Aflibercept 8 mg in Diabetic Macular Edema: 156-Week Results From the PHOTON Extension Study

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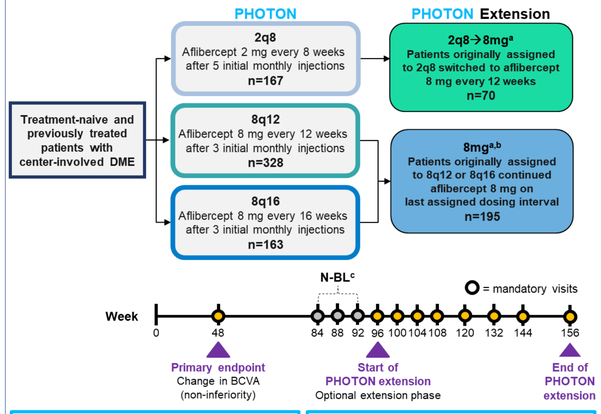
BACKGROUND & PURPOSE

- At Week 48 of the pivotal PHOTON study (NCT04429503), aflibercept 8 mg every 12 and 16 weeks (8q12 and 8q16) after 3 initial monthly doses demonstrated comparable best-corrected visual acuity (BCVA) gains and reductions in central retinal thickness (CRT) to aflibercept 2 mg every 8 weeks (2q8) after 5 initial monthly doses in patients with diabetic macular edema (DME)[1]
  - Similar visual and anatomic improvements were maintained across treatment groups at Week 96, and 93% of patients in the combined aflibercept 8-mg group had a last assigned dosing interval of ≥12 weeks[2]
- An optional 1-year PHOTON extension was conducted through Week 156 to evaluate treatment outcomes in patients who continued with aflibercept 8 mg and in patients who were switched from aflibercept 2q8 to 8 mg

METHODS

- Eligible patients completed Week 96 of the PHOTON study; had ≥1 BCVA and ≥1 CRT value at Week 84, 88, or 92; and had their Week 96 visit ≤4 weeks before the first extension study visit
- At Week 96, patients initially randomized to 8q12 or 8q16 continued to receive aflibercept 8 mg (8mg group; n=195), while patients initially randomized to 2q8 were switched to aflibercept 8 mg every 12 weeks (2q8→8mg group; n=70) (**Figure 1**)
  - Beginning at Week 100, dosing intervals were shortened or extended if patients met prespecified dose regimen modification criteria

Figure 1. PHOTON Extension Study Design



E-DRM: Interval Shortening During Year 3
- Patients were assessed at ***any visit*** beginning at Week 100
- **Criteria for interval shortening:**
  - >10-letter loss in BCVA from N-BL due to persistent or worsening DME **AND** >50-µm increase in CRT from N-BL
  - **OR**
  - ≥15-letter loss from N-BL due to worsening DME
- Dosing intervals shortened by **2-week** increments
- Minimum interval was Q8

E-DRM: Interval Extension During Year 3
- Patients were assessed at ***dosing visits*** beginning at Week 100
- **Criteria for interval extension:**
  - <5-letter loss in BCVA from N-BL **AND**
  - CRT <300 µm (or <320 µm on Spectralis)
- Dosing intervals extended by **2-week** increments
- Maximum interval was Q24

[a]Dosing visits were scheduled as necessary based on individual dosing interval assignment. [b]Patients who were randomized to the 8q12 or 8q16 groups at the beginning of the PHOTON study and continued treatment with aflibercept 8 mg through the PHOTON extension study. [c]N-BL defined as an average of values from Week 84, 88, and 92.
E-DRM, PHOTON extension dose regimen modification; N-BL, new baseline; Q8, every 8 weeks; Q24, every 24 weeks.

RESULTS

- A total of 265 patients participated in the PHOTON extension study; 77.9% and 82.9% of patients in the 8mg and 2q8→8mg groups, respectively, completed Week 156 (**Table 1**)
- Baseline patient characteristics were balanced in both the PHOTON and PHOTON extension studies **(Table 1)**

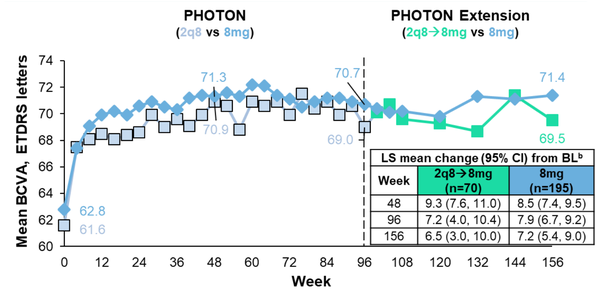
Table 1. Patient Disposition and Baseline Characteristics

	PHOTON	PHOTON extension		
	Total	2q8→8mg	8mg[a]	Total
Patients entering PHOTON study (FAS), n	658	–	–	–
Patients entering PHOTON extension (eFAS), n	–	70	195	265
Age, years	62.3 (10.4)	62.7 (8.5)	61.5 (11.3)	61.8 (10.7)
Female, %	39.1	40.0	36.4	37.4
Race, %				
White	71.6	65.7	77.4	74.3
Black or African American	9.4	8.6	6.7	7.2
Asian	15.3	21.4	14.4	16.2
Other[b]	3.7	4.3	1.5	2.3
Hispanic or Latino, %	18.1	14.3	15.9	15.5
Hemoglobin A1c, %	8.0 (1.5)	8.2 (1.4)	7.9 (1.5)	8.0 (1.5)
History of hypertension, %	78.1	70.0	77.4	75.5
BCVA, ETDRS letters	62.5 (10.9)	61.6 (11.3)	62.8 (11.1)	62.5 (11.1)
CRT, µm	454.0 (129.5)	472.3 (160.7)	460.2 (137.7)	463.4 (143.9)
Prior treatment for DME, %	43.8	51.4	43.1	45.3

Data are mean (SD) unless otherwise indicated.
[a]Patients who were randomized to the 8q12 or 8q16 groups at the beginning of the PHOTON study and continued treatment with aflibercept 8 mg through the PHOTON extension study. [b]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and unreported race.
eFAS, PHOTON extension full analysis set; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.

- Improvements in BCVA that were achieved through Week 96 were maintained in both groups at Week 156 (**Figure 2**)
  - Mean BCVA was 71.4 letters in the 8mg group and 69.5 letters in the 2q8→8mg group, and corresponding least squares (LS) mean changes from baseline in BCVA at Week 156 were +7.2 and +6.5 letters, respectively

Figure 2. Mean BCVA[a] Through Week 156



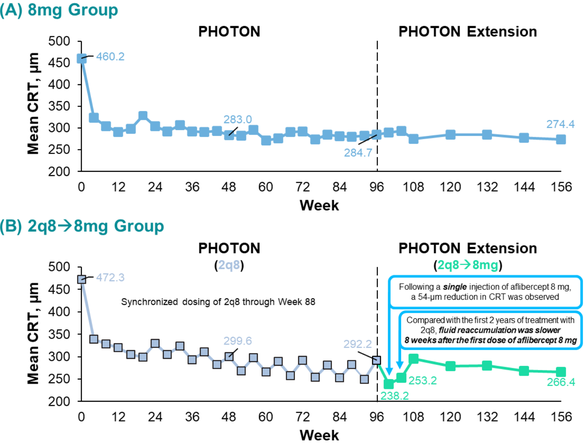
LS mean change (95% CI) from BL[b]

Week	2q8→8mg (n=70)	8mg (n=195)
48	9.3 (7.6, 11.0)	8.5 (7.4, 9.5)
96	7.2 (4.0, 10.4)	7.9 (6.7, 9.2)
156	6.5 (3.0, 10.0)	7.2 (5.4, 9.0)

[a]eFAS, observed cases. [b]LS mean values were generated using MMRM and a weighting scheme based on observed margins, with baseline BCVA measurement as a covariate, treatment group, visit, and the stratification variables (geographic region [Japan vs rest of the world]; baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME (per EDC) [yes vs no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit. [c]eFAS.
BL, baseline; EDC, electronic data capture; MMRM, mixed model for repeated measures.

- CRT reductions through Week 96 were maintained in the 8mg and 2q8→8mg groups through Week 156 (**Figure 3**)
  - After Week 108, patients in the 2q8→8mg group experienced smaller fluctuations in CRT compared with those observed in PHOTON (**Figure 3B**)

Figure 3. Mean CRT Through Week 156

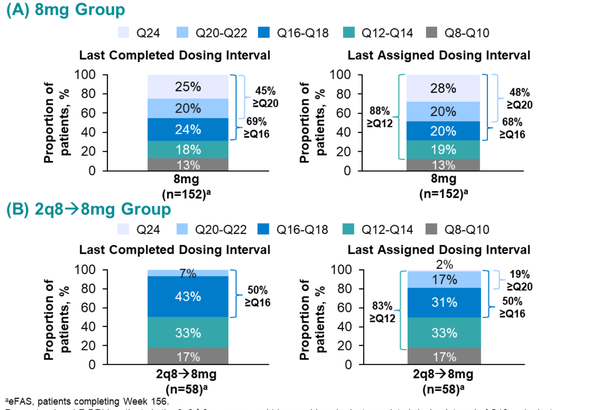


	LS mean change (95% CI) from BL (µm)[a]		
	Week 48	Week 96	Week 156
8mg (n=195)	−180.6 (−193.5, −167.7)	−178.4 (−194.2, −162.6)	−192.4 (−208.7, −176.1)
2q8→8mg (n=70)	−161.7 (−187.8, −135.6)	−169.7 (−221.8, −117.6)	−197.4 (−220.4, −174.5)

[a]LS mean values were generated using MMRM and a weighting scheme based on observed margins, with baseline CRT measurement as a covariate, treatment group, visit, and the stratification variables (geographic region [Japan vs rest of the world]; baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME (per EDC) [yes vs no]) as fixed factors, and terms for the interaction between baseline and visit and the interaction between treatment and visit.

- The majority of patients in the 8mg and 2q8→8mg groups were on extended dosing intervals through Week 156, and a last assigned dosing interval of ≥12 weeks was achieved by 88% and 83% of patients, respectively (**Figure 4**)

Figure 4. Last Completed and Last Assigned Dosing Intervals at Week 156



[a]eFAS, patients completing Week 156.
Per protocol and E-DRM, patients in the 2q8→8mg group could have achieved a last completed dosing interval of Q18 and a last assigned dosing interval of Q20 weeks by Week 156. Several patients were assigned a dosing interval that was longer than planned per E-DRM and actual dates of injections received due to late visits. Values may not add up to 100% due to rounding.

- Through Week 156, ocular safety in the study eye was comparable in the 8mg and 2q8→8mg groups (**Table 2**)
  - Ocular treatment-emergent adverse events reported in >4% of all patients included cataract, vitreous floaters, vitreous detachment, and diabetic retinal edema
  - The incidence of intraocular inflammation was low in both groups, and no cases of occlusive vasculitis were reported
- Non-ocular safety was also similar between both groups through Week 156

Table 2. Ocular and Non-ocular Safety Through Week 156[a]

	2q8→8mg (n=70)	8mg (n=195)	Total (N=265)
Ocular AEs, n (%)[b,c]	37 (52.9)	108 (55.4)	145 (54.7)
Ocular SAEs, n (%)[b,c]	3 (4.3)	4 (2.1)	7 (2.6)
Intraocular inflammation, n (%)[b,c]	1 (1.4)	3 (1.5)	4 (1.5)
Iritis	0	2 (1.0)	2 (0.8)
Iridocyclitis	1 (1.4)	0	1 (0.4)
Uveitis	1 (1.4)	0	1 (0.4)
Endophthalmitis	0	1 (0.5)	1 (0.4)
Non-ocular SAEs, n (%)[b]	24 (34.3)	58 (29.7)	82 (30.9)
APTC events, n (%)[b]	5 (7.1)	14 (7.2)	19 (7.2)
Deaths, n (%)[d]	2 (2.9)	10 (5.1)	12 (4.5)

eSAF.
[a]Cumulative events from baseline through Week 156. [b]Treatment emergent. [c]Reported in the study eye. [d]All events.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; eSAF, PHOTON extension safety analysis set; SAE, serious adverse event.

CONCLUSIONS

- Patients in the 8mg group maintained visual and anatomic improvements achieved in the first 2 years, with the majority of patients on extended dosing intervals
  - At Week 156, 45% of patients completed ≥20-week dosing intervals, and 48% had a last assigned dosing interval of ≥20 weeks
- In the 2q8→8mg group, visual and anatomic improvements achieved with fixed 2q8 dosing were maintained with aflibercept 8 mg
  - At Week 156, 83% of patients achieved ≥12-week dosing intervals
  - Longer duration of action with aflibercept 8 mg versus 2 mg was further supported by slower fluid reaccumulation following the first aflibercept 8-mg injection
- No new safety signals were reported with aflibercept 8 mg in either treatment group through Week 156

REFERENCES

1. Brown DM et al. *Lancet.* 2024;403:1153–1163.
2. Do DV. Presented at: American Academy of Ophthalmology; November 3-6, 2023; San Francisco, CA.

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