Original Article

Cost-effectiveness of anti-oxidant vitamins plus zinc treatment to prevent the progression of intermediate age-related macular degeneration. A Singapore perspective

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Purpose: To determine if providing high dose anti-oxidant vitamins and zinc treatment age-related eye disease study (AREDS formulation) to patients with intermediate age-related macular degeneration (AMD) aged 40–79 years from Singapore is cost-effective in preventing progression to wet AMD. **Methods:** A hypothetical cohort of category 3 and 4 AMD patients from Singapore was followed for 5 calendar years to determine the number of patients who would progress to wet AMD given the following treatment scenarios: (a) AREDS formulation or placebo followed by ranibizumab (as needed) for wet AMD. (b) AREDS formulation or placebo followed by bevacizumab (monthly) for wet AMD. (c) AREDS formulation or placebo followed by aflibercept (VIEW I and II trial treatment regimen). Costs were estimated for the above scenarios from the providers' perspective, and cost-effectiveness was measured by cost per disability-adjusted life year (DALY) averted with a disability weight of 0.22 for wet AMD. The costs were discounted at an annual rate of 3%. **Results:** Over 5400 patients could be prevented from progressing to wet AMD cumulatively if AREDS formulation were prescribed. AREDS formulation followed by ranibizumab was cost-effective compared to placebo-ranibizumab or placebo-aflibercept combinations (cost per DALY averted: SGD$23,662.3 and SGD$21,138.8, respectively). However, bevacizumab (monthly injections) alone was more cost-effective compared to AREDS formulation followed by bevacizumab. **Conclusion:** Prophylactic treatment with AREDS formulation for intermediate AMD patients followed by ranibizumab or for patients who progressed to wet AMD was found to be cost-effective. These findings have implications for intermediate AMD screening, treatment and healthcare planning in Singapore.

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Age-related macular degeneration (AMD) is one of the leading causes of blindness in the elderly populations around the world.[1-5] The stages of AMD are categorized as early, in which visual symptoms are inconspicuous, intermediate, in which the vision deterioration is beginning and late, in which severe loss of vision is usual.[6] Late stage AMD, also known as wet AMD is a cause for poor visual function, anxiety, depression, falls, and impaired activities of daily living.[7] Research suggests that anti-oxidant vitamins could be useful in treating patients with AMD.[8]

A large randomized controlled clinical trial conducted by the age-related eye disease study (AREDS) Research Group showed that provision of high-dose anti-oxidant vitamins and zinc (hereafter known as AREDS formulation) to certain AMD patients (category 3 - extensive intermediate drusen, geographic atrophy not involving the center of the macula, or at least one large druse or category 4 - advanced AMD or visual acuity less than 20/32 due to AMD in eye) was clinically effective in preventing the progression to wet AMD.[9] A recent report on the long-term follow-up of the patients in the AREDS clinical trial also showed a decreased risk of developing wet AMD following the long-term use of AREDS formulation, results being consistent with their previous findings.[10] Another study looking at lutein and anti-oxidant vitamins to treat atrophic AMD showed that lutein alone or lutein plus anti-oxidant vitamins was effective in improving the visual function of atrophic AMD patients.[11]

In addition to being clinically effective, studies have shown that the AREDS formulation is cost-effective in preventing the progression to late stage AMD.[12,13] However, both these studies were conducted in Caucasian population.

Singapore has a rapidly aging population with over 9% of the resident population being aged 65 years or above in 2012.[14] By the year 2030, it is estimated that one in five resident Singaporeans will be aged 65 years or above.[15] As a result of this rapid aging, the burden of ocular morbidity and visual disability due to age-related eye disorders in Singapore is set to increase. This study aims to determine if providing AREDS formulation to category 3 or 4 AMD patients aged 40–79 years from Singapore is cost-effective in preventing progression to Wet AMD. Being the first cost-effectiveness analysis (CEA)

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for anti-oxidant vitamin therapy for AMD in Singapore, this study can be used to provide cost-effectiveness information to inform ophthalmic practice for patients diagnosed with category 3 or 4 AMD.

Methods

From the 2012 Singapore population trends report,[14] the number of resident Singaporeans aged 40–79 years was obtained (1.72M people), and the proportion of AMD cases was estimated using the age and ethnicity-specific prevalence estimates from a local study conducted by Cheung *et al*.[2] From this total number of estimated AMD cases, the number of category 3 and 4 AMD patients was estimated using proportions from the AREDS report.[9] This hypothetical cohort of category 3 and 4 AMD patients (n = 66,709) was followed for 5 years to determine the number of patients progressing to wet AMD. Crude annual mortality rate of 4.5/1000 Singaporeans was included in the model.[14] Progression rates for patients receiving AREDS formulation or placebo were taken from the AREDS report (5 years progressing rate was 20% and 28% for vitamins vs. placebo respectively for category 3 and 4 patients).[9] Patients who had progressed to wet AMD were either treated with ranibizumab (on a PRN basis), bevacizumab (monthly) as per CATT study protocol,[16] or aflibercept (treatment regimen as per the VIEW I and VIEW II trials).[17] The average number of ranibizumab injections was taken from the CATT 1 and 2 years trials as well as the HORIZON trial for treatment after the initial 2 years follow-up period.[16,18,19] The treatment regimen for aflibercept was taken from the VIEW I and VIEW II trials.[17] We acknowledge that bevacizumab is an off-label treatment for wet AMD but has found widespread use across the world for this indication and has hence been included in this study for analysis. Only one eye for the patients was assumed to be affected with AMD.

Six treatment scenarios were considered, as follows:

- AREDS formulation followed by ranibizumab (as needed) for wet AMD
- Placebo followed by ranibizumab (as needed) for wet AMD
- AREDS formulation followed by bevacizumab (monthly) for wet AMD
- Placebo followed by bevacizumab (monthly) for wet AMD
- AREDS formulation followed by aflibercept (VIEW I and VIEW II treatment protocol)
- Placebo followed by aflibercept (VIEW I and VIEW II treatment protocol).

Detailed information on cost for AREDS formulation (for category 3 and 4 AMD patients), ranibizumab, bevacizumab, aflibercept, injection procedure cost, consultation costs, and diagnostics costs (for wet AMD) were obtained from Tan Tock Seng Hospital Eye Centre and the National Healthcare Group Pharmacy Department.

Cost-effectiveness of AREDS formulation was estimated by computing the cost per disability-adjusted life year (DALY) averted for the 5 years study period. DALY is calculated as the sum of the years of life lost due to disability (YLD) and the years of life lost (YLL) due to premature death (DALY = YLD + YLL). The DALY scale ranges from 0 (perfect health) to 1 (dead).

Years of life lost due to disability = disability weight associated with wet AMD X number of people with wet AMD X number of years lived with wet AMD during the course of the 5 years study period.

The disability weight associated with wet AMD was 0.22/year of life lived with wet AMD for patients within our study age group.[20]

Years of life lost = reduced life expectancy due to mortality attributed to the disease (legal blindness due to wet AMD).

Since no local data were available for the life expectancy of wet AMD patients, we assumed that patients with wet AMD dying during the 5 years study period had negligible loss of life due to premature death associated with wet AMD-related causes like vision loss. We do acknowledge that in reality, this might not be the case.

Although utility values for AMD in Singapore were available from a publication,[21] the authors had concluded that these health status utilities may not be sufficiently robust for healthcare economic analyses. In addition, applying utility values from other studies conducted in Caucasian populations might not accurately represent the disease burden to the society in Singapore.[22] Hence, we opted to use the "cost per DALY averted" measure to determine cost-effectiveness rather than the utility value based "cost per Quality Adjusted Life Year (QALY) saved." The analysis was carried out from the providers' perspective, and all costs were presented in Singapore dollars (1 SGD ≈ 0.80 USD as on September 2014). The costs were discounted at an annual rate of 3%.

Our CEA model had several assumptions; there was no dropout of patients for the 5 years of follow-up although mortality was incorporated into the model; patients were fully compliant with prescribed treatment; proportion of category 3 and 4 AMD patients and progression rates were similar to the reported proportions from the AREDS report; treatment for wet AMD with ranibizumab was similar to that reported in the CATT 1 and 2 years study as well as the HORIZON study for post-2 years follow-up and treatment with aflibercept was similar to the regimen in the VIEW I and II trials; and finally, cost of consultation, treatment and diagnostic investigations did not change during the 5 years of follow-up. As this is a simulation study, no Institutional Review Board approval was needed.

Sensitivity analysis

Sensitivity analysis was performed to assess the robustness of the CEA model.[23] The progression rates (based on treatment with AREDS formulation vs. placebo) for the hypothetical cohort of category 3 and 4 AMD patients were varied by constructing confidence intervals (CIs) for the point estimate progression rates that were obtained from the AREDS study.[9] Based on the lower and upper limits of the CI for the progression rates, the CEA model was re-analyzed for the six treatment scenarios mentioned above and cost per DALY averted was calculated for the same.

Results

Using Singapore resident population information for 2012 and recently published AMD prevalence estimates,[2] the estimated number of AMD patients aged 40–79 years was 123,537 and the corresponding number of category 3 and 4 AMD patients was 66,709 [Table 1]. This hypothetical cohort of 66,709 patients

Table 1: Projected prevalence of AMD in Singapore by age and ethnicity

Age (years)	Chinese		Malay		Indian		Other#	
	Total population*	Number of AMD cases	Total population*	Number of AMD cases	Total population*	Number of AMD cases	Total population*	Number of AMD cases
40-49	465,700	20,956	77,700	3885	59,500	3035	26,900	1264
50-59	454,300	29,984	72,500	5800	42,600	1619	12,900	800
60-69	283,700	22,696	32,900	3158	21,100	1920	5200	442
70-79	144,100	23,056	15,900	3323	9900	1257	2100	342
Total	1.34M	96,692	0.19M	16,166	0.13M	7831	47,100	2848
Number of category 3 or 4 AMD patients**	52,213		8729		4229		1538	

*Numbers obtained from the Department of Statistics, Singapore for the year 2012.[14] Age and ethnicity-specific prevalence proportions obtained from the study by Cheung *et al*.[2] #As age-specific proportions were not available for the "others" ethnic group; the overall prevalence proportions were applied (Cheung *et al*. [2012]). **Proportions obtained from the AREDS report (2001)[9]. AMD: Age-related macular degeneration, AREDS: Age-related eye disease study

was followed for 5 years, and progression to wet AMD was estimated. The input parameters for the progression model are shown in Table 2. Cumulatively, 5493 patients could have been prevented from progressing to wet AMD over 5 years, had AREDS formulation been prescribed. Details of the progression model are available in Appendix 1.

Disability-adjusted life years were computed for patients receiving AREDS formulation versus placebo [Table 3]. The cost for treatment and the corresponding DALYs accumulated over the follow-up period for the six treatment options was presented [Fig. 1]. The number of DALYs averted as a result of prescribing AREDS formulation was 2734.3 over 5 years. The cost per DALY averted as a result of prescribing AREDS formulation was $23,662.3 and $21,138.8 for the ranibizumab and aflibercept arms, respectively [Table 4]. However, bevacizumab (monthly 1 injection) alone was more cost-effective when compared to the AREDS formulation bevacizumab combination.

Sensitivity analysis

By varying the progression rates (using constructed 95% CI of the progression rates from AREDS), the number of DALYs averted ranged from 2055.6 to 3436.6 if AREDS formulation was prescribed [Table 3]. Cost per DALY averted ranged from $2432.3 to $24,209.9 if ranibizumab was prescribed for wet AMD [Table 5]. However, cost-effectiveness of AREDS formulation followed by bevacizumab or aflibercept (for wet AMD) was inconclusive after sensitivity analysis was conducted [Table 5].

Discussion

The World Health Organization (WHO) guidelines for cost-effectiveness state that an intervention is considered "extremely cost-effective" if the cost-effectiveness ratio is less than the per-capita gross domestic product (GDP) of the country.[2] The GDP per-capita for Singapore in the year 2012 was USD$51,709[24] (SGD ≈: $65,454,4). Our study shows that prescribing AREDS formulation to category 3 and 4 AMD patients is extremely cost-effective in preventing progression to wet AMD for Singaporean patients.

With an aging population, the number of AMD cases in Singapore is going to increase with time. The burden of AMD

Table 2: Input parameters for the CEA model

Parameter	Associated cost (in SGD)*
Cost component	
Drug	
Ranibizumab+injection procedure fee	$1634 per injection
Bevacizumab+injection procedure fee	$351 per injection
Aflibercept+injection procedure fee	$1643.45 per injection
Antioxidant vitamin+zinc treatment (oral tablets for category 3 and 4 AMD patients)	$25.05 per month
Consultation cost for wet AMD patient	$78 per month
Fluorescein angiography for wet AMD patient	$130-once at baseline
Optical coherence tomography for wet AMD patient	$65 per month
Progression probabilities for category 3 and 4 AMD patients**	
Receiving preventive antioxidant vitamin+Zn – 4.4% per year	
Not receiving preventive antioxidant vitamin+Zn (placebo) – 6.5% per year	
Mortality rate: 4.5 deaths per 1000 Singaporeans per year***	

*Cost information obtained from Tan Tock Seng Hospital Eye Centre, Singapore and National Healthcare Group Pharmacy Division, Singapore. **Rates computed from the AREDS report[9]. ***Department of Statistics, Singapore[14]. AMD: Age-related macular degeneration, CEA: Cost-effectiveness analysis

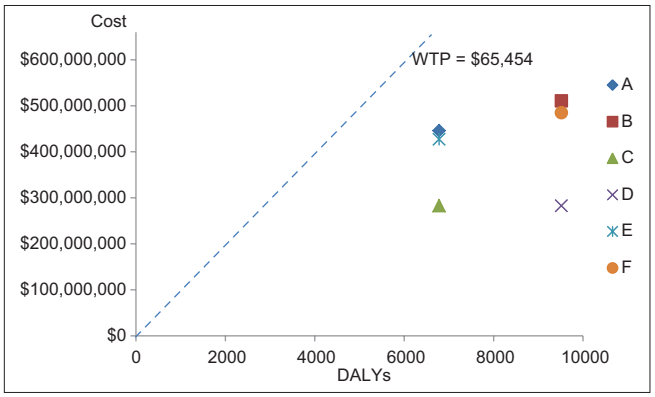

Figure 1: Cost and corresponding disability-adjusted life years for the six treatment options

Table 3: DALYs associated with wet AMD based on receipt or no receipt of AREDS formulation over 5 years

Progression rate^	Treatment	Number of wet AMD patients	YLD	YLL	DALY	DALY averted
4.4% per year (point estimate)	AREDS formulation	14,682	6780.9	0	6780.9	2734.3
6.5% per year (point estimate)	No AREDS formulation (placebo)	20,175	9515.2	0	9515.2	
2.2% per year (lower limit)	AREDS formulation	8383	3787.4	0	3787.4	2055.6
3.7% per year (lower limit)	No AREDS formulation (placebo)	12,740	5843.0	0	5843.0	
6.9% per year (upper limit)	AREDS formulation	21,167	10,022.7	0	10,022.7	3436.6
9.7% per year (upper limit)	No AREDS formulation (placebo)	27,645	13,459.3	0	13,459.3	

*Disability weight associated with wet AMD is 0.22 (scale for disability weight: 0 – perfect health, 1 – dead) obtained from the Deloitte's access economics report[20]. ^Progression rates obtained from AREDS Report (2001)[9] after constructing 95% CI for the point estimates. **The duration for this study was 5 years. Crude mortality rate of 4.5/1000 adult Singaporeans was incorporated. YLD: Years of life lost due to disability=Disability weight associated with wet AMD* × number of patients with wet AMD×average duration of case until remission or death**, YLL: Years of life lost due to wet AMD=Assumed to be zero during our study period. DALYs: Disability-adjusted life years=YLD+YLL, AREDS: Age-related eye disease study, AMD: Age-related macular degeneration, CI: Confidence interval

Table 4: Cost per DALY averted based on possible treatment options for patients with wet AMD

Follow-up of the 2012 hypothetical cohort	**Ranibizumab: Given as needed at a cost of $1634 per injection**			
5 years (till end of 2016)	Cost of treatment module A	Cost of treatment module B	(Cost of treatment module A)–(cost of treatment module B)	Cost per DALY averted
	$446.0M	$510.7M	–$64.7M	$23,662.3
Follow-up of the 2012 hypothetical cohort	**Bevacizumab: Given 12 injections a year at a cost of $351 per injection**			
5 years (till end of 2016)	Cost of treatment module C	Cost of treatment module D	(Cost of treatment module C)–(cost of treatment module D)	Cost per DALY averted*
	$282.9M	$282.8M	$0.1M	–$36.5
Follow-up of the 2012 hypothetical cohort	**Aflibercept: Given monthly for first 3 months followed by once every 2 months for the 1st year followed by a capped PRN protocol from year 2 at a cost of $1643.45 per injection**			
5 years (till end of 2016)	Cost of treatment module E	Cost of treatment module F	(Cost of treatment module E)–(cost of treatment module F)	Cost per DALY averted*
	$427.3M	$485.1M	–$57.8M	$21,138.8

Treatment module A: AREDS formulation followed by ranibizumab (as needed) for those who have progressed to wet AMD. Treatment module B: No AREDS formulation followed by ranibizumab (as needed) for those who have progressed to wet AMD. Treatment module C: AREDS formulation followed by bevacizumab (monthly) for those who have progressed to wet AMD. Treatment module D: No AREDS formulation followed by bevacizumab (monthly) for those who have progressed to wet AMD. Treatment module E: AREDS formulation followed by aflibercept (treatment as per VIEW I and II trials) for wet AMD. Treatment module F: No AREDS formulation followed by aflibercept (treatment as per VIEW I and II trials) for wet AMD. *Bevacizumab (monthly 1 injection) alone was cost-effective compared to preventive anti-oxidant vitamins+Zn followed by bevacizumab. DALYs: Disability-adjusted life years, AMD: Age-related macular degeneration

Table 5: Sensitivity analysis for CEA model

	Progression rates	Cost per DALY averted for ranibizumab	Cost per DALY averted for bevacizumab	Cost per DALY averted for aflibercept
Lower limit (%)	AREDS formulation: 2.2 Placebo: 3.7	$2432.3	–$21,554.0	–$340.5
Upper limit (%)	AREDS formulation: 6.9 Placebo: 9.7	$24,209.9	$785.6	$21,271.8

95% CI for progression rates constructed based on proportion of category 3 and 4 patients receiving treatment or placebo from AREDS report. CI: Confidence interval, AREDS: Age-related eye disease study, CEA: Cost-effectiveness analysis, DALYs: Disability-adjusted life years

on the society is tremendous. Brown *et al*. showed that mild AMD caused a 17% decrease in the quality of life of the average patient, which is similar to that encountered with moderate cardiac angina or symptomatic human immunodeficiency virus syndrome; Moderate AMD caused a 32% decrease in the average patient's quality of life, comparable to severe cardiac angina or a fractured hip. Severe AMD caused a 53% decrease in quality, which is more than that of renal hemodialysis. Very severe AMD caused a 60% decrease in the average AMD patient's quality of life, similar to that encountered with end-stage prostate cancer or a catastrophic stroke.[25]

The economic burden of AMD is also high. A study conducted by Rein *et al*. in the US showed that the direct medical cost for treating AMD in patients 40 years and older was $575 million for calendar year 2004.[26] Another study

conducted by Garattini *et al*. in Italy found the direct cost to the hospital's ophthalmology department to be, on average, € 383 (~509 USD) per AMD patient per year, with cost being the highest for patients with wet AMD.[27] Thus preventing progression to wet AMD will not only benefit the patient in terms of quality of life, but also the healthcare provider by reducing the direct costs associated with wet AMD.

To date, two studies reported the cost-effectiveness of anti-oxidant vitamins in preventing the progression to wet AMD. Hopley conducted an economic evaluation of screening for early AMD followed by prophylactic treatment with vitamins for patients who were diagnosed with the disease.[12] This study showed that the cost per QALY gained was £22,700 (~35,185 USD). Another study conducted by Rein *et al*. showed that the cost per QALY gained for anti-oxidant treatment versus no treatment was USD$21,387.[13] Based on the accepted threshold value for the "willingness to pay" to gain a QALY, both studies concluded that it was cost-effective to prescribe anti-oxidant vitamins to early AMD patients.

In our study, we used the cost per DALY averted measure to determine cost-effectiveness. Although utility values associated with AMD were available in the local setting, the authors concluded that they were not suitable to be used for health economic evaluations.[21] Hence, we used reported disability weights to compute the number of DALYs for patients receiving ARED formulation versus placebo. The accepted threshold for cost-effectiveness set by the WHO is 1–3 times the GDP per-capita.[28] Our results fall well within the WHO stated range, suggesting it is cost-effective to prescribe anti-oxidant vitamins and zinc to category 3 and 4 AMD patients from Singapore.

In our study, we noted that AREDS formulation followed by ranibizumab was cost-effective compared to placebo-ranibizumab while the reverse was true for bevacizumab. The reason for this is the high-cost difference between the two drugs (almost 1/5th of the price assuming no dose titrations are done). However, sensitivity analysis showed that the results for bevacizumab were inconclusive. A meta-analysis and systematic review conducted by Schmucker *et al*. showed that bevacizumab was associated with an increased risk of ocular and multiple systemic adverse events compared to ranibizumab for the treatment of wet AMD.[29] The CATT trial[16] showed a statistically significant higher rate of gastrointestinal adverse events for bevacizumab treated patients compared to ranibizumab treated patients. Although there are significant cost differences between bevacizumab and ranibizumab, this may perhaps be mitigated if adverse event rates for the different drugs are taken into consideration. This would be hampered, however, by a paucity of data regarding the comparative safety of anti-vascular endothelial growth factor (VEGF) treatments currently.

We acknowledge that our study suffers from several limitations. First, since no progression rates were available for Singaporean patients, we applied rates from the AREDS report to the local Singaporean context. However, in order to test our model assumptions, we did conduct a sensitivity analysis by varying the progression rates based on treatment with AREDS formulation versus placebo. Second, our model accounted for only the prevalent cases of AMD and not the incident cases as no local incidence data were available. Third, we assumed that compliance to treatment for anti-oxidant vitamins as well as anti-VEGF treatment was 100%. This might not be the case in the real world scenario. The disability weight associated with wet AMD was not available from local literature and hence we used the weight of 0.22, obtained from a foreign study, to compute the YLD in the DALY calculation.

A study conducted by Bandello *et al*. suggested that on average, 2 years of life are lost due to premature death associated with consequences of developing wet AMD.[30] As ours was a hypothetical cohort study, we had no way to estimate the YLL in our study population. Had we assumed that all cases of wet AMD dying during the study period died due to wet AMD-related causes, and that on average each patient that had died had lost 2 years of life due to premature death (maximum possible YLL for our cohort), our CEA results would still hold true. In reality, the YLL would lie between 0 and this maximum number, but as no local data are available at this point in time, we assumed YLL to be zero. Nevertheless, any value of YLL for our study period, lying between 0 and the maximum, based on Bandello *et al*.'s estimate mentioned above, would not have impacted our CEA results (data not shown).

Our study provides evidence of the effectiveness of AREDS formulation for patients with intermediate AMD. These results will help physicians make an informed decision on the treatment options for intermediate and wet AMD in Singapore. This study forms the basis for an in-depth analysis of AREDS treatment for prophylaxis use among a cohort of patients in the real world setting.

Conclusion

Prophylactic treatment with AREDS formulation for category 3 and 4 AMD patients from Singapore is cost-effective in preventing progression to wet AMD. AREDS formulation followed by ranibizumab was cost-effective compared to placebo-ranibizumab while the sensitivity analysis suggested no difference between AREDS-bevacizumab/aflibercept and placebo-bevacizumab/aflibercept. These findings have implications for intermediate AMD treatment and healthcare planning in Singapore.

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Conflicts of interest

There are no conflicts of interest.

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Appendix 1

Progression of category 3 or 4 patients based on treatment modality and the cost associated with the same: Progression rates were obtained from the AREDS trial.

Treatment module A: Age-related eye disease study formulation followed by ranibizumab (as needed) for those who have progressed to wet age-related macular degeneration

Anti-oxidant vitamin+Zn (yearly progression rate=4.4%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests	Cost for anti-oxidant vitamin+Zn treatment
Start of year 1	66,709			
End of year 1	63,474	3235	135M	20M
End of year 2	60,395	3078	102.2M	19.7M
End of year 3	57,466	2929	72.5M	19.3M
End of year 4	54,679	2787	40M	18.9M
End of year 5	52,027	2652	0	18.4M
Total		14,682	349.7M	96.3M

AMD: Age-related macular degeneration

Treatment module B: No age-related eye disease study formulation followed by ranibizumab (as needed) for those who have progressed to wet age-related macular degeneration

No anti-oxidant vitamin+Zn (yearly progression rate=6.5%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests
Start of year 1	66,709		
End of year 1	62,073	4636	193.4M
End of year 2	57,759	4314	164.3M
End of year 3	53,744	4014	99.4M
End of year 4	50,009	3735	53.5M
End of year 5	46,534	3476	0
Total		20,175	510.5M

AMD: Age-related macular degeneration

Treatment module C: Age-related eye disease study formulation followed by bevacizumab (monthly) for those who have progressed to wet age-related macular degeneration

Anti-oxidant vitamin+Zn (yearly progression rate=4.4%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests	Cost for Anti-oxidant vitamin+Zn treatment
Start of year 1	66,709			
End of year 1	63,474	3235	76.6M	20M
End of year 2	60,395	3078	55.4M	19.7M
End of year 3	57,466	2929	36.2M	19.3M
End of year 4	54,679	2787	18.4M	18.9M
End of year 5	52,027	2652	0	18.4M
Total		14,682	186.6M	96.3M

AMD: Age-related macular degeneration

Treatment module D: No age-related eye disease study formulation followed by bevacizumab (monthly) for those who have progressed to wet age-related macular degeneration

No anti-oxidant vitamin+Zn (yearly progression rate=6.5%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests
Start of year 1	66,709		
End of year 1	62,073	4636	109.7M
End of year 2	57,759	4314	98.8M
End of year 3	53,744	4014	49.5M

Contd...

Treatment module D: Contd...

No anti-oxidant vitamin+Zn (yearly progression rate=6.5%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests
End of year 4	50,009	3735	24.8M
End of year 5	46,534	3476	0
Total		20,175	282.8M

AMD: Age-related macular degeneration

Treatment module E: Age-related eye disease study formulation followed by aflibercept for those who have progressed to wet age-related macular degeneration

Anti-oxidant vitamin+Zn (yearly progression rate=4.4%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests	Cost for Anti-oxidant vitamin+Zn treatment
Start of year 1	66,709			
End of year 1	63,474	3235	125.6M	20M
End of year 2	60,395	3078	95.1M	19.7M
End of year 3	57,466	2929	67.1M	19.3M
End of year 4	54,679	2787	43.2M	18.9M
End of year 5	52,027	2652	0	18.4M
Total		14,682	331M	96.3M

AMD: Age-related macular degeneration

Treatment module F: No age-related eye disease study formulation followed by aflibercept for those who have progressed to wet age-related macular degeneration

No anti-oxidant vitamin+Zn (yearly progression rate=6.5%)	Number of category 3 or 4 patients	Number of wet AMD cases	Cost for treating wet AMD+consultation costs and diagnostic tests
Start of year 1	66,709		
End of year 1	62,073	4636	179.9M
End of year 2	57,759	4314	154.4M
End of year 3	53,744	4014	93.0M
End of year 4	50,009	3735	57.8M
End of year 5	46,534	3476	0
Total		20,175	485.1M

AMD: Age-related macular degeneration