Intravitreal Aflibercept Injection 8 mg for Diabetic Macular Edema: 48-Week Results From the Phase 2/3 PHOTON Trial

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PURPOSE

To evaluate the efficacy and safety of intravitreal aflibercept injection 8 mg versus 2 mg in patients with treatment-naïve or previously treated diabetic macular edema (DME).

METHODS

PHOTON (NCT04429503) was a double-masked, 96-week, Phase 2/3, non-inferiority trial that randomized patients with DME to receive aflibercept 8 mg (70 µL injection), every 12 or 16 weeks after three monthly doses (8q12 [n=328] or 8q16 [n=163]) or aflibercept 2 mg (50 µL injection) every 8 weeks after five monthly doses (2q8 [n=167]).

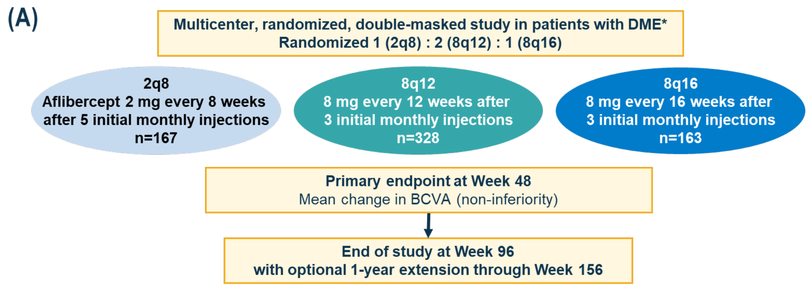
During Weeks 16–48, patients in the 8q12 or 8q16 treatment arms received aflibercept 8 mg in shorter intervals (minimum interval for all patients was every 8 weeks [Q8]) if they met prespecified dose regimen modification criteria denoting disease activity.

The primary endpoint was the mean change from baseline in best corrected visual acuity (BCVA) at Week 48 (non-inferiority margin at four letters); the key secondary endpoint was the proportion of patients with ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score at Week 48 (non-inferiority margin at 15%; **Figure 1**).

METHODS

FIGURE 1: (A) PHOTON Study Design and (B) Dosing Schedule

(A)

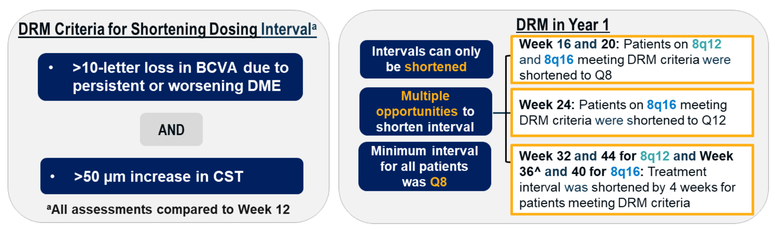


(B)

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	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

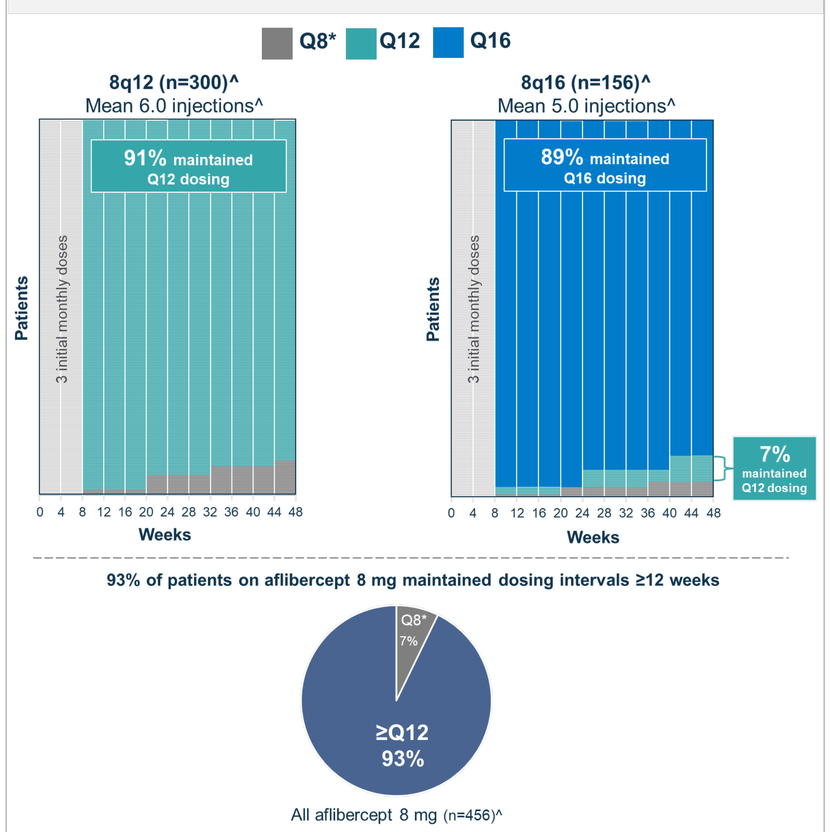
Note: Aflibercept 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections



Stippled boxes=initial treatment phase; X=active injection; o=sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
*Treatment naïve and previously treated.
^At Week 36, patients in the aflibercept 8q16 group who were previously shortened to Q12 could have been shortened to Q8.
BCVA, best corrected visual acuity; CST, central subfield thickness; DME, diabetic macular edema; DRM, dose regimen modification.

RESULTS

FIGURE 4: Proportion of Patients Who Maintained Randomized Intervals Through Week 48



*Patients shortened based on DRM assessments at some point through Week 48.
^Patients completing Week 48.
DRM, dose regimen modification; Q8, every 8 weeks; Q12, every 12 weeks; Q16, every 16 weeks.

RESULTS

Overall, 658 patients (8q12: n=328; 8q16: n=163; 2q8: n=167) were evaluated (mean±SD age, 62.3±10.4 years; 39% female; **Table 1**).

Mean BCVA change from baseline at Week 48 was +9.2, +8.8, and +7.9 letters with 2q8, 8q12, and 8q16, respectively (least squares mean difference: non-inferiority p<0.0001 for 8q12 vs 2q8 [95% CI: −2.26, 1.13]; non-inferiority p=0.0031 for 8q16 vs 2q8 [95% CI: −3.27, 0.39]; **Figure 2**). The proportion of patients with ≥2-step improvement from baseline to Week 48 in DRSS score was 27%, 29%, and 20% with 2q8, 8q12, and 8q16, respectively (8q12 group met the non-inferiority margin of 15% [95% CI vs 2q8: −6.61, 10.57] whereas the 8q16 group did not [95% CI vs 2q8: −16.88, 1.84]; **Figure 3**).

Through Week 48, 91% (8q12) and 89% (8q16) of patients maintained their original randomized dosing interval, and, in the aflibercept 8 mg combined group, 93% of patients maintained a dosing interval of ≥12 weeks after the initial monthly dosing period (**Figure 4**).

Safety outcomes for aflibercept 8 mg and aflibercept 2 mg were similar through Week 48 (**Table 2**). The reported terms for intraocular inflammation were iridocyclitis, iritis, uveitis, vitreal cells, and vitritis; there were no cases of endophthalmitis or occlusive retinal vasculitis. No clinically relevant change in intraocular pressure was observed with aflibercept 8 mg.

TABLE 1: Baseline Demographics and Ocular Characteristics

	2q8	8q12	8q16	Total
N	167	328	163	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
Race (%)				
White	67.1	70.4	78.5	71.6
Asian	18.0	14.6	14.1	15.3
Black or African American	10.8	10.7	5.5	9.4
Other*	2.4	3.0	0.6	2.4
Not reported	1.8	1.2	1.2	1.4
Ethnicity (%)				
Not Hispanic or Latino	79.6	81.1	77.3	79.8
Hispanic or Latino	18.6	16.5	20.9	18.1
Duration of diabetes (years)	15.9 (10.0)	15.1 (10.0)	15.7 (10.7)	15.5 (10.2)
Hemoglobin A_{1c} (%)	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)
CST (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: all randomized patients who received ≥1 study treatment. SAF: all patients who received study treatment.
*Other includes patients who were American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and multiracial.
BCVA, best corrected visual acuity; BMI, body mass index; CST, central subfield thickness; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; SAF, safety analysis set.

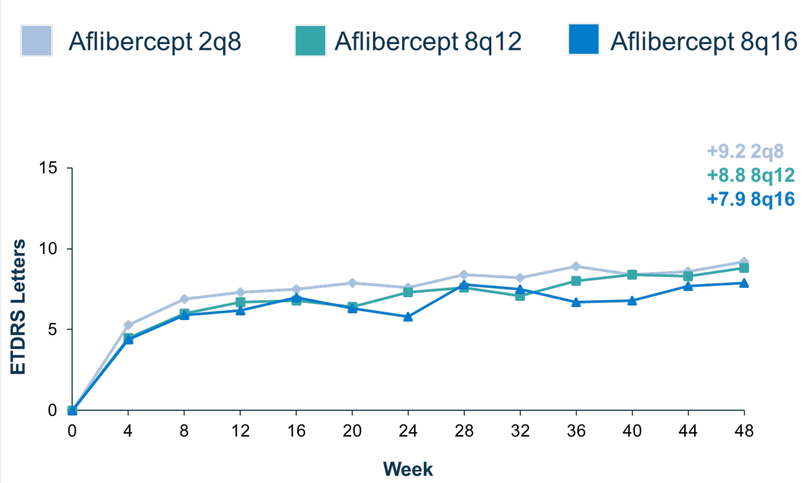
TABLE 2: Safety Through Week 48

	2q8	8q12	8q16	All 8 mg
N	167	328	163	491
Any ocular TEAE in the study eye (%)	27.5	31.7	29.4	31.0
Cataract	1.2	1.5	4.9	2.6
Conjunctival hemorrhage	3.6	4.3	3.7	4.1
Intraocular pressure increased	3.6	2.1	0.6	1.6
Punctate keratitis	0.6	1.5	3.7	2.2
Retinal hemorrhage	0.6	0.0	3.7	1.2
Vitreous floaters	2.4	4.9	1.8	3.9
Patients with ≥1 IOI TEAE (%)	0.6	1.2	0.0	0.8
Patients with IOP ≥35 mmHg pre- or post-injection (%)	1.2	0.3	0.0	0.2
Any non-ocular AEs (%)				
APTC events*	3.6	2.4	4.3	3.1
Hypertension events*	12.0	11.0	14.1	12.0
Non-ocular SAEs*	15.6	15.9	13.5	15.1
Deaths^	2.4	2.7	1.8	2.4

No cases of ischemic optic neuropathy were reported through Week 48.

*Treatment-emergent events. ^All events.
AEs, adverse events; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; IOP, intraocular pressure; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

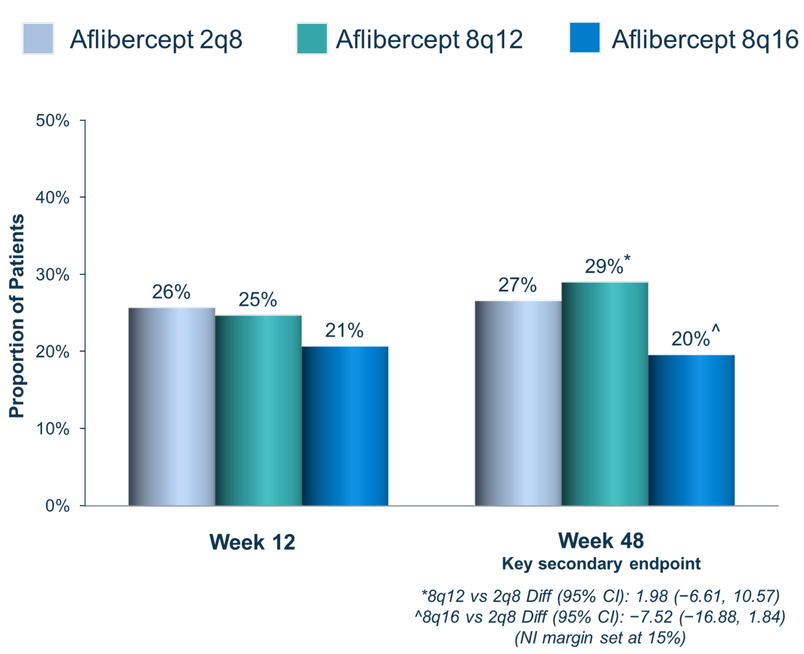
FIGURE 2: Mean Change in BCVA From Baseline Through Week 48[a]



	LS mean change from baseline[b]	Difference in LS means vs aflibercept 2q8	Two-sided 95% CI	One-sided test for non-inferiority at four-letter margin
2q8	8.7	—	—	—
8q12	8.1	−0.57	−2.26, 1.13	p<0.0001
8q16	7.2	−1.44	−3.27, 0.39	p=0.0031

[a]Based on observed values (censoring data post-ICE).
[b]Calculated using mixed model for repeated measures.
FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
CI, confidence interval; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares.

FIGURE 3: Proportion of Patients With ≥2-Step DRSS Improvement at Weeks 12 and 48



LOCF (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.
DRSS, Diabetic Retinopathy Severity Scale; FAS, full analysis set; ICE, intercurrent event; LOCF, last observation carried forward; NI, non-inferiority.

CONCLUSIONS

Aflibercept 8 mg met the primary efficacy endpoint for DME, demonstrating non-inferiority in BCVA change versus aflibercept 2 mg. The majority of patients maintained ≥12-week dosing (93% in the combined aflibercept 8 mg group) and 16-week dosing (89% in the 8q16 group). There were no new safety signals through Week 48 for aflibercept 8 mg or aflibercept 2 mg, and no cases of endophthalmitis or occlusive retinal vasculitis, or clinically relevant changes in IOP.

Diabetic eye disease, including DME, is a leading cause of blindness for people aged 20–79 years.[1] The high treatment burden associated with frequent clinic visits and injections, especially for these patients of working age, represents a considerable challenge in the routine management of DME. Furthermore, such patients may experience greater employment instability and lower work productivity, and use more healthcare resources compared with patients with diabetes without DME.[2] Aflibercept 8 mg demonstrated efficacy and safety with extended dosing intervals and may decrease treatment burden for all patients with DME.

References

1. Varma R et al. *JAMA Ophthalmol.* 2014;132:1334–40.
2. Kiss S et al. *Clin Ophthalmol.* 2016;10:2443–53.

Disclosures

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Study disclosure

This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation.

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