

NEW ZEALAND DATA SHEET

LUCENTIS[®] Ranibizumab 10 mg/mL solution for injection

Description and composition

Pharmaceutical form

Solution for injection.

Sterile, clear, colourless 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 humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology.

Active moiety

Ranibizumab.

Excipients

Alpha, alpha-trehalose dihydrate
Histidine hydrochloride, monohydrate
Histidine
Polysorbate 20
Water for injections.

Indications

Lucentis[®] is indicated for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD).
- the treatment of visual impairment due to diabetic macular oedema (DME).
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO).

Dosage and administration

Dosage

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

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

The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05mL. The interval between two doses should not be shorter than 1 month.

Treatment of wet AMD

Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment.

Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to wet AMD and continued until stable visual acuity is reached again for three consecutive monthly assessments.

Treatment of visual impairment due to DME

Treatment is given monthly and continued until visual acuity is stable for three consecutive monthly assessments, implying a minimum of two injections. Thereafter patients should be monitored monthly for visual acuity. Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to DME and continued until stable visual acuity is reached again for three consecutive monthly assessments.

Lucentis and Laser Photocoagulation in DME: Lucentis can be safely administered concomitantly with laser photocoagulation as well as in patients who have received previous laser photocoagulation. When given on the same day, Lucentis should be administered at least 30 minutes after laser photocoagulation.

Treatment of visual impairment due to macular oedema secondary to RVO

Treatment is given monthly and continued until maximum visual acuity is achieved, confirmed by stable visual acuity for three consecutive monthly assessments performed while on Lucentis treatment. If there is no improvement in visual acuity over the course of the first three injections, continued treatment is not recommended

Thereafter patients should be monitored monthly for visual acuity.

Treatment is resumed with monthly injections when monitoring indicates a loss of visual acuity due to macular oedema secondary to RVO and continued until stable visual acuity is reached again for three consecutive monthly assessments.

Lucentis and laser photocoagulation in Branch RVO (BRVO):

Lucentis has been used concomitantly with laser photocoagulation in clinical studies (see 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.

Mode 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) and the availability of sterile paracentesis (if required). The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see Contraindications). The periocular skin, eyelid and ocular surface should be disinfected. Adequate anaesthesia and a broad-spectrum topical microbicide should be administered prior to the injection.

The patient should be instructed to self-administer antimicrobial drops four times daily for 3 days before and after each injection.

For information on preparation of Lucentis, see Instructions for use and handling.

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

Special populations

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.

Renal impairment

Dose adjustment is not needed in patients with renal impairment (see Clinical pharmacology - Pharmacokinetics).

Paediatric patients

Lucentis is not recommended for use in children and adolescents due to a lack of data on safety and efficacy in these sub-populations.

Geriatric patients

No dose adjustment is required in the elderly.

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 injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see Adverse effects). 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.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis (see Adverse effects). Sustained IOP increases have also been reported. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately.

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 the benefit outweighs the potential risk.

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

The safety and efficacy of Lucentis therapy administered to both eyes concurrently have not been studied.

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

Interactions

No formal interaction studies have been performed.

For the adjunctive use of verteporfin photodynamic therapy (PDT) and Lucentis in wet AMD, see Pharmacodynamic properties.

For the adjunctive use of laser photocoagulation and Lucentis in DME, see Pharmacodynamic properties and Dosage and method of administration.

Women of child-bearing potential, pregnancy, breast-feeding and fertility

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment.

Pregnancy

For ranibizumab no clinical data on exposed pregnancies are available.

Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/foetal development (see Non-clinical safety data).

The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, ranibizumab must be regarded as potentially teratogenic and embryo-/fetotoxic. Therefore, ranibizumab should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus. For women who wish to become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

Breast-feeding

It is not known whether Lucentis is excreted in human milk. As precautionary measure, breast-feeding is not recommended during the use of Lucentis.

Fertility

There is no fertility data available.

Driving and using machines

The Lucentis treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see Adverse effects). Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.

Adverse effects

Summary of the safety profile

Wet AMD population

A total of 1,315 patients constituted the safety population in the three phase III studies in wet AMD 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 Warnings and precautions).

Other serious ocular events observed among Lucentis-treated patients included intraocular inflammation and increased intraocular pressure (see Warnings and precautions).

The adverse events listed below 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 (see definition under Pharmacodynamic properties) or verteporfin photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD phase III FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER) studies in wet AMD. 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.

Tabulated summary of adverse drug reactions from clinical trials

The adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 1 Adverse drug reactions from clinical trials

Infections and infestations	
Very common	Nasopharyngitis
Common	Influenza, urinary tract infection*
Blood and lymphatic system disorders	
Common	Anaemia
Psychiatric disorders	
Common	Anxiety
Nervous system disorders	
Very common	Headache
Common	Stroke
Eye disorders	
Very common	Intraocular inflammation, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritus.
Common	Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage,

Uncommon	conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia 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 increased

*observed only in the DME population

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 Pharmacodynamic properties).

The event of urinary tract infection, in the common frequency category, met the criteria for the table above; 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.

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 oedema secondary to Branch RVO (BRVO) and Central RVO (CRVO), respectively (see Pharmacodynamic properties). Ocular and non-ocular events in the BRAVO and CRUISE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

Overdose

Cases of accidental overdose have been reported from the clinical studies and post-marketing data. Adverse reactions most frequently associated with these reported cases were intraocular pressure increased and eye pain. If an overdose occurs,

intraocular pressure should be monitored and treated, if deemed necessary by the attending physician.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineovascularisation agents, ATC code: S01LA04

Mechanism of action (MOA)

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

Pharmacodynamics

Binding of VEGF A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, all of which are thought to contribute to the progression of the neovascular form of age-related macular degeneration and the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

Pharmacokinetics

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

Distribution and elimination

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

Special populations

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% percent (136 of 200) of

patients in a population pharmacokinetic analysis had renal impairment (46.5% mild [50 to 80 mL/min], 20% moderate [30 to 50 mL/min] and 1.5% severe [<30 mL/min]). In RVO patients, 48.2% (253 of 525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). Systemic clearance was slightly lower, but this was not clinically significant.

Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of 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 randomised, double-masked, sham*- or active-controlled studies in patients with neovascular AMD. A total of 1,323 patients (879 active and 444 control) were enrolled in these studies.

In 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). Data are available up to the end of month 24.

In 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. Sham or active verteporfin 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 (sham, 143; Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140). Data are available up to the end of month 24.

** The sham Lucentis injection control procedure involved anaesthetising 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 summarised in Tables 2, 3 and Figure 1.

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

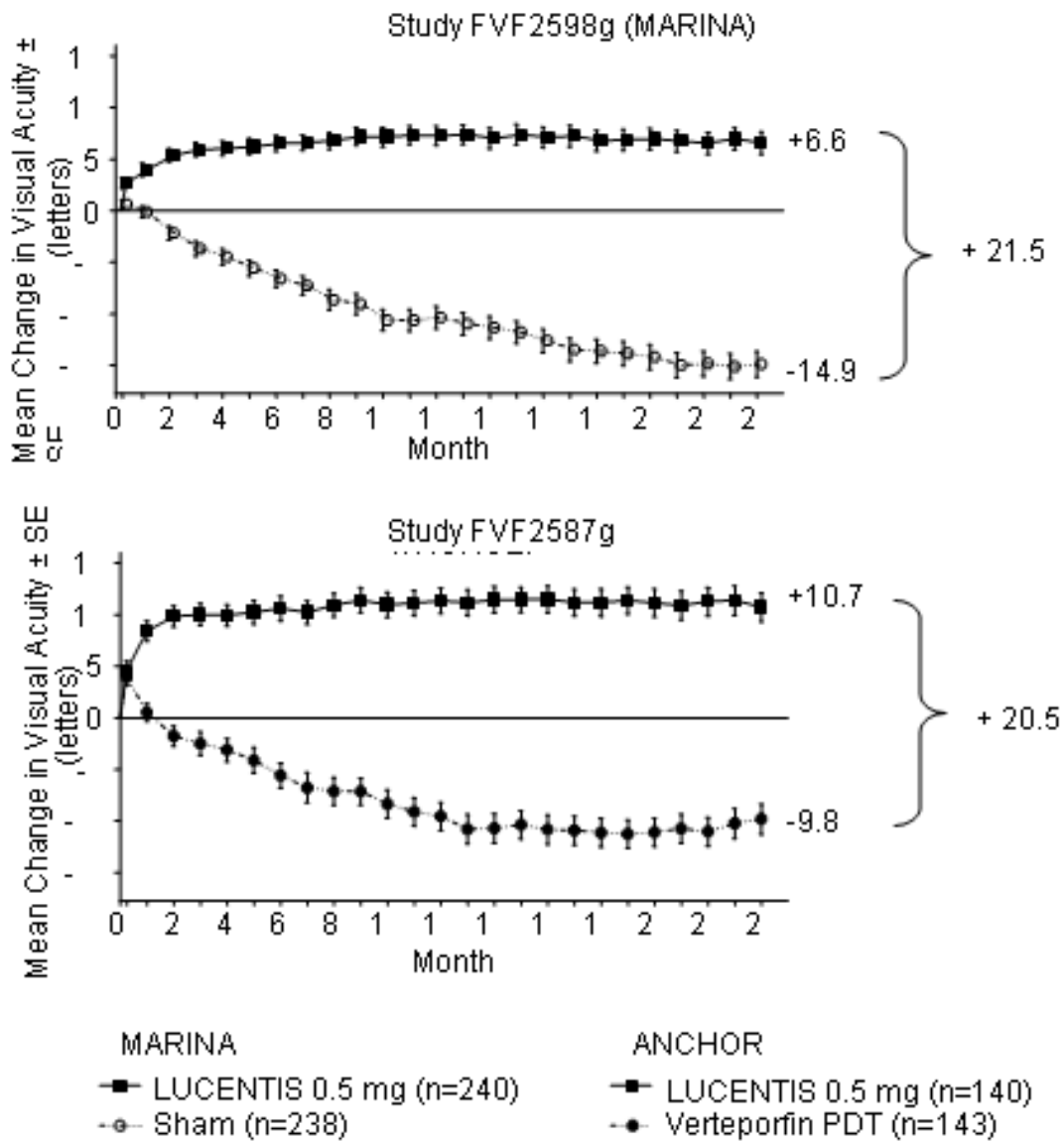
Outcome measure	Month	Sham (n=238)	Lucentis 0.5 mg (n=240)
Loss of <15 letters in visual acuity (%) ^a (Maintenance of vision)	Month 12	62%	95%
	Month 24	53%	90%
Gain of ≥15 letters in visual acuity (%) ^a	Month 12	5%	34%
	Month 24	4%	33%
Mean change in visual acuity (letters) (SD) ^a	Month 12	-10.5 (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) was a randomised, 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 total treatments. The primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline (see Figure 2). 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. In PIER, almost all Lucentis-treated patients (90%) maintained their visual acuity at month 12, and 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) 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. Two thousand three hundred seventy eight 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 as-needed re-treatment 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.

Treatment of visual impairment due to DME

Clinical safety and efficacy of Lucentis in patients with visual impairment secondary to diabetic macular oedema (DME) have been assessed in the randomised, double-masked, controlled studies D2301 (RESTORE) and D2201 (RESOLVE).

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular edema was enrolled to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation, combined ranibizumab 0.5 mg and laser photocoagulation, or sham injection and laser photocoagulation monotherapy. Treatment with ranibizumab was started with monthly intravitreal injections. Treatment was suspended when visual acuity stability was observed over the last three consecutive visits. The treatment was reinitiated when there was a reduction in best corrected visual acuity (BCVA) due to DME progression. Laser photocoagulation was administered at baseline, and then as

needed based on ETDRS criteria. The primary efficacy endpoint was mean average change in BCVA from month 1 to month 12 compared to baseline.

The 12-month results demonstrate statistically significant superiority of ranibizumab as monotherapy or adjunctive to laser photocoagulation compared to laser control, on both primary and secondary endpoints of visual acuity, and on the effect on central retinal thickness (CRT). The primary visual acuity endpoint over 12 months showed an improvement of 5.4 and 4.9 letters, respectively, for ranibizumab and ranibizumab adjunctive to laser compared to laser monotherapy. The results of the primary endpoint and additional secondary results are detailed in below Table 3 and Figures 4 and 5.

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

Outcome measure	Ranibizumab 0.5 mg (n=116)	Ranibizumab 0.5 mg + Laser (n=118)	Laser (n=111)
<i>Average change in BCVA from month 1 to month 12 compared to baseline (letters)^b</i>	6.1	5.9	0.8
<i>Mean change in BCVA at month 12 compared to baseline (letters) (SD)^b</i>	6.8	6.4	0.9
<i>Gain of ≥10 letters in BCVA (% of patients) at month 12</i>	37.4	43.2	15.5
<i>Gain of ≥15 letters in BCVA (% of patients) at month 12</i>	22.6	22.9	8.2

^b p<0.0001

Figure 2 Mean BCVA change from baseline over time in study D2301 (RESTORE)

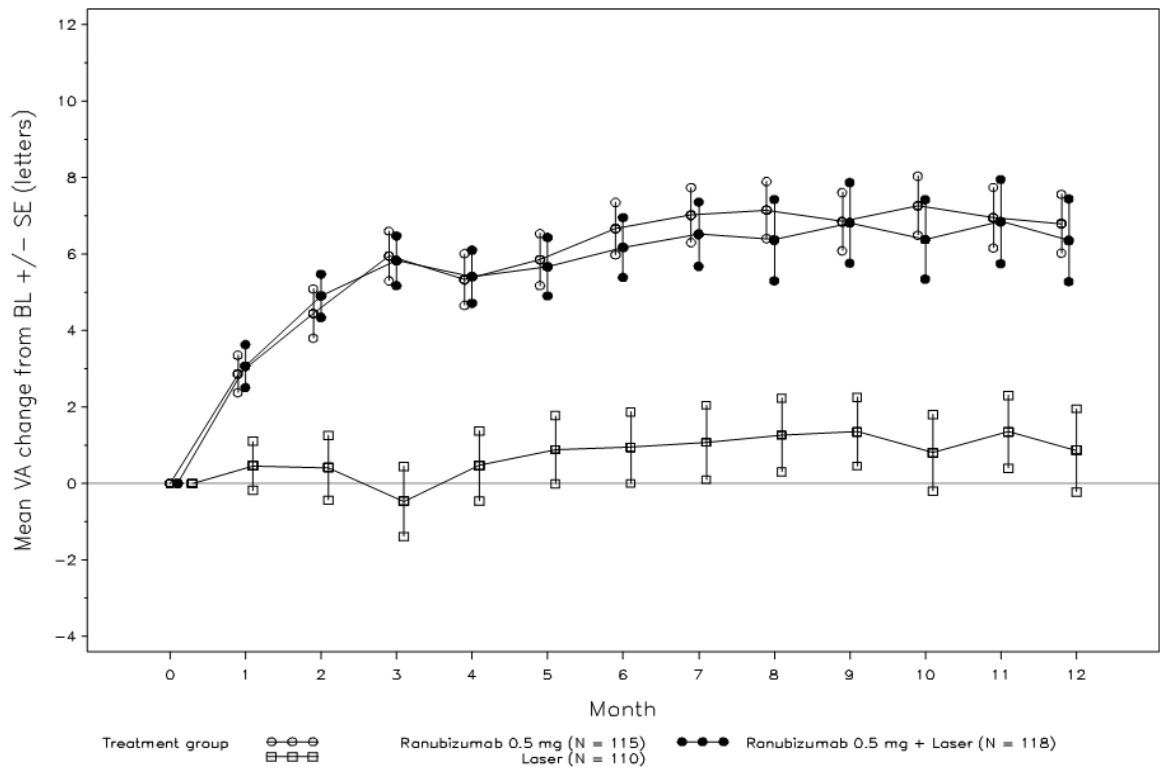
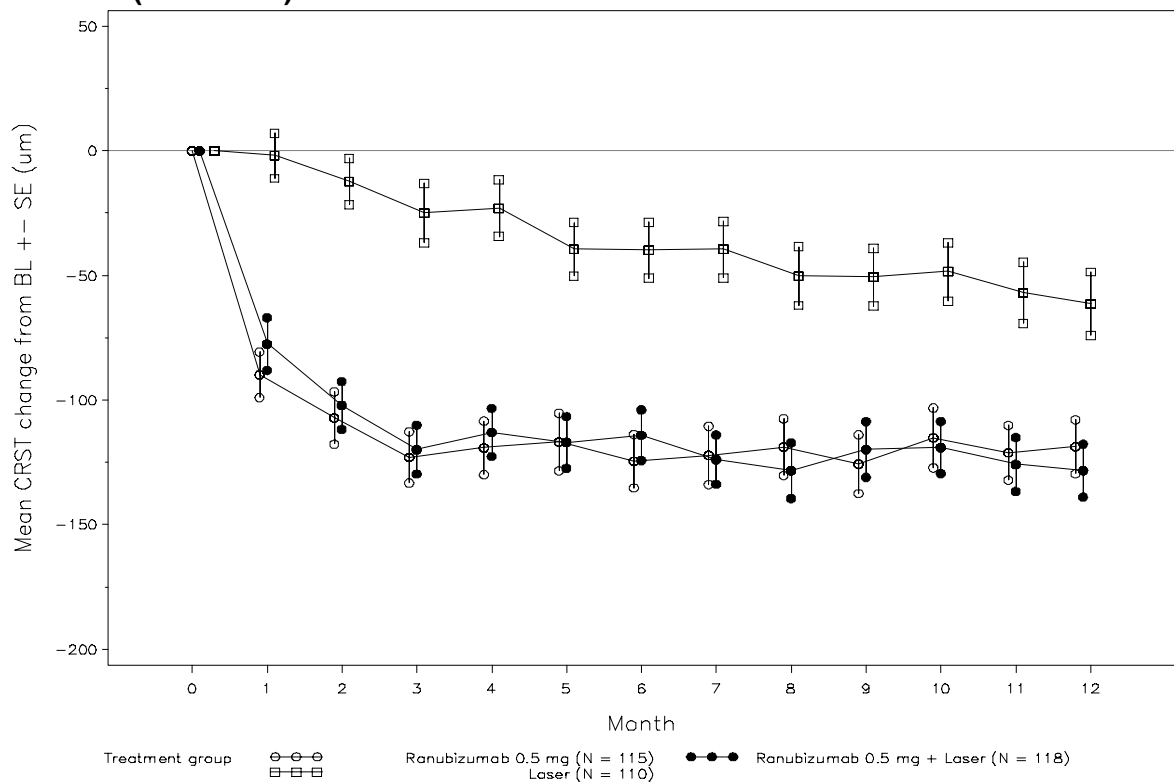


Figure 3 Mean CRT change from baseline over time in study D2301 (RESTORE)



In study D2201 (RESOLVE), a total of 151 patients with macular center involvement causing visual impairment was enrolled to receive either: 1) initial intravitreal injection of ranibizumab 0.3 mg (6 mg/mL formulation) and then monthly injection until treatment success or futility was observed (51 patients); 2) initial intravitreal injection of ranibizumab 0.5 mg (10 mg/mL formulation) and then monthly injection until treatment success or futility was observed (51 patients); 3) initial sham injection and then monthly sham injections when needed following the same treatment criteria (49 patients). The initial ranibizumab dose 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. The dose doubling was achieved by doubling of the injection volume from 0.05mL to 0.1mL. Laser photocoagulation rescue treatment was allowed at any time in the study in the active and control arms after month 3 of the study, based on the investigators' opinion.

The study comprised two parts: an exploratory part (Group A) consisting of 42 patients analysed at the interim 6 months time point, and a confirmatory part (Group B) of 109 patients that were analysed at 12 months. Data are available from both study parts up to the end of 12 months.

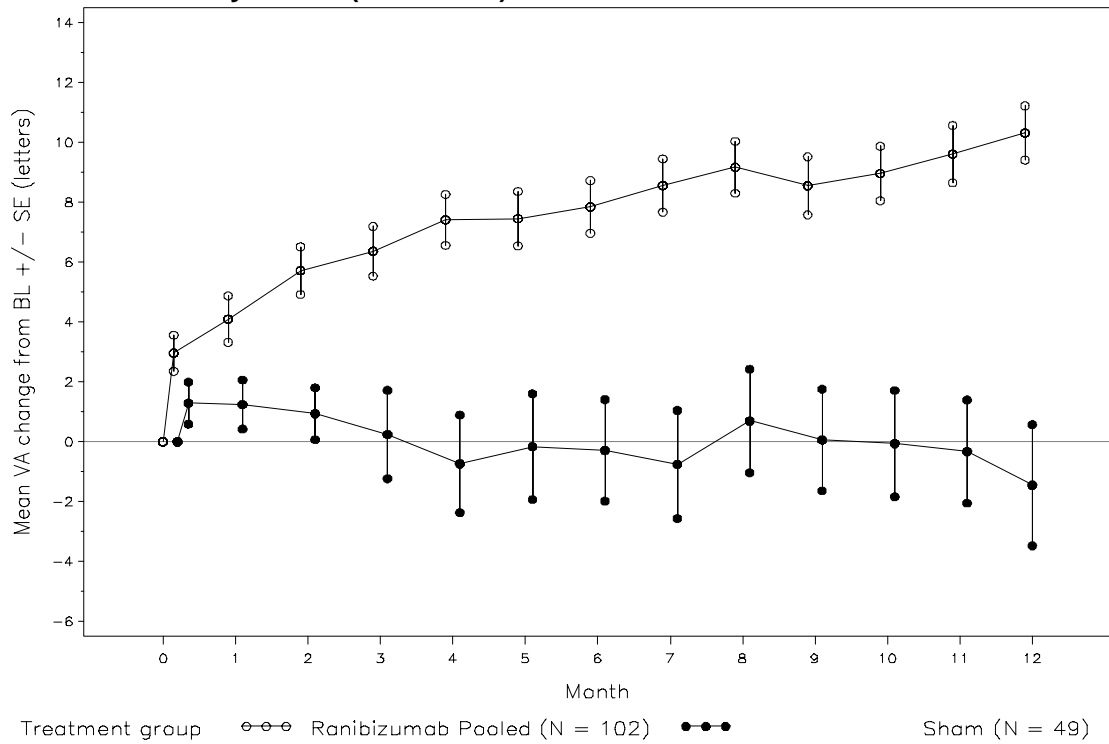
In Group A, the primary efficacy endpoint was the effect of ranibizumab treatment in reducing macular oedema as measured by central retina thickness (CRT). The superiority of ranibizumab was demonstrated in this primary endpoint. In addition, the secondary efficacy endpoint, the mean change in BCVA at month 6, demonstrated visual acuity improvement in ranibizumab-treated patients. In Group B, the primary efficacy endpoint was average change in BCVA over 12 months compared to baseline. This change was shown to be statistically superior with a gain of 7.6 letters in ranibizumab treated patients as compared to sham treatment. In the overall study population (Group A+B) this average change compared to baseline in BCVA over time was 7.8 letters. Additionally, in the overall study population (Group A+B), a mean change in BCVA at month 12 of +10.3 letters was experienced in ranibizumab-treated patients as compared to baseline. Sixty one percent of patients experienced a clinically relevant improvement in vision of ≥ 10 letters at 12 months. For thirty three percent of patients, there was an improvement of ≥ 15 letters. Detailed results are shown in Table 4 and Figure 6.

Table 5 12-month outcomes in Group A+B of study D2201 (RESOLVE)

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

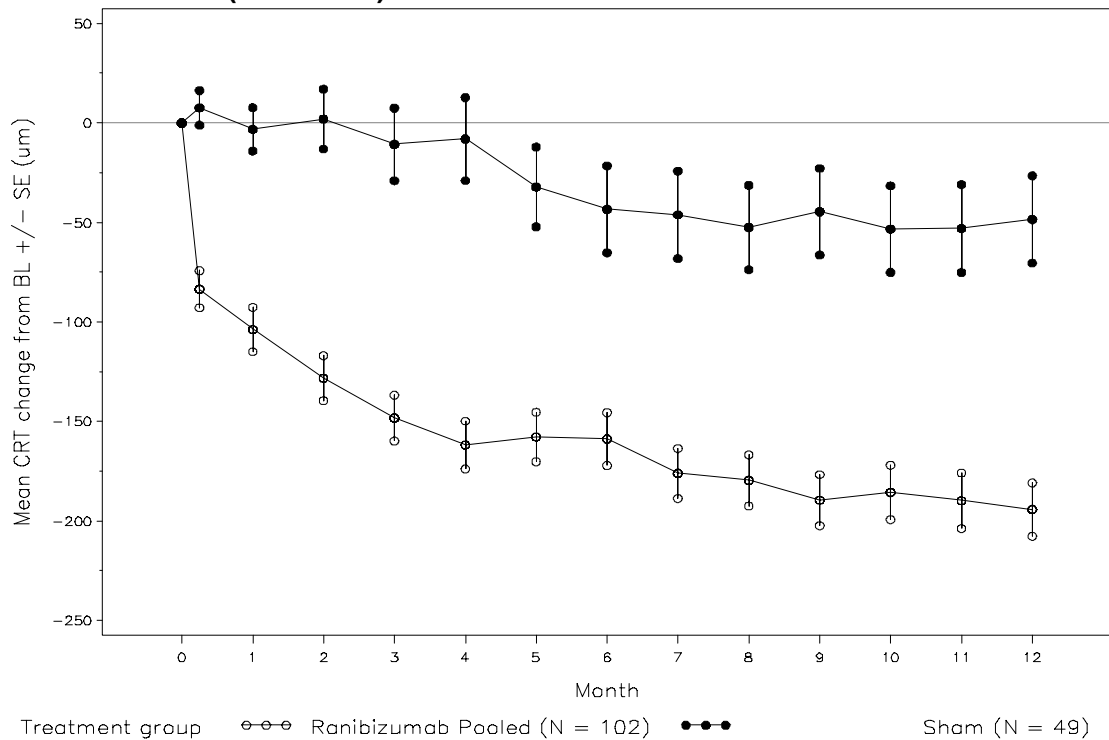
^b $p < 0.0001$

Figure 4 Mean change in visual acuity from baseline over time in Group A+B of study D2201 (RESOLVE)



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

Figure 5 Mean change in CRT from baseline over time in Group A+B of study D2201 (RESOLVE)



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.

Treatment of visual impairment due to macular oedema secondary to RVO

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

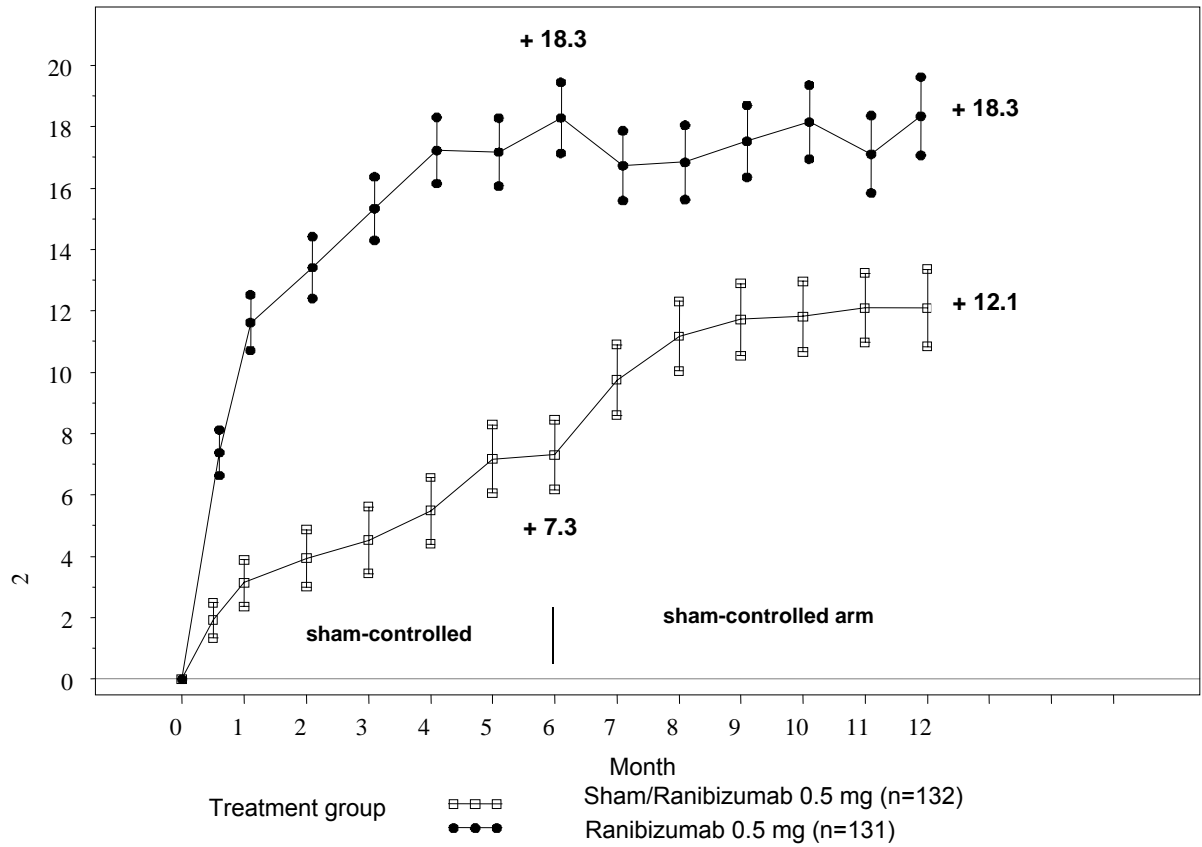
Key outcomes from BRAVO and CRUISE are summarised in Tables 4 and 5, and Figures 3 and 4.

Table 6 Outcomes at Month 6 and 12 (BRAVO)

Outcome measure	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 6 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (BRAVO)



BL=baseline; SE=standard error of mean

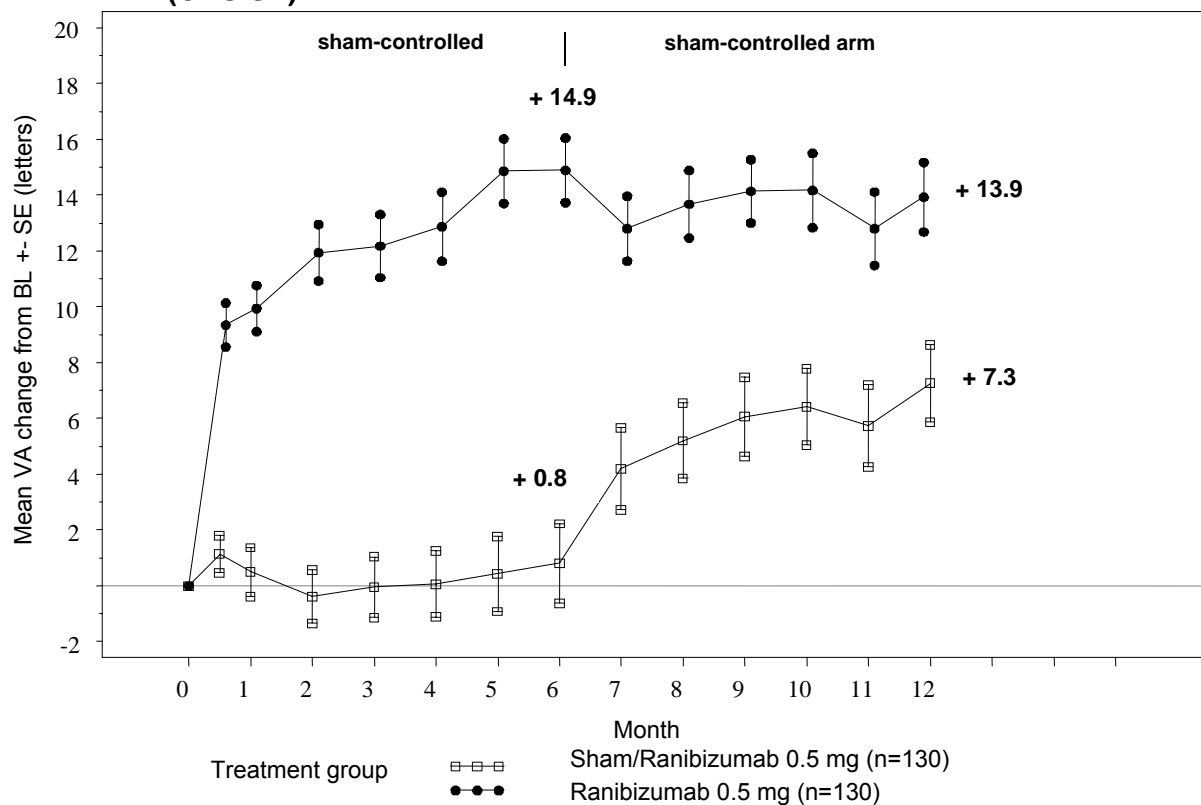
Table 7 Outcomes at Month 6 and 12 (CRUISE)

Correction of patient numbers

Outcome measure	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 7 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 oedema as measured by central retinal thickness.

The improvement in visual acuity seen with ranibizumab treatment at 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (VFQ-25) sub-scales related to near and distance activity, a pre-specified secondary efficacy endpoint. The difference between Lucentis 0.5 mg and the control group was assessed at Month 6 with p-values of 0.02 to 0.0002.

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 are available.

In pregnant monkeys, IVT ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, although, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryo-foetotoxic.

However, due to restrictions dictated by the intravitreal route of administration the feasible doses used in this study did not reach maternal toxicity but only a multiple with respect to human systemic exposure. The absence of ranibizumab-mediated effects on the embryo-foetal development is plausibly related mainly to the inability of the Fab fragment to cross the placenta.

Nevertheless, a case was described with high maternal ranibizumab serum levels and presence of ranibizumab in foetal serum, suggesting that the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer. The embryo-foetal development investigations were performed in healthy pregnant

animals and disease (such as e.g. diabetes) may modify the permeability of the placenta towards a Fab fragment (see recommendations in “Women of child-bearing potential, pregnancy, breast-feeding and fertility”).

Pharmaceutical information

Incompatibilities

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

Special precautions for storage

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.

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

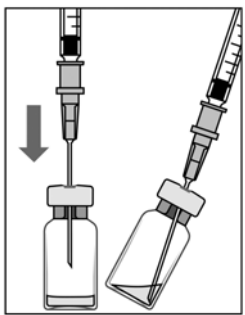
Nature and contents of container

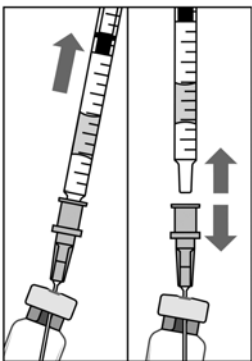
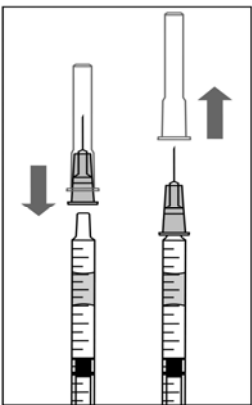
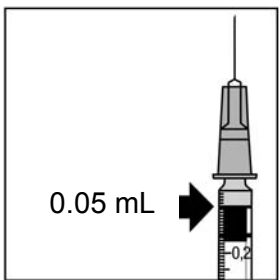
0.23 mL Lucentis solution for injection in a glass vial (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial, one filter needle for withdrawal of the vial content, one needle for intravitreal injection, one syringe for withdrawal of the vial contents and for intravitreal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

Instructions for use and handling

Vials are for single use only (see Dosage and administration).

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

<p>A.</p> 	<ol style="list-style-type: none">1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.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
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<p>B.</p> 	<p>4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.</p> <p>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.</p>
<p>C.</p> 	<p>6. Aseptically and firmly assemble the injection needle (provided) onto the syringe.</p> <p>7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.</p> <p>Note: Grip at the yellow hub of the injection needle while removing the cap.</p>
<p>D.</p> 	<p>8. Carefully expel the air from the syringe and adjust the dose to the 0.05 ml mark on the syringe. The syringe is ready for injection.</p> <p>Note: Do not wipe the injection needle. Do not pull back on the plunger.</p>

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

Medicine classification

Prescription Medicine

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