PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrRANOPTO™

Ranibizumab injection

Single Use Vials

10 mg/mL solution for injection

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

Distributed by:
Teva Canada Limited
30 Novopharm Court
M1B 2K9 Ontario CA

Manufactured for:
Teva Canada Innovation
1080 Cote du Beaver Hall
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Date of Initial Authorization:
OCT 11, 2023

Submission Control Number: 268288

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Sections or subsections that are not applicable at the time of authorization are not listed.

RANOPTO (ranibizumab injection) is a biosimilar to Lucentis (ranibizumab injection). A biosimilar is a biologic drug that was granted authorization based on a demonstration of similarity to a version previously authorized in Canada, known as the reference biologic drug.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between RANOPTO™ (ranibizumab injection) and the reference biologic drug Lucentis®.

RANOPTO™ (ranibizumab injection) is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD).
- the treatment of visual impairment due to diabetic macular edema (DME).
- the treatment of 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.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

Ranopto is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Single-use vial for intravitreal use only. Use of more than one injection from a vial can lead to contamination and subsequent infection. Ranopto (ranibizumab injection) vials do not contain any preservative agent (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

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

4.2 Recommended Dose and Dosage Adjustment

The recommended dose for Ranopto 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

Ranopto 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.

Ranopto 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, Ranopto 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 Ranopto 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.

Ranopto *and laser photocoagulation in DME:*

In clinical trials, ranibizumab was administered concomitantly with laser photocoagulation, as well as in patients who have received previous laser photocoagulation. When given on the same day, Ranopto 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 Ranopto 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.

Ranopto *and laser photocoagulation in Branch RVO (BRVO):*

Ranopto can be safely administered concomitantly with laser photocoagulation. When given on the same day, Ranopto 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 14 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 ranibizumab and other medical agents/procedures in patients diagnosed with pathologic myopia.

There are limited data on treatment with ranibizumab 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.

4.4 Administration

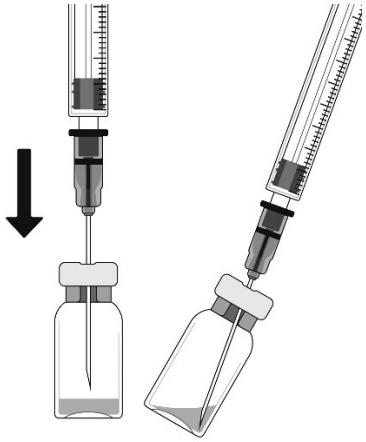
As with all medicinal products for parenteral use, Ranopto should be inspected visually for particulate matter and discoloration prior to administration.

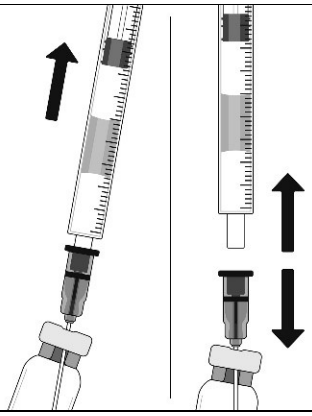
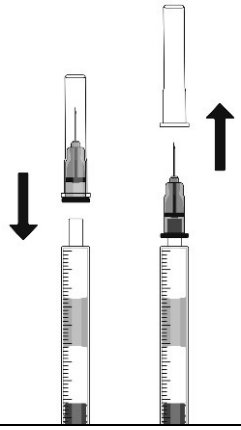
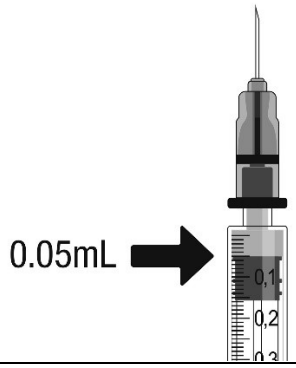
The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history for hypersensitivity reactions should be carefully evaluated prior to performing the intravitreal procedure (see 2 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.

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.

To prepare Ranopto for intravitreal administration in 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 onto the 1 mL syringe (both items are not included in Ranopto pack) using aseptic technique. Push the blunt filter needle into the centre of the vial stopper until the needle touches the bottom edge of the vial. 3. Withdraw all the liquid from the vial, keeping the vial in an upright position, slightly inclined to ease complete withdrawal.
B	4. Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle. 5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.

	
C 	6. Aseptically and firmly assemble the 30G x ½ inch Injection needle onto the syringe (both items not included in the Ranopto pack). 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 0.05 mL mark on the syringe. The syringe is ready for injection. Note**:** Do not wipe the injection needle. Do not pull back on the plunger.
E	9. 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.

4.5 Missed Dose
Not applicable.

5 OVERDOSAGE
Because Ranopto 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 ranibizumab) 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.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the Ranopto (ranibizumab injection) name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Intravitreal injection	Sterile solution / 10 mg/mL (2.3 mg/0.23 mL/vial)	α,α-trehalose dihydrate; histidine hydrochloride monohydrate; histidine; polysorbate 20; water for injection.

Ranopto (ranibizumab injection) is a sterile, clear colourless to pale yellow and preservative-free aqueous solution for injection.

Packaging

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 vial.

7 WARNINGS AND PRECAUTIONS

General
Treatment with Ranopto (ranibizumab injection) is for intravitreal injection only.

Driving and Operating Machinery
The Ranopto treatment procedure may induce temporary visual disturbances, which may affect the ability to drive or use machines (see 8 ADVERSE REACTIONS). Patients who experience these

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

Immune

Hypersensitivity

As with all therapeutic proteins, there is a potential for immunogenicity with Ranopto. 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/anaphlactoid reactions or angioedema which may occur with the use of ranibizumab (see 14.5 Clinical Trials – Reference Biologic Drug)

Ranopto has not been studied in patients with active systemic infections.

Ophthalmologic

Endophthalmitis and Retinal detachments

Intravitreal injections, including those with Ranopto, have been associated with endophthalmitis, intraocular inflammation, hypopyon, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see 8 ADVERSE REACTIONS). Proper aseptic injection techniques must always be used when administering Ranopto. 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 Ranopto (see 8 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.

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

Bilateral Treatment and Populations with Limited Data

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

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

Renal

Systemic exposure to ranibizumab may be increased in patients with renal impairment (see 10.3 Pharmacokinetics). The clinical significance of increased systemic exposure to ranibizumab is unknown.

Reproductive Health: Female and Male Potential
Fertility
There is no fertility data available.

Teratogenic Risk
Women of childbearing potential should use effective contraception during treatment.

Systemic Effects
Thromboembolic events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in the ranibizumab 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 8 ADVERSE REACTIONS**). Therefore, these patients should be carefully evaluated by their physician to determine whether treatment with Ranopto is appropriate, and the benefit outweighs the potential risk. Patients who suffer a thromboembolic event while being treated with Ranopto should be carefully evaluated by their physician who will assess if continuation of Ranopto 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 Ranopto in clinical trials for adults (see 8 ADVERSE REACTIONS), and there is a potential risk that these may relate to VEGF inhibition.

7.1 Special Populations

7.1.1 Pregnant Women

No clinical data concerning exposure to Ranopto 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 16 NON-CLINICAL TOXICOLOGY). The systemic exposure to ranibizumab is low after ocular administration, but due to its mechanism of action, Ranopto must be regarded as potentially teratogenic and embryo-/fetotoxic. Therefore, Ranopto 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 Ranopto, it is recommended to wait at least 3 months after the last dose of Ranopto before conceiving a child.

7.1.2 Breast-feeding

Based on limited data, ranibizumab is present in human milk following the intravitreal administration of ranibizumab in lactating women and may suppress VEGF levels in breast milk. The effects of VEGF suppression in breast milk on the breastfed infant or the effects of ranibizumab on milk production/excretion are unknown. As a precautionary measure, breast-feeding is not recommended during the use of Ranopto.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Ranopto (ranibizumab injection) to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.1 Adverse Reaction Overview

Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see 7 WARNINGS AND PRECAUTIONS, Ophtalmologic).

Other serious ocular events observed among ranibizumab-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 7 WARNINGS AND PRECAUTIONS, Ophtalmologic).

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 ranibizumab (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 ranibizumab. Serious ocular events other than those listed above observed among ranibizumab 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 ranibizumab treated patients was cataract, which occurred in 1.7% of patients treated with ranibizumab 0.5 mg and laser. There were no ocular serious adverse events reported in patients treated with ranibizumab monotherapy and no reports of endophthalmitis overall in the study. All serious non-ocular adverse events reported in the ranibizumab 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 ranibizumab monotherapy, as well as hypertension which occurred in 1.7% of patients treated with ranibizumab and laser.

All serious ocular and non-ocular adverse events reported in the RVO trials during the 6-month treatment period in patients receiving ranibizumab (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 ranibizumab 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 ranibizumab also occurred at a frequency of <1%. The serious ocular events observed among ranibizumab 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 ranibizumab. None of the non-ocular SAEs were suspected to be related to study treatment or ocular injection.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 ranibizumab 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 ranibizumab treatment occurring in ≥ 1% of patients receiving treatment with ranibizumab 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 Table 2 and Table 3 below.

The common ocular and non-ocular adverse events, regardless of treatment relationship to ranibizumab, with a difference in incidence rate of ≥ 2% between patients receiving treatment with 0.5 mg ranibizumab 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 4 below.

Furthermore, the ocular and non-ocular adverse events, regardless of relationship to ranibizumab treatment, occurring in ≥ 1% of patients receiving ranibizumab 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 5 and Table 6 below.

Table 2 Ocular Adverse Events in the Study Eye with Suspected Relationship to Ranibizumab Treatment Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) Safety Population Adverse Events with Incidence Rate ≥ 1% for Ranibizumab 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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 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%

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 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%
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 increasing	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%
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%

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 0.5 mg (N=61)
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 3 Non-Ocular Adverse Events with Suspected Relationship to Ranibizumab Treatment Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) Safety Population Adverse Events with Incidence Rate ≥ 1% for Ranibizumab 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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 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 4 Ocular (in the study eye) and Non-ocular Adverse Events, regardless Relationship To Treatment, with a Difference in Incidence Rate ≥ 2% between Ranibizumab 0.5 mg and the Control in at Least One Study Studies MARINA (FVF2598g), ANCHOR (FVF2587g) and PIER (FVF3192g) Safety Population

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 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%

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 0.5 mg (N=61)
Conjunctivitis allergic	1.7%	2.1%	3.8%	0.7%	0.7%	1.4%	1.6%	0.0%	3.3%
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%
Vitreous disorder	0.0%	2.1%	0.8%	0.0%	1.5%	2.1%	0.0%	1.7%	0.0%

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 0.5 mg (N=61)
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%
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%

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 0.5 mg (N=61)
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									
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									

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)	Ranibizumab 0.3 mg (N=238)	Ranibizumab 0.5 mg (N=239)	Verteporfin PDT (N=143)	Ranibizumab 0.3 mg (N=137)	Ranibizumab 0.5 mg (N=140)	Sham (N=62)	Ranibizumab 0.3 mg (N=59)	Ranibizumab 0.5 mg (N=61)
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%
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 5 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%
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%
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 6 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%
Diverticulum	1.3%	0.7%	2.1%	1.6%
Dyspepsia	3.7%	2.8%	2.1%	1.4%

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
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%

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
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%
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				

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
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				
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%

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
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				
Renal cyst	1.3%	3.5%	1.4%	1.1%
Renal failure	0.3%	1.4%	1.8%	1.1%

Preferred Term	Sham N=298 (%)	PDT N=143 (%)	Ranibizumab 0.3 mg N=434 (%)	Ranibizumab 0.5 mg N=440 (%)
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 ranibizumab 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 ranibizumab 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 ranibizumab 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 7. Although there was a low annual rate of arterial thromboembolic events observed in the ranibizumab (a VEGF inhibitor) clinical trials, there was no imbalance between treatment groups (Table 8). There is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors.

Table 7 Cerebrovascular Accident (CVA) Rates (Fatal and Non-fatal), Safety Populations (2-year Cumulative Data)

	Control	0.3 mg Ranibizumab	0.5 mg Ranibizumab
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 ranibizumab 0.5 mg group for the remainder of the study.

Table 8 Arterial Thromboembolic Events (ATE) as Defined by the Antiplatelet Trialists' Collaboration (APTC), Safety Populations (2-year Cumulative Data)

	Control	0.3 mg Ranibizumab	0.5 mg Ranibizumab
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 ranibizumab 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 ranibizumab 0.3 mg and ranibizumab 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 ranibizumab 0.5 mg compared with 0.3% for ranibizumab 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 ranibizumab 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 ranibizumab 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 ranibizumab-treated patients with visual impairment due to DME (see 14.4 Clinical Trials - Reference Biologic Drug). 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 ranibizumab 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 ranibizumab treatment occurring in ≥ 1% of patients receiving treatment with ranibizumab (any group) in at least one of the two studies RESOLVE and RESTORE are summarized in Table 9 and Table 10 below.

The common ocular and non-ocular adverse events, regardless of treatment relationship to ranibizumab, with a difference in incidence rate of > 2% between patients receiving treatment with ranibizumab (any group) and the control group in at least one of the two studies RESOLVE and RESTORE are summarized in Table 11 below.

Table 9 Ocular Adverse Events in the Study Eye with Suspected Relationship to Ranibizumab Treatment Studies RESOLVE and RESTORE Safety Population Adverse Events with Incidence Rate ≥ 1% For Ranibizumab (Any Group) in at Least One Study

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg/mL‡ (N=51)	Ranibizumab 10 mg/mL‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 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%

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg/mL‡ (N=51)	Ranibizumab 10 mg/mL‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 0.5 mg + Laser (N=120)	Laser (N=110)
Conjunctival edema	2.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%
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							

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg/mL‡ (N=51)	Ranibizumab 10 mg/mL‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 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 14.4 Clinical Trials - Reference Biologic Drug). 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 Non-ocular Adverse Events with Suspected Relationship to Ranibizumab Treatment Studies RESOLVE and RESTORE Safety Population Adverse Events with Incidence Rate ≥ 1% for Ranibizumab (any group) in at Least One Study

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg/ml‡ (N=51)	Ranibizumab 10 mg/ml‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 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							

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg/ml‡ (N=51)	Ranibizumab 10 mg/ml‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 0.5 mg + Laser (N=120)	Laser (N=110)
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 14.4 Clinical Trials - Reference Biologic Drug). 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 11 Ocular (in the study eye) and Non-ocular Adverse Events, regardless Relationship to Treatment, with a Difference in Incidence Rate > 2% between Ranibizumab (any group) and the Control, and at a Higher Rate in the Ranibizumab 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	Ranibizumab 6 mg / ml‡ (N=51)	Ranibizumab 10 mg / ml‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 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%

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg / ml‡ (N=51)	Ranibizumab 10 mg / ml‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 0.5 mg + Laser (N=120)	Laser (N=110)
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%
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%

	% of Patients Study RESOLVE (group A + B)†				% of Patients Study RESTORE		
SYSTEM ORGAN CLASS Preferred term	Ranibizumab 6 mg / ml‡ (N=51)	Ranibizumab 10 mg / ml‡ (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)	Ranibizumab 0.5 mg (N=115)	Ranibizumab 0.5 mg + Laser (N=120)	Laser (N=110)
Blood creatinine increased	0.0%	0.0%	0.0%	0.0%	2.6%	0.0%	0.0%
METABOLISM AND NUTRITION DISORDERS							
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 14.4 Clinical Trials - Reference Biologic Drug). 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 ranibizumab was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular edema secondary to Branch RVO (BRVO) and Central RVO (CRVO) (see 14.4 Clinical Trials - Reference Biologic Drug). 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 ranibizumab in the controlled RVO phase III studies BRAVO and CRUISE (pooled data) are summarized in Table 12 and Table 13 below.

Table 12 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%	1.9%
Lacrimation increased	2.7%	3.8%	1.9%
Macular edema	6.2%	3.4%	1.5%
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%
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%

SYSTEM ORGAN CLASS Preferred term	Sham N=260 (%)	Ranibizumab 0.3 mg N=266 (%)	Ranibizumab 0.5 mg N=259 (%)
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 13 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			
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	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%
INVESTIGATIONS			
Blood pressure increased	0.8%	0.8%	1.2%
METABOLISM AND NUTRITION DISORDERS			

System Organ Class Preferred term	**Sham** **N=260** **(%)**	**Ranibizumab** **0.3 mg** **N=266** **(%)**	**Ranibizumab** **0.5 mg** **N=259** **(%)**
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 ranibizumab safety profile (see14_CLINICAL_TRIALS , Post-marketing studies).

PM population

The safety data of ranibizumab as studied in the 12-month clinical study (RADIANCE), which included 224 ranibizumab-treated patients with PM (see 14.4 Clinical Trials - Reference Biologic Drug). 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 ranibizumab in the controlled PM phase III study are summarized in Table 14 and Table 15 below.

Table 14 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

	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 (%)**
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 15 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	5 (4.7)	4 (3.4)	1 (2.6)	0

Table 15 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 (%)**
SITE CONDITIONS				
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

Table 15 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 (%)**
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 ranibizumab was studied in a 12-month clinical study (MINERVA), which included 171 ranibizumab-treated patients with visual impairment due to CNV (see 14.4 Clinical Trials - Reference Biologic Drug). The safety profile in these patients was consistent with that seen in previous clinical trials with ranibizumab. 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 ranibizumab in the controlled CNV phase III study are summarized in Table 16 and Table 17 below.

Table 16 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
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

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 (%)
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 17 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

	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 (%)
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

	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 (%)
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
Pharanasal 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.

8.3 Less Common Clinical Trial Adverse Reactions

Wet AMD Population

The adverse events with suspected relationship to ranibizumab treatment listed below occurred in patients receiving treatment with ranibizumab 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, cor neal 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, etinal 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 ranibizumab treatment listed below are the events that occurred at an incidence of < 1.0% in the ranibizumab groups in the controlled study RESTORE and that are not listed in Table 9 and Table 10 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 ranibizumab treatment listed below occurred in patients receiving treatment with ranibizumab 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 ranibizumab 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 ranibizumab treatment listed below are events that occurred at an incidence of < 1.0% in the ranibizumab groups in the controlled study RADIANCE and that are not listed in Table 14 and 15 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 ranibizumab treatment listed below are events that occurred at an incidence of < 1.0% in the ranibizumabgroups in the controlled study MINERVA and that are not listed in Table 16 and 17 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.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Wet AMD population:
There were no findings to suggest a relationship between ranibizumab and the development of clinically significant abnormalities.

RVO population:
There were no findings to suggest a relationship between ranibizumab 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 ranibizumab 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.

8.5 Post-Market Adverse Reactions

The common ocular and non-ocular adverse drug reactions reported with an incidence rate of ≥ 1.0% of the total adverse reactions reported in Phase IV clinical trials and with marketed use of ranibizumab in wet AMD are summarized in Table 18 below.

Table 18 Ranibizumab 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%)

Preferred Term	Studies SECURE and EVEREST	Literature Cases	Spontaneous Reports
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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

For the adjunctive use of verteporfin photodynamic therapy (PDT) and ranibizumab injection in wet AMD and PM, see 14.4 CLINICAL TRIALS – Reference Biological Drug.

For the adjunctive use of laser photocoagulation and ranibizumab in DME, see 14.4 CLINICAL TRIALS – Reference Biological Drug and 4.2 Recommended Dose and Dosage Adjustment – Treatment of Visual Impairment Due to DME sections.

For the adjunctive use of laser photocoagulation and ranibizumab in BRVO, see 14.4 CLINICAL TRIALS – Reference Biological Drug and 4.2 Recommended Dose and Dosage Adjustment – Treatment of Visual Impairment Due to macular edema secondary to RVO sections.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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.

10.2 Pharmacodynamics

The pharmacology of ranibizumab has been evaluated in several in vitro assays and in vivoanimal studies. Ranibizumab binds with high affinity to the human VEGF isoforms (KD: ≤192 pM or VEGF110, VEGF121, and VEGF165), inhibits VEGF-induced HUVEC proliferation (IC50: ≤ 0.56 nM) and tissue factor expression (IC50: 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 (IC50: ≤ 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.

10.3 Pharmacokinetics

Following monthly intravitreal administration of 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 ranibizumab 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

- **Pediatrics:** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

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

- **Sex:** No special considerations are needed.

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

- **Renal Insufficiency:** No formal studies have been conducted to examine the pharmacokinetics of ranibizumab in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (136 of 200) had renal impairment (46.5% mild [50-80 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.

11 STORAGE, STABILITY AND DISPOSAL

Store vial 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 stored at temperatures up to a maximum of 30°C for a maximum of 24 hours.

12 SPECIAL HANDLING INSTRUCTIONS

Do not use if particles, discoloration or cloudiness are evident. Vials 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.

PART II: SCIENTIFIC INFORMATION

13 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.
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.
Physicochemical properties:	a sterile, clear colourless to pale yellow and preservative - free aqueous solution for injection.
Pharmaceutical standard:	In-house standard

Heavy Chain of Ranopto (ranibizumab injection)

001 **EVQLVESGGGLVQPGGSLRLSCAASGYDFTHYGMNWVRQAPGKGLEWVGW**
INTYTGEPTY
061 **AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPYYYGTSHWYFDVWGQGTLVT**
121 **VSS**ASTKGPSVFPLAPSSKSTSGGTAALG**C**LVKDYFPEPVTVSWNSGALTSGVHTFPAVL
181 QSSGLYSLSSVVTVPSSSLGTQTYI**C**NVNHKPSNTKVDKKVEPKS**C**DKTHL 231

Light Chain of Ranopto (ranibizumab injection)

001 **DIQLTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS**
061 **RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIK**RTVAAPSVFIFPP
121 SDEQLKSGTASVV**C**LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
181 LSKADYEKHKVYA**C**EVTHQGLSSPVTKSFNRGE**C** 214

Cysteine residue: Underlined letters
Variable region: **Bold letters**

Product Characteristics

The drug substance (DS) manufacturing process of Ranopto (ranibizumab injection) involves pre-culture, main culture, harvest of the cell culture fluid (primary downstream process), purification, and dispensing, resulting in highly purified DS of Ranopto.

The drug product (DP) manufacturing process of Ranopto involves drug substance (DS) thawing, bioburden reduction filtration and DS pooling/mixing, sterile filtration, and aseptic filling/stoppering/crimping.

14 CLINICAL TRIALS

14.5 Clinical Trials – Reference Biologic Drug

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of 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.

[1]The sham ranibizumab injection control procedure involved anesthetising the eye in a manner identical to a ranibizumab intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.

In study FVF2598g (MARINA), patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) received monthly intravitreal injections of ranibizumab 0.3 mg or 0.5 mg or sham injections. A total of 716 patients were enrolled in this study (sham, 238; ranibizumab 0.3 mg, 238; ranibizumab 0.5 mg, 240). 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 ranibizumab 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of ranibizumab 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 ranibizumab 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; ranibizumab 0.3 mg, 140; ranibizumab 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 ranibizumab in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of Month 12. Patients received ranibizumab 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for 3 consecutive doses, followed by a dose administered once every 3 months. A total of 184 patients were enrolled in this study (ranibizumab 0.3 mg, 60; ranibizumab 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 ranibizumab-treated patients (90-96%) depending on study and dose maintained their visual acuity (See Table 19 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.

Table19 Overview of the Primary Endpoints by Study, Randomized Subjects, with Last Observation Carried Forward (LOCF) Method to Impute Missing Data:

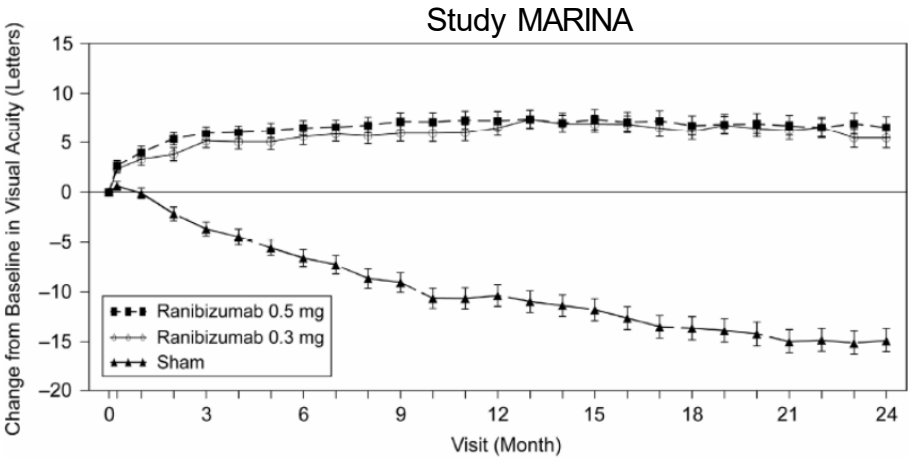
Study MARINA (Outcome at 12 and 24 months)						
Outcome Measure	Month	Sham (N=238)	Ranibizumab 0.3mg (N=238)	Estimated Difference between Sham and Ranibizumab 0.3mg	Ranibizumab 0.5mg (N=240)	Estimated Difference between Sham and Ranibizumab 0.5mg
Loss of < 15 letters in visual acuity (%) (95% CI)	12	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)	Ranibizumab 0.3mg (N=140)	Estimated Difference between PDT and Ranibizumab 0.3mg	ranibizumab 0.5mg (N=139)	Estimated Difference between PDT and Ranibizumab 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)	Ranibizumab 0.3mg (N=60)	Estimated Difference between Sham and Ranibizumab 0.3mg	Ranibizumab 0.5mg (N=61)	Estimated Difference between Sham and Ranibizumab 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, ranibizumab 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 ranibizumab, 0.5 mg ranibizumab):

- 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 ranibizumab injection control procedure involved anesthetising the eye in a manner identical to a ranibizumab intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.

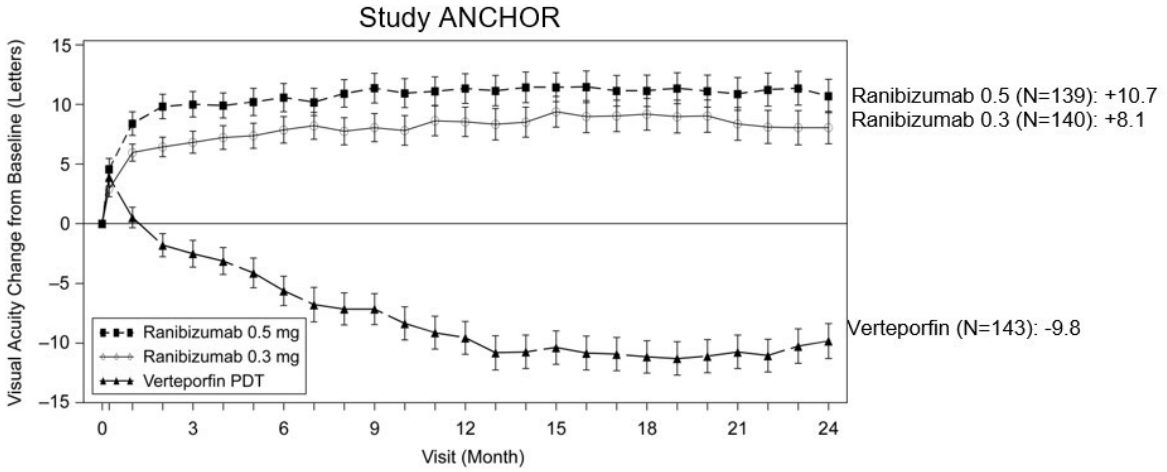
Figure 1 Mean Change in Visual Acuity from Baseline to Month 24 in Study FVF2598g (MARINA) and Study FVF2587g (ANCHOR), Randomized Subjects



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.



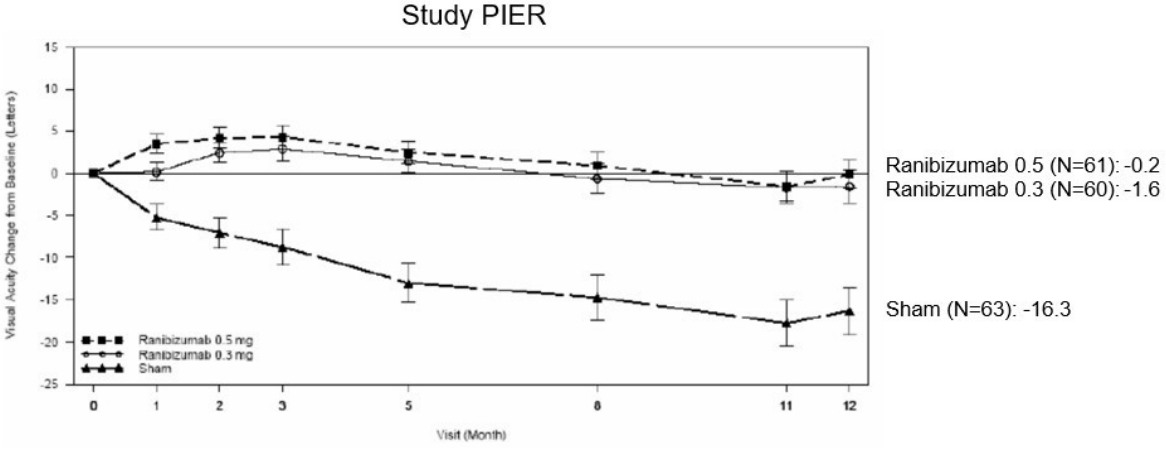
PDT = photodynamic therapy
Note: The LOCF method was used to impute missing data. Vertical bars are ± 1 standard error of the mean

Randomized subjects = all subjects randomized. Note for Study ANCHOR, ranibizumab 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 ranibizumab, 0.5 mg ranibizumab):

- 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 ranibizumab injection control procedure involved anesthetising the eye in a manner identical to a ranibizumab intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.

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 ranibizumab, 0.5 mg ranibizumab):

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

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

Thirty-four percent (34%) to 40% of ranibizumab-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 ranibizumab-treated patients (0.3 mg) experienced a clinically significant, sustained improvement in vision (Table 22). 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 ranibizumab (at Month 3) and maintained until Month 24 in both studies.

In PIER, almost all ranibizumab-treated patients (90%) maintained their visual acuity at Month 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 20 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)	Ranibizumab 0.3mg (N=238)	Estimated Difference between Sham and Ranibizumab 0.3mg	Ranibizumab 0.5mg (N=240)	Estimated Difference between Sham and Ranibizumab 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)	Ranibizumab 0.3mg (N=140)	Estimated Difference between PDT and Ranibizumab 0.3mg	Ranibizumab 0.5mg (N=139)	Estimated Difference between PDT and Ranibizumab 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)	Ranibizumab 0.3mg (N=60)	Estimated Difference between Sham and Ranibizumab 0.3mg	Ranibizumab 0.5mg (N=61)	Estimated Difference between Sham and Ranibizumab 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, ranibizumab 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 ranibizumab, 0.5 mg ranibizumab):

- 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 ranibizumab injection control procedure involved anesthetising the eye in a manner identical to a ranibizumab intravitreal injection. The tip of a needleless syringe was then pressed against the conjunctiva and the plunger of the needleless syringe depressed.

Patients in the groups treated with ranibizumab had minimal observable CNV lesion growth, on average. At Month 12, the mean change in the total area of the CNV lesion was 0.1 to 0.3 disc area for ranibizumab 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 ranibizumab.

In MARINA and ANCHOR, at month 12 patients treated with ranibizumab 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 ranibizumab: + 10.4 point increase; 0.3 mg ranibizumab: + 9.4 point increase; ANCHOR: 0.5 mg ranibizumab: + 9.1 point increase; 0.3 mg ranibizumab: + 6.6 point increase), distance vision (such as driving; MARINA: 0.5 mg ranibizumab: + 7.0 point increase; 0.3 mg ranibizumab: + 6.7 point increase; ANCHOR: 0.5 mg ranibizumab: + 9.3 point increase; 0.3 mg ranibizumab: + 6.4 point increase) and vision–specific dependency (such as seeing faces; MARINA: 0.5 mg ranibizumab: + 6.8 point increase; 0.3 mg ranibizumab: + 3.6 point increase; ANCHOR: 0.5 mg ranibizumab: + 8.9 point increase; mg ranibizumab: + 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 ranibizumab-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 ranibizumab 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 ranibizumab 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 ranibizumab has been assessed in the randomised, double-masked, controlled studies D2301 (RESTORE) and D2201 (RESOLVE).

Table 21 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.	Ranibizumab 0.5mg intravitreal injection (+ sham laser), prn‡; ranibizumab 0.5mg intravitreal injection + laser, prn; or Sham injection + laser, prn 12 month study.	Ranibizumab 0.5mg : n= 116 ranibizumab 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.	Ranibizumab 0.3mg intravitreal injection (dose doubling permitted), prn; ranibizumab 0.5mg intravitreal injection (dose doubling permitted), prn; or Sham injection, prn 12 month study.	Ranibizumab 0.3mg: n=51 ranibizumab 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.

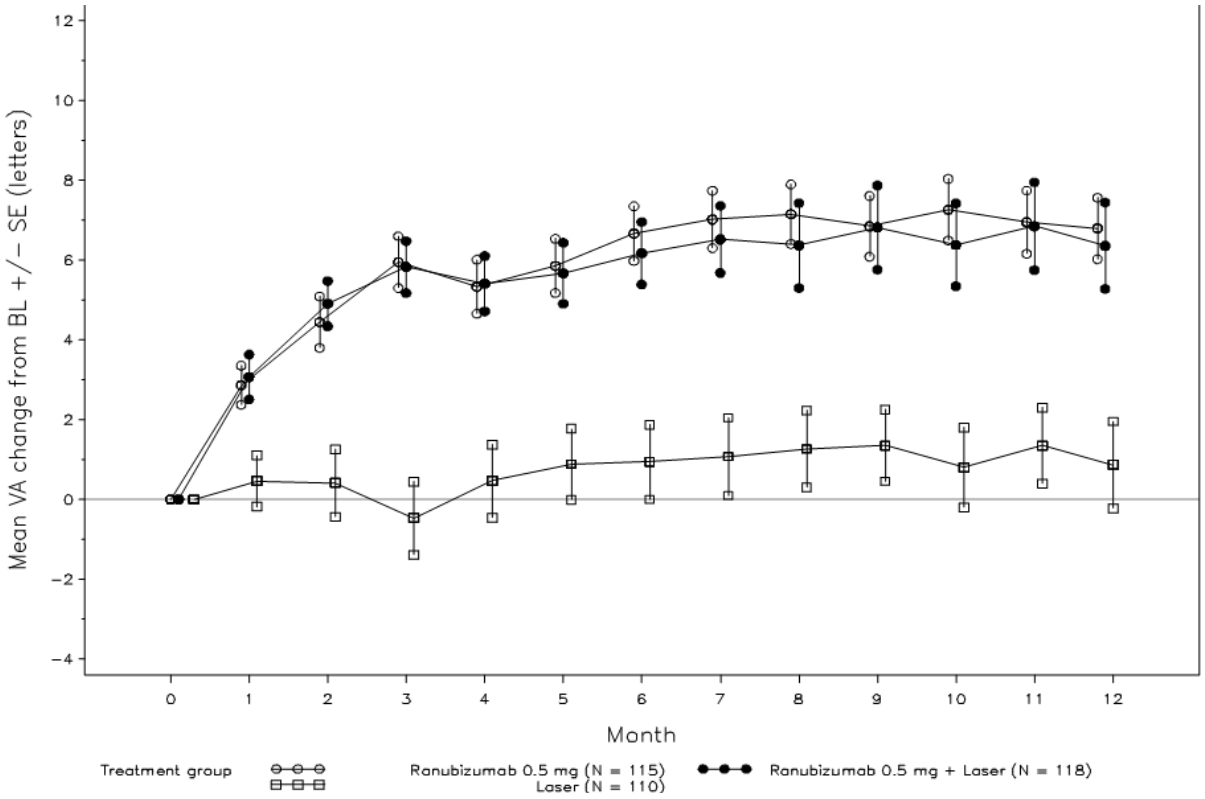
The results of the primary endpoint are detailed below in Table 22 and illustrated in Figure 3.

Table 22 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 ranibizumab 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 sham1 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.

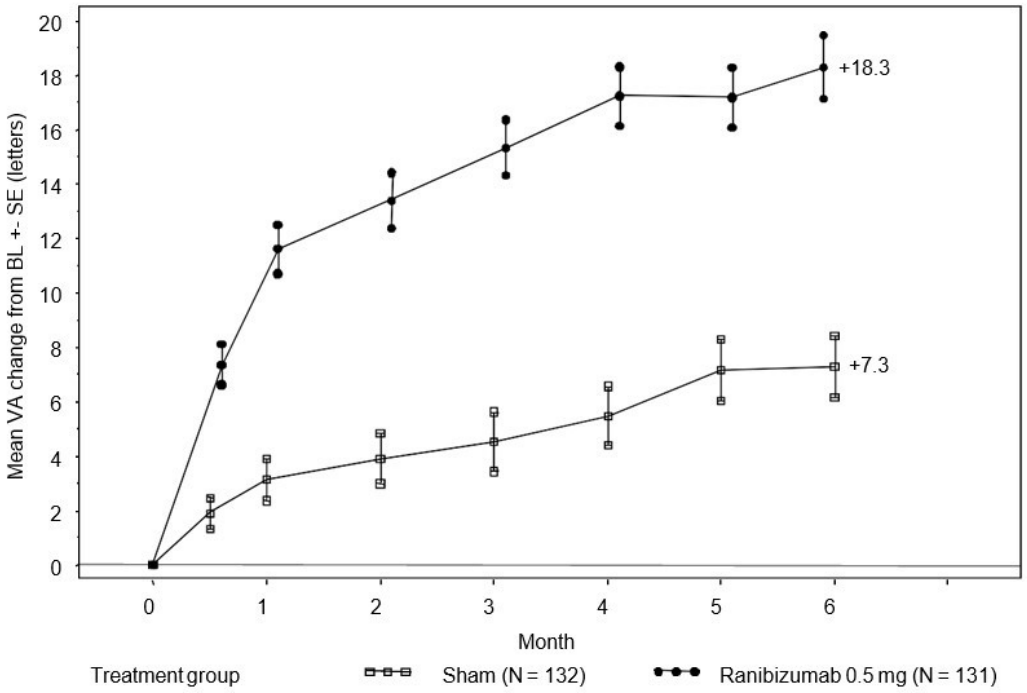
Statistically significant improvements were also observed in key secondary endpoints at Month 6, and sustained to Month 12. At month 6, 61.1% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 28.8% of patients in the sham group, which 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 23 BCVA Primary Efficacy Outcome at Month 6 (BRAVO), Randomized Patients, with Last Observation Carried Forward Method (LOCF) to Impute Missing Data

Primary endpoint	Sham (n=132)	Ranibizumab 0.5 mg (n=131)	Estimated Difference between Sham and Ranibizumab 0.5 mg
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.

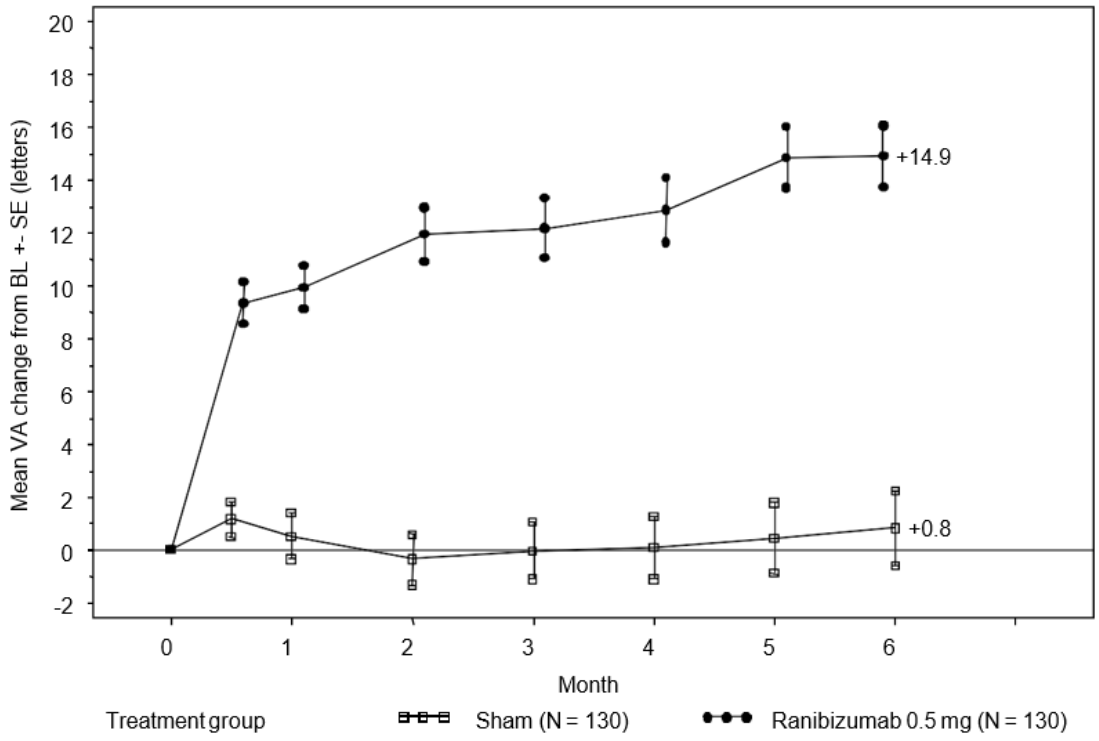
Statistically significant improvements were also observed in key secondary endpoints at Month 6 and sustained through Month 12. At month 6, 47.7% of the patients in the 0.5 mg ranibizumab group gained ≥15 letters in visual acuity score from baseline compared with 16.9% of patients in the sham group, 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 24 BCVA Primary Efficacy Outcome at Month 6 (CRUISE), Randomized Patients, with Last Observation Carried Forward Method (LOCF) to Impute Missing Data

Primary endpoint	Sham (n=130)	Ranibizumab 0.5 mg (n=130)	Estimated Difference between Sham and Ranibizumab 0.5 mg
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.

Post-marketing studies

The long term (24 month) clinical safety and efficacy of ranibizumab in patients with visual impairment due to macular edema secondary to RVO were assessed in the BRIGHTER (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 25: Outcomes at Month 6 and 24 (BRIGHTER and CRYSTAL)

	BRIGHTER			**CRYSTAL**
	Ranibizumab 0.5 mg N=180	**Ranibizumab 0.5 mg + Laser N=178**	**Laser* N=90**	**Ranibizumab 0.5 m (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 allow ed (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 ranibizumab in patients with visual impairment due to CNV in PM have been assessed based on the 12-month data of the randomized, double-masked, controlled pivotal study F2301 (RADIANCE) which was designed to evaluate two different dosing regimens of 0.5 mg ranibizumab given as intravitreal injection in comparison to verteporfin 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 26 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 4.2 Recommended Dosage and Dosage Adjustment), 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 Month1 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.

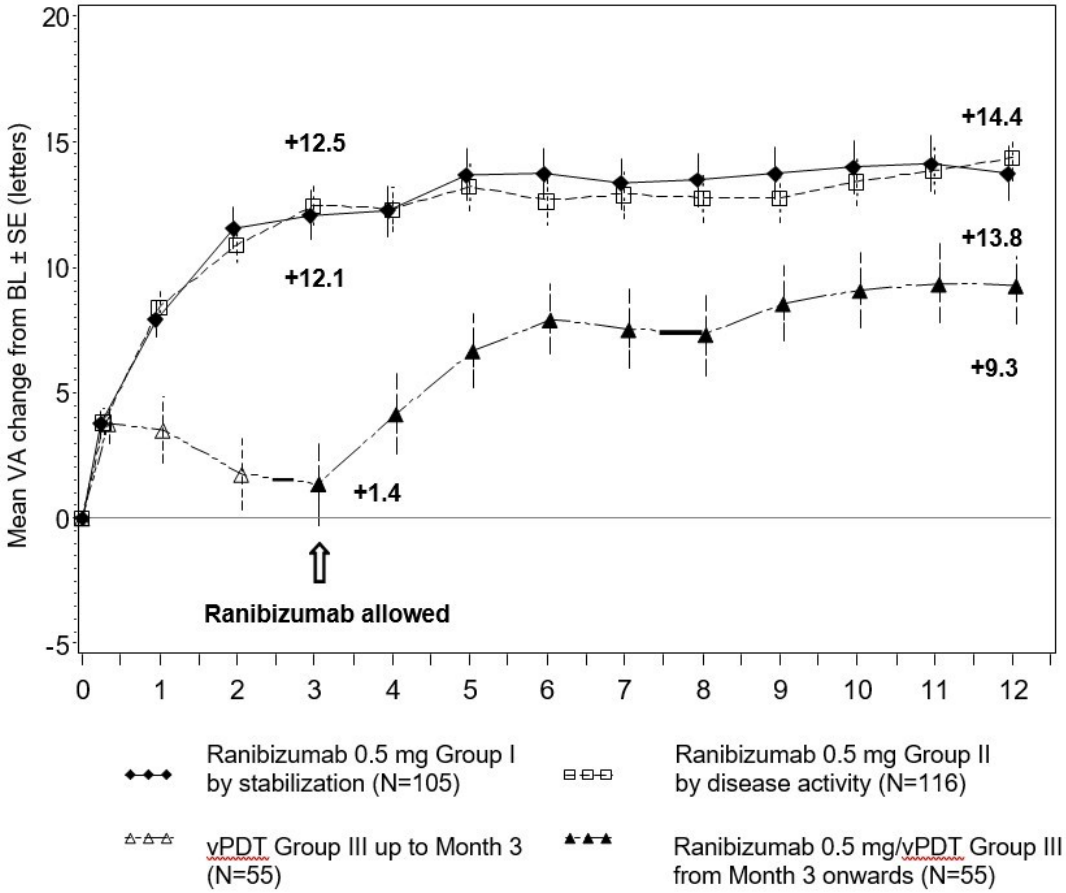
Table 27 Primary Efficacy Outcome at Month 3 in Study RADIANCE, Randomized Patients, with Modified Last Observation Carried Forward (LOCF) Method

Primary endpoint	Group I Ranibizumab 0.5 mg "Visual Acuity Stability" (n=105)	Group II Ranibizumab 0.5 mg "Disease Activity" (n=116)	Group III vPDT (n=55)†
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 ranibizumab 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 ranibizumab 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 28 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 individualized 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 29).

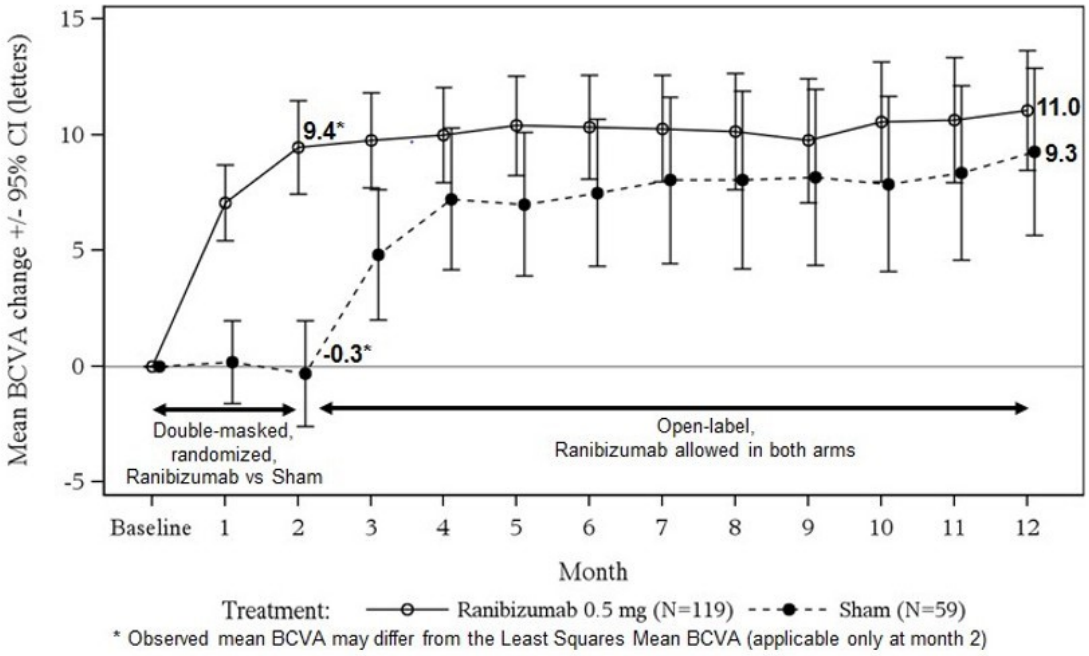
Table 29 Change in Visual Acuity at Month 2 in study MINERVA

	Ranibizumab 0.5 mg (N=119)	Sham (N=59)
n	118	57
Mean BCVA change from baseline to Month 2 (letters) (Least Squares Mean) a	+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 30 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 BCVA (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.

Immunogenicity
In the wet AMD studies, the pre-treatment incidence of immunoreactivity to ranibizumab was 0% 3% across treatment groups. After monthly dosing with ranibizumab for 12 to 24 months, low titres of antibodies to ranibizumab 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 ranibizumab in an electrochemiluminescence assay and are highly dependent on the sensitivity and specificity of the assay. The clinical significance of immunoreactivity to ranibizumab is unclear at this time, although some patients with the highest levels of immunoreactivity were noted to have iritis or vitritis.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Genotoxicity
No genotoxicity studies have been conducted with ranibizumab.

Carcinogenecity
No carcinogenicity studies have been conducted with ranibizumab.

Reproductive and Developmental Toxicology:
The potential of ranibizumab to affect embryo-fetal and/or placental development has been investigated in pregnant cynomolgus monkeys given bilateral ITV injections of ranibizumab every 14 days from Day 20 until Day 62 of gestation. The selected ITV 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 (C_{max}) about 10- and 100-fold, respectively, higher than the median C_{maxb} in humans given monthly unilateral ITV 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, ITV 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-fetotoxic. 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 7.1.1 Pregnant Women).

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.

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.

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 (unilateral, left eye)	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.

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: 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.

Study Type	Species /Strain	No./Sex /Group	Route of Admin.	Nominal Doses	Study Duration	Dosing Regimen	Findings
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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. PrLucentis® 10 mg/mL (2.3 mg/0.23 mL/vial), sterile solution for intravitreal injection, Control No. 263995, Product Monograph, Novartis Pharmaceuticals Canada Inc, September 28, 2022 .

PATIENT MEDICATION INFORMATION

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PrRANOPTO™

Ranibizumab injection

Read this carefully before you start taking Ranopto and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Ranopto.

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

Ranopto is a biosimilar biologic drug (biosimilar) to the reference biologic drug PrLucentis®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

What is Ranopto used for?

Ranopto is given as an injection into the eye by a healthcare professional under a local anesthetic.

Ranopto 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.

How does Ranopto work?

The active substance in Ranopto 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.

What are the ingredients in Ranopto?

Medicinal ingredient: ranibizumab.

Non-medicinal ingredients: α,α-trehalose dihydrate; histidine hydrochloride monohydrate; histidine; polysorbate 20; water for injection.

Ranopto contains no preservatives.

Ranopto comes in the following dosage form:

Vial:
Ranopto 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 solution.

Ranopto is supplied as a pack containing one glass vial of ranibizumab with chlorobutyl rubber stopper.

Do not use Ranopto if:

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

If any of these apply to you tell your healthcare professional. You should not be given Ranopto.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Ranopto.

Take special care with Ranopto

- **Inform your healthcare professional if you have already had a stroke or experienced transient signs of stroke (weakness or paralysis of limbs or face, difficulty speaking or understanding). This information will be taken into account to evaluate if Ranopto is the appropriate treatment for you.**
- Ranopto 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 Ranopto treatment. It is important to identify and treat such a type of infection or retinal detachment as soon as possible. **Please tell your healthcare professional 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 sustained eye pressure increases. This is something you may not notice; therefore, your healthcare professional should monitor this after each injection.
- Non-ocular hemorrhages have been reported after Ranopto treatment.

If you notice any changes after you have been given Ranopto, **please inform your healthcare professional immediately.**

BEFORE you receive Ranopto talk to your healthcare professional or pharmacist if:

- you are pregnant or planning to become pregnant. There is no clinical data on the use of Ranopto in pregnant women. Pregnancy should be avoided until at least three months after finishing Ranopto treatment. You should discuss with your healthcare professional the potential risk of Ranopto during pregnancy.
- you are using or plan to use birth control during treatment with Ranopto.
- you are breast-feeding. Ranopto is not recommended during breast-feeding because Ranopto passes into human milk. Ask your healthcare professional or pharmacist for advice before Ranopto treatment.

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Ranopto:
No relevant interactions are known.

How to take Ranopto:

All Ranopto injections will be administered by your healthcare professional.

Follow your healthcare professional's instructions carefully.

If you are treated for wet age-related macular degeneration, the injection is given once a month in the first 3 months. Afterwards, your healthcare professional will continue to monitor your vision and the frequency of dosing can be between 1 and 3 months. Ranopto 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 healthcare professional will monitor your vision monthly. If your vision remains the same while you are being given Ranopto treatment, your healthcare professional may decide to stop the treatment with Ranopto. Your healthcare professional will continue to monitor your vision monthly and will decide if treatment with Ranopto should be resumed or not. Your healthcare professional may decide that you also need to be treated with laser for these conditions, if so, laser treatment can be administered together with Ranopto.

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

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

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

If you have further questions on the use of this product, ask your healthcare professional

Usual dose:
Ranopto (ranibizumab injection) is given as a single injection into your eye. The usual dose is 0.05 mL (which contains 0.5 mg of medicine). The time between two doses injected into the same eye should not be shorter than one month.

Older people (age 65 years and over): Elderly people can receive Ranopto without adjusting the dose.

Overdose:

If you think you, or a person you are caring for, have been given too much Ranopto, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose
If you forget to attend an appointment
Contact your healthcare professional or hospital as soon as possible to reschedule your appointment.

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

If you have further questions on the use of this product, ask your healthcare professional.

What are possible side effects from using Ranopto?

As with all medicines, patients treated with Ranopto may experience side effects, although not everybody gets them. These are not all the possible side effects you may have when taking Ranopto. If you experience any side effects not listed here, tell your healthcare professional.

With administration of Ranopto, 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 Ranopto treatment. Other side effects include pain or redness and increased eye pressure. The symptoms you might experience are described in the "**Take special care with Ranopto"** Section of this leaflet. Please read this section. It tells you what to do if you have any of these symptoms.

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
- Small particles or spots in your vision
- 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
- Visual disturbance
- Swelling or infection of the eyelid margin
- 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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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. If you experience these signs, please go to the hospital emergency as immediate medical care is needed.		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
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		√	
UNCOMMON			
Infection in the eye		√	
Clouding of the lens		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Do not use Ranopto (ranibizumab injection) 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 Ranopto (ranibizumab injection) out of reach and sight of children.
- Store vial in a refrigerator (2ºC – 8ºC). DO NOT FREEZE.
- Prior to use, the unopened vial may be stored at room temperatures up to a maximum of 30°C for a maximum of 24 hours.
- Keep the vial in the outer carton in order to protect from light.

If you want more information about Ranopto:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the Canadian distributor (Teva Canada Innovation) website www.tevacanada.com
  or by calling 1-833-662-5644.

This leaflet was prepared by Teva Canada Innovation

Last Revised: OCT 11, 2023