PRODUCT MONOGRAPH

PrLUCENTIS®

(ranibizumab injection)

Single Use Vials
Single Use Pre-filled Syringes

10 mg/mL solution for injection

Anti-Vascular Endothelial Growth Factor-A (VEGF-A inhibitor)

ATC Code: S01LA04

LUCENTIS indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.
For further information for LUCENTIS please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

LUCENTIS, 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 visual impairment due to macular edema secondary to retinal vein occlusion (RVO).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to ocular conditions other than AMD or PM, including but not limited to angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy or idiopathic chorioretinopathy.

has been issued market authorization without conditions.

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Boulevard
Dorval, QC
H9S 1A9

Date of Initial Approval:
June 26, 2007

Date of Revision:
December 21, 2021

Submission Control No: 245596

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?

The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance be will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:

- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Drug Reaction Reporting and Re-Issuance of the Product Monograph

Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Health Product Safety Information Division at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 5
SUMMARY PRODUCT INFORMATION 5
INDICATIONS AND CLINICAL USE 5
CONTRAINDICATIONS 6
WARNINGS AND PRECAUTIONS 6
ADVERSE REACTIONS 10
DRUG INTERACTIONS 69
DOSAGE AND ADMINISTRATION 69
OVERDOSAGE 79
ACTION AND CLINICAL PHARMACOLOGY 80
STORAGE AND STABILITY 81
SPECIAL HANDLING INSTRUCTIONS 82
DOSAGE FORMS, COMPOSITION AND PACKAGING 82

PART II: SCIENTIFIC INFORMATION 83
PHARMACEUTICAL INFORMATION 83
CLINICAL TRIALS 85
DETAILED PHARMACOLOGY 106
TOXICOLOGY 107
REFERENCES 115

PART III: CONSUMER INFORMATION 117

PrLUCENTIS®

Ranibizumab injection

PART I: HEALTH PROFESSIONAL INFORMATION

LUCENTIS indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.
For further information for LUCENTIS please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

LUCENTIS, 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 visual impairment due to macular edema secondary to retinal vein occlusion (RVO).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to ocular conditions other than AMD or PM, including but not limited to angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy or idiopathic chorioretinopathy.

has been issued market authorization without conditions.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravitreal injection	Sterile solution / 10 mg/mL (2.3 mg/0.23 mL/vial or 1.65 mg/0.165 mL/pre-filled syringe)	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LUCENTIS® (ranibizumab injection) is indicated in adults for:

- the treatment of neovascular (wet) agerelated macular degeneration (AMD).
- the treatment of visual impairment due to diabetic macular edema (DME).
- the treatment of visual impairment due to macular edema secondary to retinal vein occlusion (RVO).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to ocular conditions other than AMD or PM, including but not limited to angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy or idiopathic chorioretinopathy.

NOC/c LUCENTIS is indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease.

The marketing authorization with conditions is primarily based on the absence of active ROP and absence of unfavorable retinal structural outcomes in both eyes (see **CLINICAL TRIALS, Treatment of ROP in preterm infants**). Change in visual acuity was not assessed during this study.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION and PACKAGING** section of the Product Monograph.
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

NOC/c WARNINGS AND PRECAUTIONS

General

- Treatment with LUCENTIS (ranibizumab injection) is for intravitreal injection only.

- The WARNINGS AND PRECAUTIONS for adults also apply to preterm infants with ROP.
- Potential systemic suppression of VEGF cannot be excluded following intravitreal administration of ranibizumab in premature infants with ROP (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pediatrics population -Preterm infants with ROP**).
- The safety in preterm infants beyond two years has not been studied. Long-term safety has not been established.

Systemic Effects

Thromboembolic events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The risk of stroke may be greater in patients with known risk factors, including history of prior stroke or transient ischemic attack [see ADVERSE REACTIONS]. Therefore, these patients should be carefully evaluated by their physician to determine whether treatment with LUCENTIS is appropriate, and 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 treatment is appropriate, i.e., if the benefit to the patient outweighs the risk.

Non-ocular hemorrhages

Non-ocular hemorrhages have been reported following intravitreal injection of VEGF inhibitors, including LUCENTIS in clinical trials for adults and preterm infants with ROP (see **ADVERSE REACTIONS**), and there is a potential risk that these may relate to VEGF inhibition.

Carcinogenesis and Mutagenesis

See TOXICOLOGY.

Hepatic

LUCENTIS has not been studied in patients with hepatic impairment.

Immune

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: In the wet AMD studies, 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 with active systemic infections.

Ophthalmologic

Endophthalmitis and Retinal detachments: Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, intraocular inflammation, hypopyon, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see ADVERSE 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 aforementioned events without delay.

Increases in Intraocular Pressure: Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of LUCENTIS (see ADVERSE REACTIONS). Sustained IOP increases have also been reported. Both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection and / or tonometry within 30 minutes following the injection.

LUCENTIS has not been studied in patients who have previously received other types of intravitreal injections. LUCENTIS should not be administered concurrently with other anti-VEGF agents (systemic or ocular).

Bilateral treatment: Available data do not suggest an increased risk of systemic adverse events with bilateral treatment. The efficacy of LUCENTIS therapy administered to both eyes concurrently has not been studied.

LUCENTIS has not been studied in patients with concurrent eye conditions such as retinal detachment or macular hole.

Additional experience has been gained from post-approval studies on a limited number of patients with prior episodes of RVO and of patients with ischemic branch RVO (BRVO) and ischemic central RVO (CRVO). In patients with RVO presenting with clinical signs of irreversible ischemic visual function loss, treatment is not recommended.

NOC/c **Neurologic**

Neurodevelopment impairment have been reported in preterm infants treated for ROP with anti-VEGF, including LUCENTIS (see **ADVERSE REACTIONS**). Long-term neurodevelopment has not been studied in preterm infants treated for ROP with LUCENTIS beyond two years.

Renal

Systemic exposure to LUCENTIS may be increased in patients with renal impairment (see ACTION AND CLINICAL PHARMACOLOGY – Special Populations and Conditions). The clinical significance of increased systemic exposure to LUCENTIS is unknown.

Special Populations

Women of childbearing potential: Women of childbearing potential should use effective contraception during treatment.

Pregnant Women: No clinical data concerning exposure to ranibizumab during human pregnancy are available.

Studies in cynomolgus monkeys do not indicate direct or indirect harmful effects with respect to pregnancy or embryonal/fetal development (see TOXICOLOGY). 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 potential 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.

Breast-feeding: It is not known whether LUCENTIS is excreted in human milk. As a precautionary measure, breast-feeding is not recommended during the use of LUCENTIS because many drugs can be excreted in human milk.

Fertility: There is no fertility data available.

Pediatrics (< 18 years of age):

Pediatric patients other that preterm infants with ROP

Health Canada has not authorized LUCENTIS for pediatric use due to insufficient data on safety and efficacy in this sub-population. Limited data from 5 adolescent patients aged 13 to 17 years with visual impairment due to CNV are available.

NOC/c ***Preterm infants with ROP***

The warnings and precautions for adults also apply to preterm infants with ROP. Potential systemic suppression of VEGF cannot be excluded following intravitreal administration of ranibizumab in premature infants. The safety profile in preterm infants has not been established beyond two years.

Geriatrics (≥ 65 years of age): No dose adjustment is necessary in the elderly.

Effects on Ability to Drive and Use Machines

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 (with frequency from 3.3% to 11.7% in the wet AMD trials) and increased intraocular pressure (with frequency from 6.6% to 18.8% in the wet AMD trials) (see WARNINGS AND PRECAUTIONS).

Overall, ocular and non-ocular events in the DME, RVO, PM and CNV trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

In the RESOLVE trial in patients with DME, all serious ocular and non-ocular adverse events reported in patients receiving LUCENTIS (pooled data) occurred at a frequency of <1%, with the exception of endophthalmitis and hypoglycemia, which both occurred in 2.0% of patients treated with LUCENTIS. Serious ocular events other than those listed above observed among LUCENTIS treated patients in the RESOLVE trial include retinal artery occlusion, retinal ischemia and vitreous hemorrhage. In the RESTORE trial, the only serious ocular adverse events that occurred in LUCENTIS treated patients was cataract, which occurred in 1.7% of patients treated with LUCENTIS 0.5 mg and laser. There were no ocular serious adverse events reported in patients treated with LUCENTIS monotherapy and no reports of endophthalmitis overall in the study. All serious non-ocular adverse events reported in the LUCENTIS arms occurred at a frequency of <1%, with the exception of angina pectoris, coronary artery disease, fall, and pulmonary embolism which each occurred at a frequency of 1.7% in patients treated with LUCENTIS monotherapy, as well as hypertension which occurred in 1.7% of patients treated with LUCENTIS and laser.

All serious ocular and non-ocular adverse events reported in the RVO trials during the 6-month treatment period in patients receiving LUCENTIS (pooled data) occurred at a frequency of <1%. Serious ocular events, other than those listed above for the wet-AMD and DME trials, observed among LUCENTIS treated patients in the RVO trials include blindness unilateral, corneal abrasion, corneal edema, iris neovascularization, macular edema, retinal vascular disorder, retinal vascular occlusion and retinal vein occlusion. No serious intraocular inflammation adverse events occurred in the RVO trials.

In the PM trial, all serious ocular and non-ocular adverse events reported in patients receiving LUCENTIS also occurred at a frequency of <1%. The serious ocular events observed among LUCENTIS treated patients, which were not listed above for the wet-AMD, DME and RVO trials,

were corneal erosion and retinoschisis. No serious intraocular inflammation adverse events occurred in the PM trial.

In the CNV trial there were no serious ocular adverse events reported in the study eye or in the fellow treated eye in patients receiving LUCENTIS. None of the non-ocular SAEs were suspected to be related to study treatment or ocular injection.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Wet AMD Population

A total of 1,315 patients constituted the safety population in the three phase III studies in wet AMD, FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER) with 24 months exposure to LUCENTIS (ranibizumab injection) and four hundred and forty (440) patients were treated with the recommended dose of 0.5 mg.

The common ocular and non-ocular adverse events with suspected relationship to LUCENTIS treatment occurring in ≥ 1% of patients receiving treatment with LUCENTIS 0.5 mg in at least one of the three controlled wet AMD phase III studies FVF2598g (MARINA; 2-year data), FVF2587g (ANCHOR; 2-year data) and FVF3192g (PIER; 2-year data) are summarized in Tables 1 and 2 below.

The common ocular and non-ocular adverse events, regardless of treatment relationship to LUCENTIS, with a difference in incidence rate of ≥ 2% between patients receiving treatment with 0.5 mg LUCENTIS and the control group in at least one of the three controlled wet AMD phase III studies FVF2598g (MARINA; 2-year data), FVF2587g (ANCHOR; 2-year data) and FVF3192g (PIER; 2-year data) are summarized in Table 3 below.

Furthermore, the ocular and non-ocular adverse events, regardless of relationship to LUCENTIS treatment, occurring in ≥ 1% of patients receiving LUCENTIS 0.5 mg in the controlled wet AMD phase III studies FVF2598g (MARINA; 2-year data), FVF2587g (ANCHOR; 2-year data) and FVF3192g (PIER; 2-year data) (pooled data) are summarized in Table 4 and 5 below.

Table 1: Ocular adverse events in the study eye with suspected relationship to LUCENTIS treatment
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS 0.5 mg in at least one study

Preferred Term	% of Patients Study MARINA (Dosage q 1 month) 2 Years			% of Patients Study ANCHOR (Dosage q 1 month) 2 Years			% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years		
	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Cataract	0.0%	0.0%	1.3%	0.0%	0.0%	1.4%	0.0%	0.0%	0.0%
Cataract nuclear	0.0%	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	1.6%
Conjunctival hemorrhage	11.9%	13.4%	18.4%	11.2%	17.5%	11.4%	0.0%	0.0%	1.6%
Conjunctival hyperemia	2.1%	0.4%	1.7%	2.1%	5.1%	2.1%	0.0%	0.0%	0.0%
Conjunctivitis	1.3%	1.3%	1.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Corneal abrasion	2.5%	1.3%	2.5%	0.7%	0.0%	1.4%	0.0%	0.0%	0.0%
Detachment of retinal pigment epithelium	0.4%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
Dry eye	0.8%	0.4%	2.1%	0.7%	0.0%	0.7%	0.0%	0.0%	0.0%
Eye discharge	3.0%	2.9%	0.4%	2.1%	0.7%	1.4%	0.0%	0.0%	0.0%
Eye irritation	11.4%	10.1%	6.7%	5.6%	4.4%	5.7%	0.0%	1.7%	1.6%
Eye pain	23.7%	26.9%	28.9%	18.2%	22.6%	17.9%	0.0%	0.0%	0.0%
Eye pruritus	4.7%	2.9%	4.2%	1.4%	7.3%	2.9%	0.0%	0.0%	0.0%
Eyelid oedema	1.3%	0.8%	1.7%	1.4%	2.2%	1.4%	0.0%	0.0%	0.0%
Eyelid pain	0.4%	0.8%	0.4%	0.7%	0.0%	1.4%	0.0%	0.0%	0.0%
Foreign body sensation in eyes	10.2%	11.8%	11.3%	6.3%	5.1%	7.9%	0.0%	0.0%	0.0%
Hypoaesthesia eye	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Incorrect route of drug administration	0.0%	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	1.6%

Table 1: Ocular adverse events in the study eye with suspected relationship to LUCENTIS treatment
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS 0.5 mg in at least one study

Preferred Term	% of Patients Study MARINA (Dosage q 1 month) 2 Years			% of Patients Study ANCHOR (Dosage q 1 month) 2 Years			% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years		
Injection site hemorrhage	0.8%	0.0%	1.7%	0.7%	2.2%	2.1%	0.0%	0.0%	0.0%
Injection site pain	0.8%	0.8%	1.3%	0.7%	0.7%	0.0%	0.0%	0.0%	0.0%
Intraocular pressure increased	3.8%	18.9%	18.8%	5.6%	17.5%	15.0%	1.6%	5.1%	6.6%
Iridocyclitis	0.4%	0.8%	1.7%	0.0%	0.0%	2.9%	0.0%	1.7%	1.6%
Iritis	3.8%	5.9%	5.4%	0.0%	2.2%	6.4%	1.6%	0.0%	1.6%
Keratopathy	0.0%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
Lacrimation increased	9.3%	11.8%	7.9%	1.4%	5.1%	5.0%	0.0%	0.0%	0.0%
Ocular discomfort	3.0%	5.9%	3.8%	1.4%	2.9%	5.0%	0.0%	0.0%	1.6%
Ocular hyperemia	7.2%	5.0%	6.3%	4.2%	6.6%	7.9%	0.0%	0.0%	0.0%
Punctate keratitis	0.8%	0.8%	1.3%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%
Uveitis	0.0%	0.4%	0.8%	0.0%	0.7%	1.4%	0.0%	0.0%	0.0%
Vision blurred	1.7%	6.3%	2.9%	1.4%	5.1%	2.9%	0.0%	0.0%	0.0%
Visual acuity reduced	0.4%	1.7%	2.9%	2.1%	0.7%	0.7%	0.0%	1.7%	0.0%
Visual disturbance	0.4%	3.8%	6.7%	0.7%	2.9%	1.4%	0.0%	0.0%	0.0%
Vitreous detachment	1.3%	4.2%	2.1%	0.0%	2.2%	0.7%	0.0%	0.0%	0.0%
Vitreous disorder	0.0%	1.3%	0.4%	0.0%	1.5%	1.4%	0.0%	0.0%	0.0%
	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Vitreous floaters	2.1%	18.9%	17.2%	1.4%	9.5%	4.3%	0.0%	1.7%	1.6%
Vitreous hemorrhage	0.0%	2.1%	1.7%	0.7%	2.2%	2.1%	0.0%	0.0%	0.0%
Vitritis	1.3%	5.5%	8.4%	1.4%	3.6%	5.0%	0.0%	0.0%	1.6%
Total intraocular inflammation[+]	5.1%	10.9%	11.7%	1.4%	5.8%	10.7%	1.6%	1.7%	3.3%

Multiple occurrences of the same event were counted once in the overall incidence
[+] Preferred terms summarized: Anterior chamber inflammation, Hypopyon, Iridocyclitis, Iritis, Uveitis and Vitritis.

Table 2: Non-ocular adverse events with suspected relationship to LUCENTIS treatment
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS 0.5 mg in at least one study

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
INVESTIGATIONS									
Blood creatinine increased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
Blood pressure diastolic increased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
Blood urea increased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS									
Pain in extremity	0.0%	0.0%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%	1.6%
NERVOUS SYSTEM DISORDERS									
Headache	0.4%	0.8%	2.5%	0.0%	0.7%	0.0%	0.0%	0.0%	0.0%

Multiple occurrences of the same event were counted once in the overall incidence.

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
BLOOD AND LYMPHATIC SYSTEM DISORDERS									
Anaemia	8.1%	7.1%	7.5%	4.2%	8.8%	8.6%	0.0%	6.8%	8.2%
CARDIAC DISORDERS									
Angina pectoris	1.7%	2.5%	1.3%	0.7%	0.0%	3.6%	0.0%	0.0%	0.0%
Cardiac failure congestive	4.2%	4.2%	2.5%	3.5%	4.4%	4.3%	3.2%	3.4%	6.6%
Sinus bradycardia	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	0.0%	0.0%	3.3%
CONGENITAL, FAMILIAL AND GENETIC DISORDERS									
Corneal dystrophy	2.5%	4.2%	2.9%	0.0%	2.9%	2.1%	0.0%	0.0%	0.0%
EAR AND LABYRINTH DISORDERS									
Vertigo	1.7%	4.2%	1.7%	7.0%	5.8%	1.4%	1.6%	0.0%	6.6%
EYE DISORDERS									
Arcus lipoides	0.0%	1.3%	2.1%	0.0%	2.2%	1.4%	0.0%	1.7%	0.0%
Blepharitis	8.9%	10.9%	13.4%	7.0%	10.2%	9.3%	6.5%	6.8%	4.9%
Cataract	6.8%	7.1%	5.4%	7.0%	9.5%	13.6%	1.6%	6.8%	6.6%
Cataract cortical	2.1%	1.3%	4.6%	1.4%	1.5%	1.4%	1.6%	1.7%	3.3%
Cataract nuclear	5.9%	4.2%	3.8%	1.4%	5.1%	5.0%	3.2%	1.7%	8.2%
Conjunctival hemorrhage	66.1%	77.3%	75.7%	50.3%	71.5%	70.0%	29.0%	50.8%	52.5%
Conjunctival hyperemia	6.8%	2.9%	7.1%	4.2%	11.7%	7.9%	0.0%	1.7%	0.0%
Conjunctivitis	3.0%	3.8%	3.3%	0.0%	2.2%	2.1%	0.0%	3.4%	3.3%
Conjunctivitis allergic	1.7%	2.1%	3.8%	0.7%	0.7%	1.4%	1.6%	0.0%	3.3%

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Detachment of retinal pigment epithelium	15.3%	11.3%	9.2%	3.5%	2.2%	4.3%	3.2%	8.5%	16.4%
Dry eye	6.4%	6.7%	10.0%	9.1%	3.6%	14.3%	8.1%	8.5%	4.9%
Eye irritation	19.9%	16.0%	19.2%	6.3%	4.4%	8.6%	4.8%	13.6%	13.1%
Eye pain	33.5%	36.1%	37.2%	23.1%	29.9%	30.0%	12.9%	18.6%	18.0%
Eyelid pain	0.4%	1.3%	1.3%	0.7%	0.0%	2.9%	0.0%	0.0%	1.6%
Foreign body sensation in eyes	14.4%	18.1%	18.8%	12.6%	8.0%	10.0%	6.5%	10.2%	9.8%
Glaucoma	0.4%	1.3%	2.9%	2.1%	1.5%	2.1%	0.0%	1.7%	1.6%
Iridocyclitis	1.3%	0.8%	1.7%	0.0%	0.0%	3.6%	1.6%	1.7%	1.6%
Iritis	7.6%	8.0%	7.9%	1.4%	5.8%	7.9%	1.6%	1.7%	1.6%
Lacrimation increased	16.1%	17.2%	16.3%	5.6%	10.2%	9.3%	0.0%	6.8%	3.3%
Maculopathy	11.4%	8.4%	9.6%	4.9%	5.1%	7.9%	3.2%	5.1%	8.2%
Ocular discomfort	4.7%	7.6%	7.1%	2.1%	4.4%	6.4%	0.0%	0.0%	8.2%
Ocular hyperemia	10.2%	10.1%	10.0%	5.6%	7.3%	12.1%	1.6%	8.5%	6.6%
Photophobia	2.5%	3.8%	2.5%	1.4%	0.7%	3.6%	0.0%	1.7%	0.0%
Posterior capsule opacification	5.1%	6.3%	7.9%	2.8%	3.6%	5.0%	0.0%	3.4%	3.3%
Retinal degeneration	6.8%	10.5%	10.0%	4.2%	2.9%	5.7%	3.2%	1.7%	1.6%
Retinal disorder	9.3%	11.3%	12.6%	2.8%	8.0%	6.4%	0.0%	0.0%	1.6%
Uveitis	0.0%	0.4%	0.8%	0.0%	0.7%	2.1%	0.0%	0.0%	0.0%
Visual disturbance	11.4%	13.9%	15.9%	5.6%	10.2%	7.9%	1.6%	3.4%	4.9%
Vitreous detachment	17.8%	21.8%	22.2%	21.7%	17.5%	18.6%	19.4%	10.2%	8.2%

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Vitreous disorder	0.0%	2.1%	0.8%	0.0%	1.5%	2.1%	0.0%	1.7%	0.0%
Vitreous floaters	9.7%	31.9%	29.7%	4.9%	19.0%	22.1%	3.2%	11.9%	13.1%
Vitreous hemorrhage	2.5%	3.4%	2.9%	2.1%	3.6%	5.0%	1.6%	0.0%	1.6%
Vitritis	3.4%	7.1%	12.6%	2.1%	6.6%	10.7%	1.6%	1.7%	4.9%
GASTROINTESTINAL DISORDERS									
Dental caries	0.8%	2.1%	0.8%	0.0%	1.5%	2.1%	1.6%	0.0%	0.0%
Diarrhoea	8.5%	7.6%	4.2%	4.9%	10.2%	5.7%	1.6%	1.7%	4.9%
Dysphagia	0.8%	2.5%	0.8%	0.0%	0.7%	1.4%	0.0%	0.0%	3.3%
Hiatus hernia	2.1%	0.8%	1.3%	0.7%	1.5%	3.6%	0.0%	1.7%	0.0%
Nausea	5.5%	8.8%	8.8%	7.0%	8.0%	10.0%	4.8%	8.5%	3.3%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS									
Asthenia	2.5%	1.7%	1.7%	2.1%	4.4%	1.4%	0.0%	3.4%	3.3%
Chest pain	5.5%	4.2%	3.8%	2.1%	5.1%	5.0%	3.2%	6.8%	3.3%
Injection site hemorrhage	1.7%	1.7%	5.0%	2.8%	5.8%	4.3%	0.0%	0.0%	0.0%
INFECTIONS AND INFESTATIONS									
Bronchitis	8.5%	9.7%	10.5%	9.8%	8.0%	12.1%	4.8%	5.1%	6.6%
Diverticulitis	2.1%	3.8%	2.9%	0.7%	1.5%	2.9%	0.0%	3.4%	1.6%
Gastroenteritis viral	2.1%	1.3%	4.2%	0.0%	2.9%	2.9%	0.0%	1.7%	3.3%
Herpes zoster	2.1%	5.5%	4.2%	2.1%	2.9%	0.0%	1.6%	1.7%	4.9%
Influenza	5.1%	9.7%	7.9%	4.2%	5.8%	6.4%	3.2%	3.4%	4.9%

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Localized infection	2.5%	2.1%	0.8%	0.0%	0.7%	1.4%	0.0%	0.0%	3.3%
Nasopharyngitis	13.1%	13.4%	15.9%	12.6%	24.8%	16.4%	9.7%	8.5%	6.6%
Sinusitis	5.5%	7.6%	8.4%	10.5%	10.5%	8.6%	4.8%	5.1%	1.6%
Upper respiratory tract infection	9.7%	15.1%	7.5%	6.3%	7.3%	11.4%	4.8%	11.9%	4.9%
Urinary tract infection	7.6%	8.8%	7.1%	10.5%	12.4%	11.4%	8.1%	8.5%	13.1%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS									
Corneal abrasion	3.4%	2.5%	2.9%	0.7%	2.2%	3.6%	1.6%	1.7%	0.0%
Foot fracture	0.4%	1.3%	0.0%	0.0%	0.7%	2.9%	1.6%	0.0%	0.0%
Procedural pain	1.7%	1.7%	1.3%	2.8%	2.2%	5.7%	1.6%	5.1%	0.0%
Wrist fracture	2.5%	1.7%	0.4%	0.0%	0.7%	2.1%	0.0%	0.0%	0.0%
INVESTIGATIONS									
Blood cholesterol increased	3.8%	0.8%	3.8%	0.7%	0.7%	2.9%	1.6%	3.4%	1.6%
Blood glucose increased	4.7%	3.4%	3.8%	1.4%	3.6%	4.3%	0.0%	1.7%	1.6%
Intraocular pressure increased	5.9%	23.9%	23.8%	7.7%	22.6%	25.0%	4.8%	23.7%	31.1%
White blood cell count increased	0.0%	0.0%	2.5%	0.0%	0.7%	0.7%	0.0%	0.0%	0.0%
METABOLISM AND NUTRITION DISORDERS									
Diabetes mellitus	1.3%	2.9%	3.8%	2.8%	4.4%	3.6%	0.0%	5.1%	1.6%
Gout	1.7%	0.8%	2.5%	0.7%	2.9%	2.9%	0.0%	0.0%	3.3%
Hypokalemia	3.0%	1.3%	1.7%	4.2%	4.4%	2.1%	0.0%	0.0%	8.2%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS									

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
Arthralgia	8.9%	10.9%	11.3%	9.8%	5.1%	10.7%	1.6%	6.8%	8.2%
Back pain	9.3%	10.1%	9.2%	13.3%	10.2%	4.3%	3.2%	1.7%	6.6%
Exostosis	0.4%	0.4%	0.4%	1.4%	1.5%	1.4%	0.0%	0.0%	3.3%
Musculoskeletal chest pain	0.0%	0.0%	0.0%	0.0%	1.5%	0.7%	0.0%	0.0%	3.3%
Osteoarthritis	4.2%	3.8%	1.7%	0.7%	2.9%	3.6%	9.7%	1.7%	4.9%
Pain in extremity	5.9%	6.3%	5.4%	4.9%	5.1%	5.0%	0.0%	5.1%	3.3%
NERVOUS SYSTEM DISORDERS									
Dementia	1.3%	0.4%	0.4%	0.7%	0.7%	0.7%	0.0%	0.0%	3.3%
Dizziness	9.7%	7.6%	4.6%	4.9%	5.1%	7.9%	1.6%	3.4%	3.3%
Headache	10.2%	16.0%	10.0%	7.0%	12.4%	15.0%	3.2%	1.7%	8.2%
Sciatica	0.8%	1.3%	1.7%	0.7%	2.2%	2.1%	0.0%	1.7%	3.3%
PSYCHIATRIC DISORDERS									
Anxiety	3.0%	4.2%	5.0%	6.3%	7.3%	3.6%	4.8%	0.0%	1.6%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS									
Chronic obstructive pulmonary disease	2.1%	2.1%	4.6%	3.5%	6.6%	7.9%	0.0%	6.8%	0.0%
Cough	7.2%	9.7%	10.5%	8.4%	12.4%	6.4%	3.2%	3.4%	3.3%
Dyspnoea	2.5%	5.0%	2.9%	3.5%	3.6%	5.7%	3.2%	6.8%	1.6%
Sinus congestion	2.5%	2.1%	2.1%	0.0%	1.5%	2.1%	1.6%	1.7%	1.6%

Table 3: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate ≥ 2% between LUCENTIS 0.5 mg and the control in at least one study
Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) safety population

	% of Patients Study MARINA (Dosage q 1 month) 2 years			**% of Patients Study ANCHOR (Dosage q 1 month) 2 Years**			**% of Patients Study PIER (Dosage q 1 month for first 3 months then q 3 months) 2 Years**		
Preferred Term	Sham (N=236)	LUCENTIS 0.3 mg (N=238)	LUCENTIS 0.5 mg (N=239)	Verteporfin PDT (N=143)	LUCENTIS 0.3 mg (N=137)	LUCENTIS 0.5 mg (N=140)	Sham (N=62)	LUCENTIS 0.3 mg (N=59)	LUCENTIS 0.5 mg (N=61)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS									
Ecchymosis	0.4%	1.7%	1.7%	0.0%	2.2%	4.3%	0.0%	1.0%	1.6%
Pruritus	2.1%	3.8%	2.5%	0.7%	0.0%	3.6%	1.6%	1.7%	0.0%
VASCULAR DISORDERS									
Hypertension	16.1%	17.2%	16.3%	16.1%	9.5%	12.1%	11.3%	10.2%	18.0%
Multiple occurrences of the same event were counted once in the overall incidence.									

Table 4: Ocular adverse events in the study eye regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
CONGENITAL, FAMILIAL AND GENETIC DISORDERS				
Corneal dystrophy	2.0%	0.0%	3.2%	2.3%
EYE DISORDERS				
Anterior chamber flare	2.0%	0.0%	2.1%	2.0%
Arcus lipoides	0.0%	0.0%	1.6%	1.6%
Blepharitis	8.4%	7.0%	10.1%	10.9%
Cataract	5.7%	7.0%	7.8%	8.2%
Cataract cortical	2.0%	1.4%	1.4%	3.4%
Cataract nuclear	5.4%	1.4%	4.1%	4.8%
Cataract subcapsular	2.3%	0.7%	3.2%	2.7%
Chalazion	0.3%	0.7%	0.7%	1.6%
Choroidal neovascularisation	16.8%	12.6%	2.5%	2.5%
Conjunctival hemorrhage	58.4%	50.3%	71.9%	70.7%
Conjunctival hyperemia	5.4%	4.2%	5.5%	6.4%
Conjunctivitis	2.3%	0.0%	3.2%	3.0%
Conjunctivitis allergic	1.7%	0.7%	1.4%	3.0%
Detachment of retinal pigment epithelium	12.8%	3.5%	8.1%	8.6%
Diplopia	0.0%	0.7%	0.9%	1.1%
Dry eye	6.7%	9.1%	6.0%	10.7%
Eye discharge	6.7%	3.5%	6.2%	3.0%
Eye hemorrhage	3.4%	0.0%	0.7%	1.1%
Eye irritation	16.8%	6.3%	12.0%	15.0%
Eye pain	29.2%	23.1%	31.8%	32.3%
Eye pruritus	10.4%	8.4%	8.5%	10.2%
Eye swelling	1.3%	1.4%	1.2%	1.4%
Eyelid edema	2.7%	2.8%	2.8%	3.0%
Eyelid pain	0.3%	0.7%	0.7%	1.8%
Foreign body sensation in eyes	12.8%	12.6%	13.8%	14.8%
Glaucoma	0.3%	2.1%	1.4%	2.5%
Iridocyclitis	1.3%	0.0%	0.7%	2.3%
Iritis	6.4%	1.4%	6.5%	7.0%
Lacrimation increased	12.8%	5.6%	13.6%	12.3%
Macular degeneration	62.4%	70.6%	43.3%	42.0%
Macular edema	10.4%	4.9%	3.2%	3.6%

Table 4: Ocular adverse events in the study eye regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
Macular scar	1.7%	2.1%	2.3%	1.8%
Maculopathy	9.7%	4.9%	6.9%	8.9%
Meibomianitis	0.3%	0.0%	0.9%	1.6%
Ocular discomfort	3.7%	2.1%	5.5%	7.0%
Ocular hyperemia	8.4%	5.6%	9.0%	10.2%
Photophobia	2.0%	1.4%	2.5%	2.5%
Photopsia	5.0%	8.4%	4.8%	4.1%
Posterior capsule opacification	4.0%	2.8%	5.1%	6.4%
Punctate keratitis	3.7%	1.4%	3.9%	3.0%
Retinal degeneration	6.0%	4.2%	6.9%	7.5%
Retinal detachment	7.0%	2.1%	3.9%	1.4%
Retinal disorder	7.4%	2.8%	8.8%	9.1%
Retinal exudates	9.7%	4.9%	5.5%	4.8%
Retinal hemorrhage	52.7%	67.8%	25.8%	25.2%
Retinal pigmentation	1.0%	0.0%	1.4%	1.1%
Retinal tear	1.0%	0.0%	0.9%	1.1%
Retinal vascular disorder	2.7%	0.7%	0.5%	1.4%
Subretinal fibrosis	15.1%	22.4%	9.2%	9.5%
Trichiasis	0.7%	0.7%	1.2%	1.6%
Uveitis	0.0%	0.0%	0.5%	1.1%
Vision blurred	7.4%	9.1%	11.5%	6.8%
Visual acuity reduced	17.8%	16.8%	11.3%	8.6%
Visual disturbance	7.4%	4.9%	9.2%	10.5%
Vitreous detachment	17.8%	21.7%	18.9%	19.1%
Vitreous disorder	0.0%	0.0%	1.8%	1.1%
Vitreous floaters	8.1%	4.9%	25.1%	25.0%
Vitreous hemorrhage	2.3%	2.1%	3.0%	3.4%
Vitritis	3.0%	2.1%	6.2%	10.9%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Injection site hemorrhage	1.3%	2.8%	2.8%	4.1%
IMMUNE SYSTEM DISORDERS				
Drug hypersensitivity	2.0%	4.2%	1.4%	1.4%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Corneal abrasion	3.0%	0.7%	2.3%	2.7%

Table 4: Ocular adverse events in the study eye regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
INVESTIGATIONS				
Intraocular pressure increased	5.7%	7.7%	23.5%	25.2%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Cutis laxa	0.7%	0.7%	1.4%	1.1%
Dandruff	0.7%	0.7%	0.7%	1.1%

Table 5: Non-ocular adverse events regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Anaemia	6.4%	4.2%	7.6%	8.0%
CARDIAC DISORDERS				
Angina pectoris	1.3%	0.7%	1.4%	1.8%
Atrial fibrillation	4.0%	3.5%	3.2%	4.5%
Bradycardia	0.7%	2.1%	0.9%	1.1%
Cardiac failure congestive	4.0%	3.5%	4.1%	3.6%
Cardiomegaly	1.7%	0.7%	1.2%	1.1%
Coronary artery disease	3.0%	0.7%	2.8%	2.3%
Myocardial infarction	1.7%	1.4%	1.2%	1.6%
EAR AND LABYRINTH DISORDERS				
Vertigo	1.7%	7.0%	4.1%	2.3%
ENDOCRINE DISORDERS				
Hypothyroidism	2.3%	2.1%	1.6%	1.1%
GASTROINTESTINAL DISORDERS				
Abdominal pain	1.7%	2.1%	2.8%	1.1%
Colonic polyp	1.0%	2.8%	1.6%	1.6%
Constipation	7.0%	5.6%	6.7%	5.2%
Dental caries	1.0%	0.0%	1.6%	1.1%
Diarrhoea	7.0%	4.9%	7.6%	4.8%

Table 5: Non-ocular adverse events regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
Diverticulum	1.3%	0.7%	2.1%	1.6%
Dyspepsia	3.7%	2.8%	2.1%	1.4%
Dysphagia	0.7%	0.0%	1.6%	1.4%
Gastritis	0.7%	0.7%	1.2%	1.6%
Gastrooesophageal reflux disease	5.0%	8.4%	6.0%	3.6%
Hemorrhoids	2.3%	1.4%	1.8%	1.8%
Hiatus hernia	1.7%	0.7%	1.2%	1.8%
Inguinal hernia	0.3%	0.0%	0.5%	1.1%
Nausea	5.4%	7.0%	8.5%	8.4%
Toothache	2.0%	1.4%	1.4%	1.6%
Vomiting	1.3%	5.6%	4.4%	2.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Asthenia	1.0%	2.1%	2.8%	1.4%
Chest pain	5.0%	2.1%	4.8%	3.9%
Fatigue	3.4%	4.9%	3.2%	3.2%
Oedema peripheral	5.7%	2.8%	6.7%	3.6%
Pain	1.7%	2.1%	2.1%	2.0%
Pyrexia	1.7%	1.4%	2.5%	2.3%
HEPATOBILIARY DISORDERS				
Cholelithiasis	3.0%	0.7%	0.7%	1.1%
IMMUNE SYSTEM DISORDERS				
Drug hypersensitivity	2.7%	1.4%	0.9%	2.0%
Hypersensitivity	1.0%	4.2%	2.8%	2.3%
Seasonal allergy	3.4%	7.0%	3.7%	3.9%
INFECTIONS AND INFESTATIONS				
Bronchitis	8.1%	9.8%	9.0%	10.5%
Cellulitis	2.3%	0.7%	2.1%	1.1%
Cystitis	2.0%	2.8%	3.0%	3.0%
Diverticulitis	1.7%	0.7%	3.0%	2.7%
Ear infection	1.3%	2.1%	1.4%	1.4%
Gastroenteritis viral	1.7%	0.0%	1.8%	3.6%
Herpes zoster	2.0%	2.1%	4.1%	3.0%

Table 5: Non-ocular adverse events regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
Influenza	4.7%	4.2%	7.6%	7.0%
Localised infection	2.0%	0.0%	1.4%	1.4%
Lower respiratory tract infection	0.7%	1.4%	1.8%	1.1%
Nasopharyngitis	12.4%	12.6%	16.4%	14.8%
Pneumonia	5.4%	4.2%	6.2%	4.5%
Sinusitis	5.4%	10.5%	8.1%	7.5%
Tooth abscess	1.7%	1.4%	1.2%	1.6%
Tooth infection	1.3%	0.0%	1.6%	1.1%
Upper respiratory tract infection	8.7%	6.3%	12.2%	8.4%
Urinary tract infection	7.7%	10.5%	9.9%	9.3%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS				
Contusion	7.4%	5.6%	3.9%	4.1%
Excoriation	1.3%	0.7%	1.6%	1.6%
Fall	4.0%	2.1%	3.2%	3.2%
Joint sprain	0.7%	0.0%	1.2%	1.1%
Procedural pain	1.7%	2.8%	2.3%	2.5%
Skin laceration	2.3%	3.5%	3.5%	1.6%
INVESTIGATIONS				
Blood cholesterol increased	3.4%	0.7%	1.2%	3.2%
Blood glucose increased	3.7%	1.4%	3.2%	3.6%
Blood pressure increased	6.0%	2.1%	4.6%	5.5%
Blood urea increased	0.3%	0.7%	0.9%	1.1%
Blood uric acid increased	1.3%	0.0%	0.7%	1.8%
White blood cell count increased	0.0%	0.0%	0.2%	1.6%
METABOLISM AND NUTRITION DISORDERS				
Dehydration	1.0%	3.5%	2.8%	2.3%
Diabetes mellitus	1.0%	2.8%	3.7%	3.4%
Gout	1.3%	0.7%	1.4%	2.7%
Hypercholesterolemia	4.4%	5.6%	5.3%	5.0%
Hyperlipidemia	2.0%	2.8%	1.8%	1.6%
Hypokalemia	2.3%	4.2%	2.1%	2.7%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				

Table 5: Non-ocular adverse events regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
Arthralgia	7.4%	9.8%	8.5%	10.7%
Arthritis	7.0%	7.0%	4.6%	5.7%
Back pain	8.1%	13.3%	9.0%	7.3%
Exostosis	0.3%	1.4%	0.7%	1.1%
Joint swelling	2.0%	1.4%	1.8%	1.1%
Muscle spasms	2.3%	2.8%	2.3%	1.6%
Musculoskeletal pain	4.4%	2.8%	2.8%	3.0%
Musculoskeletal stiffness	0.0%	0.7%	0.2%	1.1%
Myalgia	1.3%	2.8%	1.4%	1.6%
Neck pain	1.0%	0.0%	1.2%	2.0%
Osteoarthritis	5.4%	0.7%	3.2%	2.7%
Osteoporosis	2.0%	3.5%	2.8%	3.0%
Pain in extremity	4.7%	4.9%	5.8%	5.0%
Rotator cuff syndrome	1.3%	0.7%	0.9%	1.1%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
Basal cell carcinoma	3.7%	2.1%	5.1%	2.3%
Skin cancer	1.0%	0.0%	0.9%	1.1%
NERVOUS SYSTEM DISORDERS				
Balance disorder	0.3%	0.0%	0.2%	1.1%
Carpal tunnel syndrome	0.3%	0.7%	0.9%	1.4%
Cerebrovascular accident	0.7%	0.7%	0.7%	1.1%
Dizziness	8.1%	4.9%	6.2%	5.2%
Headache	8.7%	7.0%	12.4%	11.4%
Nerve compression	1.0%	0.0%	0.5%	1.1%
Sciatica	0.7%	0.7%	1.6%	2.0%
Syncope	3.0%	2.1%	1.4%	2.7%
Transient ischaemic attack	1.3%	2.8%	0.7%	1.8%
PSYCHIATRIC DISORDERS				
Anxiety	3.4%	6.3%	4.6%	4.1%
Depression	6.7%	9.1%	5.5%	5.0%
Insomnia	5.0%	4.2%	4.1%	5.2%
RENAL AND URINARY DISORDERS				

Table 5: Non-ocular adverse events regardless of relationship to treatment by system organ class and preferred term (2-year incidence at least 1.0% in ranibizumab 0.5 mg group) in MARINA, ANCHOR, and PIER (pooled data) Safety Population

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
Renal cyst	1.3%	3.5%	1.4%	1.1%
Renal failure	0.3%	1.4%	1.8%	1.1%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
Benign prostatic hyperplasia	1.3%	2.8%	2.1%	2.3%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Asthma	2.0%	2.8%	2.5%	2.3%
Chronic obstructive pulmonary disease	1.7%	3.5%	4.1%	5.0%
Cough	6.4%	8.4%	9.7%	8.2%
Dyspnoea	2.7%	3.5%	4.8%	3.6%
Emphysema	1.0%	1.4%	1.2%	1.1%
Epistaxis	1.0%	2.8%	1.8%	1.6%
Pharyngolaryngeal pain	0.7%	2.8%	2.3%	1.8%
Rhinorrhoea	1.7%	1.4%	2.3%	1.4%
Sinus congestion	2.3%	0.0%	1.8%	2.0%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Actinic keratosis	3.0%	0.7%	1.8%	1.4%
Dermatitis contact	0.7%	2.1%	0.9%	1.4%
Ecchymosis	0.0%	0.0%	0.7%	1.6%
Pruritus	1.3%	0.7%	2.1%	2.5%
Rash	3.7%	5.6%	2.8%	3.9%
VASCULAR DISORDERS				
Haematoma	1.3%	0.0%	1.4%	1.1%
Hypertension	15.1%	16.1%	13.8%	15.2%
Hypotension	2.3%	4.2%	2.3%	1.8%

Arterial thromboembolic events, as defined by the ANTIPLATELET TRIALISTS' COLLABORATION (APTC), including vascular deaths, non-fatal myocardial infarctions, non-fatal ischemic strokes and non-fatal haemorrhagic strokes, have been linked to the systemic availability of highly potent vascular endothelial growth factor (VEGF) inhibitors. When the first-year data from all three phase III studies (MARINA, ANCHOR and PIER) were combined, the overall incidence of arterial thromboembolic events was higher for patients treated with LUCENTIS 0.5 mg (2.5%) compared with control arm (1.1%). When the second year data from all three phase III (MARINA, ANCHOR and PIER) were combined, the overall incidence of

arterial thromboembolic events was similar for patients with LUCENTIS 0.5 mg (4.1%) compared with the control arm (3.6%). For (fatal and non-fatal) cerebrovascular accidents (CVAs) the results were not consistent across studies. In the MARINA study, there was a slight numerical imbalance between LUCENTIS 0.5 mg (1.3%) and the control arm (0.4%) during the first year, which was still present at the end of the 2-year treatment period (3.3% for 0.5 mg vs. 1.3% for sham treatment). The CVA incidence rate in the MARINA, ANCHOR study and PIER study are shown in Table 6. Although there was a low annual rate of arterial thromboembolic events observed in the LUCENTIS (a VEGF inhibitor) clinical trials, there was no imbalance between treatment groups (Table 7). There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

Table 6 Cerebrovascular Accident (CVA) Rates (fatal and non-fatal), safety populations (2-year cumulative data)

	Control	0.3 mg LUCENTIS	0.5 mg LUCENTIS
MARINA – 1 yr	1/236 (0.4%)	1/238 (0.4%)	3/239 (1.3%)
MARINA – 2 yr	3/236 (1.3%)	3/238 (1.3%)	8/239 (3.3%)
ANCHOR – 1 yr	1/143 (0.7%)	1/137 (0.7%)	1/140 (0.7%)
ANCHOR - 2 yr	2/143 (1.4%)	3/137 (2.2%)[a]	0/140 (0.0%)
PIER – 1 yr	0/62 (0.0%)	0/59 (0.0%)	0/61 (0.0%)
PIER -2 yr[b]	0/62 (0.0%) (before crossover) 1/39 (2.6%) (after crossover)	0/59 (0.0%)	0/61 (0.0%)

[a] Includes one serious adverse event of cerebral infarction (Year 1), one adverse event of ischemic stroke (Year 2) and one non-serious adverse event of cerebral ischemia (Year 2)
[b]After the month 12 visit in the study, patients in the sham-injection group could crossover to the LUCENTIS 0.5 mg group for the remainder of the study.

Table 7 Arterial thromboembolic events (ATE) as defined by the Antiplatelet Trialists' Collaboration (APTC), safety populations (2-year cumulative data)

	Control	0.3 mg LUCENTIS	0.5 mg LUCENTIS
MARINA – 1 yr	2/236 (0.8%)	4/238 (1.7%)	5/239 (2.1%)
MARINA – 2 yr	9/236 (3.8%)	11/238 (4.6%)	11/239 (4.6%)
ANCHOR – 1 yr	3/143 (2.1%)	3/137 (2.2%)	6/140 (4.3%)
ANCHOR 2 yr	6/143 (4.2%)	6/137 (4.4%)	7/140 (5.0%)
PIER – 1 yr	0/62 (0.0%)	0/59 (0.0%)	0/61 (0.0%)
PIER -2 yr[a]	1/62 (1.6%) (before crossover) 1/39 (2.6%) (after crossover)	1/59 (1.7%)	0/61 (0.0%)

[a] After the month 12 visit in the study, patients in the sham-injection group could crossover to the LUCENTIS 0.5 mg group for the remainder of the study.

The SAILOR study, FVF 3689g, was a Phase IIIb, Multicenter Study to Evaluate the Safety and Tolerability of Ranibizumab in Naive and Previously Treated Subjects with Choroidal Neovascularization (CNV) Secondary to Age-Related Macular Degeneration (AMD).

In the study, an interim analysis including data from almost 2400 patients (randomized to the two doses of LUCENTIS 0.3 mg and LUCENTIS 0.5 mg in a 1:1 ratio) with an average follow-up period of 230 days was performed. The overall incidence of CVAs (fatal and non-fatal) was found to be 1.1% for LUCENTIS 0.5 mg compared with 0.3% for LUCENTIS 0.3 mg (p=0.021). The rate of deaths from all causes was (1.6% on 0.5 mg vs. 0.6% on 0.3 mg, p=0.029) whereas the differences in the rate of vascular deaths (0.7% on 0.5 mg vs. 0.4% on 0.3 mg) and in the rate of combined APTC events (1.7% on 0.5 mg vs. 1.1% on 0.3 mg) were smaller.

A second interim analysis which was based on an average follow-up time of 335 days showed that the difference in the incidence of CVAs had decreased with increasing exposure to LUCENTIS treatment (1.3% on 0.5 mg vs. 0.6% on 0.3 mg). The same applied to the difference in the overall death rate (2.0% on 0.5 mg vs. 1.3% on 0.3 mg).

Upon final analysis of the incidence in strokes in SAILOR study, there exists a 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 for 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. Forty-nine deaths were reported, with 20 deaths in the 0.3-mg group (1.7%) and 29 deaths in the 0.5-mg group (2.4%). Of these, 21 were classified as vascular deaths, 11 in the 0.3-mg group (0.9%) and 10 in the 0.5-mg group (0.8%).

DME population

The safety of LUCENTIS was studied in a one-year sham-controlled trial (study D2201 - RESOLVE) and in a one year laser-controlled trial (study D2301 - RESTORE) conducted respectively in 102 and 235 LUCENTIS-treated patients with visual impairment due to DME (see CLINICAL TRIALS section – Treatment of visual impairment due to DME). The safety population is grouped by the actual treatment received and is comprised of the safety-evaluable patients from the two studies who received at least one dose of study drug (a total of 496 patients). Overall, 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. The most common ocular adverse events in patients receiving LUCENTIS monotherapy (pooled data) were eye pain (14.3%), conjunctival hemorrhage (14.3%), intraocular pressure increased (10.1%), conjunctival hyperemia (5.5%), and foreign body sensation in eyes (5.1%). The most common non-ocular events were nasopharyngitis (9.7%), hypertension (7.4%) and influenza (5.1%).

The common ocular and non-ocular adverse events with suspected relationship to LUCENTIS treatment occurring in ≥ 1% of patients receiving treatment with LUCENTIS (any group) in at least one of the two studies RESOLVE and RESTORE are summarized in Tables 8 and 9 below.

The common ocular and non-ocular adverse events, regardless of treatment relationship to LUCENTIS, with a differrence in incidence rate of > 2% between patients receiving treatment with LUCENTIS (any group) and the control group in at least one of the two studies RESOLVE and RESTORE are summarized in Table 10 below.

Table 8: Ocular adverse events in the study eye with suspected relationship to LUCENTIS treatment
Studies RESOLVE and RESTORE safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS (any group) in at least one study

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml‡ (N=51)	LUCENTIS 10 mg / ml‡ (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
EYE DISORDERS							
Conjunctival hemorrhage	19.6%	25.5%	22.5%	14.3%	7.0%	7.5%	0.0%
Eye pain	15.7%	15.7%	15.7%	16.3%	10.4%	8.3%	10.0%
Vitreous floaters	2.0%	13.7%	7.8%	0.0%	0.0%	0.0%	0.0%
Conjunctival hyperemia	3.9%	2.0%	2.9%	2.0%	7.0%	3.3%	5.5%
Foreign body sensation in eyes	5.9%	3.9%	4.9%	2.0%	3.5%	5.8%	1.8%
Lacrimation increased	3.9%	5.9%	4.9%	0.0%	1.7%	2.5%	0.9%
Eye irritation	5.9%	2.0%	3.9%	2.0%	1.7%	0.0%	1.8%
Eye pruritus	3.9%	3.9%	3.9%	0.0%	0.9%	0.8%	1.8%
Endophthalmitis	2.0%	3.9%	2.9%	0.0%	0.0%	0.0%	0.0%
Ocular hyperemia	2.0%	3.9%	2.9%	8.2%	0.9%	0.8%	0.0%
Vision blurred	2.0%	3.9%	2.9%	0.0%	1.7%	0.8%	1.8%
Vitreous hemorrhage	2.0%	3.9%	2.9%	0.0%	0.0%	0.0%	0.0%
Eye discharge	2.0%	0.0%	1.0%	0.0%	2.6%	2.5%	0.9%
Visual impairment	0.0%	0.0%	0.0%	0.0%	2.6%	1.7%	0.0%
Eyelid edema	0.0%	0.0%	0.0%	6.1%	1.7%	2.5%	0.9%
Vitreous disorder	2.0%	2.0%	2.0%	0.0%	0.0%	0.0%	0.0%
Blepharitis allergic	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Conjunctival edema	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%

Table 8: Ocular adverse events in the study eye with suspected relationship to LUCENTIS treatment
Studies RESOLVE and RESTORE safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS (any group) in at least one study

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml‡ (N=51)	LUCENTIS 10 mg / ml‡ (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
Corneal disorder	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Corneal erosion	2.0%	0.0%	1.0%	2.0%	0.9%	0.8%	0.0%
Erythema of eyelid	2.0%	0.0%	1.0%	0.0%	0.9%	0.0%	0.0%
Eye disorder	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Lenticular opacities	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Retinal artery occlusion	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Retinal disorder	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Retinal exudates	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Ulcerative keratitis	2.0%	0.0%	1.0%	0.0%	0.9%	0.0%	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS							
Sensation of foreign body	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
INFECTIONS AND INFESTATIONS							
Hypopyon	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS							
Post procedural complication	3.9%	2.0%	2.9%	0.0%	0.0%	0.0%	0.0%
Corneal abrasion	0.0%	2.0%	1.0%	0.0%	0.0%	0.8%	0.0%
Foreign body in eye	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Medication error	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
INVESTIGATIONS							

Table 8: Ocular adverse events in the study eye with suspected relationship to LUCENTIS treatment
Studies RESOLVE and RESTORE safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS (any group) in at least one study

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml‡ (N=51)	LUCENTIS 10 mg / ml‡ (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
Intraocular pressure increased	11.8%	27.5%	19.6%	0.0%	0.9%	0.8%	0.0%

†The RESOLVE study (D2201) consisted of an exploratory part (Group A) and a confirmatory part (Group B) (see CLINICAL TRIALS - Treatment of visual impairment due to DME). For the purpose of the safety analyses, only data on the overall population (Group A+B) is presented.
‡Patients in the 6 mg/ml group received an actual dose of 0.3 mg or 0.6 mg ranibizumab, and patients in the 10 mg/ml group received an actual dose of 0.5 mg or 1.0 mg ranibizumab.

Table 9: Non-ocular adverse events with suspected relationship to LUCENTIS treatment
Studies RESOLVE and RESTORE safety population
Adverse events with incidence rate ≥ 1% for LUCENTIS (any group) in at least one study

	% of Patients Study RESOLVE (group A + B) †				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml‡ (N=51)	LUCENTIS 10 mg / ml‡ (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
CARDIAC DISORDERS							
Myocardial infarction	0.0%	2.0%	1.0%	2.0%	0.0%	0.0%	0.0%
GASTROINTESTINAL DISORDERS							
Nausea	0.0%	2.0%	1.0%	0.0%	0.9%	0.0%	0.0%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS							
Facial pain	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%
Sensation of foreign body	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS							
Procedural hypertension	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
INVESTIGATIONS							
Heart rate irregular	3.9%	2.0%	2.9%	0.0%	0.0%	0.0%	0.0%
Blood pressure increased	2.0%	2.0%	2.0%	2.0%	0.0%	0.0%	0.0%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS							
Pulmonary embolism	0.0%	0.0%	0.0%	0.0%	1.7%	0.0%	0.0%
VASCULAR DISORDERS							
Hypertension	3.9%	2.0%	2.9%	4.1%	0.9%	0.0%	0.9%
Accelerated hypertension	0.0%	2.0%	1.0%	0.0%	0.0%	0.0%	0.0%

†The RESOLVE study (D2201) consisted of an exploratory part (Group A) and a confirmatory part (Group B) (see CLINICAL TRIALS - Treatment of visual impairment due to DME). For the purpose of the safety analyses, only data on the overall population (Group A+B) is presented.
‡Patients in the 6 mg/ml group received an actual dose of 0.3 mg or 0.6 mg ranibizumab, and patients in the 10 mg/ml group received an actual dose of 0.5 mg or 1.0 mg ranibizumab.

Table 10: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate > 2% between LUCENTIS (any group) and the control, and at a higher rate in the LUCENTIS group, in at least one study Studies RESOLVE and RESTORE safety population

	% of Patients Study RESOLVE (group A + B)[†]				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml[‡] (N=51)	LUCENTIS 10 mg / ml[‡] (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
BLOOD AND LYMPHATIC SYSTEM DISORDER							
Anemia	5.9%	3.9%	4.9%	0.0%	0.9%	1.7%	2.7%
EYE DISORDERS							
Conjunctival hemorrhage	19.6%	25.5%	22.5%	14.3%	7.0%	8.3%	0.0%
Vitreous floaters	2.0%	15.7%	8.8%	0.0%	0.0%	0.0%	0.0%
Lacrimation increased	7.8%	7.8%	7.8%	0.0%	1.7%	3.3%	0.9%
Conjunctival hyperemia	0.0%	0.0%	0.0%	0.0%	7.8%	5.0%	5.5%
Foreign body sensation in eyes	5.9%	5.9%	5.9%	2.0%	4.3%	6.7%	1.8%
Corneal disorder	5.9%	3.9%	4.9%	0.0%	0.0%	0.0%	0.0%
Vitreous hemorrhage	2.0%	7.8%	4.9%	0.0%	0.9%	0.8%	1.8%
Eye irritation	5.9%	2.0%	3.9%	2.0%	1.7%	0.0%	2.7%
Retinal disorder	5.9%	2.0%	3.9%	0.0%	0.0%	0.0%	0.0%
Visual disturbance	5.9%	2.0%	3.9%	2.0%	0.0%	0.0%	0.0%
Diabetic retinopathy	2.0%	0.0%	1.0%	2.0%	0.9%	5.0%	2.7%
Endophthalmitis	2.0%	3.9%	2.9%	0.0%	0.0%	0.0%	0.0%
Visual impairment	0.0%	0.0%	0.0%	0.0%	3.5%	1.7%	0.9%
Lenticular opacities	2.0%	3.9%	2.9%	0.0%	0.0%	0.0%	0.9%
Retinal hemorrhage	2.0%	3.9%	2.9%	6.1%	0.0%	0.0%	0.9%
Eye discharge	2.0%	0.0%	1.0%	0.0%	2.6%	3.3%	0.9%

Table 10: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate > 2% between LUCENTIS (any group) and the control, and at a higher rate in the LUCENTIS group, in at least one study Studies RESOLVE and RESTORE safety population

	% of Patients Study RESOLVE (group A + B)[†]				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml[‡] (N=51)	LUCENTIS 10 mg / ml[‡] (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
GASTROINTESTINAL DISORDERS							
Vomiting	3.9%	0.0%	2.0%	0.0%	0.9%	0.8%	3.6%
Constipation	0.0%	0.0%	0.0%	0.0%	0.9%	3.3%	0.9%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS							
Fatigue	0.0%	3.9%	2.0%	0.0%	0.9%	0.8%	0.9%
Sensation of foreign body	3.9%	0.0%	2.0%	0.0%	0.0%	0.0%	0.0%
INFECTIONS AND INFESTATIONS							
Nasopharyngitis	9.8%	9.8%	9.8%	2.0%	9.6%	10.0%	14.5%
Influenza	3.9%	5.9%	4.9%	2.0%	5.2%	1.7%	5.5%
Cystitis	3.9%	0.0%	2.0%	0.0%	0.9%	1.7%	0.0%
Urinary tract infection	3.9%	0.0%	2.0%	2.0%	3.5%	0.8%	0.0%
Rhinitis	0.0%	0.0%	0.0%	2.0%	2.6%	0.0%	0.0%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS							
Post procedural complication	3.9%	2.0%	2.9%	0.0%	0.0%	0.0%	0.0%
INVESTIGATIONS							
Intraocular pressure increased	11.8%	29.4%	20.6%	2.0%	0.0%	0.0%	0.0%
Heart rate irregular	3.9%	2.0%	2.9%	0.0%	0.0%	0.0%	0.0%
Blood creatinine increased	0.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.0%
METABOLISM AND NUTRITION DISORDERS							

Table 10: Ocular (in the study eye) and non ocular adverse events, regardless relationship to treatment, with a difference in incidence rate > 2% between LUCENTIS (any group) and the control, and at a higher rate in the LUCENTIS group, in at least one study Studies RESOLVE and RESTORE safety population

	% of Patients Study RESOLVE (group A + B)[†]				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	LUCENTIS 6 mg / ml[‡] (N=51)	LUCENTIS 10 mg / ml[‡] (N=51)	LUCENTIS pooled (N=102)	Sham (N=49)	LUCENTIS 0.5 mg (N=115)	LUCENTIS 0.5 mg + Laser (N=120)	Laser (N=110)
Hypoglycemia	3.9%	3.9%	3.9%	0.0%	1.7%	2.5%	3.6%
Hyperglycemia	3.9%	0.0%	2.0%	0.0%	0.9%	1.7%	0.9%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS							
Osteoarthritis	3.9%	0.0%	2.0%	0.0%	0.0%	0.0%	0.9%
Pain in extremity	0.0%	2.0%	1.0%	0.0%	2.6%	0.0%	0.0%
PSYCHIATRIC DISORDERS							
Depression	3.9%	0.0%	2.0%	0.0%	0.9%	0.8%	0.9%
Nervousness	3.9%	0.0%	2.0%	0.0%	0.0%	0.0%	0.0%

[†]The RESOLVE study (D2201) consisted of an exploratory part (Group A) and a confirmatory part (Group B) (see CLINICAL TRIALS - Treatment of visual impairment due to DME). For the purpose of the safety analyses, only data on the overall population (Group A+B) is presented.

[‡]Patients in the 6 mg/ml group received an actual dose of 0.3 mg or 0.6 mg ranibizumab, and patients in the 10 mg/ml group received an actual dose of 0.5 mg or 1.0 mg ranibizumab.

There was no significant imbalance in the incidence rate of arterial thromboembolic events in the RESOLVE and RESTORE studies between the ranibizumab and control arms. In the RESOLVE study, 3 patients reported arterial thromboembolic events in the 10 mg/mL ranibizumab arm (5.9%) and 2 in sham arm (4.1%). One of the 3 events in the treatment arm (retina artery occlusion) was classified as an ATE, however the event was reported to occur due to the pressure caused by the intraocular injection, not due to an arterial thromboembolic event. In the RESTORE study, arterial thromboembolic events were reported in 4 patients in the ranibizumab arm (3.5%), 4 patients in the ranibizumab + laser arm (3.3%), and in 3 patients in the laser arm (2.7%).

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.

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 Branch RVO (BRVO) and Central RVO (CRVO) (see CLINICAL TRIALS section – Treatment of visual impairment due to macular edema secondary to RVO). The safety population comprises all patients from the BRAVO and CRUISE studies who received at least 1 injection of study drug. 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, with no new safety signals identified from the RVO population. The most commonly reported ocular events in the ranibizumab groups during the 6-month treatment period were conjunctival hemorrhage, retinal exudates, and eye pain. The most common non-ocular adverse event reported overall during the treatment period was hypertension (8.1% in the sham group vs. 6.0% and 5.0% in the 0.3 mg and 0.5 mg groups, respectively). Overall, the cumulative 12-month safety profile of ranibizumab in both studies was consistent with that observed at month 6.

The ocular and non-ocular adverse events occurring in ≥ 1% of patients receiving LUCENTIS in the controlled RVO phase III studies BRAVO and CRUISE (pooled data) are summarized in Table 11 and 12 below.

Table 11: Ocular adverse events in the study eye regardless of relationship to treatment, during the 6-month treatment period, by primary system organ class and preferred term (at least 1.0% in ranibizumab group) in BRAVO and CRUISE (pooled data) Safety Population

SYSTEM ORGAN CLASS Preferred term	**Sham N=260 (%)**	**Ranibizumab 0.3 mg N=266 (%)**	**Ranibizumab 0.5 mg N=259 (%)**
EYE DISORDERS			
Conjunctival hemorrhage	37.3%	51.5%	47.9%
Retinal exudates	12.7%	25.9%	20.8%
Eye pain	12.3%	16.5%	17.4%
Retinal vascular disorder	9.2%	11.3%	12.4%
Retinal hemorrhage	11.2%	12.0%	11.2%
Maculopathy	7.3%	13.5%	10.8%
Retinal depigmentation	4.2%	6.4%	8.9%
Myodesopsia	2.3%	9.8%	6.9%
Foreign body sensation in eye	5.0%	3.8%	6.9%
Ocular vascular disorder	5.0%	6.4%	6.6%
Eye irritation	6.2%	5.3%	6.6%
Ocular hyperemia	2.7%	6.8%	5.0%
Vision blurred	3.1%	3.4%	4.6%
Vitreous detachment	2.3%	2.6%	3.9%
Vitreous hemorrhage	5.8%	4.1%	3.5%
Dry eye	2.7%	2.3%	2.7%
Ocular discomfort	2.3%	1.1%	2.3%
Retinal disorder	1.2%	1.1%	2.3%
Retinal pigmentation	3.5%	3.0%	2.3%
Lacrimation increased	2.7%	3.8%	1.9%
Macular edema	6.2%	3.4%	1.9%
Cataract	0.4%	1.1%	1.5%
Punctate keratitis	0.8%	1.9%	1.5%
Optic atrophy	0.4%	0.0%	1.5%
Photopsia	1.2%	1.5%	1.5%
Conjunctivitis	0.0%	0.0%	1.2%

Table 11: Ocular adverse events in the study eye regardless of relationship to treatment, during the 6-month treatment period, by primary system organ class and preferred term (at least 1.0% in ranibizumab group) in BRAVO and CRUISE (pooled data) Safety Population

SYSTEM ORGAN CLASS Preferred term	**Sham N=260 (%)**	**Ranibizumab 0.3 mg N=266 (%)**	**Ranibizumab 0.5 mg N=259 (%)**
Keratitis	0.0%	0.4%	1.2%
Eye pruritus	2.3%	2.6%	1.2%
Visual acuity reduced	1.2%	0.0%	1.2%
Metamorphosia	1.2%	1.9%	1.2%
Iritis	2.7%	1.1%	0.8%
Eye discharge	1.2%	1.1%	0.8%
Papilloedema	1.9%	1.1%	0.8%
Optic disc vascular disorder	3.1%	4.1%	0.8%
Retinal degeneration	0.0%	1.1%	0.8%
Diplopia	0.4%	1.5%	0.8%
Visual impairment	1.2%	2.3%	0.8%
Conjunctival hyperemia	0.4%	1.5%	0.4%
Blepharitis	1.2%	1.1%	0.4%
Eye swelling	0.0%	1.5%	0.4%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Corneal abrasion	1.5%	1.5%	0.4%
INVESTIGATIONS			
Intraocular pressure increased	2.3%	6.8%	6.6%

Table 12: Non-ocular adverse events regardless of relationship to treatment, during the 6-month treatment period, by system organ class and preferred term (at least 1.0% in ranibizumab monotherapy group) in BRAVO and CRUISE (pooled data) Safety Population

System Organ Class Preferred term	**Sham N=260 (%)**	**Ranibizumab 0.3 mg N=266 (%)**	**Ranibizumab 0.5 mg N=259 (%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS			

Table 12: Non-ocular adverse events regardless of relationship to treatment, during the 6-month treatment period, by system organ class and preferred term (at least 1.0% in ranibizumab monotherapy group) in BRAVO and CRUISE (pooled data) Safety Population

System Organ Class Preferred term	**Sham N=260 (%)**	**Ranibizumab 0.3 mg N=266 (%)**	**Ranibizumab 0.5 mg N=259 (%)**
Anemia	1.2%	1.1%	1.2%
EAR AND LABYRINTH DISORDERS			
Vertigo	2.7%	1.1%	0.4%
GASTROINTESTINAL DISORDERS			
Nausea	1.5%	0.8%	1.2%
Vomiting	1.5%	0.4%	1.2%
Gastroesophageal reflux disease	0.4%	1.1%	0.8%
Diarrhea	2.7%	1.9%	0.4%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Pain	0.8%	1.1%	0.8%
Fatigue	0.8%	1.1%	0.0%
IMMUNE SYSTEM DISORDERS			
Hypersensitivity	0.4%	0.8%	1.5%
Seasonal allergy	1.9%	1.5%	0.4%
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	3.8%	5.3%	5.4%
Influenza	1.9%	1.5%	3.1%
Sinusitis	1.9%	5.3%	3.1%
Upper respiratory tract infection	1.5%	2.6%	2.3%
Cystitis	0.4%	0.4%	1.2%
Urinary tract infection	1.5%	1.9%	0.8%
Bronchitis	1.5%	1.1%	0.4%
Pneumonia	1.5%	1.5%	0.4%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Fall	2.3%	0.8%	1.9%
Contusion	1.9%	0.8%	1.5%
Upper limb fracture	0.0%	1.1%	0.0%

Table 12: Non-ocular adverse events regardless of relationship to treatment, during the 6-month treatment period, by system organ class and preferred term (at least 1.0% in ranibizumab monotherapy group) in BRAVO and CRUISE (pooled data) Safety Population

System Organ Class Preferred term	**Sham N=260 (%)**	**Ranibizumab 0.3 mg N=266 (%)**	**Ranibizumab 0.5 mg N=259 (%)**
INVESTIGATIONS			
Blood pressure increased	0.8%	0.8%	1.2%
METABOLISM AND NUTRITION DISORDERS			
Hypercholesterolemia	1.2%	1.5%	0.8%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Back pain	0.8%	1.5%	2.7%
Arthralgia	0.8%	1.1%	2.3%
Osteoporosis	0.4%	0.0%	1.2%
Arthritis	0.4%	1.1%	0.8%
Pain in extremity	0.8%	1.1%	0.8%
Neck pain	0.4%	1.1%	0.0%
Osteoarthritis	0.4%	1.5%	0.0%
NERVOUS SYSTEM DISORDERS			
Headache	3.5%	4.9%	2.7%
Sinus headache	0.4%	0.0%	1.2%
Dizziness	3.5%	2.3%	0.8%
PSYCHIATRIC DISORDERS			
Depression	0.4%	0.8%	1.2%
Anxiety	1.5%	1.5%	0.8%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	1.5%	1.1%	1.5%
Sinus congestion	0.4%	0.8%	1.5%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Hyperhidrosis	0.0%	0.0%	1.2%
VASCULAR DISORDERS			
Hypertension	8.1%	6.0%	5.0%

Sinusitis occurred in 5/260 (1.9%) of patients on sham and in 8/259 (3.1%) of patients on 0.5 mg

of ranibizumab in the pooled BRAVO and CRUISE trials.

There was no significant imbalance in the incidence rate of arterial thromboembolic events during the 6-month treatment period of the BRAVO and CRUISE studies between the ranibizumab and control arms. In the BRAVO study, the rate of APTC arterial thromboembolic events during the 6-month treatment period was similar between treatment groups, with 1 subject (0.8%) in the sham group experiencing a non-fatal hemorrhagic cerebrovascular accident, no subjects in the 0.3-mg group experiencing an arterial thromboembolic event, and 2 subjects (1.5%) in the 0.5-mg group experiencing one arterial thromboembolic event each (non-fatal myocardial infarction and fatal hemorrhagic cerebrovascular accident). In the CRUISE study, the rate of APTC arterial thromboembolic events during the 6-month treatment period were also balanced between treatment groups, with 1 subject (0.8%) in the sham group, 1 subject (0.8%) in the 0.3-mg group, and 1 subject (0.8%) in the 0.5-mg group experiencing one such event each (non-fatal myocardial infarction). Low rates of these events (<2.5%) were observed at 12 months in both 0.3 and 0.5-mg groups.

The long term safety profile of ranibizumab observed in the BRIGHTER and CRYSTAL 24-month studies was consistent with the known LUCENTIS safety profile (see CLINICAL TRIALS, Post-marketing studies).

PM population

The safety data of LUCENTIS was studied in the 12-month clinical study (RADIANCE), which included 224 ranibizumab-treated patients with PM (see CLINICAL TRIALS section – Treatment of visual impairment due to CNV secondary to PM). The safety population includes all randomized patients who received at least 1 application of study treatment (ranibizumab (sham) and/or vPDT (sham)) and had at least 1 post-baseline safety assessment during the study. Ocular and non-ocular events in this trial were reported with a frequency and severity consistent with those seen in the wet-AMD trials. Up to Month 12, the most frequently reported ocular adverse events following ranibizumab treatment were conjunctival hemorrhage, punctate keratitis, intraocular pressure increased, eye pain, and injection site hemorrhage. The most common non-ocular adverse events up to Month 12 in the ranibizumab groups were nasopharyngitis, headache, hypertension, upper respiratory tract infection, urinary tract infection, back pain, influenza and abdominal pain.

The ocular and non-ocular adverse events occurring in ≥ 1% of patients receiving LUCENTIS in the controlled PM phase III study are summarized in Table 13 and 14 below.

Table 13: Ocular adverse events of the study eye up to Month 12, regardless of relationship to treatment, by primary system organ class and preferred term (at least 1.0% in ranibizumab groups [Group I and II]) in study RADIANCE (Safety Set)				
	Ranibizumab 0.5 mg		**Verteporfin PDT**	
SYSTEM ORGAN CLASS Preferred term	**Group I by stabilization N=106 n (%)**	**Group II by disease activity N=118 n (%)**	**Group III with Ranibizumab 0.5 mg from Month 3 N=38 n (%)**	**Group III without Ranibizumab 0.5 mg from Month 3 N=15 n (%)**
EYE DISORDERS	39 (36.8)	36 (30.5)	12 (31.6)	4 (26.7)
Conjunctival hemorrhage	12 (11.3)	12 (10.2)	2 (5.3)	0
Punctate keratitis	8 (7.5)	3 (2.5)	2 (5.3)	0
Vitreous floaters	5 (4.7)	1 (0.8)	0	0
Dry eye	4 (3.8)	2 (1.7)	0	1 (6.7)
Eye pain	4 (3.8)	4 (3.4)	1 (2.6)	1 (6.7)
Blepharitis	2 (1.9)	2 (1.7)	0	0
Conjunctivitis	2 (1.9)	1 (0.8)	0	0
Eyelid edema	2 (1.9)	0	0	0
Retinal tear	2 (1.9)	1 (0.8)	0	0
Cataract	1 (0.9)	2 (1.7)	0	1 (6.7)
Conjunctivitis allergic	1 (0.9)	5 (4.2)	1 (2.6)	0
Ocular hyperemia	1 (0.9)	2 (1.7)	1 (2.6)	0
Retinal hemorrhage	1 (0.9)	3 (2.5)	0	0
Metamorphopsia	0	3 (2.5)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (3.8)	3 (2.5)	2 (5.3)	0
Injection site hemorrhage	3 (2.8)	3 (2.5)	2 (5.3)	0
INVESTIGATIONS	3 (2.8)	7 (5.9)	4 (10.5)	0
Intraocular pressure increased	3 (2.8)	7 (5.9)	4 (10.5)	0

PDT = photodynamic therapy

Table 14: Non-ocular adverse events up to Month 12, regardless of relationship to treatment, by primary system organ class and preferred term (at least 1.0% in ranibizumab groups [Groups I and II]) in study RADIANCE (Safety Set)

	Ranibizumab 0.5 mg		Verteporfin PDT	
SYSTEM ORGAN CLASS Preferred term	Group I by stabilization N=106 n (%)	Group II by disease activity N=118 n (%)	Group III with Ranibizumab 0.5 mg from Month 3 N=38 n (%)	Group III without Ranibizumab 0.5 mg from Month 3 N=15 n (%)
EAR AND LABYRINTH DISORDERS	2 (1.9)	4 (3.4)	0	1 (6.7)
Tinnitus	0	2 (1.7)	0	1 (6.7)
GASTROINTESTINAL DISORDERS	11 (10.4)	16 (13.6)	3 (7.9)	1 (6.7)
Abdominal pain	3 (2.8)	1 (0.8)	0	0
Nausea	2 (1.9)	1 (0.8)	1 (2.6)	0
Toothache	2 (1.9)	1 (0.8)	0	0
Vomiting	2 (1.9)	1 (0.8)	0	0
Dental caries	0	2 (1.7)	0	1 (6.7)
Hemorrhoids	0	2 (1.7)	0	0
Tooth disorder	0	2 (1.7)	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (4.7)	4 (3.4)	1 (2.6)	0
Fatigue	0	2 (1.7)	0	0
IMMUNE SYSTEM DISORDERS	1 (0.9)	2 (1.7)	0	0
Seasonal allergy	0	2 (1.7)	0	0
INFECTIONS AND INFESTATIONS	25 (23.6)	24 (20.3)	8 (21.1)	5 (33.3)
Nasopharyngitis	12 (11.3)	12 (10.2)	1 (2.6)	2 (13.3)
Upper respiratory tract infection	3 (2.8)	4 (3.4)	1 (2.6)	0
Urinary tract infection	3 (2.8)	3 (2.5)	0	0
Bacteriuria	2 (1.9)	0	0	0
Influenza	2 (1.9)	4 (3.4)	1 (2.6)	0
Pharyngitis	2 (1.9)	0	0	0
Bronchitis	1 (0.9)	4 (3.4)	1 (2.6)	0

METABOLISM AND NUTRITION DISORDERS	3 (2.8)	6 (5.1)	1 (2.6)	0
Diabetes mellitus	2 (1.9)	1 (0.8)	1 (2.6)	0
Hypercholesterolemia	1 (0.9)	2 (1.7)	0	0
Hyperglycemia	0	2 (1.7)	0	0
Hyperlipidemia	0	2 (1.7)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	12 (11.3)	9 (7.6)	1 (2.6)	1 (6.7)
Back pain	2 (1.9)	4 (3.4)	0	0
Intervertebral disc protrusion	2 (1.9)	0	0	0
Osteoporosis	2 (1.9)	0	0	0
Pain in extremity	2 (1.9)	1 (0.8)	0	1 (6.7)
Arthralgia	1 (0.9)	2 (1.7)	0	0
Tendonitis	1 (0.9)	2 (1.7)	0	0
NERVOUS SYSTEM DISORDERS	13 (12.3)	16 (13.6)	1 (2.6)	0
Headache	8 (7.5)	11 (9.3)	1 (2.6)	0
Migraine	2 (1.9)	1 (0.8)	1 (2.6)	0
Sciatica	1 (0.9)	2 (1.7)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (3.8)	5 (4.2)	2 (5.3)	0
Cough	1 (0.9)	2 (1.7)	1 (2.6)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1.9)	5 (4.2)	0	0
Urticaria	0	2 (1.7)	0	0
VASCULAR DISORDERS	5 (4.7)	6 (5.1)	3 (7.9)	0
Hypertension	3 (2.8)	5 (4.2)	3 (7.9)	0

PDT = photodynamic therapy

CNV population

The safety of LUCENTIS was studied in a 12-month clinical study (MINERVA), which included 171 ranibizumab-treated patients with visual impairment due to CNV (see CLINICAL TRIALS section - Treatment of visual impairment due to CNV). The safety profile in these patients was consistent with that seen in previous clinical trials with LUCENTIS. The safety population includes those adult patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Safety and tolerability of ranibizumab 0.5 mg were

compared to safety and tolerability of sham injections up to Month 2 and over time up to Month 12 (overall safety).

Up to Month 12, the most commonly reported ocular adverse events were conjunctival hemorrhage (7 (5.9%) ranibizumab patients and 6 (11.5%) sham with ranibizumab patients), choroidal neovascularization (3 (2.5%) ranibizumab patients and 0 sham with ranibizumab patients), visual acuity reduced (3 (2.5%) ranibizumab patients and 1 (1.9%) sham with ranibizumab patients) and conjunctivitis (2 (1.7%) ranibizumab patients and 3 (5.8%) sham with ranibizumab patients). The most commonly reported non-ocular adverse event up to Month 12 was nasopharyngitis (14 (11.8%) ranibizumab patients and 9 (17.3%) sham with ranibizumab patients).

The ocular and non-ocular adverse events occurring in ≥ 1% of patients receiving LUCENTIS in the controlled CNV phase III study are summarized in Table 15 and 16 below.

Table 15: Ocular adverse events of the study eye up to Month 12, regardless of relationship to treatment, by primary system organ class and preferred term (at least 1.0% in ranibizumab groups) in study MINERVA (Safety Set)

SYSTEM ORGAN CLASS Preferred term	**Ranibizumab 0.5 mg** **N=119** **n (%)**	**Sham with ranibizumab 0.5 mg** **N=52** **n (%)**	**Sham without ranibizumab 0.5 mg** **N=7** **n (%)**
EYE DISORDERS	25 (21.0)	16 (30.8)	3 (42.9)
Conjunctival hemorrhage	7 (5.9)	6 (11.5)	0
Choroidal neovascularisation	3 (2.5)	0	1 (14.3)
Visual acuity reduced	3 (2.5)	1 (1.9)	1 (14.3)
Ocular hypertension	2 (1.7)	0	0
Retinal hemorrhage	2 (1.7)	1 (1.9)	0
Vision blurred	2 (1.7)	1 (1.9)	0
Vitreous detachment	2 (1.7)	0	0
Vitreous floaters	2 (1.7)	0	0
Eye irritation	1 (0.8)	1 (1.9)	0
Eye pain	1 (0.8)	1 (1.9)	0
Foreign body sensation in eyes	1 (0.8)	1 (1.9)	1 (14.3)
Ocular discomfort	1 (0.8)	1 (1.9)	0
Ocular hyperemia	1 (0.8)	1 (1.9)	1 (14.3)
Conjunctival edema	0	1 (1.9)	0
Diplopia	0	1 (1.9)	0
Dry eye	0	1 (1.9)	0
Eye discharge	0	1 (1.9)	0
Eye hemorrhage	0	1 (1.9)	0
Eyelid cyst	0	1 (1.9)	0
Eyelid edema	0	2 (3.8)	0
Lacrimation increased	0	1 (1.9)	0
Retinal pigment epithelial tear	0	1 (1.9)	0
Uveitis	0	1 (1.9)	0
Visual impairment	0	1 (1.9)	0
IMMUNE SYSTEM DISORDERS	0	1 (1.9)	0

Table 15: Ocular adverse events of the study eye up to Month 12, regardless of relationship to treatment, by primary system organ class and preferred term (at least 1.0% in ranibizumab groups) in study MINERVA (Safety Set)

SYSTEM ORGAN CLASS Preferred term	**Ranibizumab 0.5 mg** **N=119** **n (%)**	**Sham with ranibizumab 0.5 mg** **N=52** **n (%)**	**Sham without ranibizumab 0.5 mg** **N=7** **n (%)**
Reaction to preservatives	0	1 (1.9)	0
INFECTIONS AND INFESTATIONS	3 (2.5)	4 (7.7)	0
Conjunctivitis	2 (1.7)	3 (5.8)	0
Adenoviral conjunctivitis	1 (0.8)	1 (1.9)	0
INVESTIGATIONS	3 (2.5)	1 (1.9)	0
Intraocular pressure increased	2 (1.7)	1 (1.9)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (1.9)	0
Sjogren's syndrome	0	1 (1.9)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (1.9)	0
Scab	0	1 (1.9)	0

Table 16: Non-ocular adverse events up to Month 12, regardless of relationship to treatment, by primary system organ class and preferred term (at least 1.0% in ranibizumab groups) in study MINERVA (Safety Set)			
	Ranibizumab 0.5 mg **N=119** **n (%)**	**Sham with ranibizumab 0.5 mg** **N=52** **n (%)**	**Sham without ranibizumab 0.5 mg** **N=7** **n (%)**
SYSTEM ORGAN CLASS Preferred term			
GASTROINTESTINAL DISORDERS	13 (10.9)	2 (3.8)	0
Diarrhea	4 (3.4)	0	0
Toothache	3 (2.5)	0	0
Abdominal pain upper	2 (1.7)	0	0
Dyspepsia	2 (1.7)	0	0
Nausea	1 (0.8)	1 (1.9)	0
Faecaloma	0	1 (1.9)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.8)	1 (1.9)	0
Pyrexia	0	1 (1.9)	0
IMMUNE SYSTEM DISORDERS	2 (1.7)	2 (3.8)	0
Seasonal allergy	1 (0.8)	1 (1.9)	0
Allergy to arthropod bite	0	1 (1.9)	0
INFECTIONS AND INFESTATIONS	37 (31.1)	17 (32.7)	1 (14.3)
Nasopharyngitis	14 (11.8)	9 (17.3)	1 (14.3)
Influenza	9 (7.6)	0	0
Bronchitis	3 (2.5)	1 (1.9)	0
Cystitis	3 (2.5)	2 (3.8)	0
Otitis media	2 (1.7)	0	0
Rhinitis	2 (1.7)	0	0
Sinusitis	2 (1.7)	3 (5.8)	0
Urinary tract infection	2 (1.7)	1 (1.9)	0
Dermatophytosis	0	1 (1.9)	0
Latent turberculosis	0	1 (1.9)	0
Tonsillitis	0	1 (1.9)	0
Urosepsis	0	1 (1.9)	0

INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4 (3.4)	4 (7.7)	0
Foot fracture	1 (0.8)	1 (1.9)	0
Ligament sprain	1 (0.8)	1 (1.9)	0
Head injury	0	1 (1.9)	0
Laceration	0	1 (1.9)	0
Muscle strain	0	1 (1.9)	0
INVESTIGATION	10 (8.4)	3 (5.8)	0
Bacterial test positive	2 (1.7)	0	0
Blood pressure increased	2 (1.7)	0	0
Blood alkaline phosphatase increased	1 (0.8)	1 (1.9)	0
Alanine aminotransferase increased	0	1 (1.9)	0
Hepatic enzyme increased	0	1 (1.9)	0
Prostatic specific antigen increased	0	1 (1.9)	0
Transaminases increased	0	1 (1.9)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (7.6)	4 (7.7)	1 (14.3)
Back pain	6 (5.0)	0	1 (14.3)
Arthralgia	1 (0.8)	1 (1.9)	0
Musculoskeletal pain	0	1 (1.9)	0
Osteoarthritis	0	1 (1.9)	0
Polyarthritis	0	1 (1.9)	0
Rheumatic disorder	0	1 (1.9)	0
Tenosynovitis	0	1 (1.9)	0
NEOPLASM BENIGN, MALIGNANT AND UNSPECIFIED (incl cysts and polyps)	7 (5.9)	1 (1.9)	0
Hepatocellular carcinoma	0	1 (1.9)	0
NERVOUS SYSTEM DISORDERS	9 (7.6)	3 (5.8)	1 (14.3)
Dizziness	3 (2.5)	0	0
Sciatica	2 (1.7)	0	0
Headache	1 (0.8)	3 (5.8)	1 (14.3)
PSYCHIATRIC DISORDERS	2 (1.7)	2 (3.8)	0
Depression	2 (1.7)	1 (1.9)	0
Fear of injection	0	1 (1.9)	0
Sleep disorder	0	1 (1.9)	0

RENAL AND URINARY DISORDERS	0	1 (1.9)	0
Oliguria	0	1 (1.9)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (1.7)	1 (1.9)	0
Benign prostatic hyperplasia	1 (0.8)	1 (1.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (2.5)	5 (9.6)	0
Chronic obstructive pulmonary disease	0	1 (1.9)	0
Cough	0	1 (1.9)	0
Oropharyngeal pain	0	1 (1.9)	0
Paranasal cyst	0	1 (1.9)	0
Pharyngeal inflammation	0	1 (1.9)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1.7)	1 (1.9)	0
Actinic keratosis	0	1 (1.9)	0
VASCULAR DISORDERS	6 (5.0)	1 (1.9)	1 (14.3)
Hypertension	5 (4.2)	1 (1.9)	1 (14.3)

In the study MINERVA (Safety Set), only 1 patient (0.8%) in the ranibizumab arm experienced a non-ocular risk of non-myocardial arterial thromboembolic events up to Month 2.

NOC/c **Retinopathy of Prematurity (ROP) population**

The safety of LUCENTIS 0.2 mg and 0.1 mg was studied in the 6-month clinical trial (RAINBOW), which included 149 ranibizumab-treated preterm infants with ROP (see CLINICAL TRIALS section). Up to Month 6, the most commonly reported (>5% incidence) ocular adverse events in the LUCENTIS groups were conjunctival hemorrhage, retinal hemorrhage, conjunctivitis and vitreous hemorrhage.

The ocular SAEs reported in the ranibizumab groups by one patient each included cataract, endophthalmitis, orbital infection, eye disorder, nystagmus and exophthalmos.

The most frequently reported (>5% incidence) non-ocular AEs that occurred more frequently in any of the LUCENTIS groups than in the laser group were pyrexia, diaper dermatitis,

nasopharyngitis, upper respiratory tract infection, cough, bronchiolitis, apnea, respiratory failure, anemia, urinary tract infection, diarrhea, bradycardia, inguinal hernia and osteopenia.

The most common non-ocular SAEs (in >2 patients [3%]) that occurred more frequently in any of the LUCENTIS groups than in the laser group were pneumonia, bronchiolitis, respiratory failure, necrotising colitis.

Brain edema and necrotising colitis were the most common adverse events leading to permanent discontinuation of ranibizumab treatment.

The ocular and non-ocular adverse events occurring in ≥ 1% of patients and reported more frequently in any of the LUCENTIS groups than in the laser group in the controlled ROP phase III study are summarized in Table 17 and 18 below.

Table 17: Ocular adverse events up to Month 6, regardless of relationship to treatment, (greater than or equal to 1% and more frequently reported in any of the LUCENTIS groups than in the laser group) in study RAINBOW (Safety Set)			
	Ranibizumab 0.2 mg **N=73** **n (%)**	**Ranibizumab 0.1 mg** **N=76** **n (%)**	**Laser** **N=69** **n (%)**
SYSTEM ORGAN CLASS Preferred term MedDRA version: 20.1 was used for reporting			
EYE DISORDERS			
Conjunctival hemorrhage	6 (8.2)	6 (7.9)	2 (2.9)
Retinal hemorrhage	6 (8.2)	10 (13.2)	7 (10.1)
Astigmatism	1 (1.4)	1 (1.3)	0
Cataract	1 (1.4)	0	0
Corneal epithelium defect	1 (1.4)	1 (1.3)	0
Eyelid oedema	1 (1.4)	1 (1.3)	0
Hypermetropia	1 (1.4)	0	0
Iris adhesions	1 (1.4)	0	0
Miosis	1 (1.4)	0	0
Refraction disorder	1 (1.4)	1 (1.3)	0
Retinal detachment	1 (1.4)	0	0
Atrophy of the globe	0	1 (1.3)	0
Corneal disorder	0	1 (1.3)	0
Exophthalmos	0	1 (1.3)	0
Eye disorder	0	1 (1.3)	0
Eye hemorrhage	0	2 (2.6)	1 (1.4)
Retinal scar	0	1 (1.3)	0
Vitreous hemorrhage	0	4 (5.3)	0
INFECTIONS AND INFESTATIONS			
Conjunctivitis	1 (1.4)	6 (7.9)	3 (4.3)
Adenoviral conjunctivitis	0	1 (1.3)	0
Endophthalmitis	0	1 (1.3)	0
Hypopyon	0	1 (1.3)	0
Orbital infection	0	1 (1.3)	0

INVESTIGATIONS			
Intraocular pressure increased	0	1 (1.3)	0
NERVOUS SYSTEM DISORDERS			
Nystagmus	1 (1.4)	1 (1.3)	0

Table 18: Non-ocular adverse events up to Month 6, regardless of relationship to treatment, (greater than or equal to 1% and more frequently reported in any of the LUCENTIS groups than in the laser group) in study RAINBOW (Safety Set)			
	Ranibizumab 0.2 mg **N=73** **n (%)**	**Ranibizumab 0.1 mg** **N=76** **n (%)**	**Laser** **N=69** **n (%)**
SYSTEM ORGAN CLASS Preferred term MedDRA version: 20.1 was used for reporting			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia	5 (6.8)	8 (10.5)	5 (7.2)
Anemia neonatal	2 (2.7)	4 (5.3)	1 (1.4)
Thrombocytopenia	1 (1.4)	0	0
Hypersplenism	0	1 (1.3)	0
Leukocytosis	0	1 (1.3)	0
Splenomegaly	0	1 (1.3)	0
CARDIAC DISORDERS			
Bradycardia	2 (2.7)	5 (6.6)	1 (1.4)
Cardiac failure acute	1 (1.4)	0	0
Cardiopulmonary failure	1 (1.4)	1 (1.3)	0
Pericardial effusion	1 (1.4)	0	0
Ventricular extrasystoles	1 (1.4)	0	0
Arrhythmia	0	1 (1.3)	0
Cardiac failure	0	1 (1.3)	0
Cardio-respiratory arrest	0	2 (2.6)	0
Cardiogenic shock	0	1 (1.3)	0
CONGENITAL, FAMILIAL AND GENETIC DISORDERS			
Deafness congenital	1 (1.4)	0	0
Ileal atresia	1 (1.4)	0	0
Hemoglobin C trait	0	1 (1.3)	0
Hypertrophic cardiomyopathy	0	1 (1.3)	0
EAR AND LABYRINTH DISORDERS			
Deafness	2 (2.7)	0	0
Deafness transitory	1 (1.4)	0	0

Deafness unilateral	1 (1.4)	0	0
Hypoacusis	1 (1.4)	0	0
ENDOCRINE DISORDERS			
Hypothyroidism	1 (1.4)	2 (2.6)	0
Adrenocortical insufficiency acute	0	1 (1.3)	0
GASTROINTESTINAL DISORDERS			
Gastroesophageal reflux disease	5 (6.8)	6 (7.9)	5 (7.2)
Diarrhea	4 (5.5)	2 (2.6)	1 (1.4)
Inguinal hernia	4 (5.5)	2 (2.6)	2 (2.9)
Flatulence	2 (2.7)	3 (3.9)	2 (2.9)
Incarcerated inguinal hernia	2 (2.7)	0	0
Vomiting	2 (2.7)	5 (6.6)	4 (5.8)
Abdominal discomfort	1 (1.4)	0	0
Abdominal distension	1 (1.4)	0	0
Anal inflammation	1 (1.4)	0	0
Ascites	1 (1.4)	1 (1.3)	0
Constipation	1 (1.4)	3 (3.9)	2 (2.9)
Gastric fistula	1 (1.4)	0	0
Gastrointestinal disorder	1 (1.4)	0	0
Gastrointestinal hemorrhage	1 (1.4)	0	0
Gastrointestinal oedema	1 (1.4)	0	0
Hiatus hernia	1 (1.4)	0	0
Intestinal prolapse	1 (1.4)	0	0
Necrotising colitis	1 (1.4)	3 (3.9)	1 (1.4)
Stress ulcer	1 (1.4)	0	0
Teething	1 (1.4)	0	0
Gastritis	0	1 (1.3)	0
Ileus	0	1 (1.3)	0
Large intestinal stenosis	0	1 (1.3)	0
Stomatitis	0	1 (1.3)	0
Umbilical hernia	0	3 (3.9)	2 (2.9)
Varices oesophageal	0	1 (1.3)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Pyrexia	9 (12.3)	6 (7.9)	4 (5.8)

Cyst	1 (1.4)	0	0
Face oedema	1 (1.4)	0	0
Peripheral swelling	1 (1.4)	0	0
Drug withdrawal syndrome	0	1 (1.3)	0
HEPATOBILIARY DISORDERS			
Hepatic fibrosis	1 (1.4)	0	0
Hepatomegaly	1 (1.4)	1 (1.3)	0
Cholestasis	0	1 (1.3)	0
Jaundice	0	1 (1.3)	0
IMMUNE SYSTEM DISORDERS			
Food allergy	1 (1.4)	0	0
Allergy to immunoglobulin therapy	0	1 (1.3)	0
INFECTIONS AND INFESTATIONS			
Nasopharyngitis	7 (9.6)	7 (9.2)	4 (5.8)
Upper respiratory tract infection	6 (8.2)	3 (3.9)	1 (1.4)
Urinary tract infection	4 (5.5)	2 (2.6)	2 (2.9)
Bronchiolitis	3 (4.1)	4 (5.3)	2 (2.9)
Bronchitis	3 (4.1)	3 (3.9)	2 (2.9)
Escherichia urinary tract infection	3 (4.1)	1 (1.3)	0
Rhinitis	3 (4.1)	0	2 (2.9)
Viral infection	3 (4.1)	1 (1.3)	1 (1.4)
Abscess limb	1 (1.4)	0	0
Bacteremia	1 (1.4)	0	0
Bacterial disease carrier	1 (1.4)	1 (1.3)	0
Bacterial sepsis	1 (1.4)	0	0
Device related infection	1 (1.4)	1 (1.3)	0
Enterococcal infection	1 (1.4)	1 (1.3)	0
Enterococcal sepsis	1 (1.4)	0	0
Fungal infection	1 (1.4)	0	0
Gastrointestinal fungal infection	1 (1.4)	0	0
Genital candidiasis	1 (1.4)	0	0
Klebsiella infection	1 (1.4)	0	0
Klebsiella sepsis	1 (1.4)	0	0
Lower respiratory tract infection	1 (1.4)	1 (1.3)	0

Peritonitis	1 (1.4)	0	0
Pneumonia cytomegaloviral	1 (1.4)	0	0
Pneumonia staphylococcal	1 (1.4)	1 (1.3)	0
Roseola	1 (1.4)	0	0
Septic shock	1 (1.4)	1 (1.3)	0
Skin infection	1 (1.4)	1 (1.3)	0
Staphylococcal sepsis	1 (1.4)	1 (1.3)	0
Urinary tract infection pseudomonal	1 (1.4)	0	0
Bacterial tracheitis	0	1 (1.3)	0
Bacteriuria	0	1 (1.3)	0
Candida infection	0	1 (1.3)	0
Cellulitis	0	1 (1.3)	0
Enteritis infectious	0	1 (1.3)	0
Enterobacter infection	0	1 (1.3)	0
Enterovirus infection	0	1 (1.3)	0
Escherichia sepsis	0	1 (1.3)	0
Febrile infection	0	1 (1.3)	0
Infection	0	1 (1.3)	0
Lower respiratory tract infection viral	0	1 (1.3)	0
Lung infection	0	1 (1.3)	0
Pathogen resistance	0	1 (1.3)	0
Post procedural infection	0	1 (1.3)	0
Respiratory tract infection	0	2 (2.6)	1 (1.4)
Respiratory tract infection bacterial	0	1 (1.3)	0
Staphylococcal bacteremia	0	1 (1.3)	0
Urinary tract infection enterococcal	0	1 (1.3)	0
Varicella	0	1 (1.3)	0
Viral upper respiratory tract infection	0	2 (2.6)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Greenstick fracture	1 (1.4)	0	0
Post procedural complication	1 (1.4)	0	0
Procedural pain	1 (1.4)	0	0
Stoma site erythema	1 (1.4)	0	0

Wound	1 (1.4)	0	0
Postoperative fever	0	2 (2.6)	0
INVESTIGATIONS			
Blood albumin decreased	1 (1.4)	0	0
Platelet count decreased	1 (1.4)	1 (1.3)	0
Protein total decreased	1 (1.4)	0	0
Pseudomonas test positive	1 (1.4)	0	0
Weight decreased	1 (1.4)	0	0
White blood cell count decreased	1 (1.4)	0	0
Blood albumin abnormal	0	1 (1.3)	0
Blood chloride decreased	0	1 (1.3)	0
Blood iron decreased	0	1 (1.3)	0
Blood potassium abnormal	0	1 (1.3)	0
Blood potassium increased	0	1 (1.3)	0
C-reactive protein increased	0	1 (1.3)	0
Cardiac murmur	0	1 (1.3)	0
Electroencephalogram abnormal	0	1 (1.3)	0
Hematocrit decreased	0	1 (1.3)	0
Protein total abnormal	0	1 (1.3)	0
Serum ferritin decreased	0	1 (1.3)	0
Vitamin D decreased	0	1 (1.3)	0
Vitamin D increased	0	1 (1.3)	0
METABOLISM AND NUTRITION DISORDERS			
Dehydration	1 (1.4)	0	0
Failure to thrive	1 (1.4)	0	0
Hyperphosphatasemia	1 (1.4)	0	0
Hypochloremia	1 (1.4)	0	0
Hypoglycemia	1 (1.4)	1 (1.3)	0
Hypoproteinemia	1 (1.4)	0	0
Vitamin D deficiency	1 (1.4)	0	0
Electrolyte imbalance	0	1 (1.3)	0
Hypercalcemia	0	1 (1.3)	0
Hypernatremia	0	2 (2.6)	0
Hyponatremia	0	1 (1.3)	0

Hypophagia	0	1 (1.3)	0
Malnutrition	0	3 (3.9)	0
Underweight	0	1 (1.3)	0
Zinc deficiency	0	1 (1.3)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Bone disorder	1 (1.4)	0	0
Bone metabolism disorder	1 (1.4)	0	0
Osteoporosis	1 (1.4)	0	0
Osteopenia	0	4 (5.3)	2 (2.9)
Positional plagiocephaly	0	2 (2.6)	0
Torticollis	0	1 (1.3)	0
NEOPLASM BENIGN, MALIGNANT AND UNSPECIFIED (incl cysts and polyps)			
Hemangioma	1 (1.4)	2 (2.6)	0
NERVOUS SYSTEM DISORDERS			
Brain oedema	2 (2.7)	0	0
Cerebellar hemorrhage	1 (1.4)	0	0
Intraventricular hemorrhage neonatal	1 (1.4)	0	0
Partial seizure	1 (1.4)	0	0
Periventricular hemorrhage neonatal	1 (1.4)	0	0
Seizure	1 (1.4)	2 (2.6)	1 (1.4)
Cognitive disorder	0	1 (1.3)	0
Developmental coordination disorder	0	1 (1.3)	0
Hemorrhage intracranial	0	1 (1.3)	0
Hypoxic-ischaemic encephalopathy	0	1 (1.3)	0
Peroneal nerve palsy	0	1 (1.3)	0
PSYCHIATRIC DISORDERS			
Autism spectrum disorder	0	1 (1.3)	0
Breath holding	0	1 (1.3)	0
Insomnia	0	1 (1.3)	0
Neurodevelopmental disorder	0	1 (1.3)	0
Psychomotor retardation	0	1 (1.3)	0
Restlessness	0	2 (2.6)	0

Stress	0	1 (1.3)	0
RENAL AND URINARY DISORDERS			
Pyelocaliectasis	1 (1.4)	0	0
Vesicoureteric reflux	1 (1.4)	0	0
Nephrolothiasis	0	1 (1.3)	0
Pelvi-ureteric obstruction	0	1 (1.3)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Ovarian cyst	1 (1.4)	0	0
Penile hemorrhage	1 (1.4)	0	0
Scrotal oedema	1 (1.4)	0	0
Balanoposthitis	0	1 (1.3)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	4 (5.5)	2 (2.6)	1 (1.4)
Bronchospasm	3 (4.1)	0	1 (1.4)
Atelectasis	2 (2.7)	0	1 (1.4)
Respiratory distress	2 (2.7)	2 (2.6)	0
Apnea	1 (1.4)	6 (7.9)	3 (4.3)
Aspiration	1 (1.4)	0	0
Bronchial dysplasia	1 (1.4)	0	0
Hypercapnia	1 (1.4)	0	0
Pneumothorax	1 (1.4)	0	0
Respiratory failure	1 (1.4)	4 (5.3)	1 (1.4)
Rhinitis allergic	1 (1.4)	0	0
Apnoeic attack	0	1 (1.3)	0
Dyspnea	0	2 (2.6)	1 (1.4)
Pneumonia aspiration	0	3 (3.9)	2 (2.9)
Pneumonitis	0	1 (1.3)	0
Respiratory arrest	0	2 (2.6)	0
Respiratory tract edema	0	2 (2.6)	0
Tracheomalacia	0	1 (1.3)	0
Vocal cord cyst	0	1 (1.3)	0
Wheezing	0	2 (2.6)	1 (1.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Dermatitis diaper	8 (11.0)	6 (7.9)	4 (5.8)

Dermatitis contact	1 (1.4)	0	0
Erythema	1 (1.4)	0	0
Hemorrhage subcutaneous	1 (1.4)	1 (1.3)	0
Purpura	1 (1.4)	0	0
Skin maceration	1 (1.4)	1 (1.3)	0
Skin oedema	1 (1.4)	0	0
Petechiae	0	1 (1.3)	0
Seborrhoeic dermatitis	0	1 (1.3)	0
SOCIAL CIRCUMSTANCES			
Dependence on oxygen therapy	1 (1.4)	0	0
VASCULAR DISORDERS			
Phlebitis	0	1 (1.3)	0
Shock	0	1 (1.3)	0
Superior vena cava syndrome	0	1 (1.3)	0

Deaths

There were 12 deaths through 24-week controlled period: 4 patients (5.5%) in the ranibizumab 0.2 group, 4 patients (5.3%) in the ranibizumab 0.1 mg group and 4 patients (5.8%) in the laser group. Six (6) deaths were due to respiratory complications including 3 patients in the ranibizumab 0.2 group, 1 patient in the ranibizumab 0.1 mg group and 2 patients in the laser group.

Arterial thromboembolic events (ATEs) and Non-ocular hemorrhages

Non-myocardial arterial thromboembolic events (4.1%, and 2.6%) and non-ocular hemorrhage (11.0% and 3.9%) were observed in the ranibizumab 0.2 mg and 0.1 mg groups, respectively. None of these events occurred in the laser group.

Neurodevelopmental impairment

A total of 37 patients (68 events) were identified as reporting events that may be broadly considered as related to overall developmental impairment associated with central nervous system (CNS) disorders. Amongst these 37 patients, AEs of developmental delay (including developmental delay, motor developmental delay, developmental coordination disorder, motor dysfunction, psychomotor skills impaired/psychomotor retardation, failure to thrive) occurred in 7 patients (11.5%) in the ranibizumab 0.2 mg group, 4 patients (6.2%) in the ranibizumab 0.1 mg group and 4 patients (7.4%) in the laser group. These events were predominantly reported in

patients born extremely premature, i.e. with an extremely low birth weight (≤1000g), and a history of CNS lesions prior to first treatment at baseline.

Less Common Clinical Trial Adverse Drug Reactions

Wet AMD Population

The adverse events with suspected relationship to LUCENTIS treatment listed below occurred in patients receiving treatment with LUCENTIS 0.5 mg for up to 2 years in the controlled Phase III studies MARINA (FVF2598g) and ANCHOR (FVF2587g) at an incidence of < 1.0%. The safety data described below also includes procedure and potential drug related ocular (in the study eye) and non-ocular adverse events in the 379 patients of the combined 0.5 mg treatment groups.

Cardiac disorders: Atrial fibrillation.

Ear and labyrinth disorders: Ear pain.

Eye disorders: Abnormal sensation in eye, angle closure glaucoma, anterior chamber flare, blepharitis, blindness, cataract subcapsular, conjunctival edema, conjunctivitis allergic, corneal deposits, corneal edema, corneal epithelium defect, corneal striae, dellen, detachment of retinal pigment epithelium, endophthalmitis, episcleritis, erythema of eyelid, eye hemorrhage, eye swelling, eyelid irritation, eyelid ptosis, glaucoma, hyphema, iris adhesions, keratopathy, lenticular pigmentation, macular degeneration, maculopathy, photophobia, photopsia, pigmentary glaucoma, posterior capsule opacification, pupillary reflex impaired, retinal artery occlusion, retinal disorder, retinal scar, retinal tear, scleral hyperemia, subretinal fibrosis, vitreous degeneration, vitreous opacities.

Gastrointestinal disorders: Nausea.

General disorders and administration site conditions: Asthenia, facial pain, injection site irritation, pain.

Infections and infestations: Hypopyon.

Injury, poisoning and procedural complications: Cataract traumatic, contusion, eye injury, scratch.

Investigations: Intraocular pressure decreased.

Musculoskeletal and connective tissue disorders: Pain in jaw.

Nervous System disorders: Dizziness.

Psychiatric disorders: Anticipatory anxiety, anxiety.

Respiratory, thoracic and mediastinal disorders: Cough, increased upper airway secretion, rhinorrhea, wheezing.

Skin and subcutaneous tissue disorders: Dermatitis allergic, lichenoid ketatosis.

DME population

The adverse events with suspected relationship to LUCENTIS treatment listed below are the events that occurred at an incidence of < 1.0% in the LUCENTIS groups in the controlled study RESTORE and that are not listed in Table 8 and 9 above. The safety data described below includes ocular (in the study eye) and non-ocular adverse events that were either considered related to the injection procedure or to the study medication.

Cardiac disorders: Coronary artery occlusion.

Gastrointestinal disorders: Intestinal obstruction.

Eye disorders: Anterior chamber inflammation, corneal epithelium defect, eye allergy, lid margin discharge, maculopathy, photophobia, cataract subcapsular, corneal edema, eyelid pain, metamorphosia, ocular discomfort, visual acuity reduced.

General disorders and administration site conditions: Influenza like illness.

Infections and infestations: Influenza.

Metabolism and nutrition disorders: Hypoglycemia.

Musculoskeletal and connective tissue disorders: Arthralgia, back pain.

Nervous system disorders: Dizziness

Psychiatric disorders: Anxiety

Respiratory, thoracic and mediastinal disorders: Dyspnea, rhinorrhea.

Skin and subcutaneous tissue disorders: Urticaria.

Vascular disorders: Arterial thrombosis limb.

RVO population

The adverse events with suspected relationship to LUCENTIS treatment listed below occurred in patients receiving treatment with LUCENTIS 0.5 mg for up to 6 months in the controlled Phase III studies BRAVO and CRUISE (pooled data) at an incidence of < 1.0%. The safety data described below includes procedure and potential drug related ocular (in the study eye) and non-ocular adverse events in the 259 patients treated with LUCENTIS 0.5 mg.

Cardiac disorders: Myocardial infarction.

Eye disorders: Anterior chamber disorder, cataract, vitreous hemorrhage, vitreous detachment, conjunctival edema, conjunctivitis, keratitis, corneal erosion, keratopathy, iritis, eyelid edema, eye hemorrhage, retinal disorder, eye discharge, photophobia, maculopathy, diplopia, metamorphosia, visual impairment.

Immune system disorders: Drug hypersensitivity.

Infections and infestations: Endophthalmitis, sinusitis.

Injury, poisoning and procedural complications: Corneal abrasion.

Nervous System disorders: Cerebral hemorrhage, hyperaesthesia, presyncope.

PM population

The adverse events with suspected relationship to LUCENTIS treatment listed below are events that occurred at an incidence of < 1.0% in the LUCENTIS groups in the controlled study RADIANCE and that are not listed in Table 13 and 14 above. The safety data described below includes ocular (in the study eye) and non-ocular adverse events that were either considered related to the injection procedure or to the study medication.

Eye disorders: Conjunctival edema, corneal erosion, uveitis, vitreous prolapse, eye irritation, iridocyclitis.

General disorders and administration site conditions: Injection site pain.

Hepatobiliary disorders: Hepatic function abnormal.

Immune system disorders: Drug hypersensitivity.

Infections and infestations: Adenoviral conjunctivitis.

Nervous System disorders: Intracranial pressure increased.

CNV population

The adverse events with suspected relationship to LUCENTIS treatment listed below are events that occurred at an incidence of < 1.0% in the LUCENTIS groups in the controlled study MINERVA and that are not listed in Table 15 and 16 above. The safety data described below includes ocular (in the study eye) and non-ocular adverse events that were either considered related to the injection procedure or to the study medication.

Cardiac disorders: Arrhythmia.

Eye disorders: Blepharitis, conjunctival hyperemia, conjunctivitis allergic, iritis, retinal cyst.

NOC/c

ROP population

The adverse events with suspected relationship to LUCENTIS treatment listed below are events that occurred in patients receiving treatment with LUCENTIS 0.2 mg or 0.1 mg for up to 6 months in the controlled study RAINBOW at an incidence of < 1.0% and that are not listed in Tables 17 and 18 above. The safety data described below includes ocular (in the study eye) events that were either considered related to the injection procedure or to the study medication. There were no suspected non-ocular adverse events in patients receiving treatment with LUCENTIS 0.2 mg or 0.1 mg for up to 6 months in the controlled study RAINBOW.

Eye disorders: Corneal edema.

Abnormal Hematologic and Clinical Chemistry Findings

Wet AMD population:

There were no findings to suggest a relationship between LUCENTIS and the development of clinically significant abnormalities.

RVO population:

There were no findings to suggest a relationship between LUCENTIS and the development of clinically significant abnormalities. There was no imbalance among treatment groups regarding the hematology and biochemistry post-baseline values.

PM population

There were no findings to suggest a relationship between LUCENTIS and the development of clinically significant abnormalities. There was no imbalance among treatment groups regarding the hematology and biochemistry post-baseline values.

CNV population

Overall, there were no meaningful shifts in laboratory parameters over 12 months in the MINERVA study. There were no patients with newly occurring notable values or with reported laboratory abnormalities which were classified as serious adverse events.

Post-Market Adverse Drug Reactions

The common ocular and non-ocular adverse drug reactions been reported with an incidence rate of ≥ 1.0% of the total adverse reactions reported in Phase IV clinical trials and with marketed use of LUCENTIS in wet AMD are summarized in Table 19 below.

Table 19: LUCENTIS Post-market ocular and non-ocular adverse reactions: Phase IV Studies [SECURE (CRFB002A2402) and EVEREST (CBPD952A2308)], literature cases and spontaneous reports. Adverse reactions with incidence rate ≥ 1% of total adverse reactions reported (n=4074)

Preferred Term	Studies SECURE and EVEREST	Literature Cases	Spontaneous Reports
EYE DISORDERS			
Visual acuity reduced	5 (0.1%)	31 (0.8%)	226 (5.5%)
Eye pain	2 (0.0%)	0 (0.0%)	182 (4.5%)
Visual impairment	1 (0.0%)	2 (0.0%)	125 (3.1%)
Endophthalmitis	5 (0.1%)	12 (0.3%)	77 (1.9%)
Ocular hyperemia	0 (0.0%)	0 (0.0%)	93 (2.3%)
Vision blurred	0 (0.0%)	0 (0.0%)	80 (2.0%)
Myodesopsia	0 (0.0%)	0 (0.0%)	57 (1.4%)
Foreign body sensation in eyes	0 (0.0%)	0 (0.0%)	51 (1.2%)
Eye hemorrhage	0 (0.0%)	1 (0.0%)	45 (1.1%)
Lacrimation increased	0 (0.0%)	0 (0.0%)	45 (1.1%)
Retinal pigment epithelial tear	0 (0.0%)	11 (0.3%)	34 (0.8%)
Eye irritation	0 (0.0%)	0 (0.0%)	43 (1.1%)
GASTROINTESTINAL DISORDERS			
Nausea	0 (0.0%)	0 (0.0%)	39 (1.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Drug ineffective	0 (0.0%)	3 (0.1%)	82 (2.0%)
INVESTIGATIONS			
Blood pressure increased	0 (0.0%)	0 (0.0%)	50 (1.2%)
NERVOUS SYSTEM DISORDERS			
Cerebrovascular accident	0 (0.0%)	1 (0.0%)	86 (2.1%)
Headache	0 (0.0%)	0 (0.0%)	85 (2.1%)
Dizziness	1 (0.0%)	0 (0.0%)	51 (1.2%)
SKIN AND SUBCUTANEOUS DISORDERS			
Allergic reactions[+]	1 (0.0%)	1 (0.0%)	71 (1.7%)

[+] Preferred terms summarized: Rash, Erythema, Urticaria, Pruritus and Pruritus generalized

DRUG INTERACTIONS

Overview
For the adjunctive use of verteporfin photodynamic therapy (PDT) and LUCENTIS (ranibizumab injection) in wet AMD and PM, see CLINICAL TRIALS - Treatment of Wet AMD section.

For the adjunctive use of laser photocoagulation and LUCENTIS in DME, see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION – Treatment of Visual Impairment Due to DME sections.

For the adjunctive use of laser photocoagulation and LUCENTIS in BRVO, see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION – Treatment of Visual Impairment Due to macular edema secondary to RVO sections.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose
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 (ranibizumab injection) vials and pre-filled syringes do not contain any preservative agent (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

LUCENTIS (ranibizumab injection) must be administered by a qualified ophthalmologist experienced in intravitreal injections.

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

Treatment of wet AMD

LUCENTIS 0.5 mg is recommended to be administered by intravitreal injection once a month. Treatment may be reduced to one injection every 3 months after the first three injections if monthly dosing is not feasible. Compared to monthly dosing, dosing every 3 months will lead to an approximate 5-letter (1 line) loss of visual acuity benefit, on average, over the following 9 months. Patients should be evaluated regularly.

LUCENTIS treatment is initiated with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase in which patients should be monitored for visual acuity on a regular basis. If the patient experiences a loss of greater than 5 letters in visual acuity (Early Treatment Diabetic Retinopathy Study (ETDRS) or one Snellen line equivalent), or clinical or diagnostic evidence of disease activity, LUCENTIS should be administered.

Treatment of visual impairment due to DME

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.

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:

In clinical trials, LUCENTIS was 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 edema 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.

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 edema 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 can be safely administered concomitantly with 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 CNV secondary to PM

Treatment is initiated with a single injection.

If monitoring reveals signs of disease activity, e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended.

Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) or fluorescein angiography (FA).

While many patients may only need one or two injections during the first year, some patients may need more frequent treatment (see CLINICAL TRIALS). Therefore, monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician.

There is no clinical trial experience of concomitant administration of LUCENTIS and other medical agents/procedures in patients diagnosed with pathologic myopia.

There are limited data on treatment with LUCENTIS in patients previously treated with verteporfin PDT.

Treatment of visual impairment due to CNV

Treatment is initiated with a single injection.

If monitoring reveals signs of disease activity, e.g. reduced visual acuity and/or signs of lesion activity, further treatment is recommended.

Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) or fluorescein angiography (FA).

Frequent monitoring is recommended, the treating physician should determine frequency of monitoring.

NOC/c ***Preterm infants***

Treatment of ROP in preterm infants

The recommended dose for LUCENTIS in **preterm infants** is 0.1 mg administered by intravitreal injection. This corresponds to an injection volume of 0.01 mL.

Treatment in preterm infants is initiated with a single injection per eye and may be given bilaterally on the same day. Further treatment may be administered if there are signs of disease activity. The interval between two doses injected into the same eye should not be shorter than one month.

In the clinical trial, up to three injections per eye can be administered. Most patients (78%) received one injection per eye (see **CLINICAL TRIALS**, **Treatment of ROP in preterm infants**). The administration of more than three injections per eye has not been studied. LUCENTIS re-treatment was not administered to an eye that had developed stage 4 or stage 5 ROP.

The recurrence of ROP was observed in the clinical trial (see **CLINICAL TRIALS, Treatment of ROP in preterm infants**). Disease recurrence should be monitored closely until the ophthalmologist can be assured that reactivation of proliferative ROP will not occur.

Administration

As with all medicinal products for parenteral use, LUCENTIS should be inspected visually for particulate matter and discoloration prior to administration.

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see 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, in accordance with local practice guidelines.

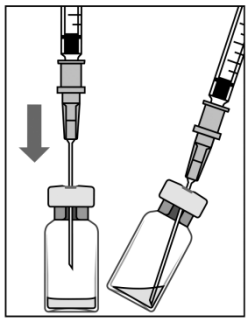
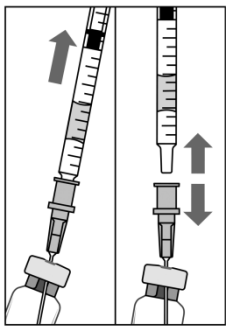
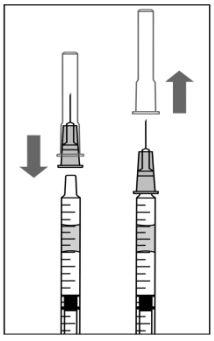
Vial (adults and preterm infants)

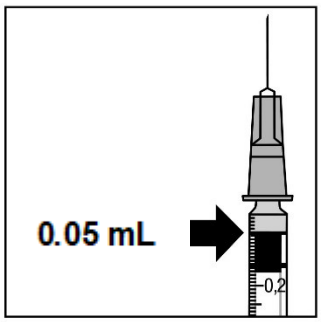
Vials are for single use only. After injection any unused product must be discarded.

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.

Adults

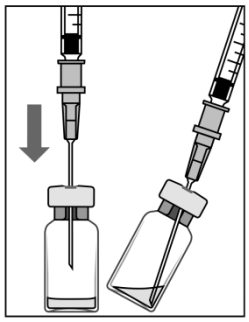
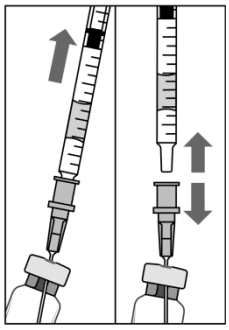
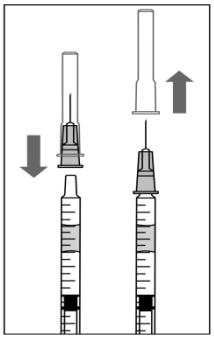
To prepare LUCENTIS for intravitreal administration **to adults**, please adhere to the following instructions:

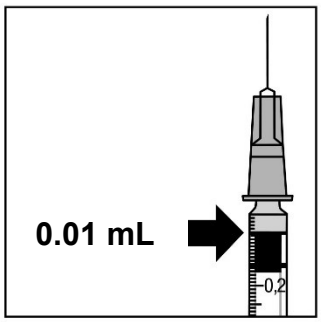
A. 	1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected. 2. Assemble the 5 micrometer filter needle (included in LUCENTIS pack) onto the 1 mL syringe (not included in LUCENTIS pack) using aseptic technique. Push the blunt filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal
B. 	4. Ensure that the plunger rod is drawn 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 (not included in LUCENTIS pack) onto the syringe. 7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe. Note**:** Grip at the 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 syringe is ready for injection. Note**:** Do not wipe the injection needle. Do not pull back on the plunger.

	
E.	9. 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. 10. The injection volume of **0.05 mL**, is then delivered. 11. The scleral site should be rotated for subsequent injections. 12. 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.

NOC/c ***Preterm infants***

To prepare LUCENTIS for intravitreal administration to **preterm infant**, please adhere to the following instructions:

A. 	1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected. 2. Assemble the 5 micrometer filter needle (included in LUCENTIS pack) onto the 1 mL syringe (not included in LUCENTIS pack) using aseptic technique. Push the blunt filter needle into the center of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal
B. 	4. Ensure that the plunger rod is drawn 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 (not included in LUCENTIS pack) onto the syringe. 7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe. Note**:** Grip at the 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 preterm infants is 0.01 ml. The syringe is ready for injection. Note**:** Do not wipe the injection needle. Do not pull back on the plunger.

	
E.	9. 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. 10. The injection volume of **0.01 mL** is then delivered. 11. If further treatment is administered the scleral site should be rotated for subsequent injections. 12. 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)

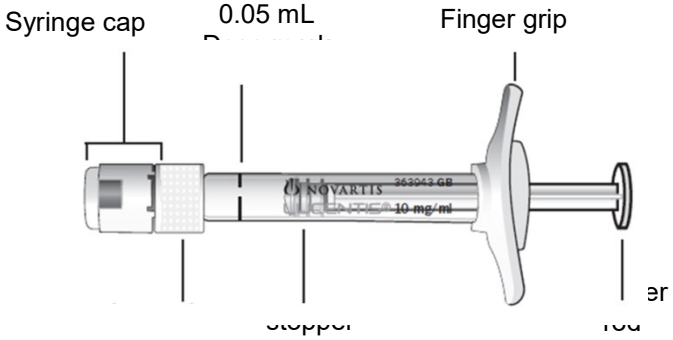
The pre-filled syringe is for single use only.

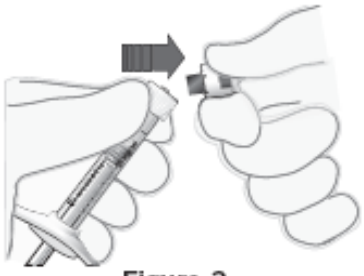
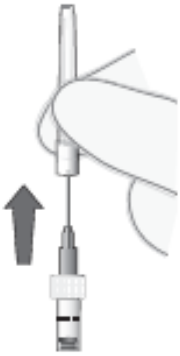
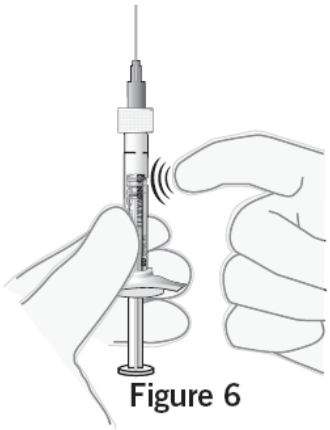
The pre-filled syringe is sterile. Do not use the pre-filled syringe if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discolored, cloudy, or contains particulates.

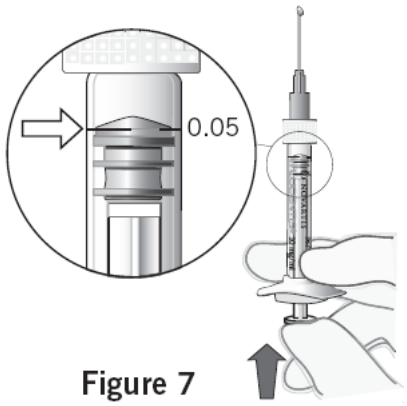
For the intravitreal injection, a 30G x 1/2 inch injection needle should be used.

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

Introduction	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.	
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, colourless to pale yellow to brown and does not contain any particulates. 4. If any of the above is not true, use a new pre-filled syringe.	

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 1/2 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

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 centre 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.	

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Because LUCENTIS (ranibizumab injection) is administered by qualified ophthalmologists experienced in intravitreal injections, the likelihood of an overdose is very low. Cases of accidental overdose (injection of volumes greater than the recommended 0.05 mL LUCENTIS) 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor-A (VEGF-A). Ranibizumab is designed to penetrate all retinal layers. It binds with high affinity to all active 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. 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, of macular edema causing visual impairment in diabetes and retinal vein occlusion, and of choroidal neovascularization secondary to pathologic myopia.

Pharmacokinetics

Following monthly intravitreal administration of LUCENTIS (ranibizumab injection) to patients with neovascular AMD, serum concentrations of ranibizumab were generally low. Maximum serum levels (C_{max}), measured after single administration and estimated using population pharmacokinetics (PK) for repeated administration, were generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). Following single administration, C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Serum ranibizumab concentrations in RVO patients were similar to those observed in wet AMD patients. Although the PK data suggest that serum ranibizumab levels remain below the level necessary to inhibit the biological activity of VEGF by 50%, an assessment of additional time points around the C_{max} would be required to confirm that serum ranibizumab levels do not exceed this threshold at any timepoint upon monthly intravitreal injection of 0.5 mg LUCENTIS in humans.

Based on analysis of limited population pharmacokinetics data from patients with wet AMD treated with the 0.5 mg dose, 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.

Special Populations and Conditions

NOC/c **Pediatrics population (preterm infants with ROP):** Following intravitreal administration of LUCENTIS to preterm infants with ROP at a dose of 0.1 mg or 0.2 mg (per eye), serum ranibizumab concentrations reached highest level within 24 hours after injection. The mean (±SD)

maximum concentrations were 12.1 (±25.5) ng/mL and 24.7 (±52.4) ng/mL respectively, about 7- and 14.5-fold higher than in neovascular AMD adult patients receiving 0.5 mg in one eye. Change from baseline in the plasma free VEGF concentrations was observed. The median free VEGF levels in the plasma of infants with ROP decreased from 130 – 136 pg/mL at the baseline to 67.0 - 68.7 pg/mL after ranibizumab 0.1 mg or 0.2 mg intravitreal injection.

Geriatrics (65 years or above): No dose adjustment is required in the elderly.

Gender: No special considerations are needed.

Hepatic Insufficiency: No formal studies have been conducted to examine the pharmacokinetics of LUCENTIS in patients with hepatic impairment.

Renal Insufficiency: 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 [50-80 mL/min], 20% moderate [30-50 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 in patients with mild and moderate renal impairment. Three patients with severe renal impairment had a clearance that was reduced by approximately 42%. The clinical significance of these findings is unknown.

STORAGE AND STABILITY

Vial (adults and preterm infants)

Store in a refrigerator (2°C - 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 (adults only)

Store in a refrigerator (2°C - 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 must be kept out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

Do not use if particles, discolouration or cloudiness are evident.

Vials and pre-filled syringes are for single use only.

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form and Composition

LUCENTIS (ranibizumab injection) is a sterile, clear colourless to pale yellow to brown and preservative-free aqueous solution for injection. Each mL of LUCENTIS contains:

Medicinal Ingredient: 10 mg ranibizumab.
Nonmedicinal Ingredients: α,α-trehalose dihydrate; histidine hydrochloride monohydrate; histidine; polysorbate 20; water for injection.

Packaging

Vial (adults and preterm infants)

Single-use glass vial (colourless type I glass) with chlorobutyl rubber stopper containing 2.3 mg ranibizumab in 0.23 mL solution for injection. One pack contains one 0.23 mL vial and one filter needle for withdrawal of the vial contents.

Pre-filled syringe (adults only)

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, containing 1.65 mg ranibizumab in 0.165 mL sterile solution for injection. 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.

PART II: SCIENTIFIC INFORMATION

LUCENTIS indicated in preterm infants for:

- the treatment of retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.
For further information for LUCENTIS please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

LUCENTIS, 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 visual impairment due to macular edema secondary to retinal vein occlusion (RVO).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM).
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to ocular conditions other than AMD or PM, including but not limited to angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy or idiopathic chorioretinopathy.

has been issued market authorization without conditions.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ranibizumab

Chemical name: Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ-chain

Molecular formula and molecular mass:
The molecular weight of the light and of the heavy chain deduced from the amino acid sequence is 23,433 and 24,957 Da, respectively. The molecular weight of the Fab fragment is 48 kDa and is produced by an *E. coli* expression system in a nutrient medium containing the antibiotic tetracycline. Tetracycline is not detectable in the final product.
Structural formula:

Ranibizumab is a humanised monoclonal antibody fragment produced in *Escherichia coli* cells by recombinant DNA technology. It consists of a 214-residue light chain linked by a disulfide bond at its C-terminus to the 231-residue N-terminal segment of the heavy chain. The expected amino acid sequences of the heavy and light chains are shown below. Ranibizumab is not glycosylated.

The amino acid sequence of the heavy chain of ranibizumab:

```
         10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGWINTYTGEPTY
         70        80        90        100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT
        130       140       150       160       170       180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
        190       200       210       220       230
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL
```

Complementarity-determining regions (CDRs) are underlined.

The amino acid sequence of the light chain of ranibizumab:

```
         10        20        30        40        50        60
DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
         70        80        90        100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
        130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
        190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Complementarity-determining regions (CDRs) are underlined.

CLINICAL TRIALS

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of LUCENTIS (ranibizumab injection) have been assessed in three randomised, double-masked, sham[1]- 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 choroidal neovascularisation (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 photodynamic therapy (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.

Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of LUCENTIS in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of Month 12. 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. A total of 184 patients were enrolled in this study (LUCENTIS 0.3 mg, 60; LUCENTIS 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study.

In both studies MARINA and ANCHOR the primary efficacy endpoint was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity at 12 months compared with baseline. Almost all LUCENTIS-treated patients (90-96%) depending on study and dose maintained their visual acuity (See Table 20 and Figure 1). In study FVF3192g (PIER), the primary efficacy endpoint was mean change in BCVA from baseline at Month 12 (see Figure 2). In both dose groups, visual acuity was maintained, on average.

Table 20 Overview of the primary endpoints by study, randomized subjects, with last observation carried forward (LOCF) method to impute missing data:

Study MARINA (Outcome at 12 and 24 months)						
Outcome Measure	Month	Sham (N=238)	LUCENTIS 0.3mg (N=238)	Estimated Difference Between Sham and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=240)	Estimated Difference Between Sham and LUCENTIS 0.5mg
Loss of < 15 letters in visual acuity (%) (95% CI)	12	62.2 (56.0 , 68.3)	94.5 (91.7 , 97.4)	32.4 (25.5 , 39.2)	94.6 (91.7 , 97.4)	32.4 (25.6 , 39.2)
	24	52.9 (46.6 , 59.3)	92.0 (88.6 , 95.5)	39.1 (31.9 , 46.3)	90.0 (86.2 , 93.8)	37.1 (29.7 , 44.4)

Study ANCHOR (Outcome at 12 and 24 months)						
Outcome Measure	Month	PDT (N=143)	LUCENTIS 0.3mg (N=140)	Estimated Difference Between PDT and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=139)	Estimated Difference Between PDT and LUCENTIS 0.5mg
Loss of < 15 letters in visual acuity (%) (95% CI)	12	64.3 (56.5 , 72.2)	94.3 (90.4 , 98.1)	30.0 (21.2 , 38.7)	96.4 (93.3 , 99.5)	32.1 (23.6 , 40.5)
	24	65.7 (58.0 , 73.5)	90.0 (85.0 , 95.0)	24.3 (15.0 , 33.5)	89.9 (84.9 , 94.9)	24.2 (14.9 , 33.4)

Study PIER (Outcome at 12 months)						
Outcome Measure	Month	Sham (N=63)	LUCENTIS 0.3mg (N=60)	Estimated Difference Between Sham and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=61)	Estimated Difference Between Sham and LUCENTIS 0.5mg
Mean change (SD) in BCVA[#] from Baseline (Letters) (95% CI)	12	-16.3 (22.3) (-21.9 , -10.7)	-1.6 (15.1) (-5.4 , 2.3)	14.8 (7.9 , 21.6)	-0.2 (13.1) (-3.5 , 3.2)	16.2 (9.6 , 22.7)

[#]Best Corrected Visual Acuity

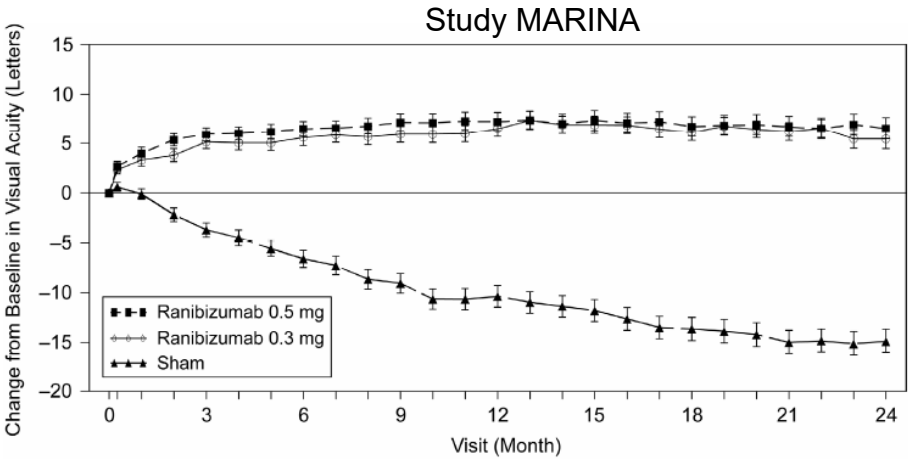
Randomized subjects = all subjects randomized. Note for Study ANCHOR, LUCENTIS 0.5 mg group, 140 subjects were randomized, however one subject did not have a BCVA baseline value, therefore, data from 139 patients are included in the results for this group.

Patient withdrawal rates (control, 0.3 mg LUCENTIS, 0.5 mg LUCENTIS):

- MARINA 1 year (discontinued study on or prior to Month 12): 8.8%, 2.5%, 2.5%
- MARINA 2 year (discontinued from study): 20.2%, 11.8%, 10.4%
- ANCHOR 1 year (discontinued study on or prior to Month 12): 7.0%, 7.1%, 3.6%
- ANCHOR 2 year (discontinued from study): 23.1%, 16.4%, 17.1%
- PIER 1 year (discontinued study on or prior to Month 12): 12.7%, 1.7%, 3.3%

The sham LUCENTIS injection control procedure involved anesthetising 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.

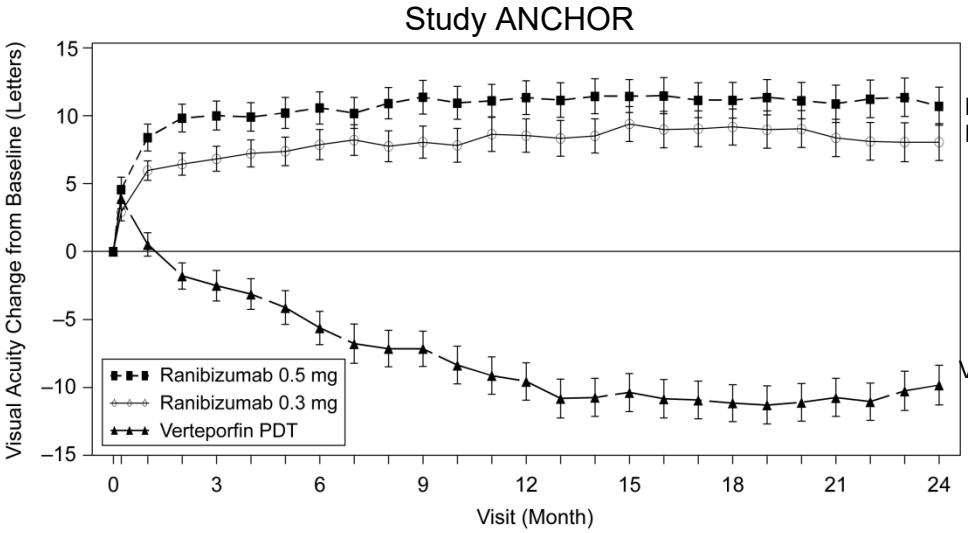
Figure 1 Mean Change in Visual Acuity from Baseline to Month 24 in Study FVF2598g (MARINA) and Study FVF2587g (ANCHOR), Randomized Subjects



Ranibizumab 0.5 (N=240): +6.6
Ranibizumab 0.3 (N=238): +5.4

Sham (N=238): -14.9

Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean.



Ranibizumab 0.5 (N=139): +10.7
Ranibizumab 0.3 (N=140): +8.1

Verteporfin (N=143): -9.8

PDT = photodynamic therapy
Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean

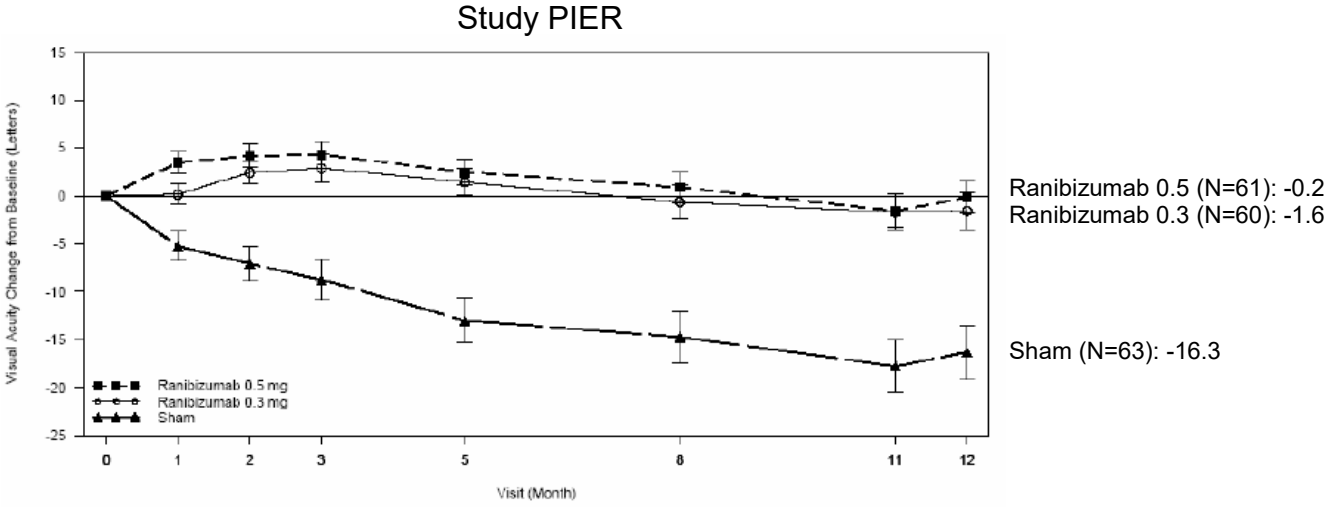
Randomized subjects = all subjects randomized. Note for Study ANCHOR, LUCENTIS 0.5 mg, 140 subjects were randomized, however one subject did not have a BCVA baseline value, therefore, data from 139 patients are included in the results for this group.

Patient withdrawal rates (control, 0.3 mg LUCENTIS, 0.5 mg LUCENTIS):

- MARINA 1 year (discontinued study on or prior to Month 12): 8.8%, 2.5%, 2.5%
- MARINA 2 year (discontinued from study): 20.2%, 11.8%, 10.4%
- ANCHOR 1 year (discontinued study on or prior to Month 12): 7.0%, 7.1%, 3.6%
- ANCHOR 2 year (discontinued from study): 23.1%, 16.4%, 17.1%

The sham LUCENTIS injection control procedure involved anesthetising 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.

Figure 2 Mean Change in Visual Acuity from Baseline to Month 12 in Study FVF3192g (PIER), Randomized Subjects



Note: The LOCF method was used to impute missing data. Vertical bars are ±1 standard error of the mean.

Randomized subjects = all subjects randomized

Patient withdrawal rates (control, 0.3 mg LUCENTIS, 0.5 mg LUCENTIS):

- PIER 1 year (discontinued study on or prior to Month 12): 12.7%, 1.7%, 3.3%

The sham LUCENTIS injection control procedure involved anesthetising 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.

Thirty-four percent (34%) to 40% of LUCENTIS-treated patients in studies MARINA and ANCHOR, (0.5 mg) experienced a clinically significant, sustained improvement in vision, defined as gaining 15 or more letters at 24 months ($p<0.01$), regardless of lesion type. Twenty-five percent (25%) to 36% of LUCENTIS-treated patients (0.3 mg) experienced a clinically significant, sustained improvement in vision (Table 21). In both studies, mean changes in BCVA from baseline at Month 24 demonstrated an improvement of vision by 6.6-11.3 letters (0.5 mg) and 5.4-8.5 letters (0.3 mg) respectively. The gain in BCVA was essentially achieved after the first 3 injections with LUCENTIS (at Month 3) and maintained until Month 24 in both studies.

In PIER, almost all LUCENTIS-treated patients (90%) maintained their visual acuity at Month 12. In study FVF3192g (PIER), the proportion of patients who lost fewer than 15 letters of BCVA at Month 12 was 90% on 0.5 mg and 83% on 0.3mg.

Table 21 Overview of the main secondary endpoints by study, randomized subjects, with last observation carried forward (LOCF) method to impute missing data

Study MARINA (Outcomes at 12 and 24 months)						
Outcome Measure	Month	Sham (N= 238)	LUCENTIS 0.3mg (N=238)	Estimated Difference Between Sham and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=240)	Estimated Difference Between Sham and LUCENTIS 0.5mg
Gain of ≥ 15 letters in visual acuity (%) (95% CI)	12	4.6 (2.0 , 7.3)	24.8 (19.3 , 30.3)	20.2 (14.1 , 26.3)	33.8 (27.8 , 39.7)	29.1 (22.6 , 35.7)
	24	3.8 (1.4 , 6.2)	26.1 (20.5 , 31.6)	22.3 (16.2 , 28.3)	33.3 (27.4 , 39.3)	29.6 (23.1 , 36.0)
Mean change (SD) in BCVA[#] from Baseline (Letters) (95% CI)	12	-10.5 (16.6) (-12.6 , -8.3)	6.5 (12.7) (4.9 , 8.1)	17.0 (14.3 , 19.6)	7.2 (14.4) (5.4 , 9.1)	17.7 (14.9 , 20.5)
	24	-14.9 (18.7) (-17.3 , -12.5)	5.4 (15.2) (3.5 , 7.4)	20.3 (17.3 , 23.4)	6.6 (16.5) (4.5 , 8.7)	21.4 (18.3 , 24.6)
Study ANCHOR (Outcomes at 12 and 24 months)						
Outcome Measure	Month	PDT (N=143)	LUCENTIS 0.3mg (N=140)	Estimated Difference Between PDT and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=139)	Estimated Difference Between PDT and LUCENTIS 0.5mg
Gain of ≥ 15 letters in visual acuity (%) (95% CI)	12	5.6 (1.8 , 9.4)	35.7 (27.8 , 43.7)	30.1 (21.3 , 38.9)	40.3 (32.1 , 48.4)	34.7 (25.7 , 43.7)
	24	6.3 (2.3 , 10.3)	34.3 (26.4 , 42.1)	28.0 (19.2 , 36.8)	41.0 (32.8 , 49.2)	34.7 (25.6 , 43.8)
Mean change (SD) in BCVA[#] from Baseline (Letters) (95% CI)	12	-9.5 (16.4) (-12.3 , -6.8)	8.5 (14.6) (6.1 , 11.0)	18.1 (14.4 , 21.7)	11.3 (14.6) (8.9 , 13.8)	20.9 (17.2 , 24.5)
	24	-9.8 (17.6) (-12.7 , -6.9)	8.1 (16.2) (5.4 , 10.7)	17.9 (13.9 , 21.8)	10.7 (16.5) (7.9 , 13.5)	20.5 (16.5 , 24.5)

Study PIER (Outcomes at 12 months)						
Outcome Measure	Month	Sham (N=63)	LUCENTIS 0.3mg (N=60)	Estimated Difference Between Sham and LUCENTIS 0.3mg	LUCENTIS 0.5mg (N=61)	Estimated Difference Between Sham and LUCENTIS 0.5mg
Loss of < 15 letters in visual acuity (%) (95% CI)	12	49.2 (36.9 , 61.6)	83.3 (73.9 , 92.8)	34.1 (18.6 , 49.7)	90.2 (82.7 , 97.6)	41.0 (26.5 , 55.4)

[#] Best Corrected Visual Acuity

Randomized subjects = all subjects randomized. Note for Study ANCHOR, LUCENTIS 0.5 mg, 140 subjects were randomized, however one subject did not have a BCVA baseline value, therefore, data from 139 patients are included in the results for this group.

Patient withdrawal rates (control, 0.3 mg LUCENTIS, 0.5 mg LUCENTIS):

- MARINA 1 year (discontinued study on or prior to Month 12): 8.8%, 2.5%, 2.5%
- MARINA 2 year (discontinued from study): 20.2%, 11.8%, 10.4%
- ANCHOR 1 year (discontinued study on or prior to Month 12): 7.0%, 7.1%, 3.6%
- ANCHOR 2 year (discontinued from study): 23.1%, 16.4%, 17.1%
- PIER 1 year (discontinued study on or prior to Month 12): 12.7%, 1.7%, 3.3%

The sham LUCENTIS injection control procedure involved anesthetising 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.

Patients in the groups 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 disc area for LUCENTIS versus 2.3 to 2.6 disc area 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.

The size of the lesion did not significantly affect the results. In general, patients with poor visual acuity (<20/200) at the onset of treatment experienced a benefit of treatment. However, neovascular AMD that has evolved into lesions characterised by subretinal fibrosis and advanced geographic atrophy is not likely to respond to LUCENTIS.

In MARINA and ANCHOR, at month 12 patients treated with LUCENTIS reported, on average, a statistically ($p<0.01$) and clinically meaningful improvement in their ability to perform activities related to near vision (such as reading; MARINA: 0.5 mg LUCENTIS: + 10.4 point increase; 0.3 mg LUCENTIS: + 9.4 point increase; ANCHOR: 0.5 mg LUCENTIS: + 9.1 point increase; 0.3 mg LUCENTIS: + 6.6 point increase), distance vision (such as driving; MARINA: 0.5 mg LUCENTIS: + 7.0 point increase; 0.3 mg LUCENTIS: + 6.7 point increase; ANCHOR: 0.5 mg LUCENTIS: + 9.3 point increase; 0.3 mg LUCENTIS: + 6.4 point increase) and vision–specific dependency (such as seeing faces; MARINA: 0.5 mg LUCENTIS: + 6.8 point increase; 0.3 mg LUCENTIS: + 3.6 point increase; ANCHOR: 0.5 mg LUCENTIS: + 8.9 point increase; 0.3 mg LUCENTIS: + 7.6 point increase), as measured by the National Eye Institute (NEI) Visual Functioning Questionnaire-25 (VFQ-25). Sham-treated patients reported a decrease in their ability to perform these activities (MARINA: near vision: - 2.6 point decrease; distance vision: -5.9 point decrease; vision-specific dependency: -4.7 point decrease) and verteporfin PDT-treated patients reported a small increase or decrease (ANCHOR: near vision: + 3.7 point increase; distance vision: + 1.7 point increase; vision-specific dependency: - 1.4 point decrease).

In MARINA, this increase from baseline in each of the three VFQ-25 subscales at Month 12 was maintained at Month 24 for LUCENTIS-treated patients, while in the sham-injection group the mean change from baseline decreased further from Month 12 to Month 24 in each of these subscales. Therefore, the treatment benefit of LUCENTIS over the sham control at Month 24 was greater than that at Month 12.

In the verteporfin PDT group, the mean improvement from baseline in the near activities and distance activities subscale scores at Month 12 were lost at Month 24, while the mean decrease from baseline in the vision-specific dependency subscale score at Month 12 was maintained at Month 24. These changes between Months 12 and 24 within each treatment group resulted in either maintained or greater treatment benefit of ranibizumab over verteporfin PDT compared with Month 12, while the treatment benefit of ranibizumab in the vision-specific dependency subscale was smaller at Month 24 compared with Month 12 (p-values ranging from 0.0023 to 0.0006).

Treatment of visual impairment due to DME

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

Table 22 –Summary of patient demographics for clinical trials in visual impairment due to DME

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
D2301† (RESTORE)	Randomized, double-masked, multicenter, laser-controlled study.	LUCENTIS 0.5mg intravitreal injection (+ sham laser), prn‡; LUCENTIS 0.5mg intravitreal injection + laser, prn; or Sham injection + laser, prn 12 month study.	LUCENTIS 0.5mg : n= 116 LUCENTIS 0.5mg + laser: n=118 Sham injection + laser: n=111	63.5 (37-87 years)	Male: 58.3% Female: 41.7%
D2201 (RESOLVE)	Randomized, double-masked, multicenter, sham-controlled study.	LUCENTIS 0.3mg intravitreal injection (dose doubling permitted), prn; LUCENTIS 0.5mg intravitreal injection (dose doubling permitted), prn; or Sham injection, prn 12 month study.	LUCENTIS 0.3mg: n=51 LUCENTIS 0.5mg: n=51 Sham injection: n=49	63.6 (32-85 years)	Male: 53.6% Female: 46.4%

† a. There is only limited experience in the treatment of subjects with DME due to Type I diabetes.
b. There is limited experience in patients older than 75 years of age with DME.
c. Patients with the HbA1c > 10% were not included in the clinical trial.

‡ prn: pro re nata (as needed)

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular edema were 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 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). Clinical significance of the effect on central retinal thickness in this population is unknown. A rapid improvement in BCVA was observed as early as the first follow-up visit and was maintained through the 12-month period (Figure 3). The mean average change in BCVA 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, and in the laser arm, a maintenance of the baseline BCVA of about + 1 letter over the 12 months study period.

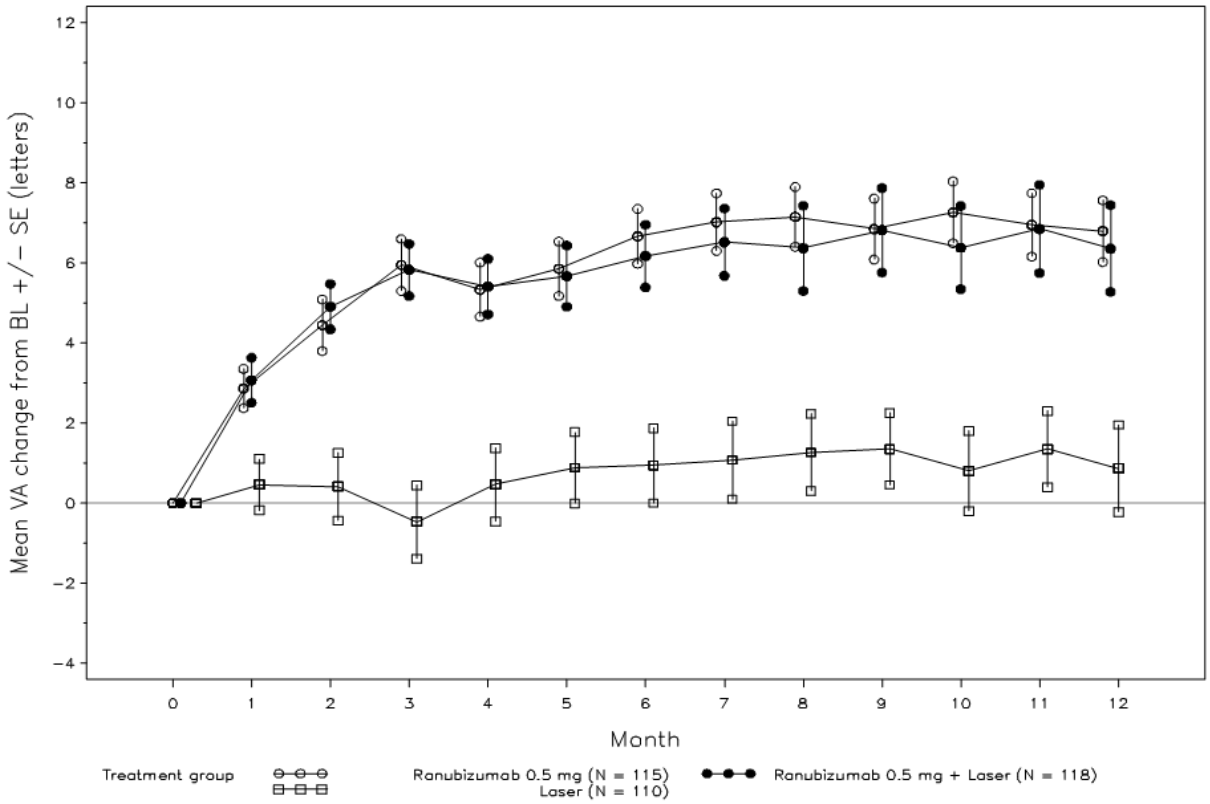
The results of the primary endpoint are detailed below in Table 23 and illustrated in Figures 3.

Table 23 Outcomes at month 12 in study D2301 (RESTORE), full analysis set, with last observation carried forward (LOCF)

Primary Endpoint					
Outcome measure	**Ranibizumab 0.5 mg (n=116)**	**Ranibizumab 0.5 mg + Laser (n=118)**	**Laser (n=111)**	**Estimated difference Between Laser and Ranibizumab 0.5 mg**	**Estimated difference Between Laser and Ranibizumab 0.5 mg + Laser**
Mean average change in BCVA from month 1 to month 12 compared to baseline (letters) (SD) (95% CI)[b]	6.1 (6.43) (4.9, 7.3)	5.9 (7.92) (4.4, 7.3)	0.8 (8.56) (-0.8, 2.4)	5.4 (3.5, 7.4)	4.9 (2.8, 7.0)

[b] $p<0.0001$

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



The results for the key secondary efficacy endpoints based on BCVA were consistent with those obtained for the primary endpoint and showed statistically significant treatment differences in ranibizumab treated patients compared to laser. At Month 12, the mean BCVA improvement compared to baseline for patient treated with ranibizumab and ranibizumab adjunctive to laser was 6.8 and 6.4 letters, compared to 0.9 letters in the laser treated patients. The proportion of ranibizumab treated patients who gained at least 15 letters from baseline at 12 months was 22.6% (ranibizumab) and 22.9% (ranibizumab + laser) compared to 8.2% in laser control.

The improvement in the visual acuity outcomes was also accompanied by a rapid and sustained decrease in the macular edema as assessed by the central retinal thickness. Clinical significance of the effect on central retinal thickness in this population is unknown.

In study D2201 (RESOLVE), a total of 151 patients with macular center involvement causing visual impairment were 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 0.05 to 0.1 mL. 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.

Treatment of visual impairment due to macular edema secondary to RVO

Clinical safety and efficacy of LUCENTIS in patients with visual impairment due to macular edema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE.

In the BRAVO study, a total of 397 patients with visual impairment due to macular edema secondary to Branch RVO were enrolled to receive either 0.3 mg or 0.5 mg intravitreal ranibizumab or sham[1] injections. Laser photocoagulation standard of care was allowed in all three arms and was administered, based on protocol defined criteria, as rescue treatment beginning at Month 3. A proportion of 57.6% of patients in the sham-control arm and 20.1% and 21.4% in the ranibizumab-treated arms (0.3 mg and 0.5 mg, respectively) received at least one laser treatment during the first 6 months of the study.

After 6 months, the patients in the sham-control arm were crossed-over to 0.5 mg ranibizumab. The proportion of patients receiving at least one laser treatment during the entire 12 months study period was as follows: 61.4% in the sham/0.5 mg ranibizumab arm, 41.0% in the 0.3 mg ranibizumab arm, and 34.4% in the 0.5 mg ranibizumab arm.

The primary endpoint was the mean change from baseline in best-corrected visual acuity (BCVA) at Month 6: treatment with 0.5 mg ranibizumab, on average, showed a statistically significant improvement of 18.3 letters compared to a gain of 7.3 letters in the control group ($p<0.0001$). Improvement in BCVA was rapid (as early as day 7, $p<0.0001$), and sustained over the next months through Month 12 (secondary endpoint), with a mean improvement from baseline in BCVA score at Month 12 of 18.3 letters for the 0.5 mg ranibizumab group, compared to 12.1 letters for the sham/0.5 mg group.

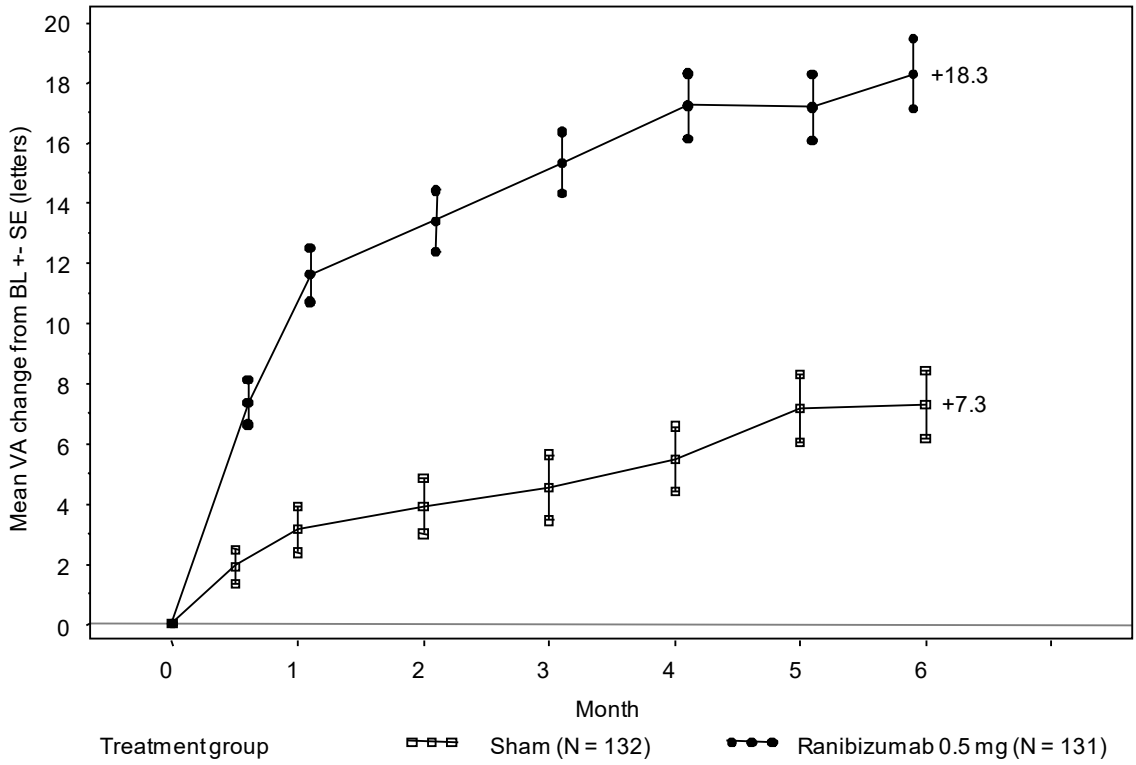
Statistically significant improvements were also observed in key secondary endpoints at Month 6, and sustained to Month 12. At month 6, 61.1% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 28.8% of patients in the sham group, which represents an estimated difference of 31.3% between the two groups. At month 12, 60.3% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 43.9% of patients in the sham/0.5 mg ranibizumab arm. For the crossover sham/0.5-mg group, improvements in visual acuity were also observed during the 6-month observation period.

Table 24 BCVA primary efficacy outcome at Month 6 (BRAVO), randomized patients, with last observation carried forward method (LOCF) to impute missing data

	Sham (n=132)	LUCENTIS 0.5 mg (n=131)	Estimated difference between sham and LUCENTIS 0.5 mg
Primary endpoint			
Mean change in BCVA from baseline ETDRS[a] (letters) (SD) (95% CI) [b]	+7.3 (13.0) (5.1, 9.5)	+18.3 (13.2) (16.0,20.6)	10.6 (7.6,13.6)

a: Early Treatment Diabetic Retinopathy Study
b: p<0.0001

Figure 4 Mean Change from Baseline BCVA over Time to Month 6 (BRAVO)



In the CRUISE study, a total of 392 patients with visual impairment due to macular edema secondary to Central RVO were enrolled to receive either 0.3 mg or 0.5 mg intravitreal ranibizumab or sham injections. After 6 months, the patients in the sham-control arm were crossed-over to 0.5 mg ranibizumab.

The primary endpoint was the mean change from baseline in BCVA at Month 6: treatment with 0.5 mg ranibizumab, on average, showed a statistically significant improvement of 14.9 letters compared to 0.8 letter gain in the control group (p<0.0001). Improvement in BCVA was rapid (as

early as day 7, p<0.0001), and sustained over the next months through month 12, with a mean improvement from baseline in BCVA score at Month 12 of 13.9 letters for the 0.5 mg ranibizumab group, compared to 7.3 letters for the sham/0.5 mg group.

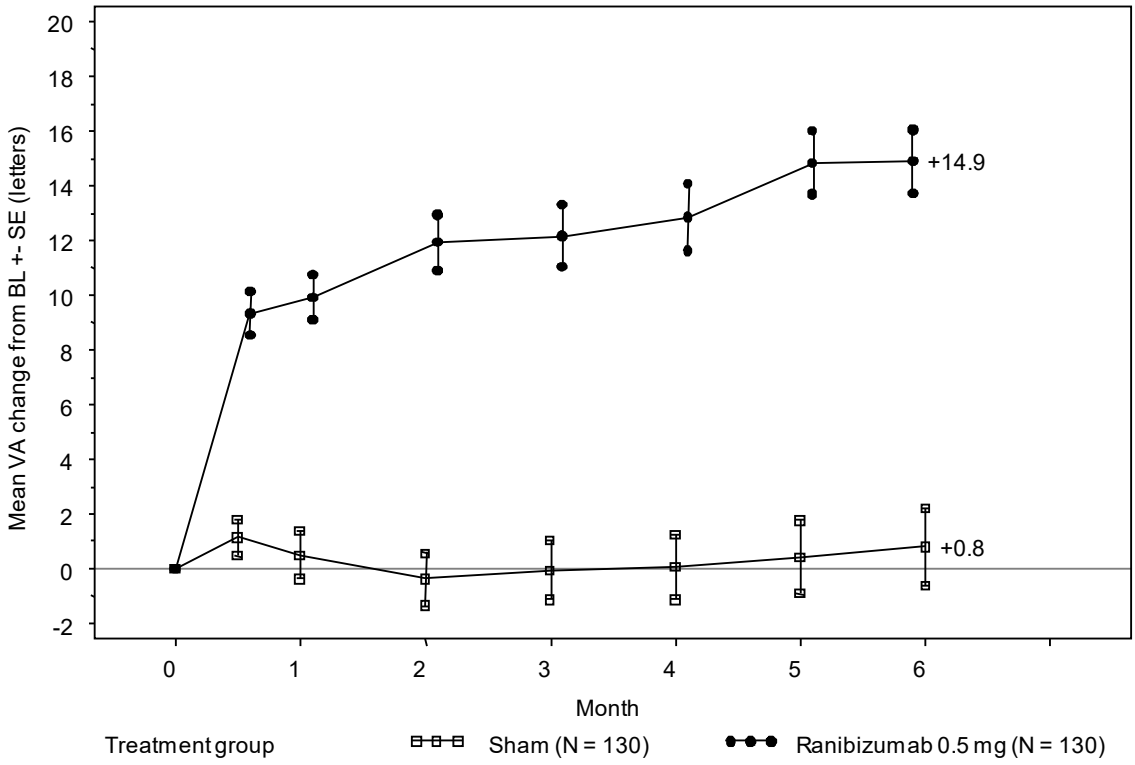
Statistically significant improvements were also observed in key secondary endpoints at Month 6 and sustained through Month 12. At month 6, 47.7% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 16.9% of patients in the sham group, which represents an estimated difference of 30.3% between the two groups. At month 12, 50.8% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 33.1% of patients in the sham/0.5 mg ranibizumab arm. For the crossover sham/0.5 mg group, improvements in visual acuity were also observed during the 6-month observation period.

Table 25 BCVA primary efficacy outcome at Month 6 (CRUISE), randomized patients, with last observation carried forward method (LOCF) to impute missing data

	Sham (n=130)	**LUCENTIS 0.5 mg (n=130)**	**Estimated difference between sham and LUCENTIS 0.5 mg**
Primary endpoint			
Mean change in BCVA from baseline ETDRS[a] (letters) (SD) (95% CI) [b]	+0.8 (16.2) (-2.0, 3.6)	+14.9 (13.2) (12.6, 17.2)	13.8 (10.3, 17.4)

a: Early Treatment Diabetic Retinopathy Study
b: p<0.0001

Figure 5 Mean Change from Baseline BCVA over Time to Month 6 (CRUISE)



In both studies, the improvement in the visual acuity outcomes were accompanied by a rapid and sustained decrease in the macular edema as assessed by the central retinal thickness, both at Month 6 and Month 12.

In both studies, the improvement in visual acuity outcomes seen with ranibizumab treatment at both 6 and 12 months was accompanied by patient-reported benefits as measured by the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), and particularly in the sub-scales related to near and distance activities, as pre-specified secondary efficacy endpoints.

In BRAVO and CRUISE, patients treated with ranibizumab achieved statistically significant improvements at Month 6 in near activities (BRAVO: ranibizumab 0.5 mg: +13.7; sham: +7.3; p=0.0002; CRUISE: ranibizumab 0.5 mg: +9.3; sham: +5.1; p=0.0099) and distance activities (BRAVO: ranibizumab 0.5 mg: +11.3; sham: +6.3; p=0.0014; CRUISE: ranibizumab 0.5 mg: +6.7; sham: +2.8; p=0.0199). In both studies, this increase from baseline in each of the two VFQ-25 subscales at Month 6 was sustained at Month 12.

[1] The sham LUCENTIS injection control procedure involved anesthetising 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.

Post-marketing studies

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 (BRVO) and CRYSTAL (CRVO) studies. 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.

The key outcome measures from BRIGHTER and CRYSTAL are shown in the Table below.

Table 26: Outcomes at Month 6 and 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 (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 (letters) (SD)	+15.5 (13.91)	+17.3 (12.61)	+11.6 (16.09)	+12.1 (18.60)

* Starting at Month 6 treatment with ranibizumab 0.5 mg was allowed (24 patients were treated with laser only).

The effect 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.

Treatment of visual impairment due CNV secondary to PM

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 photodynamic therapy PDT (vPDT). PM is characterized by abnormal and progressive elongation of the eyeball, usually to an axial length greater than 26 mm and refractive error of more than -6.0 Diopters, with concomitant degenerative changes in the posterior segment of the eye such as posterior staphyloma, chorioretinal atrophy, Bruch's membrane (lacquer) cracks, subretinal hemorrhage, retinal detachment, and CNV.

Table 27 – Summary of patient demographics for clinical trials in visual impairment due to CNV secondary to PM

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
F2301 (RADIANCE)	Randomized, double-masked, multicenter, active-controlled study.	Group I: Ranibizumab 0.5 mg intravitreal injection (VA stabilization) Group II: Ranibizumab 0.5 mg intravitreal injection (disease activity) Group III: vPDT† 12 month study	Group I: n= 106 Group II: n=116 Group III: n=55	55.5 (18-87 years)	Male: 24.5% Female: 75.5%

†Patients in the vPDT were allowed to receive ranibizumab treatment as of Month 3.

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

- Group I (ranibizumab 0.5 mg, dosing regimen driven by "stability" criteria defined as no change in best corrected visual acuity (BCVA) compared to two preceding monthly evaluations)
- Group II (ranibizumab 0.5 mg, 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 (median 4.0, range 1-12) in Group I and 3.5 (median 2.0, range 1-12) injections in Group II. In Group II (in which patients received the recommended treatment regimen based on disease activity, see DOSAGE 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.

The primary efficacy endpoint was the mean average change in BCVA from baseline to Month 1 through Month 3. Both ranibizumab treatment arms demonstrated statistically significant superior efficacy compared with vPDT: the mean average BCVA score of the study eye from Month 1 to Month 3 exceeded baseline by 10.5 letters (Group I; min-max: -19.3 to +31.0) and 10.6 letters (Group II; min-max: -8.3 to +32.0) in the ranibizumab groups and by 2.2 letters in the vPDT group (min-max: -24.7 to +24.3). The treatment benefit was maintained for the 12-month duration of the study. The mean average change in BCVA from baseline to Month 1 through Month 12 was 12.8 letters and 12.5 letters in Group I and Group II, respectively.

Table 28 Primary efficacy outcome at Month 3 in study RADIANCE, randomized patients, with modified last observation carried forward (LOCF) method

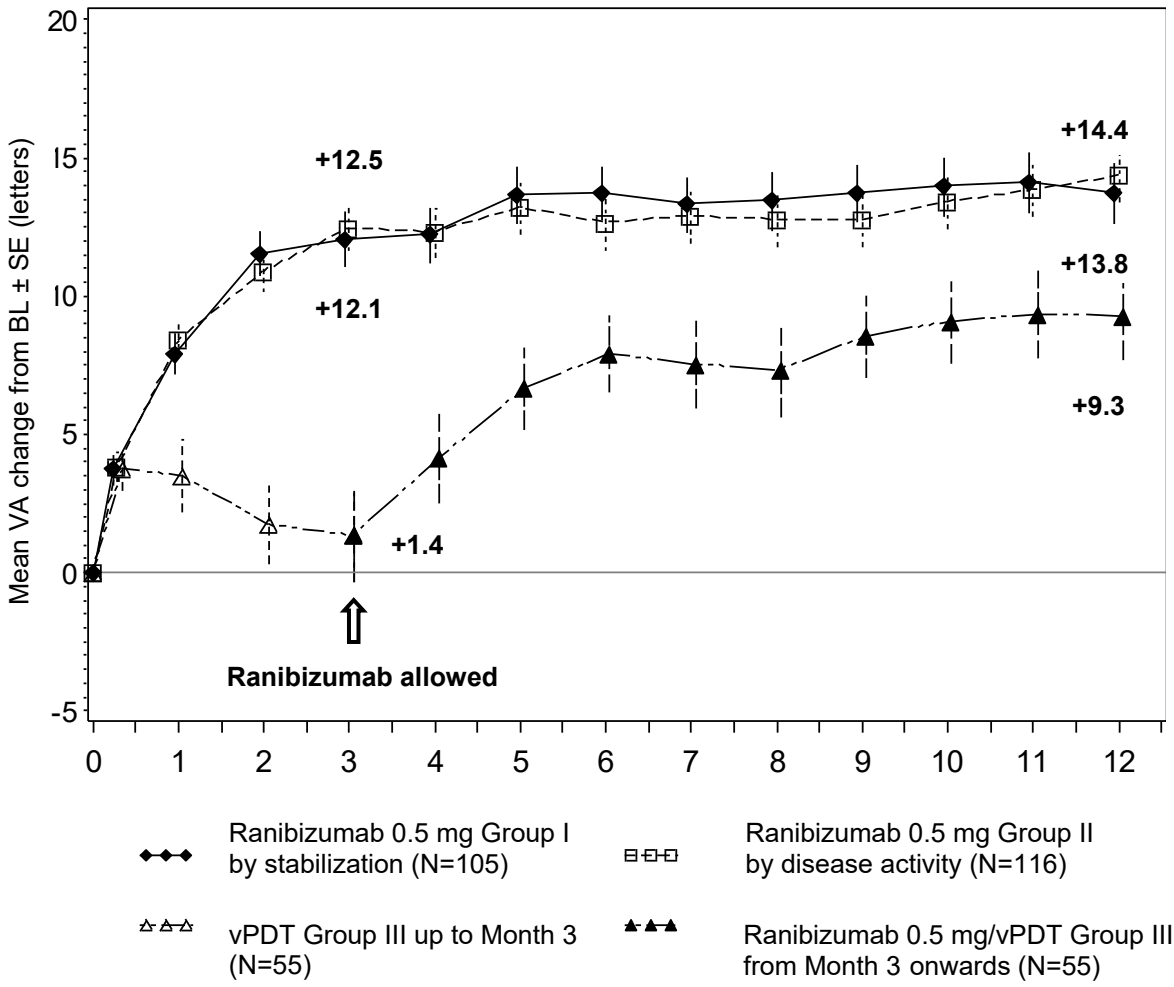
	Group I Ranibizumab 0.5 mg "visual acuity stability"	Group II Ranibizumab 0.5 mg "disease activity"	Group III vPDT (n=55)†

	(n=105)	(n=116)	
Primary endpoint Mean average BCVA change from Month 1 to Month 3 compared to baseline[a] (letters) (SD)	+10.5 (8.16)	+10.6 (7.26)	+2.2 (9.47)

† Comparative control up to Month 3. Patients randomized to vPDT were allowed to receive ranibizumab treatment as of Month 3, as per Investigator discretion (in Group III, 38 patients received ranibizumab from Month 3 onwards)
a: $p<0.00001$ comparison with vPDT control

Results for secondary endpoint were consistent with those of the primary endpoint. The time course of mean change BCVA from baseline through Month 12 showed a rapid improvement, most of it reached by Month 2. The improvement in BCVA continued through Month 12 achieving a mean change in BCVA of about 14 letters gain in both ranibizumab arms (Figure 6). At Month 3, the proportion of patients who gained ≥10 letters (or reached a BCVA of ≥84 letters) from baseline was 61.9% and 65.5% in Group I and II, compared to 27.3% in the vPDT group; and the proportion of patients who gained ≥15 letters (or ≥84 letters total) was 38.1% and 43.1% in Group I and II, compared to 14.5% in the vPDT group. At Month 12, the proportion of patients who gained ≥10 letters (or ≥84 letters total) from baseline was 69.5% and 69.0% in Group I and II; and the proportion of patients who gained ≥15 letters (or ≥84 letters total) from baseline was 53.3% and 51.7% in Group I and II, respectively.

Figure 6 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.

There are limited data regarding treatment with LUCENTIS in PM patients with extrafoveal lesions.

The improvement of vision was accompanied by a reduction in central retinal thickness; however, the clinical significance of this is yet to be determined.

Treatment of visual impairment due to CNV

The clinical safety and efficacy of LUCENTIS in patients with visual impairment due to CNV secondary to etiologies other than wet AMD and PM have been assessed based on a Phase 3 multi-center study G2301 (MINERVA), which was randomized, double-masked, sham controlled for 2 months followed by an open-label extension of 10 months.

Table 29 – Summary of patient demographics for clinical trials in visual impairment due to CNV

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
G2301 (MINERVA)	Randomized, double-masked, sham-controlled, multicenter, study.	Arm 1: Ranibizumab 0.5 mg intravitreal injection Arm 2: Sham intravitreal injection (up to Month 2) As of Month 2, treatment was open-label 12 month study	Arm 1: n= 119 Arm 2: n=59	53.7 years (19 to 86 years)	Male: 49.4% Female: 50.6%

In this study, 178 adult patients were randomized in a 2:1 ratio to one of the following arms, stratified by the presence of angioid streaks at baseline (yes/no):

- ranibizumab 0.5 mg at baseline followed by an individualized dosing regimen based on evidence of disease activity.
- sham injection at baseline followed by an individualized treatment regimen based on evidence of disease activity.

Starting at Month 2, all patients received open-label individualised treatment with ranibizumab based on disease activity. The primary endpoint was assessed by the best corrected visual acuity (BCVA) change from baseline to Month 2.

The primary outcome measure, demonstrated statistically superior efficacy in ranibizumab-treated patients compared to patients randomized to sham (Table 30).

Table 30 Change in Visual Acuity at Month 2 in study MINERVA

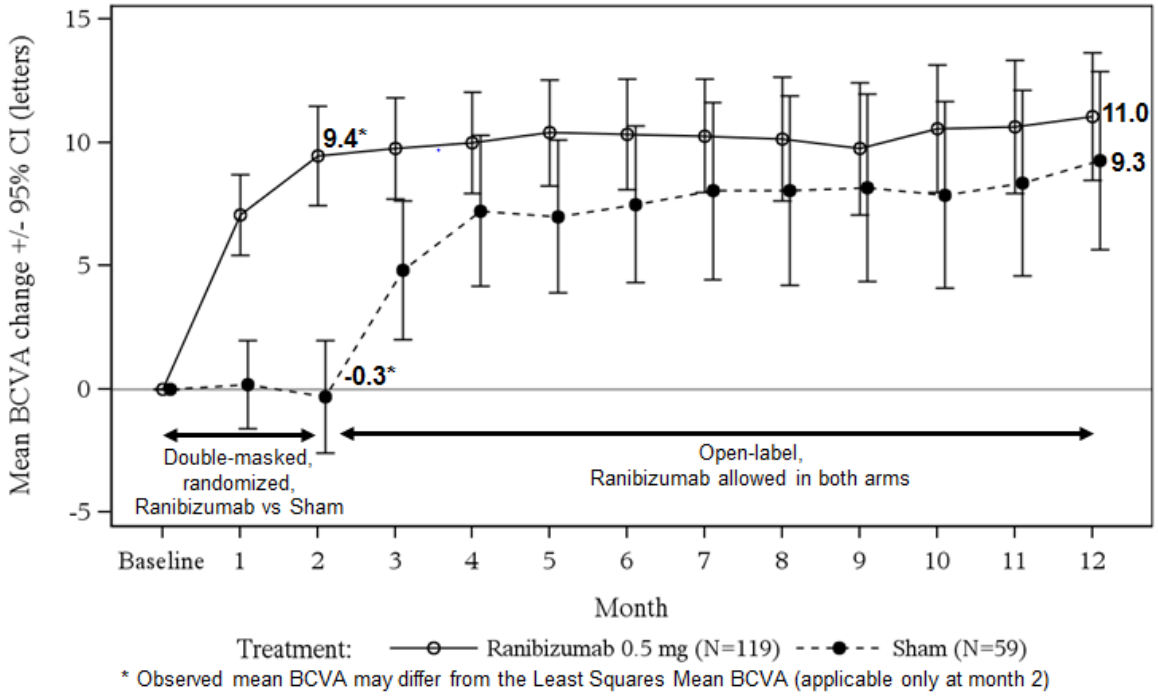
	Ranibizumab 0.5 mg (N=119)	**Sham (N=59)**
n	118	57
Mean BCVA change from baseline to Month 2 (letters) (Least Squares Mean)	+9.5 (0.95)	-0.4 (1.16)
95% CI for LS mean	(7.6,11.4)	(-2.8, 1.9)
Difference in LS means (Ranibizumab minus Sham) (SE)	9.94 (1.502)	
95% CI for difference	(6.97, 12.91)	
One-sided p-value for treatment difference [(1)]	< 0.001	

n is the number of patients with data available in the analysis

[(1)] Analyzed using MMRM, which contains scheduled visit, the type of underlying pathophysiologic mechanism (angioid streaks vs. others) and treatment group as fixed effect factors, centered baseline BCVA as a continuous covariate and treatment group by visit and visit by centered baseline BCVA interactions.

The mean BCVA change from baseline over time to Month 12 is shown in Figure 7.

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



A difference was observed in the change from baseline to Month 2 in BCVA (13.0 letters vs 4.2 letters) for the 2 age groups (patients <= 60 years vs patients > 60 years, respectively).

A subgroup analysis for the primary variable was conducted using the following subgroups of type of underlying ocular pathophysiological mechanism (baseline etiology) in the study eye: (i) angioid streaks; (ii) post-inflammatory retinochoroidopathy; (iii) idiopathic chorioretinopathy; (iv) central serous chorioretinopathy (CSC) and (v) miscellaneous (any etiology that does not belong to the above subgroups). The subgroups were based on data entered in the eCRF, and the definition of each baseline etiology subgroup was determined prior to database lock. Within the "Miscellaneous" baseline etiology subgroup, there were 15 different etiologies causing CNV. In total, the study enrolled patients with 19 different etiologies. Results from the subgroup analysis for the primary variable by baseline etiology are shown in Table 31, and suggest that the treatment effect varies by baseline etiology.

Table 31: Overall results on change in visual acuity and per baseline etiology at Month 2 (MINERVA)

Overall and per baseline etiology	Change from baseline to Month 2 in BVCA (letters)	Treatment difference over sham (letters)

	ranibizumab		sham		
	n	LS mean	n	LS mean	
Overall	118*	9.5	57*	-0.4	9.9
Angioid streaks	18	11.0	9	-3.5	14.6
Post-inflammatory retinochoroidopathy	18	7.0	9	0.4	6.5
Central serous chorioretinopathy	17	6.6	6	1.6	5.0
Idiopathic chorioretinopathy	37	12.5	25	1.1	11.4
Miscellaneous etiologies[a]	28	7.5	8	-3.0	10.6

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

* number of patients with data available in the analysis

The mean number of ranibizumab injections given in the study eye over 12 months was 5.8 (range 1-12) in the ranibizumab arm versus 5.4 (range 1-10) over 10 months 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.

NOC/c **Treatment of ROP in preterm infants**

The clinical safety and efficacy of LUCENTIS 0.2 mg and 0.1 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

Table 32: Summary of patient demographics for clinical trial in the treatment of retinopathy of prematurity (ROP)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean gestational age (Range)	Sex

Study H2301 (RAINBOW)	Randomized, controlled, multicenter, study	Arm 1: Ranibizumab 0.2 mg intravitreal injection Arm 2: Ranibizumab 0.1 mg intravitreal injection Arm 3: Laser therapy 6 month study	Arm 1: n= 74 Arm 2: n=77 Arm 3: n=74	26.1 weeks (23 – 32 weeks)	Male: 47.6% Female: 52.4%

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

The primary endpoint was defined as treatment success measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after initiation of treatment, taking into account death and treatment switch at or before Week 24 also as treatment failure. The study failed to achieve its primary objective.

Results of the comparison of the event rate difference are shown in the Table 33 below.

Table 33: Absence of active ROP and absence of structural outcomes in both eyes 24 weeks after the first study treatment (Full Analysis Set)

Treatment	**n/M (%)**	**95% CI**	**Event rate difference (%) (compared to Laser group)**	**95% CI**	**p-value[a]**
Ranibizumab 0.2 mg (N=74)	56/70 (80.0)	(0.6873, 0.8861)	14.7	(0.3, 29.2)	0.0254
Ranibizumab 0.1 mg (N=77)	57/76 (75.0)	(0.6374, 0.8423)	9.3	(-5.5, 24.1)	0.1118[b]
Laser (N=74)	45/68 (66.2)	(0.5368, 0.7721)			

CI-Confidence Interval
- n: Number of subjects with absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment (including imputed values); M: The total number of subjects with non-missing value on primary efficacy outcome (including imputed values using 2-step single imputation approach).
- 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.
-Difference and 95% CI for response are using Cochran-Mantel-Haenszel weight to stratify ROP Zone at baseline.
- [a] The pre-specified significance level for the one sided p-value is 0.025.
- [b] P-values for pairwise comparisons are one-sided, without adjusting for multiplicity.

In a sensitivity analysis of primary endpoint, in which missing response was considered as treatment failure, the percentage of patients with absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after the first study treatment was 75.7%, 74.0% and 60.8% in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser group, respectively.

At Week 24, the recurrence of ROP (defined as patients receiving any post-baseline intervention i.e., ranibizumab re-treatment or switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group) was 31.1%, 31.2% and 18.9% in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively. At week 40, these percentages were 31.1%, 33.8% and 20.4% in the ranibizumab 0.2 mg, ranibizumab 0.1 mg and laser groups, respectively.

DETAILED PHARMACOLOGY

Mechanism of Action

Ranibizumab is a humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor-A (VEGF-A). Ranibizumab is designed to penetrate all retinal layers. It binds with high affinity to all active 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. 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, of macular edema causing visual impairment in diabetes and retinal vein occlusion, and of choroidal neovascularization secondary to pathologic myopia.

Pharmacodynamics

The pharmacology of ranibizumab has been evaluated in several *in vitro* assays and *in vivo* animal studies. Ranibizumab binds with high affinity to the human VEGF isoforms (K_D: ≤192 pM for $VEGF_{110}$, $VEGF_{121}$, and $VEGF_{165}$), inhibits VEGF-induced HUVEC proliferation (IC_{50}: ≤ 0.56 nM) and tissue factor expression (IC_{50}: 0.31 nM), and does not bind to complement C1q and Fc gamma receptors that mediate complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, respectively. Ranibizumab also inhibits VEGF-induced changes in vascular permeability in a guinea pig skin model (IC_{50}: ≤ 1.2 nM). In the non-human primate model of laser-induced CNV, intravitreal injection of ranibizumab alone at 0.5 mg/eye can prevent formation of clinically significant CNV membranes and decreases leakage of already formed CNV membranes. Ranibizumab in combination with verteporfin PDT causes a reduction in CNV leakage compared to verteporfin PDT alone, irrespective of the order of treatment.

Pharmacokinetics

Following monthly intravitreal administration of LUCENTIS (ranibizumab injection) to patients with neovascular AMD, serum concentrations of ranibizumab were generally low. Maximum serum levels (C_{max}), measured after single administration and estimated using population pharmacokinetics (PK) for repeated administration, were generally below the ranibizumab concentration necessary to inhibit the biological activity of VEGF by 50% (11-27 ng/mL, as assessed in an *in vitro* cellular proliferation assay). Following single administration, C_{max} was dose proportional over the dose range of 0.05 to 1.0 mg/eye. Serum ranibizumab concentrations in RVO patients were similar to those observed in wet AMD patients. Although the PK data suggest that serum ranibizumab levels remain below the level necessary to inhibit the biological activity of

VEGF by 50%, an assessment of additional time points around the C_{max} would be required to confirm that serum ranibizumab levels do not exceed this threshold at any timepoint upon monthly intravitreal injection of 0.5 mg LUCENTIS in humans.

Based on analysis of limited population pharmacokinetics data from patients with wet AMD treated with the 0.5 mg dose, 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.

TOXICOLOGY

The non-clinical safety of ranibizumab was assessed primarily in cynomolgus monkeys, because of the close homology between the cynomolgus monkey and human VEGF. All repeat-dose toxicology studies were conducted in cynomolgus monkeys, whilst rabbits were employed for single-dose local tolerance studies.

The toxicology program was designed to support ITV administration and included 4-, 13-, and 26-week repeat-dose ITV toxicity studies in cynomolgus monkeys. Because transient ocular inflammation was observed in the toxicity studies, a 16-week study was conducted to investigate the non-clinical safety of different ITV dosing regimens (various dose escalation and dose frequency regimens), as well as the effect of oral and topical corticosteroid treatment on ocular inflammation. The non-clinical safety of ranibizumab/verteporfin/PDT combination treatments was assessed in cynomolgus monkeys with laser-induced CNV. Human tissue cross-reactivity, hemolytic potential, and blood compatibility were also investigated.

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.

The potential of ranibizumab to affect embryo-fetal and/or placental development has been investigated in pregnant cynomolgus monkeys given bilateral IVT injections of ranibizumab every 14 days from Day 20 until Day 62 of gestation. The selected IVT doses were 0.125 and 1.0 mg/eye, administered in a 50 µL volume, and were chosen as to give predicted maximum maternal serum levels (Cmax) about 10- and 100-fold, respectively, higher than the median Cmax in humans given monthly unilateral IVT injection of 0.5 mg ranibizumab/eye. The dose of 1.0 mg/eye was considered to be the highest dose that could be administered to pregnant animals, based on the ocular inflammation observed in the previously performed 4-26 weeks toxicity studies in non-pregnant monkeys. In those studies, no systemic toxicity was observed up to the highest investigated dose of 2.0 mg/eye. The dose-escalation regimen used in non-pregnant monkeys was considered to be inappropriate for an embryo-fetal development (EFD) study.

In the EFD study, fetal (cord blood) serum was sampled at caesarian section (on gestation day 100 ± 1), 32 ± 1 days (i.e. approximately 7-9 half-lives, based on an "apparent" serum ranibizumab half-life of 3.5-4.5 days in monkeys) after the last administration of ranibizumab (on gestation day 62). With one exception, fetal serum ranibizumab concentrations were below the limit of quantitation, irrespective of the dose. The exception was in a high dose (1.0 mg/eye) animal that was positive for anti-ranibizumab antibodies and that had an unusually high maternal serum ranibizumab concentration (1990 ng/mL, presumably due to the presence of anti-ranibizumab antibodies) after the last dose on gestation day 62. In this animal, fetal (cord blood) serum ranibizumab concentrations at caesarian section were 230 pg/mL, which is approximately twice the "minimum quantifiable concentration" (MQC) of the analyte (equal to the lower limit of quantitation multiplied by the minimum dilution factor required for accurate quantitation of the analyte in the sample matrix) of 100 pg/mL.

In this animal, anti-ranibizumab antibodies may have acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance, and enabling its placental transfer. However, the EFD study in monkeys was not designed to address this question and the collected data do not allow for an unambiguous answer.

In pregnant monkeys, IVT ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta. However, based on its pharmacological effect, ranibizumab should be regarded as potentially teratogenic and embryo-foetotoxic. The absence of ranibizumab-mediated effects on the embryo-fetal development is plausibly related to the inability of the Fab fragment to cross the placenta. The embryo-fetal

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 WARNINGS AND PRECAUTIONS – Special Populations).

Repeated-Dose Toxicity Studies

Species/ Strain	No./Sex/ Group	Route of Admin.	Nominal Doses (mg/eye)	Study Duration	Dosing Regimen	Findings
Cynomolgus monkey	2-4/M 2-4/F	ITV (bilateral)	0 0.5 2.0	4 weeks dosing / 4 weeks recovery	Once every 14 days	No test material-related systemic (non-ocular) effects. *Ocular findings*: Dose-dependent, transient ocular inflammation, characterized by anterior chamber cells and flare and by vitreous cells. Evidence of scleral weakening due to repeated ITV dosing and vitreous fluid sampling at identical sites. Retinal perivascular infiltrates and/or sheathing that may have been test material-related in 2 animals at the highest dose. The intensity of the inflammatory responses partially or completely diminished upon recovery. Increase in intraocular pressure, most plausibly due to the increase in intraocular volume related to the injection procedure. No test material-related-related changes in fluorescein angiography nor effects on scotopic/photopic electroretinography (ERG). Anti-drug antibody in the serum, but not in the vitreous, of 4/16 ranibizumab-treated animals.
Cynomolgus monkey	4-6/M 4-6/F	ITV (bilateral)	0 0.25 0.5/0.75 0.5/2.0	13 weeks dosing / 4 weeks recovery	Once every 14 days	No test material-related systemic (non-ocular) effects. *Ocular findings (to minimize the degree of transient ocular inflammation a dose-ramping design was used*): Dose-dependent, transient ocular inflammation, characterized by anterior chamber cells and flare and by vitreous cells, that diminished with subsequent injections. The intensity of the inflammatory response diminished during the recovery. Retinal perivascular sheathing in 9/24 eyes given 2.0 mg and in 3/16 eyes given 0.75 mg ranibizumab. White exudate over the surface of the optic disc in 3 cases and into the macular/foveal region in 1 case. Optic disc changes, characterized by a primarily perivascular inflammatory cell infiltrate. Small vitreal floaters in eyes of both vehicle- and ranibizumab-treated animals. Increase in intraocular pressure, most plausibly due to the increase in intraocular volume related to the injection procedure. No effects on scotopic/photopic ERG or on cortical visual evoked potentials. Vitreous and serum anti-drug antibodies in 3/28 and 15/28, respectively, ranibizumab-treated animals.

Repeated-Dose Toxicity Studies (cont.)

Species/ Strain	No./Sex/ Group	Route of Admin.	Nominal Doses (mg/eye)	Study Duration	Dosing Regimen	Findings
Cynomolgus monkey	4-6/M 4-6/F	ITV (bilateral)	0 0.5 0.5/1.0 0.5/1.0/2.0	26 weeks dosing / 8 weeks recovery	Once every 14 days	No test material-related systemic (non-ocular) effects. *Ocular findings (to minimize the degree of transient ocular inflammation a dose-ramping design was used)*: Dose-dependent, transient ocular inflammation, characterized by anterior chamber cells and flare and by vitreous cells, that diminished with subsequent injections. The intensity of the inflammatory response diminished when dosing was stopped or during the recovery. Two types of inflammatory responses in the posterior portion of the eye: single to multifocal perivenous retinal hemorrhages, typically with white centers in the far peripheral retina, and focal to multifocal, white, perivascular sheathing around peripheral retinal venules. Ocular inflammation tended to increase in severity with subsequent doses suggesting that the 2-week dosing interval did not allow the eye to fully recover before the next dose was administered. Cataracts after relatively long periods of intense inflammation only and in the 1.0 or 2.0 mg/eye groups only, suggesting that they were secondary to severe inflammation. No observations suggesting degenerative processes in any ocular structure. Color fundus photographs revealed venous dilatation and tortuosity, venous beading, possible peripapillary retinal thickening, macular thickening, possible papillary swelling, avascular papillary tuft, and small preretinal droplets. With the exception of preretinal droplet (considered artifacts related to the injection procedure) these findings were associated with the observed inflammation and tended to be dose related. Retinal function, as assessed by ERG, was not affected Antibodies to ranibizumab in the serum of 15/28 ranibizumab-treated animals.

Repeated-Dose Toxicity Studies (cont.)

Species/ Strain	No./Sex/ Group	Route of Admin.	Nominal Doses (mg/eye)	Study Duration	Dosing Regimen	Findings
Cynomolgus monkey	4/M 4/F	ITV (bilateral)	0.25/0.5/2.0 /2.0 or 0.25/2.0/2.0 or 0.5/2.0/2.0	9 weeks dosing / 7 weeks recovery	ITV injections on Days 1, 15, 29, and 57; or on Days 1, 29,and 57	No test material-related systemic (non-ocular) effects. *Ocular findings*: Transient anterior chamber inflammatory that was most intense after the first injection. Subsequent doses at the same dose level or with two-fold increase or administered 2 weeks apart resulted in a lesser inflammatory reaction. When the dose was increased four-fold from the previous dosing or dosing was 4 weeks from the previous dose, inflammation was not diminished. Systemic and topical corticosteroids administered both prior to and after dosing did not mitigate the inflammatory response. Increase in intraocular pressure, most plausibly due to the increase in intraocular volume related to the injection procedure. *Changes of the posterior segment of the eye*: Acute focal or multifocal, perivenous retinal hemorrhages with or without white centers in the venules of the far peripheral retina following the first dose; resolved within 1 week, and were diminished or did not reoccur with subsequent treatments. Focal or multifocal, white, perivascular sheathing around peripheral retinal venules. Repeated dosing at 2.0 mg/eye resulted in more prominent sheathing. Infiltrates in various ocular structures among all groups. Systemic and topical corticosteroids given both before and after dosing did not appreciably mitigate the inflammatory response. Low to moderate anti- ranibizumab antibody titers in the serum of 11/24 animals

Local Tolerance Studies

Species/ Strain	No./Sex/ Group	Route of Admin.	Nominal Doses (mg/eye)	Dosing Regimen	Findings
Rabbit Hra(NZW) SPF	9/M	ITV (unilateral, left eye)	2.0 (right eye: vehicle)	Single dose (necropsy 1, 3 and 7 days post dose)	No signs of active inflammation such as flare or inflammatory cells in the anterior segment. Vitreous floaters in 1/9 and iris inflammation in 1/9 ranibizumab-treated eyes 1 day following dose administration. Decreased intraocular pressure in 4/9 ranibizumab-treated eyes, which may have been associated with a mild, transient cyclitis. Microscopical changes limited to subacute inflammation in the vitreous, visible as an infiltration of neutrophils and mononuclear cells in the vitreous adjacent to but not including the retina, ciliary body, or iris. The severity increased slightly between Day 2 and Day 8.
Rabbit Hra(NZW) SPF	9/M	ITV (bilateral)	2.5 (right eye: Lot M4-TOX8 left eye: Lot M4-TOX14)	Single dose (necropsy 1, 3 and 7 days post dose)	On Day 4, vitreous floaters in 3/6 eyes given ranibizumab Lot M4-TOX14 and 1/6 eyes given ranibizumab Lot M4-TOX8. On Day 2 vitreous flare in 1/9 eyes given ranibizumab Lot M4-TOX8. Findings are indicative of low grade cyclitis, part of which may be induced by the ITV injection. Microscopical observations consisted of inflammatory cell infiltrates into various locations in the globe. Lot M4-TOX8 and Lot M4-TOX14 caused very similar overall responses with slight differences in the time course and the extent of the responses.
Rabbit Hra(NZW) SPF	9/M	ITV (bilateral)	2.0 (right eye: Lot M4-TOX14 left eye: Lot M4-TOX61)	Single dose (necropsy 1, 3 and 7 days post dose)	Transient inflammation of the iris and vitreous flare 1 day post-dose, associated with the ITV injection. Low intraocular pressure on Days 2 and 4 in some animals given ranibizumab Lot M4-TOX14 or Lot M3-TOX61. Vitreous floaters on Days 2, 4, and 8 in 1/9, 2/6, and 1/3 eyes given Lot M4-TOX14, respectively. Vitreous flare on Days 2 and 8 in 2/9 and 1/3 eyes given Lot M4-TOX14, respectively. Vitreous findings coupled with low intraocular pressures are indicative of low-grade cyclitis, part of which may have been induced by ITV injection. Inflammatory cell infiltrates observed in several intraocular locations and in the conjunctiva/eyelids of the eyes given Lot M4-TOX14 or Lot M3-TOX61. In other observations from M4-TOX14, the cellular composition of the infiltrates did not differ between the two lots.

Other Toxicity Studies

Study Type	Species/ Strain	No./Sex/ Group	Route of Admin.	Nominal Doses	Study Duration	Dosing Regimen	Findings
Safety in combination with i.v. verteporfin/ PDT following laser-induced CNV	Cynomolgus monkey	2-7/M&F	ITV (unilateral, vehicle in contralateral eye)	0.5→2.0 mg/eye (verteporfin: 6 mg/m^2)	42-63 days	Once every 14 days; either before, after, or at the same time as PDT	Combination treatment with ranibizumab and PDT, by any regimen, either in normal eyes or eyes with laser-induced CNV lesions, did not alter the inflammatory response induced by ranibizumab. Anti-drug antibody in the serum, but not in the vitreous, of 2/21 animals.
Tissue cross-reactivity	Human	--	In vitro	0.01, 0.025, or 0.4 mg/mL rhuMAb VEGF (full length antibody counterpart of ranibizumab)	--	--	No target antigen-specific or cross-reactive binding of rhuMAb VEGF was observed in any of the normal human tissues examined.
Hemolytic potential/ Blood and vitreous fluid compatibility	Human; Cynomolgus monkey	--	In vitro	0, 2.5, 7.5, or 20 mg/mL (final conc.)	--	--	Ranibizumab did not cause hemolysis of human erythrocytes, and were compatible with cynomolgus monkey and human serum and plasma, and with human vitreous fluid. The weak positive hemolytic response for ranibizumab vehicle and the ranibizumab samples from one, but not a second, cynomolgus donor was not considered to be caused by the ranibizumab protein. It is possible that the red blood cells from the animal with the weak positive response were atypically sensitive to the ranibizumab Vehicle in this test.

REFERENCES

1. Brown DM, Kaiser PK, Michels M et al. Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration N Engl J Med 2006; 355: 1432-1444.
2. Chen Y, Wiesmann C, Fuh G et al. Selection and analysis of an optimized anti-VEGF antibody: crystal structure of an affinity-matured Fab in complex with antigen. JMol Biol; 1999; 293(4):865-881.
3. Ferrara N, Damico L, Shams N et al. Development of Ranibizumab, an Anti-vascular Endothelial Growth Factor Antigen Binding Fragment, as Therapy for Neovascular Age-related Macular Degeneration. Retina 2006; 26:859-870.
4. Gaudreault J, Fei D, Rusit J et al. Preclinical pharmacokinetics of Ranibizumab (rhuFabV2) after a single intravitreal administration. Invest Ophthalmol Vis Sci; 2005; 46(2):726-733.
5. Husain D, Kim I, Gauthier D et al. Safety and efficacy of intravitreal injection of ranibizumab in combination with verteporfin PDT on experimental choroidal neovascularization in the monkey. Arch Ophthalmol; 2005; 123:509-516.
6. Keyt BA, Nguyen HV, Berleau LT et al. Identification of vascular endothelial growth factor determinants for binding KDR and FLT-1 receptors. Generation of receptor-selective VEGF variants by site-directed mutagenesis. J Biol Chem; 1996; 271(10):5638-5646.
7. Krzystolik MG, Afshari MA, Adamis AP et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol 2002; 120:338-346.
8. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD. Development of the 25-Item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 2001; 119:1050-8.
9. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric Properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ). Arch Ophthalmol. 1998; 116:1496-1504.
10. Mangione CM, Berry S, Spritzer K, Janz NK, Klein R, Owsley C, Lee PP. Identifying the content area for the 51-Item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 1998; 116:227-233.
11. Mitchell P, Bandello F, Schmidt-Erfurth U et al. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011; 118:615-25.
12. Mordenti J, Cuthbertson RA, Ferrara N et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. Toxicol Pathol 1999; 27:536-544.
13. Muller YA, Chen Y, Christinger HW et al. VEGF and the Fab fragment of a humanized neutralizing antibody: crystal structure of the complex at 2.4 A resolution and mutational analysis of the interface. Structure 1998; 6(9):1153-1167.

14. Ozaki H, Hayashi H, Vinores SA et al. Intravitreal sustained release of VEGF causes retinal neovascularization in rabbits and breakdown of the blood-retinal barrier in rabbits and primates. Exp Eye Res 1997; 64(4):505-517.

15. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY. Ranibizumab for Neovascular Age-Related Macular Degeneration. N Engl J Med 2006; 355:1419-1431.

PART III: CONSUMER INFORMATION

PrLUCENTIS®
ranibizumab injection

This leaflet is part III of a three-part "Product Monograph" published when LUCENTIS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LUCENTIS. Contact your doctor, ophthalmologist or pharmacist if you have any questions about the drug.

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects affects you severely, or if you notice any side effects not listed in the leaflet, please tell your doctor.

If you have difficulties with reading this document, ask someone for help with reading it.

ABOUT THIS MEDICATION

What the medication is used for:
LUCENTIS (pronounced "loo-SEN-tis") is given as an injection into the eye by a doctor under a local anesthetic.

In adults, LUCENTIS is used to treat damage to the retina (the light-sensitive back part of the eye) caused by growth of leaky abnormal blood vessels (choroidal neovascularization, CNV) in diseases that may cause decreased vision such as:
- Wet age-related macular degeneration (AMD),
- Diabetic macular edema (DME), or edema due to retinal vein occlusion (RVO), where fluid accumulates in the back of the eye, causing swelling ("edema"),
- CNV secondary to pathologic myopia (PM),
- CNV due to other causes.

In preterm infants, LUCENTIS is used to treat retinopathy of prematurity (ROP).

If you are the parent or guardian of a baby who is being treated with LUCENTIS, the following also applies to your baby.

LUCENTIS has been shown to slow down the progression of vision loss, improve vision, as well as the ability to perform related activities (e.g. reading, driving, etc.).

For the following indication LUCENTIS has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.
- treat retinopathy of prematurity (ROP) with zone I [stage 1 with plus disease (1+), stage 2 with plus disease (2+), or stage 3 with or without plus disease (3 or 3+)], or zone II [stage 3 with plus disease (3+)] or aggressive posterior ROP (AP-ROP) disease.

For the following indications LUCENTIS has been approved without conditions. This means it has passed Health Canada's review and can be bought and sold in Canada.
- Wet age-related macular degeneration (AMD),
- Diabetic macular edema (DME), or edema due to retinal vein occlusion (RVO), where fluid accumulates in the back of the eye, causing swelling ("edema"),
- CNV secondary to pathologic myopia (PM),
- CNV due to other causes.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

What it does:
The active substance in LUCENTIS is ranibizumab which is part of an antibody. Antibodies are proteins which specifically recognize and bind to other unique proteins in the body. Ranibizumab binds selectively to all active forms of a protein called human vascular endothelial growth factor A (VEGF-A), which is present in the retina. Ranibizumab helps to stop the growth and leakage of new blood vessels in the eye, abnormal processes that contribute to several eye diseases that may cause decreased vision.

When it should not be used:
LUCENTIS must not be used

- If you are allergic to ranibizumab or any of the other ingredients of LUCENTIS listed below. If you think you may be allergic, ask your doctor for advice.
- If you have already experienced an allergic reaction tell your doctor before receiving LUCENTIS.
- If you have or suspect you have an infection in or around your eye.
- If you have pain or redness in your eye.

If any of these apply to you tell your doctor. You should not be given LUCENTIS.

Your baby must not receive LUCENTIS
- If your baby is allergic to ranibizumab or any of the other ingredients of this medicine listed below.
- If your baby has an infection in or around his/her eye.
- If your baby has pain or redness in his/her eye.

What the medicinal ingredient is:
The active substance in LUCENTIS is ranibizumab.

What the important nonmedicinal ingredients are:
The other inactive ingredients are: α,α-trehalose dihydrate; histidine hydrochloride monohydrate; histidine; polysorbate 20; water for injection.

What dosage forms it comes in:

Vial (adults and preterm infants):
LUCENTIS is a solution for injection supplied in a clear, colourless glass vial. The vial contains 0.23 mL of a sterile clear colourless to pale yellow to brown solution.

LUCENTIS is supplied as a pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper and one filter needle for withdrawal of the vial contents.

Pre-filled syringe (adults only):
LUCENTIS is a solution for injection supplied in a pre-filled syringe. The pre-filled syringe contains 0.165 mL of a sterile, clear, colourless to pale yellow to brown aqueous solution.

LUCENTIS is supplied as packs containing one sterile pre-filled syringe.

WARNINGS AND PRECAUTIONS

The warnings and precautions for adults also apply to preterm infants with ROP.
Potential systemic suppression of VEGF cannot be excluded following intravitreal administration of ranibizumab in premature infants with ROP.
The long-term safety profile in preterm infants with ROP has not been established.

Take special care with LUCENTIS

- **Inform your doctor if you have already had a stroke or experienced short-lasting signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding). This information will be taken into account to evaluate if LUCENTIS is the appropriate treatment for you**.
- LUCENTIS is given as an injection into the eye. Occasionally, an infection in the internal portion of the eye, pain or redness, detachment or tear of retina, or clouding of the lens may occur after LUCENTIS treatment. It is important to identify and treat such a type of infection or retinal detachment as soon as possible. Please tell your doctor immediately if you develop signs such as eye pain or increased discomfort, worsening eye redness, blurred or decreased vision, an increased number of small particles in your vision or increased sensitivity to light.
- In some patients the eye pressure may increase for a short period directly after the injection. There have also been reports of a long-lasting increase in eye pressure. This is something you may not notice; therefore your doctor should check for this after each injection.
- Non-ocular hemorrhages have been reported after LUCENTIS treatment.
- Neurodevelopment impairment have been reported in preterm infants treated for ROP with anti-VEGF, including LUCENTIS.

If you notice any changes after you have been given LUCENTIS, **please inform your doctor immediately**.

Talk to your baby's doctor before your baby is given LUCENTIS.
- LUCENTIS is given as an injection into the eyes. Occasionally, an infection in the internal portion of the eye, pain or redness, detachment or tear of one of retina, or clouding of the lens may occur after LUCENTIS treatment. It is important to identify and treat such an infection or retinal detachment as soon as possible.
- In some patients the eye pressure may increase for a short period directly after the injection. Your baby's doctor may monitor this after each injection.

If you notice any changes after your baby has been given LUCENTIS, **please inform your baby's doctor immediately**

BEFORE LUCENTIS is given to your baby, tell your baby's doctor if your baby is receiving, has recently received or might receive any other medicines.

BEFORE you use LUCENTIS talk to your doctor or pharmacist if:

- you are taking or have recently taken any other medicines, including medicines bought without a prescription (over-the-counter) or natural health products.
- you are pregnant or planning to become pregnant. There is no clinical data on the use of LUCENTIS in pregnant women.

Pregnancy should be avoided until at least three months after finishing LUCENTIS treatment. You should discuss with your doctor the potential risk of LUCENTIS during pregnancy.
- you are using or plan to use birth control during treatment with LUCENTIS.
- you are breast-feeding. LUCENTIS is not recommended during breast-feeding because it is not known whether LUCENTIS passes into human milk. Ask your doctor or pharmacist for advice before LUCENTIS treatment.

The use of LUCENTIS in children and adolescents has not been studied and is therefore not recommended.

PROPER USE OF THIS MEDICATION

All LUCENTIS injections will be administered by your doctor.

Follow your doctor's instructions carefully.

LUCENTIS is given as a single injection into your eye. For adults, the usual dose is 0.05 mL (which contains 0.5 mg of medicine). In preterm infants, the usual dose is 0.01 mL (which contains 0.1 mg of medicine). The time between two doses injected into the same eye should not be shorter than one month.

If you are treated for wet age-related macular degeneration, the injection is given once a month in the first 3 months. Afterwards, your doctor will continue to check your vision and the frequency of dosing can be between 1 and 3 months. LUCENTIS given every 3 months was not as effective as when given once a month.

If you are treated for visual loss due to diabetic macular edema or macular edema in RVO, the injection is given once a month. Your doctor will monitor your vision monthly. If your vision remains the same while you are being given LUCENTIS treatment, your doctor may decide to stop the treatment with LUCENTIS. Your doctor will continue to monitor your vision monthly and will decide if treatment with LUCENTIS should be resumed or not. Your doctor may decide that you also need to be treated with laser for these conditions, if so, laser treatment can be administered together with LUCENTIS.

If you are treated for visual loss due to CNV secondary to PM, the treatment is started with one injection of LUCENTIS. Your doctor will continue to monitor the condition of your eye. Depending on how you respond to the treatment, your doctor will decide whether and when you need to receive the next injection of LUCENTIS.

If you are treated for visual loss due to CNV, the treatment is started with one injection of LUCENTIS. Your doctor will continue to monitor frequently the condition of your eye. Depending on how you respond to the treatment, your doctor will decide whether and when you need to receive the next injection of LUCENTIS.

Before the injection, your doctor will use an eye drop that kills germs or wash your eye carefully to prevent infection. Your doctor will also give you a local anesthetic to reduce or prevent any pain you might have with the injection.

If your baby is treated for retinopathy of the prematurity (ROP), LUCENTIS is administered as a single injection into your baby's eyes by the eye doctor under a local anaesthetic. If ROP is present in both eyes, a second injection of LUCENTIS can be given to your baby on the same day. The usual dose of an injection is 0.01 ml (which contains 0.1 mg of active substance). The interval between two doses injected into the same eyes should be at least four weeks. All injections will be administered by the eye doctor.

Before the injection, your baby's doctor will wash your baby's eyes carefully to prevent infection. The doctor will also give your baby a local anaesthetic to reduce or prevent any pain it might have with the injection.

The doctor will monitor the condition of your baby's eye and, depending on how your baby responds to the treatment, will decide if and when your baby will need to receive further injection of LUCENTIS.

Older people (65 years or above): Elderly people can receive LUCENTIS without adjusting the dose.

If you forget to attend an appointment
Contact your doctor or hospital as soon as possible to reschedule your appointment.

Before stopping LUCENTIS treatment
If you are considering stopping LUCENTIS treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with LUCENTIS.

If you are considering stopping LUCENTIS treatment, please go to your next appointment and discuss this with your baby's doctor. Your baby's doctor will advise you and decide how long your baby should be treated with LUCENTIS.

If you have further questions on the use of this product, ask your doctor or your baby's doctor.

Overdosage:

For management of a suspected drug overdose, contact your regional Poison Control Centre.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients treated with LUCENTIS may experience side effects, although not everybody gets them.

With administration of LUCENTIS, there may be some side effects, mostly in the eye and due to the injection procedure.

Occasionally an infection in the internal portion of the eye, detachment or tear of the retina, or clouding of the lens may occur in the two weeks after LUCENTIS treatment. Other side effects include pain or redness and increased eye pressure. The symptoms you might experience are described in the WARNINGS and PRECAUTIONS Section of this leaflet. Please read this section. It tells you what to do if you have any of these symptoms.

The most common side effects in babies born prematurely are described below:
Visual side effects include: Bleeding in the back of the eye (retinal bleeding), bloodshot eye (conjunctival bleeding), bleeding into the thick fluid that fills the center of the eye (vitreous hemorrhage) and inflammation or infection of the transparent membrane (conjunctivitis).

Non-visual side effects include fever, nasal congestion, runny nose and cough (upper respiratory tract infection), low red blood cell counts (with symptoms such as tiredness, breathlessness, pale skin), urinary tract infection, allergic reactions like rash and skin reddening, diarrhea and slow heart rate (bradycardia).

Additional side effects that have been observed with LUCENTIS in adults are listed below. These side effects may also occur in babies born prematurely.

Very common side effects *(These may affect more than 1 in every 10 patients)*
The most common side effects in the eye reported to be possibly caused by the medicinal product or by the injection procedure include:
- bloodshot eye
- eye pain
- seeing spots or cobwebs (floaters)
- increased pressure inside the eye
- displacement of the jelly-like portion inside the eye (vitreous body)
- swelling of the eye
- blurred vision
- eye irritation
- clouding of the lens
- a feeling of having something in the eye
- vision change
- swelling or infection of the rim of the eye
- formation of fibrous tissue under the retina
- redness of the eye
- blurred or decreased sharpness of vision
- dry eye
- inflammation of the jelly-like portion inside the eye
- temporary blindness
- increased tear production
- itching of the eye
- detachment of a layer of the retina

The most common non-visual side effects reported to be possibly caused by the medicinal product or by the injection procedure include:
- headache
- elevated blood pressure
- sore throat
- pain in the joints

Common side effects *(These may affect between 1 and 10 in every 100 patients)*
Other common side effects in the eye reported to be possibly caused by the medicinal product or by the injection procedure include:
- discomfort of the eye
- clouding of a part of the lens
- deposits in the back of the eye
- infection of the surface of the eye
- changes in the part of the retina responsible for central vision
- bleeding in the back of the eye
- degeneration of the retina
- small scratches on the cornea (front part of the eye)
- bleeding in the eye or at the site of injection
- tear or detachment of the retina
- redness of the eye
- light sensitivity
- swelling of the eyelid
- eyelid pain
- eye discharge
- bleeding in the jelly-like portion inside the eye

Other common non-visual side effects reported to be possibly caused by the medicinal product or by the injection procedure include:
- stroke
- infection of the lower part of the airways
- reduced number of red blood cells (you may experience tiredness, breathlessness, dizziness, pale skin)
- feeling of tension or fullness in the nose, cheeks and behind the eyes sometimes with a throbbing ache
- urinary tract (bladder) infection
- flu
- cough
- nausea
- back pain
- inflammation of the joints
- fatigue
- general feeling of being unwell
- allergic reactions (rash, hives, itching, skin reddening)
- changes in heart rhythm

Uncommon side effects *(These may affect between 1 and 10 in every 1000 patients)*
Uncommon side effects in the eye reported to be possibly caused by the medicinal product or by the injection procedure include:
- irritation and edema of the eyelids

- blindness
- inflammatory deposits in the front part of the eye
- reactions at the site of injection
- abnormal sensation in the eye
- blurred vision with light sensitivity
- Double vision
- Visual loss
- Distorted vision
- Serious allergic reaction

Other uncommon non-visual side effects reported to be possibly caused by the medicinal product or by the injection procedure include:

- wheezing
- increased secretion of the upper airways
- inflammatory disease of the skin
- heart attack
- inflammation of the sinuses
- increased skin sensitivity
- feeling faint
- low blood sugar
- anxiety

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Pain or redness in the eye		√
	Detachment of the layer in the back of the eye		√
	Tear of the layer in the back of the eye		√
	Increased pressure in the eye		√
	Signs of stroke, such as weakness or paralysis of limbs or face, difficulty speaking or understanding.		√
	Signs of non-ocular hemorrhage, such as black or tarry stool, vomit that looks like coffee grounds, weakness, headache of abrupt onset, nausea and vomiting, purplish bruises on the skin, etc.		√
	If you experience these signs, please go to the hospital emergency as immediate medical care is needed.		
Uncommon	Infection in the eye		√
	Clouding of the lens		√

This is not a complete list of side effects. If any of the side effects you experience gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Driving and using machines: After LUCENTIS treatment you may experience some short term vision blurring. If this happens, do not drive or use machines until this resolves.

HOW TO STORE IT

- Do not use LUCENTIS after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.
- Do not use any pack that is damaged.
- Keep LUCENTIS out of reach and sight of children.

Vial:

- Store in a refrigerator (2ºC – 8ºC). DO NOT FREEZE.
- Prior to use, the unopened vial may be kept at room temperature (25°C) for up to 24 hours.
- Keep the vial in the outer carton in order to protect from light.

Pre-filled syringe:

- Store in a refrigerator (2ºC – 8ºC). DO NOT FREEZE.
- Prior to usage, the unopened tray may be kept at room temperature (25°C) for up to 24 hours.
- Keep the pre-filled syringe in its sealed tray in the carton in order to protect from light.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.novartis.ca

This leaflet was prepared by
Novartis Pharmaceuticals Canada Inc.
385 Bouchard Boulevard
Dorval, QC
H9S 1A9

Last revised: December 21, 2021

This document is available in large print format by contacting the Sponsor, Novartis Pharmaceuticals Canada at: 1-800-363-8883