PULSAR Extension: Intraocular Inflammation-related Events with 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

Primary endpoint
Change from baseline in BCVA (non-inferiority)

N-BL[b]

Start of PULSAR Extension[c]

Dosing interval modifications through W152

End of PULSAR Extension

Week: 0, 48, 84, 88, 92, 96, 100, 104, 108, 120, 132, 144, 156

= mandatory visits

[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 full analysis set; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **SD**, standard deviation.

Ocular Safety in the Study Eye

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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
Total number of injections	4007	968	5711	1550
Patients with any ocular TEAE, n (%)	**181 (53.9)**	**67 (32.2)**	**345 (51.3)**	**113 (27.1)**
Mild	129 (38.4)	48 (23.1)	226 (33.6)	74 (17.7)
Moderate	46 (13.7)	16 (7.7)	107 (15.9)	35 (8.4)
Severe	6 (1.8)	3 (1.4)	12 (1.8)	4 (1.0)
Patients with any serious ocular TEAE, n (%)	**4 (1.2)**	**4 (1.9)**	**20 (3.0)**	**9 (2.2)**
Mild	1 (0.3)	0	0	4 (1.0)
Moderate	1 (0.3)	2 (1.0)	13 (1.9)	2 (0.5)
Severe	2 (0.6)	2 (1.0)	7 (1.0)	3 (0.7)

- **Aflibercept 8 mg demonstrated comparable safety to 2 mg for up to 96 weeks during PULSAR**
- **Ocular safety in the study eye was comparable between the 2q8→8mg arm and 8mg arm during the PULSAR Extension**
- **Ocular TEAEs reported in ≥2% of patients in PULSAR Extension (N=625) include cataract, retinal hemorrhage, increased intraocular pressure, macular edema, posterior capsule opacification, and reduced visual acuity**
- **No cases of occlusive vasculitis were reported**

[a]SAF; [b]eSAF. **eSAF**, PULSAR Extension safety analysis set; **SAF**, safety analysis set in the PULSAR; **TEAE**, treatment-emergent adverse event.

Ocular TEAEs with Severe Maximum Intensity in the Study Eye Through Week 156

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Ocular TEAE event	Patients, n	Treatment arm	Treatment status
Blindness transient	1	8q12/8q16[a]	Dose Not changed
Cataract	2	8q12/8q16[a,b] 8mg	Dose not changed Dose not changed
Circulatory collapse	1	2q8→8mg[a]	Dose not changed
Corneal abrasion	1	2q8→8mg[a]	Dose not changed
Detachment of retinal pigment	1	2q8[c,e]	Dose not changed
Endophthalmitis	2	2q8[a] 2q8→8mg[a,d]	Interrupted Dose not changed
IOP increase	1	8q12/8q16[a]	Dose not changed
Macular detachment	1	8q12/8q16	Interrupted
Macular hole	1	2q8[b]	Withdrawn
Pain	1	8q12/8q16	Dose not changed
Photopsia	1	8q12/8q16[c]	Dose not changed
Retinal detachment	3	8q12/8q16 8q12/8q16 8mg	Dose not changed Interrupted Dose not changed
Retinal hemorrhage	6	2q8[e] 2q8 8q12/8q16[b] 8q12/8q16[f] 8q12/8q16[b,e] 8mg[b]	Dose not changed Dose not changed Withdrawn Withdrawn Dose not changed Dose not changed
Transient loss of arterial circulation	1	2q8[a]	Dose not changed
Vasculitis	1	2q8[a,d]	Withdrawn
Visual acuity reduced	2	8q12/8q16[b,e] 8mg	Dose not changed Dose not changed
Visual impairment	1	8q12/8q16[b]	Withdrawn

Severe ocular TEAEs (n=27) were reported for:

- PULSAR:
  - 6 patients in the **2q8** arm
  - 12 patients in the **8q12/8q16** arm
- PULSAR Extension:
  - 3 patients in the **2q8→8mg** arm
  - 4 patients in the **8mg** arm

Most were not considered to be study drug (25/27) or injection (19/27) related

- 2 were considered study drug related
- 8 were considered injection related

Most patients (20/27) recovered from the event

- 1 recovered with sequalae
- 2 were recovering/the event was resolving at the time of analysis
- 7 had not recovered/the event had not resolved at the time of analysis

SAF/eSAF. [a]Event was considered injection related. [b]Event was not resolved at the time of the analysis. [c]Event was resolving at the time of analysis. [d]Event was considered study drug related. [e]Patient experienced 2 different ocular TEAEs. [f]Resolved with sequelae.

Serious Ocular TEAEs with Severe Maximum Intensity in the Study Eye

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Serious ocular TEAE event	Patients, n	Treatment arm	Treatment status
Cataract	1	8mg	Dose not changed
Corneal abrasion	1	2q8→8mg[a]	Dose not changed
Endophthalmitis	2	2q8[a] 2q8→8mg[a,b]	Interrupted Dose not changed
IOP increased	1	8q12/8q16[a]	Dose not changed
Retinal detachment	4	8q12/8q16 8q12/8q16 8q12/8q16 8mg	Interrupted Dose not changed Interrupted Dose not changed
Retinal hemorrhage	5	2q8 8q12/8q16[c] 8q12/8q16[d] 8q12/8q16[c] 8mg[c]	Dose not changed Withdrawn Withdrawn Dose not changed Dose not changed

Serious ocular TEAEs of severe maximum intensity (n=14) were reported for:

- PULSAR:
  - 2 patients in the **2q8** arm
  - 7 patients in the **8q12/8q16** arm
- PULSAR Extension:
  - 2 patients in the **2q8→8mg** arm
  - 3 patients in the **8mg** arm

Most were not considered to be study drug (13/14) or injection (10/14) related

- 1 was considered study drug related
- 4 were considered injection related

Most resolved (10/14) at the time of analysis

- 1 resolved with sequalae
- 3 had not resolved

SAF/eSAF. [a]Event was considered injection related. [b]Event was considered study drug related. [c]Event was not resolved at the time of the analysis. [d]Resolved with sequelae.

IOI-related Events in the Study Eye

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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
Total number of injections	4007	968	5711	1550
IOI-related event, n (n/1000 injections)	**11 (2.7)**	**3 (3.1)**	**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)	1 (1.0)	1 (0.2)	0
Vitreal 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)	2 (2.1)	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 the PULSAR Extension and comparable in both the 2q8→8mg and 8mg arms during the PULSAR Extension

[a]SAF. [b]eSAF. **IOI**, intraocular inflammation.

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

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IOI-related event	Patients, n	Treatment arm	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	3	2q8[b,c]	Moderate	Withdrawn
		2q8→8mg[b]	Moderate	Withdrawn
		8q12/8q16[c]	Moderate	Study ended
Vitritis	1	8q12/8q16[a]	Moderate	Dose not changed

Most IOI-related events, 74.2% (23/31), were mild

IOI-related events with moderate or severe maximum intensity (n=8) were reported for:

- PULSAR (n=5):
  - 2 patients in the **2q8** arm
  - 3 patients in the **8q12/8q16** arm
- PULSAR Extension (n=3):
  - 3 patients in the **2q8→8mg** arm
  - 0 patients in the **8mg** arm

Of the events with moderate or severe maximum intensity:

- 4 were considered study drug related
- 3 were considered injection related
- 3 events that occurred during PULSAR had not resolved at the time of the PULSAR analysis
- All events that occurred during the PULSAR Extension resolved or were resolving at the time of the analysis

SAF/eSAF. [a]Event was considered injection related. [b]Event was considered study drug related. [c]Event was not resolved at the time of the analysis.

Conclusions

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Incidence of IOI-related events	• **There was a low incidence of IOI-related events** in both aflibercept 2q8→8mg and 8mg treatment arms during the PULSAR Extension • One case of endophthalmitis was reported with aflibercept 2q8→8mg and **none were reported** with aflibercept 8mg during the PULSAR Extension
Severity of IOI-related events	• **Most IOI-related events were mild in severity**, with 1 case of severe endophthalmitis reported with aflibercept 2q8→8mg during the PULSAR Extension • **All patients** who developed IOI-related events during the PULSAR Extension **recovered or were recovering** at the time of the analysis
Safety profile	• The safety profiles of the 2q8→8mg and 8mg treatment arms during the PULSAR Extension were generally **consistent with the known safety profile of aflibercept 8 mg in PULSAR**