

Title

Intravitreal aflibercept for diabetic macular edema in real-world clinical practice in Japan: 24-month outcomes

Journal

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Supplementary Information 1 Safety specification definitions

Important risks identified	
Intraocular inflammatory response	Anterior chamber cell, anterior chamber fibrin, anterior chamber flare, anterior chamber inflammation, aqueous fibrin, autoimmune uveitis, candida endophthalmitis, choroiditis, chorioretinitis, cyclitis, endophthalmitis, eye infection, eye infection bacterial, eye infection chlamydial, eye infection fungal, eye infection intraocular, eye infection staphylococcal, eye inflammation, hypopyon, infectious iridocyclitis, infective iritis, infective uveitis, iridocyclitis, iritis, mycotic endophthalmitis, non-infectious endophthalmitis, noninfective chorioretinitis, pseudoendophthalmitis, uveitis, vitreal cells, vitreous fibrin, vitritis, necrotizing retinitis
Increased intraocular pressure	Intraocular pressure increased, ocular hypertension
Retinal tear and retinal detachment	Macular detachment, retinal tear, retinal detachment, rhegmatogenous retinal detachment, serous retinal detachment, tractional retinal detachment
Traumatic cataract	Atopic cataract, cataract, cataract cortical, cataract diabetic, cataract nuclear, cataract operation, cataract subcapsular, cataract traumatic, intraocular lens implant, lens capsulotomy, lens discoloration, lens extraction, lenticular injury, lenticular opacities, lenticular operation, posterior lens capsulotomy, radiation cataract, toxic cataract
Important potential risk	
Arterial thromboembolic events	[SMQ] Ischemic central nervous system vascular conditions (SMQ) [Narrow] [SMQ] Ischemic heart disease (SMQ) [Broad]
Important information deficiency	
Events that occurred when used in combination with PRP	–

MedDRA Medical Dictionary for Regulatory Activities; *PRP* panretinal photocoagulation; *SMQ* standardized MedDRA queries

Supplementary Information 2 Prior treatments

	Patients, n (%) ^a
Presence of prior treatment	471 (100)
Panretinal photocoagulation	357 (75.8)
Corticosteroids	184 (39.1)
Other anti-VEGF agents	116 (24.6)
Direct coagulation	75 (15.9)
Surgery	58 (12.3)
Grid coagulation	9 (1.9)
Other	5 (1.1)

VEGF vascular endothelial growth factor

^aCounted under all applicable categories

Supplementary Information 3 Medical history

	Patients, <i>n</i> (%)^a
Safety analysis set	646 (100)
Ocular	270 (41.8)
Cataract	254 (39.3)
Ocular hypertension	8 (1.2)
Conjunctivitis	8 (1.2)
Glaucoma	6 (0.9)
Uveitis	2 (0.3)
Other	17 (2.6)
Non-ocular	135 (20.9)
Hypertension	51 (7.9)
Renal impairment	26 (4.0)
Hypercholesterolemia	16 (2.5)
Old cerebral infarction	16 (2.5)
Angina pectoris	8 (1.2)
Old myocardial infarction	6 (0.9)
Hypertriglyceridemia	5 (0.8)
Acute myocardial infarction	3 (0.5)
Impaired liver function	2 (0.3)
Cerebral hemorrhage	2 (0.3)
Subarachnoid hemorrhage	1 (0.2)
Other	49 (7.6)

^aCounted under all applicable categories

Supplementary Information 4 Combination therapies^a

	Patients, n (%)^b
Safety analysis set	646 (100)
Absence of combination therapies	434 (67.2)
Presence of combination therapies^a	201 (31.1)
Panretinal photocoagulation	80 (12.4)
Corticosteroids	55 (8.5)
Surgery	52 (8.0)
Direct coagulation	45 (7.0)
Grid coagulation	3 (0.5)
Other	10 (1.5)

^aDrug treatment other than IVT-AFL, photocoagulation or surgery, performed for DME after the first dose of IVT-AFL

^bCounted under all applicable categories

Supplementary Information 5 Comorbidities at baseline

	Patients, <i>n</i> (%) ^a
Safety analysis set	646 (100)
Ocular	209 (32.4)
Cataract	165 (25.5)
Glaucoma	38 (5.9)
Ocular hypertension	9 (1.4)
Conjunctivitis	9 (1.4)
Retinal pigment epitheliopathy	2 (0.3)
Other	23 (3.6)
Non-ocular	222 (34.4)
Hypertension	159 (24.6)
Renal impairment	66 (10.2)
Hypercholesterolemia	57 (8.8)
Hypertriglyceridemia	21 (3.3)
Angina pectoris	12 (1.9)
Impaired liver function	7 (1.1)
Old cerebral infarction	3 (0.5)
Old myocardial infarction	1 (0.2)
Other	47 (7.3)

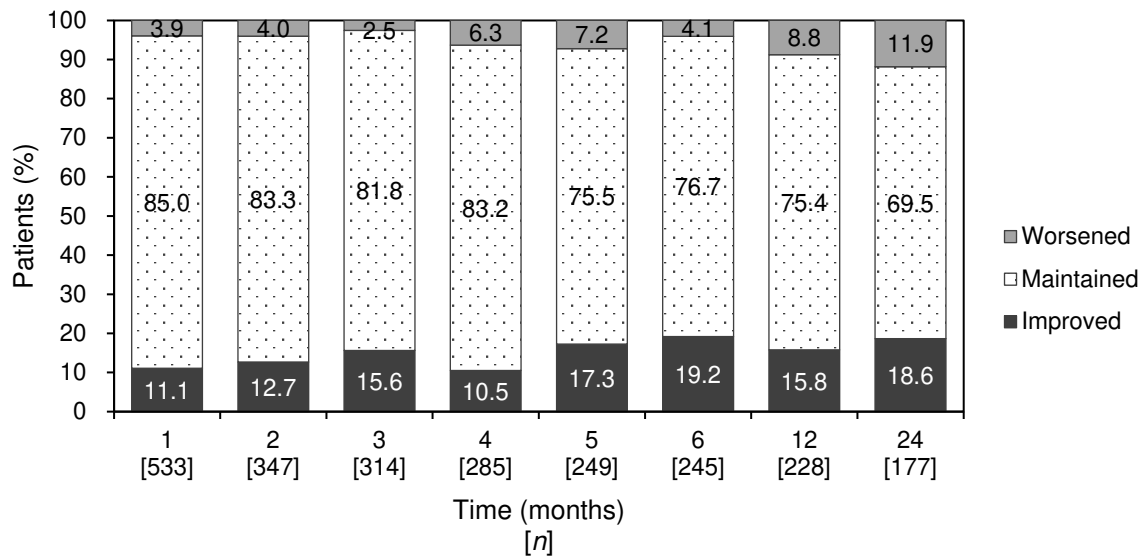
^aCounted under all applicable categories

Supplementary Information 6 Incidence of adverse events and adverse drug reactions

Safety analysis set (n =646)	Patients, n (%)			
	AE	SAE	ADR	SADR
Total events	42 (6.50) ^a	24 (3.72) ^a	12 (1.86)	7 (1.08)
Ocular events, total	27 (4.18) ^a	9 (1.39) ^a	8 (1.24)	4 (0.62)
Eye disorders	22 (3.41) ^a	7 (1.08)	6 (0.93)	3 (0.46)
Vitreous hemorrhage	5 (0.77)	0	0	0
Cataract	4 (0.62)	2 (0.31)	3 (0.46)	1 (0.15)
Conjunctivitis allergic	3 (0.46)	0	0	0
Glaucoma	2 (0.31)	1 (0.15)	0	0
Posterior capsule opacification	2 (0.31)	0	0	0
Retinal artery occlusion	1 (0.15)	1 (0.15)	1 (0.15)	1 (0.15)
Tractional retinal detachment	1 (0.15)	1 (0.15)	1 (0.15)	1 (0.15)
Eye pain	1 (0.15)	0	1 (0.15)	0
Iris adhesions	1 (0.15)	1 (0.15)	0	0
Retinal detachment	1 (0.15)	1 (0.15)	0	0
Asthenopia	1 (0.15)	0	0	0
Conjunctival deposit	1 (0.15)	0	0	0
Dry eye	1 (0.15)	0	0	0
Keratitis	1 (0.15)	0	0	0
Ocular hypertension	1 (0.15)	0	0	0
Ulcerative keratitis	1 (0.15)	0	0	0
Investigations	4 (0.62)	1 (0.15)	1 (0.15)	0
Intraocular pressure increased	4 (0.62)	1 (0.15)	1 (0.15)	0
Injury, poisoning, and procedural complications	1 (0.15)	1 (0.15)	1 (0.15)	1 (0.15)
Lenticular injury	1 (0.15)	1 (0.15)	1 (0.15)	1 (0.15)
Infections and infestations	1 (0.15)	1 (0.15)	0	0
Dacryocystitis	1 (0.15)	1 (0.15)	0	0
Nervous system disorders	1 (0.15)	0	0	0
Facial paralysis	1 (0.15)	0	0	0
Non-ocular events, total	18 (2.79) ^a	15 (2.32) ^a	4 (0.62)	3 (0.46)
Nervous system disorders	6 (0.93)	4 (0.62)	3 (0.46)	2 (0.31)
Cerebral infarction	4 (0.62)	4 (0.62)	2 (0.31)	2 (0.31)
Facial paralysis	1 (0.15)	0	1 (0.15)	0
Migraine	1 (0.15)	0	0	0
Infections and infestations	4 (0.62)	4 (0.62)	0	0
Gangrene	2 (0.31)	2 (0.31)	0	0
Peritonitis	1 (0.15)	1 (0.15)	0	0
Sepsis	1 (0.15)	1 (0.15)	0	0
Renal and urinary disorders	3 (0.46)	3 (0.46)	0	0
Chronic kidney disease	3 (0.46)	3 (0.46)	0	0
Cardiac disorders	2 (0.31)	2 (0.31)	1 (0.15)	1 (0.15)
Myocardial infarction	1 (0.15)	1 (0.15)	1 (0.15)	1 (0.15)
Cardiac failure	1 (0.15)	1 (0.15)	0	0
Injury, poisoning, and procedural complications	2 (0.31)	2 (0.31)	0	0
Injury	1 (0.15)	1 (0.15)	0	0
Road traffic accident	1 (0.15)	1 (0.15)	0	0
Investigations	2 (0.31)	0	0	0
Glycosylated hemoglobin increased	2 (0.31)	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.15)	1 (0.15)	0	0
Colon cancer	1 (0.15)	1 (0.15)	0	0
Blood and lymphatic system disorders	1 (0.15)	0	0	0
Anemia	1 (0.15)	0	0	0

^aIncluding patients with multiple events

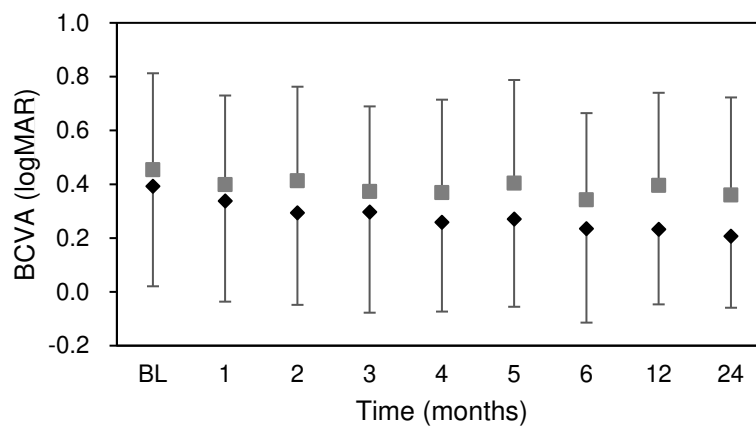
AE adverse event; *SAE* serious adverse event; *ADR* adverse drug reaction; *SADR* serious adverse drug reaction



Supplementary Information 7 Proportions of patients with improved, maintained, or worse BCVA. The logMAR BCVA change from baseline was classified as follows: “improved”, logMAR BCVA change ≤ -0.3 ; “maintained”, logMAR BCVA change between -0.3 and 0.3 ; and “worse”, logMAR BCVA change ≥ 0.3 .

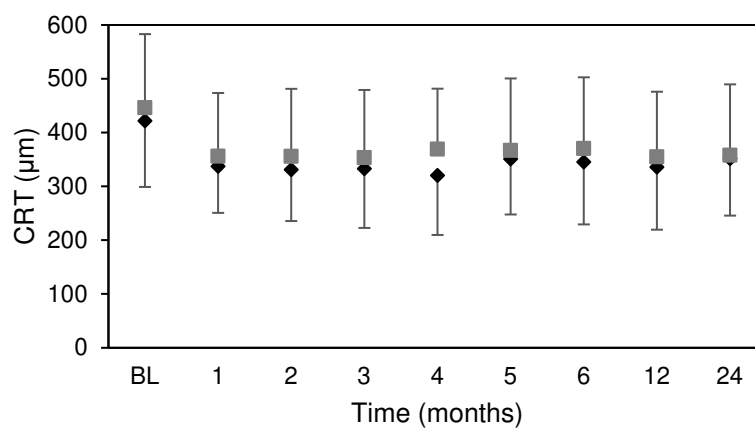
BCVA best-corrected visual acuity; logMAR logarithm of the minimum angle of resolution

a



■ With previous treatment	BCVA (logMAR)	0.454							0.342	0.396	0.360
	[n]	[459]	[395]	[252]	[232]	[211]	[187]	[182]	[167]	[132]	
◆ Without Previous treatment	BCVA (logMAR)	0.393							0.235	0.233	0.207
	[n]	[155]	[133]	[91]	[80]	[71]	[59]	[60]	[59]	[42]	

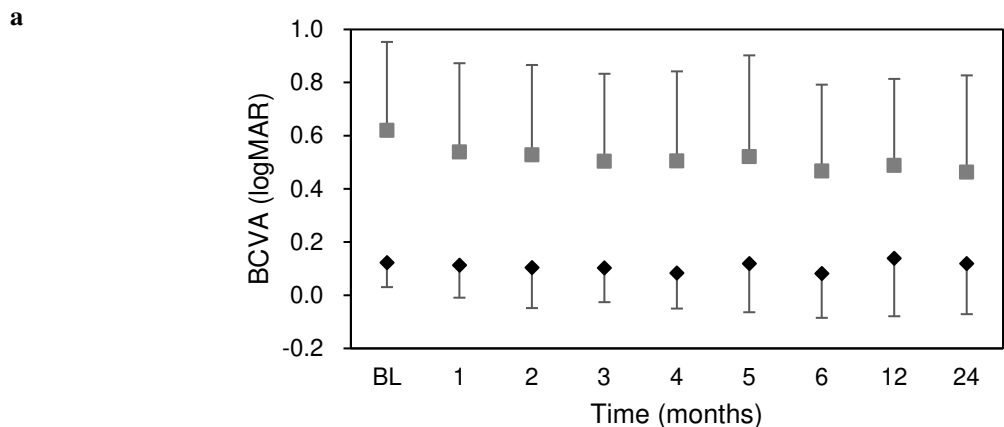
b



■ With previous treatment	CRT (μm)	446.2							370.4	354.9	357.8
	[n]	[343]	[301]	[207]	[193]	[161]	[139]	[146]	[134]	[109]	
◆ Without previous treatment	CRT (μm)	421.7							345.4	335.9	351.7
	[n]	[98]	[85]	[66]	[58]	[43]	[36]	[39]	[43]	[30]	

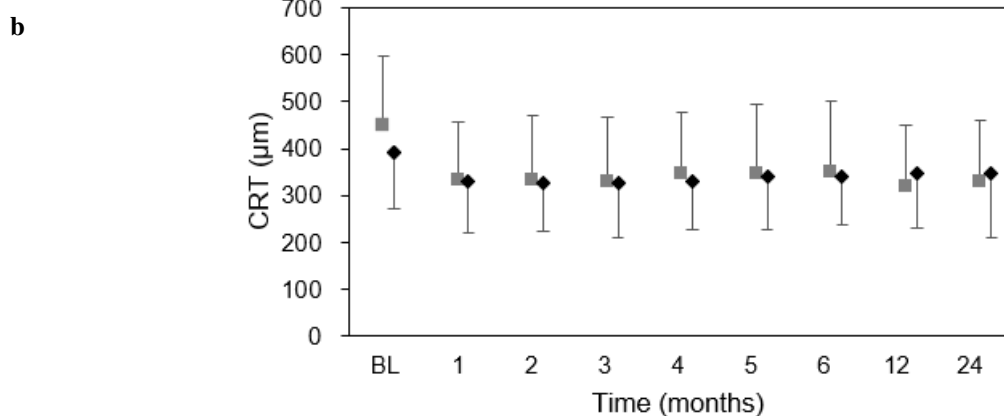
Supplementary Information 8 Subgroup analysis based on the presence/absence of previous treatment. (a) LogMAR BCVAs and numbers of patients during the 24-month study period. (b) CRTs (μm) and numbers of patients during the 24-month study period. The mean and standard deviation are indicated with markers and whiskers, respectively.

BCVA best-corrected visual acuity; BL baseline; CRT central retinal thickness; logMAR logarithm of the minimum angle of resolution



■ BL decimal	BCVA (logMAR)	0.620								0.467	0.488	0.463
	BCVA ≤ 0.5	[n]	[393]	[337]	[225]	[194]	[173]	[154]	[147]	[139]	[104]	

◆ BL decimal	BCVA (logMAR)	0.123										0.082	0.139	0.119
	BCVA > 0.5	[n]	[229]	[196]	[122]	[120]	[112]	[95]	[98]	[89]	[73]			



■ BL decimal	CRT (μm)	464.0										369.1	341.3	349.8
	BCVA ≤ 0.5	[n]	[268]	[234]	[170]	[146]	[117]	[108]	[111]	[107]	[81]			

◆ BL decimal	CRT (μm)	405.4										357.0	361.9	363.4
	BCVA > 0.5	[n]	[176]	[155]	[106]	[107]	[87]	[69]	[76]	[71]	[59]			

Supplementary Information 9 Subgroup analysis based on the baseline decimal BCVA. (a) LogMAR BCVAs and numbers of patients during the 24-month study period. (b) CRTs (μm) and numbers of patients during the 24-month study period. The mean and standard deviation are indicated with markers and whiskers, respectively.

BCVA best-corrected visual acuity; BL baseline; CRT central retinal thickness; logMAR logarithm of the minimum angle of resolution