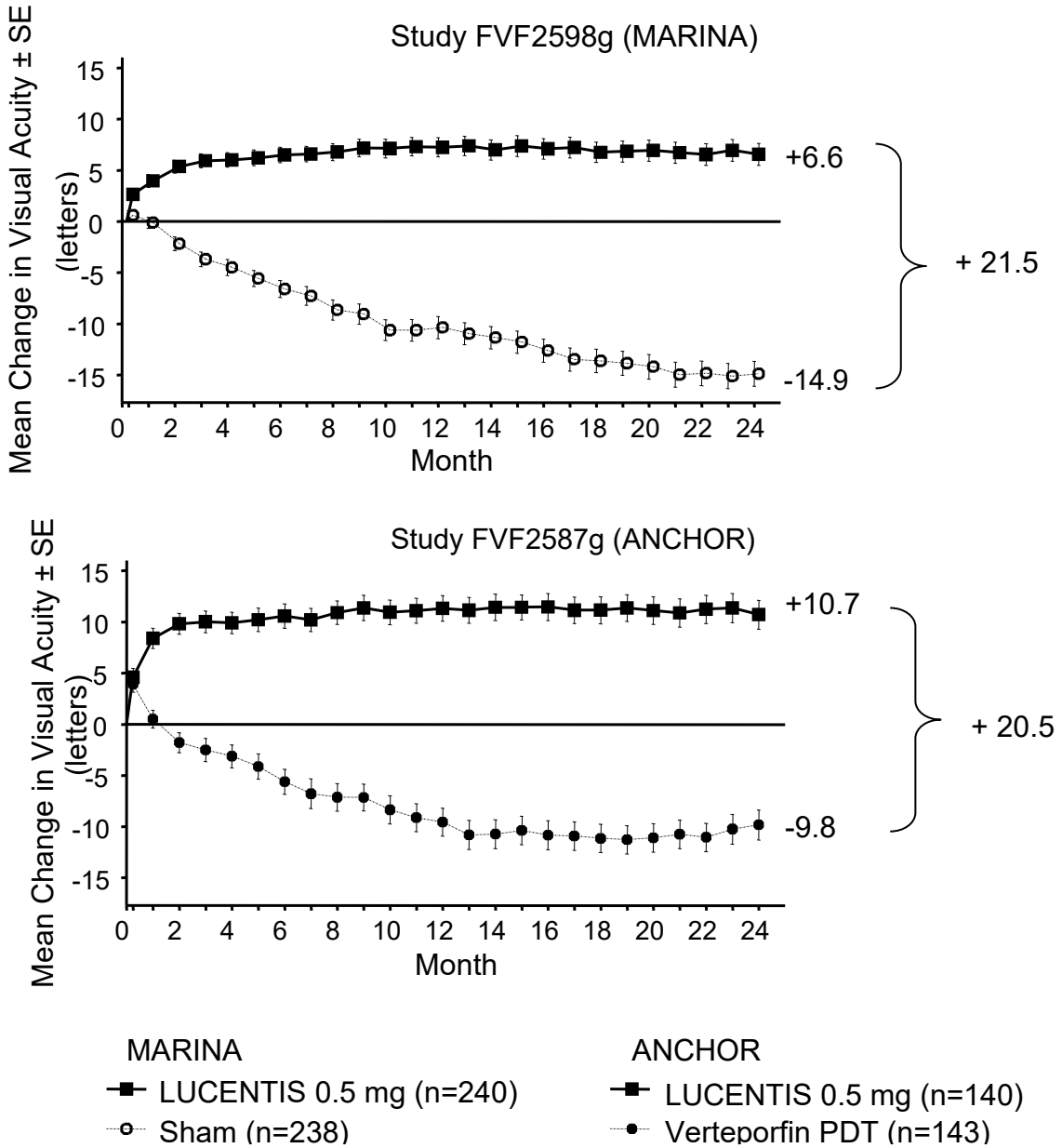
[a] $p<0.01$.

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

Outcome measure	Month	Verteporfin PDT (n=143)	Lucentis 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 Lucentis had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1 to 0.3 DA for Lucentis versus 2.3 to 2.6 DA for the control arms.

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 Lucentis 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 Lucentis 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 Lucentis in 184 patients with neovascular AMD (with or without a classic CNV component). Patients received Lucentis 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 Lucentis 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 Lucentis lost visual acuity, returning to baseline at Month 12. This effect was maintained in most Lucentis-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 Lucentis 0.5 mg monotherapy vs. Lucentis 0.5 mg in combination with verteporfin photodynamic therapy (vPDT) in 322 Asian patients with symptomatic macular polypoidal choroidal vasculopathy (PCV), a subtype of wet AMD. Patients in both study arms initiated treatment with three monthly Lucentis injections, plus

sham or active vPDT given with the first Lucentis injection only. Following treatment initiation, Lucentis monotherapy and Lucentis administered with vPDT were given pro re nata (PRN) based on ocular clinical assessments, including imaging techniques (e.g. OCT, FA, ICGA). Primary results at Month 12 demonstrated that Lucentis administered with vPDT was superior to Lucentis monotherapy with respect to the BCVA change from baseline (8.3 letters versus 5.1 letters, p=0.013) and complete polyp regression (69.3% versus 34.7%, p<0.001). Patients administered Lucentis with vPDT received on average 2.3 Lucentis injections less than patients administered Lucentis monotherapy (5.1 vs. 7.4 injections).

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

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

Treatment of visual impairment due to DME

The efficacy and safety of Lucentis have been assessed in two randomized, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular edema (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.

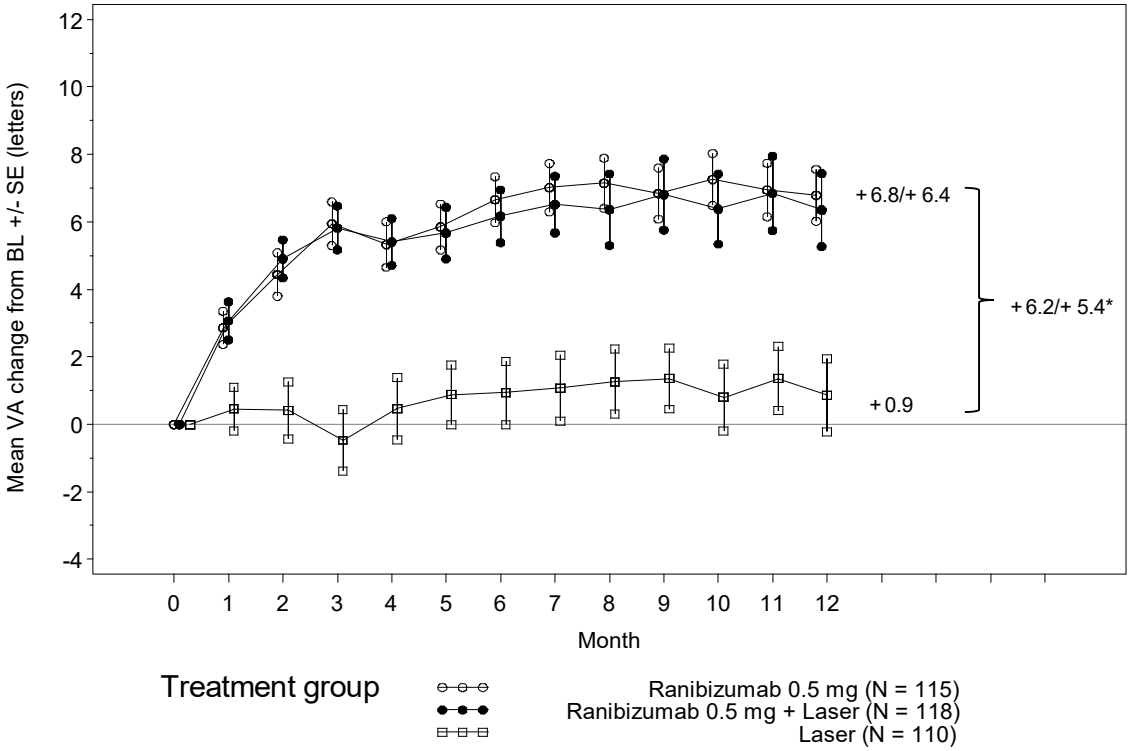
Table 4 Outcomes at Month 12 in study D2301 (RESTORE)

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

[b]p<0.0001, [c]p=0.0004, [d]p=0.0001, [e]p=0.0032, [f]p=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 Lucentis safety profile.

Study D2201 (RESOLVE)

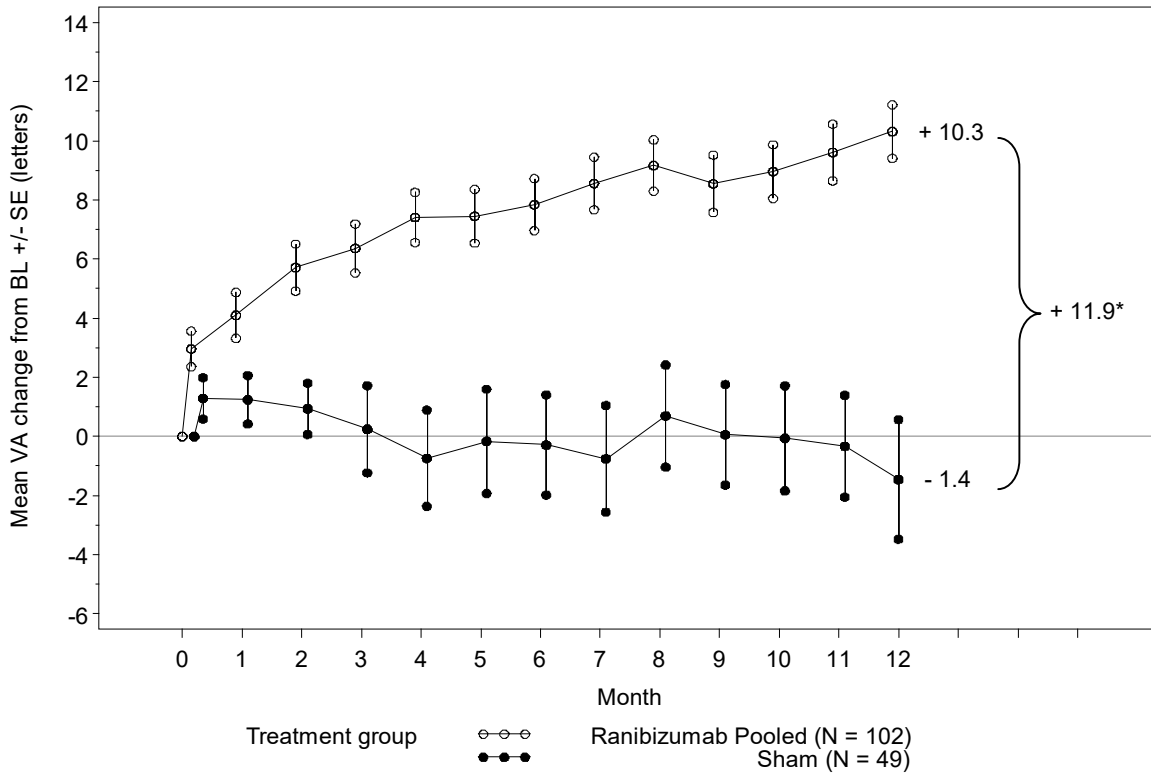
In study D2201 (RESOLVE), a total of 151 patients with macular center involvement causing visual impairment were treated with ranibizumab (6 mg/ml, n=51, 10 mg/ml, n=51) or sham (n=49) by monthly intravitreal injections until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (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 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 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

[b] $p<0.0001$

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.

Treatment of moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

The clinical safety and efficacy of Lucentis in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) have been assessed in 4 studies that evaluated treatment with ranibizumab 0.5 mg intravitreal injections compared to standard treatment with either active laser or panretinal photocoagulation (PRP). Change in diabetic retinopathy severity was assessed based on fundus photographs using the ETDRS Diabetic Retinopathy Severity Score (DRSS).

Protocol S

Protocol S was a multicenter, randomized, active-controlled, parallel-assignment, non-inferiority Phase 3 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. A total of 306 eyes (77.7%) did not have baseline DME: 149 (78.0%) and 157 (77.3%) eyes in the ranibizumab and PRP groups, respectively.

In this study, 41.8% of eyes experienced a ≥2 -step improvement in the DRSS at month 12 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]).

Study D2301 (RESTORE), Study D2303 (REVEAL), and Study D2305 (REFINE)

Studies D2301 (RESTORE), D2303 (REVEAL), and D2305 (REFINE) were randomized, double masked, active-controlled Phase 3 studies of similar design in patients with visual impairment due to DME that included a total of 875 patients treated with ranibizumab 0.5 mg PRN or laser. In a meta-analysis of these studies, 48.4% of the 315 patients in the subgroup of

patients with moderately severe to severe NPDR or PDR 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]) (see Table 8).

Table 8 DRSS improvement or worsening of ≥2 or ≥3 steps at year 1 in Protocol S and pooled Novartis studies (LOCF Method)

Categorized change from baseline	Protocol S			Pooled Novartis studies[1]		
	Ranibizumab 0.5 mg (N=189)	PRP (N=199)	Difference in proportion (%), CI	Ranibizumab 0.5 mg N= 192	Laser N= 123	Difference in proportion (%), CI
≥2-step improvement						
n (%)	79 (41.8)	29 (14.6)	27.4 (18.9, 35.9)	93 (48.4)	18 (14.6)	29.9 (20.0, 39.7)
≥3-step improvement						
n (%)	54 (28.6)	6 (3.0)	25.7 (18.9, 32.6)	42 (21.9)	8 (6.5)	13.4 (5.8, 21.0)
≥2-step worsening						
n (%)	3 (1.6)	23 (11.6)	-9.9 (-14.7, -5.2)	4 (2.1)	10 (8.1)	-6.0 (-11.3, -0.8)
≥3-step worsening						
n (%)	1 (0.5)	8 (4.0)	-3.4 (-6.3, -0.5)	2 (1.0)	6 (4.9)	-3.7 (-7.7, 0.3)

DRSS= diabetic retinopathy severity score, n= number of patients who satisfied the condition at the visit, N= total number of study eyes.

[1] Pooled patient population includes patients with moderately severe NPDR or worse at baseline in the Full analysis set in specific treatment group.

Differences in proportion are based on stratified analysis using CMH weights. Stratification factors for Protocol S includes number of study eyes and baseline DME status, Stratification factors for Novartis studies include study ID.

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 edema secondary to RVO

Study FVF4165g (BRAVO) and study FVF4166g CRUISE

The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular 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.

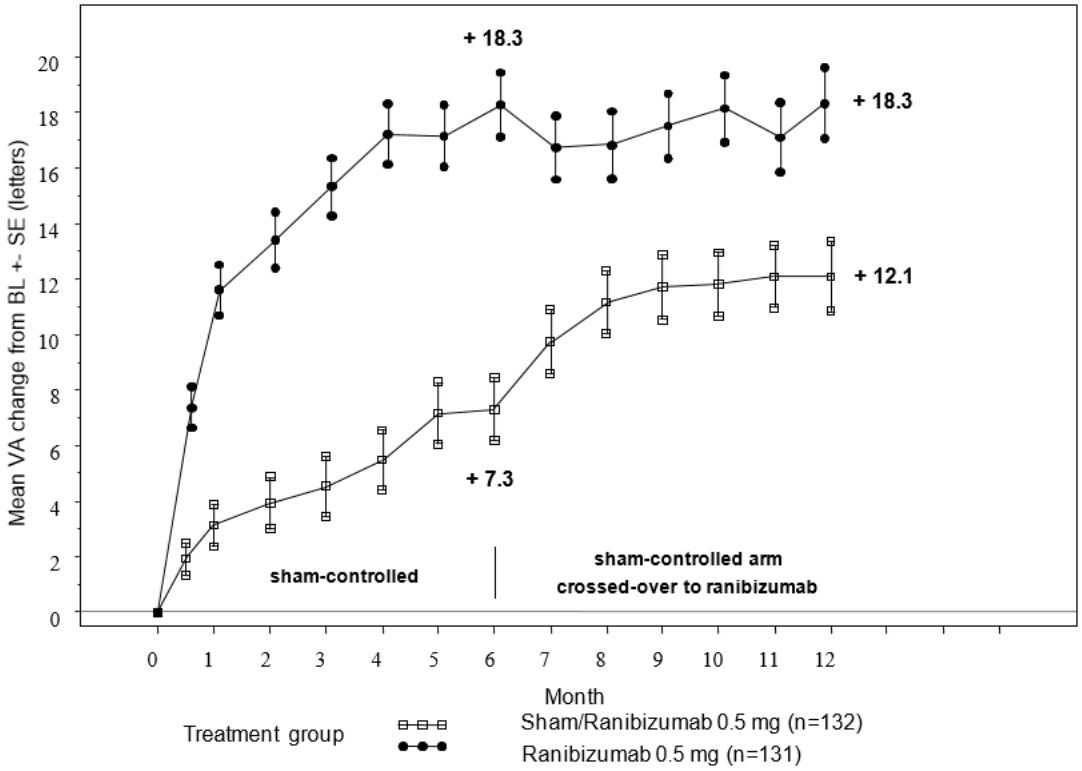
Key outcomes from BRAVO and CRUISE are summarized in Tables 9 and 10, and Figures 4 and 5.

Table 9 Outcomes at Month 6 and 12 (BRAVO)

	Sham/Lucentis 0.5 mg (n=132)	**Lucentis 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)



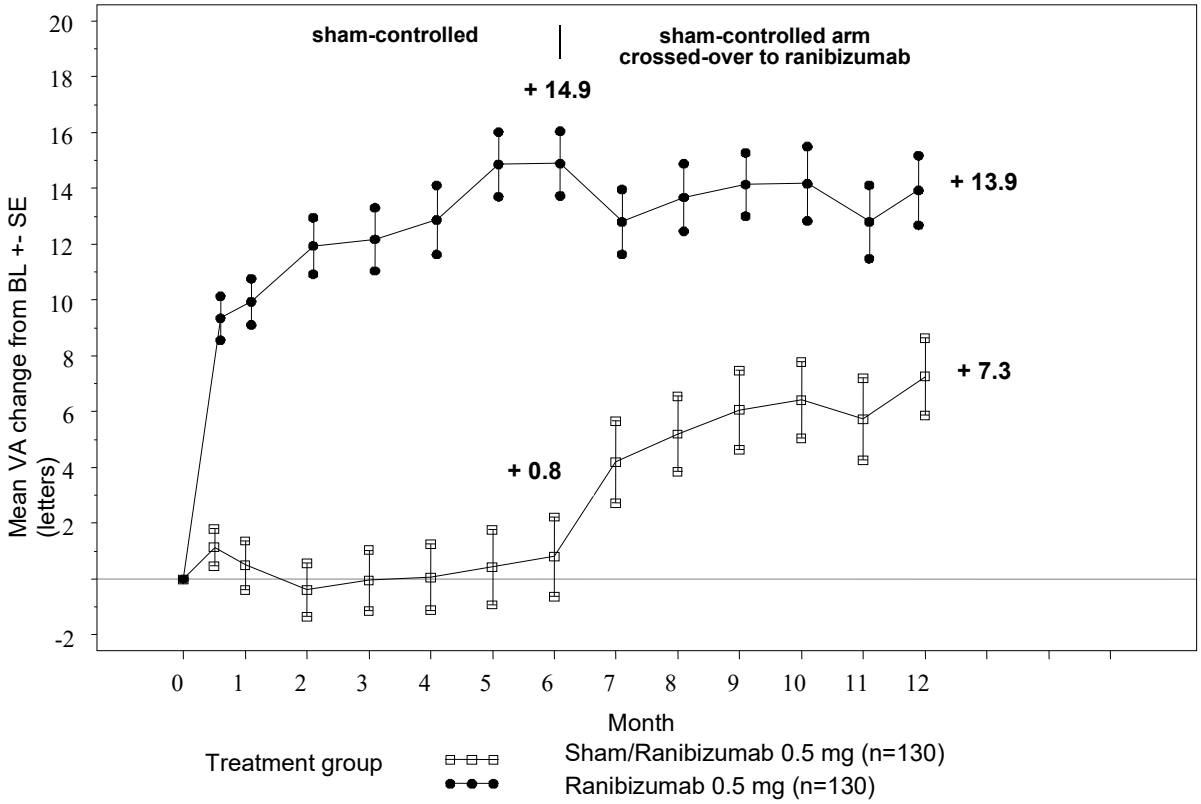
BL=baseline; SE=standard error of mean

Table 10 Outcomes at Month 6 and 12 (CRUISE)

	Sham/Lucentis 0.5 mg (n=130)	**Lucentis 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 Lucentis 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 Lucentis in patients with visual impairment due to macular edema secondary to RVO were assessed in the BRIGHTER and CRYSTAL studies, which recruited subjects with BRVO (n=455) and CRVO (n=357), respectively. In both studies, subjects received a 0.5 mg ranibizumab PRN dosing regimen driven by individualized stabilization criteria. BRIGHTER was a 3-arm, 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
	Lucentis 0.5 mg N=180	**Lucentis 0.5 mg + Laser N=178**	**Laser* N=90**	**Lucentis 0.5 mg (N=356)**
Mean change in BCVA at Month 6[b] (letters) (SD)	+14.8 (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: Lucentis 0.5 mg vs Laser and Lucentis 0.5 mg + Laser vs Laser.

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

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

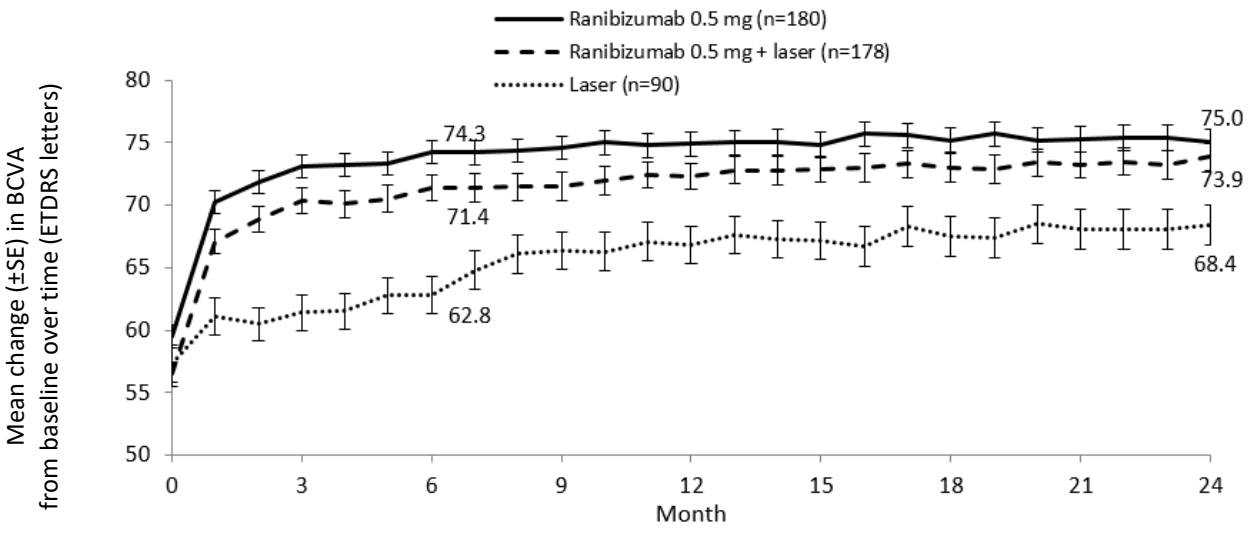
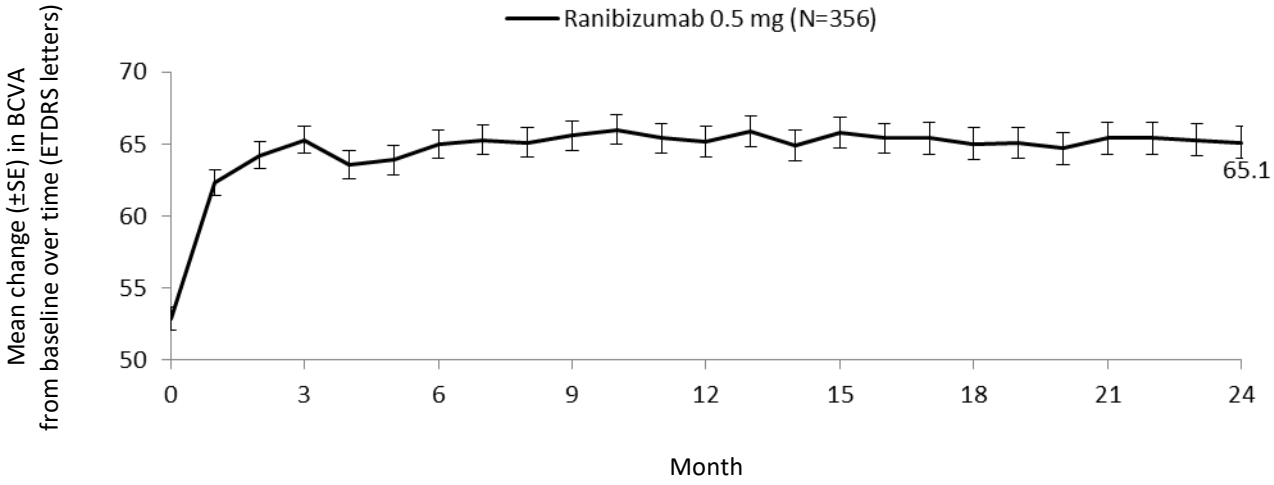


Figure 7 CRYSTAL: Mean change in BCVA from baseline over 24 months



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 Lucentis safety profile.

Treatment of visual impairment due to CNV

Study G2301 (MINERVA)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV secondary to etiologies other than nAMD and PM have been assessed 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.

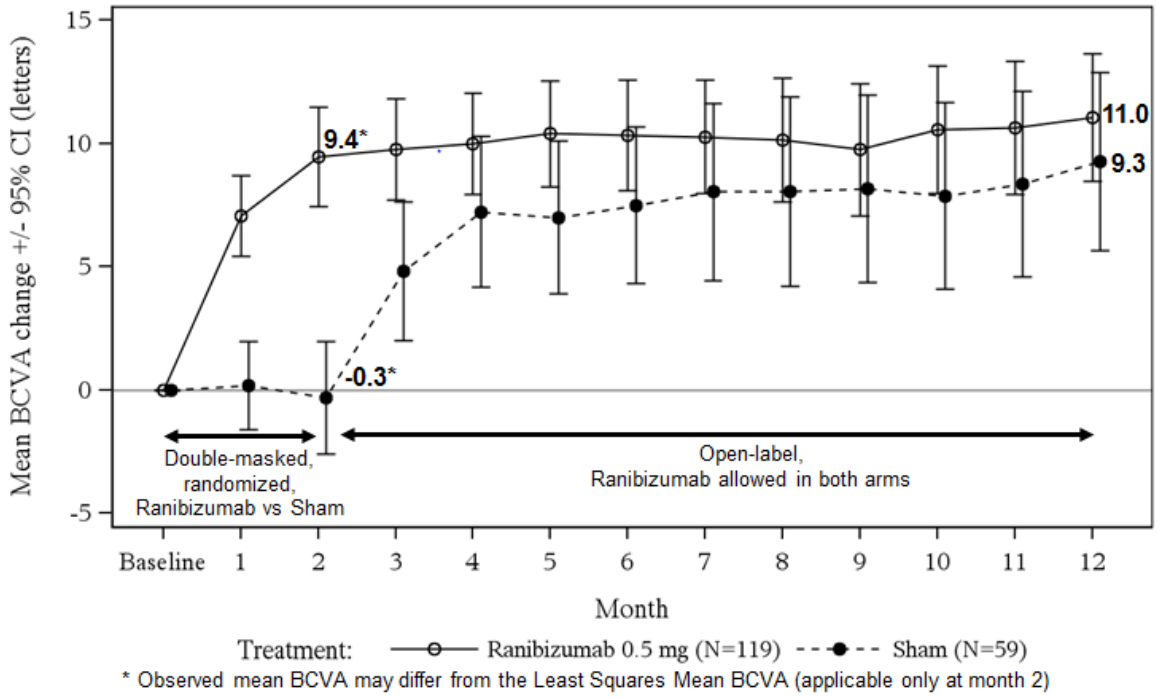
Table 12 Outcomes at Month 2 (MINERVA)

	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 Lucentis 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.

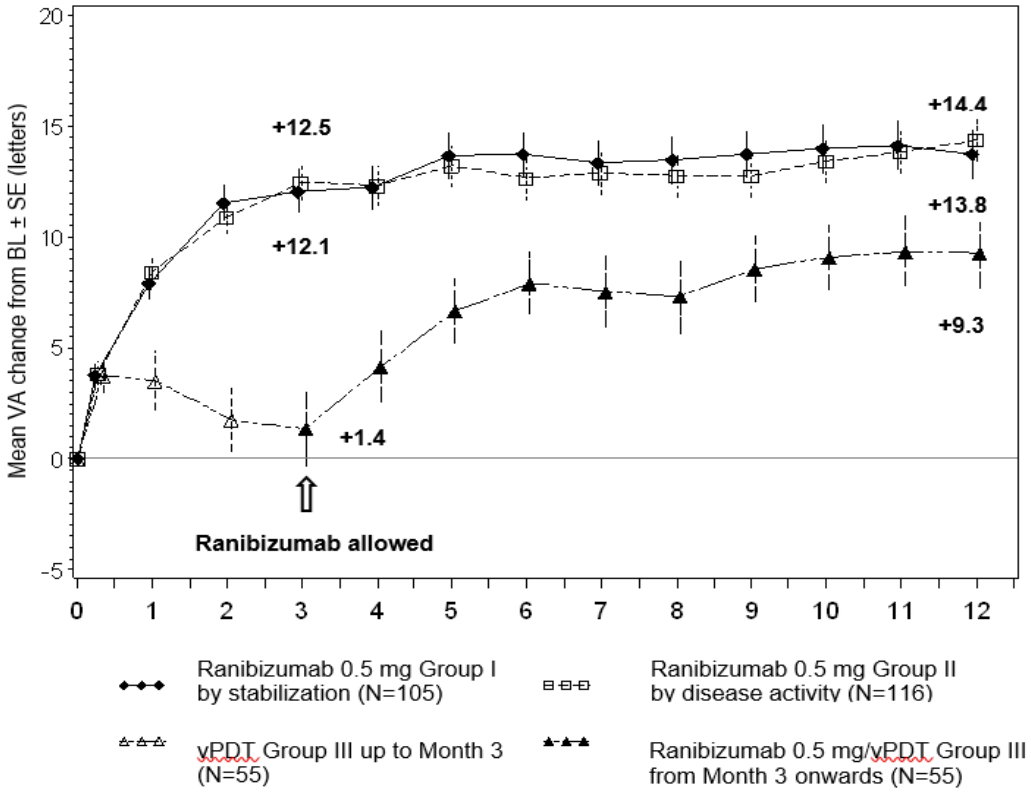
Table 14 Outcomes at Month 3 and Month 12 (RADIANCE)

	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[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[a] (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

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 Lucentis 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%). The majority of patients treated with ranibizumab 0.2 mg (78.1%) did not require re-treatment with ranibizumab. The difference between ranibizumab 0.2 mg and laser was clinically relevant with an odds ratio (OR) of 2.19 (95% confidence interval (CI) [0.9932, 4.8235]). The primary endpoint did not reach statistical significance (see Table 15).

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.

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%). Unfavorable structural outcomes were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4%) compared with laser therapy (7 patients, 10.1%). In addition, 75% of patients achieved resolution of plus disease within 8 days with ranibizumab 0.2 mg compared to 22.5 days in patients treated with laser.

Study H2301E1 (RAINBOW extension)

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).

A higher proportion of patients in the ranibizumab 0.2 mg arm had an ETDRS score of ≥71 letters (20 patients, 32.8%) compared to the laser arm (11 patients, 20.4%).

Table 16 Visual acuity outcomes in the better-seeing eye[1] at the patient's 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 and mutagenicity data are available.

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.

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

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

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

INSTRUCTIONS FOR USE AND HANDLING

Vial (adults and preterm infants)

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.

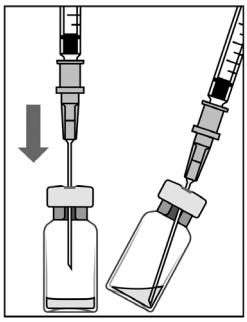
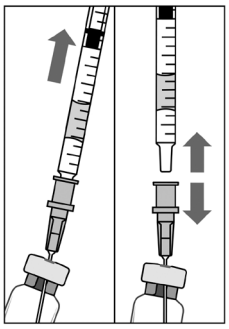
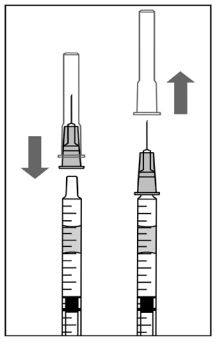
For preparation and intravitreal injection, the following single-use medical devices are needed:

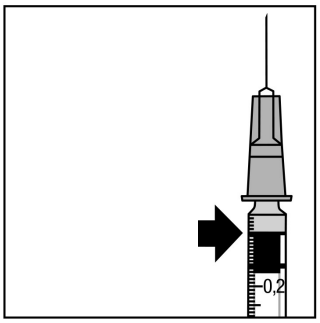
- a 5 micrometer filter needle (18G)
- a 1 mL sterile syringe
- an injection needle (30G x 1/2 inch)

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

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

To prepare Lucentis for intravitreal 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 appropriate mark on the syringe. The dose for adults is 0.05 mL. The dose for preterm infants is 0.02 mL. 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.

Manufacturer:

See folding box.

International Package Leaflet

Information issued: May-2023

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Novartis Pharma AG, Basel, Switzerland