Aflibercept 8 mg for Diabetic Macular Edema: 96-Week Results From the Phase 2/3 PHOTON Trial

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Paul Chous, MA, OD, FAAO, on behalf of the PHOTON study investigators
Chous Eyecare Associates, Tacoma, Washington

INTRODUCTION

- Aflibercept 8 mg, a novel intravitreal formulation that delivers a 4-times higher molar dose than aflibercept 2 mg, has demonstrated improved functional and anatomic outcomes at dosing intervals of ≥12 weeks in ongoing clinical trials
- These findings supported regulatory approval of aflibercept 8 mg for the treatment of neovascular age-related macular degeneration, diabetic macular edema (DME), and diabetic retinopathy in the United States[1]
- Herein, the 96-week results from the phase 2/3 randomized, double-masked, non-inferiority PHOTON trial (NCT04429503) evaluating the efficacy and safety of intravitreal aflibercept 8 mg versus 2 mg in patients with DME are reported

METHODS

- Eligible patients with DME (**Table 1**) were randomized to receive aflibercept 8 mg, every 12 or 16 weeks after 3 monthly doses (8q12 or 8q16) or aflibercept 2 mg every 8 weeks after 5 monthly doses (2q8) (**Figure 1A**)
- Patients in the 8q12 and 8q16 groups were eligible for dose regimen modifications (DRM) criteria. As noted in **Figure 1B**, patients meeting pre-specified DRM criteria were eligible for:
  - Dosing interval shortening from Weeks 16 through 96
  - Dosing interval extension from Weeks 52 through 96

Table 1. Key Study Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Adults (≥18 years of age) with type 1 or type 2 diabetes • DME with central involvement with CRT ≥300 µm (or ≥320 µm on Spectralis) in the study eye as determined by the reading center • BCVA of 78-24 ETDRS letters (Snellen equivalent 20/32-20/320) with decreased vision due to DME	• Active PDR in the study eye • PRP or laser photocoagulation in the study eye within 12 weeks of screening visit • Intravitreal anti-VEGF treatment in the study eye within 12 weeks of screening visit • Intraocular or periocular steroids in the study eye within 16 weeks of the screening visit

BCVA, best-corrected visual acuity; CRT, central retinal thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor.

Figure 1. (A) PHOTON Study Design and (B) Dosing Schedule

(A)

Multicenter, randomized, double-masked study in patients with DME[a]
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)

- **2q8** — Aflibercept 2 mg every 8 weeks after 5 initial monthly injections n=167
- **8q12** — 8 mg every 12 weeks after 3 initial monthly injections n=328
- **8q16** — 8 mg every 16 weeks after 3 initial monthly injections n=163

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

End of study at Week 96
with optional 1-year extension through Week 156

(B)

Primary Endpoint

	Day 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o[b]	X[b]	o	o	X[b]	o	o	X[b]	o
8q16	X	X	X	o	o[b]	o[b]	X[b]	o	o	o	X[b]	o	o

	Week 52	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96
2q8	o	X	o	X	o	X	o	X	o	X	o	o
8q12	o	X[b, c]	o	o	X[b, c]	o	o	X[b, c]	o	o	X[b, c]	o
8q16	o	X[b, c]	o	o	o	X[b, c]	o	o	o	X[b, c]	o	o

DRM: Interval Shortening During Years 1 and 2

- **Criteria for interval shortening:**
  - >10-letter loss in BCVA from Week 12 due to persistent or worsening DME **AND**
  - >50 µm increase in CRT from Week 12
- 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 interval was Q8

DRM: Interval Extension During Year 2

- **Criteria for interval extension:**
  - <5-letter loss in BCVA from Week 12 **AND**
  - CRT <300 µm (or <320 µm on Spectralis)
- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
  - The maximum assigned interval was Q24

Stippled boxes=initial treatment phase; X=active injection; o=sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
[a]Treatment naïve and previously treated. [b]Interval shortening was permitted for patients meeting pre-specified DRM criteria from Weeks 16 through 96. [c]Interval extension was permitted for patients meeting pre-specified DRM criteria only from Weeks 52 through 96.

RESULTS

- The study completion rates through Weeks 96 for 2q8, 8q12, and 8q16 were 83.2%, 77.8%, and 84.8%, respectively
- Baseline demographics were balanced across treatment groups (**Table 1**)

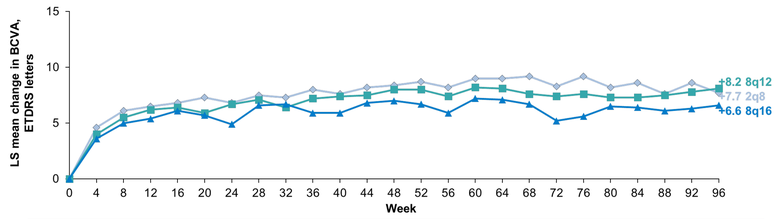
Table 1. Baseline Demographics and Ocular Characteristics

	2q8 (n=167)	8q12 (n=328)	8q16 (n=163)	Total (n=658)
Age (years)	63.0 (9.8)	62.1 (11.1)	61.9 (9.5)	62.3 (10.4)
Female (%)	44.9	36.0	39.3	39.1
Duration of diabetes (years)	15.9 (10.0)	15.1 (10.0)	15.7 (10.7)	15.5 (10.2)
Hemoglobin A1c (%)	8.1 (1.5)	7.9 (1.5)	7.8 (1.5)	8.0 (1.5)
BMI (kg/m²)	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)
BCVA (ETDRS letters)	61.5 (11.2)	63.6 (10.1)	61.4 (11.8)	62.5 (10.9)
CRT (µm)	457.2 (144.0)	449.1 (127.4)	460.3 (117.8)	454.0 (129.5)
Prior treatment for DME (%)	44.3	43.6	43.6	43.8
DRSS categories (%)				
Better or equal to level 43	62.9	60.1	65.6	62.2
Level 47 or worse	31.7	34.5	28.2	32.2
Missing/ungradable	5.4	5.5	6.1	5.6

FAS/SAF. Data are mean (SD) unless otherwise indicated.
FAS comprised all randomized patients who received ≥1 study treatment. SAF comprised all patients who received study treatment.
BMI, body mass index; DRSS, Diabetic Retinopathy Severity Scale; FAS, full analysis set; SAF, safety analysis set, SD, standard deviation.

- Both aflibercept 8-mg groups met the primary endpoint, with 8q12 and 8q16, demonstrating non-inferior BCVA gains to 2q8 at Week 48 (BCVA mean change from baseline [SD]: 8.8 [9.0] and 7.9 [8.4] vs 9.2 [9.0] letters)
- At Week 96, both aflibercept 8-mg groups maintained non-inferior BCVA gains to aflibercept 2q8 (**Figure 2**)

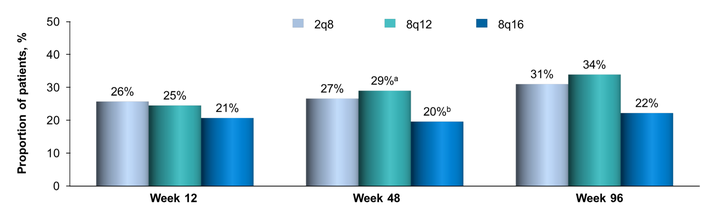
Figure 2. Mean Change in BCVA From Baseline Through Week 96



	Mean number of injections[a]	LS mean change from baseline at Week 96 (MMRM)	Difference in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	13.8	7.7			
8q12	9.5	8.2	+0.5	–1.6, 2.5	*P*<0.0001
8q16	7.8	6.6	–1.1	–3.3, 1.1	*P*=0.0044

Data shown in the figure represent LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit.
[a]Patients completing Week 96: 2q8 n=139; 8q12 n=256; 8q16 n=139.
CI, confidence interval; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

Figure 3. Proportion of Patients With ≥2-Step DRSS Improvement at Weeks 12, 48, and 96

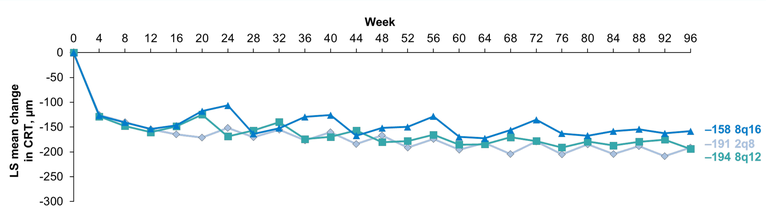


Key secondary endpoint (15% NI margin):
[a]8q12 vs 2q8 difference (95% CI): 1.98 (–6.61, 10.57)
[b]8q16 vs 2q8 difference (95% CI): –7.52 (–16.88, 1.84)

LOCF (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.
LOCF, last observation carried forward; NI, non-inferiority.

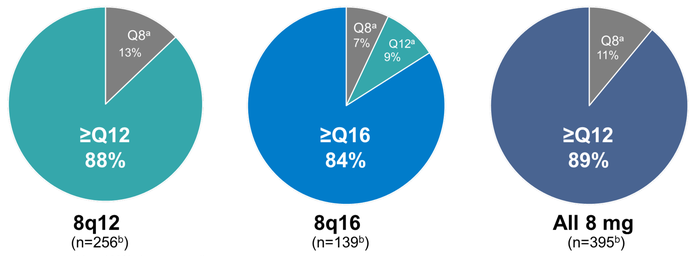
- In relation to the key secondary endpoint, the 8q12 group demonstrated non-inferiority to 2q8, with 29% of patients achieving ≥2-step DRSS improvement at Week 48 compared with 27% in the 2q8 group (**Figure 3**)
- Fluid reaccumulation between doses in the aflibercept 8-mg groups decreased over time, particularly from Weeks 48 to 96 (**Figure 4**)

Figure 4. Mean Change in CRT Through Week 96



LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline CRT as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit.

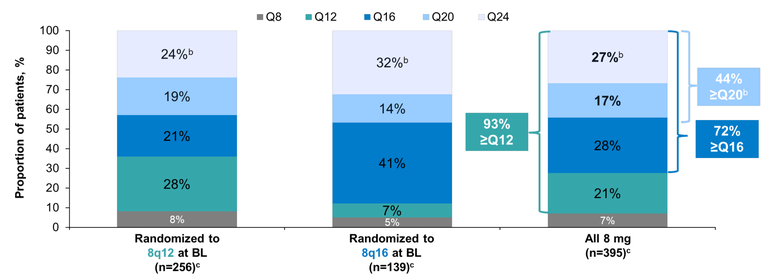
Figure 5. Proportion of Patients Who Maintained Randomized Intervals Through Week 96



Values may not add to 100% due to rounding.
[a]Patients with dosing intervals shortened based on DRM assessments at some point through Week 96.
[b]Patients completing Week 96.

- 89% of the 8 mg patients maintained dosing intervals ≥12 weeks (**Figure 5**)
- 44% of the 8 mg patients had assigned dosing intervals of ≥20 weeks at Week 96 (**Figure 6**)

Figure 6. Last Assigned Dosing Interval at Week 96[a]



Values may not add up to 100% due to rounding.
[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 **AND** CRT <300 µm (or <320 µm on Spectralis).
[b]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within the 96-week study period. [c]Patients completing Week 96.

- Safety of aflibercept 8 mg was consistent with the established safety profile of aflibercept 2 mg through Week 96 (**Table 2**)
  - No cases of ischemic optic neuropathy, retinal vasculitis, or occlusive retinitis were reported through Week 96
  - Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 96 in any treatment group

Table 2. Safety Through Week 96

	2q8 (n=167)	8q12 (n=328)	8q16 (n=163)	All 8 mg (n=491)
Ocular safety				
Patients with ≥1 ocular TEAE (%)	37.1	43.9	45.4	44.4
Patients with ≥1 IOI TEAE (%)	1.2	1.5	0.6	1.2
Patients with IOP ≥35 mmHg pre- or post-injection (%)[a]	1.2	0.6	0	0.4
Non-ocular safety				
APTC events (%)[b]	7.2	6.7	6.7	6.7
Hypertension events (%)[b]	16.2	15.5	20.9	17.3
Non-ocular serious TEAEs (%)	25.1	22.9	23.9	23.2
Deaths (%)[c]	5.4	5.5	3.1	4.7

[a]IOP was measured in the study eye. [b]Treatment-emergent events. [c]All events.
APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; IOP, intraocular pressure; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- 8q12 and 8q16 groups had non-inferior BCVA compared with 2q8 at Week 96, with up to 6 fewer injections
- Through Week 96, 89% of 8 mg patients maintained ≥12-week dosing intervals
- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks

REFERENCE

1. EYLEA® HD (aflibercept) injection, for intravitreal use. Highlights of prescribing information. Regeneron Pharmaceuticals, Inc.; 2023. Accessed September 14, 2023. https://www.regeneron.com/downloads/eyleahd_fpi.

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