



pulsar

Extension

PULSAR Extension: Safety analysis of aflibercept 8 mg through 156 weeks in patients with neovascular age-related macular degeneration

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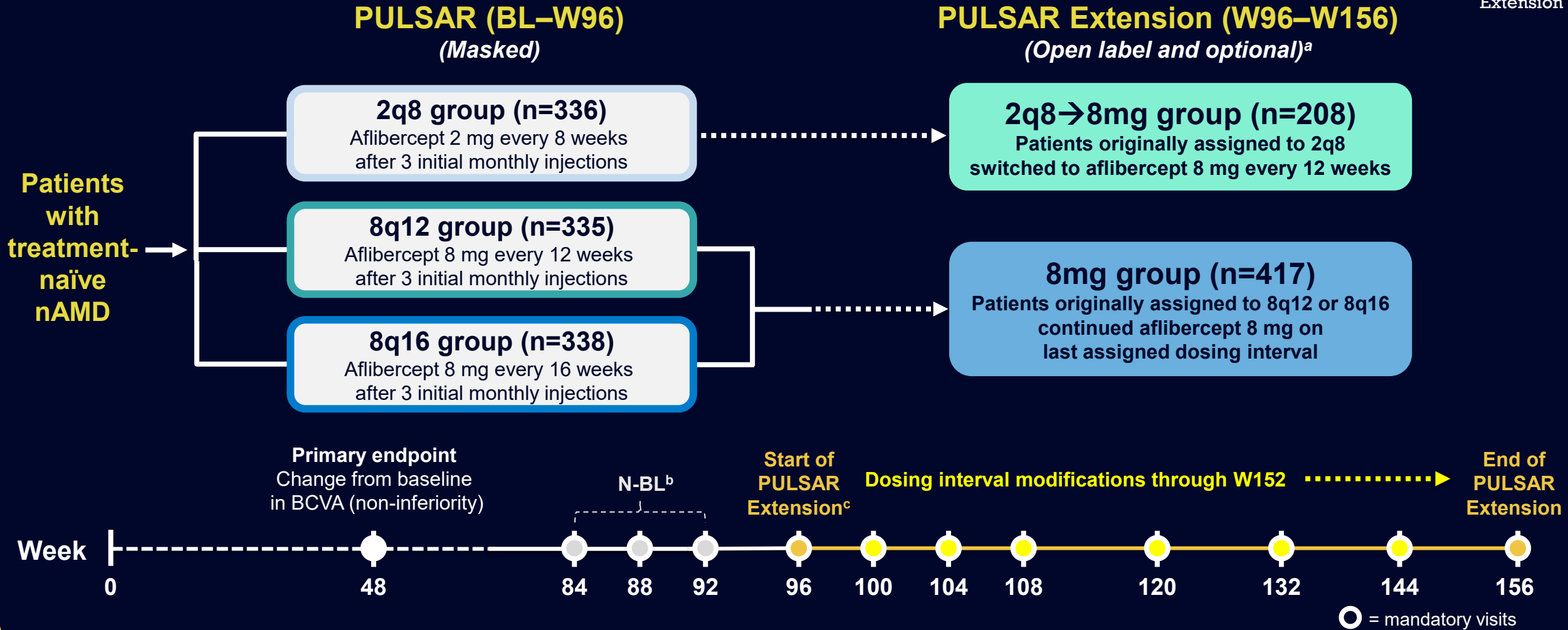
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PULSAR Extension Design



^aTo be eligible for PULSAR Extension, patients were required to have ≥ 1 BCVA and CRT assessments between Week 84 and Week 92. Masked transition period (W96–108) was followed by open-label part (W108–W156). ^bN-BL was an average of values from W84, W88, and W92. ^cOptional phase added while PULSAR was ongoing; therefore, not all patients were able to enroll due to time constraints. **2q8**, aflibercept 2 mg every 8 weeks; **8q12**, aflibercept 8 mg every 12 weeks; **8q16**, aflibercept 8 mg every 16 weeks; **BCVA**, best-corrected visual acuity; **BL**, baseline; **CRT**, central subfield retinal thickness; **nAMD**, neovascular age-related macular degeneration; **N-BL**, new baseline; **W**, week.

Patient Disposition and Baseline Characteristics



	PULSAR	PULSAR Extension		
	Total	2q8→8mg	8mg	Total
Patients entering PULSAR study (FAS), n	1009	–	–	–
Patients entering PULSAR Extension (eFAS), n (%)	–	208 (61.9)^a	417 (62.0)^a	625 (61.9)^a
Completion rate at Week 96, %	85.9	–	–	–
Completion rate at Week 156, %	–	89.9 ^b	90.4 ^b	90.2 ^b
Age, years	74 (8.4)	73.9 (8.2)	74.0 (8.1)	74.0 (8.1)
Female, %	54.5	58.7	55.2	56.3
Race, %				
White	75.8	77.4	77.5	77.4
Black or African American	0.4	0.5	0.5	0.5
Asian	23.2	22.1	21.1	21.4
Other ^c	0.6	0	1.0	0.6
History of hypertension, %	64.3	63.0	65.0	64.3
BCVA, ETDRS letters	59.6 (13.3)	59.6 (13.7)	60.6 (12.7)	60.3 (13.0)
CRT, μm^d	369 (130)	365 (139)	375 (132)	371 (134)
Total lesion area, mm²	6.7 (5.4)	6.8 (5.0)	6.4 (5.2)	6.6 (5.1)
Lesion type, %^e				
Type 1	59.1	58.7	58.3	58.4
Type 2	19.3	21.6	19.2	20.0
Type 1 and Type 2	20.0	17.8	20.9	19.8

Data are mean±SD unless otherwise stated; data are for patients in the FAS (PULSAR) and eFAS (PULSAR Extension) at the main study baseline. ^aProportions were calculated based on the number of patients who initially entered the main PULSAR study. ^bCompletion rate for PULSAR Extension based on eFAS. ^cOther includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and unreported race. ^dData as assessed by reading center. ^eType 3 was observed in <2% of cases in PULSAR and PULSAR Extension.
eFAS, PULSAR Extension FAS analysis set; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **SD**, standard deviation.

AEs in the Study Eye Through Week 156



	PULSAR^a 2q8 (n=336) W0-96	PULSAR Ext^b 2q8→8mg (n=208) W96-156	PULSAR^a 8q12/8q16 (n=673) W0-96	PULSAR Ext^b 8mg (n=417) W96-156
Dosage of aflibercept^c	2 mg	8 mg	8 mg	8 mg
Patients with any ocular TEAE, n (%)	181 (53.9)	67 (32.2)	345 (51.3)	113 (27.1)
Patients with any serious ocular TEAE, n (%)	4 (1.2)	4 (1.9)	20 (3.0)	9 (2.2)
Patients with any ocular drug-related TEAE, n (%)	16 (4.8)	10 (4.8)	40 (5.9)	5 (1.2)
Patients with any ocular TEAE leading to discontinuation, n (%)	4 (1.2)	1 (0.5)	8 (1.2)	0
Patients with any non-ocular TEAE, n (%)	257 (76.5)	102 (49.0)	500 (74.3)	195 (46.8)
Patients with any serious non-ocular TEAE ^d , n (%)	66 (19.6)	21 (10.1)	137 (20.4)	44 (10.6)
Patients with any non-ocular drug-related TEAE, n (%)	7 (2.1)	0	6 (0.9)	5 (1.2)
Patients with any non-ocular TEAE leading to discontinuation, n (%)	5 (1.5)	1 (0.5)	4 (0.6)	0
Patients with any TE APTC-defined arterial thromboembolic events^e, n (%)	11 (3.3)	1 (0.5)	12 (1.8)	4 (1.0)
Patients with IOI-related event, n (%)	7 (2.1)	3 (1.4)	9 (1.3)	4 (1.0)
Patients with any TEAE of hypertension ^e , n (%)	27 (8.0)	7 (3.4)	55 (8.2)	12 (2.9)
Death, n (%)	12 (3.6)	4 (1.9)	17 (2.5)	9 (2.2)

^aSAF. ^beSAF. ^cThe total number of injections for 2q8, 2q8→8mg, 8q12/8q16 and 8mg groups was: 4007, 968, 5711 and 1550, respectively. ^dIn the PULSAR Extension, 4 serious non-ocular TEAEs were considered to be related to study drug treatment: acute myocardial infarction, basal ganglia infarction, coronary artery disease, and pulmonary embolism (all n=1). ^eIn the PULSAR Extension, reported TE APTC events included: myocardial infarction (n=6), acute myocardial infarction, cerebrovascular accident, and death (all n=3), cerebral infarction (n=2), and acute coronary artery, acute coronary syndrome, arteriosclerosis coronary artery, cardiac arrest, carotid aneurysm rupture, cerebral hematoma, myocardial ischemia, and stroke in evolution (all n=1). ^fIn the PULSAR Extension, reported events pertaining to hypertension included: hypertension (n=17), hypertensive heart disease and hypertensive nephropathy (both n=1). **AE**, adverse event; **APTC**, Antiplatelet Trialists' Collaboration; **TE**, treatment emergent; **TEAE**, treatment-emergent adverse event.

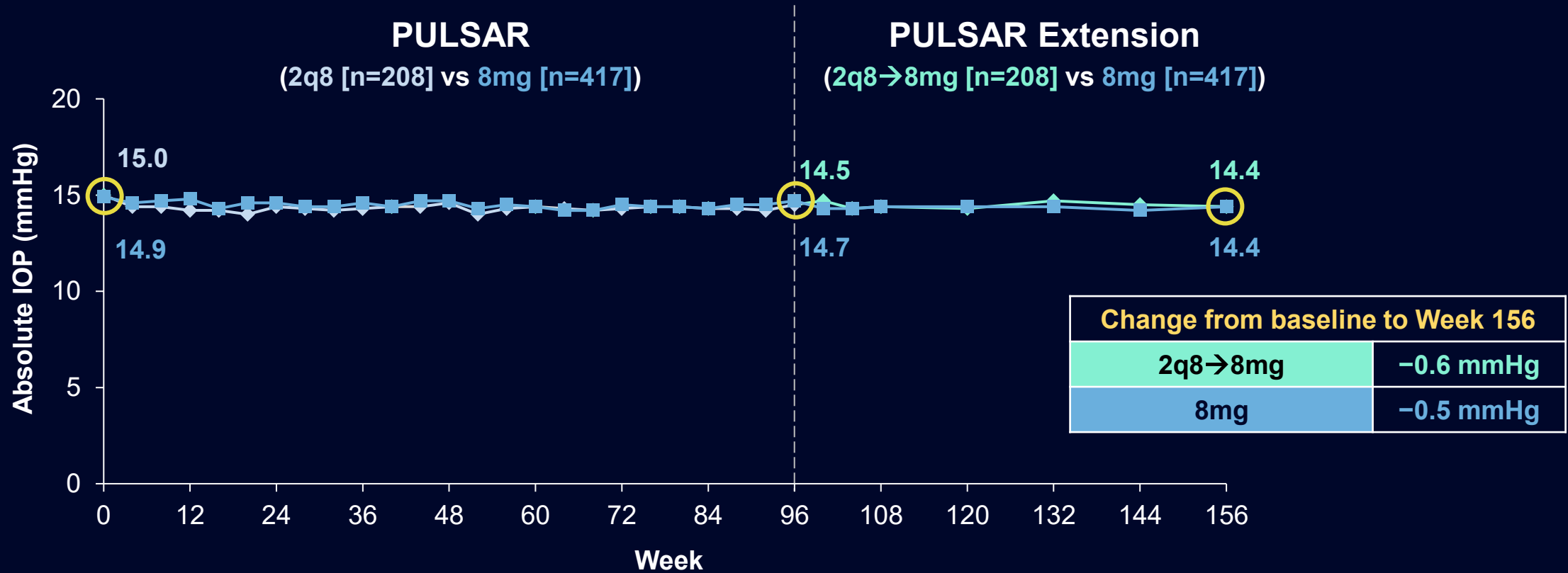
Ocular TEAEs in the Study Eye Through Week 156

Ocular TEAEs reported in $\geq 2\%$ of patients in any group, n (%)	PULSAR ^a 2q8 (n=336) W0-96 2 mg	PULSAR Ext ^b 2q8→8mg (n=208) W96-156 8 mg	PULSAR ^a 8q12/8q16 (n=673) W0-96 8 mg	PULSAR Ext ^b 8mg (n=417) W96-156 8 mg
Cataract	22 (6.5)	8 (3.8)	63 (9.4)	28 (6.7)
Conjunctivitis	9 (2.7)	3 (1.4)	13 (1.9)	5 (1.2)
Conjunctival hemorrhage	9 (2.7)	3 (1.4)	18 (2.7)	3 (0.7)
Dry AMD	7 (2.1)	1 (0.5)	8 (1.2)	3 (0.7)
Dry eye	11 (3.3)	2 (1.0)	16 (2.4)	2 (0.5)
Increased IOP	10 (3.0)	6 (2.9)	23 (3.4)	10 (2.4)
Macular edema	10 (3.0)	5 (2.4)	14 (2.1)	4 (1.0)
Macular thickening	7 (2.1)	2 (1.0)	19 (2.8)	1 (0.2)
nAMD	3 (0.9)	1 (0.5)	18 (2.7)	6 (1.4)
Posterior capsule opacification	2 (0.6)	5 (2.4)	12 (1.8)	3 (0.7)
Retinal hemorrhage	19 (5.7)	8 (3.8)	37 (5.5)	6 (1.4)
Sensation of foreign body	7 (2.1)	1 (0.5)	7 (1.0)	0
Subretinal fluid	16 (4.8)	4 (1.9)	23 (3.4)	2 (0.5)
Visual acuity reduced	24 (7.1)	4 (1.9)	44 (6.5)	10 (2.4)
Vitreous detachment	7 (2.1)	1 (0.5)	20 (3.0)	3 (0.7)
Vitreous floaters	16 (4.8)	2 (1.0)	22 (3.3)	2 (0.5)

Serious Ocular TEAEs in the Study Eye Through Week 156

	PULSAR ^a 2q8 (n=336) W0-96 2 mg	PULSAR Ext ^b 2q8→8mg (n=208) W96-156 8 mg	PULSAR ^a 8q12/8q16 (n=673) W0-96 8 mg	PULSAR ^b Ext 8mg (n=417) W96-156 8 mg
Patients with any serious ocular TEAE, n (%)	4 (1.2)	4 (1.9)	20 (3.0)	9 (2.2)
Angle-closure glaucoma	1 (0.3)	0	1 (0.1)	0
Cataract	0	2 (1.0)	4 (0.6)	5 (1.2)
Cataract operation	0	0	0	1 (0.2)
Corneal abrasion	0	1 (0.5)	0	0
Dry AMD	0	0	1 (0.1)	0
Endophthalmitis	1 (0.3)	1 (0.5)	0	0
Increased IOP	0	0	2 (0.3)	1 (0.2)
Macular detachment	0	0	1 (0.1)	0
Retinal detachment	1 (0.3)	0	5 (0.7)	1 (0.2)
Retinal hemorrhage	1 (0.3)	0	4 (0.6)	1 (0.2)
Retinal tear	0	0	1 (0.1)	0
Skin laceration	0	0	1 (0.1)	0
Vitreous hemorrhage	0	0	1 (0.1)	0
Severity of any serious ocular TEAE, n (%)				
Mild	1 (0.3)	0	0	3 (0.7)
Moderate	1 (0.3)	2 (1.0)	13 (1.9)	3 (0.7)
Severe	2 (0.6)	2 (1.0)	7 (1.0)	3 (0.7)
Any serious ocular drug-related TEAE, n (%)	0	3 (1.4)	1 (0.1)	0
Angle-closure glaucoma	0	0	1 (0.1)	0
Cataract	0	2 (1.0)	0	0
Endophthalmitis	0	1 (0.5)	0	0

PULSAR Extension: Absolute Pre-injection IOP Through Week 156



The mean pre-injection IOP values were comparable across treatment groups, with no sustained increase in IOP through Week 156

IOP-related TEAEs Through Week 156

	PULSAR ^a 2q8 (n=336) W0-96 2 mg	PULSAR Ext ^b 2q8→8mg (n=208) W96-156 8 mg	PULSAR ^a 8q12/8q16 (n=673) W0-96 8 mg	PULSAR Ext ^b 8mg (n=417) W96-156 8 mg
Patients with ≥1 IOP-related TEAE^c, n (%)	13 (3.9)	7 (3.4)	33 (4.9)	13 (3.1)
Angle-closure glaucoma	1 (0.3)	0	2 (0.3)	0
Glaucoma	1 (0.3)	0	4 (0.6)	1 (0.2)
Increased IOP	10 (3.0)	6 (2.9)	23 (3.4)	10 (2.4)
Ocular hypertension	1 (0.3)	1 (0.5)	8 (1.2)	2 (0.5)
Open-angle glaucoma	1 (0.3)	0	0	0

No cases of borderline glaucoma, glaucomatous optic neuropathy, optic nerve cupping, or trabeculectomy were reported through Week 156

^aSAF. ^beSAF. ^cTEAEs in the study eye. An IOP-related TEAE was defined based on the following preferred terms: "Angle closure glaucoma", "Borderline glaucoma", "Glaucoma", "Glaucomatous optic neuropathy", "Intraocular pressure increased", "Ocular hypertension", "Open angle glaucoma", "Optic nerve cupping", and "Trabeculectomy".

IOI-related Events in the Study Eye

	PULSAR ^a 2q8 (n=336) W0-96 2 mg	PULSAR Ext ^b 2q8→8mg (n=208) W96-156 8 mg	PULSAR ^a 8q12/8q16 (n=673) W0-96 8 mg	PULSAR Ext ^b 8mg (n=417) W96-156 8 mg
Total number of injections	4007	968	5711	1550
IOI-related event, n (n/1000 injections)	11 (2.7)	2 (2.1)	12 (2.1)	5 (3.2)
Anterior chamber cell	0	0	1 (0.2)	0
Chorioretinitis	0	0	1 (0.2)	0
Endophthalmitis	2 (0.5)	1 (1.0)	0	0
Eye inflammation	2 (0.5)	0	0	0
Hypopyon	1 (0.2)	0	0	0
Iridocyclitis	2 (0.5)	1 (1.0)	5 (0.9)	2 (1.3)
Iritis	0	0	2 (0.4)	2 (1.3)
Uveitis	1 (0.2)	0	1 (0.2)	0
Vitreous cells	3 (0.7)	0	1 (0.2)	1 (0.6)
Vitritis	0	0	1 (0.2)	0
Occlusive vasculitis	0	0	0	0
Severity of IOI-related events, n (n/1000 injections)				
Mild	9 (2.2)	0	9 (1.6)	5 (3.2)
Moderate	1 (0.2)	1 (1.0)	3 (0.5)	0
Severe	1 (0.2)	1 (1.0)	0	0

The incidence of IOI-related events per 1000 aflibercept injections was low (2-3/1000 injections) in PULSAR and PULSAR Extension and comparable in both the 2q8→8mg and 8mg groups during PULSAR Extension

IOI-related Events with Moderate or Severe Intensity in the Study Eye

Most IOI-related events, 23/30 (76.7%), were mild

IOI-related events with moderate or severe maximum intensity (n=7)

IOI-related event	Patients, n	Treatment group	Severity	Treatment status
Endophthalmitis	2	2q8 ^a	Severe	Interrupted
		2q8→8mg ^{a,b}	Severe	Dose not changed
Iridocyclitis	2	2q8→8mg	Moderate	Dose not changed
		8q12/8q16 ^{b,c}	Moderate	Withdrawn
Uveitis	2	2q8 ^b	Moderate	Withdrawn
		8q12/8q16 ^c	Moderate	Study ended
Vitritis	1	8q12/8q16 ^a	Moderate	Dose not changed

All events that occurred during PULSAR Extension resolved or were resolving at the time of the analysis

Conclusions

Ocular TEAEs

- The rates of ocular TEAEs and serious ocular TEAEs in the study eye were **comparable** between the aflibercept 2q8→8mg and 8mg groups during PULSAR Extension

Rates of IOP increase and APTC events

- The rates of IOP increase and APTC-defined arterial thromboembolic events were **similar** for the aflibercept 2q8→8mg and 8mg groups during PULSAR Extension

Incidence and severity of IOI-related events

- **During PULSAR Extension**, both the aflibercept 2q8→8mg and 8mg treatment groups experienced a **low incidence of IOI-related events**
- **Most events were mild in severity**; patients with moderate or severe events in the study eye had **recovered or were recovering** at the time of analysis

Safety profile

- The **safety profile of aflibercept 8 mg** from baseline to W156 was **comparable** between patients who were **switched** from **aflibercept 2 mg to 8 mg** at W96 and those who **received aflibercept 8 mg continuously** through W156
- The results were **consistent** with the **overall safety profile** of aflibercept 8 mg