NOVARTIS

Lucentis®

Anti-neovascularisation agent

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Solution for injection.

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

Vial

Sterile, clear, colourless to pale brownish-yellow and preservative-free aqueous solution for injection.

Pre-filled syringe

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

Active substance

Vial

One mL contains 10 mg ranibizumab. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Pre-filled syringe

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

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

Not all presentations may be available locally

Excipients

alpha, alpha-trehalose dihydrate, 1-histidine hydrochloride, l-histidine free base, polysorbate 20, water for injection

INDICATIONS

Lucentis is indicated in adults 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 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).

Lucentis is indicated in preterm infants for:

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

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

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

Lucentis must be administered by a qualified ophthalmologist experienced in intravitreal injections. The recommended dose for Lucentis in adults is 0.5 mg (0.05 mL) or 0.3mg (0.03mL) given monthly as a single intravitreal injection. The interval between two doses injected into the same eye should not be shorter than one month.

The recommended maximal dose (0.5mg) should not be exceeded. One eye only should be injected on each occasion and post-injection monitoring is recommended (see section WARNINGS AND PRECAUTIONS).

The treat-and-extend regimen and the treatment of PDR is only pertaining to the 0.5mg dose.

The recommended dose for Lucentis in preterm infants is 0.2 mg given as an intravitreal injection. This corresponds to an injection volume of 0.02 mL. In preterm infants treatment of ROP is initiated with a single injection per eye and may be given bilaterally on the same day. In the clinical study (RAINBOW), up to three ranibizumab injections per eye (i.e. 6 injections in total per subject) were allowed within six months of treatment initiation if there were signs of disease activity. Most patients (57 (78%.1)) in the clinical study received a total of one injection per eye. Ten (13.7%) patients received a total of two injections per eye and two (2.7%) received a total of three injections per eye. The administration of more than three injections per eye has not been studied. The interval between two doses injected into the same eye should be at least four weeks.

The pre-filled syringe can only deliver a dose of 0.5mg (0.05mL) due to a fixed dose mark. The single-use vial must be used when a dose of 0.3mg (0.03mL) or 0.2mg (0.02mL) is required.

General target population

Treatment of wet AMD, DME, 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. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity as assessed by visual acuity and/or anatomic parameters. If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

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

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 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. 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,(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

Lucentis and Verteporfin photodynamic therapy in CNV secondary to PM

There is no experience of concomitant administration of Lucentis and Verteporfin.

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

Treatment of ROP in preterm infants

Treatment in preterm infants is initiated with a single injection per eye and may be given bilaterally on the same day.

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 of age)

The safety and efficacy of Lucentis in children and adolescents for indications other than retinopathy of prematurity have not been established. 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 of age and 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 should be carefully evaluated for hypersensitivity reactions 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 more 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 centre of the globe. The injection volume of 0.03ml or 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.

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

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

Intravitral 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.

Bilateral treatment

Limited data on bilateral use of Lucentis (including same-day administration) do not suggest an increased risk of systemic adverse events with unilateral treatment. The efficacy of Lucentis therapy administered to both eyes concurrently has not been studied (see section DOSAGE AND ADMINISTRATION).

Immunogenicity

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

Patients should be instructed to report if an intraocular inflammation increases in severity, which may be a clinical sign attributable to intraocular antibody formation. There is a theoretical risk of hypersensitivity reactions including anaphylaxis/anaphylactoid reactions or angioedema which may occur with the use of Lucentis.

Immunogenicity: The pre-treatment incidence of immunoreactivity to Lucentis was 0%-3% across treatment groups. After monthly dosing with Lucentis for 12 to 24 months, low titres of antibodies to Lucentis were detected in approximately 1%-6% of patients. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to Lucentis in an electrochemiluminescence assay and are highly dependent on the sensitivity and specificity of the assay. The clinical significance of immunoreactivity to Lucentis is unclear

at this time, although some patients with the highest levels of immunoreactivity were noted to have iritis or vitritis.

Lucentis has not been studied in patients who have previously received intravitreal injections

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

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 ≥30mmHg

- A retinal break

- A subretinal haemorrhage involving the centre of the fovea, or if the size of the haemorrhage is ≥50% of the total lesion area

- Performed or planned intraocular surgery within the previous or next 28 days.

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

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.

There is insufficient data to conclude on the effect of Lucentis in patients with RVO presenting with irreversible ischemic visual function loss.

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

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.

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 established for up to 5 years in the RAINBOW extension study and showed no new safety signals. The safety profile of ranibizumab 0.2mg during the RAINBOW extension study was consistent with that observed in the RAINBOW core study at 24 weeks (see section CLINICAL STUDIES).

Instructions for caregivers of preterm infants

The ophthalmologist should advise the parent/caregiver of the preterm infant to immediately contact the ophthalmologist if the baby develops symptoms such as increased irritability, excessive crying, or worsening eye redness.

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 0.5mg.

Serious adverse events related to the injection procedure and occurring in <0.1% of intravitreal injections 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 and occurring in <2% of subjects 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 patients of the combined 0.5 mg treatment groups in wet AMD.

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 12 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 study (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

Cardiac disorders	
Uncommon	Atrial fibrillation
Blood and lymphatic system disorders	
Common	Anaemia
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very Common	Headache
Common	Stroke
Eye disorders	
Very common	Conjunctival haemorrhage, eye pain, vitreous floaters, retinal hemorrhage, vitreous detachment, intraocular inflammation, eye irritation, foreign body sensation in eyes, visual disturbance, lacrimation increased, blepharitis, ocular hyperaemia, dry eye, vitritis, eye pruritus
Common	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous hemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctuate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site hemorrhage, eye hemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid edema, eyelid pain, conjunctival hyperemia

Uncommon	Blindness, endophthalmitis, hypopyon, hyphema, keratopathy, iris adhesions, corneal deposits, corneal edema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation
Respiratory, thoracic and mediastinal disorders	
Common	Cough
Uncommon	Wheezing, increased upper airway secretion
Gastrointestinal disorders	
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Allergic reactions (rash, urticaria, pruritus, erythema)
Uncommon	Lichenoid keratosis
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia
Common	Back pain
Infections and Infestations	
Very common	Nasopharyngitis
Common	Bronchitis, anaemia, influenza, urinary tract infection*
Vascular disorders	
Very common	Hypertension/elevated blood pressure
Investigations	
Very common	Intraocular pressure increased

*observed only in the DME population

A meta-analysis of pooled safety data from completed, randomized, double masked global studies showed a higher incidence rate of non-serious, non-ocular wound infection/inflammation in DME patients treated with ranibizumab 0.5 mg (1.85/100 patient years) compared to control (0.27/100 patient years). The relationship to ranibizumab remains unknown.

Product-class-related adverse reactions

In the wet AMD phase III studies, the overall frequency of non-ocular hemorrhages, an adverse event potentially related to systemic VEGF (vascular endothelial growth factor) inhibition, was slightly increased in ranibizumab-treated patients. However, there was no consistent pattern among the different hemorrhages. There is a theoretical risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. A low incidence rate of arterial thromboembolic events was observed in the Lucentis clinical trials in patients with AMD, DME and RVO and there were no major differences between the groups treated with ranibizumab compared to control.

Arterial Thromboembolic events

There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF 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 with neovascular (wet) age-related macular degeneration treated with 0.5mg intravitreal ranibizumab compared to 0.3mg intravitreal ranibizumab(1.2% versus 0.7% respectively). 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. Patients who suffer a thromboembolic event while being treated with Lucentis should be carefully evaluated by their physician who will assess if continuation of Lucentis is appropriate ie. if the benefit to the patient continues to justify the risk.

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 CLINICAL STUDIES). Ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2mg were retinal haemorrhage and conjunctival haemorrhage. Non-ocular adverse reactions reported in more than one patient treated with ranibizumab 0.2mg were nasopharyngitis, anemia, cough, urinary tract infection and allergic reactions. Adverse reactions established for adult indications are considered applicable to preterm infants with ROP, though not all were observed in the RAINBOW trial. Long-term safety in preterm infants with ROP has been established up to the age of 5 years in the RAINBOW extension study and showed no new safety signals. The safety profile of ranibizumab 0.2mg during the RAINBOW extension study was consistent with that observed in the RAINBOW core study at 24 weeks (see section CLINICAL STUDIES).

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 verteporfin photodynamic therapy (PDT) and Lucentis in wet AMD and PM see section CLINICAL STUDIES.

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see sections CLINICAL STUDIES and DOSAGE 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 of ranibizumab did not elicit developmental toxicity or teratogenicity and had no effect on the weight or structure of the placenta. However due to restrictions dictated by the IVT route of administration, the doses used in the 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 levels. The effects of ranibizumab on the breastfed infant or the effects of ranibizumab on milk production/excretion are unknown. As a precautionary measure, breast-feeding is not recommended during the use of Lucentis. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lucentis and any potential adverse effects on the breastfed child from ranibizumab.

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 0.05mL Lucentis) have been reported from the clinical studies in wet AMD and post-marketing data. Adverse reactions associated with these reported cases were intraocular pressure increased, transient blindness, reduced visual acuity, corneal oedema, corneal pain, and eye pain. If an overdose occurs, intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

In clinical trials doses up to 2 mg of ranibizumab have been administered to patients with wet AMD and DME in an injection volume of 0.05 mL to 0.10 mL. 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

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 neovascularisation, as well as vascular leakage, which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, to the development of CNV, including CNV secondary to pathologic myopia, or to the macular edema causing visual impairment in diabetes, retinal vein occlusion and retinopathy of prematurity in preterm infants.

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 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).

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)

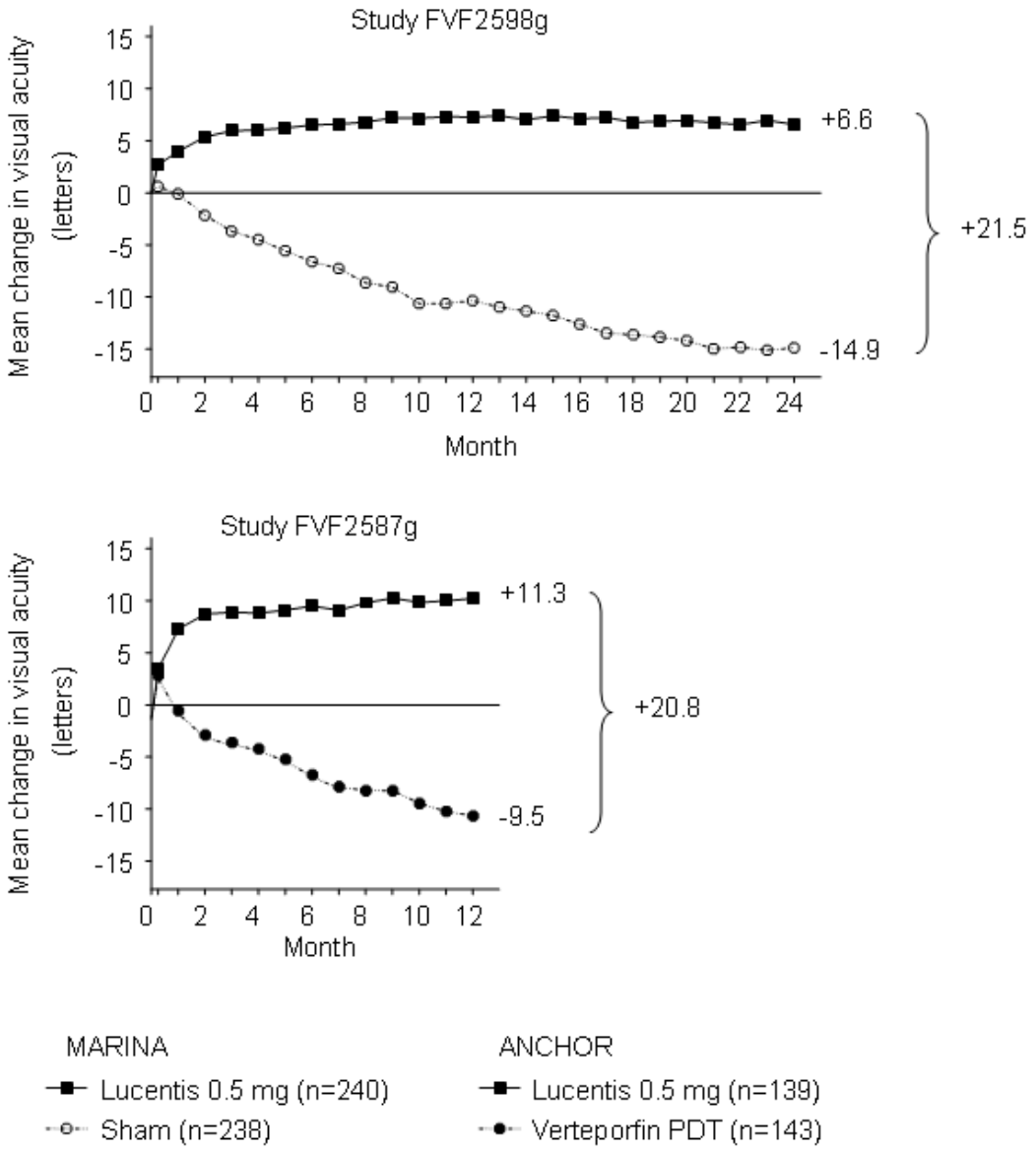
[a] $p<0.01$.

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 to Month 12 in 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.

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.

Table 4 Mean Change from Baseline in VFQ-25 Near Activities, Distance Activities, and Vision-Specific Dependency Subscale Scores at Month 24: Randomized Subjects

Change in VFQ-25 Scores at Month 24	Verteporfin PDT (n=143)	Ranibizumab 0.3mg (n=140)	Ranibizumab 0.5mg (n=140)
N	142	137	139
Near Activities			
Mean (SD)	0.2 (23.0)	7.8 (24.3)	7.1 (25.2)
95% CI of the mean [a]	(-3.6, 4.0)	(3.7, 11.9)	(2.8, 11.3)
Difference in LS means (vs. verteporfin PDT) [b]		9.0	8.1
95% CI of the difference [b]		(3.9, 14.1)	(2.9, 13.3)
p-value (vs verteporfin PDT) [b]		0.0006	0.0023
Distance activities			
Mean (SD)	-1.1 (22.6)	5.6 (22.0)	6.3 (24.3)
95% CI of the mean [a]	(-4.9, 2.6)	(1.8, 9.3)	(2.3, 10.4)
Difference in LS means (vs. verteporfin PDT) [b]		8.5	9.0
95% CI of the difference [b]		(3.5, 13.4)	(3.9, 14.0)
p-value (vs verteporfin PDT) [b]		0.0008	0.0006
Vision-specific dependency			
Mean (SD)	-2.2 (28.3)	3.0 (27.7)	6.2 (30.4)
95% CI of the mean [a]	(-6.9, 2.5)	(-1.6, 7.7)	(1.1, 11.3)
Difference in LS means (vs. verteporfin PDT) [b]		7.7	9.8
95% CI of the difference [b]		(1.8, 13.7)	(3.9, 15.8)
p-value (vs verteporfin PDT) [b]		0.0107	0.0013

CI=confidence interval; LS=least squares; PDT=photodynamic therapy; SD=standard deviation
[a] Based on the t-distribution
[b] Based on pairwise ANCOVA models adjusted for the stratification variable and baseline value of the corresponding endpoint

Study FVF3689 (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 24 month, randomized, double-masked phase IV multi-center 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 analysis 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 vs. 5.1 letters, p=0.013) and complete polyp regression (69.3% versus 34.7%, p<0.001). Patients administered Lucentis in combination with vPDT received 2.3 Lucentis injections less than patients administered Lucentis monotherapy on average (5.1 vs. 7.4injections).

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 in combination with vPDT received 4.2 Lucentis injections less than patients administered Lucentis monotherapy on average (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 injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham** injection and laser photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments visits. 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.

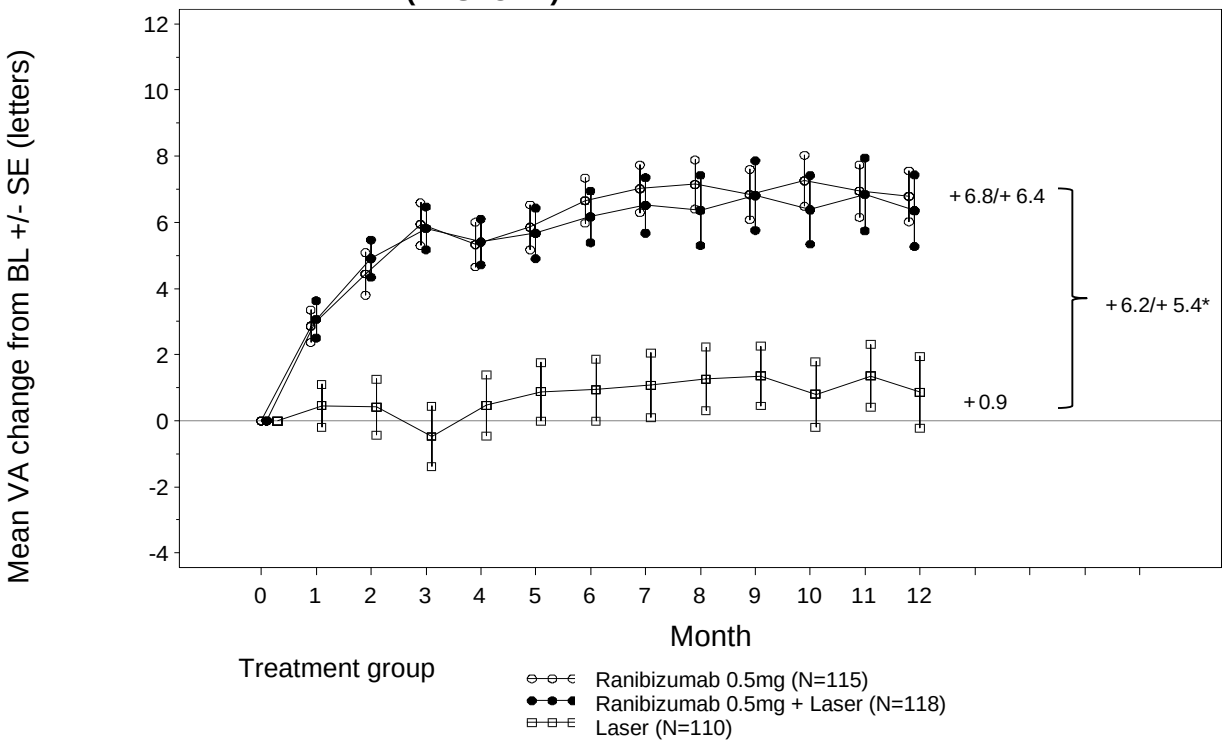
Key outcomes are summarized in Table 5 and Figure 2.

Table 5 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) [b]	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 6.

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

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

n = 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 (Group A) consisting of 42 patients analyzed at Month 6, and a confirmatory part the remaining 109 patients analysed at Month 12.

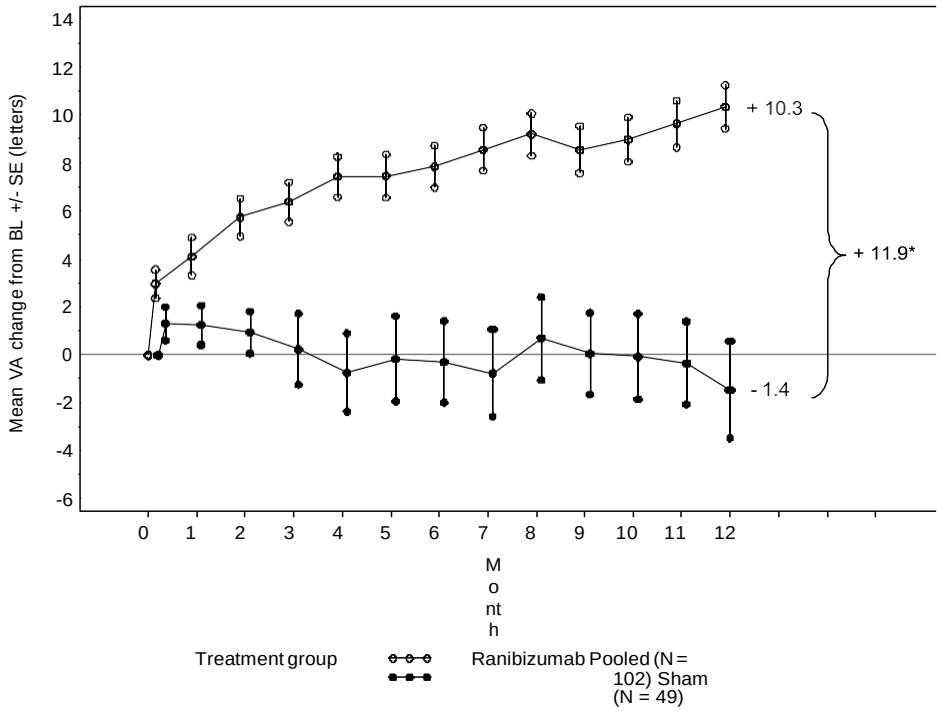
Key outcomes from the confirmatory part of the study (2/3 of the patients) are summarized in Table 7 and Figure 3.

Table 7 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, after 3 initial monthly treatment visits, the number of scheduled treatment visits required by the TE regimen was 13 compared to the 20 monthly visits required by the PRN regimen. 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 8.

Table 8 Outcomes in study D2304 (RETAIN)

Outcome measure compared to baseline	TE Ranibizumab 0.5 mg + Laser n=117	TE Ranibizumab 0.5 mg 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 CSFT in all the treatment groups.

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 average change in visual acuity at Month 12 compared to baseline were +5.9 letters in the ranibizumab monotherapy group, +5.7 letters in the ranibizumab plus laser group and +1.4 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 proliferative diabetic retinopathy (PDR)

The clinical safety and efficacy of Lucentis in patients with 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]).

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.

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 9).

Table 9 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.

Treatment of visual impairment due to macular edema secondary to RVO

Study FVF4165g (BRAVO) and study FVF4166g (CRUISE)

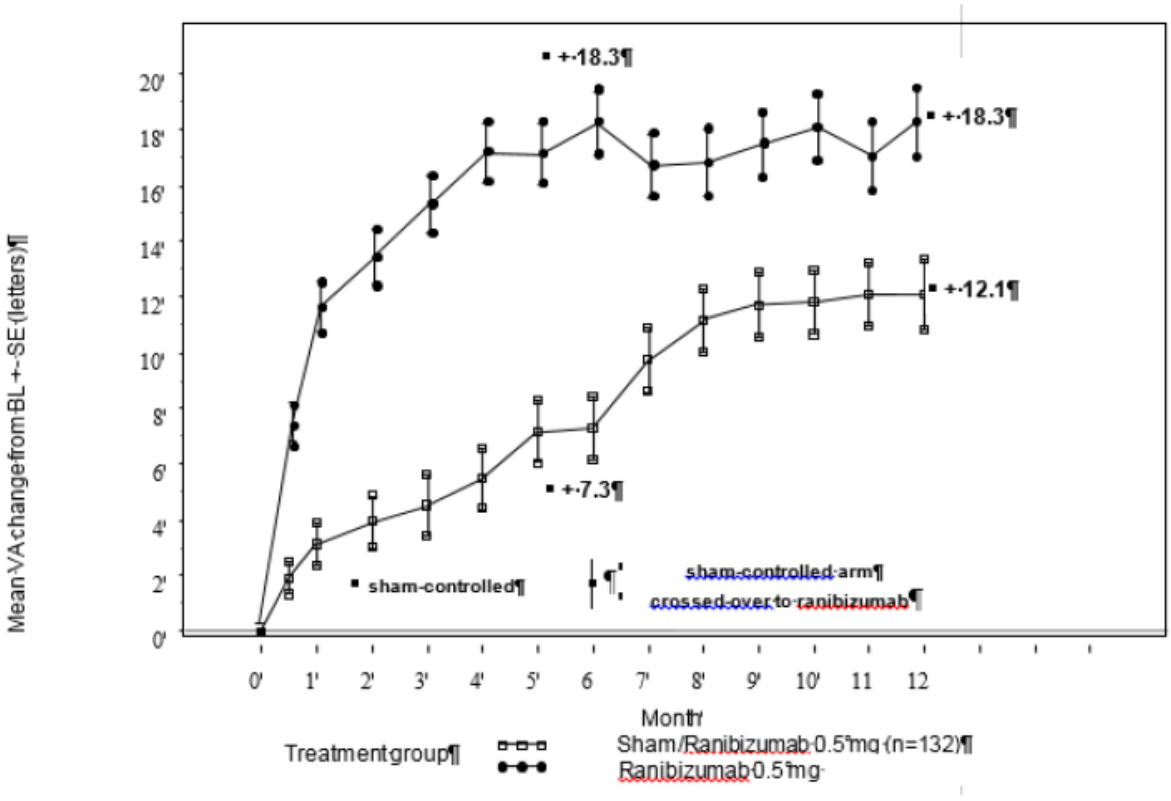
The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular edema secondary to RVO have been assessed in the randomized, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects 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 10 and 11, and Figures 4 and 5.

Table 10 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)



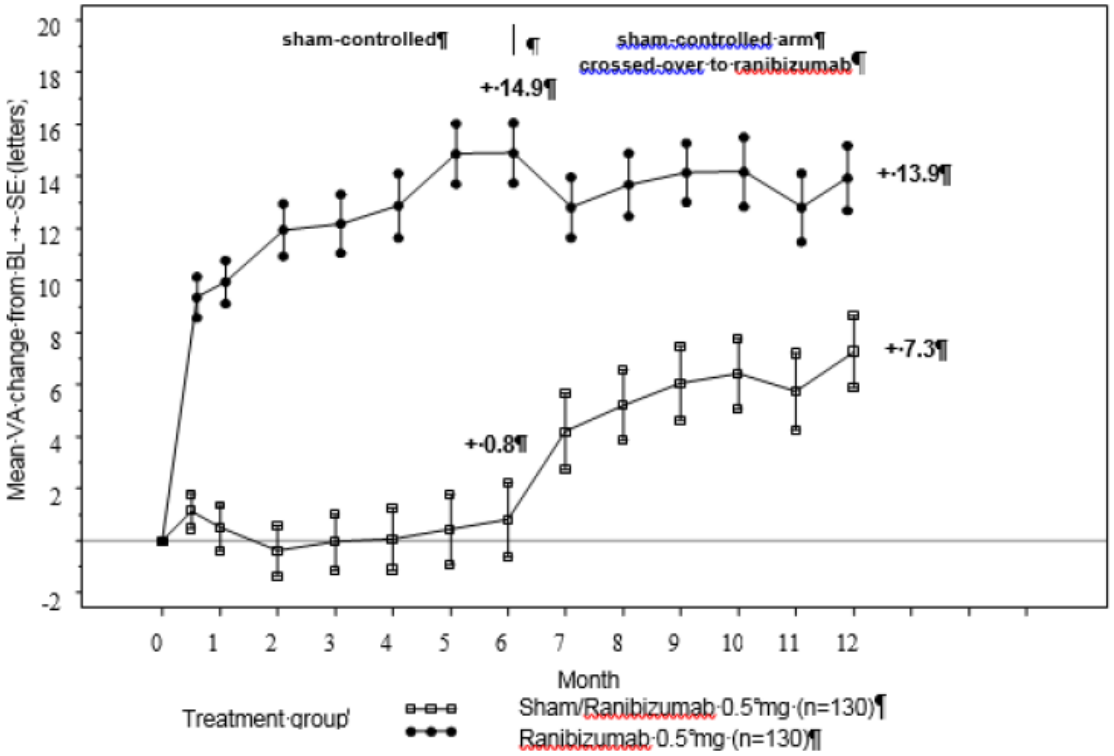
BL=baseline; SE=standard error of mean

Table 11 Outcomes at Month 6 and 12 (CRUISE)

	Sham (n=132)	Lucentis 0.5 mg (n=131)
Mean change in visual acuity from baseline at Month 6[b] (letters)[d]	+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	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.

*** 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.*

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 12.

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

	BRIGHTER			CRYSTAL
	Lucentis 0.5 mg N=180	**Lucentis 0.5 mg + Laser N=178**	**Laser* N=90**	**Lucentis 0.5 mg (N=356)**
Mean change in BCVA at Month 6[b] (letters) (SD)	+14.8 (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.

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.

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

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

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

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

Treatment of visual impairment due to CNV

Study G2301 (MINERVA)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV secondary to etiologies other than nAMD and PM have been assessed 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 13 and 14 and Figure 6.

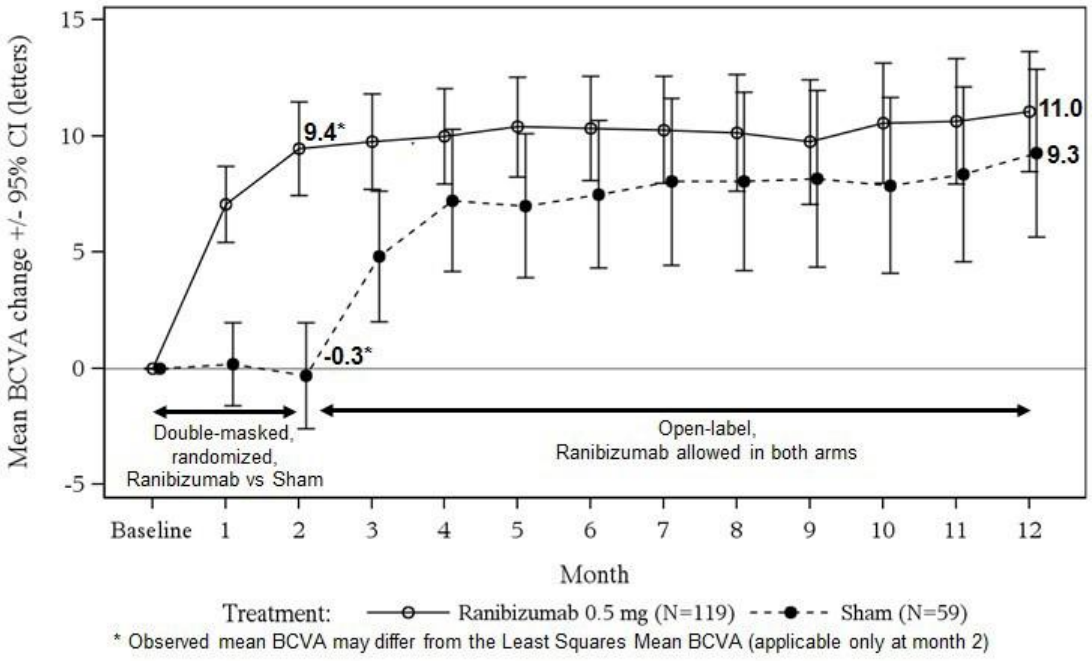
Table 13 Outcomes at Month 2 (MINERVA)

	Ranibizumab 0.5 mg (n=119)	Sham (n=59)
Mean BCVA change from baseline to Month 2 (letters) (Least Squares Mean) [a]	+9.5	-0.4
Proportion of patients who gained ≥10 letters from baseline or reached 84 letters at Month 2	42.4%	14.0%
Proportion of patients who gained ≥15 letters from baseline or reached 84 letters at Month 2	31.4%	12.3%
Reduction in CSFT from baseline to Month 2 (Least Squares Mean) [a]	77 µm	-9.8 µm

CSFT=central subfield thickness

[a]: One sided p<0.001 comparison with sham control

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



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

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

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

[a] comprises CNV etiologies which do not fall under the other subgroups

* number of patients with data available in the analysis

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

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

An improvement 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 REGIMENAND 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 photodynamictherapy).

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 15 and Figure 7.

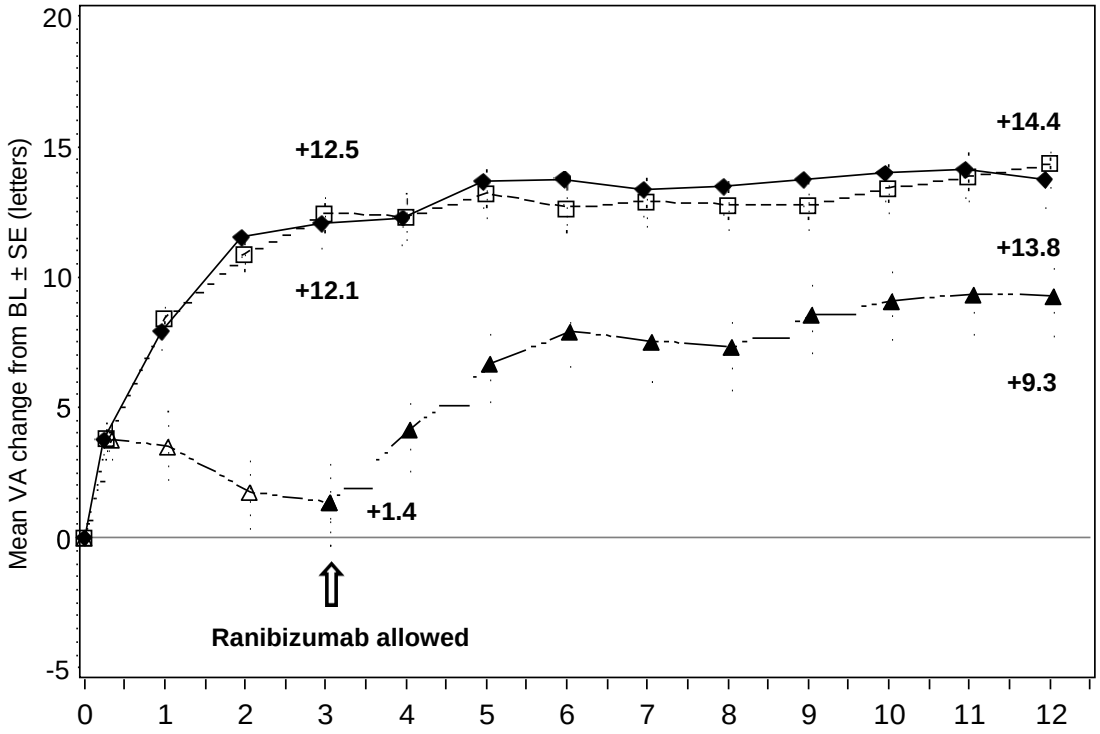
Table 15 Outcomes at Month 3 and Month 12 (RADIANCE)

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



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

Patients randomized to vPDT were allowed to receive ranibizumab from Month 3 onwards.

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

Patient-reported benefits were observed with 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 preterm infants (birth weight <1,500 grams with bilateral ROP) 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). Both eyes received treatment at baseline. Re-treatment with ranibizumab could be administered if there were signs of ROP worsening. A maximum of 3 ranibizumab injections in each eye was allowed.

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 ranibizumab 0.1 mg (75.0%), and laser therapy (66.2%). The majority of patients treated with ranibizumab 0.2 mg (78.1%) did not require re-treatment with ranibizumab.

Of the remaining patients, 19.2% received two injections in at least one eye, and 2.7 % received three injections per eye.

Table 16 Outcomes at Week 24 (RAINBOW)

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

[c] Ranibizumab 0.1 mg is not the dose authorized for treatment of ROP. Only the ranibizumab dose of 0.2 mg is authorized for treatment of ROP.

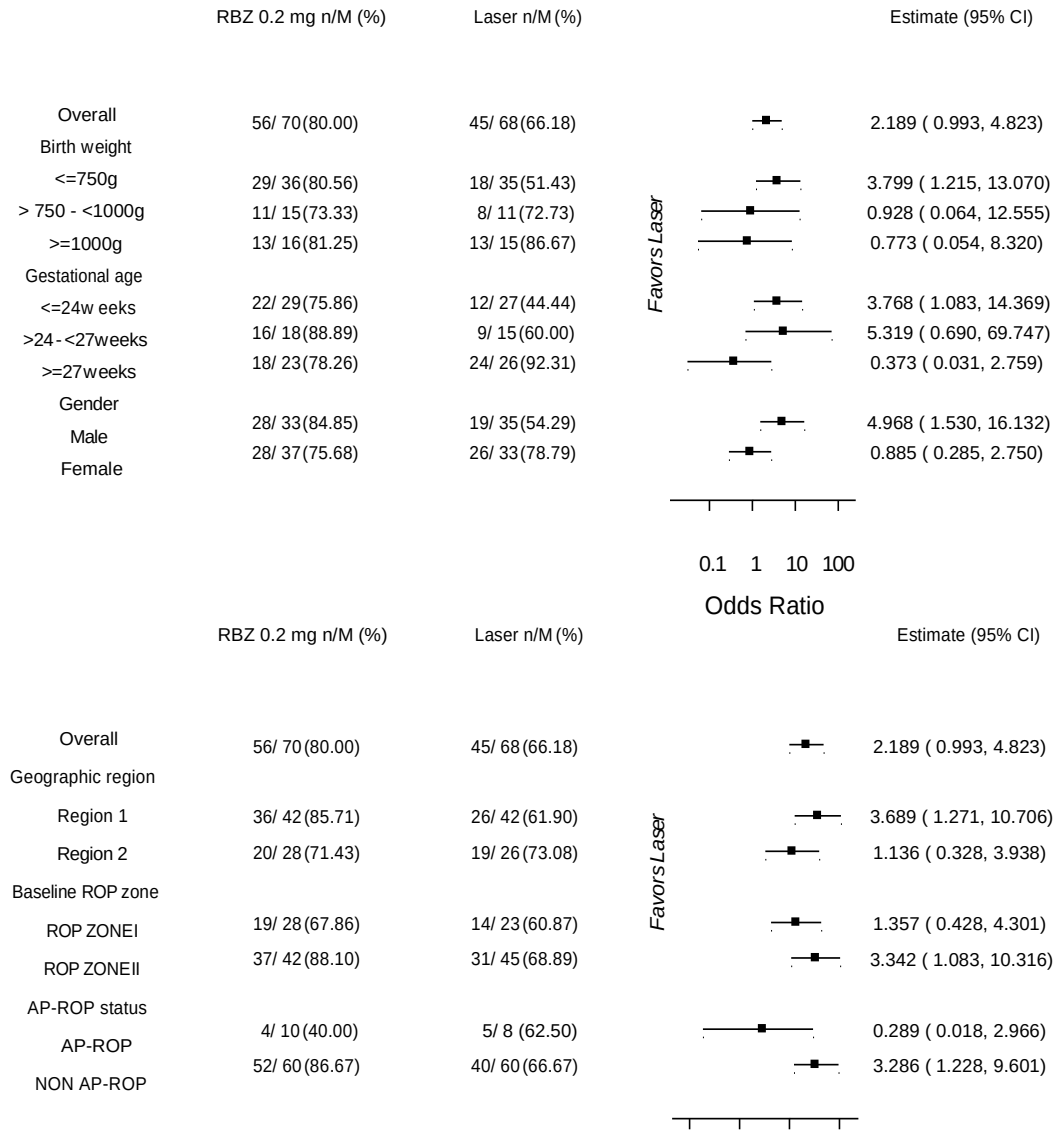
[d] the p value for ranibizumab 0.1 mg was not adjusted for multiplicity.

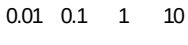
During the 24 weeks of the study, fewer patients in the ranibizumab 0.2 mg group (14.9%) switched to another treatment modality due to lack of response compared with the 0.1 mg group (16.9%) and laser group (24.3%). Unfavorable structural outcomes were less frequently reported for ranibizumab 0.2 mg (1 patient, 1.4%) compared with ranibizumab 0.1 mg (5 patients, 6.7%) and laser therapy (7

patients, 10.1%). In addition, 75% of patients achieved resolution of plus disease within 8 days with ranibizumab 0.2 mg and ranibizumab 0.1 mg compared to 22.5 days in patients treated with laser.

The following forest plot shows the pairwise comparisons of the primary endpoint, i.e., proportion of treatment success between ranibizumab 0.2 mg and laser treatment groups, based on the odds ratio scale, by subgroups of birth weight, gestational age, gender, geographical region, baseline ROP zone, and AP-ROP status. Caution is needed when interpreting the results due to small sample sizes of the subgroups, which may lead to large variability in the point estimates and wide confidence intervals.

Figure 8 Absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment: forest plot for subgroup analysis





- The binary logistic model with treatment arm and ROP zone at baseline was fitted to each subgroup level separately and the odds ratio of the primary efficacy variable with its two-sided 95% confidence interval will be presented. The p-values from these models will not be presented.
- Each subgroup factor was considered individually. Multiplicity was not controlled here.
- If a subject died or switched study treatment before or at week 24, then the subject will be considered as having active ROP and unfavorable structural outcomes at week 24.

Study H2301E1 (RAINBOW extension)

The long-term efficacy and safety of Lucentis 0.2mg 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 17 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.

INCOMPATIBILITIES

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

SPECIAL PRECAUTIONS FOR STORAGE

Vial

Store in a refrigerator (2°C to 8°C).

Do not freeze.

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

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

Pre-filled syringe kit

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the pre-filled syringe in its sealed tray in the carton in order to protect from light.

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

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

Nature and contents of container

Vial kit

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

one needle for intravitreal injection, one syringe for withdrawal of the vial contents and for intravitreal injection.

Vial with filter needle

0.23 mL Lucentis 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.

Pre-filled syringe

0.165 mL sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger

stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap and a Luer Lock adapter. The pre-filled syringe has a plunger rod and a finger grip, and is packed in a sealed tray. One pack contains one pre-filled syringe.

INSTRUCTIONS FOR USE AND HANDLING

Vial

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.

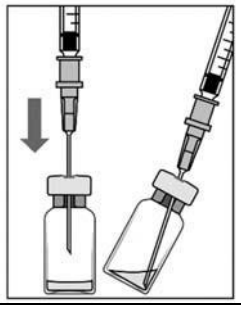
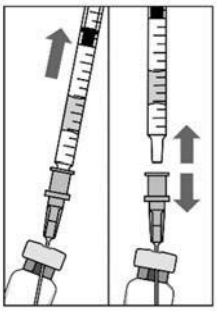
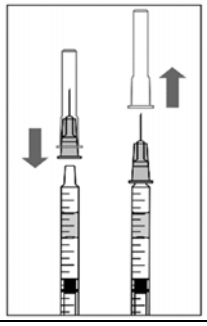
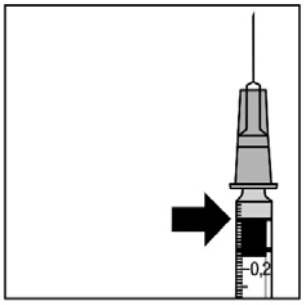
For preparation and intravitreal injection, the following single-use medical devices are needed:

- 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. Assemble the 5 micrometer filter needle (provided) onto the 1 mL syringe (provided) using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal
B. 	4. Ensure that the plunger rod is drawn sufficiently back 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 assemble the injection needle (provided) onto the syringe. 7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe. Note**:** Grip at the yellow hub of the injection needle while removing the cap.
D.  	8. Carefully expel the air from the syringe and adjust the dose to the appropriate mark on the syringe. The 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.

Pre-filled syringe (adults only)

The pre-filled syringe is for single use only (see section DOSAGE REGIMEN AND ADMINISTRATION).

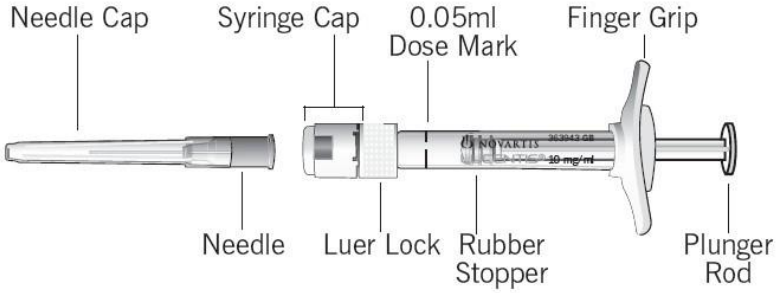
The pre-filled syringe is sterile. Do not use the pre-filled syringe if the packaging is damaged. The

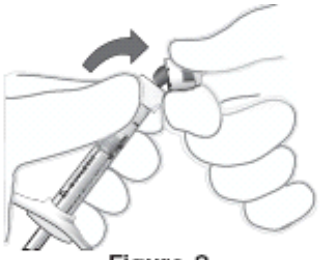
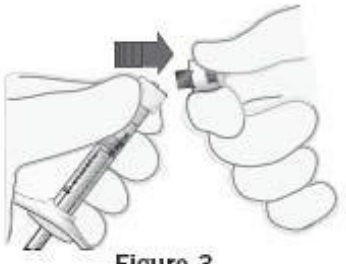
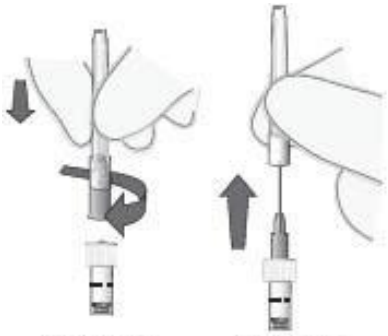
sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discolored, cloudy, or contains particulates.

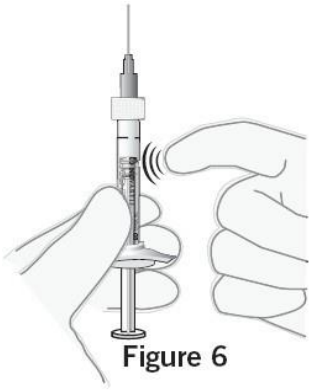
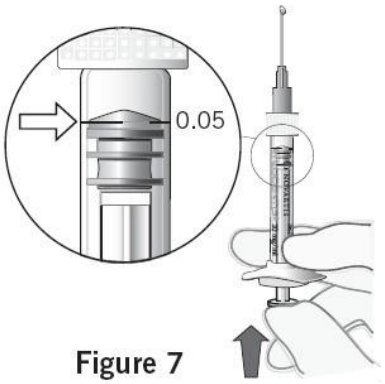
For intravitreal injection, a 30G x ½ inch injection needle should be used.

The pre-filled syringe contains more than the recommended dose of 0.5mg. The extractable volume of the pre-filled syringe (0.1ml) is not to be used in total. The excess volume should be expelled prior to injection. Injecting the entire volume of the pre-filled syringe could result in overdose. To expel the air bubble along with the excess medicinal product, slowly push the plunger until the edge below the dome of the rubber stopper is aligned with the black dosing line on the syringe (equivalent to 0.05ml, ie 0.5mg ranibizumab).

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

Heading	Instructions	Diagram/Image
	Read all the instructions carefully before using the pre-filled syringe. The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions. **Note: The dose must be set to 0.05 mL**	
Pre-filled syringe description	 Figure 1	
Prepare	1. Make sure that your pack contains: • a sterile pre-filled syringe in a sealed tray. 2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe.	*(no diagram/image)*

Check syringe	3. Check that: • the syringe cap is not detached from the Luer Lock. • the syringe is not damaged. • the drug solution looks clear, colorless to pale brownish-yellow and does not contain any particulates. 4. If any of the above is not true, discard the pre-filled syringe and use a new one.	
Heading	**Instructions**	**Diagram/Image**
Remove syringe cap	5. Snap off (do not turn or twist) the syringe cap (see Figure 2). 6. Dispose of the syringe cap (see Figure 3).	 Figure 2  Figure 3
Attach needle	7. Attach a 30G x ½ inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer Lock (see Figure 4). 8. Carefully remove the needle cap by pulling it straight off (see Figure 5). **Note: Do not wipe the needle at any time.**	 Figure 4 Figure 5

Dislodge air bubbles	9. Hold the syringe upright. 10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6).	 Figure 6
Heading	**Instructions**	**Diagram/Image**
Set dose	11. Hold the syringe at eye level and carefully push the plunger until the **edge below the dome of the rubber stopper** is aligned with the dose mark (see Figure 7). • This will expel the air and the excess solution and set the dose to 0.05 mL. **Note: the plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.**	 Figure 7
Inject	The injection procedure should be carried out under aseptic conditions 12. The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. 13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL. 14. A different scleral site should be used for subsequent injections. 15. After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.	

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

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