Aflibercept 8 mg for Diabetic Macular Edema: 2-Year Results of the Phase 2/3 PHOTON Trial

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Disclosures

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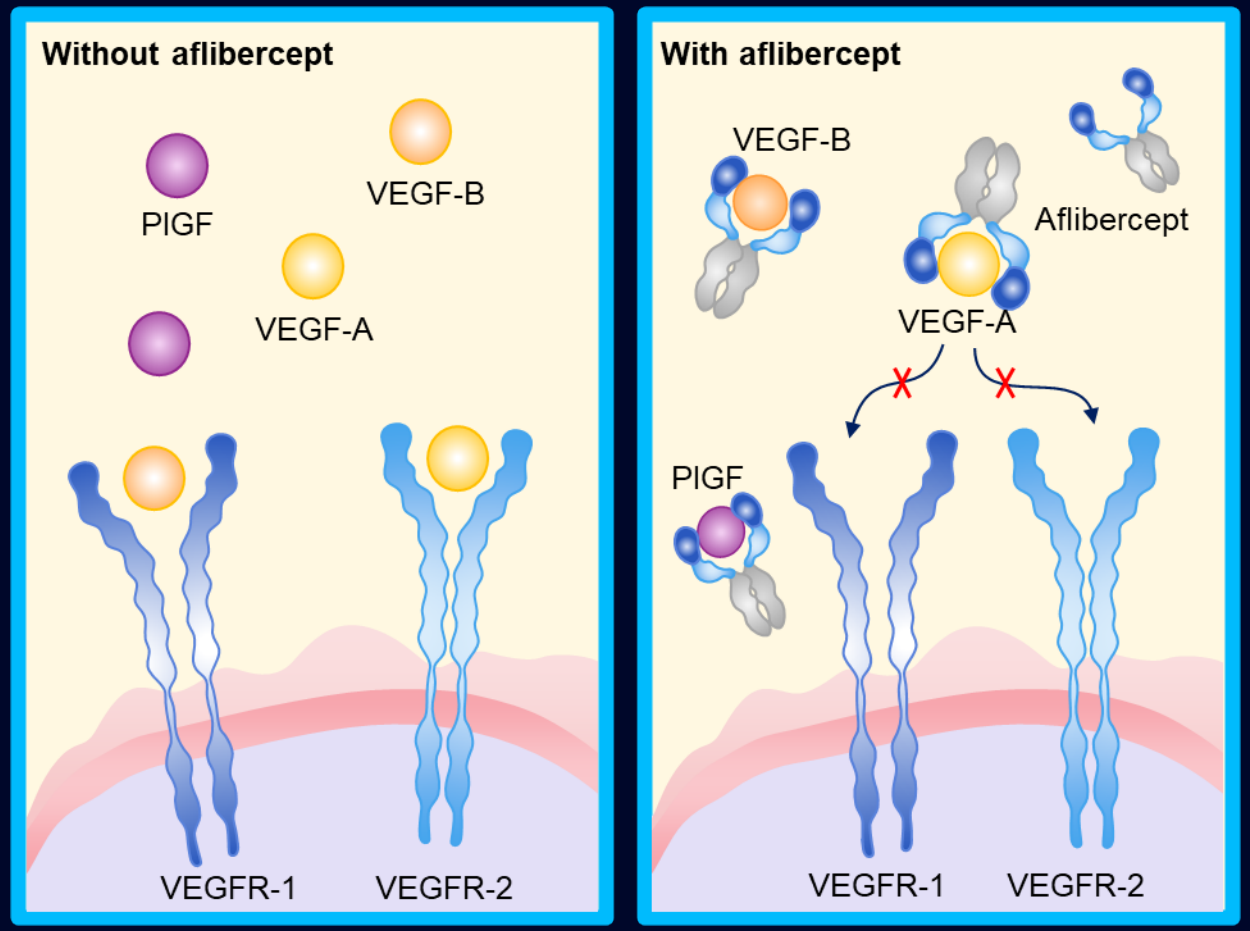
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation

Aflibercept 8 mg

- Aflibercept is a fully human recombinant fusion protein that binds VEGF-A, VEGF-B, and PIGF, thereby inhibiting the activation of cognate VEGF receptors[1,2]
- **Aflibercept 8 mg** is a novel intravitreal formulation, delivering a **4-fold higher molar dose** than aflibercept 2 mg in a 70-µL injection
- Aflibercept 8 mg has demonstrated improved functional and anatomic outcomes at dosing intervals of ≥12 weeks in ongoing clinical trials in nAMD, DME, and DR[3,4]



DME, diabetic macular edema; DR, diabetic retinopathy; nAMD, neovascular age-related macular degeneration; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

1. Holash J et al. *Proc Natl Acad Sci.* 2002;99(17):11393-11398. 2. Papadopoulos N et al. *Angiogenesis*. 2012;15(2):171-185. 3. Lanzetta P. Intravitreal aflibercept injection 8 mg for nAMD: results from the phase 3 PULSAR trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL. 4. Brown DM. Intravitreal aflibercept injection 8 mg for DME: results from the phase 2/3 PHOTON trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL.

PHOTON Study Design

Multi-center, randomized, double-masked study in patients with 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.
BCVA, best-corrected visual acuity; DME, diabetic maula edema.

Key Eligibility Criteria

Inclusion Criteria

- Adults (≥18 years of age) with type 1 or type 2 diabetes
- DME with central involvement with CRT ≥300 µm (or ≥320 µm on Spectralis) in the study eye as determined by the reading center
- BCVA of 78-24 letters (Snellen equivalent 20/32-20/320) with decreased vision due to DME

Exclusion Criteria

- Active PDR in the study eye
- PRP or laser photocoagulation in the study eye within 12 weeks of screening visit
- IVT anti-VEGF treatment in the study eye within 12 weeks of screening visit
- Intraocular or periocular steroids in the study eye within 16 weeks of the screening visit

CRT, central retinal thickness; IVT, intravitreal; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

PHOTON: Dosing Schedule and Dose Regimen Modification

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[a]	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 from **Weeks 52 through 96** 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 at Week 96

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
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 at Week 96 (%)	16.8%	22.2%	15.2%	19.1%
Reasons for discontinuation (%)				
Consent withdrawal	5.4%	5.2%	4.9%	5.2%
Death	5.4%	5.5%	3.0%	4.8%
Lost to follow-up	3.0%	5.8%	4.3%	4.7%
Decision by the investigator	1.2%	2.7%	1.8%	2.1%
Adverse event	0.6%	2.7%	1.2%	1.8%
Noncompliance with protocol	1.2%	0.3%	0	0.5%

Baseline Demographics

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	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%
Black or African American	10.8%	10.7%	5.5%	9.4%
Asian	18.0%	14.6%	14.1%	15.3%
Other	2.4%	3.0%	0.6%	2.4%
Not reported	1.8%	1.2%	1.2%	1.4%
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)
History of hypertension (%)	77.8%	77.4%	79.8%	78.1%
BMI (kg/m^2)	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)

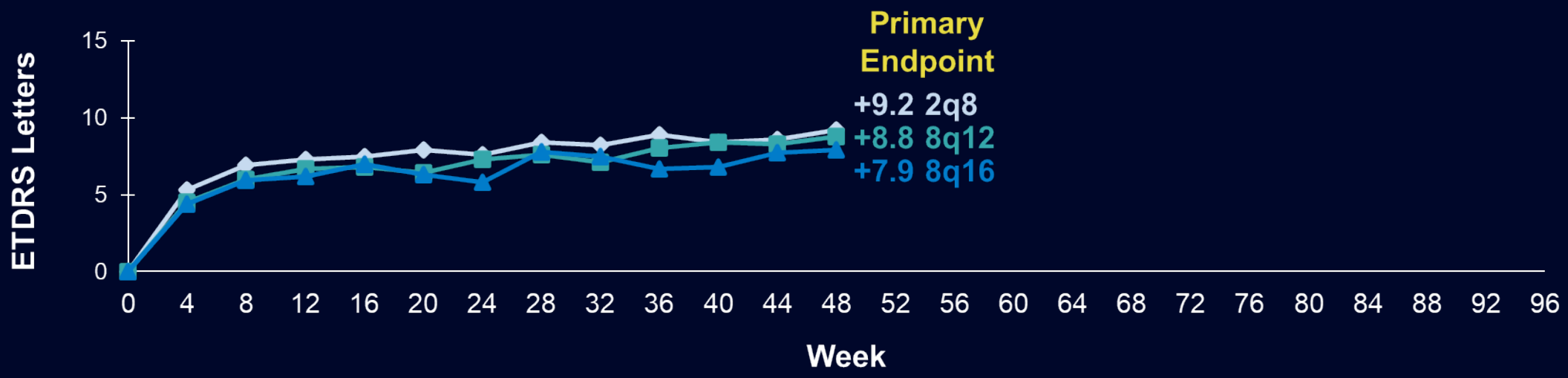
Data are mean (SD) unless otherwise indicated.
BMI, body mass index; FAS, full analysis set; SAF, safety analysis set; SD, standard deviation.

Baseline Characteristics of the Study Eye

	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)	12.0%	18.0%	14.1%	15.5%
20/40 or worse (≤73 letters)	88.0%	82.0%	85.9%	84.5%
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%
Missing/Ungradable	5.4%	5.5%	6.1%	5.6%

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

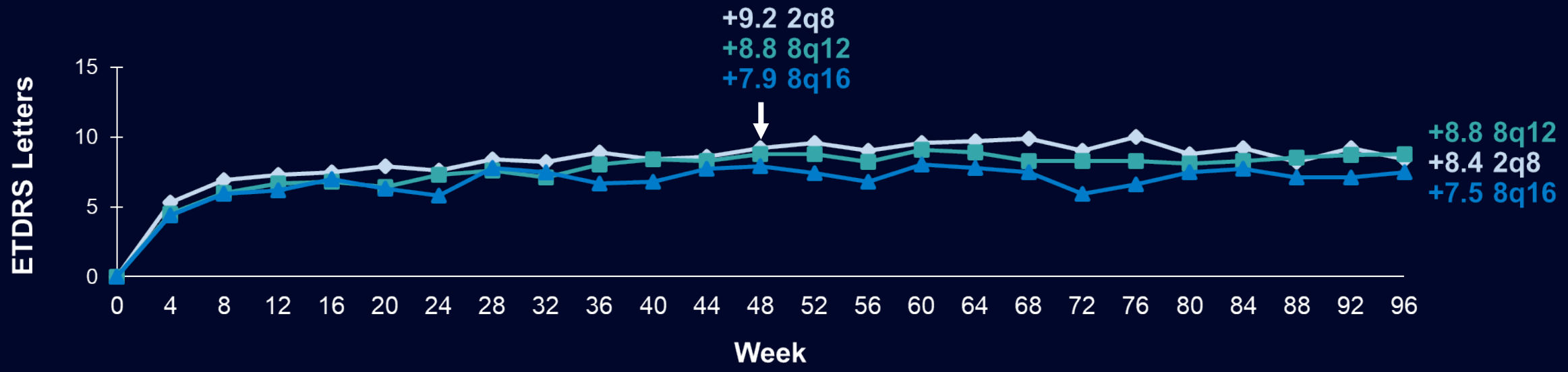
Mean Change in BCVA at Week 96



	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	8.7			
8q12	8.1	**-0.6**	**-2.3, 1.1**	**p < 0.0001**
8q16	7.2	**-1.4**	**-3.3, 0.4**	**p = 0.0031**

Data shown in the figure represent observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

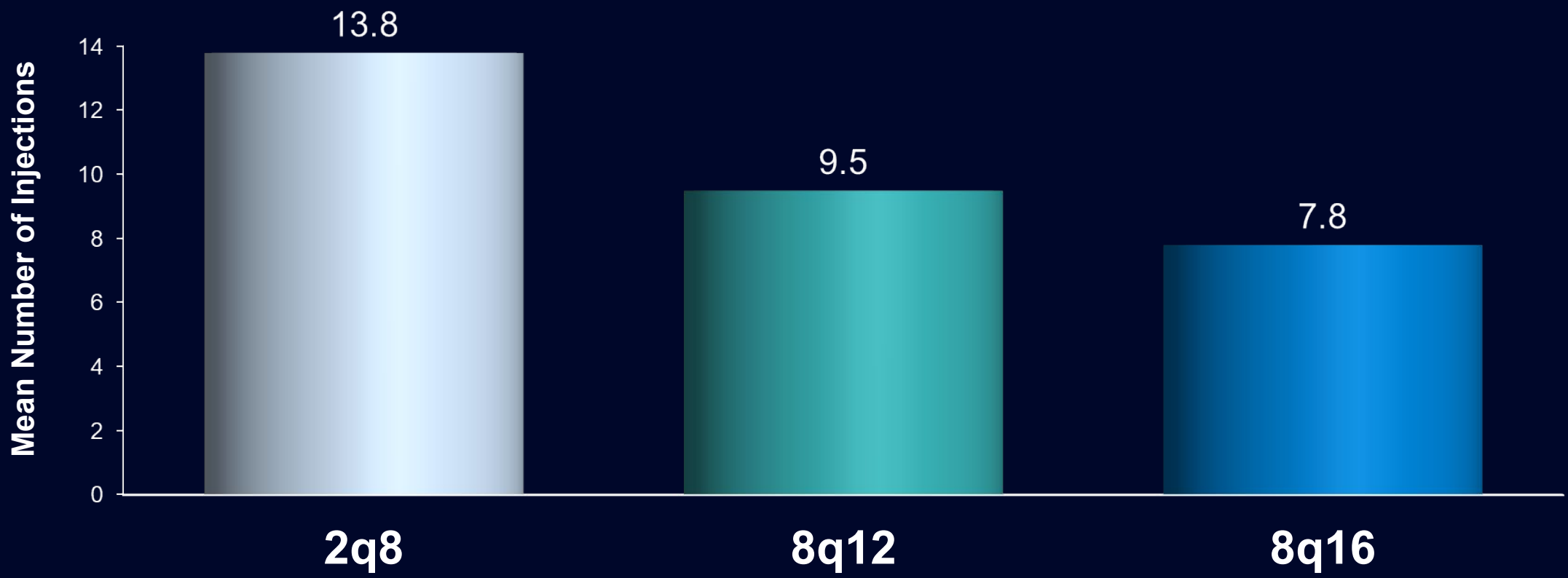
Mean Change in BCVA at Week 96



	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	7.7			
8q12	8.2	+0.5	-1.6, 2.5	p < 0.0001
8q16	6.6	-1.1	-3.3, 1.1	p = 0.0044

Data shown in the figure represent observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

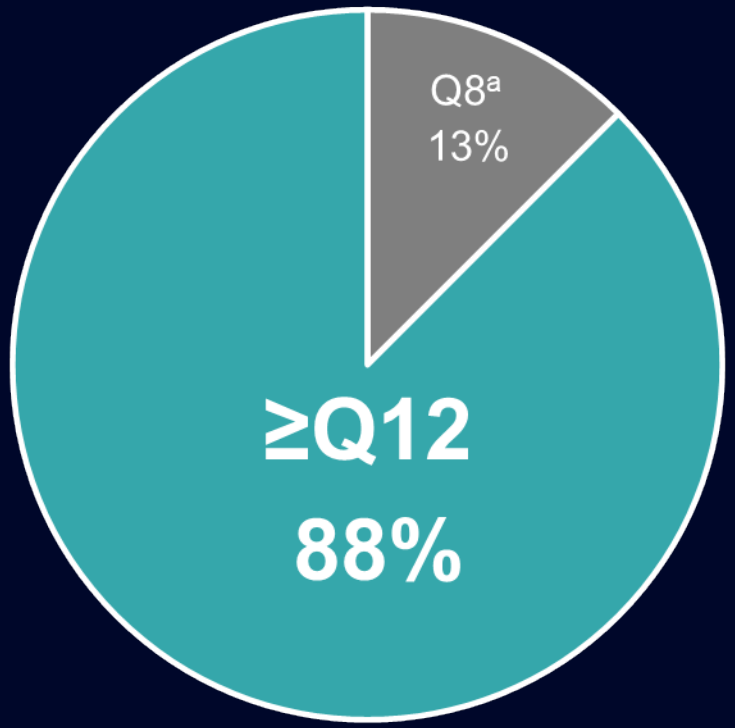
Mean Number of Injections Through Week 96



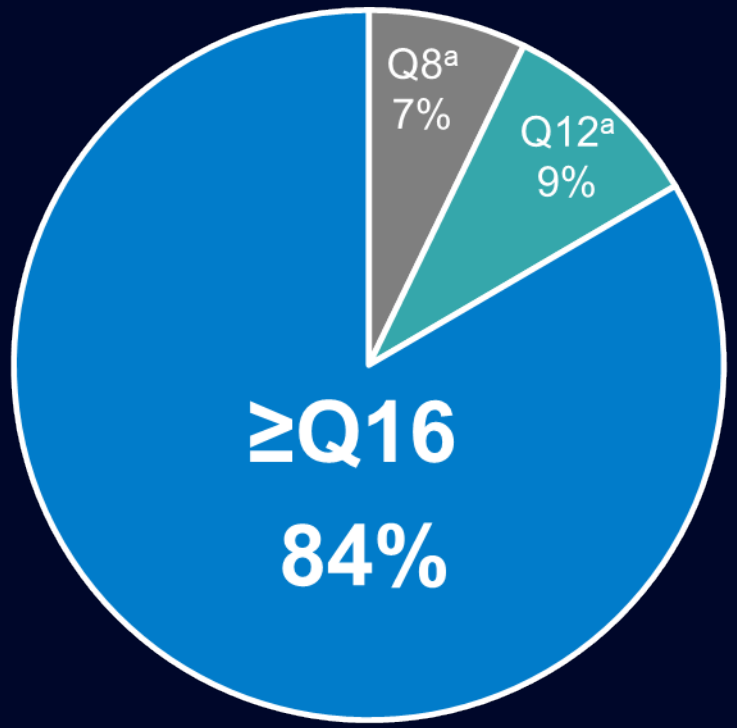
FAS, patients completing Week 96: 2q8 n=139; 8q12 n=256; 8q16 n=139.

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

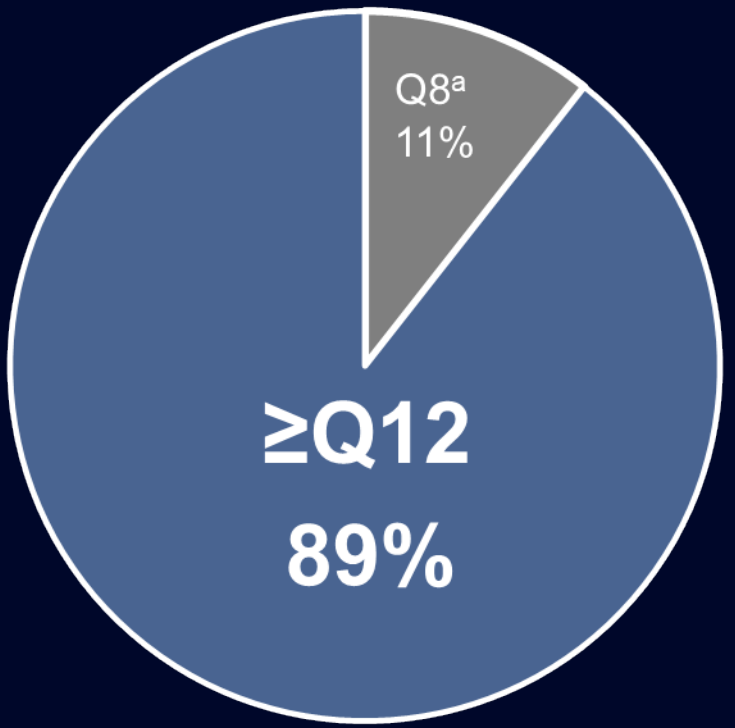
89% of 8 mg patients maintained dosing intervals ≥12 weeks



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



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

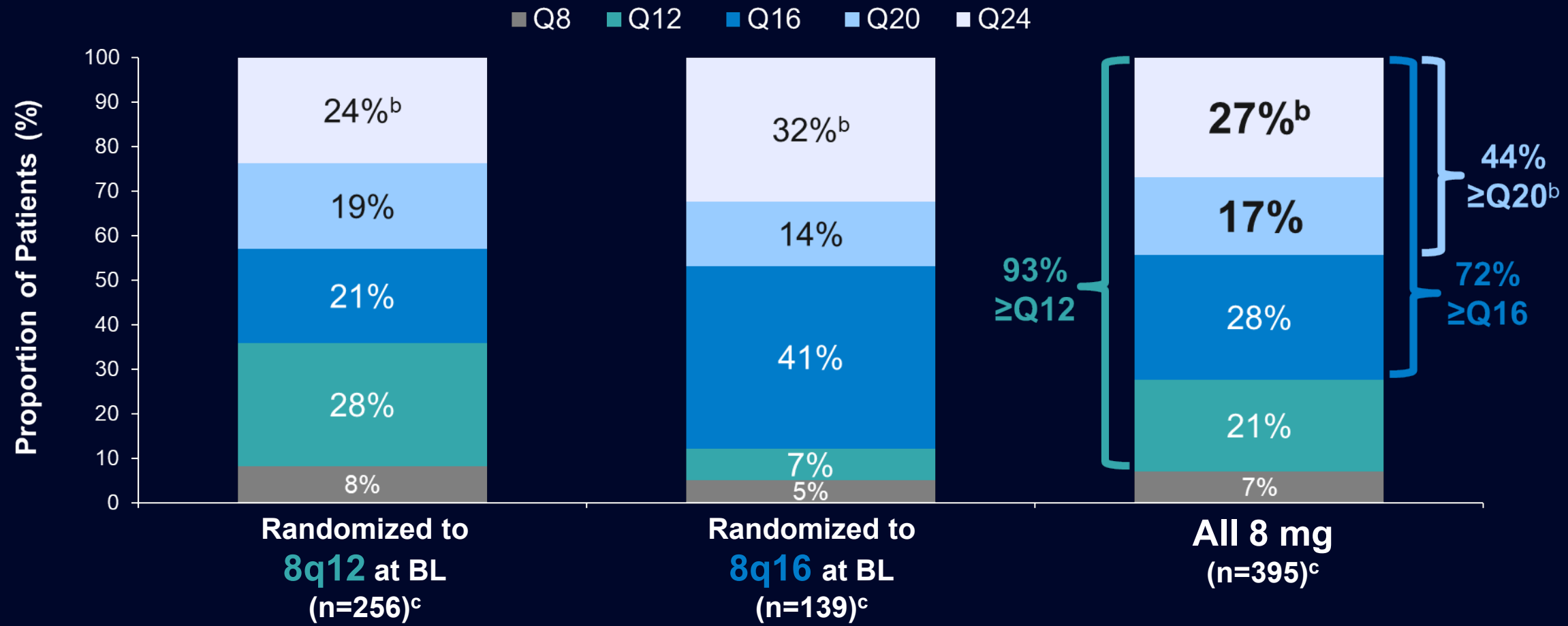


All 8 mg (n=395)[b]

[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.

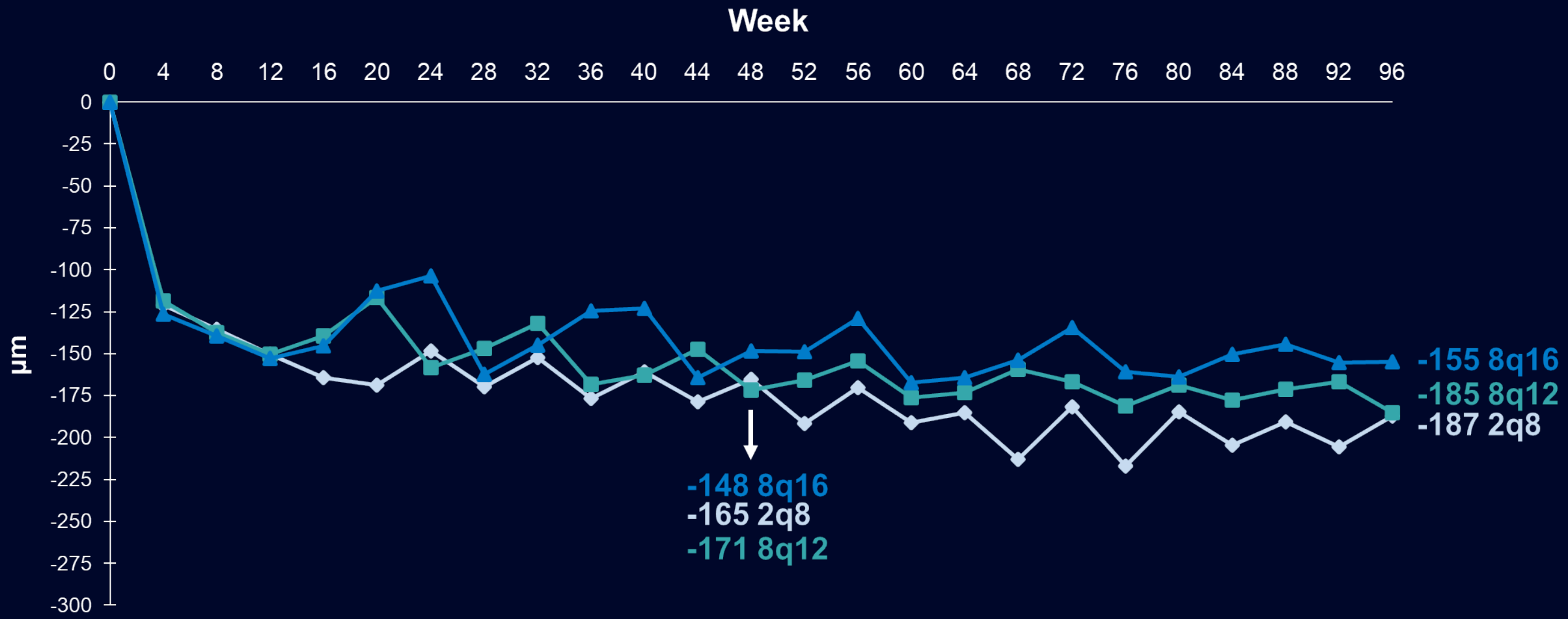
Last Assigned Dosing Interval at Week 96

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 did not have enough 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.

Mean Change in Central Retinal Thickness



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

Ocular AEs Through Week 96

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
Patients with ≥1 AE (%)[a]	37.1%	43.9%	45.4%	44.4%

- 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

[a]Ocular treatment-emergent AEs in the study eye.
AE, adverse event.

Intraocular Inflammation Through Week 96

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
Patients with ≥1 IOI AE (%)[a]	1.2%	1.5%	0.6%	1.2%

- Reported IOI terms were anterior chamber cell, iridocyclitis, iritis, uveitis, vitreal cells, and vitritis
- No cases of retinal vasculitis, occlusive retinitis, or endophthalmitis were reported through Week 96

[a]Treatment-emergent events in the study eye.
IOI, intraocular inflammation.

Intraocular Pressure Through Week 96

	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
Patients with IOP ≥35 mmHg at any time pre- or post-injection (%)[a]	1.2%	0.6%	0	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]IOP was measured in the study eye.
IOP, intraocular pressure.

Non-ocular Safety Through Week 96

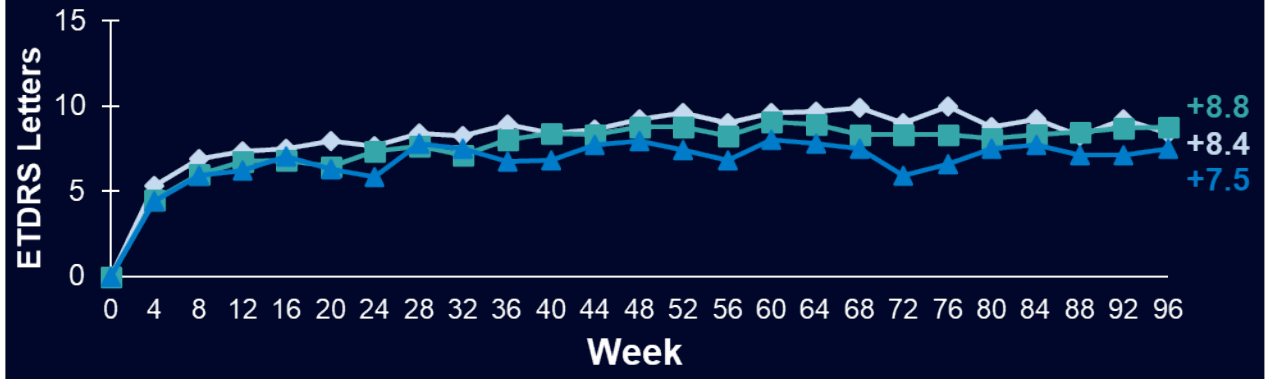
	2q8	8q12	8q16	All 8 mg
N (SAF)	167	328	163	491
APTC events[a] (%)	7.2%	6.7%	6.7%	6.7%
Hypertension events[a] (%)	16.2%	15.5%	20.9%	17.3%
Non-ocular SAEs[a] (%)	25.1%	22.9%	23.9%	23.2%
Deaths[b] (%)	5.4%	5.5%	3.1%	4.7%

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

PHOTON: 96-week Results

- 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
- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks

BCVA Change From Baseline[a]



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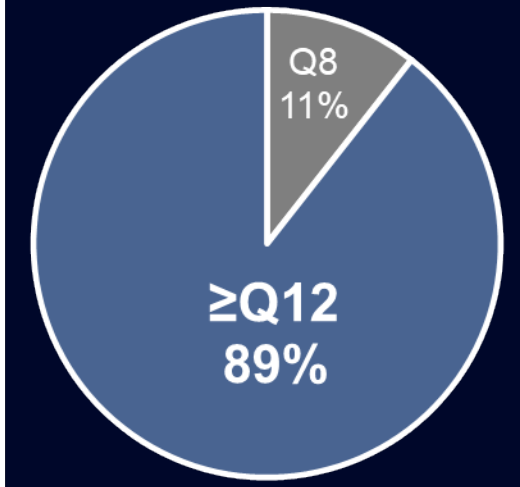
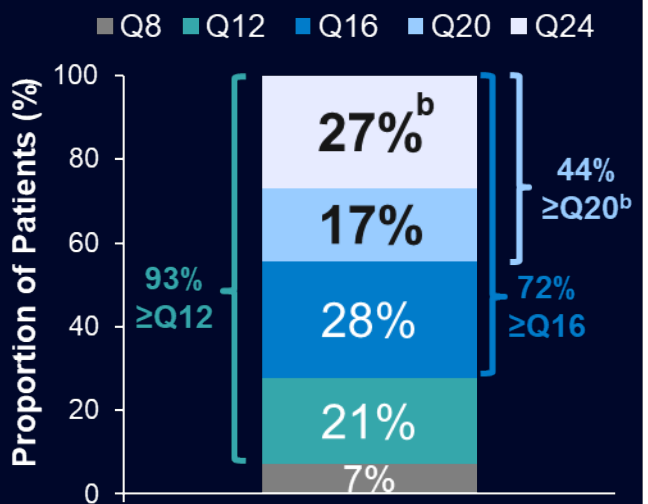
8q12	8.2	+0.5	-1.6, 2.5	p < 0.0001
8q16	6.6	-1.1	-3.3, 1.1	p = 0.0044

89% of 8 mg patients ***maintained*** ≥12-week intervals through Week 96



All 8 mg
(n=395)[c]

44% of 8 mg patients had ***assigned*** intervals of ≥20 weeks at Week 96



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