Differential Anatomic Response to Aflibercept 8 mg Versus 2 mg During the Matched Dosing Phase of the PHOTON Trial in Patients With Diabetic Macular Edema Who Subsequently Met Criteria for Shortening

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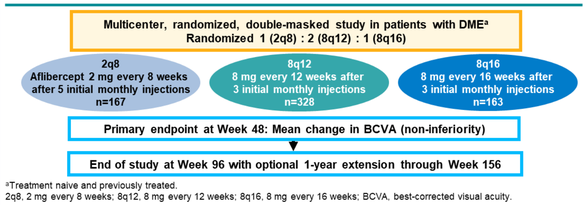
BACKGROUND

- PHOTON (NCT04429503) was a multicenter, randomized, double-masked trial that evaluated the efficacy and safety of aflibercept 8 mg versus 2 mg in patients with diabetic macular edema (DME) (**Figure 1**)

Figure 1. PHOTON Study Design

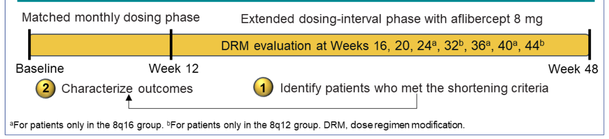


[a]Treatment naive and previously treated.
2q8, 2 mg every 8 weeks; 8q12, 8 mg every 12 weeks; 8q16, 8 mg every 16 weeks; BCVA, best-corrected visual acuity.

OBJECTIVE

- This post hoc analysis aimed to characterize visual and anatomic outcomes of patients with DME over the matched dosing phase through Week 12 among patients who did or did not meet the shortening criteria for dosing intervals any time from Week 16 through Week 48 (**Figure 2**)

Figure 2. Schematic Representation of Study Objective



[a]For patients only in the 8q16 group. [b]For patients only in the 8q12 group. DRM, dose regimen modification.

METHODS

Figure 3. PHOTON Dosing Schedule and DRM Criteria Through Week 48

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 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

DRM Criteria for Shortening Dosing Interval[a]

>10-letter loss in BCVA due to persistent or worsening DME **AND** >50-micron increase in CRT

Yellow boxes indicate visits at which patients were assessed for DRM. Intervals could only be shortened by 4-week increments, the minimum dosing interval was 8 weeks. Stippled boxes = initial treatment phase; X = active injection; o = sham injections.
[a]All assessments compared with Week 12.
CRT, central retinal thickness; Wk, Week.

- Patients in the 8q12 and 8q16 groups who met the shortening criteria in any DRM evaluation visit from Week 16 through Week 48 had their dosing intervals shortened (**Figure 3**)
  - Patients in the 2q8 group who hypothetically met shortening criteria at the scheduled dosing visit from Week 24 to Week 48 continued with every 8-week dosing

Key Outcomes

- Mean change in BCVA and CRT from baseline through Week 12
- Proportion of patients with no intraretinal fluid (IRF) and subretinal fluid (SRF) at Week 12
- Time to achieving CRT <300 µm through Week 48

RESULTS

- Through Week 48, 4.5%, 9.0%, and 10.9% of patients in the 2q8, 8q12, and 8q16 groups, respectively, met the shortening criteria versus 95.5%, 91.0%, and 89.1% who did not
- Baseline BCVA was similar across groups, except patients in 8q16 who met shortening criteria had a lower mean BCVA than the other 2 groups (**Table 1**)
  - Patients who met the shortening criteria had higher baseline CRT versus those who did not

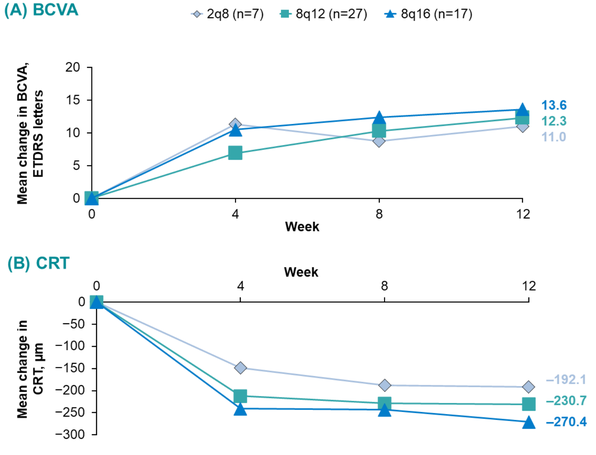
Table 1. Baseline Characteristics

	Met shortening criteria			Did not meet shortening criteria		
	2q8 (n=7)	8q12 (n=27)	8q16 (n=17)	2q8 (n=150)	8q12 (n=273)	8q16 (n=139)
Age, mean (SD), years	57.4 (10.7)	59.1 (13.9)	60.1 (9.9)	63.2 (9.6)	62.2 (10.9)	62.0 (9.6)
Duration of diabetes, mean (SD), years	19.9 (11.8)	11.1 (9.7)	15.8 (11.0)	15.6 (10.0)	15.5 (10.1)	15.6 (10.5)
HbA1c, mean (SD), %	8.4 (1.1)	7.8 (1.4)	7.8 (1.9)	8.1 (1.5)	8.0 (1.5)	7.9 (1.5)
Prior DME treatment, n (%)	5 (71.4)	15 (55.6)	8 (47.1)	66 (44.0)	116 (42.5)	62 (44.6)
BCVA, mean (SD), ETDRS letters	61.0 (7.9)	59.4 (10.0)	53.7 (12.8)	61.7 (11.3)	63.9 (10.1)	62.7 (11.2)
CRT, mean (SD), µm	558.0 (149.4)	511.4 (117.5)	534.8 (134.3)	450.9 (137.2)	444.9 (129.8)	447.1 (112.5)

FAS, patients who completed the Week 48 visit.
ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; HbA1c, hemoglobin A1c.

- Through Week 48, aflibercept 8 mg–treated patients who met shortening criteria received, on average, slightly more injections than those who did not
  - The average number of injections in those who met shortening criteria was 8.0, 6.4, and 5.5 in the 2q8, 8q12, and 8q16 groups, respectively. In those who did not meet the criteria in the 2q8, 8q12, and 8q16 groups, 7.9, 5.9, and 5.0 injections, respectively, were administered on average
- In patients who met shortening criteria, CRT improvements were relatively larger with aflibercept 8 mg than 2 mg, with similar BCVA gains observed across treatment groups (**Figure 4**)

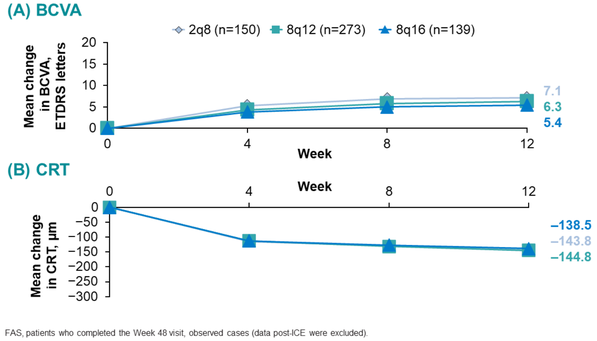
Figure 4. Mean Change in (A) BCVA and (B) CRT Through Week 12 in Patients Who Met Shortening Criteria



FAS, patients who completed the Week 48 visit, observed cases (data post-ICE were excluded).
ICE, intercurrent event.

- In patients who did not meet the shortening criteria, BCVA and CRT improvements were comparable across all treatment groups (**Figure 5**)

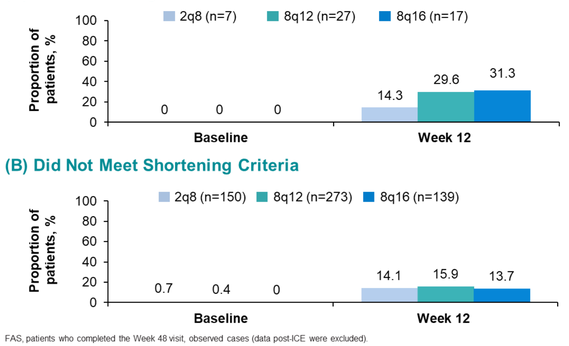
Figure 5. Mean Change in BCVA and CRT Through Week 12 in Patients Who Did Not Meet Shortening Criteria



FAS, patients who completed the Week 48 visit, observed cases (data post-ICE were excluded).

- In patients who met shortening criteria, a relatively greater proportion of patients treated with aflibercept 8 mg had no IRF or SRF at Week 12 (**Figure 6**)

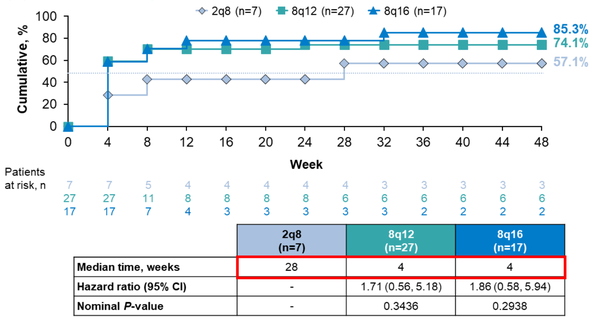
Figure 6. Proportion of Patients With No IRF and SRF in the Center Subfield at Baseline and Week 12



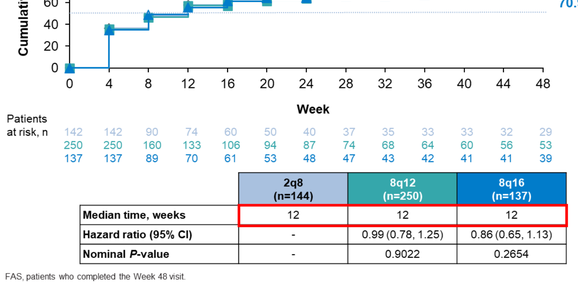
FAS, patients who completed the Week 48 visit, observed cases (data post-ICE were excluded).

- Patients treated with aflibercept 8 mg who met shortening criteria achieved CRT <300 µm relatively faster than those treated with aflibercept 2 mg in the same subgroup (**Figure 7**)

Figure 7. Time to CRT <300 µm Through Week 48



	2q8 (n=7)	8q12 (n=27)	8q16 (n=17)
Median time, weeks	28	4	4
Hazard ratio (95% CI)	-	1.71 (0.56, 5.18)	1.86 (0.58, 5.94)
Nominal *P*-value	-	0.3436	0.2938



	2q8 (n=144)	8q12 (n=250)	8q16 (n=137)
Median time, weeks	12	12	12
Hazard ratio (95% CI)	-	0.99 (0.78, 1.25)	0.86 (0.65, 1.13)
Nominal *P*-value	-	0.9022	0.2654

FAS, patients who completed the Week 48 visit.

Limitations

- This was a post hoc analysis with no adjustment for multiplicity, and findings should be considered as hypothesis-forming only
- The number of patients who met shortening criteria was low, limiting interpretation of the results

CONCLUSIONS

- In patients who met shortening criteria, aflibercept 8 mg provided relatively greater anatomic benefit (CRT improvement, more patients with no retinal fluid, and shorter time to CRT <300 µm) than aflibercept 2 mg, with similar BCVA gains
- In patients who did not meet shortening criteria, aflibercept 8 mg and 2 mg provided similar visual and anatomic outcomes
- These findings suggest that aflibercept 8 mg may provide additional anatomic benefits over aflibercept 2 mg in patients with DME who need more frequent dosing (~10%), while it may decrease treatment burden in those who do not require more frequent dosing (~90%) when compared with aflibercept 2 mg

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