PULSAR Extension: Safety Analysis of Aflibercept 8 mg Through 156 Weeks in Patients with Neovascular Age-related Macular Degeneration

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Disclosures

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PULSAR Extension Design

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PULSAR (BL–W96)
(Masked)

Patients with treatment-naïve nAMD

2q8 arm (n=336)
Aflibercept 2 mg every 8 weeks after 3 initial monthly injections

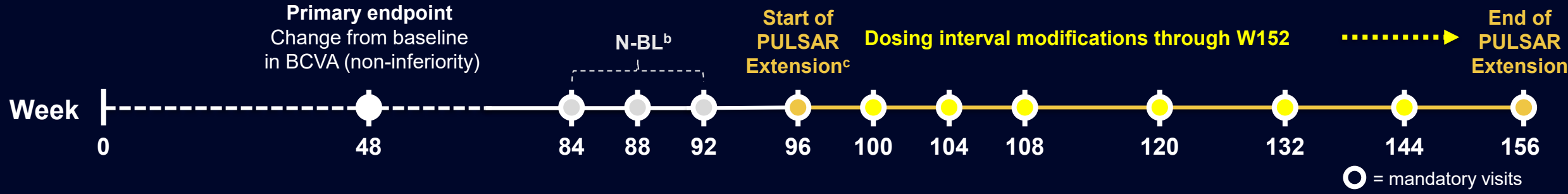
8q12 arm (n=335)
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections

8q16 arm (n=338)
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections

PULSAR Extension (W96–W156)
(Open-label and optional)[a]

2q8→8mg arm (n=208)
Patients originally assigned to 2q8 switched to aflibercept 8 mg every 12 weeks

8mg arm (n=417)
Patients originally assigned to 8q12 or 8q16 continued aflibercept 8 mg on last assigned dosing interval



[a]To be eligible for PULSAR Extension, patients had 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). [b]N-BL was an average of values from W84, 88, and 92. [c]Optional 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

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	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, %				
Occult	58.2	57.7	57.1	57.5
Predominantly classic	20.7	23.1	22.4	18.8
Minimally classic	18.6	15.9	18.1	20.3

Data are mean±SD unless otherwise stated; data are for patients in the FAS (PULSAR) and eFAS (PULSAR Extension) at the main study baseline. [a]Proportions were calculated based on the number of patients who initially entered the main PULSAR study. [b]Completion rate for PULSAR Extension based on eFAS. [c]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and unreported race. [d]Data as assessed by reading center. **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

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	PULSAR[a] 2q8 (n=336) W0–96	PULSAR Extension[b] 2q8→8mg (n=208) W96–156	PULSAR[a] 8q12/8q16 (n=673) W0–96	PULSAR Extension[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)

[a]SAF. [b]eSAF. [c]The total number of injections for 2q8, 2q8→8mg, 8q12/8q16 and 8mg groups was: 4007, 968, 5711 and 1550, respectively. [d]In the PULSAR Extension, 4 serious non-ocular TEAEs were considered related to study drug treatment: acute myocardial infarction, basal ganglia infarction, coronary artery disease, and pulmonary embolism (all n=1). [e]In 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). [f]In 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 Occurring in the Study Eye for ≥2% of Patients in Any Arm Through Week 156

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	PULSAR[a] 2q8 (n=336) W0–96	PULSAR Extension[b] 2q8→8mg (n=208) W96–156	PULSAR[a] 8q12/8q16 (n=673) W0–96	PULSAR Extension[b] 8mg (n=417) W96–156
Dosage of aflibercept	2 mg	8 mg	8 mg	8 mg
Ocular TEAEs reported in ≥2% of patients in any arm, n (%)				
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)

[a]SAF. [b]eSAF. **AMD**, age-related macular degeneration; **IOP**, intraocular pressure.

Ocular SAEs 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[b] Ext 8mg (n=417) W96–156
Dosage of aflibercept[c]	2 mg	8 mg	8 mg	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

[a]SAF. [b]eSAF. [c]The total number of injections for 2q8, 2q8→8mg, 8q12/8q16 and 8mg groups was: 4007, 968, 5711 and 1550, respectively.

PULSAR Extension: Absolute Pre-injection IOP Through Week 156

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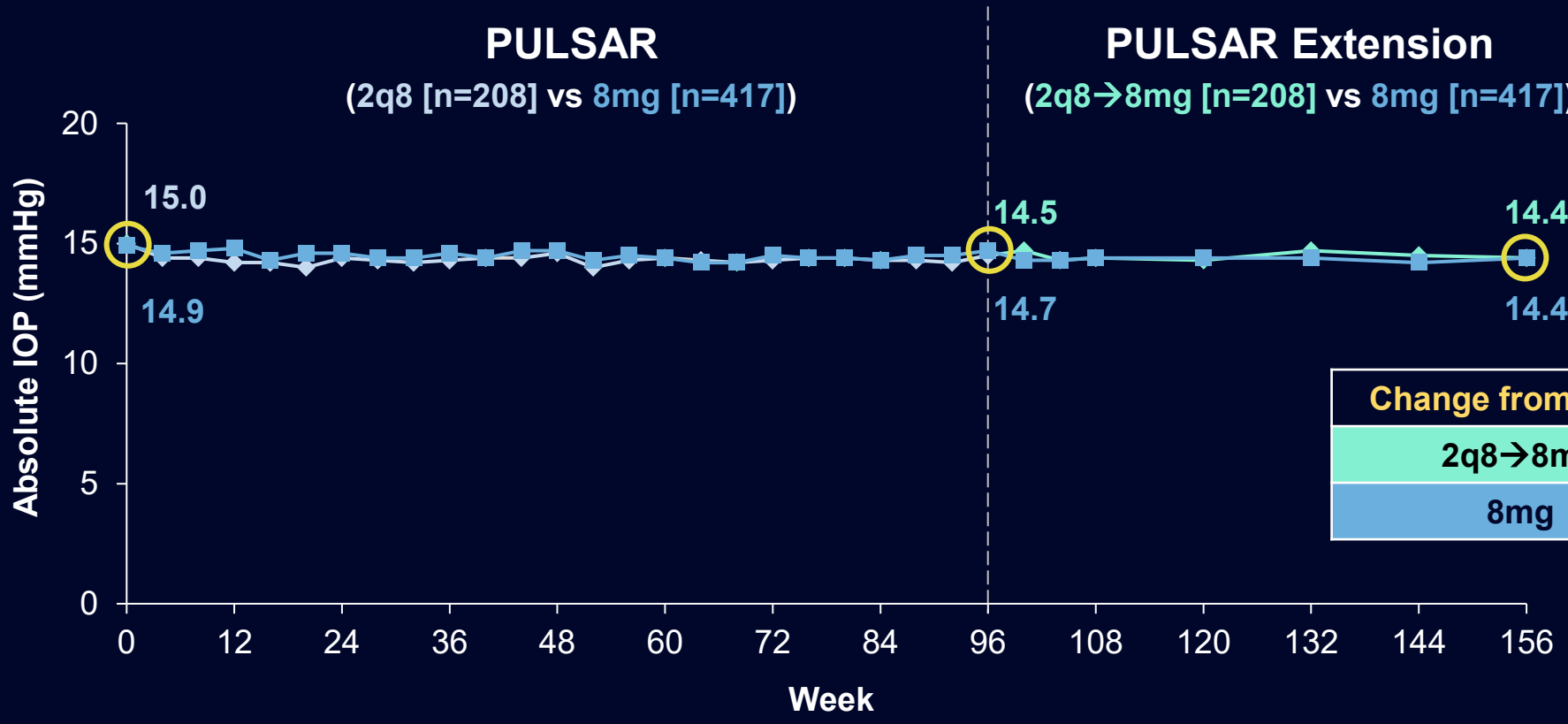

Change from baseline to Week 156	
2q8→8mg	−0.6 mmHg
8mg	−0.5 mmHg

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

eSAF. **mmHG**, millimeters of mercury.

IOP-related TEAEs Through Week 156

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	PULSAR[a] 2q8 (n=336) W0–96	PULSAR Extension[b] 2q8→8mg (n=208) W96–156	PULSAR[a] 8q12/8q16 (n=673) W0–96	PULSAR Extension[b] 8mg (n=417) W96–156
Dosage of aflibercept[c]	2 mg	8 mg	8 mg	8 mg
Patients with ≥1 IOP-related TEAE[d], 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 trabeculoplasty were reported through Week 156

[a]SAF. [b]eSAF. [c]The total number of injections for 2q8, 2q8→8mg, 8q12/8q16 and 8mg groups was: 4007, 968, 5711 and 1550, respectively. [d]TEAEs 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 “Trabeculoplasty”.

Conclusions

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Ocular TEAEs	• **Rates of ocular TEAEs and SAE in the study eye were comparable** between the aflibercept 2q8→8mg and 8mg arms during the PULSAR Extension, with **no cases of occlusive vasculitis reported**
Rates of IOP increase and APTC events	• **Rates of IOP increase and APTC-defined arterial thromboembolic events were comparable** for the aflibercept 2q8→8mg and 8mg arms during the PULSAR Extension
Safety profile	• The **safety profile was comparable through Week 156** for patients who switched from aflibercept 2 mg to 8 mg at Week 96 to that of patients who received aflibercept 8 mg from PULSAR baseline • The safety profiles of aflibercept 2q8→8mg and 8mg arms in PULSAR Extension were **consistent with the known safety profile of aflibercept 8 mg**