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

Diana V. Do, MD,[1] on behalf of the PHOTON study investigators

[1]*Byers Eye Institute, Stanford University School of Medicine, Palo Alto, CA, USA*

Presented at Angiogenesis, Exudation, and Degeneration 2024 Meeting, February 3, 2024

Disclosures

DME

- Diana V. Do is a consultant to Boehringer Ingelheim, Genentech, Kodiak Sciences, Kriya, and Regeneron Pharmaceuticals, Inc.; has received research funding from Boehringer Ingelheim, Genentech, Kriya, and Regeneron Pharmaceuticals, Inc.; and has stock options from Kodiak Sciences
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation

PHOTON Study Design

photon

DME

Multi-center, randomized, double-masked study in adult patients with center-involved DME[a]
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)
Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

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

[a]Treatment-naïve and previously treated patients aged ≥18 years with type 1 or type 2 diabetes, DME with central involvement with CRT ≥300 µm in the study eye, and BCVA of 78-24 letters (Snellen equivalent of 20/32-20/320) with decreased vision due to DME.
BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema.

PHOTON: Dosing Schedule and Dose Regimen Modification

photon

DME

Primary Endpoint

YEAR 1	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[a]	X[a]	o	o	X[a]	o	o	X[a]	o
8q16	X	X	X	o	o[a]	o[a]	X[a]	o	o	o	X[a]	o	o

YEAR 2	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[a, b]	o	o	X[a, b]	o	o	X[a, b]	o	o	X[a, b]	o
8q16	o	X[a, b]	o	o	o	X[a, b]	o	o	o	X[a, b]	o	o

[a]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

[b]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 beginning at **Week 52** had dosing intervals extended by 4-week increments
  - The maximum assigned interval was Q24

Figure does not reflect all dosing options once a patient's interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injection.
DRM, dose regimen modification.

Patient Disposition and Baseline Characteristics

photon

DME

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
Study completion rate, n (%)				
Week 48	157 (94.0)	300 (91.2)	156 (95.1)	613 (92.9)
Week 96	139 (83.2)	256 (77.8)	139 (84.8)	534 (80.9)
Baseline Characteristics				
Age (years)	63.0 (9.8)	62.1 (11.1)	61.9 (9.5)	62.3 (10.4)
Female, n (%)	75 (44.9)	118 (36.0)	64 (39.3)	257 (39.1)
White, n (%)	112 (67.1)	231 (70.4)	128 (78.5)	471 (71.6)
Hispanic or Latino, n (%)	31 (18.6)	54 (16.5)	34 (20.9)	119 (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)
History of hypertension, n (%)	130 (77.8)	254 (77.4)	130 (79.8)	514 (78.1)
BMI (kg/m^2)	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)

Data are mean (SD) unless otherwise indicated.
BMI, body mass index; FAS, full analysis set; SAF, safety analysis set; SD, standard deviation.

Baseline Characteristics of the Study Eye

photon

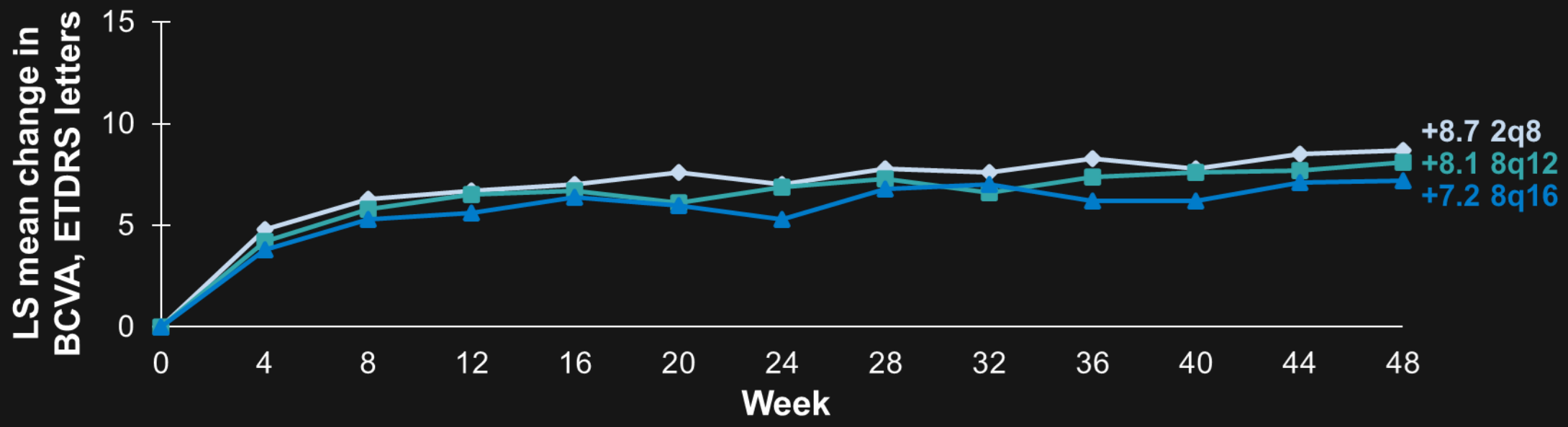
DME

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
BCVA (ETDRS letters)	61.5 (11.2)	63.6 (10.1)	61.4 (11.8)	62.5 (10.9)
Snellen equivalent	20/63	20/50	20/63	20/63
20/32 (>73 to 78 letters), n (%)	20 (12.0)	59 (18.0)	23 (14.1)	102 (15.5)
20/40 or worse (≤73 letters), n (%)	147 (88.0)	269 (82.0)	140 (85.9)	556 (84.5)
CRT (μm)	457.2 (144.0)	449.1 (127.4)	460.3 (117.8)	454.0 (129.5)
Prior treatment for DME, n (%)	74 (44.3)	143 (43.6)	71 (43.6)	288 (43.8)

Data are mean (SD) unless otherwise indicated.
ETDRS, Early Treatment Diabetic Retinopathy Study.

Primary Endpoint: Mean Change in BCVA at Week 48

DME



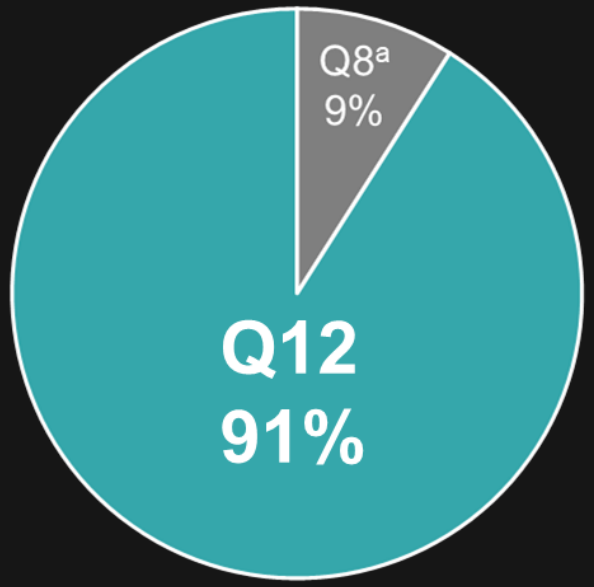
	Mean number of injections[a]	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.9	8.7			
8q12	6.0	8.1	-0.57	-2.26, 1.13	p < 0.0001
8q16	5.0	7.2	-1.44	-3.27, 0.39	p = 0.0031

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 48: 2q8 n=157; 8q12 n=300; 8q16 n=156.
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

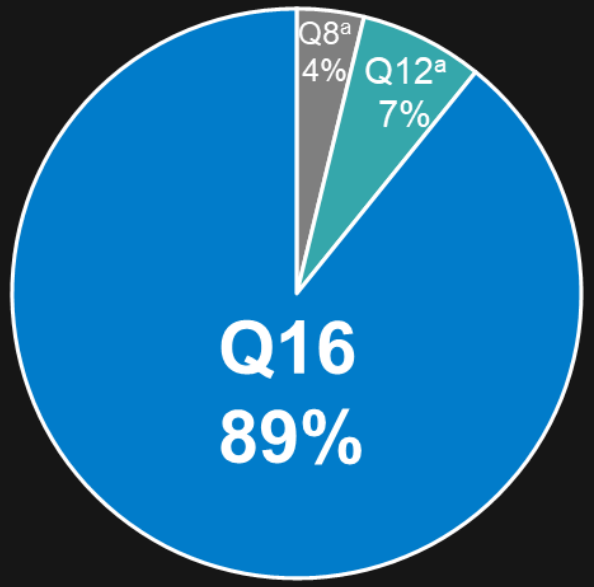
Large Majority of Aflibercept 8 mg Patients Maintained Randomized Intervals Through Week 48

photon

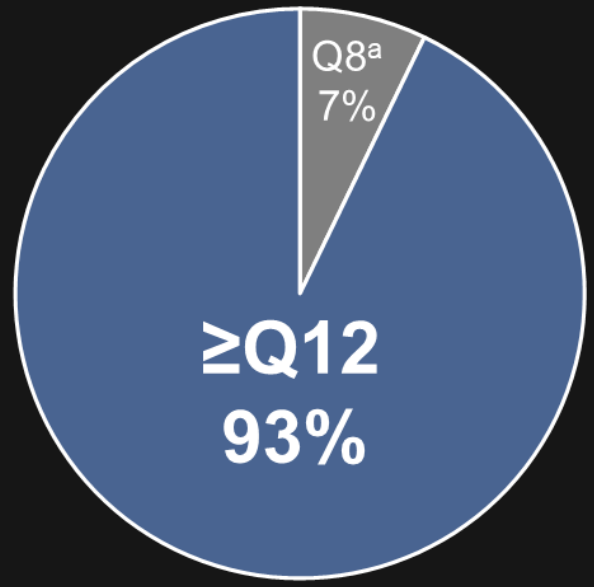
DME



8q12
(n=300)[b]



8q16
(n=156)[b]



All 8 mg
(n=456)[b]

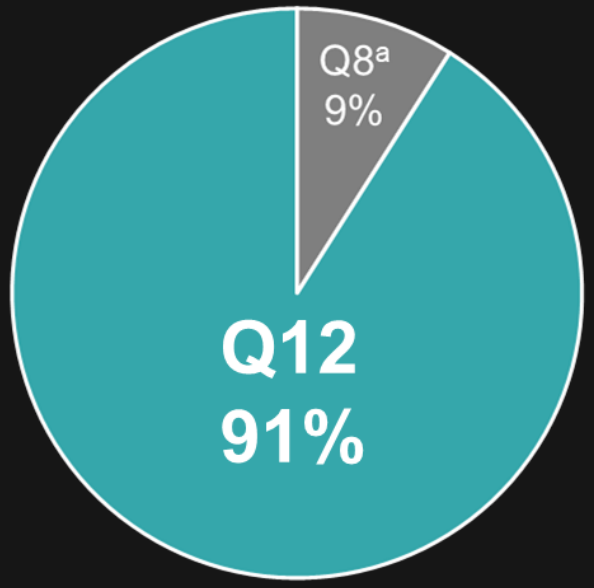
[a]Patients whose dosing intervals were shortened based on DRM assessments at some point through Week 48.
[b]Patients completing Week 48.

Exploratory Analysis of Patients Who Would Hypothetically Meet DRM Criteria for Additional Interval Shortening Through Week 48

photon

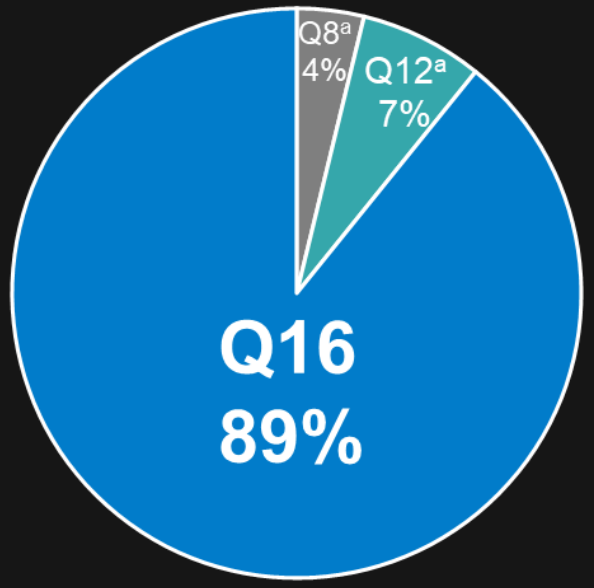
DME

1.7% of patients in the **8q12** group would have met DRM criteria for shortening to Q4



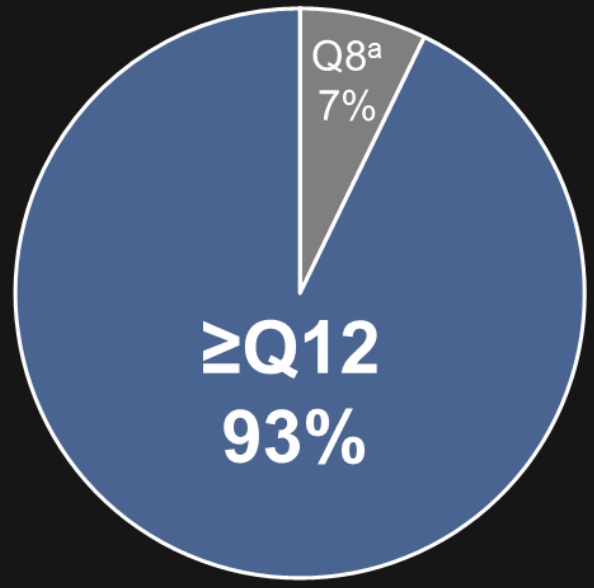
8q12
(n=300)[b]

1.3% of patients in the **8q16** group would have met DRM criteria for shortening to Q4



8q16
(n=156)[b]

1.5% of all 8 mg patients would have met DRM criteria for shortening to Q4



All 8 mg
(n=456)[b]

In this exploratory analysis, eyes with dosing intervals that were shortened to Q8 through Week 48 were further evaluated to determine if the study-specified DRM criteria would have been met for shortening to a Q4 interval. DRM criteria for interval shortening were defined as >10-letter loss in BCVA from Week 12 due to persistent or worsening DME and >50-µm increase in CRT from Week 12 (assessed using OCT data from the central reading center).

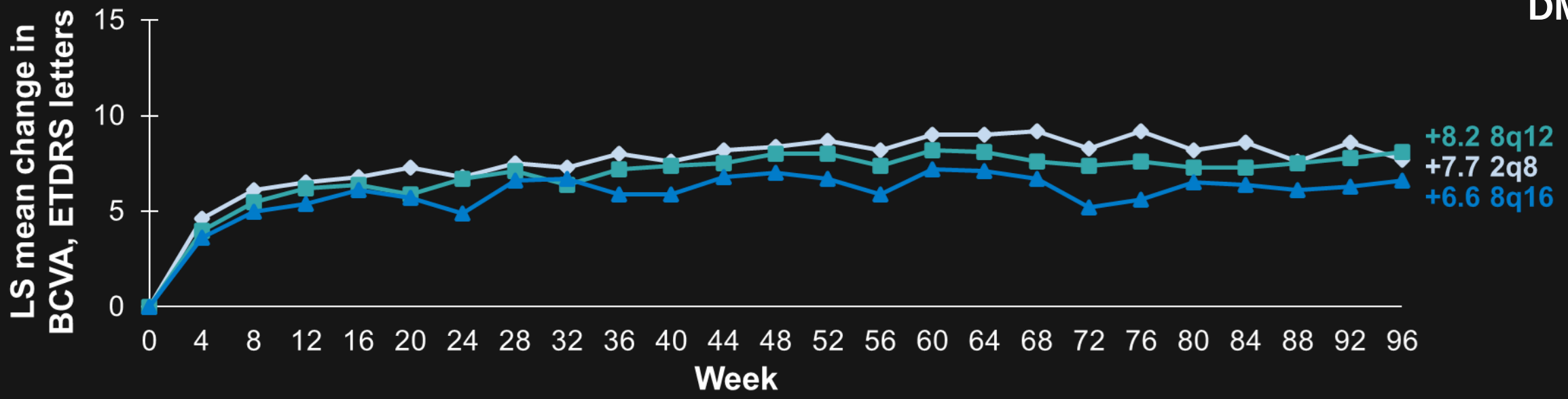
[a]Patients whose dosing intervals were shortened based on DRM assessments at some point through Week 48.

[b]Patients completing Week 48.

OCT, optical coherence tomography.

Mean Change in BCVA at Week 96

DME



	Mean number of injections[a]	LS mean change from BL at Week 96 (MMRM)	Diff. 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	**+0.45**	**-1.55, 2.45**	**p < 0.0001 (nominal)**
8q16	7.8	6.6	**-1.11**	**-3.27, 1.05**	**p = 0.0044 (nominal)**

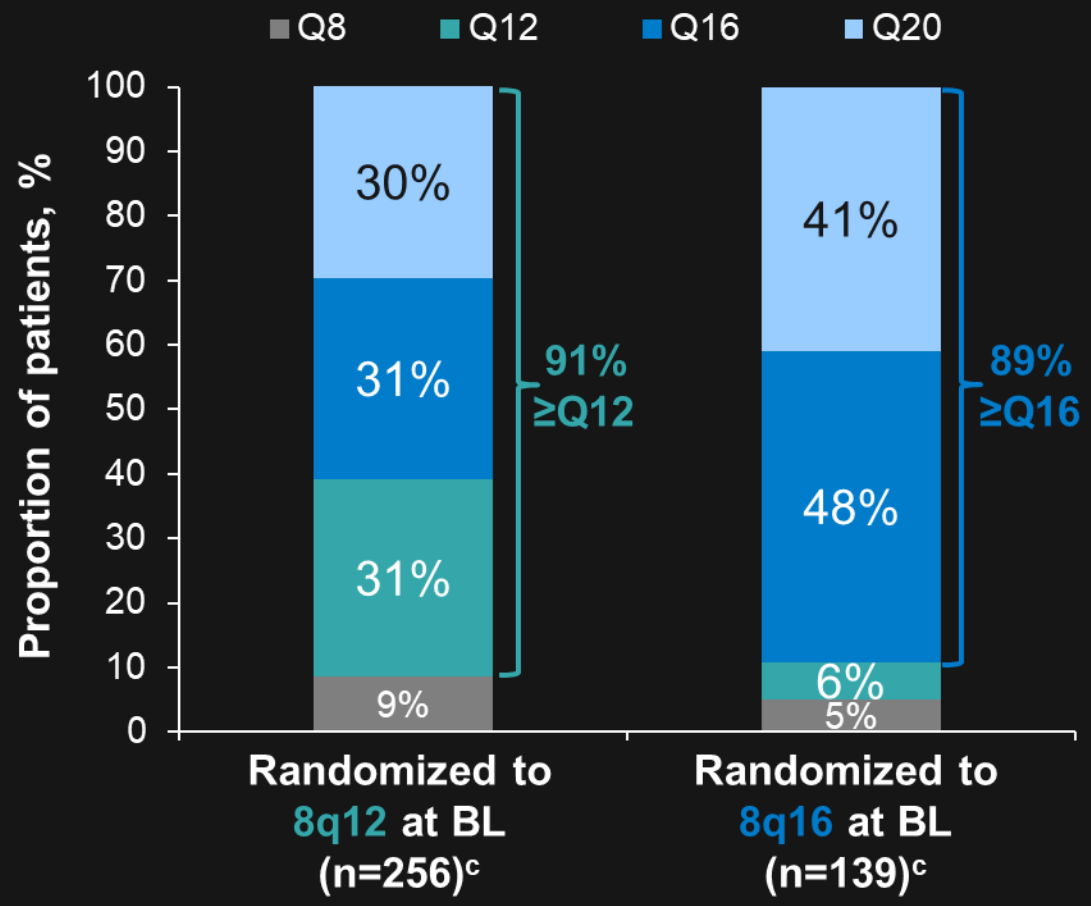
Data shown in the figure represent LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [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.
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

Large Proportion of Patients Qualified for Interval Extension in Year 2[a]

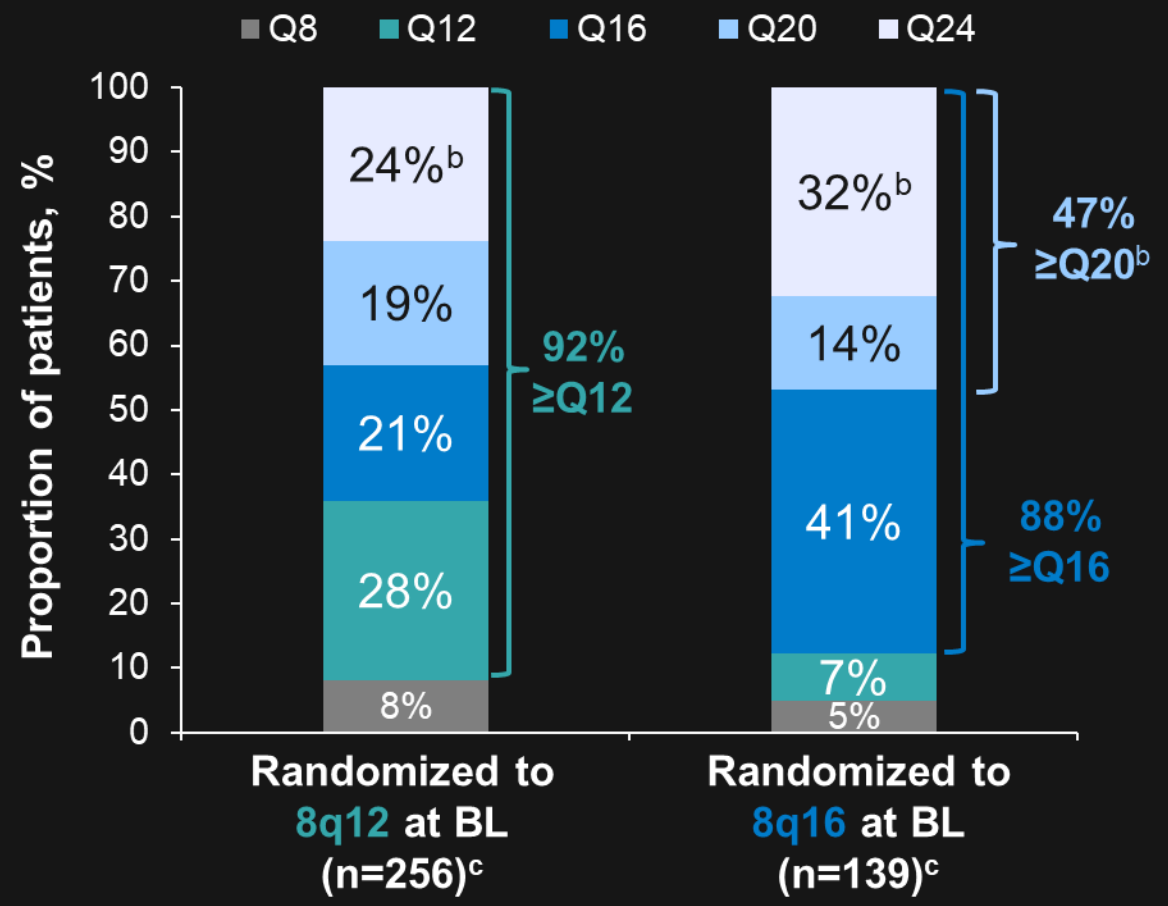
photon

DME

Last Completed



Last Assigned

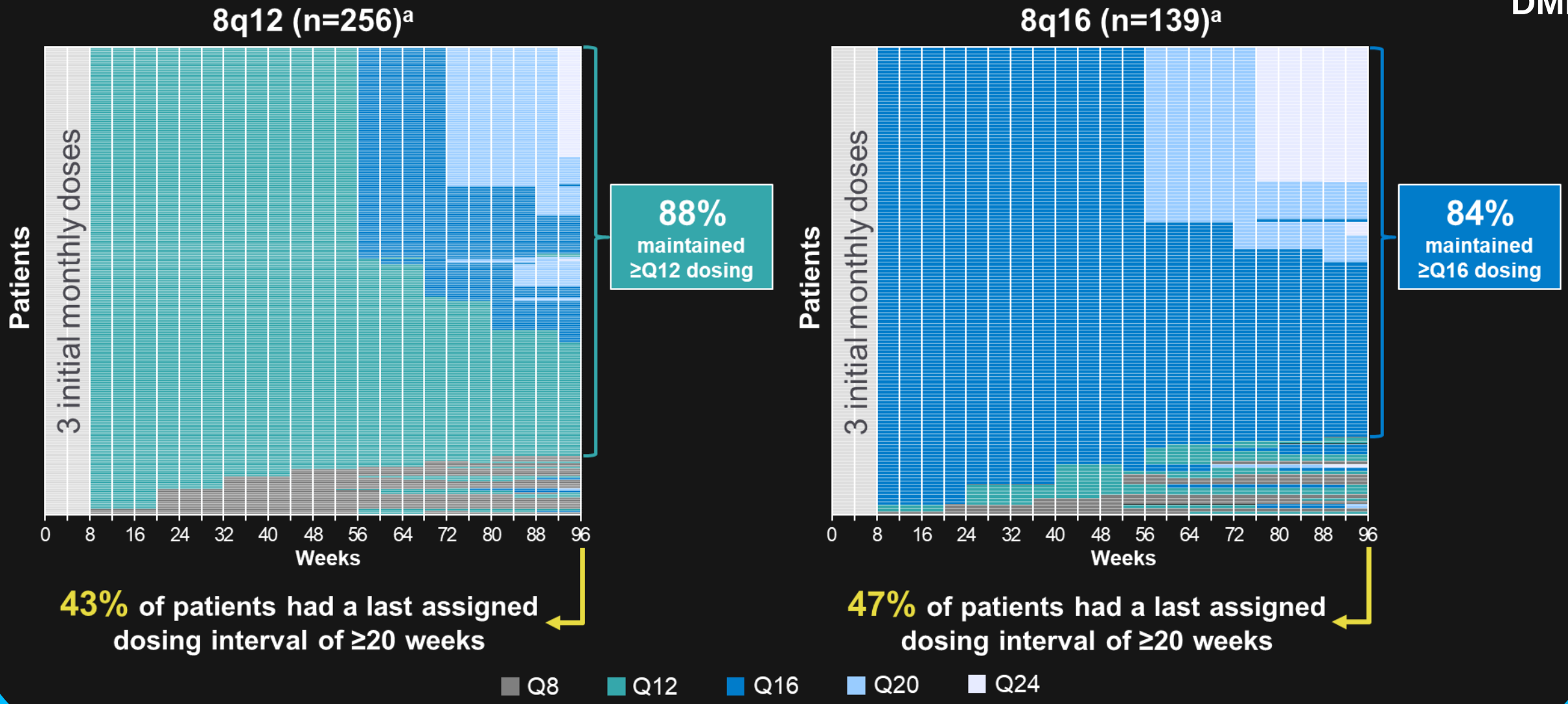


[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 and CRT <300 µm (or <320 µm on Spectralis). [b]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within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

Dosing Interval for Majority of 8 mg Patients Was Maintained or Extended Through Week 96

photon

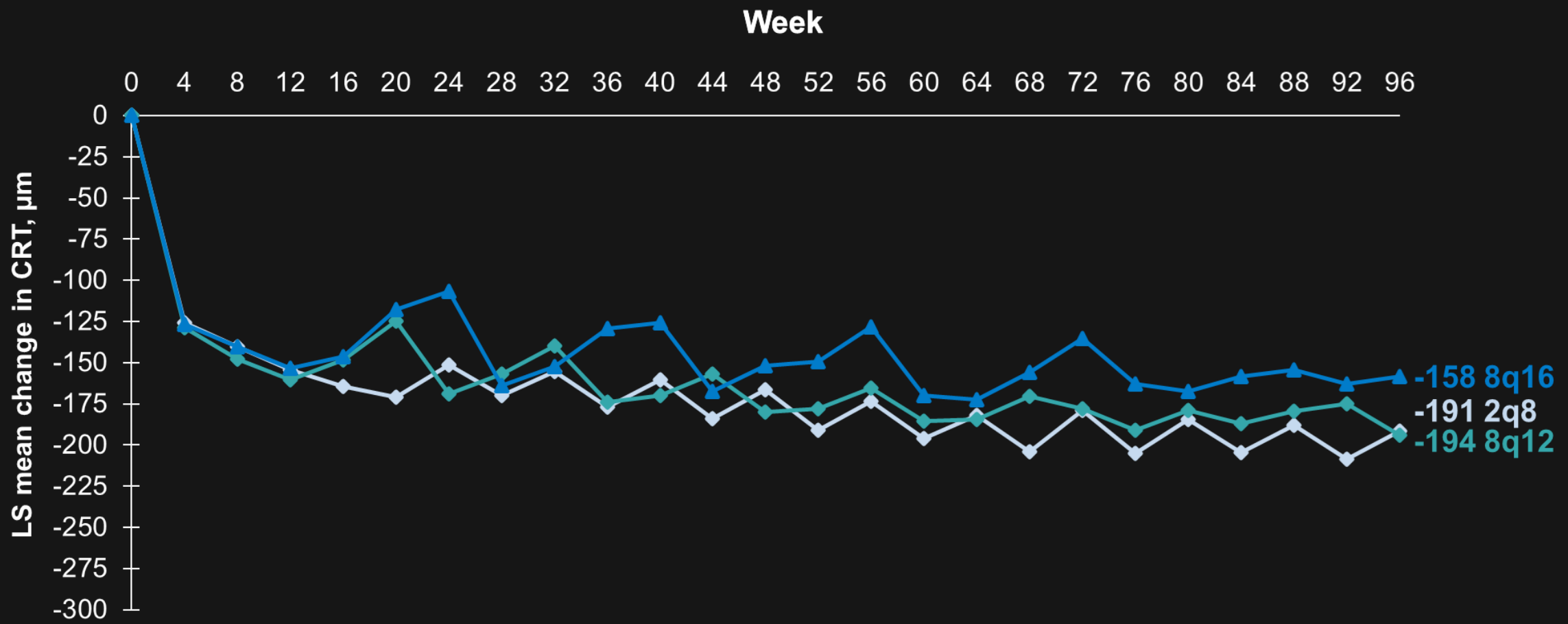
DME



[a]Patients completing Week 96.

Mean Change in Central Retinal Thickness

DME



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.

Safety Through Week 96

photon

DME

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
Ocular AEs, n (%)[a]	62 (37.1)	144 (43.9)	74 (45.4)	218 (44.4)
Non-ocular SAEs, n (%)[a]	42 (25.1)	75 (22.9)	39 (23.9)	114 (23.2)
APTC events, n (%)[a]	12 (7.2)	22 (6.7)	11 (6.7)	33 (6.7)
Hypertension events, n (%)[a]	27 (16.2)	51 (15.5)	34 (20.9)	85 (17.3)
Deaths, n (%)[b]	9 (5.4)	18 (5.5)	5 (3.1)	23 (4.7)

- Ocular AEs occurring in ≥5% of patients in any treatment group were cataract, vitreous floaters, and conjunctival hemorrhage
- No cases of ischemic optic neuropathy were reported through Week 96 in any treatment group

[a]Treatment emergent. [b]All events.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOP, intraocular pressure; SAE, serious adverse event.

IOI Through Week 96

photon

DME

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
IOI AEs, n (%)[a]	2 (1.2)	5 (1.5)	1 (0.6)	6 (1.2)
Anterior chamber cell	1 (0.6)	1 (0.3)	0	1 (0.2)
Iridocyclitis	1 (0.6)	0	1 (0.6)	1 (0.2)
Iritis	0	1 (0.3)	0	1 (0.2)
Uveitis	1 (0.6)	1 (0.3)	0	1 (0.2)
Vitreal cells	0	1 (0.3)	0	1 (0.2)
Vitritis	0	1 (0.3)	0	1 (0.2)

- No IOI events were serious, and all were considered mild or moderate in severity
- No cases of endophthalmitis or occlusive retinal vasculitis were reported through Week 96 in any treatment group

[a]Treatment emergent.
IOI, intraocular inflammation.

IOP Through Week 96

photon

DME

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
IOP increase ≥10 mmHg pre-injection from baseline, n (%)[a,b]	5 (3.0)	17 (5.2)	11 (6.7)	28 (5.7)
IOP ≥35 mmHg pre- or post-injection, n (%)[a,b]	2 (1.2)	2 (0.6)	0	2 (0.4)

- Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 96 in any treatment group

[a]Treatment emergent. [b]At any time.
IOP, intraocular pressure.

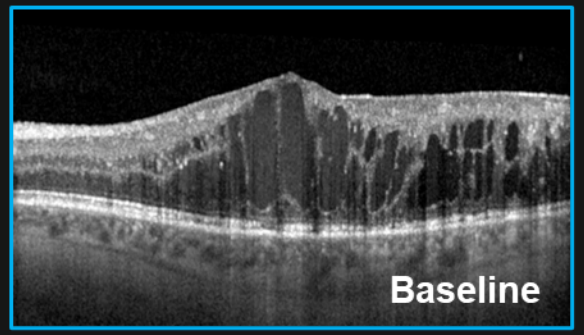
DME

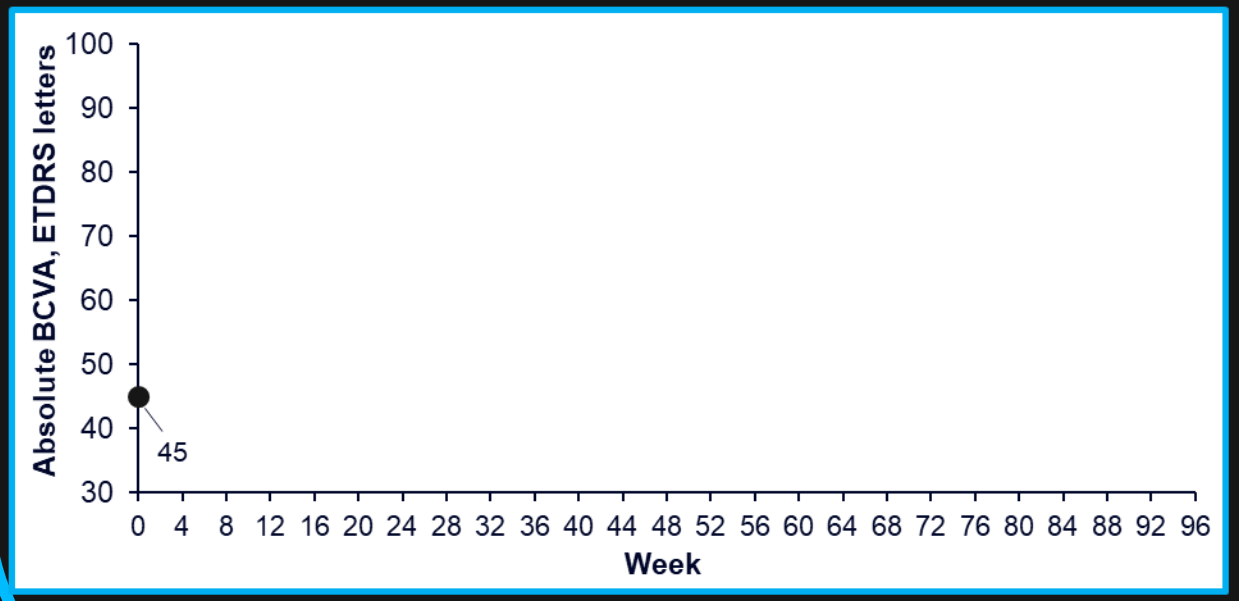
Patient Case

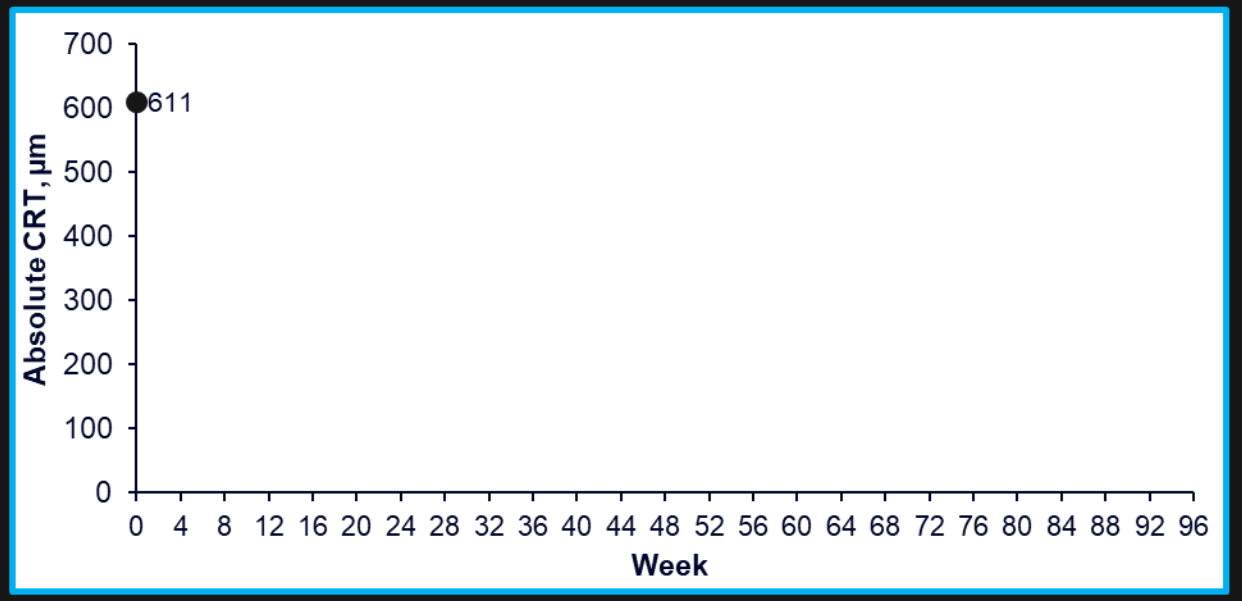
Case: Treatment-Naïve Patient Randomized to 8q16 Maintained Improvements in BCVA and CRT Through Week 96

DME

Treatment arm	8q16
Age	55 years
Sex	Male
Race	White
Baseline BCVA	45 ETDRS letters
Baseline CRT	611 µm



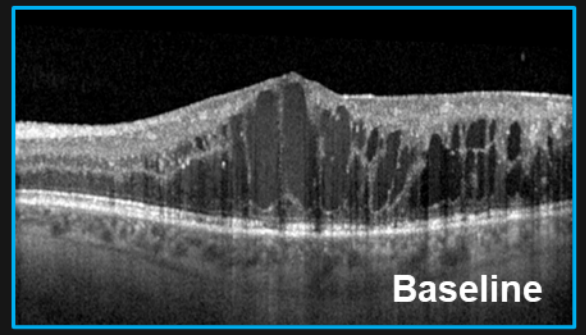


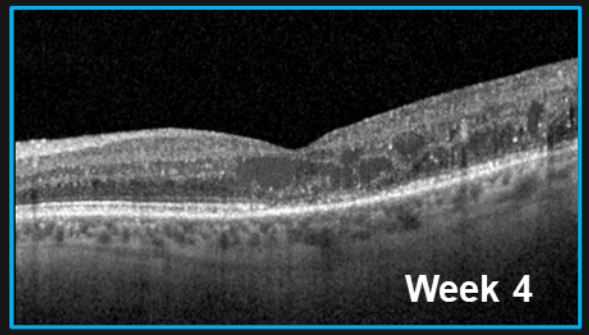


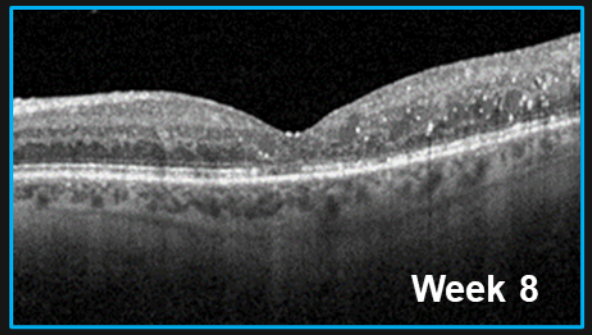
⬆ indicates active injection. ☐ indicates timepoints at which patients were assessed for interval shortening (from baseline through Week 96) or extension (from Weeks 52 through 96) based on DRM criteria.
IMD, initial monthly dosing.

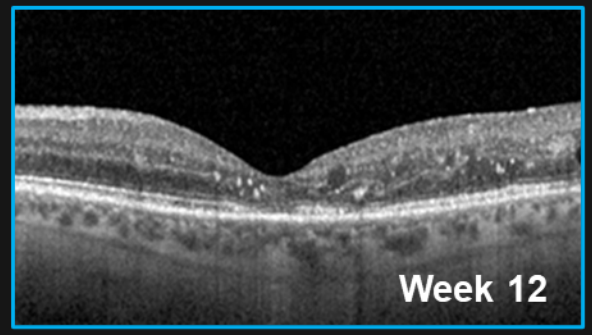
Case: Treatment-Naïve Patient Randomized to 8q16 Maintained Improvements in BCVA and CRT Through Week 96

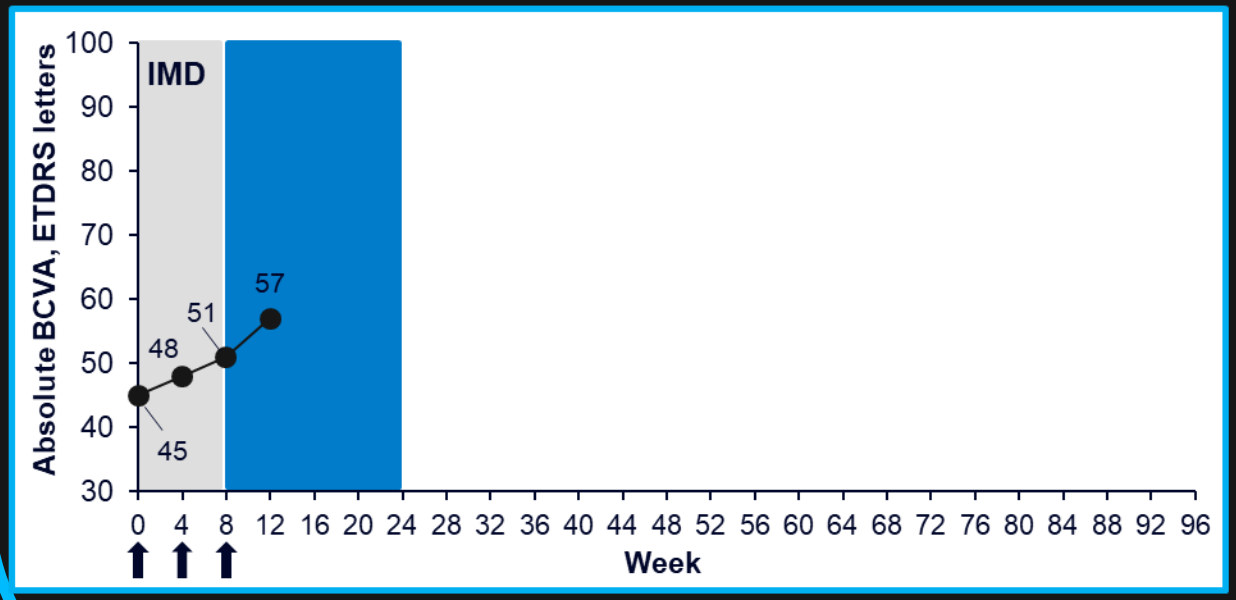
DME

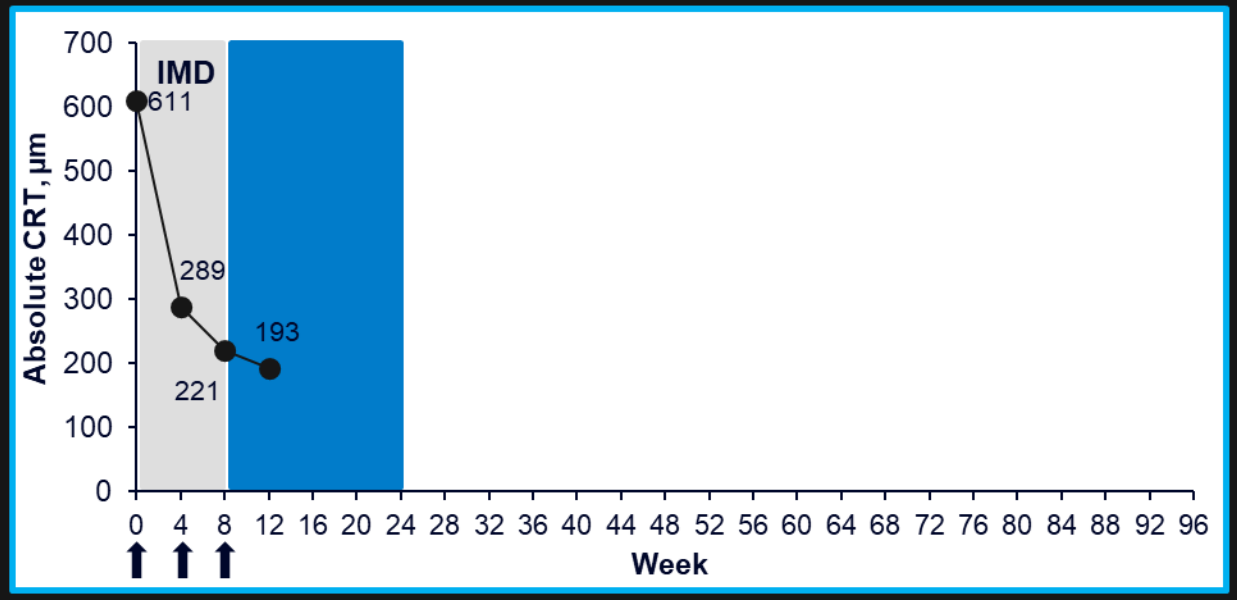










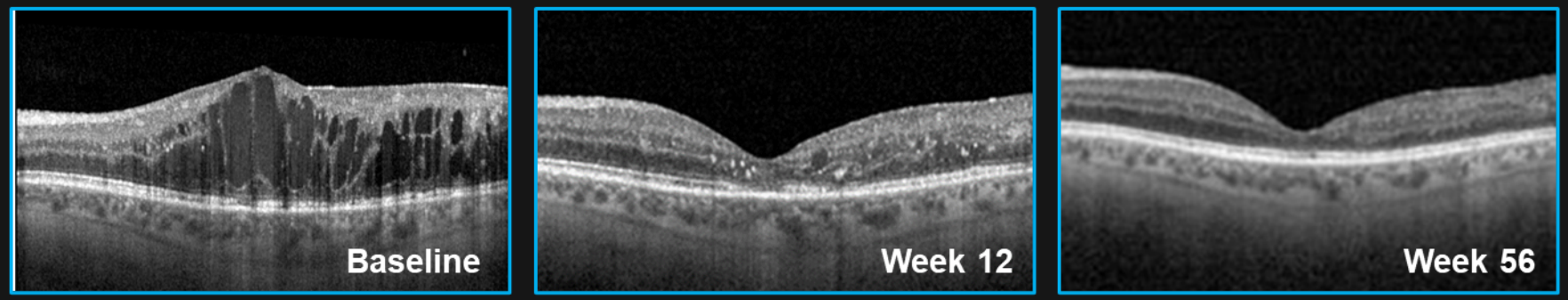


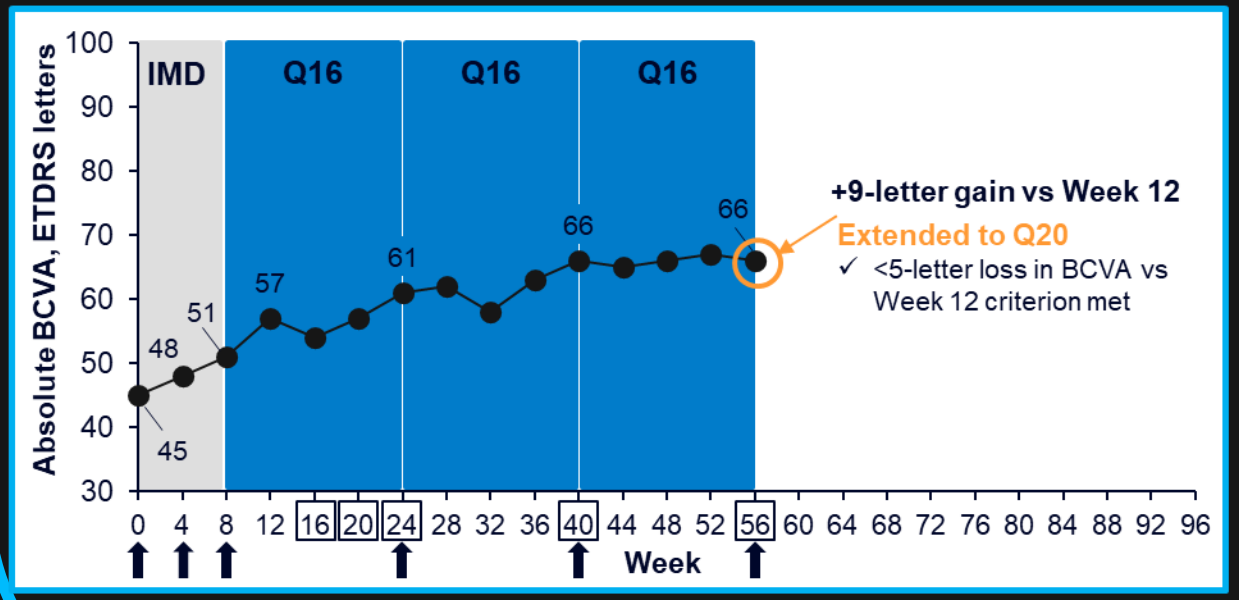
⬆ indicates active injection. ☐ indicates timepoints at which patients were assessed for interval shortening (from baseline through Week 96) or extension (from Weeks 52 through 96) based on DRM criteria.

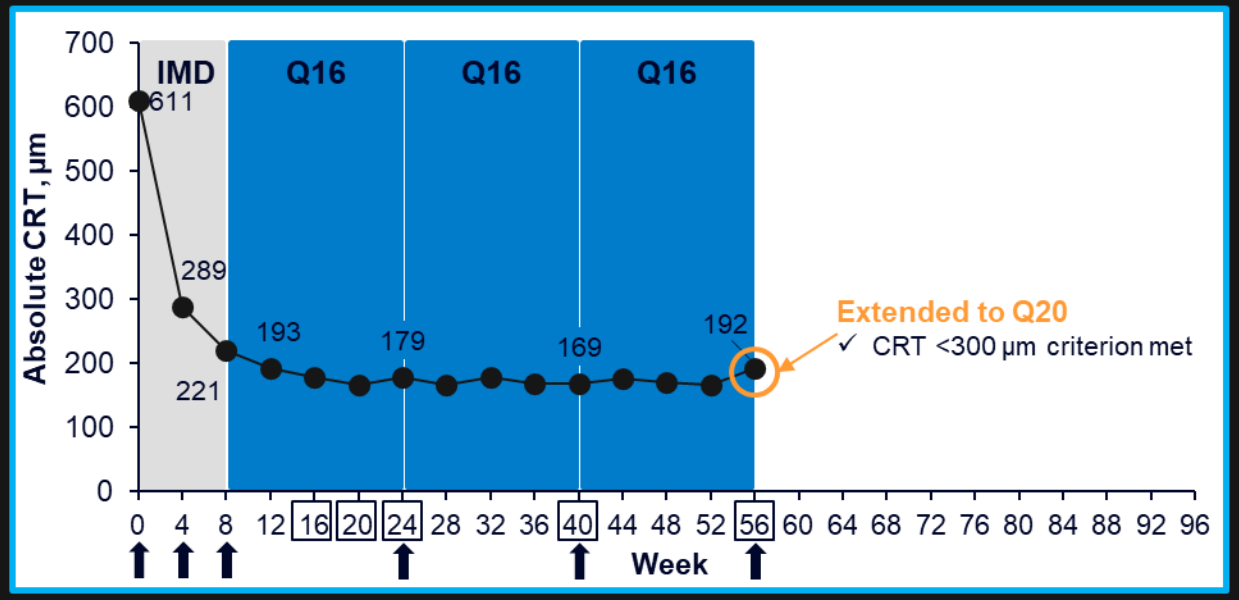
Case: Treatment-Naïve Patient Randomized to 8q16 Maintained Improvements in BCVA and CRT Through Week 96

DME

Treatment arm	8q16
Age	55 years
Sex	Male
Race	White
Baseline BCVA	45 ETDRS letters
Baseline CRT	611 µm





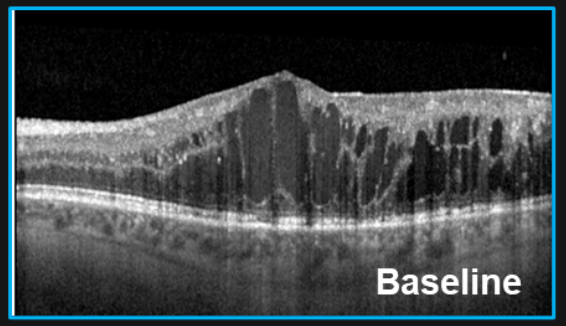


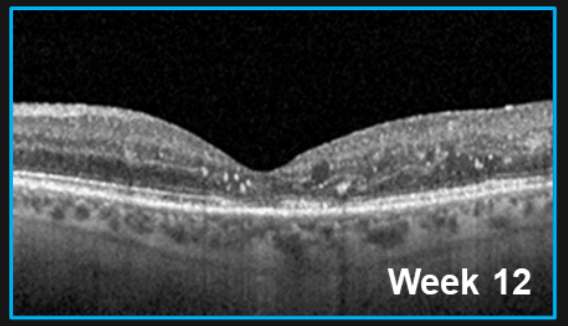
⬆ indicates active injection. ☐ indicates timepoints at which patients were assessed for interval shortening (from baseline through Week 96) or extension (from Weeks 52 through 96) based on DRM criteria.

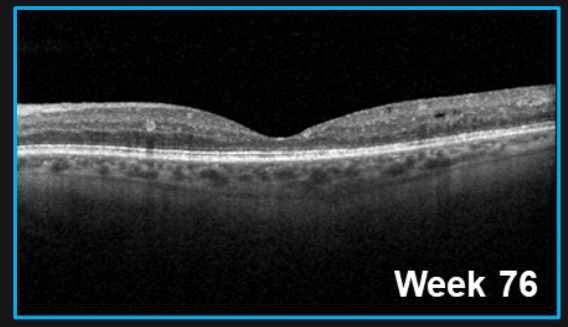
Case: Treatment-Naïve Patient Randomized to 8q16 Maintained Improvements in BCVA and CRT Through Week 96

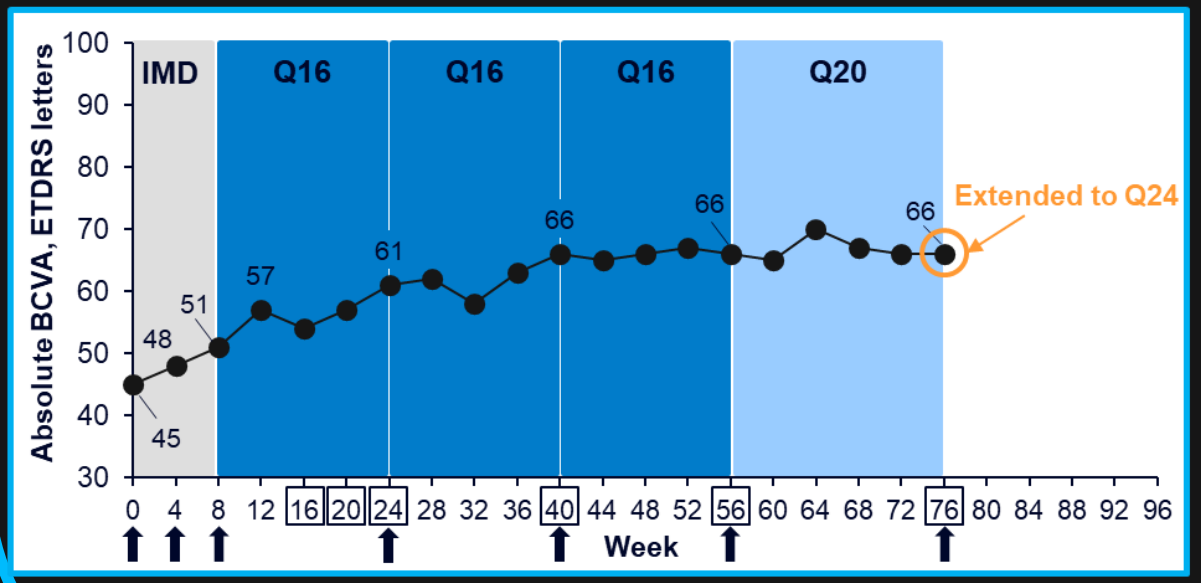
DME

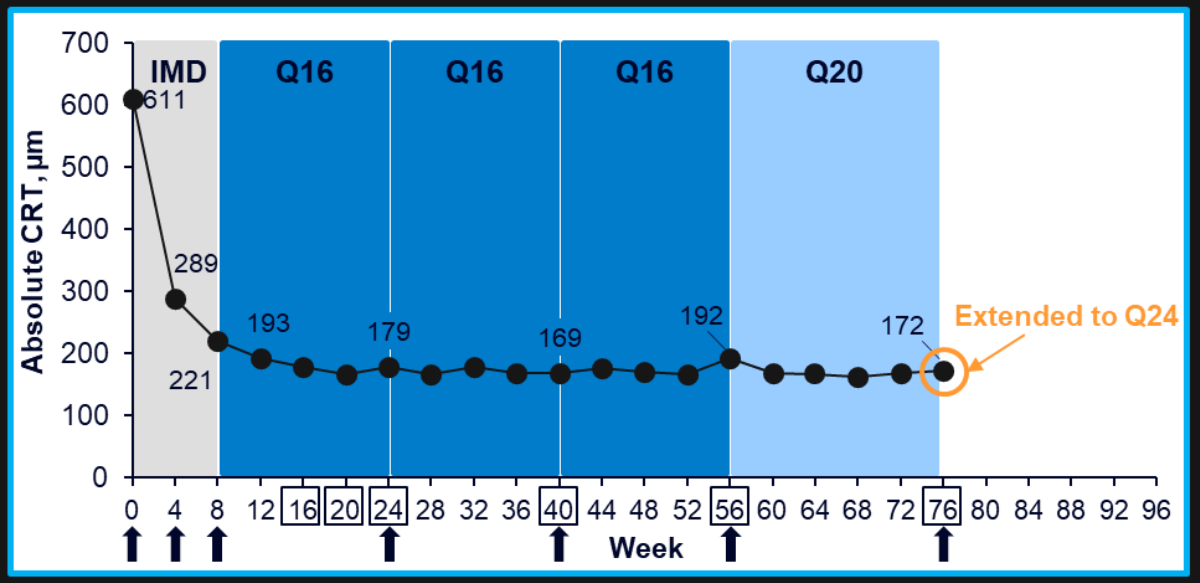
Treatment arm	8q16
Age	55 years
Sex	Male
Race	White
Baseline BCVA	45 ETDRS letters
Baseline CRT	611 µm









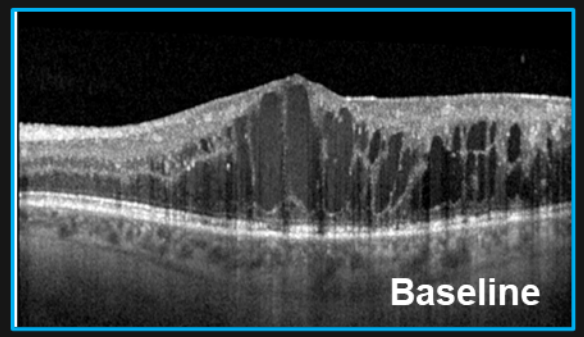


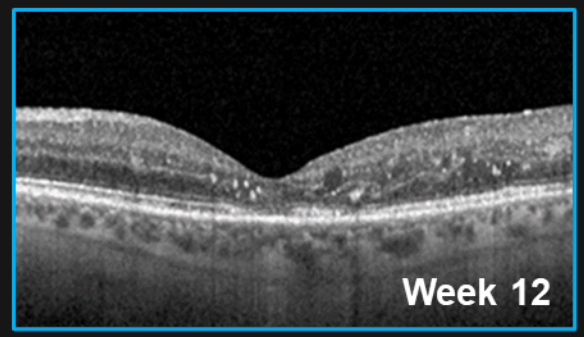
⬆ indicates active injection. ☐ indicates timepoints at which patients were assessed for interval shortening (from baseline through Week 96) or extension (from Weeks 52 through 96) based on DRM criteria.

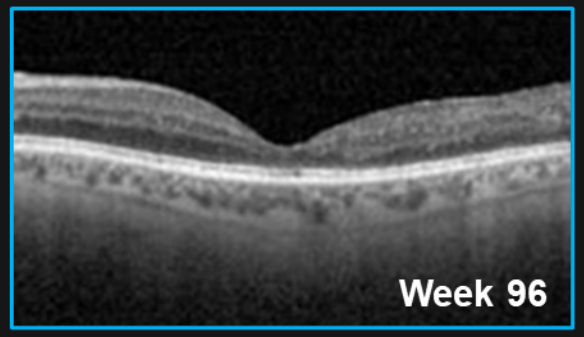
Case: Treatment-Naïve Patient Randomized to 8q16 Maintained Improvements in BCVA and CRT Through Week 96

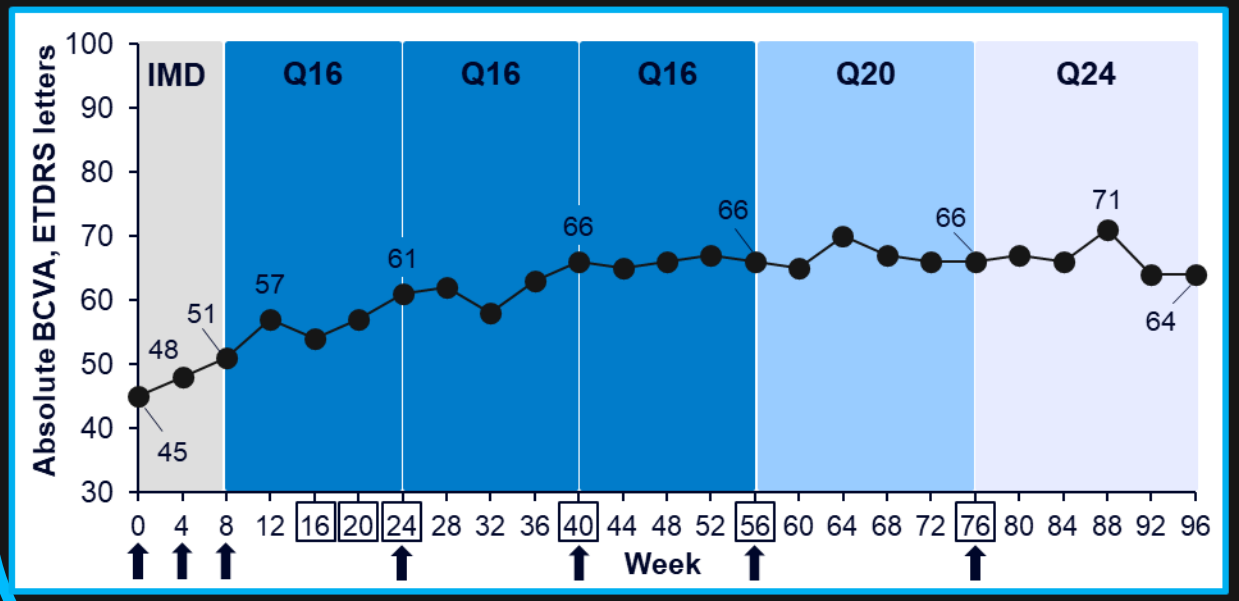
DME

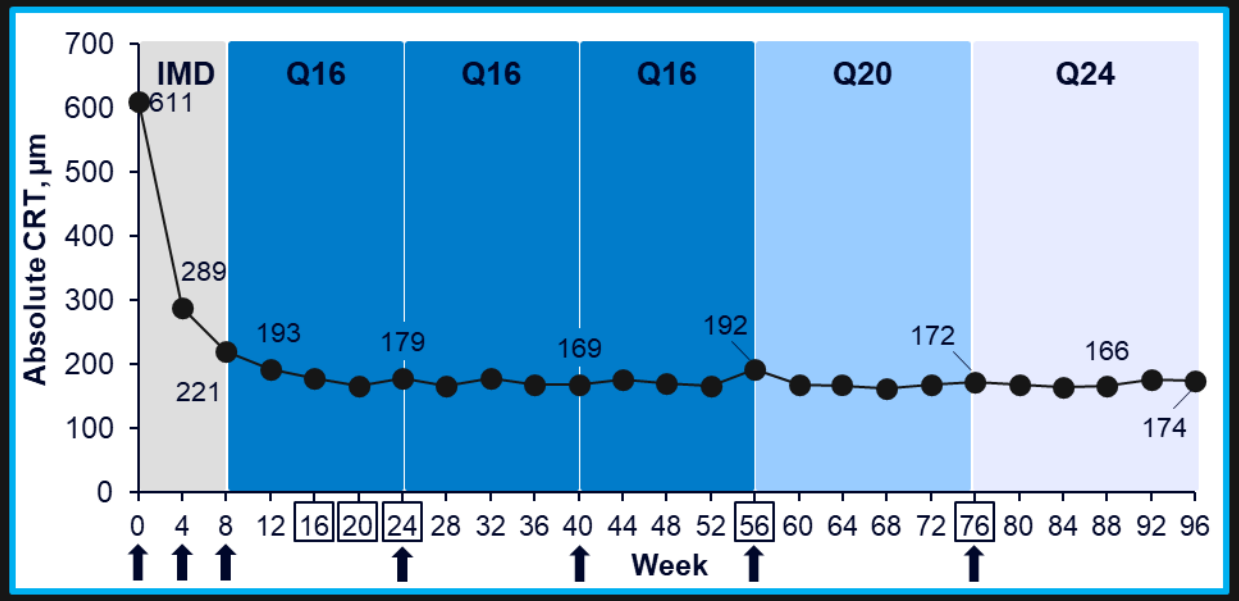
Treatment arm	8q16
Age	55 years
Sex	Male
Race	White
Baseline BCVA	45 ETDRS letters
Baseline CRT	611 µm











⬆ indicates active injection. ☐ indicates timepoints at which patients were assessed for interval shortening (from baseline through Week 96) or extension (from Weeks 52 through 96) based on DRM criteria.

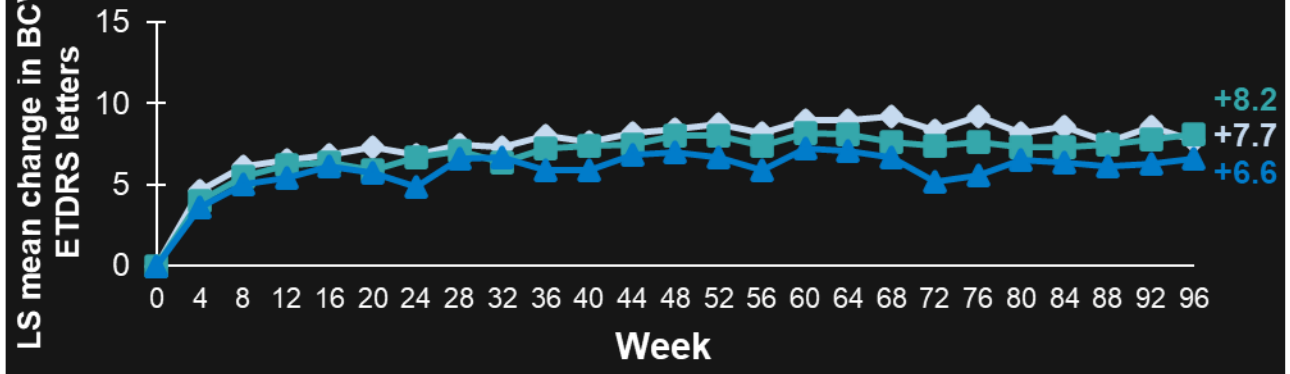
PHOTON: 96-week Results

photon

DME

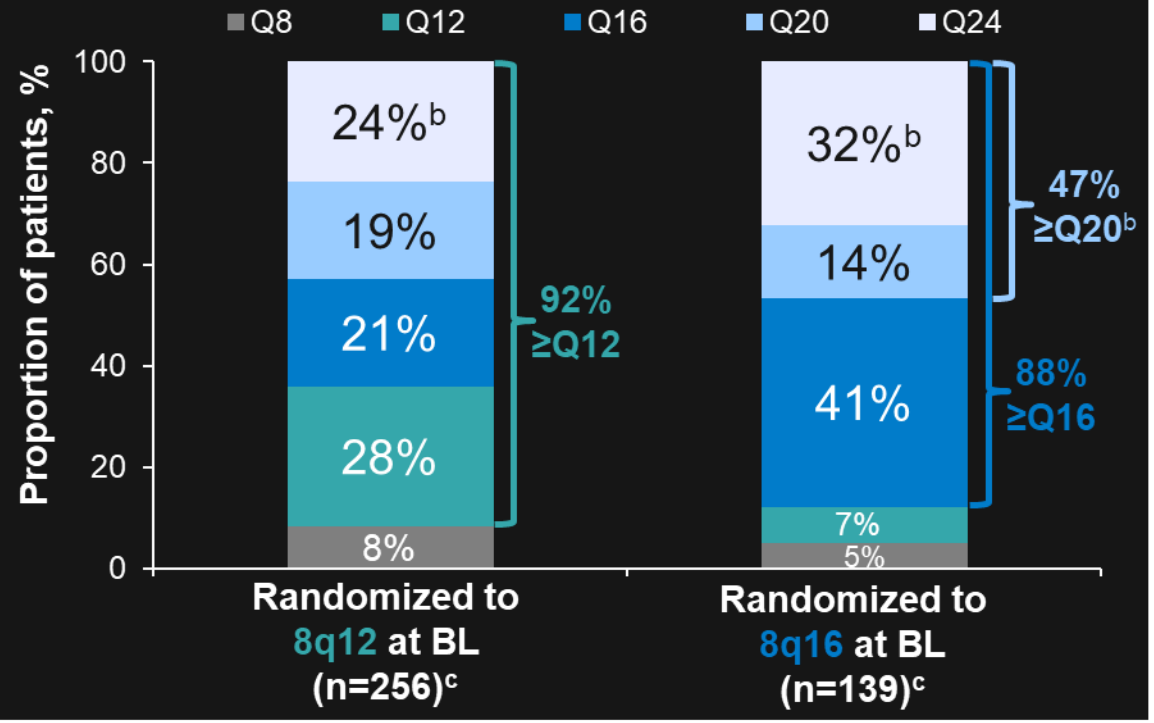
- 8q12 and 8q16 groups achieved similar BCVA gains compared to 2q8 at Week 96, with up to 6 fewer injections
- Through Week 96, 88% of 8q12 patients and 84% of 8q16 patients maintained ≥12- and ≥16-week dosing intervals, respectively
  - At Week 96, 43% of 8q12 patients and 47% of 8q16 patients had a last assigned dosing interval of ≥20 weeks
- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks

Mean Change From Baseline in BCVA[a]



	LS mean change from BL at Week 96 (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for NI at 4-letter margin
2q8	7.7			
8q12	8.2	+0.45	-1.55, 2.45	p < 0.0001 (nominal)
8q16	6.6	-1.11	-3.27, 1.05	p = 0.0044 (nominal)

Last Assigned Dosing Interval at Week 96



[a]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. [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.

Thank you to all co-investigators and patients who participated in the PHOTON trial

photon

DME