

LUCENTIS®
ranibizumab (rbe)

NAME OF THE MEDICINE

| | |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Active ingredient: | Ranibizumab |
| Chemical name: | Immunoglobulin G1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFab V2 γ 1-chain), disulfide with human-mouse monoclonal rhuFab V2 κ -chain |
| CAS number: | 347396-82-1 |
| Molecular weight: | Approximately 48kDa |
| Structure: | Ranibizumab is the Fab moiety of a high affinity version of recombinant humanised monoclonal antibody rhuMAb vascular endothelial growth factor (VEGF). 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 in Figures 1a and 1b. |

Figure 1a The amino acid sequence of the heavy chain of ranibizumab

| | | | | | |
|---------------------------------------------------------------------------------------------------------------------------|-----|-----|-----|-----|-----|
| 10 | 20 | 30 | 40 | 50 | 60 |
| EVQLVESGGGLVQPGGSLRLS <u>CAASGYDF</u> <u>THYGMNWVRQAPGKGLEWVGWINTY</u> <u>TGPEPT</u> | | | | | |
| 70 | 80 | 90 | 100 | 110 | 120 |
| <u>AADF</u> <u>KRRFTF</u> <u>SLDTSK</u> <u>STAYLQ</u> <u>MNSLRAEDTAVYYCAK</u> <u>YPYYGT</u> <u>SHWYFDVWGQ</u> <u>GLVT</u> | | | | | |
| 130 | 140 | 150 | 160 | 170 | 180 |
| VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTFPAVL | | | | | |
| 190 | 200 | 210 | 220 | 230 | |
| QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHL | | | | | |

Complementarity-determining regions (CDR) are underlined.

Figure 1b The amino acid sequence of the light chain of Ranibizumab

10 20 30 40 50 60
 DIQLTQSPSSLSASVGD^RVTTITCSSASQDISNYLNWYQKPGKAPKVLIIYFTSSLHSGVPS
 70 80 90 100 110 120
 RFSGSGSGTDFTLTISLQPEDFATYYCQQYSTVPWTFFGQGTKVEIKRTVAAPSVFIFPP
 130 140 150 160 170 180
 SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLT
 190 200 210
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Complementarity-determining regions (CDR) are underlined.

DESCRIPTION

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

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

Vial

Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution for intravitreal injection. The solution is sterile, clear, colourless to pale yellow, aqueous and preservative free.

Pre-filled syringe

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

The solution is sterile, clear, colourless to pale yellow, aqueous and preservative free.

Excipients: Trehalose dihydrate, histidine hydrochloride monohydrate, histidine, polysorbate 20, water for injections.

PHARMACOLOGY**Pharmacotherapeutic group, ATC**

Antineovascularisation agents, ATC code: S01LA04.

Mechanism of action

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

Pharmacodynamics

Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularisation, as well as vascular leakage, which are thought to contribute to the progression of the neovascular form of age-related macular degeneration, to the development of choroidal neovascularisation (CNV), including CNV secondary to pathologic myopia or to the macular oedema causing visual impairment in diabetes and retinal vein occlusion.

Pharmacokinetics

Absorption:

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

Distribution and Elimination:

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

Renal impairment: No formal studies have been conducted to examine the pharmacokinetics of Lucentis in patients with renal impairment. In a population pharmacokinetic analysis of neovascular AMD patients, 68% (136 of 200) of patients in a population pharmacokinetic analysis had renal impairment (46.5% mild [50 to 80 mL/min], 20% moderate [30 to 50 mL/min] and 1.5% severe [< 30 mL/min]). In RVO patients, 48.2% (253 of 525) had renal impairment (36.4% mild, 9.5% moderate and 2.3% severe). Systemic clearance was slightly lower, but this was not clinically significant.

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

CLINICAL TRIALS

Treatment of Wet AMD

In wet AMD, the clinical safety and efficacy of Lucentis have been assessed in three randomised, double-masked, sham** or active-controlled studies in patients with neovascular age-related macular degeneration (AMD) (FVF2598g (MARINA), FVF2587g (ANCHOR) and FVF3192g (PIER)). A total of 1,323 patients (879 active and 444 control) was enrolled in these studies.

Study FVF2598g (MARINA) and study FVF2587g (ANCHOR)

In the 24-month study FVF2598g (MARINA), patients with minimally classic or occult with no classic choroidal neovascularisation (CNV) received monthly intravitreal injections of Lucentis 0.3 mg or 0.5 mg or sham injections. A total of 716 patients was enrolled in this study (sham, 238; Lucentis 0.3 mg, 238; Lucentis 0.5 mg, 240). A total of 664 subjects (92.7%) completed month 12 (defined as having a visual acuity score for the study eye at month 12) and a total of 615 subjects (85.9%) completed the 2-year study period.

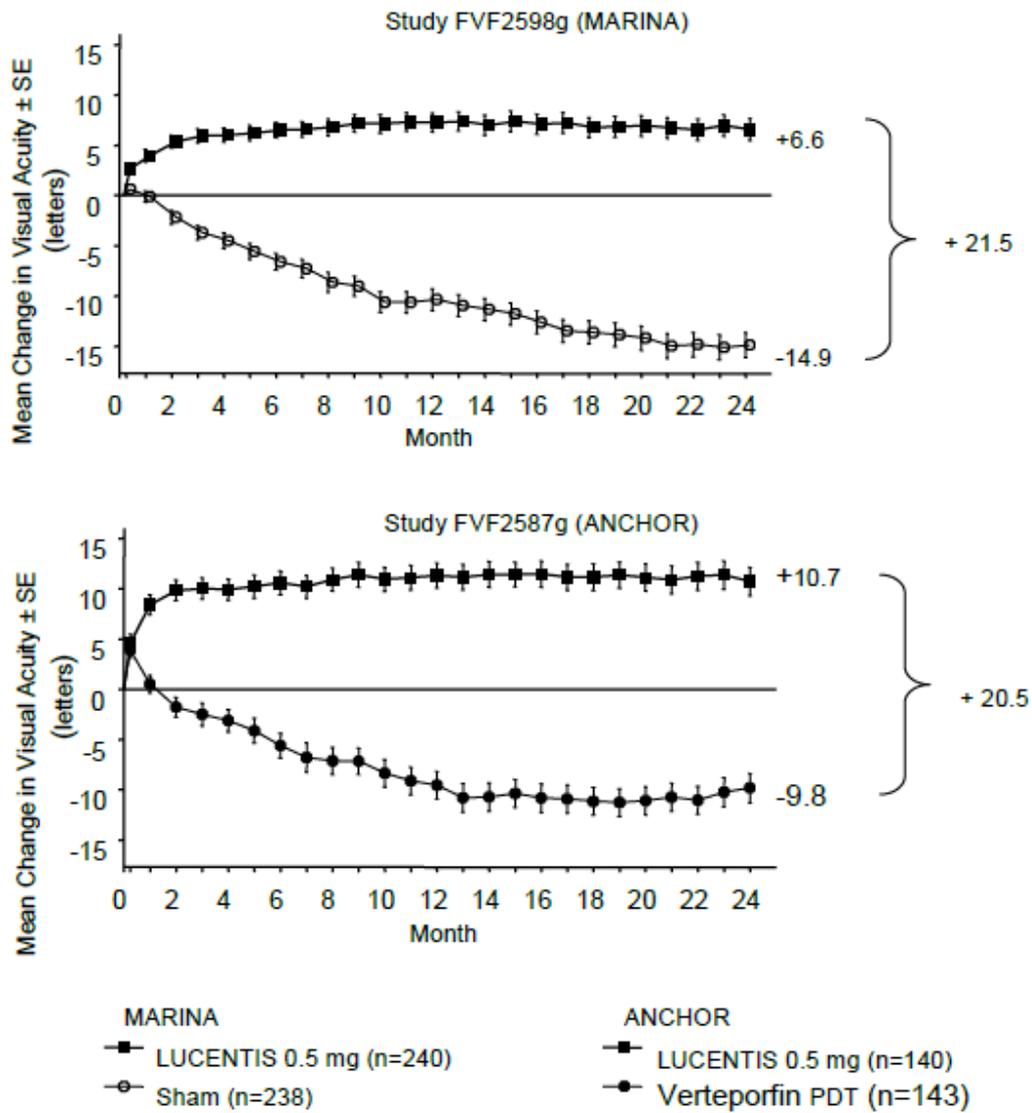
In the 24-month study FVF2587g (ANCHOR), patients with predominantly classic CNV lesions received either: 1) monthly intravitreal injections of Lucentis 0.3 mg and sham photodynamic therapy (PDT); 2) monthly intravitreal injections of Lucentis 0.5 mg and sham PDT; or 3) sham intravitreal injections and active verteporfin PDT. Verteporfin (or sham) PDT was given with the initial Lucentis (or sham) injection and every 3 months thereafter if fluorescein angiography showed persistence or recurrence of vascular leakage. A total of 423 patients was enrolled in this study (Lucentis 0.3 mg, 140; Lucentis 0.5 mg, 140; Verteporfin PDT, 143). A total of 386 subjects (91.3%) completed month 12 of the study and 343 subjects (81.1%) completed month 24 of the study.

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

In MARINA, the visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 24, compared to a gradual deterioration in the sham treatment group, as shown in Figure 2.

In ANCHOR, the visual acuity gain with ranibizumab is present at 1 month, continues to increase up to month 3, and is maintained up to month 12 compared to a gradual deterioration in the verteporfin treatment group, as shown in Figure 2.

Figure 2 Mean change in visual acuity from baseline to Month 24 in study FVF2598g (MARINA) and study FVF2587g (ANCHOR): ITT population



Detailed results are shown in the tables below:

Table 1 Outcomes at month 12 and month 24 in study FVF2598g (MARINA)

| Outcome measure | Month | Sham (n=238) | Lucentis 0.3 mg (n=238) | Lucentis 0.5 mg (n=240) |
|------------------------------------------------------------------------------------|----------|-----------------|-------------------------------|-------------------------------|
| Loss of <15 letters in visual acuity n (%) ^a (Maintenance of vision) | Month 12 | 148 (62.2%) | 225 (94.5%) | 227 (94.6%) |
| | Month 24 | 126 (52.9%) | 219 (92.0%) | 216 (90.0%) |
| Gain of ≥15 letters in visual acuity n (%) ^a | Month 12 | 11 (4.6%) | 59 (24.8%) | 81 (33.8%) |
| | Month 24 | 9 (3.8%) | 62 (26.1%) | 80 (33.3%) |
| Mean change in visual acuity (letters) (SD) ^a | Month 12 | -10.5 (16.6) | +6.5 (12.7) | +7.2 (14.4) |
| | Month 24 | -14.9 (18.7) | +5.4 (15.2) | +6.6 (16.5) |

^a p<0.01.

Table 2 Outcomes at month 12 and 24 in study FVF2587g (ANCHOR)

| Outcome measure | Month | Verteporfin PDT (n=143) | Lucentis 0.3 mg (n=140) | Lucentis 0.5 mg (n=140) |
|------------------------------------------------------------------------------------|----------|-------------------------------|-------------------------------|-------------------------------|
| Loss of <15 letters in visual acuity n (%) ^a (Maintenance of vision) | Month 12 | 92 (64%) | 132 (94%) | 134 (96%) |
| | Month 24 | 94(66%) | 126 (90%) | 125 (90%) |
| Gain of ≥15 letters in visual acuity n (%) ^a | Month 12 | 8 (6%) | 50 (36%) | 56 (40%) |
| | Month 24 | 9(6%) | 48 (34%) | 57 (41%) |
| Mean change in visual acuity (letters) (SD) ^a | Month 12 | -9.5 (16.4) | +8.5 (14.6) | +11.3 (14.6) |
| | Month 24 | -9.8 (17.6) | +8.1 (16.2) | +10.7 (16.5) |

^a p<0.01

Patients in the group treated with Lucentis had minimal observable CNV lesion growth, on average. At month 12, the mean change in the total area of the CNV lesion was 0.1 to 0.3 DA for Lucentis versus 2.3 to 2.6 DA for the control arms.

The use of Lucentis beyond 24 months has not been studied.

In MARINA, at month 12, patients treated with Lucentis reported, on average, a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency, as measured by the NEI VFQ-25, while sham-treated patients reported a decrease in their ability to perform these activities. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +10.4 point

increase (0.3 mg: +9.4), while sham-treated patients had a -2.6 point decrease ($p < 0.01$). On the distance activities scale, Lucentis 0.5 mg-treated patients had a +7.0 point increase (0.3 mg: +6.7), while sham-treated patients had a -5.9 point decrease ($p < 0.01$). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients experienced +6.8 point increase (0.3 mg: +3.6), while sham-treated patients reported a decrease of -4.7 points ($p < 0.01$).

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

In ANCHOR, at month 12, patients treated with Lucentis reported a statistically and clinically meaningful improvement in their ability to perform activities related to near vision, distance vision and vision-specific dependency compared to patients receiving verteporfin PDT treatment. On the near activities scale, patients treated with 0.5 mg Lucentis reported a +9.1 point increase (0.3 mg: +6.6), while verteporfin PDT-treated patients had a +3.7 point increase ($p < 0.01$). On the distance activities scale, Lucentis 0.5 mg-treated patients reported a +9.3 point increase (0.3 mg: +6.4), while verteporfin PDT-treated patients had a +1.7 point increase ($p < 0.01$). On the vision-specific dependency scale, Lucentis 0.5 mg-treated patients reported a +8.9 point increase (0.3 mg: +7.6), while verteporfin PDT-treated patients had a -1.4 point decrease ($p < 0.01$). 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).

Study FVF3689g (SAILOR)

Study FVF3689g (SAILOR) was a Phase IIIb, single-masked, one-year multicentre study in naïve and previously treated subjects with CNV secondary to AMD. The primary study objective was to estimate the incidence of ocular and non-ocular serious adverse events in subjects treated for 12 months. Overall, 2378 patients were randomised in a 1:1 ratio to receive one intravitreal injection of 0.3 mg or 0.5 mg ranibizumab every month for three consecutive months followed by re-treatment as-needed not more often than monthly.

Overall, no imbalances between the two dose groups were observed in the frequency of ocular and non-ocular adverse events. There was a statistically non-significant trend towards a higher stroke rate in the 0.5 mg group compared to the 0.3 mg group. The respective 95% CIs for the overall stroke rate were wide (0.3% to 1.3% for the 0.3 mg group vs. 0.7% to 2.0% for the 0.5 mg group). The number of strokes was small in both dose groups, and there is not sufficient evidence to conclude (or rule out) that there is a true difference in stroke

rates among the treatment groups. The difference in stroke rates may be greater in patients with known risk factors for stroke, including history of prior stroke and transient ischaemic attack.

Study FVF3192g (PIER)

Quarterly Dosing after Three Consecutive Monthly Doses: Study FVF3192g (PIER) was a randomised, double-masked, sham-controlled, two-year study designed to assess the safety and efficacy of Lucentis in patients with neovascular AMD (with or without a classic CNV component). Data are available up to the end of month 12. Patients received Lucentis 0.3 mg or 0.5 mg intravitreal injections or sham injections once a month for three consecutive doses, followed by a dose administered once every 3 months. A total of 184 patients was enrolled in this study (Lucentis 0.3 mg, 60; Lucentis 0.5 mg, 61; sham, 63); 171 (93%) completed 12 months of this study. Patients treated with Lucentis in PIER received a mean of 6 total treatments out of possible 6 from day 0 to month 12.

In PIER, the primary efficacy endpoint was mean change in visual acuity at 12 months compared with baseline. After an initial increase in visual acuity (following monthly dosing), on average, patients dosed once every three months with Lucentis **lost the initial visual acuity gain**, returning to **baseline** at month 12. In PIER, almost all Lucentis-treated patients (90%) maintained their visual acuity at month 12.

Interpretation of PIER: Although less effective, treatment might be reduced to one injection every 3 months after the first three injections (e.g. if monthly injections are not feasible) but, compared to continued monthly doses, dosing every 3 months may lead to an approximate 5-letter (1-line) loss of visual acuity benefit, on average, over the following nine months. Patients should be evaluated regularly.

Treatment of Visual Impairment Due to DME

The efficacy and safety of Lucentis have been assessed in two randomized, double-masked, sham- or active controlled studies of 12 months duration in patients with visual impairment due to diabetic macular oedema (Study D2301 (RESTORE) and D2201 (RESOLVE)). A total of 496 patients (336 active and 160 control) was enrolled in these studies, the majority had type II diabetes, 28 patients treated with ranibizumab had type I diabetes.

Study D2301 (RESTORE)

In study D2301 (RESTORE), a total of 345 patients with visual impairment due to macular oedema was randomised to receive either initial intravitreal injection of ranibizumab 0.5 mg as monotherapy and sham laser photocoagulation (n=116), combined ranibizumab 0.5 mg and laser photocoagulation (n=118), or sham** injection and laser photocoagulation (n=111). Treatment with ranibizumab was started with monthly intravitreal injections and continued until visual acuity was stable for at least three consecutive monthly assessments. The treatment was reinitiated when there was a reduction in best corrected visual acuity (BCVA) due to DME progression. Laser photocoagulation was administered at baseline on the same day, at least 30 minutes before the injection of ranibizumab, and then as needed based on Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.

Key outcomes are summarised in Tables 3 and 4 and Figure 3.

**Table 3 Primary Efficacy Outcomes at month 12 in study D2301 (RESTORE)
Visual acuity of the study eye (letters)**

Mean average change from Month 1 to Month 12 compared to baseline (Full analysis set / LOCF)

| Parameter | Statistic | Ranibizumab | Ranibizumab | Laser |
|---------------------------------|----------------------------|----------------------|-----------------------------|------------------|
| | | 0.5 mg N = 115 | 0.5mg + Laser N = 118 | Laser N = 110 |
| Baseline | n | 115 | 118 | 110 |
| | Mean (SD) | 64.7 (10.07) | 63.4 (9.99) | 62.6 (11.01) |
| | Median | 68.0 | 65.0 | 65.0 |
| | Min - Max | 38.0 - 81.0 | 38.0 - 79.0 | 36.0 - 78.0 |
| Average Month 1 to Month 12 | n | 115 | 118 | 110 |
| | Mean (SD) | 70.8 (10.53) | 69.2 (11.44) | 63.4 (12.26) |
| | Median | 73.7 | 71.5 | 66.2 |
| | Min - Max | 38.6 - 88.7 | 28.5 - 93.3 | 32.0 - 84.2 |
| Average change from baseline | n | 115 | 118 | 110 |
| | Mean (SD) | 6.1 (6.43) | 5.9 (7.92) | 0.8 (8.56) |
| | Median | 6.1 | 6.0 | 1.3 |
| | Min - Max | -10.9 - 25.2 | -26.7 - 27.6 | -37.8 - 26.8 |
| | 95% CI for mean (1) | (4.9, 7.3) | (4.4, 7.3) | (-0.8, 2.4) |
| Comparison vs. Laser | Difference in LS means (2) | 5.4 | 4.9 | |
| | 95% CI for difference (2) | (3.5, 7.4) | (2.8, 7.0) | |
| | p-value (3) | <.0001 | <.0001 | |

- n is the number of patients with a value for both baseline and average Month 1 to Month 12.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score

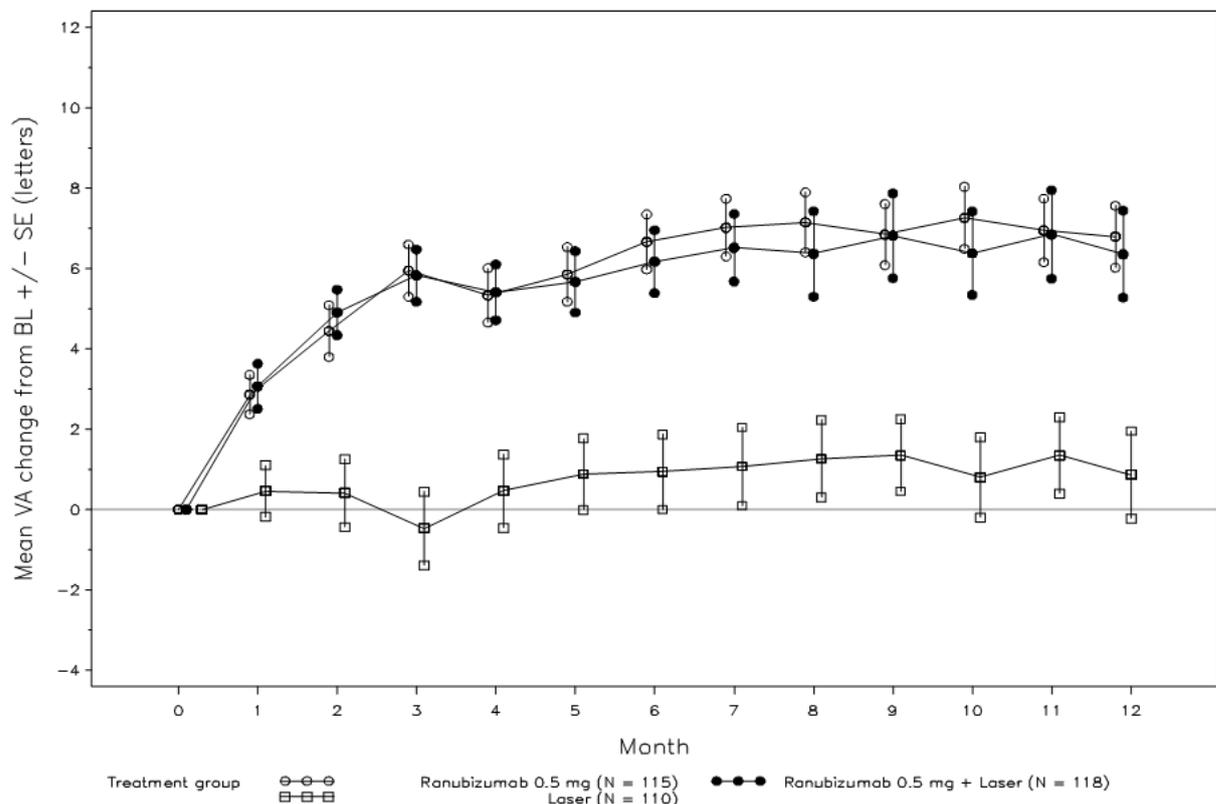
Table 4 Secondary Efficacy Outcomes at month 12 in study D2301 (RESTORE)

Visual acuity of the study eye (letters): Categorized change from baseline at Month 12 (FAS / LOCF)

| Categorized change from baseline | Ranibizumab 0.5 mg N = 115 | Ranibizumab 0.5mg + Laser N = 118 | Laser N = 110 |
|----------------------------------|----------------------------------|-----------------------------------------|------------------|
| N | 115 | 118 | 110 |
| Gain of ≥ 10 letters [1] | 43 (37.4) | 51 (43.2) | 17 (15.5) |
| Loss of ≥ 10 letters | 4 (3.5) | 5 (4.2) | 14 (12.7) |
| Gain of ≥ 15 letters [1] | 26 (22.6) | 27 (22.9) | 9 (8.2) |
| Loss of ≥ 15 letters | 1 (0.9) | 4 (3.4) | 9 (8.2) |

- N is the number of patients with a value at both baseline and the Month 12 visit.

- [1] specified gain, or BCVA of 84 letters or more

Figure 3 Mean BCVA change from baseline over time in study D2301 (RESTORE)***Study D2301E1 (RESTORE Extension)***

Study D2301E1 (RESTORE Extension) was an open-label, multi-center, 24-month extension study. 240 patients who had completed the 12-month core study entered the extension study and were treated with ranibizumab 0.5 mg pro re nata (PRN) in the same eye that was selected as the study eye in the core study. Treatment was re-initiated at monthly intervals upon a decrease in BCVA due to DME and continued until stable BCVA was reached. In addition, laser treatment was administered, if deemed necessary by the investigator, and based on ETDRS guidelines.

On average, 6.4 ranibizumab injections were administered per patient in the 24-month extension period in patients who were treated with ranibizumab, with or without laser treatment, in study D2301. Of the 74 patients from the core study laser treatment arm, 59 (80%) patients received ranibizumab at some point during the extension phase. On average, these 59 patients received 8.1 ranibizumab injections per patient over the 24 months of the extension study. The proportions of patients who did not require any ranibizumab treatment during the extension phase were 19%, 25% and 20% in the prior ranibizumab, prior ranibizumab + laser, and prior laser group, respectively.

Secondary outcome measures are summarized in Table 5.

Table 5 Outcomes at Month 36 in study D2301E1 (RESTORE Extension)

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

n is the number of patients with a value both at D2301 (RESTORE) baseline (Month 0) and at the Month 36 visit.

* Of the 74 patients with prior laser treatment, 59 (80%) patients received ranibizumab in the extension study

The long-term safety profile of ranibizumab observed in this 24-month extension study is consistent with the known Lucentis safety profile.

Study D2201 (RESOLVE)

In a supportive, partly exploratory study D2201 (RESOLVE), a total of 151 patients with macular centre involvement in at least one eye, including those with focal or diffuse DME, causing visual impairment were treated with ranibizumab (6 mg/mL, n=51, 10 mg/mL, n=51) or sham (n=49) by monthly intravitreal injections until pre-defined treatment stopping criteria were met. The initial ranibizumab dose (0.3 mg or 0.5 mg) could be doubled at any time during the study after the first injection if at the Month 1 visit, retinal thickness in the study eye remained $> 300 \mu\text{m}$; or if at any monthly visit after Month 1, retinal thickness in the study eye was $> 225 \mu\text{m}$ and reduction in retinal oedema from the previous assessment was $< 50 \mu\text{m}$. Laser photocoagulation rescue treatment was allowed from month 3 in both treatment arms.

The average injection doses in the 6 mg/mL group, 10 mg/mL group, and pooled group, were 0.47 mg, 0.76 mg and 0.62 mg, respectively. A total of 86% of patients in the ranibizumab

treated groups received doses of 0.5 mg/injection or higher, of which 69% received doses of 0.6 mg/injection or higher.

The study was comprised of two parts: an exploratory part (the first 42 patients analysed at months 6), and a confirmatory part (the remaining 109 patients analysed at months 12).

The exploratory analysis revealed no sign of a clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of this study therefore do not support the concept of dose doubling where response to the recommended dose is considered inadequate. Key outcomes from the confirmatory part of the study (2/3 patients) are summarised in Tables 6 and Figure 4.

Table 6 Overall Population, treatment comparisons key secondary efficacy variables; FAS (LOCF) of study D2201 (RESOLVE)

| Variable | Ran 6mg/mL (n=51) | Ran 10mg/mL (n=51) | Ran Pooled (n=102) | Sham (n=49) |
|----------------------------------------------------------------|----------------------|-----------------------|-----------------------|----------------|
| Gain \geq 15 letters [Δ BL to month 12] ¹ | 35.3% (n=18) | 29.4% (n=15) | 32.4% (n=33) | 10.2% (n=5) |
| Loss \geq 15 letters [Δ BL to month 12] ¹ | 0% | 5.9% (n=3) | 2.9% (n=2) | 20.4% (n=10) |
| Gain \geq 10 letters [Δ BL to month 12] ² | 72.5% (n=37) | 49.0% (n=25) | 60.8% (n=62) | 18.4% (n=9) |
| Loss \geq 10 letters [Δ BL to month 12] ² | 0% | 9.8% (n=5) | 4.9% (n=5) | 24.5% (n=12) |
| CRT μ m mean (SE) [Δ BL to month 12] ³ | -200.7 (17.11) | -187.6 (20.70) | -194.2 (13.38) | -48.4 (21.92) |
| CRT < 225 μ m (%) at month 12 ⁴ | 31.4% (n=16) | 39.2% (n=20) | 35.3% (n=36) | 10.2% (n=5) |

Δ BL = change from baseline

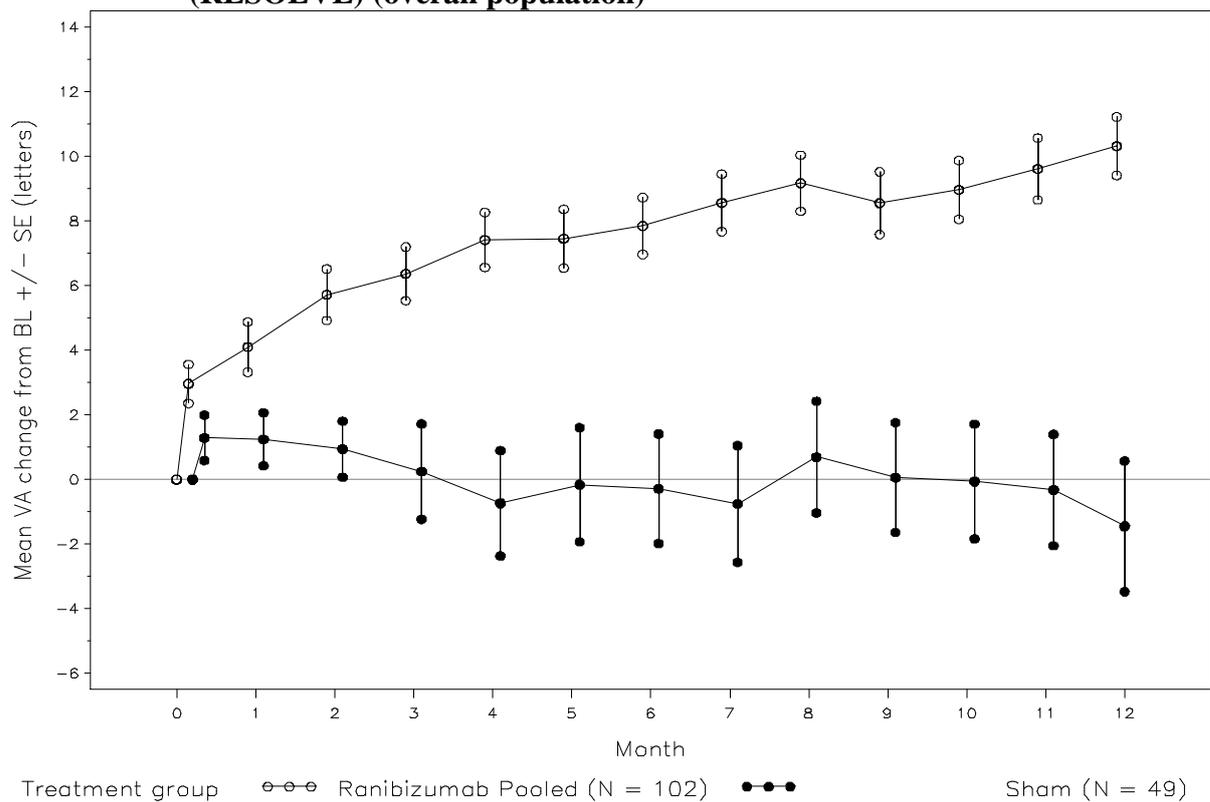
¹CMH test, stratified: 6 mg/mL vs sham p=0.0001; 10 mg/mL vs sham p=0.0037; and pooled p=0.0001

²CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p=0.0010; and pooled p<0.0001

³CMH test, stratified: 6 mg/mL vs sham p<0.0001; 10 mg/mL vs sham p<0.0001; and pooled p<0.0001

⁴CMH test, stratified: 6 mg/mL vs sham p=0.0108; 10 mg/mL vs sham p=0.0007; and pooled p=0.0011

Figure 4 Mean change in visual acuity from baseline over time in study D2201 (RESOLVE) (overall population)



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

Overall, ocular and non-ocular safety findings in DME patients of both studies D2201 and D2301 were comparable with the previously known safety profile observed in wet AMD patients.

Study D2303 (REVEAL)

The study D2303 (REVEAL), was a 12 month, randomized, double-masked Phase IIIb trial conducted in Asian patients. Similar to the RESTORE 12 month core study in trial design and inclusion/exclusion criteria, 390 patients with visual impairment due to macular oedema were randomized to receive either ranibizumab 0.5 mg injection as monotherapy and sham laser photocoagulation (n=133), ranibizumab 0.5 mg injection and laser photocoagulation (n=129), or sham injection and laser photocoagulation (n=128). Mean change in visual acuity at Month 12 compared to baseline were +6.6 letters in the ranibizumab monotherapy group, +6.4 letters in the ranibizumab plus laser group and +1.8 letters in the laser group. Overall, the efficacy and safety results of the REVEAL study in Asian DME patients are consistent with those of the RESTORE study in Caucasian DME patients.

Study D2304 (RETAIN)

In the phase IIIb study D2304 (RETAIN), 372 patients with visual impairment due to DME were randomized to receive intravitreal injection of either:

- ranibizumab 0.5 mg with concomitant laser photocoagulation on a ‘treat-and-extend’ (TE) regimen (n=121), or
- ranibizumab 0.5 mg monotherapy on a TE regimen (n=128), or
- ranibizumab 0.5 mg monotherapy on a pro re nata (PRN) regimen (n=123).

In all groups, treatment with ranibizumab was initiated with monthly intravitreal injections and continued until BCVA was stable for at least three consecutive monthly assessments. Laser photocoagulation was administered at baseline on the same day as the first ranibizumab injection and then as needed based on ETDRS criteria. On the ‘treat-and-extend’ (TE) regimen, ranibizumab was then administered, at scheduled treatment, at intervals of 2-3 months. On the PRN regimen, BCVA was assessed monthly and ranibizumab was then administered during the same visit, if needed. In all groups, monthly treatment was re-initiated upon a decrease in BCVA due to DME progression and continued until stable BCVA was reached again. The duration of the study was 24 months.

In the RETAIN study, after 3 initial monthly treatment visits, the number of scheduled treatment visits required by the TE regimen was 13 compared to the 20 monthly visits required by the PRN regimen. Over 24 months the mean (median) number of injections was 12.4 (12.0) in TE ranibizumab + laser, 12.8 (12.0) in TE ranibizumab alone, and 10.7 (10.0) for the PRN ranibizumab treatment groups. The addition of laser was not associated with a reduced mean number of ranibizumab injections in the TE regimen. On average, patients in both TE groups maintained BCVA over 24 months of treatment. In the TE groups, over 70% of patients had a visit frequency of ≥ 2 months.

Key outcome measures are summarised in Table 7.

Table 7 Outcomes in study D2304 (RETAIN)

| Outcome measure compared to baseline | TE Ranibizumab 0.5 mg + Laser n=117 | TE Ranibizumab 0.5 mg alone n=125 | PRN Ranibizumab 0.5 mg n=117 |
|------------------------------------------------------------------------|-------------------------------------|-----------------------------------|------------------------------|
| Mean average change in BCVA from Month 1 to Month 12 (SD) ^b | 5.9 (5.5) ^a | 6.1 (5.7) ^a | 6.2 (6.0) |
| Mean average change in BCVA from Month 1 to Month 24 (SD) ^c | 6.8 (6.0) | 6.6 (7.1) | 7.0 (6.4) |
| Mean change in BCVA at Month 24 (SD) ^c | 8.3 (8.1) | 6.5 (10.9) | 8.1 (8.5) |
| Gain of ≥10 letters or BCVA ≥84 (%) at Month 24 ^c | 43.6 | 40.8 | 45.3 |
| Gain of ≥15 letters or BCVA ≥84 (%) at Month 24 ^c | 25.6 | 28.0 | 30.8 |

^ap<0.0001 for assessment of non-inferiority to PRN

^b difference in BCVA over month 1 to month12 was a primary efficacy variable

^c outcomes up to 24 months were secondary efficacy variables

There was no difference in the BCVA or CRT outcomes of patients in RETAIN study who received or did not receive concomitant thiazolidinediones.

In DME studies, the improvement in BCVA was accompanied by a reduction over time in mean CRT in all the treatment groups.

Treatment of visual impairment due to macular oedema secondary to RVO

Study FVF4165g (BRAVO) and study FVF4166g (CRUISE)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to macular oedema secondary to RVO have been assessed in the randomised, double-masked, controlled studies BRAVO and CRUISE that recruited subjects with BRVO (n=397) and CRVO (n=392), respectively. In both studies, subjects received either 0.3 mg or 0.5 mg intravitreal ranibizumab or sham** injections. Patients were initially treated monthly for 6 months. Neither study compared a flexible versus fixed dosing regimen. Thereafter, treatment was given as needed following pre-specified re-treatment criteria. After 6 months, patients in the sham-control arms were crossed over to 0.5 mg ranibizumab. In BRAVO, laser photocoagulation as rescue was allowed in all arms from Month 3.

Laser therapy was not used as a comparative treatment. During the first six months, laser rescue treatment was administered to 27 (20.1%) patients in the ranibizumab 0.3 mg group, 28 (21.4%) in the ranibizumab 0.5 mg group and 76 (57.6%) in the sham group.

In the first six months, ranibizumab was given monthly. In the second six month period, all patients were given only ranibizumab as needed i.e. were given only active treatment as required (0.5mg monthly if previously on sham treatment) and at monthly intervals as

necessary, the latter determined by a best corrected visual acuity of 20/40 - or worse - or mean central subfield thickness ≥ 250 μm on optical coherence tomography.

Out of the 525 patients who received active treatment in the first 6 months, 501 patients entered into the observation period, with 87.2% (n=437) of them receiving at least one injection. Overall, patients received from 0 to 6 injections, with the lowest percentage of patients (10%) receiving 1 injection and the highest percentage of patients (20.8%) receiving 6 injections. The average number of injections was 3.3.

While numerically the better results were seen for 0.5 mg the differences between the two doses of Lucentis are not clinically significant. Key outcomes from BRAVO and CRUISE are summarised in Tables 8 and 9 and Figures 5 and 6.

Table 8 Outcomes at Month 6 and 12 (BRAVO)

| | Sham/Lucentis 0.5 mg (n=130) | Lucentis 0.3 mg (n=134) | Lucentis 0.5 mg (n=130) |
|-------------------------------------------------------------------------------------------------|---------------------------------------------|------------------------------------|------------------------------------|
| Mean change in visual acuity from baseline at Month 6 ^a (letters) (primary endpoint) | +7.3 | +16.6 | +18.3 |
| Mean change in visual acuity from baseline at Month 12 (letters) | +12.1 | +16.4 | +18.3 |
| Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 ^a | 28.8 % | 55.2% | 61.1 % |
| Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12 | 43.9 % | 56.0% | 60.3 % |
| Proportion of patients receiving laser rescue over 12 months | 61.4 % | 41.0% | 34.4 % |

^a p<0.0001

Figure 5 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (BRAVO)

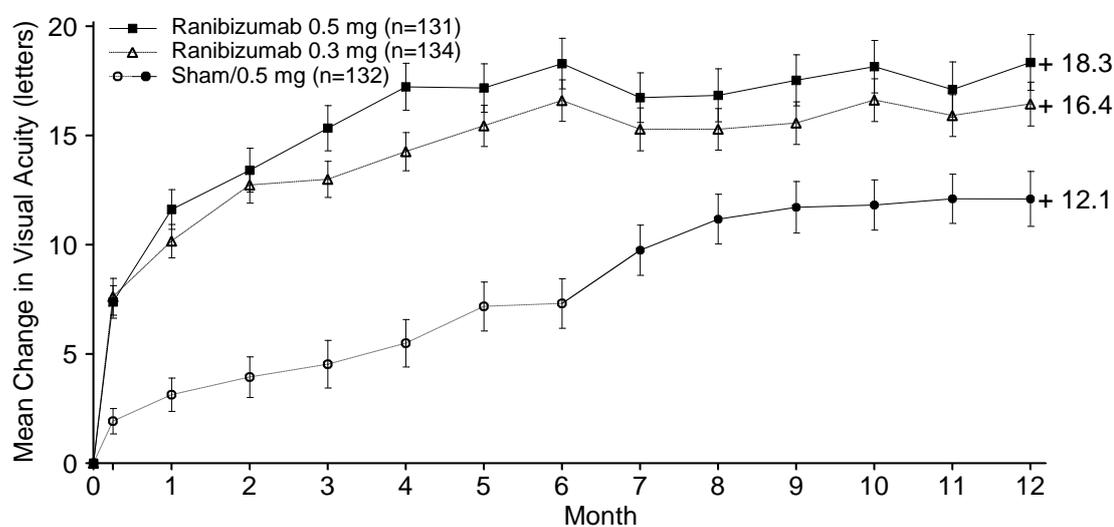
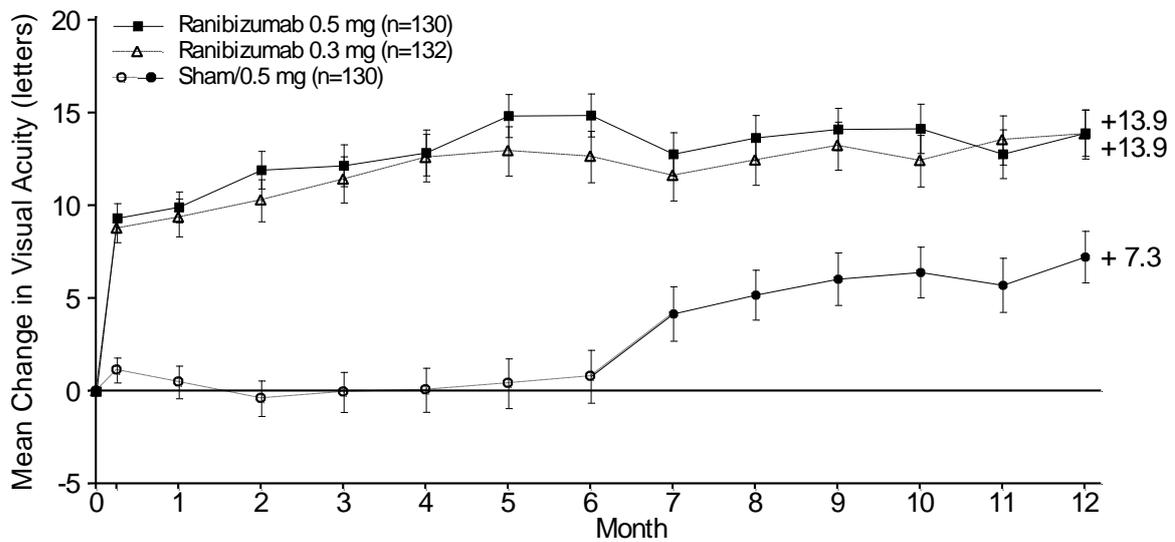


Table 9 Outcomes at Month 6 and 12 (CRUISE)

| | Sham/Lucentis 0.5 mg (n=130) | Lucentis 0.3 mg (n=132) | Lucentis 0.5 mg (n=130) |
|-----------------------------------------------------------------------------------------------|------------------------------------|-------------------------------|-------------------------------|
| Mean change in visual acuity from baseline at Month 6 (letters) ^a | +0.8 | +12.7 | +14.9 |
| Mean change in visual acuity from baseline at Month 12 (letters) | +7.3 | +13.9 | +13.9 |
| Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 6 ^a | 16.9 % | 46.2% | 47.7 % |
| Proportion of patients gained ≥ 15 letters in BCVA from baseline at Month 12 | 33.1 % | 47.0% | 50.8 % |

^a p<0.0001

Figure 6 Mean Change from Baseline BCVA over time to Month 6 and Month 12 (CRUISE)



In both studies, the improvement of vision was accompanied by a continuous decrease in the macular oedema as measured by central retinal thickness.

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

Efficacy and safety of Lucentis for treatment of visual impairment due to macular oedema secondary to RVO has not been evaluated beyond 12 months.

Treatment of visual impairment due to CNV

Study G2301 (MINERVA)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV secondary to etiologies other than nAMD and PM have been assessed in the pivotal study G2301 (MINERVA), which was randomized, double-masked, sham controlled for 2 months, followed by an open label extension of 10 months. Due to the multiple baseline etiologies involved, five subgroups (angioid streaks, post-inflammatory retinochoroidopathy, central serous chorioretinopathy, idiopathic chorioretinopathy, and miscellaneous etiology) were pre-defined for analysis. In this study, 178 patients were randomized in a 2:1 ratio to one of the following arms:

- ranibizumab 0.5 mg at baseline followed by an individualized dosing regimen driven by disease activity.
- sham injection at baseline followed by an individualized treatment regimen driven by disease activity.

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

Key outcomes from MINERVA are summarized in Tables 10 and 11 and Figure 7.

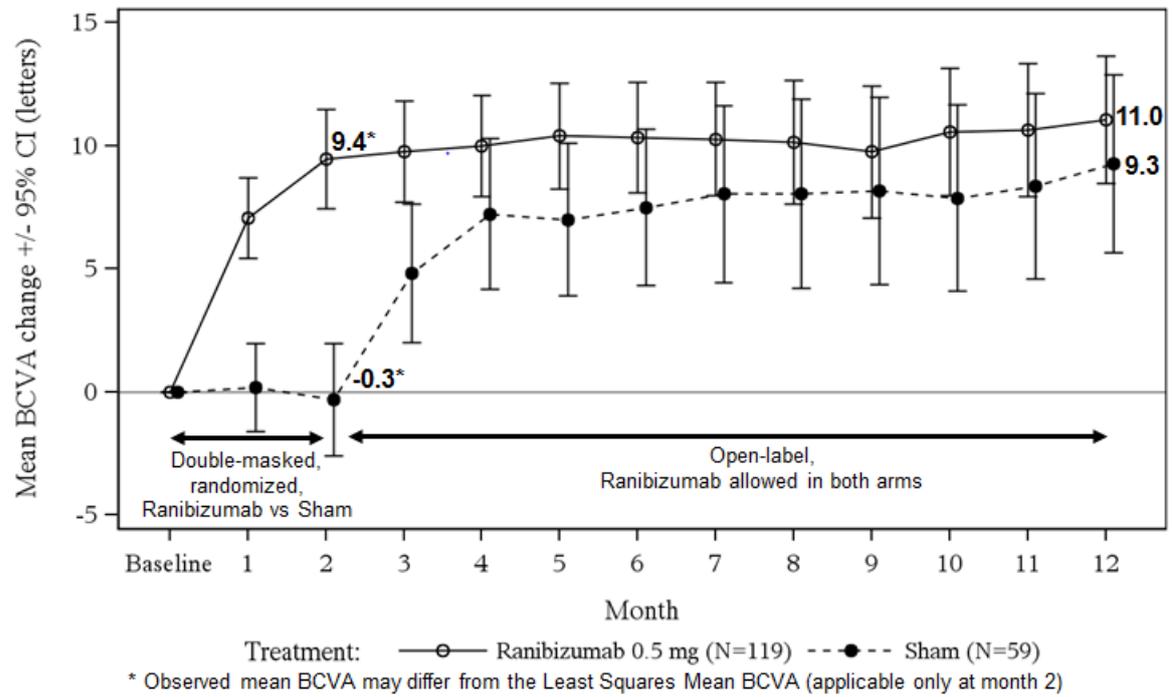
Table 10 Outcomes at Month 2 (MINERVA)

| | Ranibizumab 0.5 mg (n=119) | Sham (n=59) |
|----------------------------------------------------------------------------------------------|---------------------------------------|------------------------|
| Mean BCVA change from baseline to Month 2 (letters) (Least Squares Mean) ^a | +9.5 | -0.4 |
| Proportion of patients who gained ≥10 letters from baseline or reached 84 letters at Month 2 | 42.4% | 14.0% |
| Proportion of patients not losing >10 letters from baseline at Month 2 | 99.2% | 91.2% |
| Reduction in CSFT from baseline to Month 2 (Least Squares Mean) ^a | 77 μm | -9.8 μm |

CSFT=central subfield thickness

^a: One sided p<0.001 comparison with sham control

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



When comparing ranibizumab versus sham control at Month 2, a statistically significant treatment effect for patients in ranibizumab arm was observed.

Table 11 Overall treatment effect and treatment effect across baseline etiology subgroups for primary variable at Month 2 (MINERVA)

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

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

* number of patients with data available in the analysis

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

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

Pediatric patients

Five adolescent patients aged 12 to 17 years with visual impairment secondary to CNV received open-label treatment with ranibizumab 0.5 mg at baseline followed by an individualized treatment regimen based on evidence of disease activity (e.g. VA impairment, intra/sub-retinal fluid, hemorrhage or leakage). BCVA change from baseline to Month 12 improved in all five patients, ranging from +5 to +38 letters (mean of 16.6 letters). The improvement of vision was accompanied by a stabilization or reduction in central subfield thickness over the 12-month period. The mean number of ranibizumab injections given in the study eye over 12 months was three (see **PRECAUTION Children and Adolescents (below 18 years of age)**).

Treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to Pathologic myopia (PM)

Study F2301 (RADIANCE)

The clinical safety and efficacy of Lucentis in patients with visual impairment due to CNV in PM have been assessed based on the 12-month data of the randomized, double-masked, controlled pivotal study F2301 (RADIANCE) which was designed to evaluate two different dosing regimens of 0.5 mg ranibizumab given as intravitreal injection in comparison to verteporfin PDT (vPDT, Visudyne photodynamic therapy).

Patients with retinal detachment, cataract, pre-retinal membrane of the macula, history of panretinal or focal/grid laser photocoagulation with involvement of the macular area, history of intraocular treatment with any anti-VEGF or vPDT, history of intra-ocular surgery or treatment with corticosteroids in preceding 3 months were excluded from the trial.

A total of 277 eligible patients participated in the trial. The mean (SD) age of all randomized patients was 55.5 (13.94) years. At baseline, the mean (SD) BCVA was 55.4 (13.11) letters. The mean (SD) axial length was 29.07 (1.892) mm and the mean refraction-sphere was -12 diopters (range -6 to ~-30) at baseline. A total of 68.6% patients had subfoveal, 23.8% patients had juxtafoveal and 4.0% patients had extrafoveal lesions. The patients were randomised to the following three treatment groups:

- Group I (ranibizumab 0.5mg, dosing regimen driven by “stability” criteria defined as no change in BCVA compared to two preceding monthly evaluations)
- Group II (ranibizumab 0.5mg, dosing regimen driven by “disease activity” criteria defined as vision impairment attributable to intra-or-subretinal fluid or active leakage due to the CNV lesion as assessed by Optical Coherence Tomography (OCT) and/or Fluorescein Tomography (FA))
- Group III (vPDT - patients were allowed to receive ranibizumab treatment as of Month 3)

Over the 12 months of the study patients received on average 4.6 injections (range 1-11) in Group I and 3.5 injections (range 1-12) in Group II. In Group II (in which patients received the recommended treatment regimen based on disease activity, see **DOSAGE AND ADMINISTRATION**), 50.9% of patients required 1 or 2 injections, 34.5% required 3 to 5 injections and 14.7% required 6 to 12 injections over the 12-month study period. In Group II, 62.9% of patients did not require injections in the second 6 months of the study.

Key outcomes from RADIANCE are summarised in Table 12 and Figure 8.

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

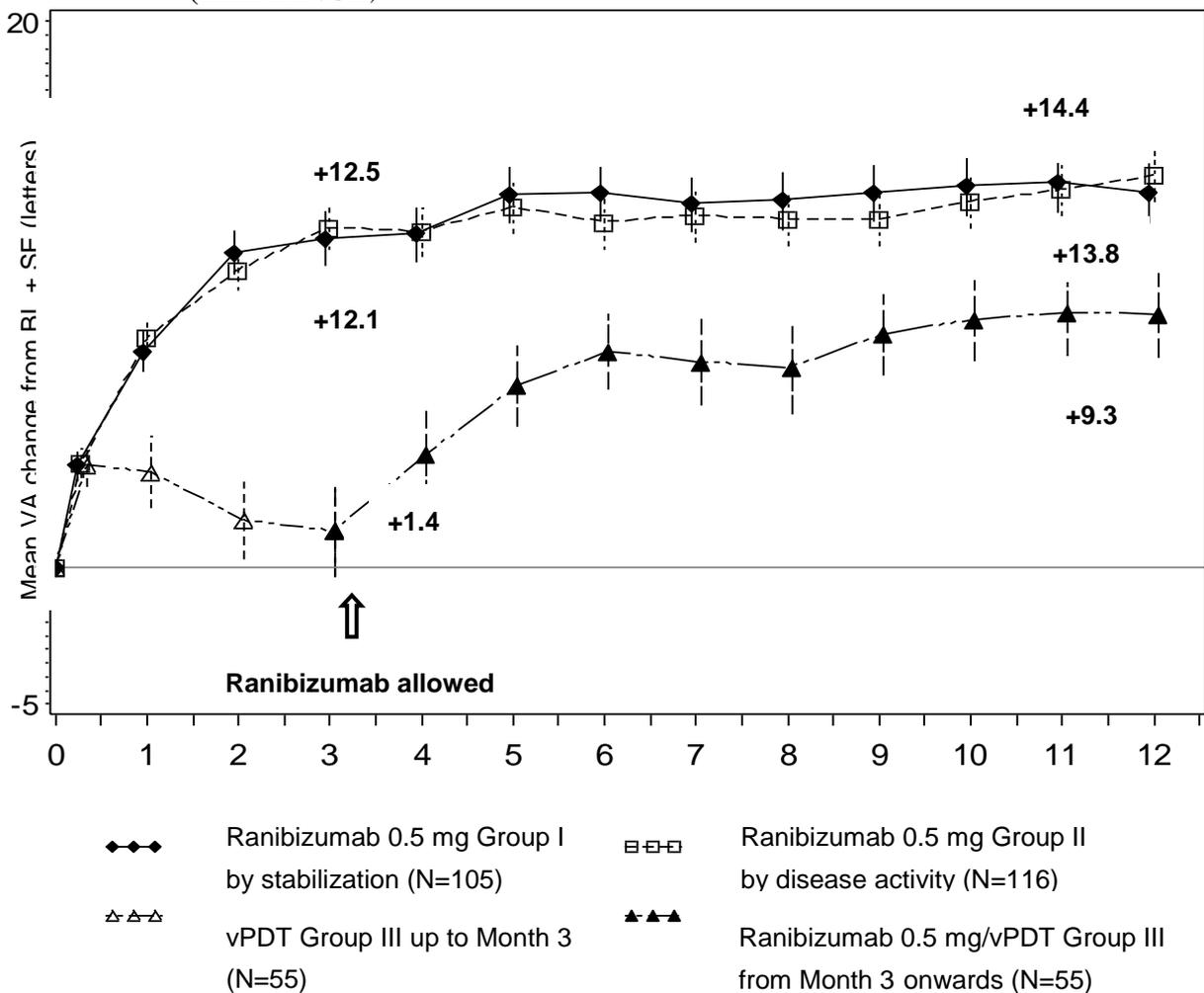
| | Group I Ranibizumab 0.5mg `visual acuity stability` (n=105) | Group II Ranibizumab 0.5mg `disease activity` (n=116) | Group III vPDT* (n=55) |
|----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------|
| Month 3 | | | |
| Mean average BCVA change from Month 1 to Month 3 compared to baseline ^a (letters) | +10.5 | +10.6 | +2.2 |
| Proportion of patients who gained | | | |
| ≥ 10 letters, or reached ≥ 84 letters in BCVA | 61.9 % | 65.5 % | 27.3 % |
| ≥ 15 letters, or reached ≥ 84 letters in BCVA | 38.1 % | 43.1 % | 14.5 % |
| Month 12 | | | |
| Number of injections up to Month 12: | | | |
| Mean | 4.6 | 3.5 | N/A |
| Median | 4.0 | 2.0 | N/A |
| Mean average BCVA change from Month 1 to Month 12 compared to baseline (letters) | +12.8 | +12.5 | N/A |
| Proportion of patients who gained | | | |

| | Group I Ranibizumab 0.5mg `visual acuity stability` (n=105) | Group II Ranibizumab 0.5mg `disease activity` (n=116) | Group III vPDT* (n=55) |
|-----------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------|------------------------------|
| ≥ 10 letters, or reached ≥ 84 letters in BCVA | 69.5 % | 69.0 % | N/A |
| ≥ 15 letters, or reached ≥ 84 letters in BCVA | 53.3 % | 51.7 % | N/A |

* Comparative control up to Month 3. Patients randomized to vPDT were allowed to receive ranibizumab treatment as of Month 3 (in Group III, 38 patients received ranibizumab from month 3 onwards)

a: p<0.00001 comparison with vPDT control

Figure 8 Mean change from Baseline BCVA over time up to Month 12 (RADIANCE)



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

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

The improvement of vision was accompanied by a reduction in central retinal thickness. Patient-reported benefits were observed with the ranibizumab treatment arms over vPDT (p-value <0.05) in terms of improvement in the composite score and several subscales (general vision, near activities, mental health and dependency) of the VFQ-25.

INDICATIONS

Lucentis (ranibizumab) is indicated in adults for:

- the treatment of neovascular (wet) age-related macular degeneration (AMD),
- the treatment of visual impairment due to choroidal neovascularisation,
- the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathologic myopia (PM)
- the treatment of visual impairment due to diabetic macular oedema (DME),
- the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with active or suspected ocular or periocular infections.
- Patients with active intraocular inflammation.

PRECAUTIONS

Intravitreal injection-related reactions

Intravitreal injections, including those with Lucentis, have been associated with endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, iatrogenic traumatic cataract and increased intraocular pressure (see **ADVERSE EFFECTS**). Symptoms of these adverse effects should be explained and the patient should be given a copy of the consumer medicine information document. The patient should be given contact details in the case of adverse effects.

Proper aseptic injection techniques must always be used when administering Lucentis. In addition, patients should be reviewed during the week following the injection to permit early treatment if an infection occurs. Patients should be instructed to report any symptoms suggestive of endophthalmitis or any of the above-mentioned events without delay.

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of injection of Lucentis (see **ADVERSE EFFECTS**). Sustained IOP increases have also been reported but the frequency is unclear. Both intraocular pressure and the perfusion of the optic nerve head must therefore be monitored and managed appropriately. Patients should be reviewed for IOP rise pre-injection and 60 minutes post-injection. The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of an intraocular pressure of ≥ 30 mmHg.

Bilateral treatment

Limited data on bilateral use of Lucentis (including same day administration) do not suggest an increased risk of systemic adverse events compared with unilateral treatment.

Arterial thromboembolic events

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

Immunogenicity

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

Patient populations with limited data

There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, proliferative diabetic retinopathy, or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is also no experience of treatment with Lucentis in diabetic patients with an HbA1c over 12% and uncontrolled hypertension.

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

Effects on Fertility

No study has been conducted to investigate the effects of ranibizumab on male or female fertility. In animal studies with bevacizumab, a closely related recombinant anti-VEGF monoclonal antibody, a reversible inhibition of ovarian function was observed in rabbits and cynomolgus monkeys following intravenous treatment. This finding is thought to be associated with inhibitory effects of bevacizumab on angiogenesis. The clinical relevance of this finding to Lucentis is unclear.

Use in Pregnancy (Category D)

For ranibizumab, no clinical data on exposed pregnancies are available. The potential risk for humans is unknown.

In pregnant monkeys, intravitreal ranibizumab treatment did not elicit developmental toxicity or teratogenicity, and had no effect on weight or structure of the placenta, at doses up to 1 mg/eye/fortnight, yielding systemic exposure levels estimated to be up to 58-times those expected clinically. However, based on its pharmacological effect ranibizumab should be regarded as potentially teratogenic and embryo-foetotoxic. For women who wish to

become pregnant and have been treated with ranibizumab, it is recommended to wait at least 3 months after the last dose of ranibizumab before conceiving a child.

The absence of ranibizumab-mediated effects on the embryo-foetal development is plausibly related to the expected inability of the Fab fragment to cross the placenta. Nevertheless, ranibizumab was detected in a foetus coincident with high maternal ranibizumab and anti-ranibizumab antibody serum levels, possibly because the anti-ranibizumab antibody acted as a (Fc region containing) carrier protein for ranibizumab, thereby decreasing its maternal serum clearance and enabling its placental transfer.

As the embryo-foetal development investigations were performed in healthy pregnant animals and disease (such as diabetes) may modify the permeability of the placenta towards a Fab fragment, ranibizumab should be used with caution in women of child bearing potential in general, and during pregnancy in particular.

Women of Childbearing Potential

Women of childbearing potential should use effective contraception during treatment (see **PRECAUTIONS Use in Pregnancy**).

Use in Lactation

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

Children and Adolescents (below 18 years of age)

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

Elderly (65 years and above)

No dose adjustment is required in the elderly.

Hepatic Impairment

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

Renal Impairment:

Dose adjustment is not needed in patients with renal impairment (see **PHARMACOLOGY, Pharmacokinetics**).

Carcinogenicity

No carcinogenicity studies were performed with ranibizumab.

Genotoxicity

No genotoxicity studies were performed with ranibizumab.

INTERACTIONS WITH OTHER MEDICINES

No formal interaction studies have been performed (see **CLINICAL TRIALS**).

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

For the adjunctive use of laser photocoagulation and Lucentis in DME and BRVO, see **CLINICAL TRIALS** and **DOSAGE AND ADMINISTRATION**.

Effects on Ability to Drive and Use Machines

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

ADVERSE EFFECTS

Wet AMD Population

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

Serious adverse events related to the injection procedure included endophthalmitis, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract (see **PRECAUTIONS**). The cumulative 2-year incidence of endophthalmitis (serious and non-serious) in the pooled pivotal trials (i.e. studies FVF2598g (MARINA), FVF2587g (ANCHOR), and FVF3192g (PIER)) was about 1%.

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

The adverse events listed in Table 12 occurred at a higher rate (at least 2 percentage points) in patients receiving treatment with Lucentis 0.5 mg than in those receiving control treatment (sham injection (see definition under **CLINICAL TRIALS**) or verteporfin photodynamic therapy (PDT)) in the pooled data of the three controlled wet AMD phase III studies. They were therefore considered potential adverse drug reactions. The safety data described below also include all adverse events suspected to be at least potentially related to the injection procedure or medicinal product in the 440 wAMD patients treated with 0.5 mg Lucentis. The adverse event rates for the 0.3 mg dose were comparable to those for 0.5 mg.

DME population

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

The event of urinary tract infection, in the common frequency category, met the criteria for the table above; otherwise ocular and non-ocular events in the RESOLVE and RESTORE trials were reported with a frequency and severity similar to those seen in the wet AMD trials.

Post-Registration Study in DME population

An analysis of 24-month data from two Phase III studies in DME, RIDE and RISE, is available. Both studies are randomised, sham-controlled studies of monthly intravitreal ranibizumab injections (0.5 mg or 0.3 mg) for a total of 36 months in patients with clinically significant macular oedema with centre involvement secondary to diabetes mellitus (type 1 or type 2). The patients are treated using a fixed dosing regimen which requires monthly injections as opposed to the approved individualised dosing regimen (see **DOSAGE AND ADMINISTRATION**). A total of 500 patients were exposed to ranibizumab treatment in the pooled studies (250 patients in each pooled ranibizumab 0.3mg and 0.5mg arm as well as the sham arm).

The pooled safety analysis showed a numerically higher, but not statistically significant, number of deaths and cerebrovascular events in the 0.5mg group as compared to the 0.3mg or sham groups. The stroke rate at 2 years was 3.2% (8/250) with 0.5mg ranibizumab, 1.2% (3/250) with 0.3mg ranibizumab, and 1.6% (4/250) with sham. Fatalities in the first 2 years occurred in 4.4% (11/250) of patients treated with 0.5mg ranibizumab, in 2.8% (7/250) treated with 0.3mg ranibizumab, and in 1.2% (3/250) of control patients.

RVO population

The safety of Lucentis was studied in two 12-month trials (BRAVO and CRUISE) conducted respectively in 264 and 261 ranibizumab-treated patients with visual impairment due to macular oedema secondary to BRVO and CRVO, respectively (see **CLINICAL TRIALS**). Ocular and non-ocular events in the BRAVO and CRUISE trials were reported with a frequency and severity similar to those seen in the wet-AMD trials.

CNV population

The safety of Lucentis was studied in a 12-month clinical trial (MINERVA), which included 171 ranibizumab-treated patients with visual impairment due to CNV (see **CLINICAL TRIALS**). The safety profile in these patients was consistent with that seen in previous clinical trials with Lucentis.

Pathologic Myopia (PM) population

The safety of Lucentis was studied in the 12-month clinical trial (RADIANCE), which included 224 ranibizumab-treated patients with visual impairment due to CNV secondary to PM (see **CLINICAL TRIALS**). Ocular and non-ocular events in this trial were reported with a frequency and severity similar to those seen in the wet-AMD trials.

Patients with PM have an increased risk for retinal detachment and retinal tear. No case of ‘retinal detachment’ was reported in the pivotal clinical trial (RADIANCE) in PM and three events coded as ‘retinal tear’ were reported. This incidence (1.3%) is higher than that seen in other approved indications for ranibizumab (0 to 1.1% in wet AMD, 0 to 0.8% in DME and in RVO) and consistent with the reporting rate for retinal tear described in Table 13.

Tabulated summary of adverse effects from clinical trials

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

Table 13 Adverse Effects from Clinical Trials

| | |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Infections and Infestations | |
| <i>Very common</i> | Nasopharyngitis |
| <i>Common</i> | Influenza, urinary tract infection* |
| Blood and lymphatic system disorders | |
| <i>Common</i> | Anaemia |
| Psychiatric disorders | |
| <i>Common</i> | Anxiety |
| Nervous system disorders | |
| <i>Very common</i> | Headache |
| <i>Common</i> | Stroke |
| Eye disorders | |
| <i>Very common</i> | Intraocular inflammation, vitritis, vitreous detachment, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, foreign body sensation in eyes, lacrimation increased, blepharitis, dry eye, ocular hyperaemia, eye pruritis. |
| <i>Common</i> | Retinal degeneration, retinal disorder, retinal detachment, retinal tear, detachment of the retinal pigment epithelium, retinal pigment epithelium tear, visual acuity reduced, vitreous haemorrhage, vitreous disorder, uveitis, iritis, iridocyclitis, cataract, cataract subcapsular, posterior capsule opacification, punctate keratitis, corneal abrasion, anterior chamber flare, vision blurred, injection site haemorrhage, eye haemorrhage, conjunctivitis, conjunctivitis allergic, eye discharge, photopsia, photophobia, ocular discomfort, eyelid oedema, eyelid pain, conjunctival hyperaemia. |
| <i>Uncommon</i> | Blindness, endophthalmitis, hypopyon, hyphaema, keratopathy, iris adhesions, corneal deposits, corneal oedema, corneal striae, injection site pain, injection site irritation, abnormal sensation in eye, eyelid irritation. |
| Respiratory, thoracic and mediastinal disorders | |
| <i>Common</i> | Cough |
| Gastrointestinal disorders | |
| <i>Common</i> | Nausea |
| Skin and subcutaneous tissue disorders | |
| <i>Common</i> | Allergic reactions (rash, urticaria, pruritis, erythema) |
| Musculoskeletal and connective tissue disorders | |
| <i>Very common</i> | Arthralgia |
| Investigations | |
| <i>Very common</i> | Intraocular pressure increase |

*Observed only in the DME population

A meta-analysis of pooled safety data from completed, randomized, double masked global studies showed a higher incidence rate of non-serious, non-ocular wound infection/inflammation in DME patients treated with ranibizumab 0.5 mg (1.85/100 PY; 20 events in 936 patients) compared to sham/laser treatment (0.27/100 PY; 2 events in 58 patients); HR 8.07 (95% CI 1.88, 34.74). The relationship to ranibizumab remains unknown.

DOSAGE AND ADMINISTRATION

Dosage

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

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

The recommended dose for Lucentis is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks.

The recommended maximal dose (0.5 mg) should not be exceeded. Post-injection monitoring is recommended (see **PRECAUTIONS**).

General target population

Treatment of wet AMD, visual impairment due to DME or due to macular oedema secondary to RVO, visual impairment due to CNV or due to CNV secondary to PM

Treatment is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

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

Treatment has been described with either fixed (e.g. monthly) or variable dosing regimens. Variable dosage regimens include 'pro re nata' (PRN) where patients are seen at regular intervals and the lesion is treated when it is active, and 'treat-and-extend' where the interval may be extended as described below.

If patients are being treated according to a treat-and-extend regimen, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by no more than two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. If disease activity recurs, the treatment interval should be shortened accordingly.

There was no sign of clinically relevant response to dose doubling (in terms of efficacy neither for visual acuity nor for central retinal thickness). The results of clinical studies do not support the concept of dose doubling where response to the recommended dose is considered inadequate (see **CLINICAL TRIALS**).

The treatment of visual impairment due to CNV should be determined individually per patient based on disease activity. In the treatment of visual impairment due to CNV secondary to Pathologic Myopia (PM), many patients may only need one or two injections during the first year, while some patients may need more frequent treatment (see **CLINICAL TRIALS**).

Lucentis and laser photocoagulation in DME and Branch RVO (BRVO)

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

Lucentis and Visudyne photodynamic therapy in CNV secondary to PM

There is no experience in using Lucentis in combination with Visudyne.

Mode of Administration

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

The injection procedure should be carried out under aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent). Sterile paracentesis equipment should be available as a precautionary measure. The patient's medical history should be carefully evaluated for hypersensitivity reactions prior to performing the intravitreal procedure (see **CONTRAINDICATIONS**). Adequate anaesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface should be administered prior to the injection.

For information on preparation of Lucentis, see **Instructions for Use and Handling**.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe. The

injection volume of 0.05 mL is then delivered; the scleral site should be rotated for subsequent injections.

Instructions for Use and Handling

Vial

Vials are for single use only (see Dosage and administration). The vial is sterile. After injection any unused product must be discarded.

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 discoloured, cloudy, or contains particulates.

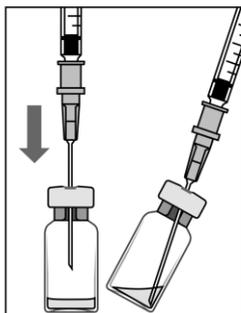
For preparation and intravitreal injection, the following single-use medical devices are needed:

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

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

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

A.

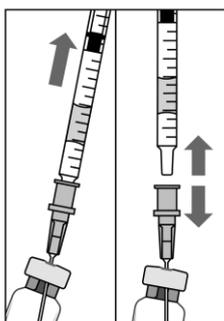


1. Before withdrawal, the outer part of the rubber stopper of the vial should be disinfected.

2. Attach a 5 μ m filter needle (18G) to a 1 mL syringe using an 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.



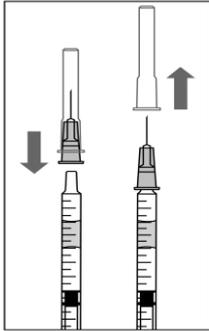
4. Ensure that the plunger rod is drawn back sufficiently when emptying the vial in order to completely empty the filter needle.

5. Leave the blunt filter needle in the vial and disconnect the syringe from the blunt filter needle. The filter needle should be discarded after withdrawal of the vial contents and should not be used for the intravitreal injection.

C.

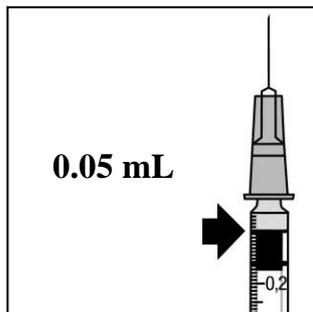
6. Aseptically and firmly attach an injection needle (30G x 1/2 inch) onto the syringe.

7. Carefully remove the cap from the injection needle without disconnecting the injection needle from the syringe.



Note: Grip at the yellow hub of the injection needle while removing the cap.

D.



8. Carefully expel the air from the syringe and adjust the dose to the 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.

After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.

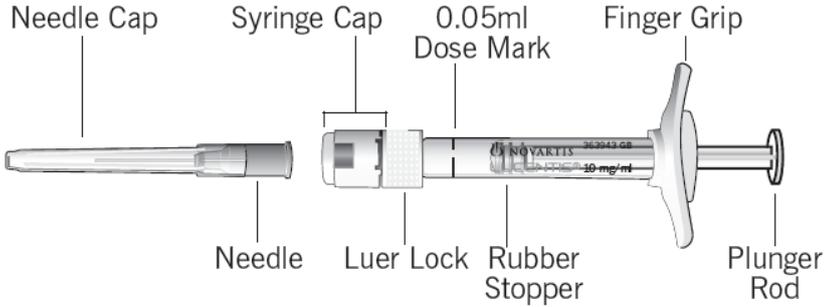
Pre-filled syringe pack

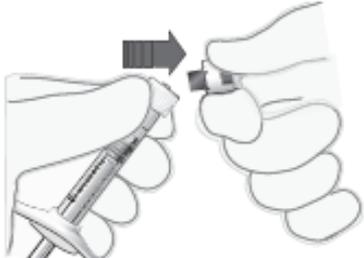
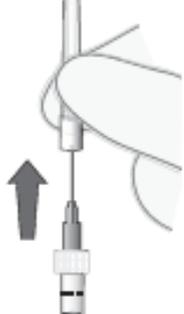
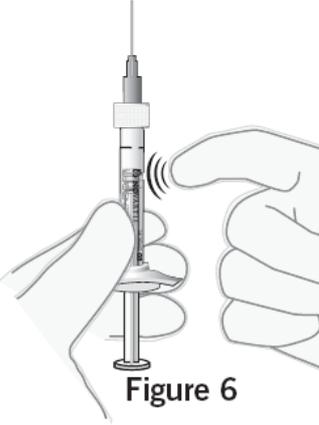
The pre-filled syringe is for single use only (see Dosage and administration).

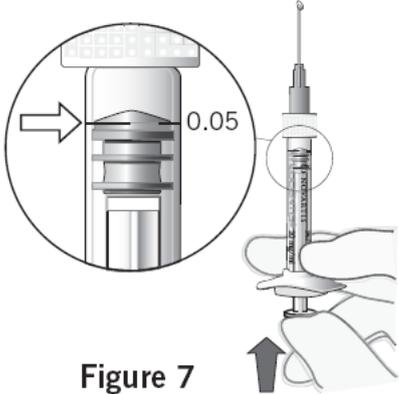
The pre-filled syringe is sterile. Do not use the pre-filled syringe if the packaging is damaged. The sterility of the pre-filled syringe cannot be guaranteed unless the tray remains sealed. Do not use the pre-filled syringe if the solution is discoloured, cloudy, or contains particulates.

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

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

| Heading | Instructions | Diagram/Image |
|---------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| | <p>Read all the instructions carefully before using the pre-filled syringe.</p> <p>The pre-filled syringe is for single use only. The pre-filled syringe is sterile. Do not use the product if the packaging is damaged. The opening of the sealed tray and all subsequent steps should be done under aseptic conditions.</p> <p>Note: The dose must be set to 0.05 mL</p> | |
| Pre-filled syringe description |  <p style="text-align: center;">Figure 1</p> | |
| Prepare | <ol style="list-style-type: none"> 1. Make sure that your pack contains: <ul style="list-style-type: none"> • a sterile pre-filled syringe in a sealed tray. 2. Peel the lid off the syringe tray and, using aseptic technique, carefully remove the syringe. | |
| Check syringe | <ol style="list-style-type: none"> 3. Check that: <ul style="list-style-type: none"> • the syringe cap is not detached from the Luer Lock. • the syringe is not damaged. • the drug solution looks clear, colourless to pale yellow and does not contain any particulates. 4. If any of the above is not true, discard the pre-filled syringe and use a new one. | |

| Heading | Instructions | Diagram/Image |
|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Remove syringe cap | 5. Snap off (do not turn or twist) the syringe cap (see Figure 2). 6. Dispose of the syringe cap (see Figure 3). |  Figure 2  Figure 3 |
| Attach needle | 7. Attach a 30G x 1/2 inch sterile injection needle firmly onto the syringe by screwing it tightly onto the Luer Lock (see Figure 4). 8. Carefully remove the needle cap by pulling it straight off (see Figure 5). Note: Do not wipe the needle at any time. |  Figure 4  Figure 5 |
| Dislodge air bubbles | 9. Hold the syringe upright. 10. If there are any air bubbles, gently tap the syringe with your finger until the bubbles rise to the top (see Figure 6). |  Figure 6 |

| Heading | Instructions | Diagram/Image |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Set dose | <p>11. Hold the syringe at eye level and carefully push the plunger until the edge below the dome of the rubber stopper is aligned with the dose mark (see Figure 7).</p> <ul style="list-style-type: none"> This will expel the air and the excess solution and set the dose to 0.05 mL. <p>Note: the plunger rod is not attached to the rubber stopper – this is to prevent air being drawn into the syringe.</p> |  <p>Figure 7</p> |
| Inject | <p>The injection procedure should be carried out under aseptic conditions.</p> <p>12. The injection needle should be inserted 3.5 - 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the centre of the globe.</p> <p>13. Inject slowly until the rubber stopper reaches the bottom of the syringe to deliver the volume of 0.05 mL.</p> <p>14. A different scleral site should be used for subsequent injections.</p> <p>15. After injection, do not recap the needle or detach it from the syringe. Dispose of the used syringe together with the needle in a sharps disposal container or in accordance with local requirements.</p> | |

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

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

OVERDOSAGE

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

In clinical trials doses up to 2 mg of ranibizumab in an injection volume of 0.05 mL to 0.10 mL have been administered to patients with wet AMD and DME. The type and frequency of ocular and systemic adverse events were consistent with those reported for the 0.5 mg (in 0.05 mL) Lucentis dose.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Vial pack

Lucentis is supplied as 0.23 mL solution for injection in glass vials (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial, one filter needle for withdrawal of the vial contents, one needle for intravitreal injection and one syringe for withdrawal of the vial contents and for intravitreal injection. Each vial contains 2.3 mg of ranibizumab in 0.23 mL solution.

Vial and filter needle pack*

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

Vial only*

Lucentis is supplied as 0.23 mL solution for injection in glass vials (colourless type I glass) with chlorobutyl rubber stopper. One pack contains one vial.

Pre-filled syringe pack

Lucentis is supplied as 0.165 mL sterile solution in a pre-filled syringe (type I glass) with a bromobutyl rubber plunger stopper and a syringe cap consisting of a white, tamper-evident rigid seal with a grey bromobutyl rubber tip cap and a Luer Lock adapter. The pre-filled syringe has a plunger rod and a finger grip, and is packed in a sealed tray. One pack contains one pre-filled syringe. Each pre-filled syringe contains 1.65 mg of ranibizumab in 0.165mL solution.

*Not all presentations may be marketed.

Storage:**Vial**

Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.

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

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

Pre-filled syringe pack

Store at 2°C to 8°C (refrigerate - do not freeze). Protect from light.

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

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

POISON SCHEDULE OF THE MEDICINE

Poisons Schedule: Schedule 4

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER
OF THERAPEUTIC GOODS (THE ARTG)**

27 February 2007

DATE OF MOST RECENT AMENDMENT

22 August 2017

® = Registered trademark

Internal document code

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