SUPPLEMENTARY MATERIALS

Title: Cost-effectiveness Analysis of Ranibizumab Biosimilar for Neovascular Age-related Macular Degeneration in Japan

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Supplementary Table S1: Overview of transition probabilities and treatment frequencies

Time Period	Treatment and Regimen	Source
Induction (first 3 months)	RBZ BS TAE RBZ TAE	RIVAL [1]
	RBZ PRN	CATT [2]
	AFL TAE	(Base case) RIVAL [1]
		(Scenario) Ohji et al. [3]
Maintenance: Year 1–2	RBZ BS TAE RBZ TAE	RIVAL [1]
	RBZ PRN	CATT [2, 4]
	AFL TAE	(Base case) RIVAL [1]
		(Scenario) Ohji et al. [3]
Maintenance: Year ≥3	RBZ BS TAE RBZ TAE	CANTREAT [5]
	RBZ PRN	CATT [6]
	AFL TAE	CANTREAT [5]
BSC and off-treatment		Wong et al. (2008) [7]

AFL: aflibercept; BS: biosimilar; BSC: best supportive care; PRN: pro re-nata; RBZ: ranibizumab; TAE: treat-and-extend.

Supplementary Table S2: Transition probabilities

Sub-health State-transition	RBZ BS TAE	RBZ BS PRN	RBZ TAE	RBZ PRN	AFL TAE	AFL to RBZ BS TAE	BSC
Base case							
Induction (for the first 3 months)							
Improving 1 health state	17.50%	17.50%	17.50%	17.50%	13.65%	13.65%	0.00%
Improving 2 health states	1.17%	1.17%	1.17%	1.17%	0.68%	0.68%	0.00%
Worsening 1 health state	3.07%	3.07%	3.07%	3.07%	4.02%	4.02%	14.10%
Worsening 2 health states	0.06%	0.06%	0.06%	0.06%	0.08%	0.08%	10.10%
Maintenance: Year 1 (Months 4–12)							
Improving 1 health state	12.75%	13.66%	12.75%	13.66%	13.43%	12.75%	0.00%
Improving 2 health states	1.04%	1.48%	1.04%	1.48%	1.33%	1.04%	0.00%
Worsening 1 health state	8.35%	9.58%	8.35%	9.58%	9.06%	8.35%	12.90%
Worsening 2 health states	0.51%	0.81%	0.51%	0.81%	0.68%	0.51%	18.20%
Maintenance: Year 2							
Improving 1 health state	12.51%	13.09%	12.51%	13.09%	11.90%	12.51%	0.00%
Improving 2 health states	1.74%	1.96%	1.74%	1.96%	1.23%	1.74%	0.00%
Worsening 1 health state	13.54%	13.35%	13.54%	13.35%	11.63%	13.54%	27.00%
Worsening 2 health states	1.99%	2.03%	1.99%	2.03%	1.18%	1.99%	28.30%
Maintenance: ≥Year 3							
Improving 1 health state	2.20%	0.16%	2.20%	0.16%	2.20%	2.20%	0.00%
Improving 2 health states	0.01%	0.00%	0.01%	0.00%	0.01%	0.01%	0.00%
Worsening 1 health state	4.10%	4.83%	4.10%	4.83%	4.10%	4.10%	27.00%
Worsening 2 health states	0.02%	0.00%	0.02%	0.00%	0.02%	0.02%	28.30%
Scenario by the indirect treatment comparison [3]							

Sub-health State-transition	RBZ BS TAE	RBZ BS PRN	RBZ TAE	RBZ PRN	AFL TAE	AFL to RBZ BS TAE	BSC
Induction (for the first 3 months)							
Improving 1 health state	17.50%	17.50%			17.29%		
Improving 2 health states	1.17%	1.17%			1.14%		
Worsening 1 health state	3.07%	3.07%			3.13%		
Worsening 2 health states	0.06%	0.06%			0.06%		
Maintenance: Year 1 (Months 4–12)							
Improving 1 health state	12.75%	12.75%			12.59%		
Improving 2 health states	1.04%	1.04%			1.02%		
Worsening 1 health state	8.35%	8.35%			8.47%		
Worsening 2 health states	0.51%	0.51%			0.52%		
Maintenance: Year 2							
Improving 1 health state	12.51%	12.51%			12.38%		
Improving 2 health states	1.74%	1.74%			1.71%		
Worsening 1 health state	13.54%	13.54%			13.67%		
Worsening 2 health states	1.99%	1.99%			2.03%		
Maintenance: ≥Year 3							
Improving 1 health state	2.20%	2.20%			2.20%		
Improving 2 health states	0.01%	0.01%			0.01%		
Worsening 1 health state	4.10%	4.10%			4.10%		
Worsening 2 health states	0.02%	0.02%			0.02%		

AFL: aflibercept; BS: biosimilar; BSC: best supportive care; PRN: pro re-nata; RBZ: ranibizumab; TAE: treat-and-extend.

Supplementary Table S3: Treatment frequencies

Treatment	Frequency in Induction Phase (for the First 3 Months)	Frequency in Maintenance Phase (per cycle)		
		Year 1	Year 2	Year ≥3
Base case				
RBZ BS TAE	3.0	2.23	2.23	1.83
RBZ BS PRN	3.0	1.30	1.43	1.28
RBZ TAE	3.0	2.23	2.23	1.83
RBZ PRN	3.0	1.30	1.43	1.28
AFL TAE	3.0	2.23	2.08	1.83
AFL to RBZ BS TAE	3.0	2.23	2.23	1.83
Scenario by the indirect treatment comparison [3]				
RBZ BS TAE	3.0	2.23	2.23	1.83
RBZ TAE	3.0	2.23	2.23	1.83
AFL TAE	3.0	1.23	1.48	1.48

AFL: aflibercept; BS: biosimilar; PRN: pro re-nata; RBZ: ranibizumab; TAE: treat-and-extend.

Supplementary Table S4: Annual incidence of fellow-eye involvement and annual discontinuation rate

Parameter	Values	Source
Annual incidence of fellow-eye involvement		
Year 1	3.40%	Ueta et al. [8]
Year 2	2.95%	
Year 3	2.95%	
Annual discontinuation rate		
Induction: for the first 3 months	1.88%	Expert opinion
Maintenance: Year 1	5.63%	
Maintenance: Year 2	15.00%	
Maintenance: Year ≥ 3	15.00%	

Supplementary Table S5: Annual rate of adverse events

Adverse Events Affecting Utility	Disutility	RBZ BS TAE	RBZ TAE	RBZ PRN	RBZ BS PRN	AFL TAE	AFL to RBZ BS TAE	BSC
Retinal artery embolism/occlusion	0.14	0.70%	0.70%	0.70%	0.70%	0.00%	0.70%	0.00%
End-ophthalmitis	0.30	0.00%	0.00%	0.00%	0.00%	0.70%	0.00%	0.00%
Traumatic lens injury	0.14	0.35%	0.35%	0.00%	0.00%	0.00%	0.35%	0.00%
Retinal detachment	0.27	0.00%	0.00%	0.00%	0.00%	0.70%	0.00%	0.00%

AFL: aflibercept; BS: biosimilar; BSC: best supportive care; PRN: pro re-nata; RBZ: ranibizumab; TAE: treat-and-extend.

Supplementary Table S6: Health utility data (Yanagi et al. [9])

Health State	Single Eye[*]	Both Eye[†]
No visual impairment (1≥BCVA>0.8)	0.777	0.777
Mild impairment (0.8≥BCVA>0.4)	0.752	0.741
Moderate impairment (0.4≥BCVA>0.2)	0.727	0.686
Severe impairment (0.2≥BCVA>0.05)	0.702	0.614
Blindness (0.05≥BCVA≥0)	0.677	0.500
Death	0.000	0.000

BCVA: best-corrected visual acuity.
[*]Utility is derived based on the worse-seeing eye.
[†]Utility is derived based on the better-seeing eye.

Supplementary Table S7: Drug acquisition cost, intravitreal injection fee and adverse event cost

Item	Details	Cost (JPY, as of April 2022)	Source
Drug acquisition cost			
RBZ BS	Ranibizumab BS intravitreal injection kit 10 mg/mL	79,348.0	MHLW [10]
RBZ (Lucentis®)	Lucentis kit for intravitreal injection 10 mg/mL	113,702.0	
AFL (Eylea®)	Eylea kit for intravitreal injection 40 mg/mL	137,292.0	
Intravitreal Injection fee			
Intravitreal injection	Code G016 (intravitreal injection)	5,800/time	MHLW, Physician fee schedule as of fiscal year 2022 [11]
Adverse event cost			
Retinal artery embolism/occlusion	Assuming vasodilators, thrombolytics, IOP-lowering eye drops or surgery (expert opinion)	9086.5	Expert opinion and the Physician Fee Schedule as of 2022 [11]
End-ophthalmitis	Code K279 (vitrectomy anterior approach and vitrectomy pars plana approach)	156,622.0	
Traumatic lens injury	Procedure used: inpatient ophthalmology stay (1–2 days, depends on patient vs. nurse ratio)	178,400.0	
Retinal detachment	Code K277 (cryotherapy to region of the retina)	389,500.0	

AFL: aflibercept; BS: biosimilar; IOP: intraocular pressure; JPY: Japanese Yen; MHLW: Ministry of Health, Labour and Welfare; RBZ: ranibizumab

Supplementary Table S8: Costs and resource utilization regarding monitoring and management

Cost by Category	Unit Cost (JPY, as of April 2022)	Resource Utilisation (per Cycle)					Source
		RBZ BS TAE & RBZ TAE	RBZ BS PRN & RBZ PRN	AFL TAE	AFL to RBZ BS TAE	BSC	
Year 1							
Physician visit	740.0	2.00	3.00	2.00	2.00	1.00	Expert opinion and the Physician Fee Schedule as of 2022 [11]
OCT	2,000.0	2.00	3.00	2.00	2.00	1.00	
Slit-lamp biomicroscopy	1,120.0	2.00	3.00	2.00	2.00	1.00	
Fluorescence angiography	4,000.0	0.25	0.25	0.25	0.25	0.5	
Year ≥2							
Physician visit	740.0	1.50	2.25	1.50	1.50	1.00	Expert opinion and the Physician Fee Schedule as of 2022 [11]
OCT	2,000.0	1.50	2.25	1.50	1.50	1.00	
Slit-lamp biomicroscopy	1,120.0	1.50	2.25	1.50	1.50	1.00	
Fluorescence angiography	4,000.0	0.25	0.25	0.25	0.25	0.5	

AFL: aflibercept; BS: biosimilar; BSC: best supportive care; JPY: Japanese Yen; OCT: optical coherence tomography; PRN: pro re-nata; RBZ: ranibizumab; TAE: treat-and-extend.

Supplementary Table S9: Societal costs (productivity loss of informal caregivers)

Parameter	Single Eye	Both Eyes	Source
Physician visit (annual)			
No visual impairment	No	No	• Physician visit was calculated based on (Transportation cost) + (Visiting physician [one day loss]) • Average daily wage in the Japanese labours: ¥15,218.2 (Basic Survey on Wage Structure in 2021 [12])
Mild impairment	No	Yes	
Moderate impairment	Yes	Yes	
Severe impairment	Yes	Yes	
Blindness	Yes	Yes	
Daily care costs (annual) (JPY)			
No visual impairment (1≥BCVA>0.8)	0.0	0.0	• Based on expert opinions for productivity loss of caregivers • Average daily wage in the Japanese labours: ¥15,218.2 (Basic Survey on Wage Structure in 2021 [12])
Mild impairment (0.8≥BCVA>0.4)	0.0	913,091.0	
Moderate impairment (0.4≥BCVA>0.2)	547,855.0	1,095,709.0	
Severe impairment (0.2≥BCVA>0.05)	1,095,709.0	2,739,273.0	
Blindness (0.05≥BCVA≥0)	1,826,182.0	5,478,545.0	

BCVA: best-corrected visual acuity; JPY: Japanese Yen.

Supplementary Table S10: PSA distributions by parameter

Parameter	PSA distribution
Treatment-specific parameters	
Transition probabilities	Beta
Treatment frequencies	Gamma
Adverse event rate	Beta
Discontinuation rate	Beta
Incidence of fellow-eye involvement	Beta
Resource use parameters	
Monitoring and management resource use	Gamma
Cost parameters	
Treatment administration costs	Gamma
Monitoring and management resource use	Gamma
Adverse event costs	Gamma
Societal costs	Gamma
Utility parameters	
Utilities	Beta

PSA: probabilistic sensitivity analysis.

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