Intravitreal Aflibercept 8 mg for Diabetic Macular Edema: Week 48 Efficacy Outcomes by Baseline Demographics in the Phase 2/3 PHOTON Trial

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BACKGROUND & PURPOSE

- Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is a standard of care for the treatment of center-involved diabetic macular edema (DME)[1]
- Aflibercept 8 mg, a novel intravitreal formulation with a 4-times higher molar dose than aflibercept 2 mg, is hypothesized to provide longer effective vitreal concentration and enable a more sustained effect on VEGF signaling
- The ongoing phase 2/3 PHOTON trial (NCT04429503) evaluates the efficacy and safety of aflibercept 8 mg versus 2 mg in patients with DME
- In this analysis, treatment effects of aflibercept 8 mg versus 2 mg at Week 48 were evaluated by baseline demographics

METHODS

- Patients aged ≥18 years with type 1 or type 2 diabetes, DME with central involvement with central retinal thickness (CRT) ≥300 µm in the study eye as determined by the reading center, and best-corrected visual acuity (BCVA) of 78-24 letters (Snellen equivalent 20/32-20/320) with decreased vision due to DME were enrolled
- Patients meeting the following criteria in the study eye were excluded: active proliferative diabetic retinopathy, intravitreal anti-VEGF treatment or panretinal or laser photocoagulation within 12 weeks of screening, or intraocular or periocular steroids within 16 weeks of screening
- Patients were randomized 1:2:1 to receive aflibercept 2 mg every 8 weeks (2q8) after 5 initial monthly injections or aflibercept 8 mg every 12 or 16 weeks (8q12 or 8q16) after 3 initial monthly injections (**Figure 1A**)
- Starting at Week 16, patients in the aflibercept 8q12 and 8q16 groups had their randomized dosing intervals shortened if dose regimen modification (DRM) criteria were met (**Figure 1B**)
- The primary endpoint, the mean change from baseline in BCVA at Week 48, was evaluated in the overall population and by subgroups of age, sex, race, and ethnicity

RESULTS

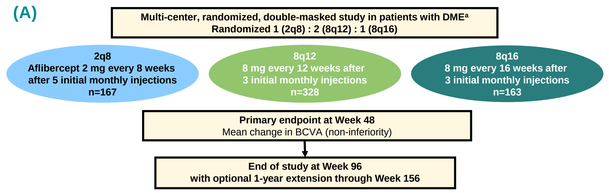
- Overall, 658 patients (aflibercept 2q8: n=167; aflibercept 8q12: n=328; aflibercept 8q16: n=163) were treated and evaluated
- Baseline demographics and ocular characteristics were generally balanced across treatment groups (**Table 1**)

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
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 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	32.4
Ungradable	5.4	5.5	6.1	5.6

FAS/SAF. Data are mean (SD) unless otherwise indicated.
The FAS and SAF were identical and defined as all randomized patients who received ≥1 study treatment.
BMI, body mass index; DRSS, Diabetic Retinopathy Severity Score; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; SAF, safety analysis set; SD, standard deviation.

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



(B)

	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
													Primary Endpoint
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[b]
- >10-letter loss in BCVA due to persistent or worsening DME
- AND
- >50-µm increase in CRT

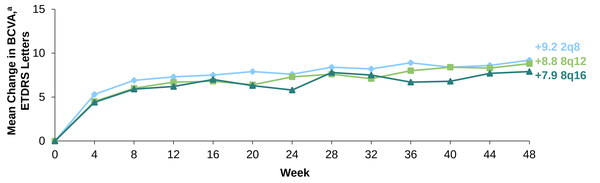
DRM in Year 1
- Intervals can only be shortened
- Multiple opportunities to shorten interval
- Minimum interval for all patients was q8

Week 16 and 20: Patients on 8q12 and 8q16 meeting DRM criteria were shortened to q8
Week 24: Patients on 8q16 meeting DRM criteria were shortened to q12
Week 32 and 44 for 8q12 and Week 36[c] and 40 for 8q16: Treatment interval was shortened by 4 weeks for patients meeting DRM criteria

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 naive and previously treated.
[b]All assessments compared to Week 12.
[c]At Week 36, patients in the aflibercept 8q16 group who were previously shortened to q12 could have been shortened to q8.

- In the overall population, the primary endpoint was met, with both aflibercept 8q12 and 8q16 groups demonstrating non-inferior BCVA gains to aflibercept 2q8 at Week 48 (**Figure 2**)

Figure 2. Mean Change in BCVA Through Week 48[a]

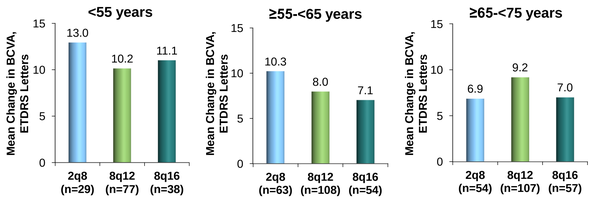


	LS mean change from baseline[b]	Difference in LS means vs. aflibercept 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	8.7	—	—	—
8q12	8.1	-0.57	-2.26, 1.13	p < 0.0001
8q16	7.2	-1.44	-3.27, 0.39	p = 0.0031

[a]Based on observed values (censoring data post-ICE).
[b]Estimated using MMRM.
FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.
CI, confidence interval; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

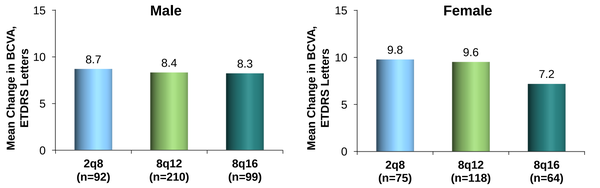
- The mean change from baseline in BCVA at Week 48 was generally similar across treatment groups when evaluated within subgroups of age, sex, race, and ethnicity (**Figures 3–6**)

Figure 3. Mean Change in BCVA at Week 48 by Age



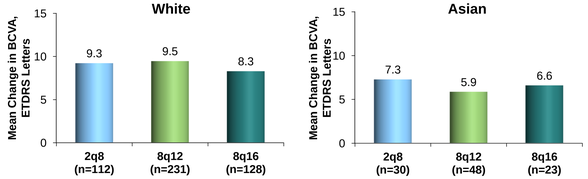
FAS. Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

Figure 4. Mean Change in BCVA at Week 48 by Sex



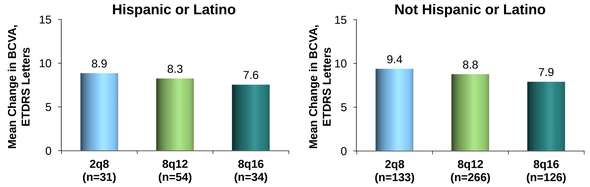
FAS. Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

Figure 5. Mean Change in BCVA at Week 48 by Race



FAS. Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

Figure 6. Mean Change in BCVA at Week 48 by Ethnicity



FAS. Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

Limitations

- This analysis was not designed to evaluate statistical differences within subgroups
- Select subgroups (age ≥75 years and Black or African American race) could not be evaluated due to small sample size

CONCLUSIONS

- Aflibercept 8 mg achieved meaningful BCVA gains from baseline at Week 48 in patients with DME across evaluable subgroups of age, sex, race, and ethnicity

REFERENCE

1. Flaxel CJ et al. *Ophthalmology*. 2020;127(1):P66-P145.

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