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Extension

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

David M. Brown, MD,[1] on behalf of the PHOTON extension study investigators

[1]Retina Consultants of America, Houston, TX, USA

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Disclosures

- David M. Brown has served as scientific advisor for Regeneron/Bayer and Genentech/Roche and as a member of the Regeneron Combination Products Steering Committee
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of this study, data interpretation, and preparation of this presentation
- This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to initiation of the study

PHOTON Extension Study Design

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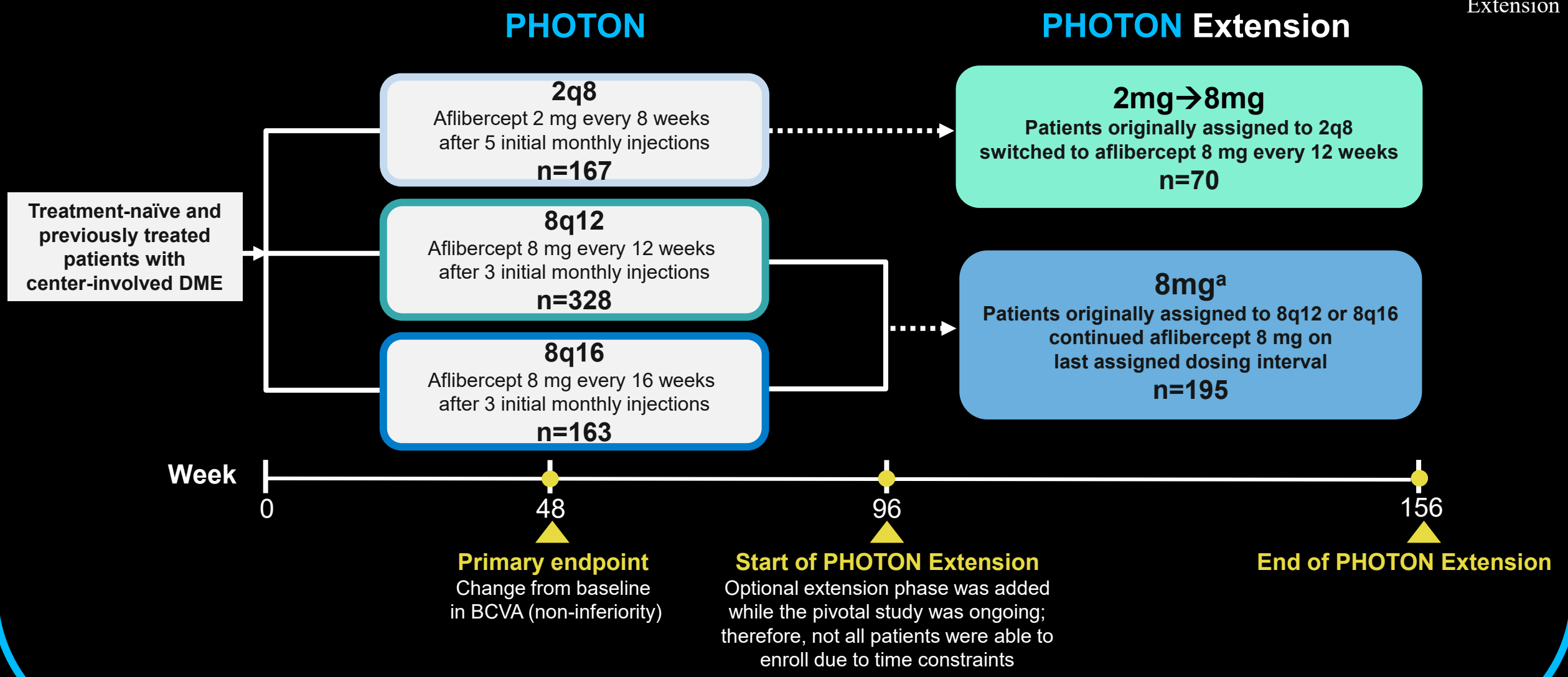

[a]Patients who were randomized to the 8q12 or 8q16 groups at the beginning of the PHOTON study and continued treatment with aflibercept 8 mg through the PHOTON extension study.
BCVA, best-corrected visual acuity; DME, diabetic macular edema.

PHOTON Extension Study Design

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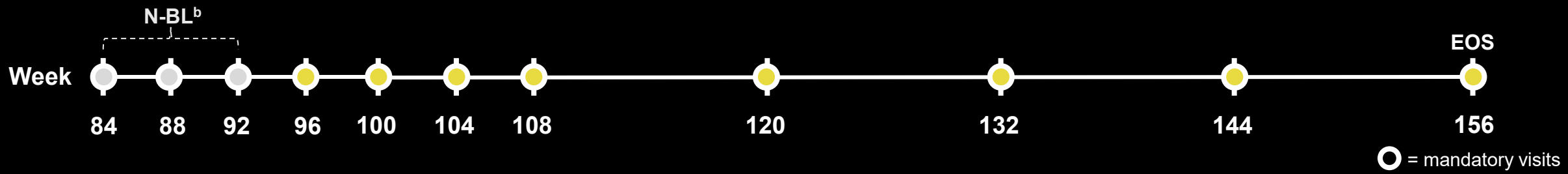
2mg→8mg
n=70

8mg[a]
n=195

- All patients received aflibercept 8 mg through Week 156
  - Patients who were treated with aflibercept 2q8 were switched to aflibercept 8 mg at Week 96 and immediately assigned to a 12-week dosing interval
- Mandatory visits were every 4 weeks through Week 108, then were quarterly through Week 156
- Dosing visits were scheduled as necessary based on individual dosing interval assignment



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]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]N-BL defined as an average of values from Week 84, 88, and 92.
CRT, central retinal thickness; DRM, dosing regimen modification; EOS, end of study; N-BL, new baseline.

Patient Disposition and Baseline Characteristics

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	PHOTON	PHOTON Extension		
	Total	2q8→8mg	8mg[a]	Total
Patients entering PHOTON study (FAS)	658	-	-	-
Patients entering PHOTON extension (eFAS)	-	70	195	265
Completion rate at Week 96 (%)	80.9	100	100	100
Completion rate at Week 156 (%)	-	82.9[b]	77.9[b]	79.2[b]
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[c]	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

[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]Completion rate for PHOTON extension study based on eFAS. [c]Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, multiple races, and unreported race.
Data are mean (SD) unless otherwise indicated.
eFAS, PHOTON extension full analysis set; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.

Mean BCVA[a] Through Week 156

2q8→8mg and 8mg[b] Patients

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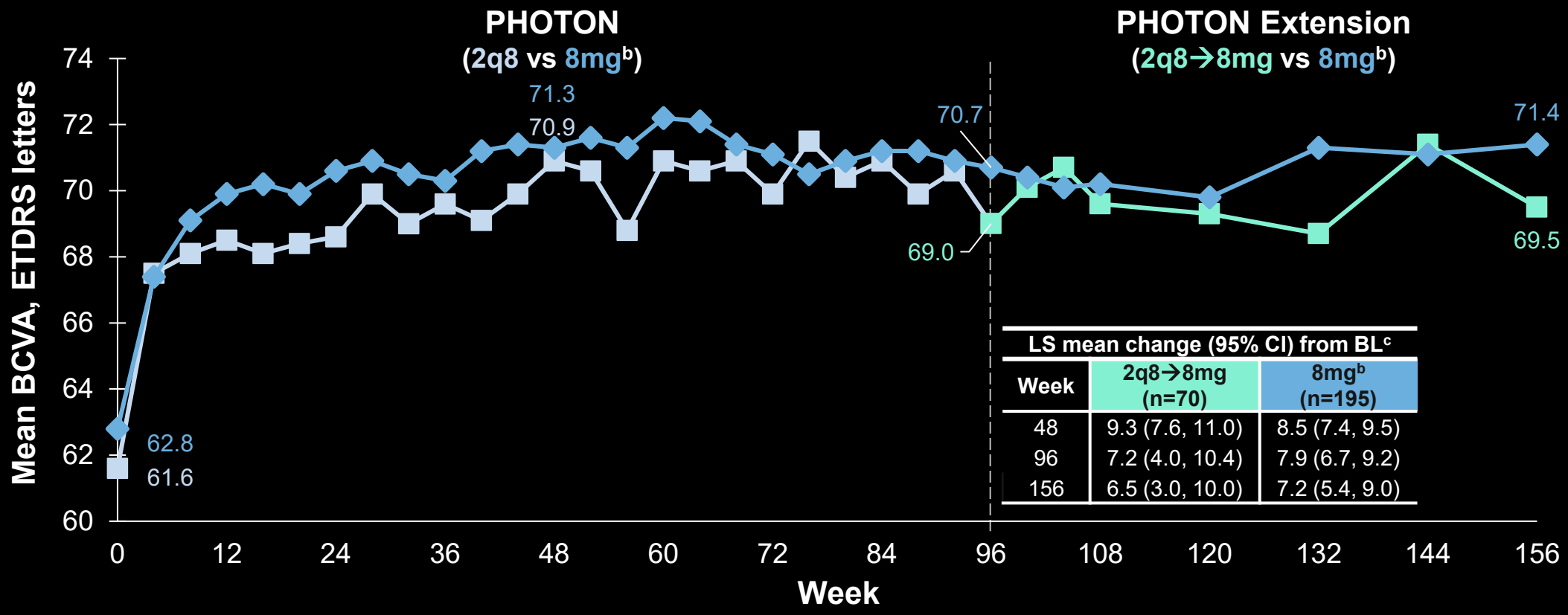

LS mean change (95% CI) from BL[c]		
Week	2q8→8mg (n=70)	8mg[b] (n=195)
48	9.3 (7.6, 11.0)	8.5 (7.4, 9.5)
96	7.2 (4.0, 10.4)	7.9 (6.7, 9.2)
156	6.5 (3.0, 10.0)	7.2 (5.4, 9.0)

Mean number of injections from baseline to Week 96[d]

2q8: 13.8

8mg[b]: 8.9

Mean number of injections from Week 96 to Week 156[d]

2q8→8mg: 4.4

8mg[b]: 3.3

[a]eFAS, observed cases. [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]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. [d]eFAS.

Mean CRT Through Week 156

8mg[a] Patients

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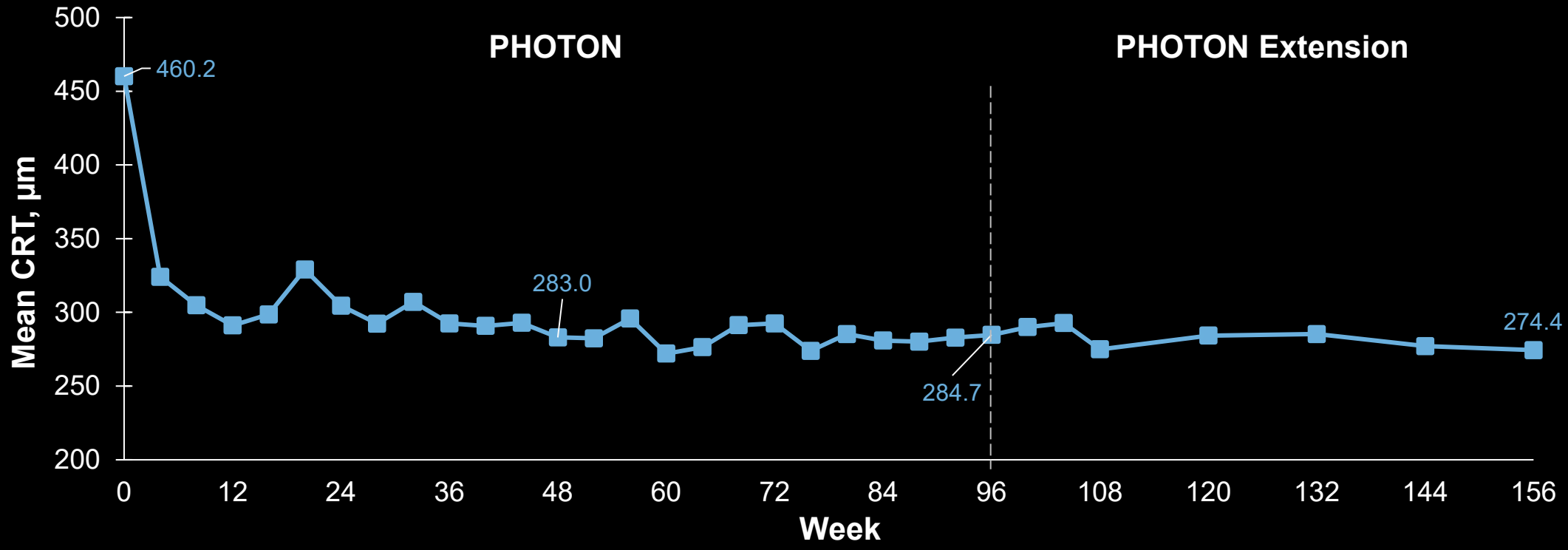
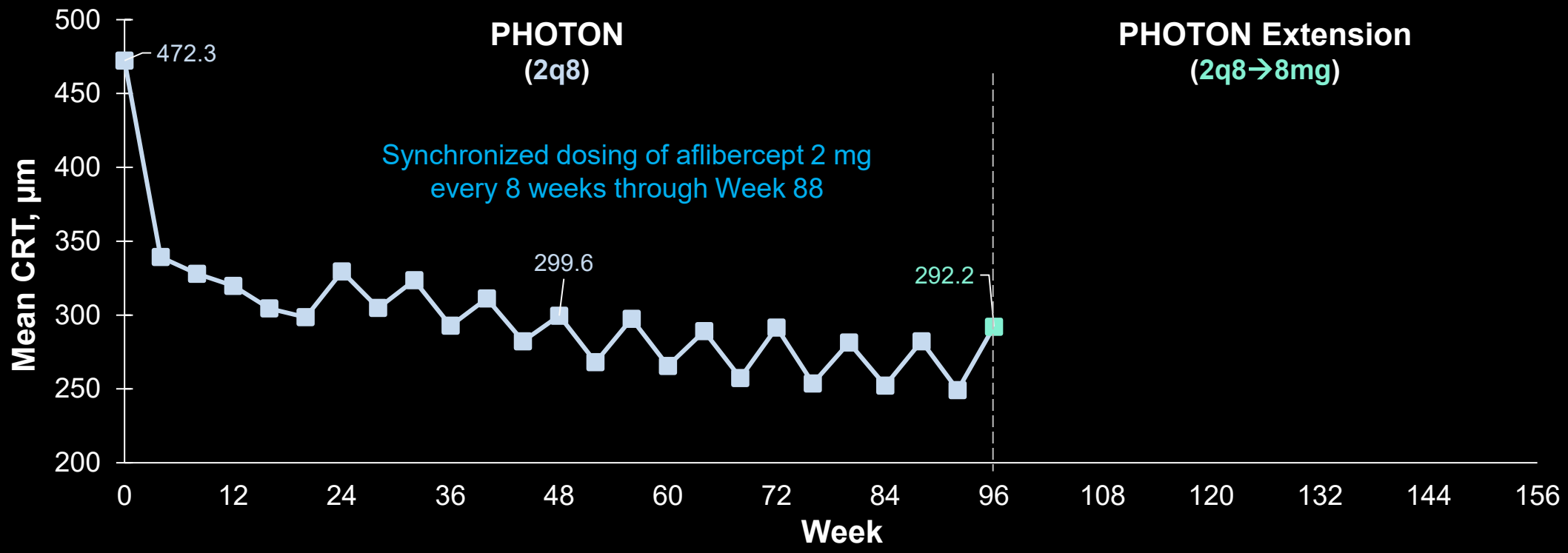


	LS mean change (95% CI) from baseline (µm)		
	Week 48	Week 96	Week 156
8mg[a] (n=195)	-180.6 (-193.5, -167.7)	-178.4 (-194.2, -162.6)	-192.4 (-208.7, -176.1)

[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.
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.
eFAS, observed cases.

Mean CRT Through Week 156

2q8→8mg Patients

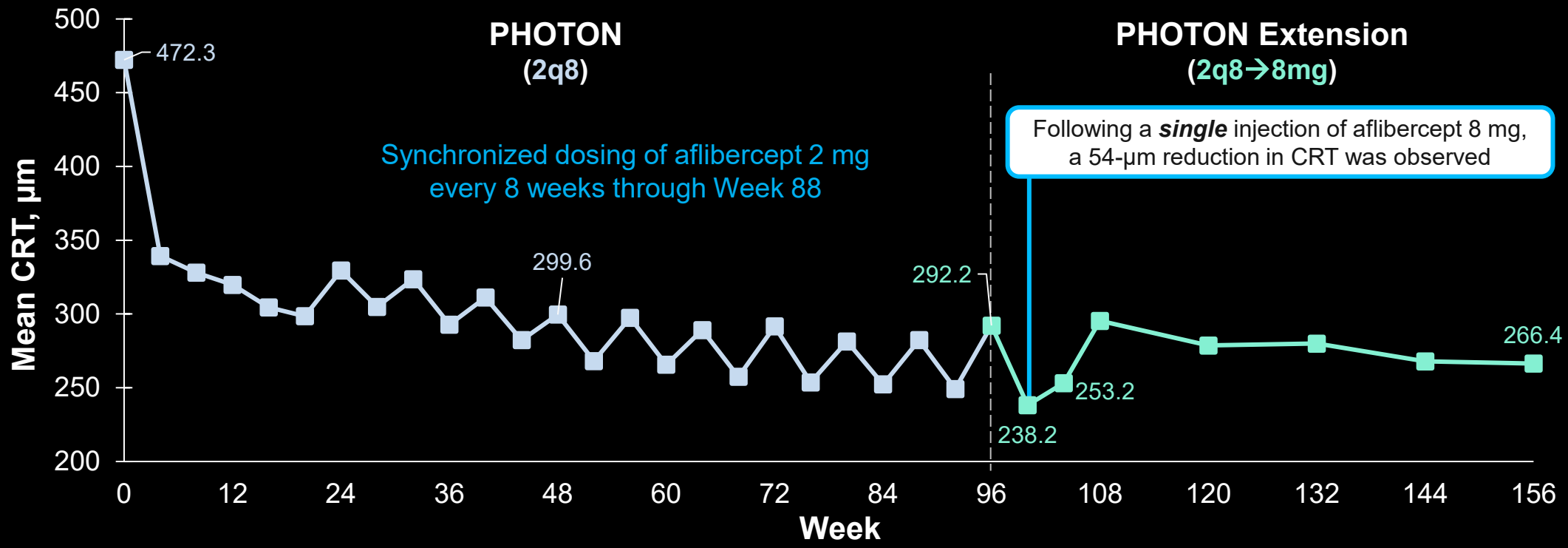


	LS mean change (95% CI) from baseline (µm)	
	Week 48	Week 96
2q8→8mg (n=70)	-161.7 (-187.8, -135.6)	-169.7 (-221.8, -117.6)

eFAS, observed cases.
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.

Mean CRT Through Week 156

2q8→8mg Patients



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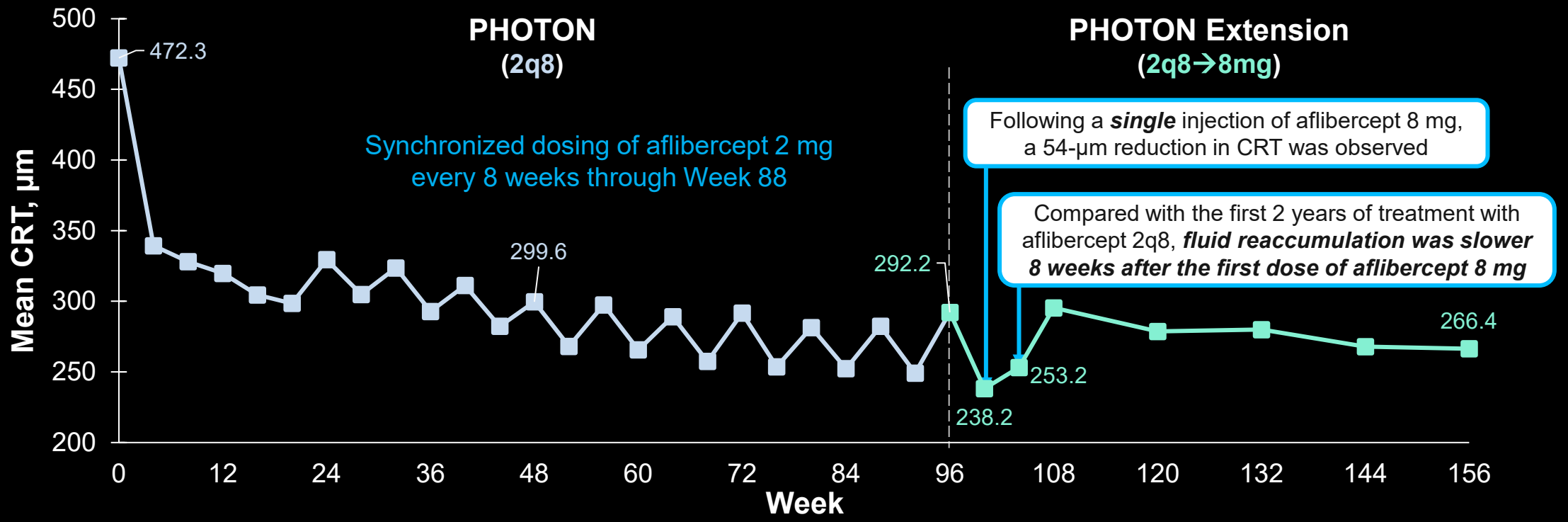
Mean CRT Through Week 156

2q8→8mg Patients



	LS mean change (95% CI) from baseline (µm)		
	Week 48	Week 96	Week 156
2q8→8mg (n=70)	-161.7 (-187.8, -135.6)	-169.7 (-221.8, -117.6)	-197.4 (-220.4, -174.5)

Numerically greater reduction in CRT was observed at Week 156 after switching to aflibercept 8 mg compared with aflibercept 2q8

eFAS, observed cases. 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.

Majority of Aflibercept 8 mg-treated Patients Achieved Extended Dosing Intervals at Week 156

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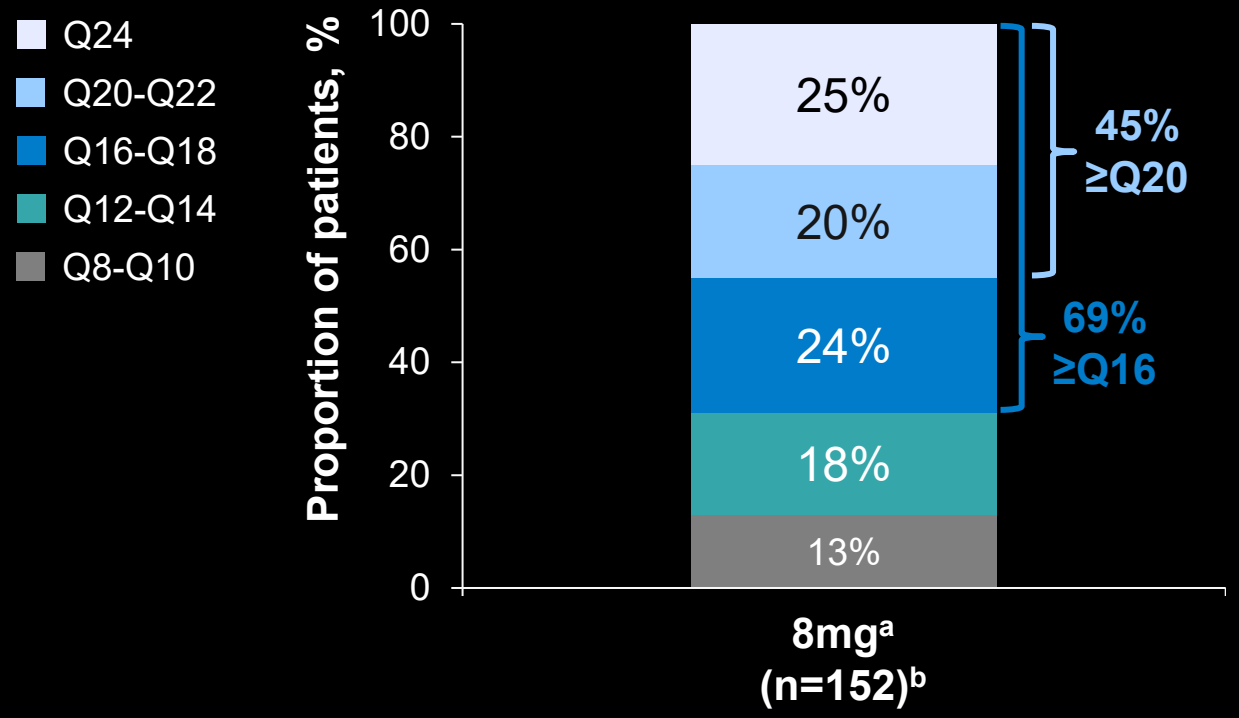
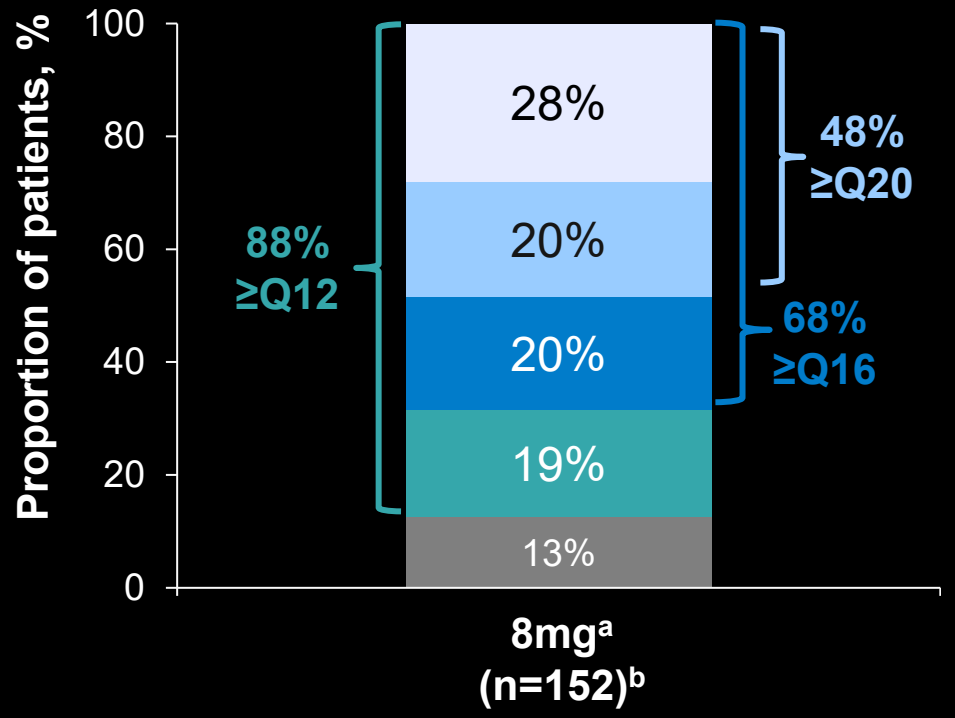
Last Completed Dosing Interval



Last Assigned Dosing Interval



88% of patients had a last assigned dosing interval of ≥12 weeks at Week 156

[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]eFAS, patients completing Week 156.
Values may not add up to 100% due to rounding.

Majority of Patients in the 2q8→8mg Group Achieved Extended Dosing Intervals at Week 156

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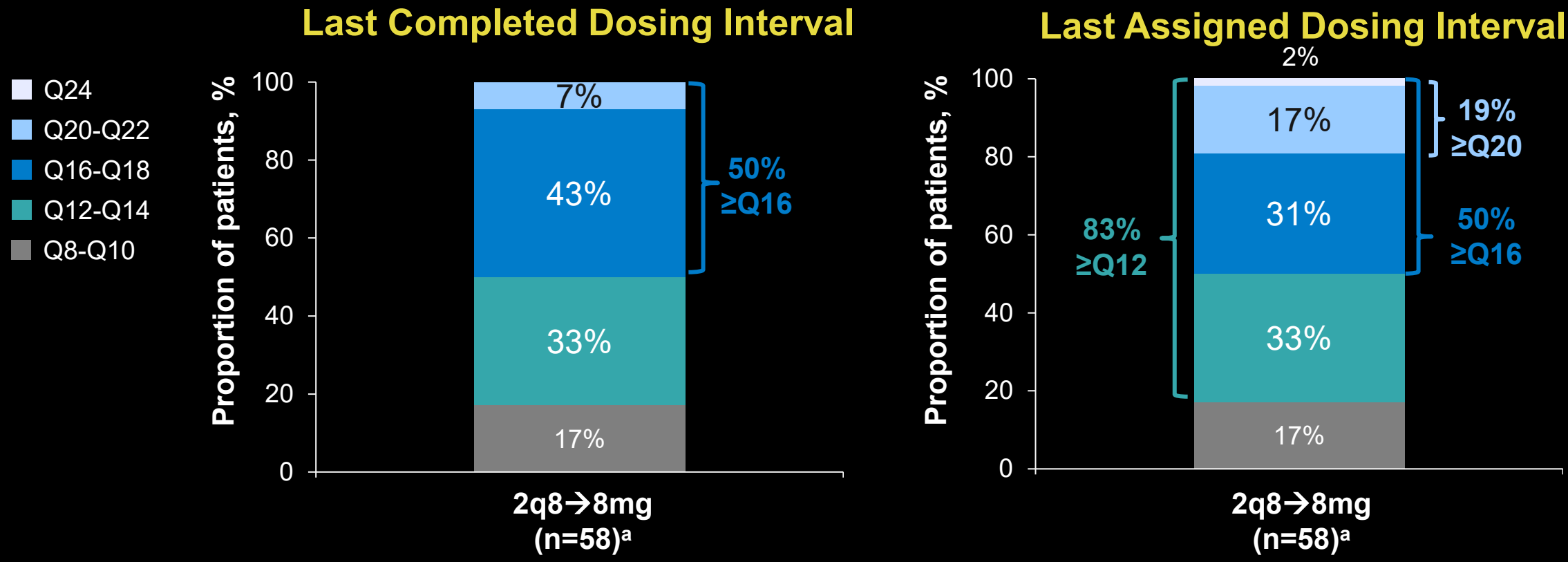

83% of patients had a last assigned dosing interval of ≥12 weeks at Week 156

[a]eFAS, patients completing Week 156.
Patients in the 2q8→8mg group were unable to complete a 24-week dosing interval during the study period.
Values may not add up to 100% due to rounding.

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

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	2q8→8mg	8mg[b]	Total
N (eSAF)	70	195	265
Ocular AEs, n (%)[c]	37 (52.9)	108 (55.4)	145 (54.7)
Ocular SAEs, n (%)[c]	3 (4.3)	4 (2.1)	7 (2.6)
Intraocular inflammation, n (%)[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 (%)[c]	24 (34.3)	58 (29.7)	82 (30.9)
APTC events, n (%)[c]	5 (7.1)	14 (7.2)	19 (7.2)
Deaths, n (%)[d]	2 (2.9)	10 (5.1)	12 (4.5)

- Ocular TEAEs reported in >4% of all patients included cataract, vitreous floaters, vitreous detachment, and diabetic retinal edema
- No cases of occlusive vasculitis were reported

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

PHOTON Extension: Key Week 156 Results

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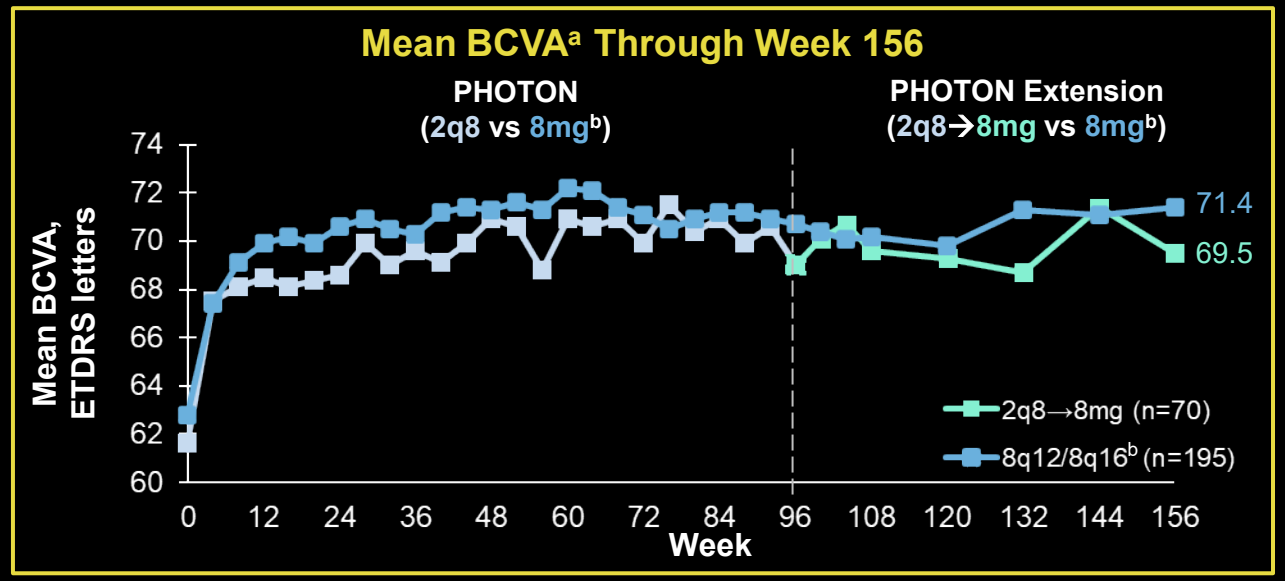
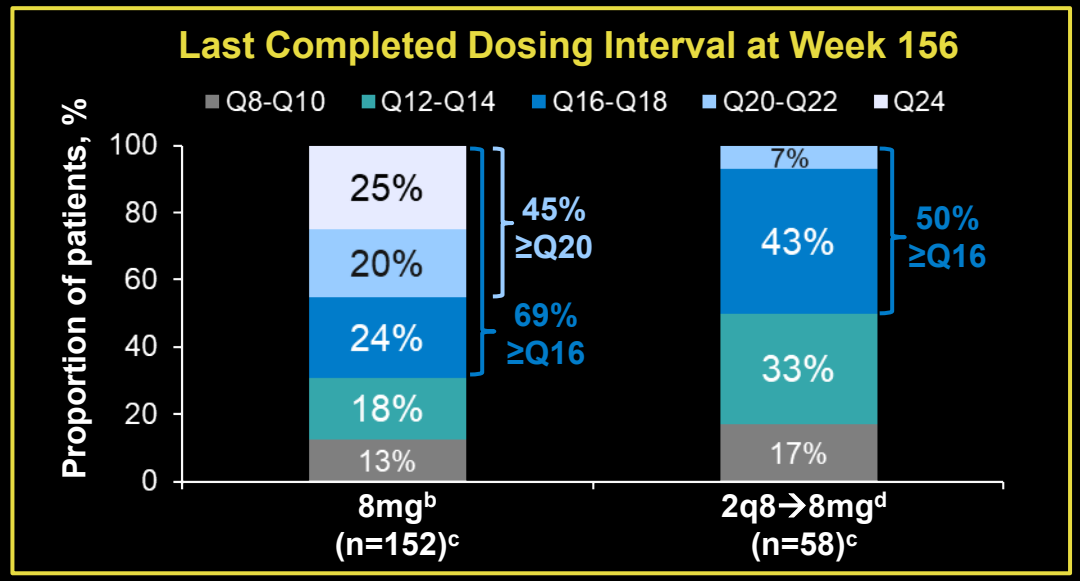
- Patients in the **8mg group** maintained visual and anatomic improvements achieved in the first 2 years, with the majority of patients on extended dosing intervals
  - 45% completed ≥20-week dosing intervals and 48% had a last assigned dosing interval of ≥20 weeks at Week 156
- In the **2q8→8mg group**, visual and anatomic improvements achieved with fixed 2q8 dosing were maintained with aflibercept 8 mg
  - 83% of patients achieved ≥12-week dosing intervals at Week 156
  - ***Longer duration of action with aflibercept 8 mg*** vs 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 through Week 156

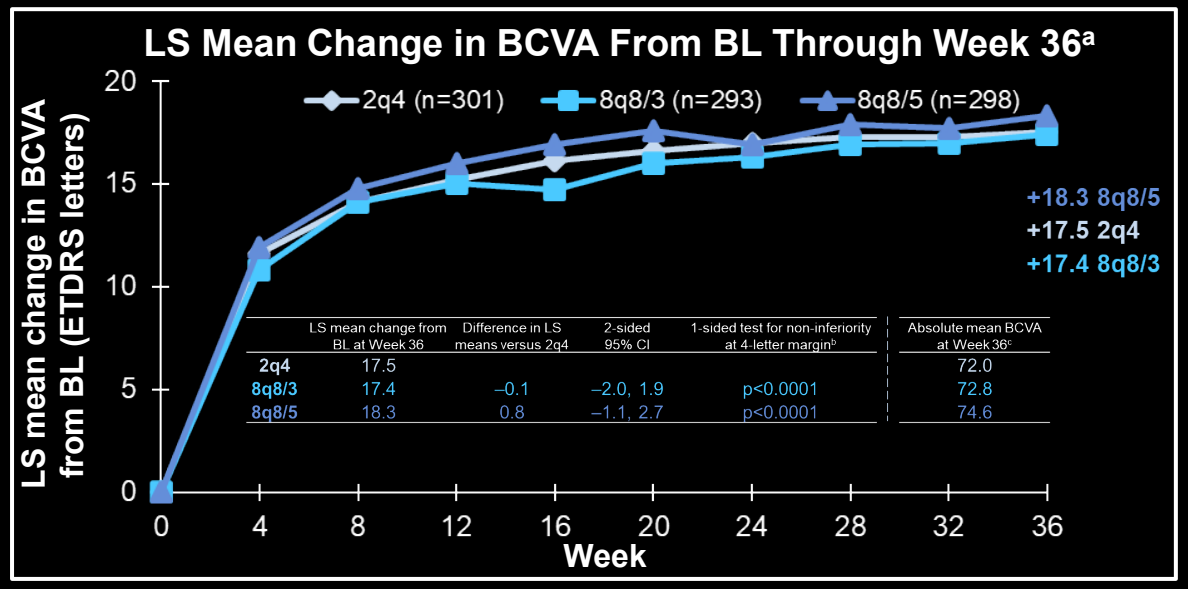




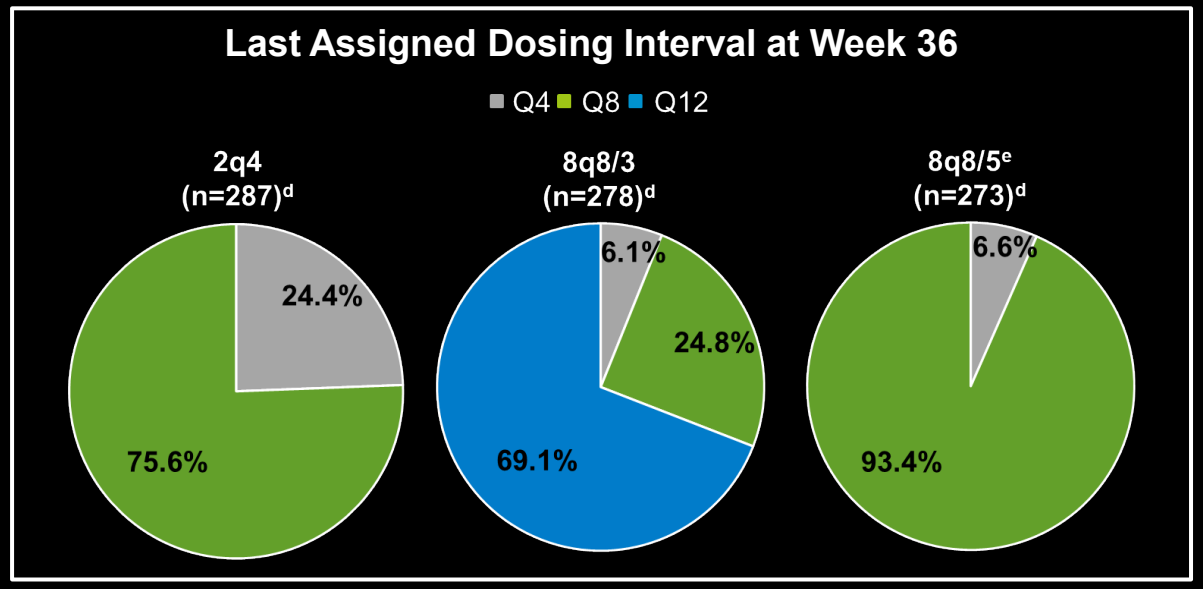
[a]eFAS, observed cases.
[b]Patients who were randomized to the 8q12 or 8q16 groups at the beginning of the PHOTON study and continued treatment with aflibercept 8 mg through the PHOTON extension study.
[c]eFAS, patients completing Week 156.
[d]Patients in the 2q8→8mg group were unable to complete a 24-week dosing interval during the study period.

Primary Endpoint Met by Both Aflibercept 8-mg Groups in RVO

- Patients who received aflibercept 8q8 after 3 or 5 initial monthly doses achieved **robust visual outcomes** and **non-inferior BCVA gains with fewer injections** compared with those who received aflibercept 2q4 after 3 initial monthly doses at Week 36
- Most patients in the aflibercept 8-mg groups **maintained their assigned Q8 intervals** through Week 36
- **Early, robust reductions in CRT** were maintained through Week 36
- The safety profile of aflibercept 8 mg was consistent with the established safety profile of aflibercept 2 mg in patients with macular edema secondary to RVO, with **no new safety signals**



	LS mean change from BL at Week 36	Difference in LS means versus 2q4	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin[b]	Absolute mean BCVA at Week 36[c]
2q4	17.5				72.0
8q8/3	17.4	–0.1	–2.0, 1.9	p<0.0001	72.8
8q8/5	18.3	0.8	–1.1, 2.7	p<0.0001	74.6



[a]Full analysis set. LS means were generated using a mixed model for repeated measures with baseline BCVA as a covariate; treatment group (aflibercept 8q8/3, 8q8/5, 2q4), visit, and stratification variables (geographic region [Japan vs Asian-Pacific vs Europe vs America], BL BCVA [<60 vs ≥60 letters], RVO type [CRVO/HRVO vs BRVO]) as fixed factors; and terms for the interaction between baseline BCVA and visit and treatment and visit. [b]p-values for the one-sided non-inferiority test at a margin of 4 letters (based on adjusted means derived using a mixed model for repeated measures). [c]Observed values (censoring data post-ICE). [d]Patients completing Week 36. [e]Per DRM criteria, dosing interval extension was not possible in the 8q8/5 group until Week 40.

2q4, aflibercept 2 mg every 4 weeks; 8q8/3, aflibercept 8 mg every 8 weeks after 3 initial monthly doses; 8q8/5, aflibercept 8 mg every 8 weeks after 5 initial monthly doses; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; HRVO, hemiretinal vein occlusion; RVO, retinal vein occlusion.