Comparable efficacy with aflibercept 8 mg at extended dosing intervals beyond q16 versus 2 mg q8 in Asian patients with nAMD in PULSAR through Week 96

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PURPOSE

In the PULSAR (NCT04423718) double-masked, 96-week, Phase 3 trial in patients with neovascular age-related macular degeneration (nAMD), aflibercept 8 mg every 12 weeks (8q12) and every 16 weeks (8q16) demonstrated non-inferior (NI) gains versus aflibercept 2 mg every 8 weeks (2q8) in best-corrected visual acuity (BCVA; NI margin of 4 letters) from baseline at Week 48 (primary endpoint). Evaluation of the primary endpoint in a subpopulation of Asian patients was pre-specified at Week 48 and evaluated through Week 96 in a post-hoc analysis.

METHODS

Patients were randomly assigned 1:1:1 to receive aflibercept 8q12, 8q16, or 2q8, each after 3 monthly injections. Dosing intervals for patients in the aflibercept 8q12 and 8q16 groups could be shortened from Week 16 and extended from Week 52 based on protocol criteria (**Figure 1**). Outcomes for Asian patients were assessed at Weeks 48, 60, and 96 using a last observation carried forward (LOCF) approach.

FIGURE 1: PULSAR dosing schedule and regimen modification in Years 1 and 2

	YEAR 1													YEAR 2										
	Day	Week												Week										
	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96
2q8	X	X	X		X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	–
8q12	X	X	X		o[a]	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	–
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	–

[a]DRM: Interval Shortening During Years 1 and 2

Criteria for interval shortening
- >5-letter loss in BCVA compared with Week 12 due to persistent or worsening nAMD **AND**
- >25 µm increase in CRT compared with Week 12, **OR** new foveal neovascularization, **OR** new foveal hemorrhage

- Patients who met DRM criteria had dosing intervals shortened to q8 at **Weeks 16** and **20** or by 4-week increments from **Week 24**
  - The minimum assigned dosing interval was q8

[b]DRM: Interval Extension During Year 2

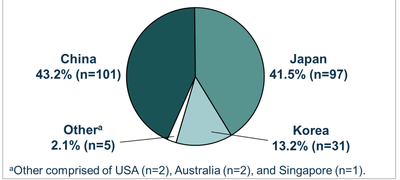
Criteria for interval extension
- <5-letter loss in BCVA compared with Week 12 **AND**
- No fluid at the central subfield on OCT **AND**
- No new foveal hemorrhage or foveal neovascularization

- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
  - The maximum assigned dosing interval was q24

Figure does not reflect all dosing options once a patient's dosing interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injections. **q8**, every 8 weeks; **q24**, every 24 weeks; **CRT**, central subfield retinal thickness; **DRM**, dose regimen modification; **OCT**, optical coherence tomography.

RESULTS

FIGURE 2: Asian patients by enrollment country



[a]Other comprised of USA (n=2), Australia (n=2), and Singapore (n=1).

Overall, 234 of the 1009 patients in the PULSAR study were identified as Asian, enrolled mainly from China, Japan, and Korea (**Figure 2**).

Disease characteristics in Asian patients were generally balanced across treatment groups (**Table 1**) and were similar to those of the overall PULSAR population (**data not shown**).

RESULTS cont'd

TABLE 1: Baseline demographics and disease characteristics of the Asian subgroup

	2q8	8q12	8q16	All 8 mg
	n=83	n=74	n=77	n=151
Age, years	70.7 (8.9)	71.5 (7.3)	71.6 (8.1)	71.5 (7.7)
Female, %	31.3	35.1	23.4	29.1
BCVA, ETDRS letters	59.2 (14.1)	57.7 (13.9)	58.1 (12.2)	57.9 (13.0)
CRT, µm	365 (149)	366 (128)	347 (131)	356 (130)
CNV size, mm²	5.4 (4.6)	5.7 (4.9)	6.0 (5.1)	5.9 (5.0)
PCV (confirmed by ICGA), %	48.2	39.2	36.4	37.7

FAS. Data are mean (SD) unless otherwise indicated. **CNV**, choroidal neovascularization; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **ICGA**, indocyanine green angiography; **PCV**, polypoidal choroidal vasculopathy; **SD**, standard deviation.

At Week 48, BCVA gains from baseline were comparable across treatment groups and maintained through Weeks 60 and 96 in the Asian subgroup (**Figure 3A**).

From baseline to Week 96, mean change in CRT in the Asian subgroup was comparable across treatment groups (**Figure 4A**).

These BCVA gains and CRT reductions were comparable to the overall PULSAR population (**Figures 3B and 4B**).

At Week 96, 90% (8q12) and 84% (8q16) of Asian patients were assigned dosing intervals ≥12 and ≥16 weeks, respectively (**Figure 5**); 55% of patients receiving 8 mg had treatment intervals extended to ≥20 weeks and 33% to 24 weeks.

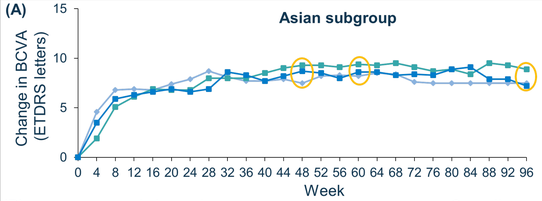
The safety profile of aflibercept 8q12 and 8q16 was comparable to 2q8 and consistent with the overall population (**Table 2**).

Ocular treatment-emergent adverse events (TEAEs) occurring in ≥5% of patients in any treatment arm in the Asian subgroup were increased intraocular pressure, retinal hemorrhage, cataract, conjunctival hemorrhage, dry eye, reduced visual acuity, and conjunctivitis.

Three cases of intraocular inflammation (IOI) occurred in the Asian subgroup (**Table 2**): eye inflammation (2q8), iritis (8q12), and endophthalmitis (2q8); none were considered serious, and all IOI cases were mild or moderate in severity.

FIGURE 3: Change in BCVA through Week 96 for the Asian subgroup

(A)



	W48	W60	W96
2q8	+7.5	+8.2	+7.5
8q12	+9.3	+9.4	+8.9
8q16	+8.8	+8.7	+7.2

(B)

Asian subgroup

	Mean ± SD change from BL to W96	Two-sided 95% CI
2q8 (n=83)	+7.5 ± 12.5	4.8, 10.3
8q12 (n=74)	+8.9 ± 16.6	5.1, 12.8
8q16 (n=77)	+7.2 ± 10.5	4.8, 9.6

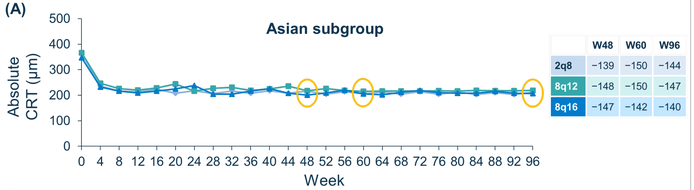
Overall population

	Mean ± SD change from BL to W96	Two-sided 95% CI
2q8 (n=336)	+7.1 ± 13.0	5.7, 8.5
8q12 (n=335)	+5.5 ± 14.9	3.9, 7.1
8q16 (n=338)	+5.4 ± 13.3	4.0, 6.8

FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints). **BL**, baseline; **CI**, confidence interval; **ICE**, intercurrent event; **W**, Week.

FIGURE 4: Change in CRT through Week 96 for the Asian subgroup

(A)



	W48	W60	W96
2q8	−139	−150	−144
8q12	−148	−150	−147
8q16	−147	−142	−140

(B)

Asian subgroup

	Mean ± SD change from BL to W96	Two-sided 95% CI
2q8 (n=83)	−144 ± 146	−176, −111
8q12 (n=74)	−147 ± 137	−179, −115
8q16 (n=77)	−140 ± 125	−169, −112

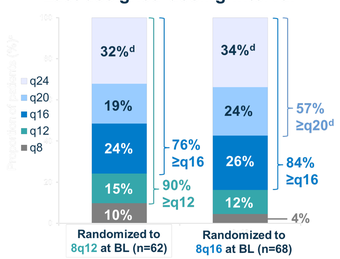
Overall population

	Mean ± SD change from BL to W96	Two-sided 95% CI
2q8 (n=336)	−141 ± 132	−155, −126
8q12 (n=335)	−147 ± 128	−161, −133
8q16 (n=338)	−145 ± 135	−160, −131

FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints). **W**, Week.

FIGURE 5: Patients in the Asian subgroup who qualified for an extended dosing interval at Week 96

Last assigned dosing interval[a,b,c]



Mean number of injections

	Weeks 0–48[e]	Weeks 0–60[f]	Weeks 0–96[b]
2q8	6.8	8.4	12.6
8q12	5.7	6.6	9.4
8q16	4.8	5.8	7.8

[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 AND no fluid at the central retinal AND no new foveal hemorrhage or neovascularization. [b]Patients completing Week 96. Asian subgroup: 2q8 n=69, 8q12 n=62, 8q16 n=68. [c]Values may not add up due to rounding. [d]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period. [e]Patients completing Week 48. Asian subgroup: 2q8 n=74, 8q12 n=66, 8q16 n=71. [f]Patients completing Week 60. Asian subgroup: 2q8 n=73, 8q12 n=66, 8q16 n=72. **q12**, every 12 weeks; **q16**, every 16 weeks; **q20**, every 20 weeks.

TABLE 2: Ocular TEAEs in study eye through Week 96 in the Asian subgroup

	Asian subgroup				Overall population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
Any ocular TEAE	40 (48.2)	33 (44.6)	39 (50.6)	72 (47.7)	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Any IOI TEAE	2 (2.4)	1 (1.4)	0	1 (0.7)	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)

Data are from the safety analysis set. TEAEs are adverse events occurring from the first injection to 30 days after the last injection (active or sham); ocular TEAEs are those occurring in the study eye

CONCLUSIONS

In Asian patients with nAMD in the PULSAR trial, robust BCVA gains were observed with aflibercept 8q12, 8q16, and 2q8 at Week 48, which were maintained through Week 96.

A robust and comparable decrease in CRT from baseline was observed in all 3 treatment arms at Week 48, with minimal fluctuations through Week 96.

With fewer injections on average compared with aflibercept 2 mg over 2 years, aflibercept 8 mg resulted in stabilized BCVA gains and robust decreases in CRT.

At Week 96, 57% of Asian patients randomly assigned to aflibercept 8q16 qualified for extension of the dosing interval to 20 weeks or more, suggesting extended durability compared with aflibercept 2 mg.

The safety profile of aflibercept 8 mg in Asian patients was similar to that of aflibercept 2 mg and to the overall PULSAR population.

In summary, aflibercept 8 mg demonstrated comparable BCVA gains at Week 48 versus aflibercept 2 mg, and these gains were maintained with fewer injections and no new safety signals through Week 96.

Disclosures

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