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

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Disclosures

- Charles C. Wykoff: 4DMT (C, R), Abbvie (C), Adverum (C, R), Aerie (C), AffaMed (R), AGTC (C), Alcon (C), Alexion (R), Alimera (R), Annexin (R), Annexon (C, R), Apellis (C, R), Ascidian (C), Asclepix (R), Bausch + Lomb (C), Bayer (C, R), Boehringer Ingelheim (C, R), Clearside (C, R), Curacle (C, R), Eyebiotech (C, R), EyePoint (C, R), Genentech (C, R), Gyroscope (C, R), IONIS (R), IVERIC Bio (C, R), Janssen (C, R), Kato (C), Kiora (C), Kodiak (C, R), Merck (C), Nanoscope (C, R), Neurotech (C, R), NGM (C, R), Notal Vision (C), Novartis (C, R), Ocular Therapeutix (C, R), Ocuphire (C, R), OcuTerra (C, R), OliX (R), ONL (C, SO), Opthea (C, R), Oxular (C, R), Palatin (C), PerceiveBio (C, R), PolyPhotonix (SO), Ray (C), RecensMedical (C, SO), Regeneron (C, R), RegenXBio (C, R), Resonance (C), Roche (C, R), Sandoz (C, R), Sanofi (C), SciNeuro (C), Stealth (C), Surrozen (C), Suzhou Raymon (C), THEA (C), Therini (C), TissueGen (SO), Valo (C), Visgenx (SO), Vitranu (SO)

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- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation

C, consultant; R, research support ; SO, stock ownership/options.

PHOTON Study Design

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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

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DME

Primary Endpoint

	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

	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

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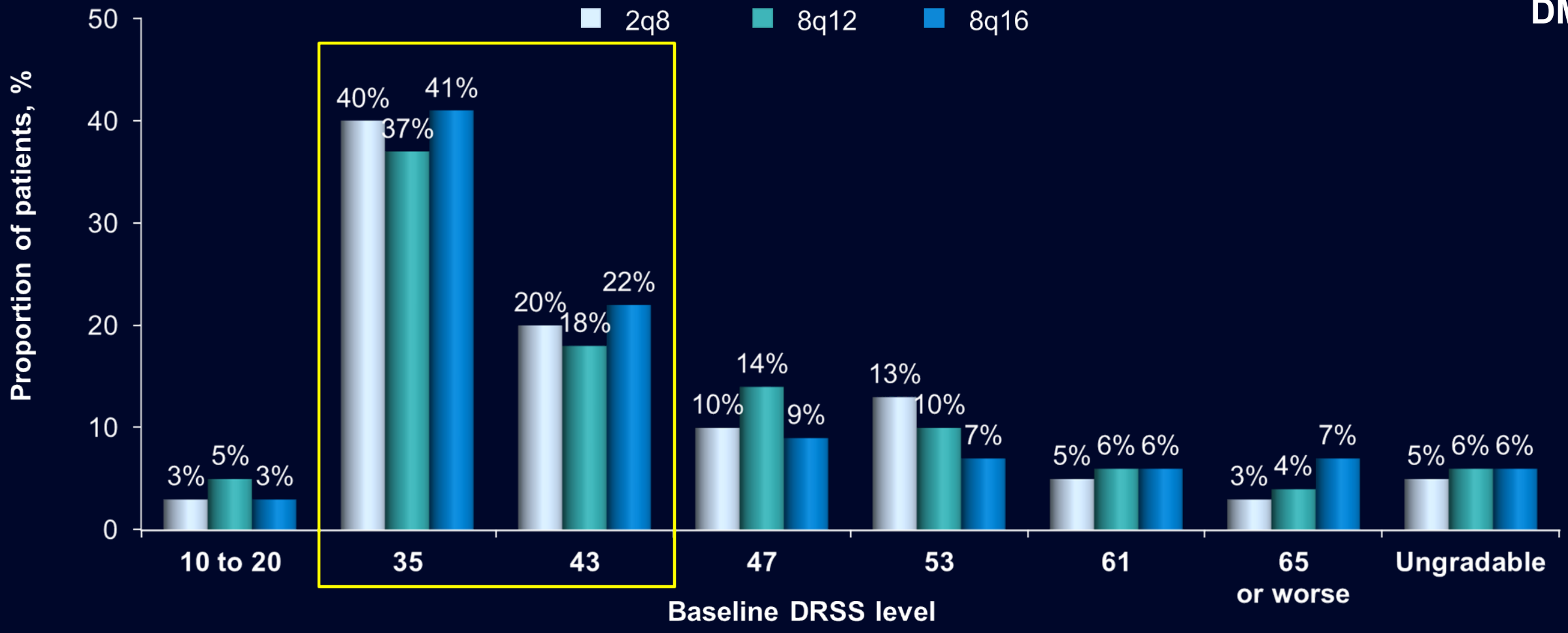
DME

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
Patient disposition				
Completion rate at Week 48 (%)	94.0%	91.2%	95.1%	92.9%
Completion rate at Week 96 (%)	83.2%	77.8%	84.8%	80.9%
Discontinuation rate due to COVID-19	0	0.6%	0	0.3%
Baseline characteristics				
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%
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)
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
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%

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

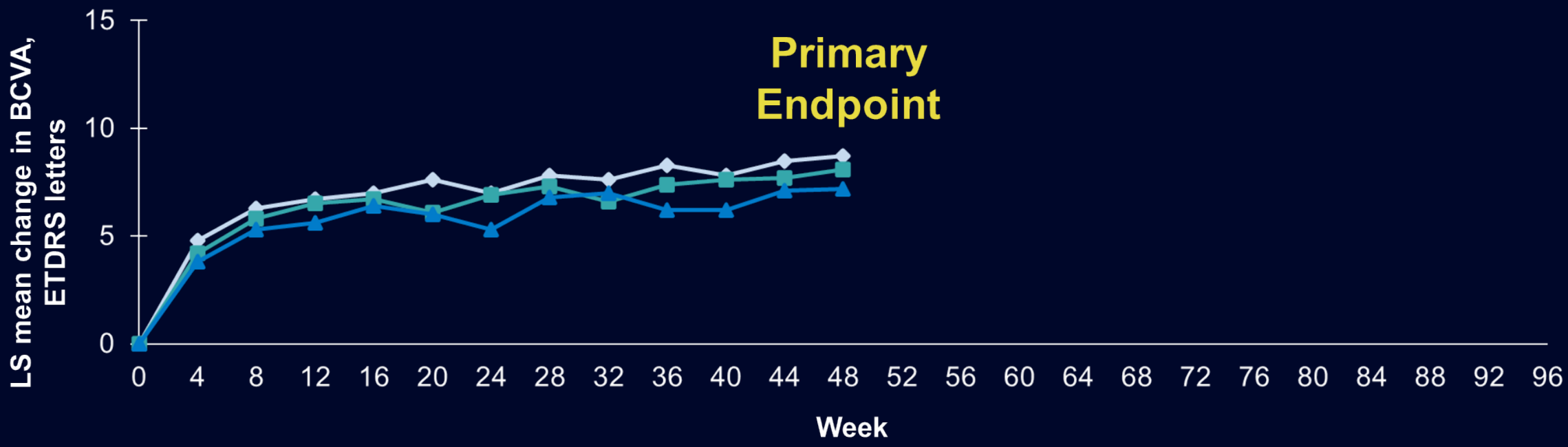
Baseline DRSS Level of the Study Eye



FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.

Mean Change in BCVA at Week 96

DME

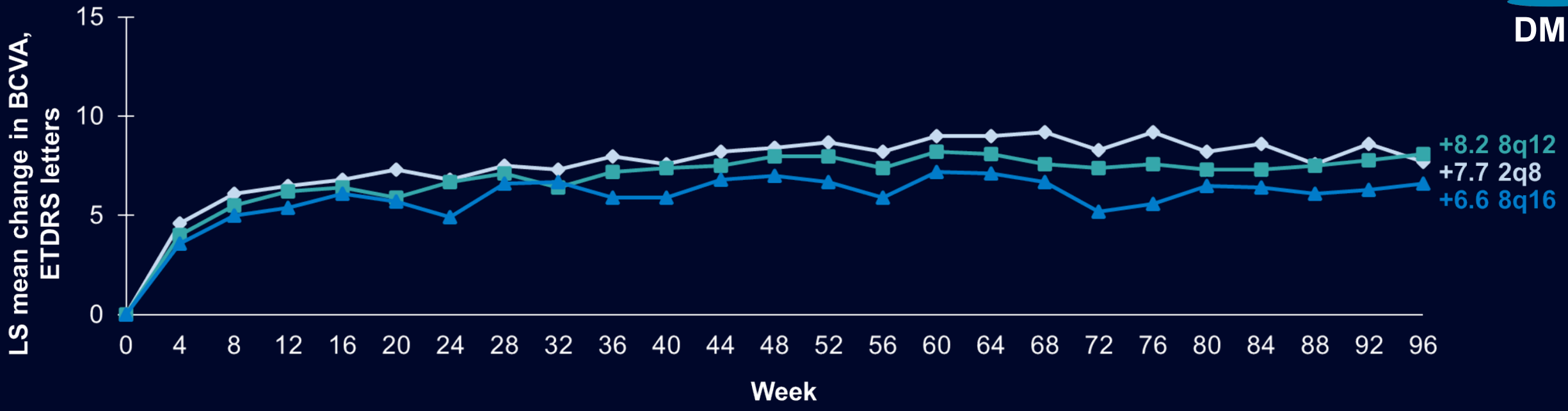


	Mean number of injections[a]	LS mean change from BL at **Week 48** (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.9	8.7			
8q12	6.0	8.1	**-0.57**	**-2.26, 1.13**	**p < 0.0001**
8q16	5.0	7.2	**-1.44**	**-3.27, 0.39**	**p = 0.0031**

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.

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**
8q16	7.8	6.6	**-1.11**	**-3.27, 1.05**	**p = 0.0044**

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 Majority of Aflibercept 8 mg Patients Maintained Randomized Intervals Through Week 96

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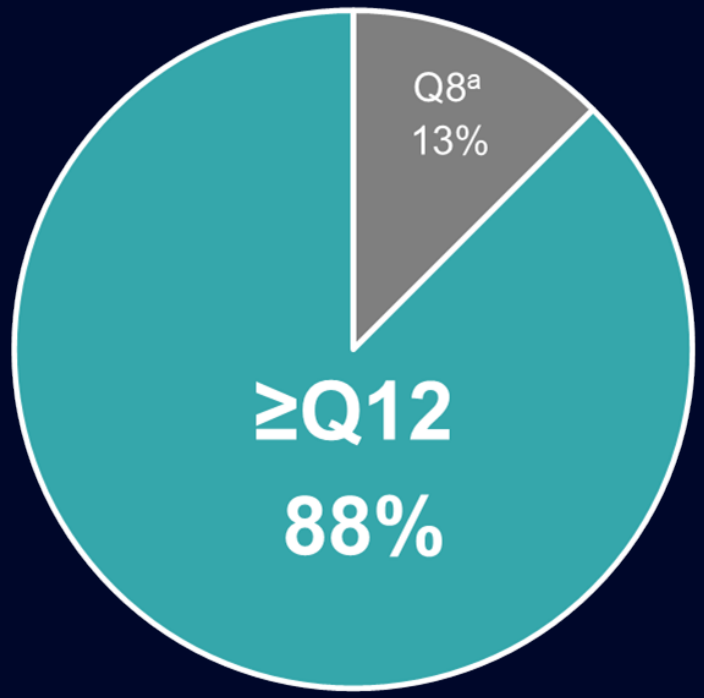
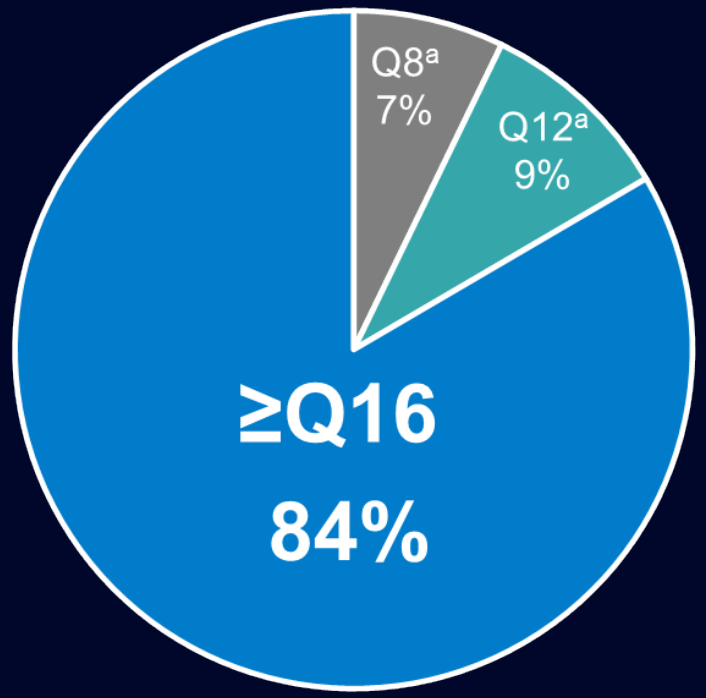
DME

88% of patients in the 8q12 group maintained ≥12-week intervals

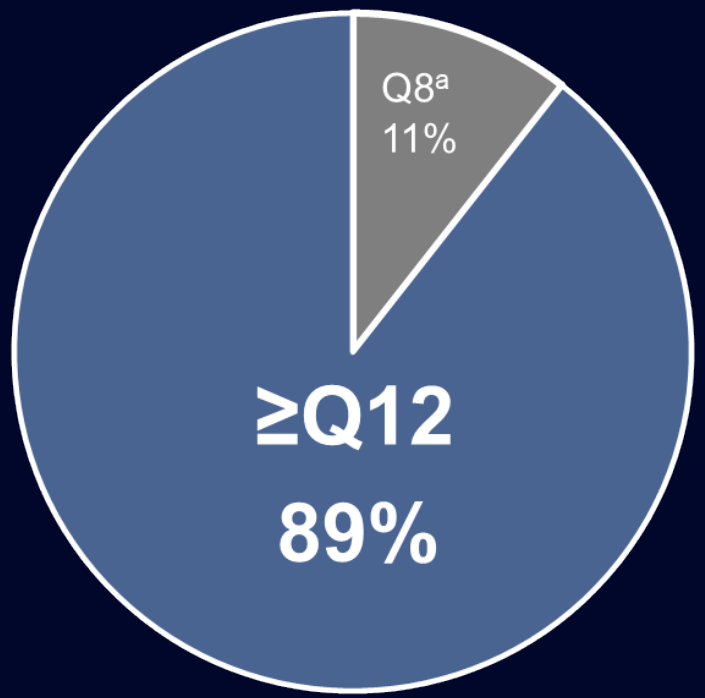
84% of patients in the 8q16 group maintained ≥16-week intervals



Randomized to **8q12** at BL
(n=256)[b]



Randomized to **8q16** at BL
(n=139)[b]

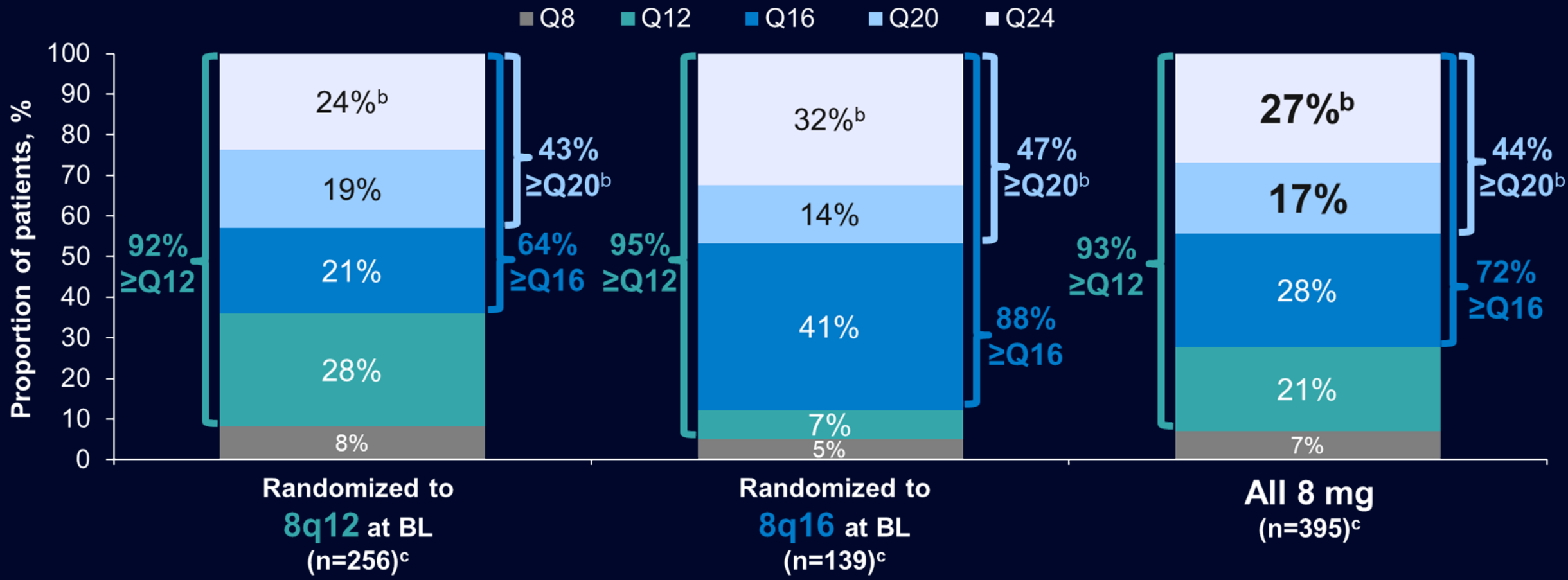


All 8 mg
(n=395)[b]

[a]Patients met DRM criteria for dosing interval shortening at some point through Week 96. [b]Patients completing Week 96.
Values may not add up to 100% due to rounding.

Last Assigned Dosing Interval at Week 96

44% of 8 mg patients had assigned dosing intervals of ≥20 weeks at Week 96[a]



[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.

Proportion of Patients With ≥2-step DRSS Improvement at Weeks 12, 48, and 96

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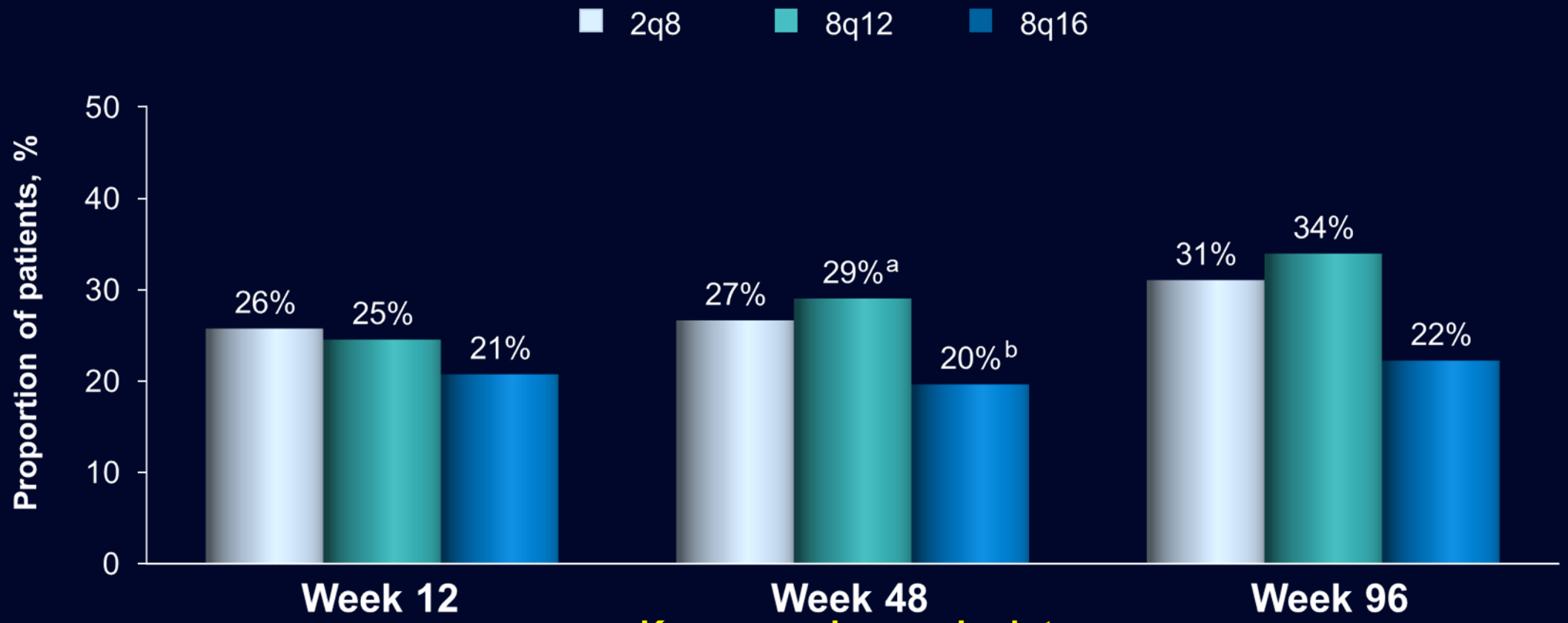
DME



Key secondary endpoint:

8q12 but not 8q16 demonstrated NI to 2q8 (NI margin: 15%)

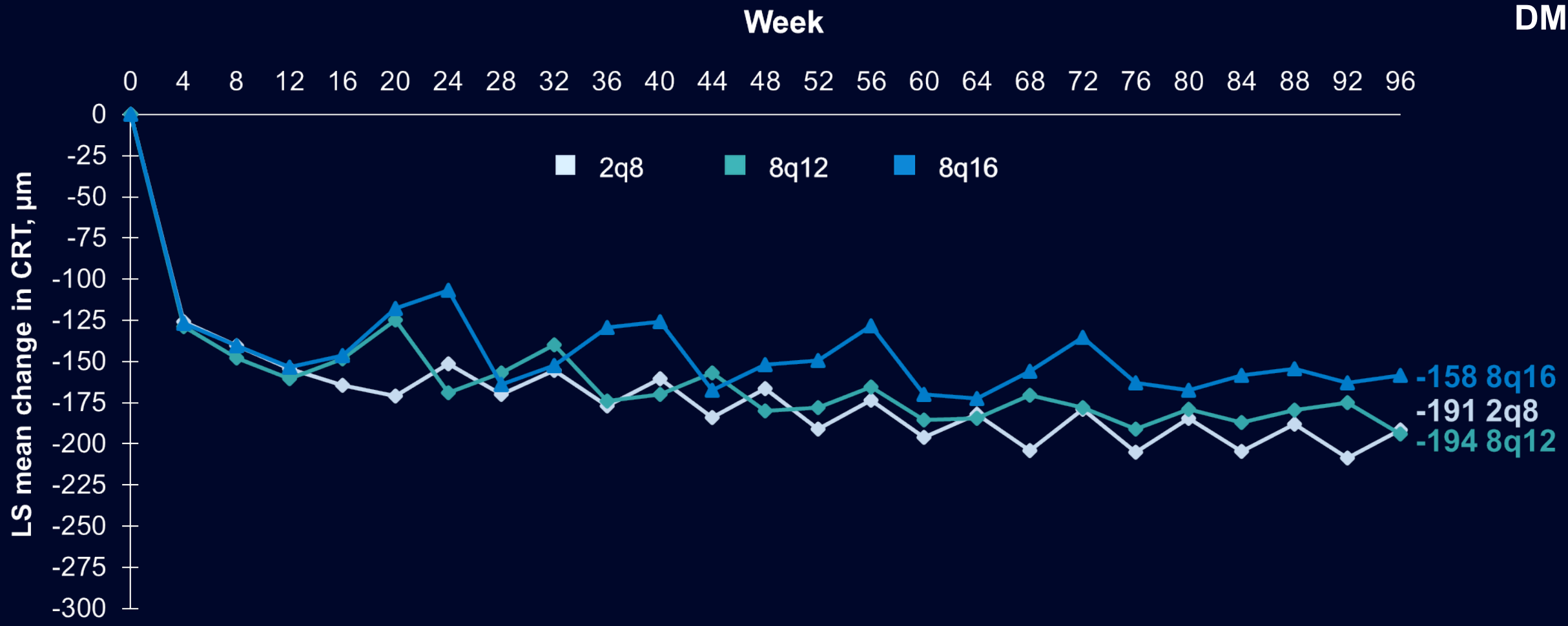
[a]8q12 vs. 2q8 Diff (95% CI): 1.98 (-6.61, 10.57)

[b]8q16 vs. 2q8 Diff (95% CI): -7.52 (-16.88, 1.84)

LOCF (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.
LOCF, last observation carried forward; NI, non-inferiority.

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

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DME

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
Ocular safety				
Patients with ≥1 ocular AE (%)[a]	37.1%	43.9%	45.4%	44.4%
Patients with ≥1 IOI AE (%)[a]	1.2%	1.5%	0.6%	1.2%
Patients with IOP ≥35 mmHg pre- or post-injection (%)[b]	1.2%	0.6%	0	0.4%
Non-ocular safety				
APTC events (%)[a]	7.2%	6.7%	6.7%	6.7%
Hypertension events (%)[a]	16.2%	15.5%	20.9%	17.3%
Non-ocular SAEs (%)[a]	25.1%	22.9%	23.9%	23.2%
Deaths (%)[c]	5.4%	5.5%	3.1%	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, retinal vasculitis, or occlusive retinitis were reported through Week 96
- 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]IOP was measured in the study eye. [c]All events.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; SAE, serious adverse event.

PHOTON: 96-week Results

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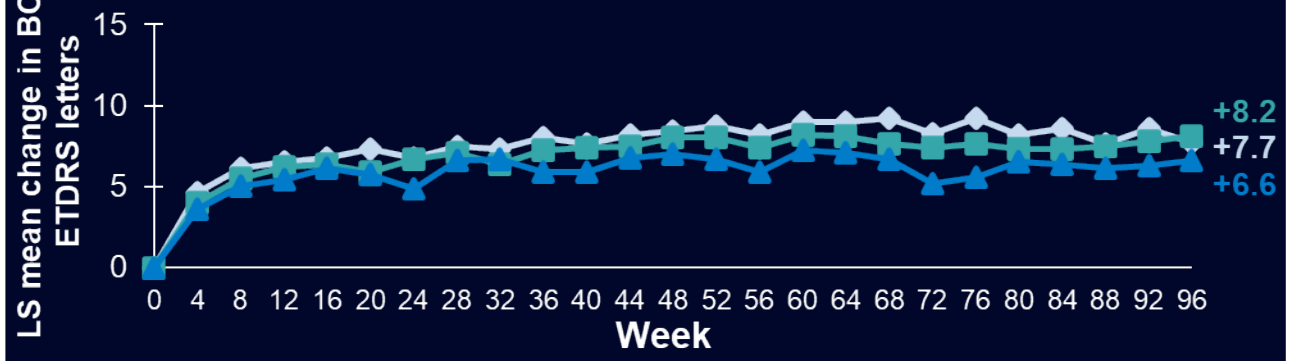
DME

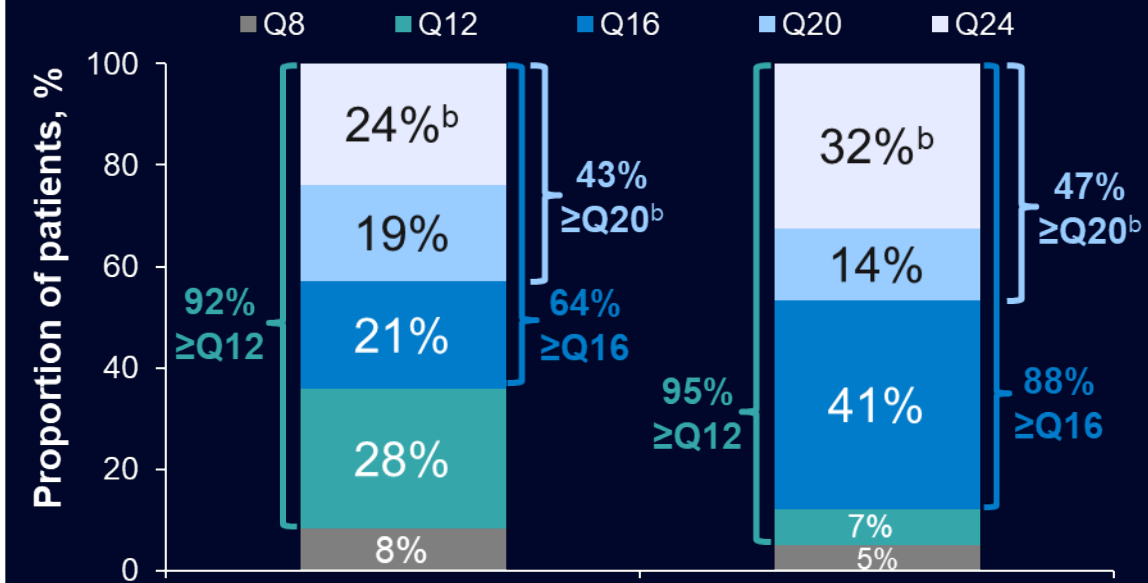
- 8q12 and 8q16 groups had non-inferior BCVA compared to 2q8 at Week 96, with up to 6 fewer injections
- Through Week 96, 89% of 8 mg patients maintained ≥12-week dosing intervals
  - At Week 96, 44% of 8 mg patients had a last assigned dosing interval of ≥20 weeks
- Safety of aflibercept 8 mg was comparable 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
8q16	6.6	-1.11	-3.27, 1.05	p = 0.0044

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

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DME