



TITLE: Long-Term Use of Ranibizumab for the Treatment of Age-Related Macular Degeneration: A Review of the Clinical and Cost-Effectiveness and Guidelines

DATE: 11 March 2014

CONTEXT AND POLICY ISSUES

Age-related macular degeneration (AMD) is a common cause of vision loss and blindness in elderly patients around the world.¹ Ranibizumab is a recombinant human monoclonal antibody fragment targeted against vascular endothelial growth factor-A (VEGF-A) and is indicated for the treatment of neovascular (wet) AMD.² Patients receive intravitreal injections of ranibizumab 0.5 mg (0.05 mL) once a month. After the first three injections treatment may be reduced to once every three months if monthly dosing is not feasible.²

In 2008, the Canadian Expert Drug Advisory Committee (CEDAC) recommended “that ranibizumab be listed for the treatment of neovascular AMD when drug plan coverage is limited to a maximum of 15 vials per patient used to treat the better seeing affected eye.”² In the same year, the National Institute for Health and Clinical Evidence (NICE)³ in the UK made a similar recommendation regarding coverage of ranibizumab for AMD and determined the treatment was cost-effective if the manufacturer were to pay for any drug costs beyond 14 injections in the treated eye.

The purpose of this review is to evaluate the clinical evidence, cost information, and guidelines to determine if there is evidence to support dosing regimens of 15 or more injections of ranibizumab for the treatment of AMD.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of the long-term use of ranibizumab for the treatment of age-related macular degeneration?
2. What is the cost-effectiveness of the long-term use of ranibizumab for the treatment of age-related macular degeneration?
3. What are the evidence-based guidelines regarding the long-term use of ranibizumab for the treatment of age-related macular degeneration?

KEY FINDINGS

Treatment of AMD with ranibizumab and bevacizumab appeared to have similar effects on visual acuity. Monthly dosing with ranibizumab resulted in a greater gain in visual acuity than as needed dosing. In long-term follow-up, ranibizumab was well-tolerated for 4 or more years and remained more effective than no treatment.

Incremental cost-effectiveness ratios (ICERs) were reported in two cost studies. Treatment with monthly ranibizumab was dominated by monthly bevacizumab. The results varied depending on the dosing regimen and length of treatment with the drugs. However, bevacizumab does not have a Health Canada indication for the treatment of AMD.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies, guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and February 7, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	patients with neovascular (wet) age-related macular degeneration (AMD)
Intervention	15 or more doses of ranibizumab (Lucentis)
Comparator	Fewer than 15 doses of ranibizumab bevacizumab (Avastin) – off-label use no comparator
Outcomes	Clinical benefit (change in visual acuity) Safety and harms Cost-effectiveness Guidelines and recommendations (length/frequency of dosing)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, economic studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008.

Critical Appraisal of Individual Studies

The included the randomized studies were critically appraised using the Downs and Black instrument,⁴ and the included economic studies were assessed using the Drummond checklist.⁵ Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 593 citations were identified in the literature search. Following screening of titles and abstracts, 563 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 26 publications were excluded for various reasons, while seven publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Study Design

One multicenter RCT,⁶ one non-randomized, open-label, multicenter extension study,⁷ two cost-effectiveness analyses,^{8,9} and three cost-utility analyses¹⁰⁻¹² examining the use of 15 or more doses of ranibizumab were included in the review.

Country of Origin

All seven studies⁶⁻¹² included in the review were conducted in the United States.

Patient Population

The clinical studies included adult patients with eyes that had active choidal neovascularization secondary to AMD.^{6,7} The patient populations for the cost studies were created using patient data from previously published clinical trials^{11,12} or were hypothetical patient cohorts treated with the protocols of previously published trials.^{8,9} One study used characteristics of patients from their clinical institution to input into the model.¹⁰

Interventions and Comparators

Ranibizumab was compared with bevacizumab,^{6,8-10} best supportive care,¹² sham treatment (no treatment),¹¹ or had no comparative treatment group.⁷

Mean Number of Injections

In the Martin study,⁶ only patients who were in the monthly ranibizumab or monthly bevacizumab for the full two years definitely received an average number of injections greater than 15 over the two years. Patients who were initially randomized to receive ranibizumab in the original RCT received a mean of 27.8 (SD = 5.4) injections of ranibizumab by the end of the HORIZON study.⁷ Patients who crossed over to ranibizumab treatment after the previous RCT or did not receive ranibizumab received fewer than 15 injections.

Outcomes

The main clinical outcomes were mean change in visual acuity and incidence and severity of ocular and non-ocular adverse events.^{6,7} The cost studies reported costs per quality-adjusted life year⁹⁻¹² and incremental cost-effectiveness ratios.^{8,10}

Characteristics of Economic Studies

Four cost studies were undertaken from the payer perspective⁹⁻¹² and one from the societal perspective.⁸ Analyses were conducted over time horizons of five,¹² 10,⁹ 12,¹¹ and 20 years.^{8,10} All studies used an annual discount rate of 3%. Willingness-to-pay thresholds of \$50,000 per quality-adjusted life year (QALY)^{9,10,12} and \$100,000 per QALY^{8,11} were used to evaluate cost-effectiveness.

Summary of Critical Appraisal

The strengths and limitations of the included studies are summarized in Appendix 3.

Inclusion criteria, study interventions, and outcome measures were well described in the included clinical studies.^{6,7} In the Martin study⁶ image graders, visual acuity examiners and the medical monitor were blinded to both the drug and dosing regimen. Ophthalmologists were blinded to the study drug but not the dosing regimen and the clinic coordinators were not blinded at all. It is possible that patients enrolled in the Martin study were able to discern which treatment they were receiving based on insurance forms they were provided that indicated if

they were receiving ranibizumab as part of the study. At the end of the study, 36.7% of patients indicated they were aware of which study drug they had been receiving and more than 97% of those patients were correct in identifying their study group. The re-allocation of some patients to new treatment groups at the end of year one resulted in six smaller treatment groups which may have lowered the statistical power of the analyses. Because of the re-allocation, the efficacy analyses were based only on data from year two of the study. Adverse events were reported only by study drug, not by dosing regimen. It is possible that patients who were switched from monthly to as needed treatment received more than 15 injections; however, the means were reported by year and were not cumulative.

All participants in the HORIZON⁷ study were aware of treatment and dosing schedules as it was an open-label, observational follow-up of patients who had previously completed a randomized study and re-treatment was at the discretion of the investigator. The “as needed” nature of the dosing schedule in this study may have introduced selection bias. Because retreatment was at the discretion of the treating physician, and there was no set follow-up regimen, patients with better visual acuity likely did not require as much retreatment and may not have been followed as closely or treated as often as those patients with worse visual acuity. As needed dosing may have contributed to undertreating patients in comparison to the dosing schedules indicated in clinical guidelines and general clinical practice at the end of the study.

The research questions, interventions, comparators, perspectives, outcomes, costs, discounting rates, and time horizons were well described for the included cost studies.⁸⁻¹² For all of the cost studies, relatively short term clinical data was extrapolated and used to populate long-term clinical and safety outcomes. The authors indicated that the clinical data used to populate the models might not accurately represent a real-world clinical population and could impact true costs incurred over time.^{8,9,11} When accounting for the costs of safety events, the assumption was made that the all adverse events were treatment-related.⁹ In the Patel study,¹⁰ the authors identified a high degree of heterogeneity between the studies they used to create their efficacy estimates. Additionally, their assumption of continuous treatment through the 20 year time horizon may have inflated treatment benefit, and both treatment and drug costs. The patient population assessed in the Stein study⁸ differed substantially to the other cost studies, with 80 year old patients modelled over a 20 year time horizon. The resulting incremental cost-effectiveness ratio (ICER) of greater than \$10,000,000 per QALY differed substantially from the other studies, which used younger patient populations in their models.

Summary of Findings

A summary of study findings is provided in Appendix 4.

What is the clinical effectiveness of the long-term use of ranibizumab for the treatment of age-related macular degeneration?

Visual Acuity

In year two of the Martin study,⁶ six treatment groups existed. Patients received either two years of monthly ranibizumab, monthly bevacizumab, as needed ranibizumab, as needed bevacizumab, or were switched from monthly ranibizumab or bevacizumab to as needed treatment with the same drug. Mean visual acuity at two years was not significantly different between all groups. For patients whose dosing regimen was reassigned at one year, mean visual acuity for patients remaining on monthly treatment did not show significant change from

year one. In the groups switched from monthly to as needed dosing, mean letter losses were significantly different between the ranibizumab and bevacizumab groups (-1.8 vs -3.6; $P = 0.03$). At two years, as needed dosing (mean number of dosing < 15) resulted in a mean gain of 2.4 letters less than monthly dosing (mean number of injections >15) ($P = 0.046$). Visual acuity for those who were switched to as needed dosing after year one was similar to those who received as needed dosing for the whole study.

In the HORIZON study,⁷ patients who were initially randomized to ranibizumab (mean number of injections = 27.8) had a mean change in visual acuity from baseline of the initial study of 9.0 letters at 24 months, 4.1 letters at 36 months, 2.0 letters at 48 months, and -0.1 letters at 60 months. The results for patients who crossed over to (mean number of injections = 5.4), or never received, ranibizumab were pooled. They demonstrated a gain of -9.6 letters at 24 months, -11.8 letters at 36 months, -11.8 letters at 48 months, and -16.1 letters at 60 months. The authors of the study concluded that, on average, patients receiving ranibizumab maintained their gain in vision for four or more years.

Safety and Harms

In the Martin study,⁶ AEs were reported at two years and were divided only by drug, not by dosing regimen or number of injections received. The most commonly reported systemic events in both groups (ranibizumab vs bevacizumab) were all-cause death (32/599 vs 36/586), arteriothrombotic events (28/599 vs 29/586), venous thrombotic events (3/599 vs 10/586), and hypertension (3/599 vs 4/586). The most commonly reported ocular events reported in the study eye were endophthalmitis (4/599 vs 7/586) and pseudo-endophthalmitis (1/599 vs 0/586). There was no significant difference in the occurrence of individual AEs between groups. However, there were significantly more patients reporting one or more serious systemic AEs in the bevacizumab group (31.7% vs 39.9%; $P = 0.004$).

In the HORIZON study,⁷ ocular adverse events were reported in 474 (79%) of ranibizumab initiated patients and in 31 (49.2%) treatment naïve patients. There were 48 (8.0%) serious ocular adverse events in the ranibizumab group and 9 events lead to discontinuation of study treatment. Non-ocular adverse events were reported in 488 (81.3%) of ranibizumab initiated patients and in 45 (71.4%) treatment naïve patients. There were 190 (31.7%) serious systemic adverse events in the ranibizumab group and 29 (4.8%) events lead to discontinuation of study treatment. There were 39 deaths (6.5%) in the ranibizumab and 7 (11.1%) in the treatment naïve group. The most commonly reported events in both groups are outlined in Table A3. No statistical analyses were presented comparing safety outcomes between groups.

What is the cost-effectiveness of the long-term use of ranibizumab for the treatment of age-related macular degeneration?

The included cost analyses and results are summarized in Table 2. More information regarding the cost study characteristics and study outcomes and conclusions are presented in Appendix 2 and 4, respectively.

Incremental cost-effectiveness ratios (ICERs) were reported in two cost studies^{8,10} In Patel,¹⁰ treatment with monthly ranibizumab was dominated by monthly bevacizumab, meaning bevacizumab was both more effective and less costly than ranibizumab.¹⁰ When comparing monthly ranibizumab with as needed bevacizumab, the resulting ICER was \$10,708,377 per QALY gained.⁸ The difference in cost-effectiveness results may be related to the differences in

populations or treatment regimens used in the models. Treatment with ranibizumab was considered to be cost-effective in one study¹¹ where it was compared with sham treatment with a willingness-to-pay threshold of \$100,000 per QALY. When compared with best-supportive care,¹² monthly bevacizumab,¹⁰ or as needed bevacizumab,^{8,9} ranibizumab was not considered to be a cost-effective treatment option at willingness-to-pay thresholds of \$50,000^{9,12} or \$100,000^{8,11} per QALY.

Given the greater cost per dose associated with ranibizumab as compared with bevacizumab, it was suggested in the included cost studies that ranibizumab would have to be decreased to a cost of between \$44¹⁰ and \$158⁹ per dose in order to be considered cost-effective as compared to bevacizumab. Alternatively, the incidence⁸ or cost of managing⁹ adverse events would have to increase substantially in order to demonstrate cost-effectiveness of ranibizumab.

Table 2: Summary of Results of Included Cost Studies

Author, Year	Analysis	Intervention/Comparator	Discounting/ Horizon	Results
Stein, 2014 ⁸	CEA	monthly Rb PRN Rb monthly Bb PRN Bb -for lifetime	3%/20 years	ICER monthly Rb/PRN Bb = \$10,708,377/QALY
Nwanze, 2012 ⁹	CEA	monthly Rb PRN Rb monthly Bb PRN Bb -for lifetime	3%/10 years	CER monthly Rb = \$63,333/QALY PRN Rb = \$18,571/QALY monthly Bb = \$2,676/QALY PRN Bb = \$3,333/QALY
Patel, 2010 ¹⁰	CUA	monthly Rb monthly Bb -for lifetime	3%/20 years	ACER monthly Rb = \$12,177/QALY monthly Bb = \$1,405/QALY ICER monthly Bb/monthly Rb = -\$54,649/QALY
Brown, 2010 ¹¹	CUA	22 injections of Rb over 24 months sham	3%/12 years	CER of Rb by model 2 nd eye = \$50,691/QALY 1 st eye = \$123,887/QALY combined = \$37,763/QALY
Fletcher, 2008 ¹²	CUA	24 injections of Rb over 24 months BSC	3%/5 years	CER Rb = \$88,250/QALY BSC = \$12,549/QALY

ACER = average cost-effectiveness ratio; AMD = age-related macular degeneration; Bb = bevacizumab; BSC = best supportive care; CEA = cost-effectiveness analysis; CER = cost-effectiveness ratio; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; PRN = as needed; QALY = quality-adjusted life-year; yo = years old

What are the evidence-based guidelines regarding the long-term use of ranibizumab for the treatment of age-related macular degeneration?

No evidence-based guidelines were identified regarding the long-term use of ranibizumab for the treatment of AMD.

Limitations

In Canada, bevacizumab is approved for use as a treatment for cancer and does not have Health Canada authorization for the treatment of AMD. Its use for this indication is off-label. The studies included in the review were all conducted in the United States. The results may not be directly applicable to the Canadian setting due to possible differences in AMD population, drug and medical costs, and clinical treatment guidelines.

There is a large variation in the results of the cost studies. This may be due to the variation in drug costs used in the models, as well as the use of different patient cohorts, dosing regimens, and time horizons. The incidence of adverse events was reported by drug treatment group, not by number of treatments.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

In the identified RCT,⁶ the authors concluded that treatment with ranibizumab and bevacizumab had similar effects on visual acuity. Monthly dosing with ranibizumab resulted in a greater gain in visual acuity than as needed dosing. In the long-term follow-up study, gains in visual acuity related to ranibizumab compared with no treatment were, on average, maintained for four or more years with retreatment as necessary.⁷ Ranibizumab was generally well-tolerated. In the RCT,⁶ rates of death and arteriothrombotic events were similar between the ranibizumab and bevacizumab groups. Overall, there was a higher rate of adverse events reported in the bevacizumab group; however, these cannot be definitively linked to the study drug.⁶ In the long-term follow-up study,⁷ systemic and ocular adverse events were uncommon in all treatment groups.

Incremental cost-effectiveness ratios (ICERs) were reported in two cost studies^{8,10} Treatment with monthly ranibizumab was dominated by monthly bevacizumab¹⁰ and, when comparing monthly ranibizumab with as needed bevacizumab, the resulting ICER was \$10,708,377 per QALY gained.⁸ The results varied depending on the dosing regimen and length of treatment with the drugs. However, bevacizumab does not have a Health Canada indication for the treatment of AMD.

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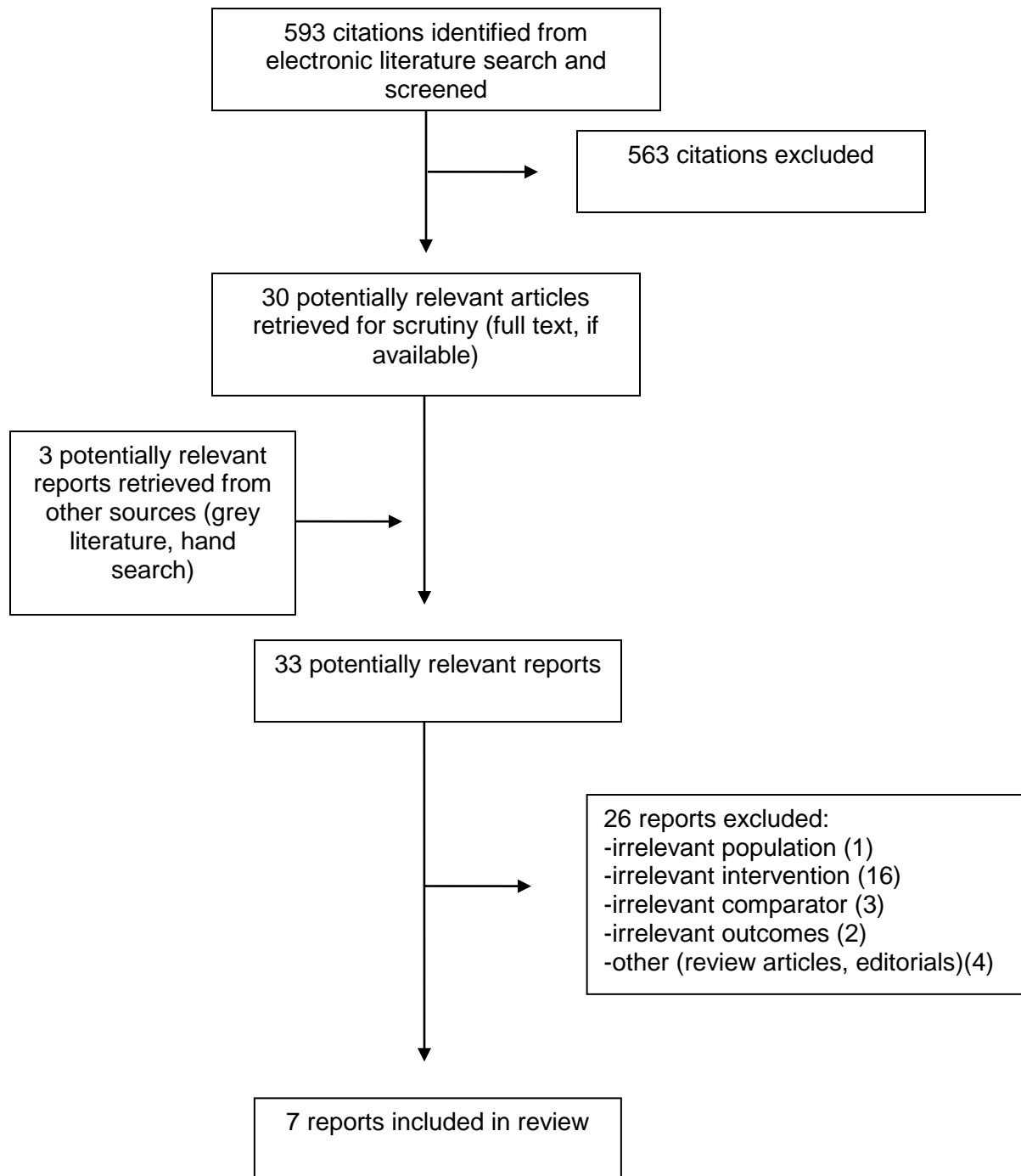
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention	Comparator Group	Clinical Endpoints
Martin, 2012 ⁶ USA CATT	Multicenter, randomized controlled trial <u>Year 1</u> Patients were equally assigned to receive monthly ranibizumab, PRN ranibizumab, monthly bevacizumab, PRN bevacizumab <u>Year two</u> Patients who were initially assigned to monthly dosing were randomized to continue monthly dosing or switch to PRN dosing of the same drug as year one	Eligible eyes had active choidal neovascularization secondary to AMD, no previous treatment, VA between 20/25 and 20/320, and neovascularization, fluid, or hemorrhage under the fovea.	Monthly (every 4 weeks) or PRN ranibizumab (0.05 mg in 0.05 mL solution) Patients who remained in the PRN groups for the full two years were eligible to receive a maximum of 26 injections	Monthly (every 4 weeks) or PRN bevacizumab (1.25 mg in 0.05 mL solution)	<u>Primary</u> Mean change in visual acuity <u>Secondary</u> Proportion of patients with change in VA ≥15 letters, number of injections, drug costs, presence of fluid and change in foveal retinal thickness, change in lesion size on fluorescein angiography, incidence of systemic and ocular AEs
Singer, 2012 ⁷ USA HORIZON	Open-label multicenter extension of three prospective, randomized controlled trials of ranibizumab	Patients with primary or recurrent choroidal neovascularization secondary to AMD who completed the MARINA, FOCUS, or ANCHOR studies	Multiple open-label intravitreal injections of 0.5 mg ranibizumab at ≥ 30 day intervals and no more than 12 injections per year.	For efficacy outcomes: pooled ranibizumab treated crossover group and the ranibizumab untreated group	<u>Primary</u> Incidence and severity of ocular and non-ocular AEs <u>Secondary</u> BCVA

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention	Comparator Group	Clinical Endpoints
		<p>Study eye from the initial study was continued in HORIZON</p> <p>Analysis groups included:</p> <ul style="list-style-type: none"> • patients initially randomized to ranibizumab in the RCTs • patients who crossed over to ranibizumab in the initial study or HORIZON • patients never treated with ranibizumab <p>Only patients in the initially randomized treatment group received more than 15 injections of ranibizumab</p>	<p>Retreatment was at the discretion of the investigator.</p>		

AEs = adverse events; BCVA = best-corrected visual acuity; CATT = Comparison of Age-related macular degeneration Treatment Trial; mg = milligram; mL = milliliter; PRN = as needed; VA = visual acuity

Table A2: Characteristics of Included Cost Studies

First author, Year	Type of analysis, Country, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Stein, 2014 ⁸	Cost-effectiveness analysis USA societal perspective	Monthly ranibizumab, PRN ranibizumab, monthly bevacizumab, PRN bevacizumab	Hypothetical cohort of 80 year old patients with neovascular AMD treated using the CATT study protocol	20 years 3% annual discount rate	<ul style="list-style-type: none"> in base-case, used distribution of BCVA from CATT and was unchanged after years 2 for all treatment groups in sensitivity analyses, BCVA in each group declined each year included direct medical costs WTP of \$100,000/QALY
Nwanze, 2012 ⁹	Cost-effectiveness analysis USA third-party payer or insurance company	Monthly ranibizumab, PRN ranibizumab, monthly bevacizumab, PRN bevacizumab	cohort of 65 year old patients treated using the CATT study protocol	10 years 3% annual discount rate	<ul style="list-style-type: none"> direct costs and utilities considers treatment costs of SAEs frequency of PRN dosing assumed to be the same as in the CATT trial used 2 years of MARINA follow-up to model gains of vision in monthly bevacizumab group WTP threshold of \$50,000/QALY
Patel, 2010 ¹⁰	Cost utility analysis USA payer perspective	monthly injections of ranibizumab 0.5 mg for the lifetime of the patient monthly injections of	Hypothetical cohort of 1000 65 year old patients with neovascular AMD	20 years 3% annual discount rate	<ul style="list-style-type: none"> efficacy data from previously published trials direct costs assumed patients

First author, Year	Type of analysis, Country, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
		bevacizumab 1.25 mg for the lifetime of the patient			<ul style="list-style-type: none"> were treated continuously through 20 years WTP threshold of \$50,000/QALY
Brown, 2008 ¹¹	Cost utility analysis USA third-party insurer perspective	22 injections of 0.5 mg ranibizumab administered over 2 years Sham treatment group (no treatment)	participants from the MARINA study using primary published data	12 years (life expectancy of the average patient with AMD) 3% annual discount rate	<ul style="list-style-type: none"> based on 2 year study outcomes modeled only AEs from the MARINA trial each of the AEs accounted for in VA data lasted for 5 days after each injection societal costs excluded WTP of \$100,000/QALY
Fletcher, 2008 ¹²	Cost utility analysis USA payer's perspective	Ranibizumab (24 doses over 24 months) Best supportive care (no active treatment)	Participants of existing published clinical trials of ranibizumab for AMD (MARINA, PIER) visual acuity data obtained from 2 year published trial data	5 years 3% annual discount rate	<ul style="list-style-type: none"> assumes a similar cohort of patients to previously published economic and clinical studies includes variable incremental costs fixed costs are excluded includes medical costs of blindness after vision falls below 35 letters WTP of \$50,000/QALY

AE = adverse event; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CATT = Comparison of Age-related macular degenerations Treatment Trial; mg = milligram; PRN = as needed; QALY = quality-adjusted life year; SAEs = severe adverse events; VA = visual acuity; WTP = willingness to pay

APPENDIX 3: Summary of Critical Appraisal of Included Clinical and Cost Studies

Table A3: Summary of Critical Appraisal

Strengths	Limitations
Downs and Black⁴	
Martin, 2012 ⁶ CATT	
<ul style="list-style-type: none"> • image graders, visual acuity examiners, and medical monitor were double blinded • inclusion criteria, study treatments, and outcome measures were well described • statistical methods, non-inferiority margin, and power size calculation were well described • adjustments for covariables and three different methods of handling missing data were provided as sensitivity analyses • ITT analysis • baseline characteristics were similar between study groups • safety analysis included all patients seen in years one and two 	<ul style="list-style-type: none"> • randomization methods were not adequately described • ophthalmologists were blinded to drug allocation but not dosing • clinic coordinators were not blinded • patients lost to follow-up were not adequately described • patients could have discovered drug allocation based on insurance forms that specified if they were receiving ranibizumab but not study-supplied bevacizumab • at the end of the study, 36.7% of patients indicated they were aware of which study drug they were assigned to. More than 97% of those patients were able to correctly identify the study drug they were assigned to • re-randomization at the end of year one resulted in six smaller treatment groups and may have lowered the statistical power of the study and increased the likelihood of inconclusive non-inferiority results • the efficacy analysis includes only patients seen within year two • AEs were reported only by study drug, not by dosing regimen
Singer, 2012 ⁷ HORIZON	
<ul style="list-style-type: none"> • inclusion criteria, study interventions, outcome measures, and discontinuation criteria were well described • all enrolled patients were included in the safety and efficacy analyses • statistical methods used for the analyses were described • baseline characteristics were similar between study groups, except for better baseline BCVA in the initially treated ranibizumab group which was to be expected due to the continuous treatment throughout the initial study 	<ul style="list-style-type: none"> • open-label, unblinded study design may have introduced bias into the results • The authors indicated possible selection bias in the study. Due to the as needed dosing schedule, “patients with better visual acuity outcomes did not receive as many injections or were not followed as frequently compared with patients with worse visual acuity outcomes who were selected to have more injections or were monitored more closely.” p. 1182 • treatment decisions made in the first year of HORIZON occurred before the unblinding of patients from MARINA and

	<p>ANCHOR</p> <ul style="list-style-type: none"> • selection bias likely introduced due to the way patients were chosen for inclusion from the original RCTs by selecting patients who responded well or need to receive continuous injections • drop-out rate may have been influenced by public availability of ranibizumab that started within the trial period • Using as needed dosing, patients may have been undertreated as compared to treatment guidelines in practice at the end of the study period
<p>Drummond⁵</p>	
<p>Stein, 2014⁸</p>	
<ul style="list-style-type: none"> • research question posed in a clear and answerable form • clear description of interventions and rationale was provided • relied on data from the CATT trial for disease outcomes and AEs to populate the model • methods to value health states and progression rates were described • societal perspective was used in the analysis • outcomes and costs were measured accurately and in appropriate units • 3% discounting rate was applied over a 20 year time horizon • one- and two-way sensitivity analyses were applied • currency and price data are reported (2012 USD) 	<ul style="list-style-type: none"> • two year data from the CATT trial was extrapolated over 20 years • patients used in the model were not well described beyond age and initial disease state • 80 year old patients modeled over 20 year time horizon • participants included in the trial may be very different than real-world patients and could therefore impact the estimated costs over time • assumption that BCVA is an acceptable surrogate for the impact of AMD on HRQoL
<p>Nwanze, 2012⁹</p>	
<ul style="list-style-type: none"> • research question posed in a clear and answerable form • clear description of interventions and rationale was provided • patients used in the model were well described • relied on data from the CATT trial to populate the model • methods to value health states were described • third-party payer perspective was used in the analysis • outcomes and costs were measured 	<ul style="list-style-type: none"> • authors indicated uncertainty in study outcomes and variables which may not accurately represent real-world information • assumption that the causal relationship between SAEs and the study drugs is true • examined only cost-effectiveness of individual regimens, not ICERs of treatments compared to each other

<ul style="list-style-type: none"> accurately and in appropriate units • 3% discounting rate was applied over a 10 year time horizon • sensitivity analyses were applied over different life expectancies, starting ages, adverse event rates, drug efficacy, and drug costs • currency and price data are reported (2011 USD) 	
<p>Patel, 2010¹⁰</p>	
<ul style="list-style-type: none"> • research question posed in a clear and answerable form • clear description of interventions and rationale was provided • patients used in the model were well described • relied on a systematic literature search and published RCT data to populate the model • methods to value health states were described • third-party payer perspective was used in the analysis • 3% discounting rate was applied over a 20 year time horizon • univariate and probabilistic sensitivity analyses were applied for all costs, transition probabilities, and utility values • currency and price data are reported (2007 USD) • one-way and probabilistic sensitivity analyses performed to test the robustness of the model 	<ul style="list-style-type: none"> • absence of large scale RCT efficacy data for bevacizumab • lack of efficacy data from head-to-head studies of ranibizumab vs bevacizumab • the authors identified a high degree of heterogeneity in the studies used to create efficacy estimates • lack of long-term clinical vision outcomes for either treatment group • total drug costs for both groups may be overestimated due to assumption of continuous monthly treatment through the full 20 year time horizon • did not account for study discontinuation due to vision loss which may have resulted in an overestimation of direct drug costs in both groups
<p>Brown, 2008¹¹</p>	
<ul style="list-style-type: none"> • research question posed in a clear and answerable form • clear description of interventions and rationale was provided • patients used in the model were well described • relied on RCT data to populate the model • methods to value health states were described • third-party payer perspective was used in the analysis • outcomes and costs were measured accurately and in appropriate units • opportunity costs were considered in the analysis 	<ul style="list-style-type: none"> • does not include societal costs • absence of RCT VA data past two years • the MARINA trial population may differ from the real-world treatment population

<ul style="list-style-type: none"> • 3% discounting rate was applied over a 12 year time horizon • sensitivity analyses were applied to utility values, confidence intervals, costs, frequency of drug administration, discount rate, and excluding the cost of adverse events • currency and price data are reported (2006 USD) 	
<p>Fletcher, 2008¹²</p>	
<ul style="list-style-type: none"> • research question posed in a clear and answerable form • clear description of interventions and rationale was provided • relied on data from published RCTs to populate the model • methods to value health states were described • payer's perspective was used in the analysis • outcomes and costs were measured accurately and in appropriate units • 3% discounting rate was applied over a 5 year time horizon • sensitivity analyses were applied • currency and price data are reported (USD) 	<ul style="list-style-type: none"> • Five year cost projections made with two year clinical results • clinical data was taken from different studies with comparable, but different, populations • little real-world data regarding costs of blindness from macular degeneration so costs may be underestimated in the analysis • adjusted value of the USD not described

AE = adverse event; BCVA = best-corrected visual acuity; CATT = Comparison of Age-related macular degenerations Treatment Trial; HRQoL = health-related quality of life; ITT = intention-to-treat; RCT = randomized controlled trial; SAE = serious adverse event

APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A4: Clinical Studies

First Author, Publication Year	Main Study Findings	Author’s Conclusions
Martin, 2012 ⁶ CATT	<p>Patients receiving same treatment regimen for 2 years N = 778 monthly ranibizumab, n = 134 PRN ranibizumab, n = 264 monthly bevacizumab, n = 129 PRN bevacizumab, n = 251</p> <p><u>Mean number of injections (SD)</u> monthly ranibizumab = 22.4 (3.9) PRN ranibizumab = 12.6 (6.6) monthly bevacizumab = 23.4 (2.8) PRN bevacizumab = 14.1 (7.0)</p> <p>between PRN groups; <i>P</i> = 0.01</p> <p><u>Mean letters change in VA score from baseline (SD)</u> monthly ranibizumab = 8.8 (15.9) PRN ranibizumab = 6.7 (14.6) monthly bevacizumab = 7.8 (15.5) PRN bevacizumab = 5.0 (17.9) drug, <i>P</i> = 0.21 regimen, <i>P</i> = 0.046</p> <p>Patients whose dosing regimen was reassigned at 1 year N = 515 monthly ranibizumab, n = 134 ranibizumab switched, n = 130 monthly bevacizumab, n = 129 bevacizumab switched, n = 122</p> <p><u>Mean number of injections in year 2 (SD)</u> monthly ranibizumab = 10.5 (3.1) ranibizumab switched = 5.0 (3.8) monthly bevacizumab = 11.3 (2.3) bevacizumab switched = 5.8 (4.4)</p> <p><u>Mean change in VA score from 1 year (SD)</u> monthly ranibizumab = -0.3 (11.1)</p>	<ul style="list-style-type: none"> the authors determined that treatment with ranibizumab and bevacizumab resulted in similar effects on visual acuity PRN dosing resulted in less gain in visual acuity than monthly dosing rates of death and arteriothrombotic events were similar between groups overall, higher rates of AEs were reported in the bevacizumab group but they cannot be definitively linked to the study drug because of the lack of specificity to events associated with the mechanism of action of the drug

First Author, Publication Year	Main Study Findings	Author's Conclusions
	<p>ranibizumab switched = -1.8 (11.2) monthly bevacizumab = -0.6 (10.3) bevacizumab switched = -3.6 (12.1) drug; $P = 0.29$ regimen; $P = 0.03$</p> <p><u>Drug cost per patient</u> monthly ranibizumab = \$21,000 ranibizumab switched = \$10,000 monthly bevacizumab = \$565 bevacizumab switched = \$290</p>	
<p>Singer, 2012⁷ HORIZON</p>	<p>Ranibizumab treatment-initiated n = 600 Mean age (SD) = 78.1 (7.6) Female (%) = 346 (57.7) Baseline BCVA/mean ETDRS letter score (SD, range) = 60.5 (17.9, 10-96)</p> <p>Mean injections (SD): In initial study and HORIZON = 27.8 (5.4) In HORIZON only = 4.4 (5.3)</p> <p><u>Safety – Ocular events (%)</u> All AEs = 474 (79.0) SAEs = 48 (9.0) Intraocular inflammation = 10 (1.7) Glaucoma = 19 (3.2) Cataract event = 75 (12.5)</p> <p><u>Safety – Non-Ocular events (%)</u> All AEs = 488 (81.3) Nasopharyngitis = 57 (9.5) Hypertension = 52 (8.7) SAEs = 190 (31.7) AEs – discontinuation = 29 (4.8) Total deaths = 36 (6.5)</p> <p>Ranibizumab untreated n = 63 Mean age (SD) = 79.2 (8.3) Female (%) = 36 (57.1) Baseline BCVA/mean ETDRS letter score (SD, range) = 41.6 (17.2, 7-83)</p>	<ul style="list-style-type: none"> • The authors concluded that ranibizumab injections were well tolerated over four or more years • on average, patients receiving ranibizumab maintained vision for ≥ four years • systemic and ocular events were uncommon in all groups

First Author, Publication Year	Main Study Findings	Author's Conclusions
	<p>Mean injections (SD): In initial study and HORIZON = 0 In HORIZON only = 0</p> <p><u>Safety – Ocular events (%)</u> All AEs = 474 (79.0) SAEs = 48 (9.0) Intraocular inflammation = 10 (1.7) Glaucoma = 19 (3.2) Cataract event = 75 (12.5)</p> <p><u>Safety – Non-Ocular events (%)</u> All AEs = 488 (81.3) Nasopharyngitis = 57 (9.5) Hypertension = 52 (8.7) SAEs = 190 (31.7) AEs – discontinuation = 29 (4.8) Total deaths = 36 (6.5)</p> <p>Vision Results</p> <p><u>Mean change from initial study baseline (letters)</u> Ranibizumab treatment-initiated 24 months = +9.0 36 months = +4.1 48 months = +2.0 60 months = -0.1</p> <p>Pooled ranibizumab treated crossover and ranibizumab untreated 24 months = -9.6 36 months = -11.8 48 months = -11.8 60 months = -16.1</p>	

AE = adverse event; BCVA = best-corrected visual acuity; BSC = best supportive care; CATT = Comparison of Age-related macular degenerations Treatment Trial; ETDRS = Early Treatment Diabetic Retinopathy Study; ICER = incremental cost-effectiveness ratio; PRN = as needed; QALY = quality-adjusted life year; SAE = serious adverse event; SD = standard deviation; VA = visual acuity

Table A5: Cost Studies

First Author, Publication Year	Main Study Findings	Author's Conclusions
Stein, 2014 ⁸	<p>Base-case analysis</p> <p><u>20 year costs of AMD</u> monthly ranibizumab = \$257,357 PRN ranibizumab = \$163,694 monthly bevacizumab = \$79,771 PRN bevacizumab = \$65,267</p> <p><u>QALYs gained</u> monthly ranibizumab = 6.68 PRN ranibizumab = 6.64 monthly bevacizumab = 6.66 PRN bevacizumab = 6.60</p> <p><u>ICERs</u> monthly bevacizumab/PRN bevacizumab = \$242,357/QALY monthly ranibizumab/PRN bevacizumab = \$10,708,377/QALY</p> <ul style="list-style-type: none"> various sensitivity analyses did not result in very different cost-effectiveness outcomes 	<ul style="list-style-type: none"> the authors concluded that bevacizumab PRN was the most cost-effective of the four treatment options the large difference in cost per QALY is partly related to the difference in per injection drug costs between the two treatments the risk of serious vascular events would have to increase by more than 2.5 times in order for monthly ranibizumab to results in an ICER of less than \$100,000/QALY ranibizumab PRN is more costly and less effective than bevacizumab PRN in 2/3 of the sensitivity analyses conducted, bevacizumab PRN was the preferred treatment option at a WTP of \$100,000/QALY
Nwanze, 2012 ⁹	<p>Cost per QALY monthly ranibizumab = \$63,333 PRN ranibizumab = \$18,571 monthly bevacizumab = \$2,676 PRN bevacizumab = \$3,333</p> <ul style="list-style-type: none"> sensitivity analyses were undertaken with various costs of treating medical and ocular AEs with minimal impact on relative cost-effectiveness 	<ul style="list-style-type: none"> the authors concluded that monthly ranibizumab would not be cost-effective at \$2,000/dose given reasonable initiation ages or time horizons the lower rate of AEs in the ranibizumab groups helps to increase its cost-effectiveness as the rate of AEs increases the authors concluded that the price of ranibizumab would have to be reduced to a maximum of \$158 per dose in order to be as cost-effective as bevacizumab at the study price of \$2,000 per dose, ranibizumab is not cost-effective the authors suggest that monthly bevacizumab is the most cost-effective treatment option at a cost of \$2,600/QALY.

First Author, Publication Year	Main Study Findings	Author's Conclusions
Patel, 2010 ¹⁰	<p>Base-case analysis (over 20 years)</p> <p><u>treatment cost</u> ranibizumab = \$220,649 bevacizumab = \$30,349</p> <p><u>mean average QALYs gained</u> ranibizumab = 18.12 bevacizumab = 21.60</p> <p><u>average cost-effectiveness ratios</u> ranibizumab = \$12,177/QALY bevacizumab = \$1405/QALY</p> <p><u>ICER</u> bevacizumab/ranibizumab = - \$54,649/QALY</p> <p>Sensitivity analyses</p> <ul style="list-style-type: none"> • both treatments were robust when changes were made to transition probabilities and utility weights • both treatments were sensitive to drug costs • drug cost of ranibizumab would have to decrease to \$44 per injection to have a CER equivalent to bevacizumab 	<ul style="list-style-type: none"> • the authors suggested that bevacizumab was the more cost-effective treatment option for AMD • in the base-case, treatment with bevacizumab dominated ranibizumab resulting in a savings of \$54,649 per QALY gained • base-case analysis was sensitive to drug costs. The cost of ranibizumab would have to drop to \$44 per injection to result in a CER equal to bevacizumab • probabilistic sensitivity analyses demonstrated a 95% probability of bevacizumab being more cost-effective than ranibizumab at a WTP threshold of \$50,000/QALY due to increased efficacy and lower cost
Brown, 2008 ¹¹	<p>Costs over initial 2 years ranibizumab treatment = \$53,204 weighted cost of AE treatment = \$217 total discounted at 3% = \$52,652</p> <p>Cost utility discounted over 12 years second eye model = \$50,691/QALY first eye model = \$123,887/QALY combined model = \$74,169/QALY</p> <p>Sensitivity analyses</p> <p><u>11 doses over 2 years</u> second eye model = \$25,810/QALY first eye model = \$63,078/QALY</p>	<ul style="list-style-type: none"> • the authors concluded that ranibizumab offers a 15.8% value gain in quality of life • using a \$100,000/QALY WTP threshold, both the second eye and combined models can be considered cost-effective • it was assumed that reducing the number of doses to 11 injections over two years did not change the QALY gain or improvement in QoL

First Author, Publication Year	Main Study Findings	Author's Conclusions
Fletcher, 2008 ¹²	<p>combined model = \$37,763/QALY</p> <p>Visual acuity – treated eye, 53; fellow eye, 0</p> <p><u>Cost per QALY</u> Ranibizumab (24 injections in 24 months) = \$88,250 Ranibizumab (10 injections in 24 months) = \$37,712 BSC = \$12,549</p> <p><u>Cost per QALY gained over BSC</u> Ranibizumab (24 injections in 24 months) = \$992,103 Ranibizumab (10 injections in 24 months) = \$626,938 Bevacizumab (dosing unknown) = \$104,748</p>	<ul style="list-style-type: none"> • Extrapolated over five years, as the number of required treatments is reduced and vision becomes stabilized, the cost per QALY decreases for all treatments except for best supportive care • Monthly ranibizumab remains the highest cost/QALY over time • “If the cost of blindness is increased...up to \$20,000, then the cost per QALY of BSC at the end of 5 years is equal to that of ranibizumab provided on a monthly basis.” p. 2196

AMD = age-related macular degeneration; BSC = best supportive care; CER = cost-effectiveness ratio; ICER = incremental cost-effectiveness ratio; PRN = as needed; QALY = quality-adjusted life year; QoL = quality of life; WTP = willingness to pay