



North Shore Eye Centre

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Clinical Trials of Ranibizumab (Lucentis)

VEGF-A is a protein that is believed to be the main form of vascular endothelial growth factor (VEGF) involved in angiogenesis (the formation of new blood vessels) as well as and vascular permeability (the ability of blood vessels to allow passage of fluids and molecules) in the wet form of macular degeneration.

Ranibizumab is a humanised monoclonal antibody fragment that is designed to bind to and inactivate all forms of VEGF-A. Anti-VEGF therapy by means of Ranibizumab injection suppresses the effect produced by VEGF-A and as a result inhibits the development of new blood vessels under the retina and leakage that leads to the progression of macular degeneration. Ranibizumab appears to be effective for all the types of wet AMD and for all lesion sizes.

Ranibizumab is being investigated in studies for the treatment of macular degeneration. The MARINA and ANCHOR trials were designed to evaluate the effectiveness and safety of treatment with Ranibizumab. Both studies have demonstrated positive outcomes for treatment of neovascular AMD with Ranibizumab. The impressive clinical trial results indicate an encouraging chance of stabilising or gaining vision, with a very low incidence of ocular or systemic side effects, providing reassurance of safety concerns.

Ranibizumab is proven to be safe and clinically effective by controlled trials. Results have indicated that Lucentis is dramatically more effective than any other treatment. In two phase 3, randomised clinical trials, results indicated that approximately 95% of the participants with AMD that received monthly injections maintained their vision, losing less than 15 letters in 12 months compared to about 60% of patients who received the control treatment. In addition up to 40% of participants demonstrated improvements in vision of at least 15 letters (3 lines) at 12 months.

The MARINA Study

The MARINA Study Group, a total of 716 patients were enrolled in this 2 year study. The study involved monthly injections of Lucentis 0.3mg (in 238 patients), 0.5mg (in 240 patients) or sham injections (in 238 patients).

The results indicated that approximately 95% of patients receiving Ranibizumab lost less than 15 letters, as opposed to 62.2% of the sham group that lost less than 15 letters, at 12 months. In addition, up to 34% of the patients receiving Ranibizumab had an improvement in vision of 15 letters or more, compared to 4.6% of the sham group that did so at 12 months (refer to figure 1). Mean visual acuity improved by 6.5 letters in the 0.3 mg group and by 7.2 letters in the 0.5 mg group. In contrast, vision reduced by 10.4 letters in the sham-injection group.



Ranibizumab injections were tolerated well and the benefits in the visual acuities were maintained during the 24-month period of the study. The 12 month safety results indicated very low incidences of ocular side effects, which included Endophthalmitis, uveitis, retinal tear, vitreous haemorrhage, lens damage. Systemic side effects included hypertension, myocardial infarction and stroke but were also uncommon.

Summary

Intraocular administration of Ranibizumab for 24 months inhibited the growth of lesions as well as the leakage. It prevented vision loss and improved mean levels of vision with low incidences of ocular adverse events. The overall incidence of any nonocular adverse event was similar among all 3 groups.

	Lucentis 0.3 mg (n= 238)	Lucentis 0.5 mg (n=238)	Sham (n= 240)
% of patients losing < 15 letters	94.5 %	94.6 %	62.2 %
% of patients gaining 15 + letters	24.8 %	33.8 %	4.6 %

Figure 1. Phase III MARINA Study: Percentages of patients at 12 months with visual outcomes measured by the ETDRS chart.

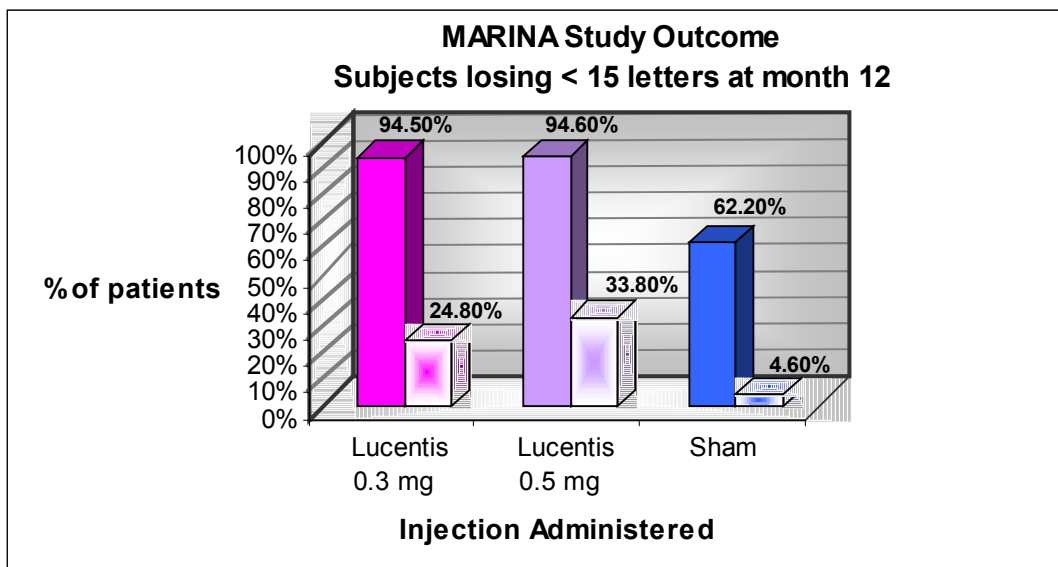


Figure 2. MARINA Study – Percentages of patients at 12 months. Single coloured columns represent the percentages of patients maintaining vision, losing 15 or less letters, measured by the ETDRS eye chart. Shaded columns represent the percentages of patients gaining 15 or more letters.



The ANCHOR Study

The ANCHOR study compared Ranibizumab with Verteporfin photodynamic therapy (PDT) in treating macular degeneration. This study enrolled a total of 423 patients, of which 143 received PDT, 140 patients received 0.3mg Ranibizumab, and 140 patients received 0.5 mg Ranibizumab. Patients were randomised to receive intravitreal injections of Ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin PDT monthly or intravitreal sham injections plus PDT every 3 months, for 24 months.

The results of the study indicated that 94-96% of patients receiving Ranibizumab lost fewer than 15 letters, compared to 64.3 % of patients in the PDT group. The level of vision improved by 15 letters or more in 36-40 % of the patients receiving Ranibizumab, and by 5.6 % in the PDT group (refer to figure 3). Mean visual acuity improved by 8.5 letters in the 0.3 mg group and by 11.3 letters in the 0.5 mg group. However, in the PDT group vision decreased by 9.5 letters.

The safety results indicated minimal incidence of adverse events. Adverse events included subconjunctival haemorrhage, eye pain, raised intraocular pressure and vitreous floaters. Serious adverse events were infrequent. Within the group of 140 patients receiving 0.5 mg of Ranibizumab, 2 developed endophthalmitis and 1 developed serious uveitis.

Summary

The study demonstrated statistically and clinically significant superior results of Ranibizumab compared to the PDT group, with a decrease in angiographic leakage, low incidence of ocular adverse events and no apparent systemic safety concerns.

	Lucentis 0.3 mg (n=140)	Lucentis 0.5 mg (n=140)	Sham (n= 143)
% of patients losing < 15 letters	94.3 %	96.4 %	64.3 %
% of patients gaining 15 + letters	35.7 %	40.3 %	-9.5 %

Figure 3. Phase III ANCHOR Study Results: Percentages of patients at 12 months with visual outcomes measured by the ETDRS chart.

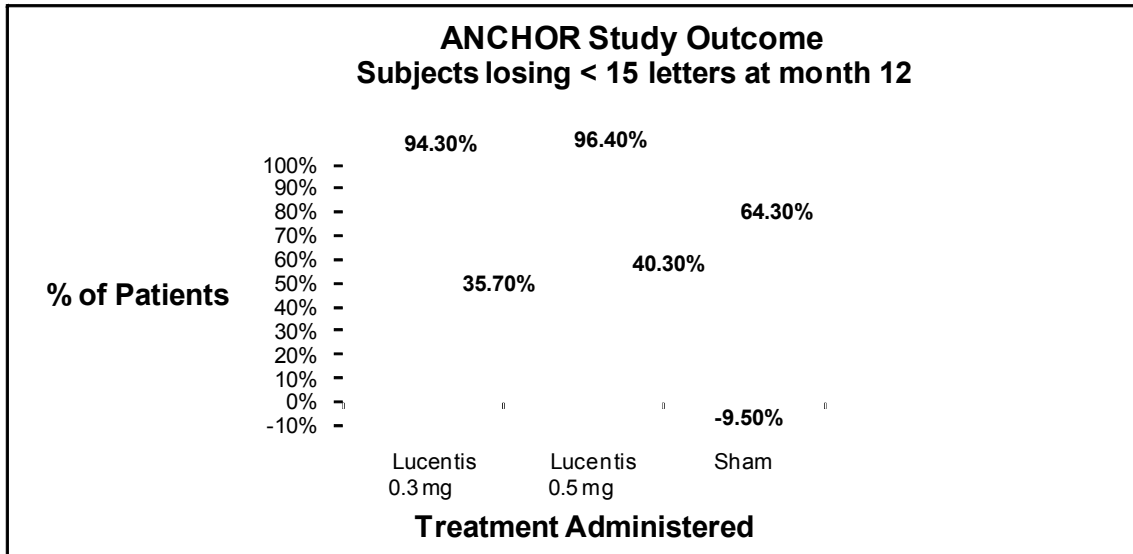


Figure 2. ANCHOR Study – Percentages of patients at 12 months, Shaded columns represent the percentages of patients gaining 15 or more letters. Single coloured columns represent the percentages of patients maintaining vision, losing less than 15 letters measured by the ETDRS eye chart.

The PIER Study

The PIER is another phase 3 study. It was designed to study the outcome of increasing the intervals between each injection. It aimed to demonstrate the benefit of administering 3 monthly injections followed by quarterly injections. The patients receiving Ranibizumab experienced an initial improvement in visual acuity, however this was not maintained throughout the following quarterly injections of Ranibizumab. Although the study indicated beneficial effects, it did not achieve an outcome reaching the visual gains obtained by the monthly injection regimens and the larger dosages.

There are several other studies that have been performed or are being designed to investigate the safety of administering Ranibizumab, as well as to clarify the ideal dosing regimen and determine the effect of varying the frequency of administering the injections.

