Impact of Baseline Central Retinal Thickness on Vision Among Patients With Diabetic Macular Edema: Post Hoc Analysis of the Phase 2/3 PHOTON Trial

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Disclosures

- Dr. Williams has worked as a consultant for AbbVie, Alcon, Alimera Sciences, Astellas Pharma, Castle Biosciences, EyePoint Pharmaceuticals, Genentech, Immunocore and Regeneron, and has stock options in Lumata Health
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- This trial includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
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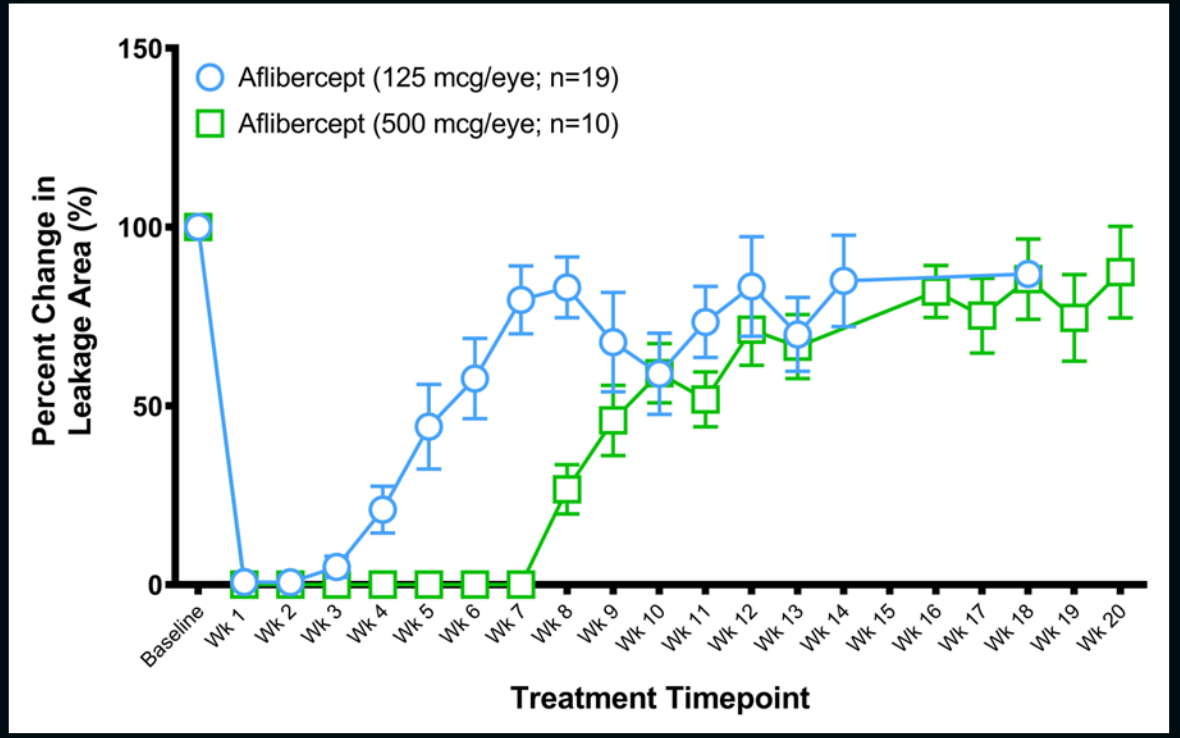
Background

- 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]

- A 4-fold increase in aflibercept dose from 125 µg to 500 µg extended the duration of complete leakage inhibition from 2 weeks to 7 weeks in the DL-AAA rabbit model[3]

Dose-dependent Duration of Leakage Inhibition[3]



Data are mean ± 1 standard error measurement.

DL-AAA, DL-α-aminoadipic acid; PIGF, placental growth factor; VEGF, vascular endothelial growth factor; Wk, week.

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. Cao J et al. *Invest Ophthalmol Vis Sci*. 2018;59(2):1033–1044.

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
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections
n=328

8q16
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections
n=163

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

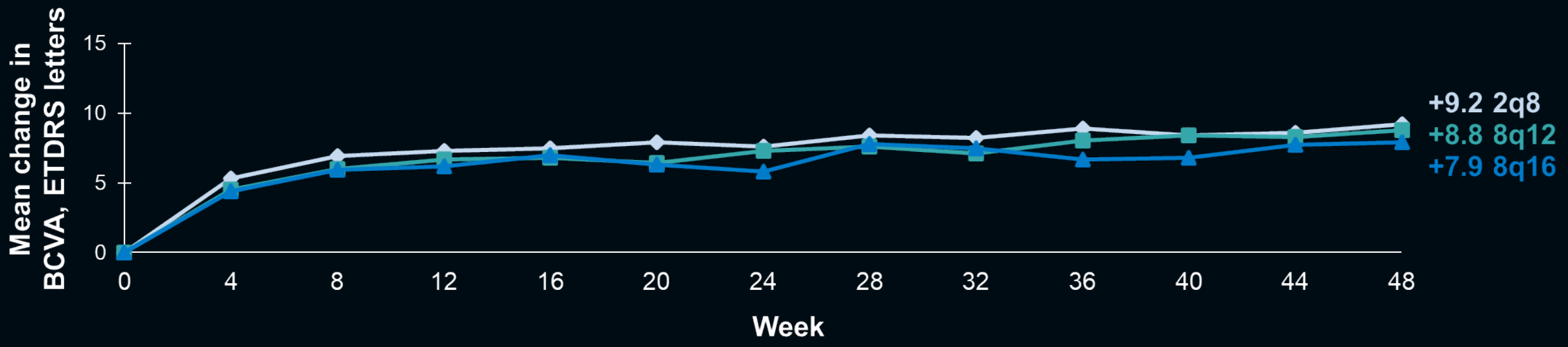
↓

End of study at Week 96
with optional 1-year extension through Week 156

[a]Treatment naive and previously treated.
2q8, 2 mg every 8 weeks; 8q12, 8 mg every 12 weeks; 8q16, 8 mg every 16 weeks; BCVA, best-corrected visual acuity; DME, diabetic macular edema.

PHOTON: 48-Week BCVA
Primary Endpoint Met in Both 8-mg Groups

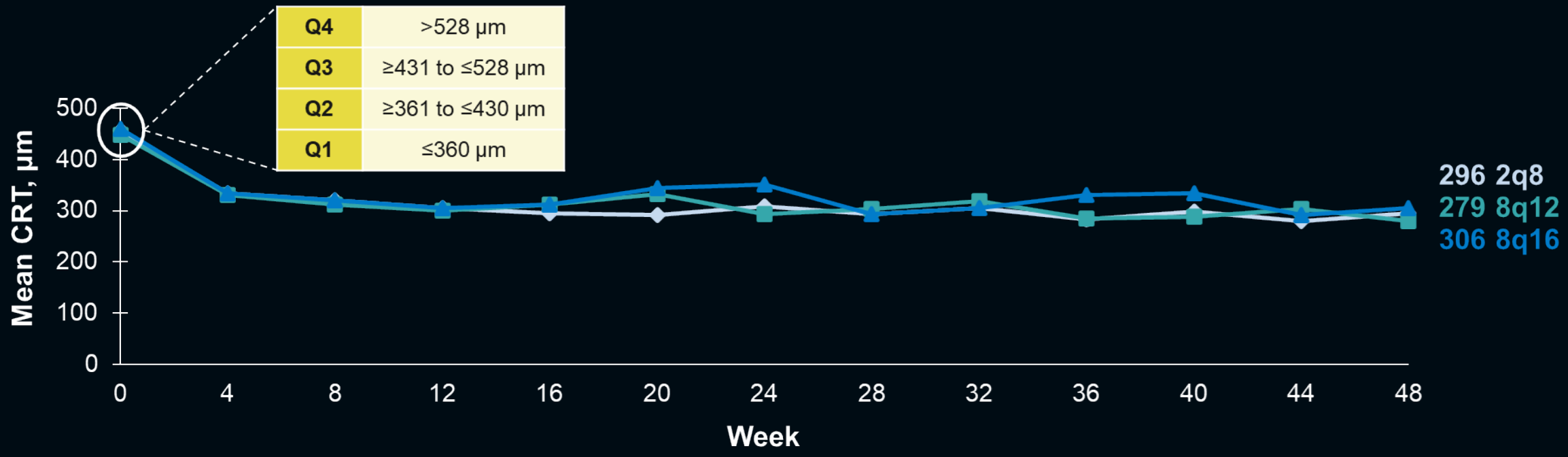
BCVA Change from Baseline[a]



	LS mean change from BL at Week 48 (MMRM)	Diff. in LS mean vs 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]Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
BL, baseline; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; Diff., difference; FAS, full analysis set; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

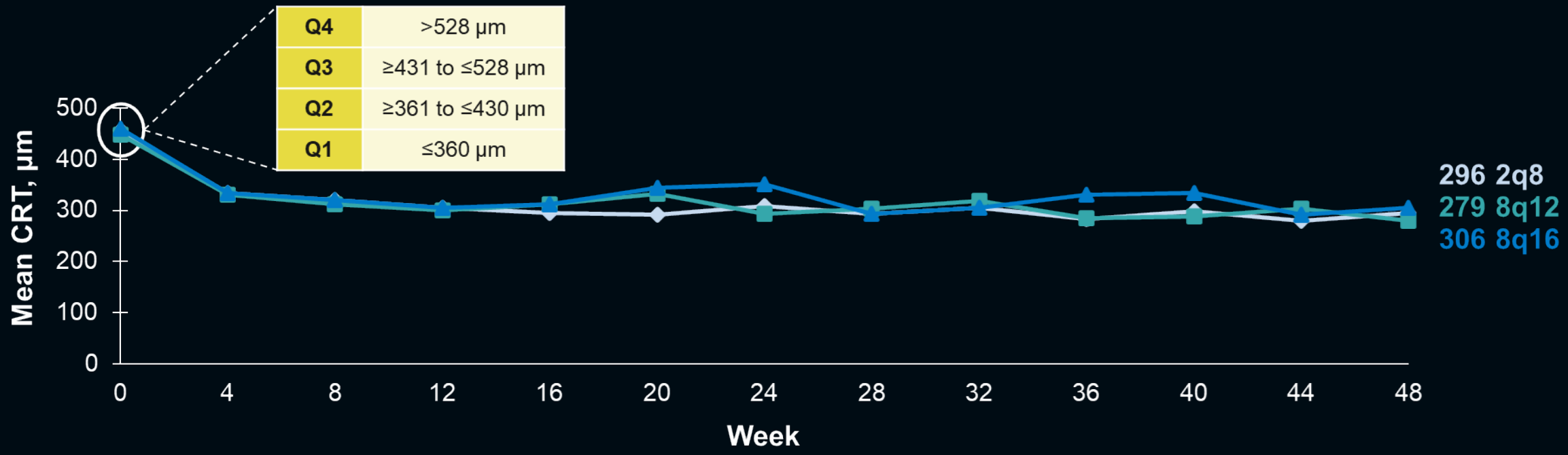
Mean CRT Through Week 48



This analysis evaluated the effect of aflibercept 8 mg versus 2 mg on clinical outcomes in patients with DME based on disease severity, as defined by baseline CRT

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
CRT, central retinal thickness; Q, quartile.

Mean CRT Through Week 48



- Analyses were descriptive and 1 patient was excluded due to missing baseline CRT
- Key outcomes assessed include:
  - Mean change in BCVA through Week 48
  - Mean change in CRT through Week 48
  - Proportion of patients who maintained their original randomized dosing intervals through Week 48

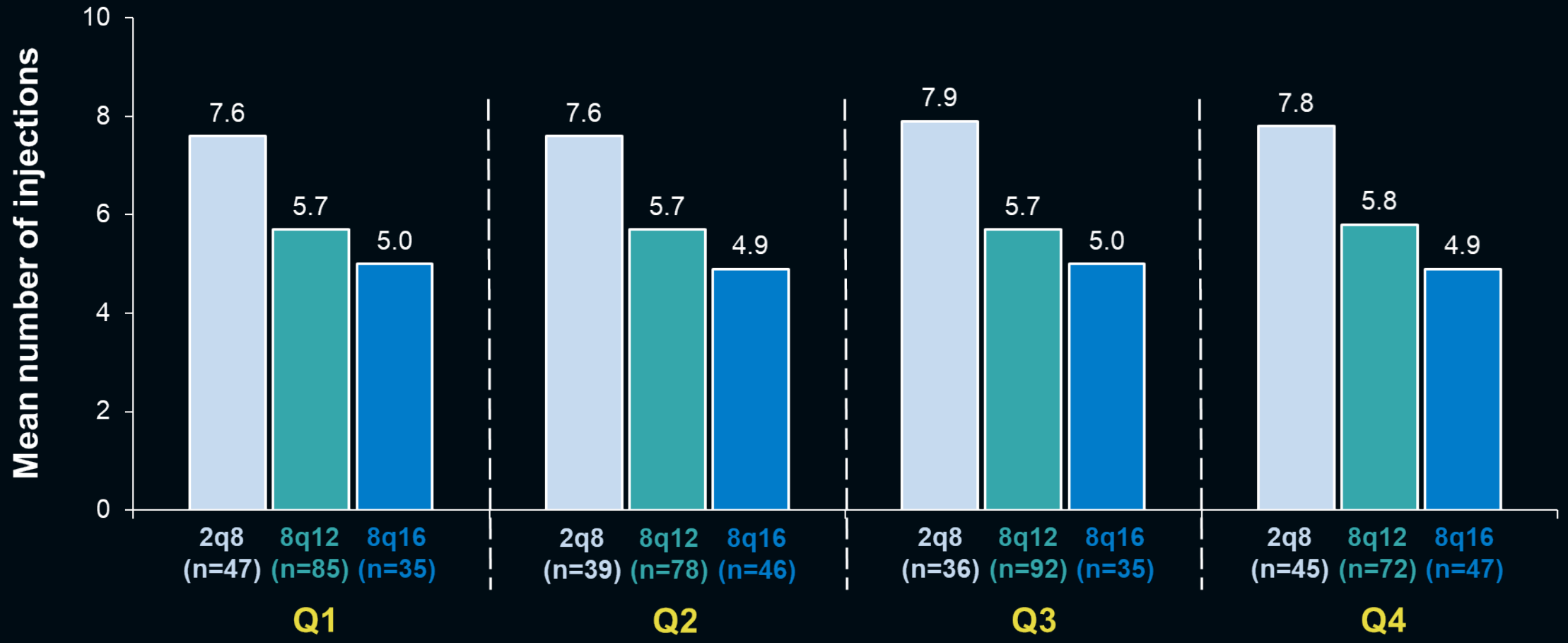
Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
CRT, central retinal thickness; Q, quartile.

Baseline Characteristics by Baseline CRT Quartiles

	Q1: ≤360 µm (n=167)			Q2: ≥361 to ≤430 µm (n=163)			Q3: ≥431 to ≤528 µm (n=163)			Q4: >528 µm (n=164)		
	2q8 (n=47)	8q12 (n=85)	8q16 (n=35)	2q8 (n=39)	8q12 (n=78)	8q16 (n=46)	2q8 (n=36)	8q12 (n=92)	8q16 (n=35)	2q8 (n=45)	8q12 (n=72)	8q16 (n=47)
Age, years	63.3 (10.7)	61.7 (10.8)	62.9 (9.5)	64.1 (8.7)	63.9 (10.8)	62.5 (9.1)	63.9 (8.5)	62.0 (9.9)	60.4 (9.8)	61.2 (10.6)	60.8 (13.2)	61.4 (9.8)
Male, n (%)	28 (59.6)	56 (65.9)	21 (60.0)	17 (43.6)	47 (60.3)	26 (56.5)	18 (50.0)	51 (55.4)	22 (62.9)	29 (64.4)	55 (76.4)	30 (63.8)
Duration of diabetes, years	18.2 (11.6)	15.3 (9.6)	18.9 (12.5)	16.8 (9.8)	16.6 (11.1)	14.4 (10.1)	14.1 (9.31)	14.3 (9.4)	14.9 (9.0)	14.3 (8.8)	14.2 (9.7)	15.1 (10.7)
BCVA, ETDRS letters	64.8 (9.9)	66.6 (7.8)	68.4 (7.1)	63.1 (10.6)	66.1 (10.1)	64.0 (11.3)	61.3 (9.8)	64.0 (8.2)	62.4 (11.3)	56.7 (12.8)	57.4 (11.5)	53.1 (10.8)
CRT, µm	320.0 (22.1)	318.7 (26.4)	326.1 (23.9)	390.3 (18.6)	391.6 (21.3)	394.2 (19.4)	475.3 (32.5)	475.0 (29.1)	479.3 (28.5)	644.2 (128.2)	632.4 (114.8)	610.9 (77.5)

FAS.
Unless otherwise specified, values shown represent mean (SD).
SD, standard deviation.

Treatment Exposure to Week 48 by Baseline CRT Quartiles



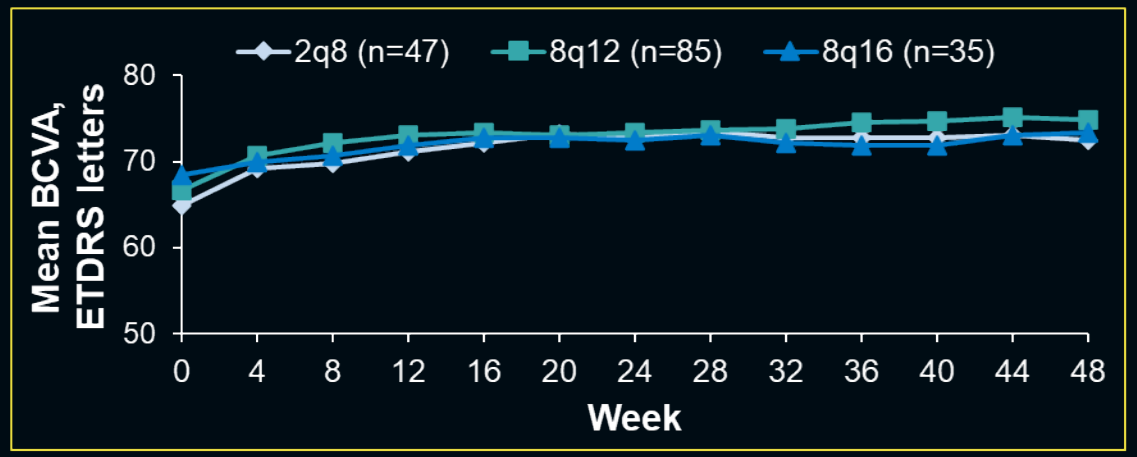
FAS, observed cases.
Q1: ≤360 µm; Q2: ≥361 to ≤430 µm; Q3: ≥431 to ≤528 µm; Q4: >528 µm.

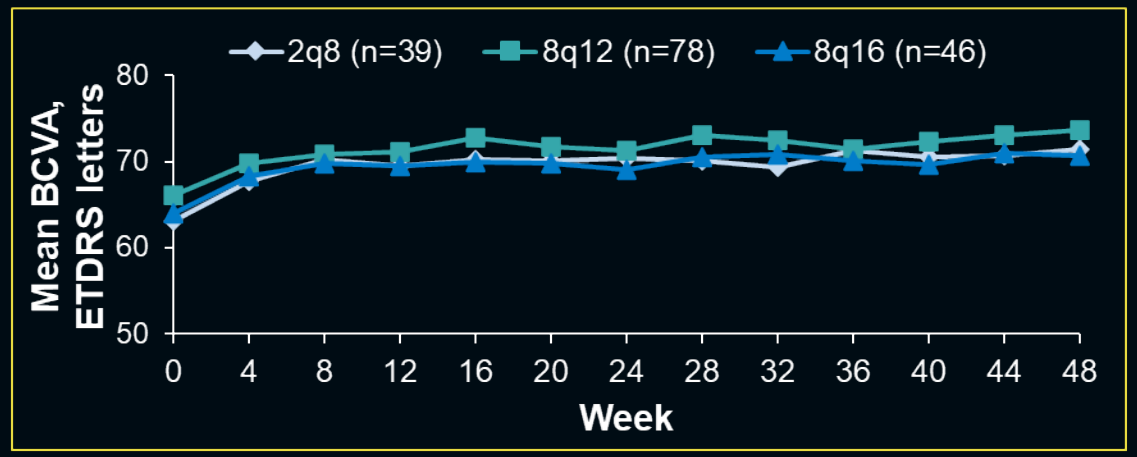
Mean BCVA and CRT Through Week 48 in Baseline CRT Q1 and Q2

Q1: ≤360 µm

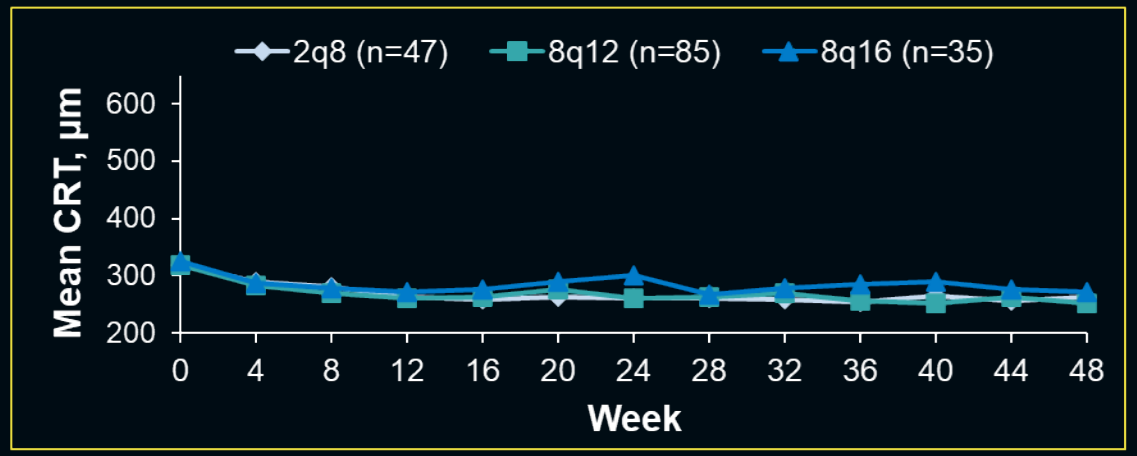
Q2: ≥361 to ≤430 µm

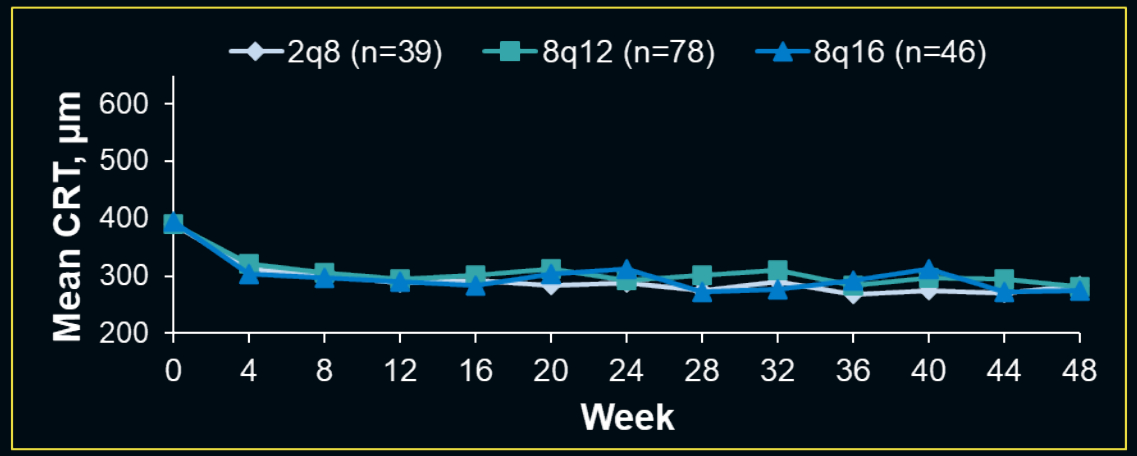
BCVA





CRT



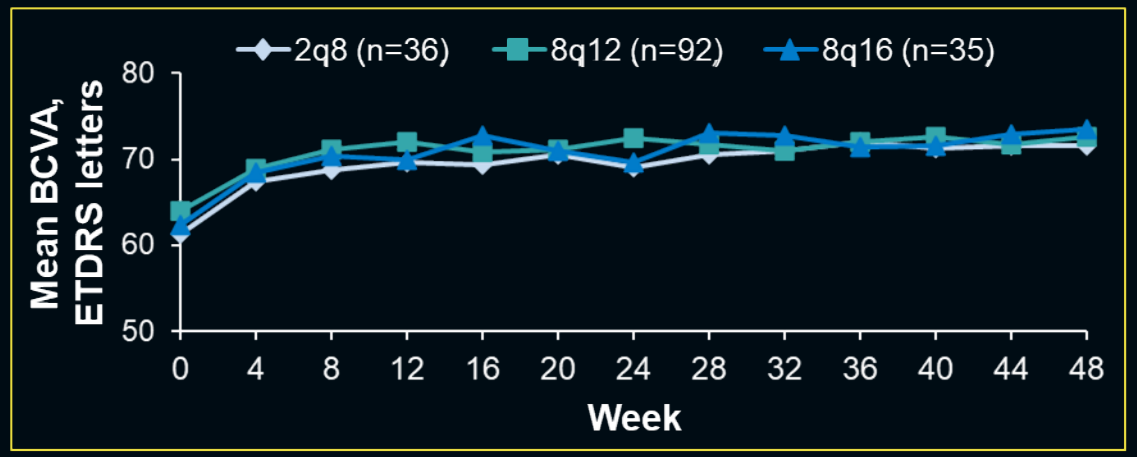


FAS, observed cases.

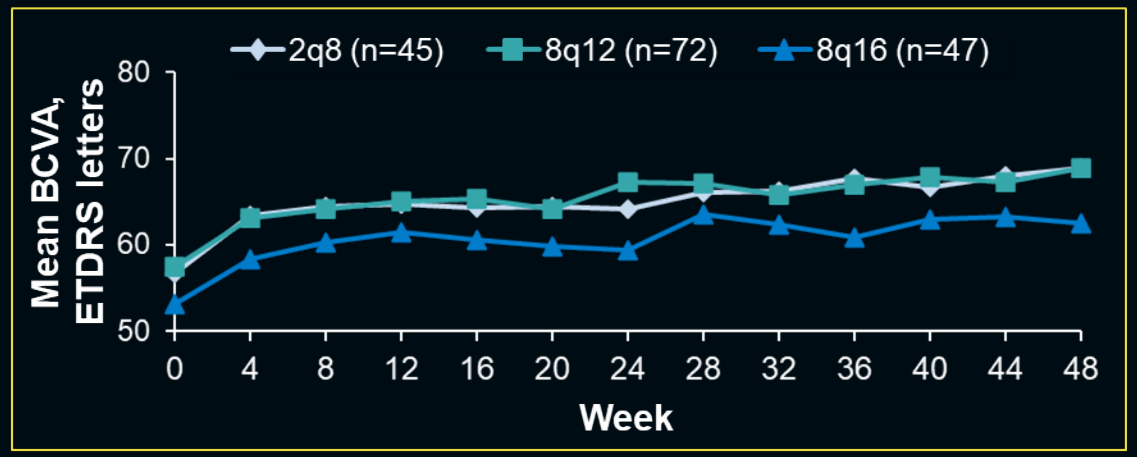
Mean BCVA and CRT Through Week 48 in Baseline CRT Q3 and Q4

BCVA

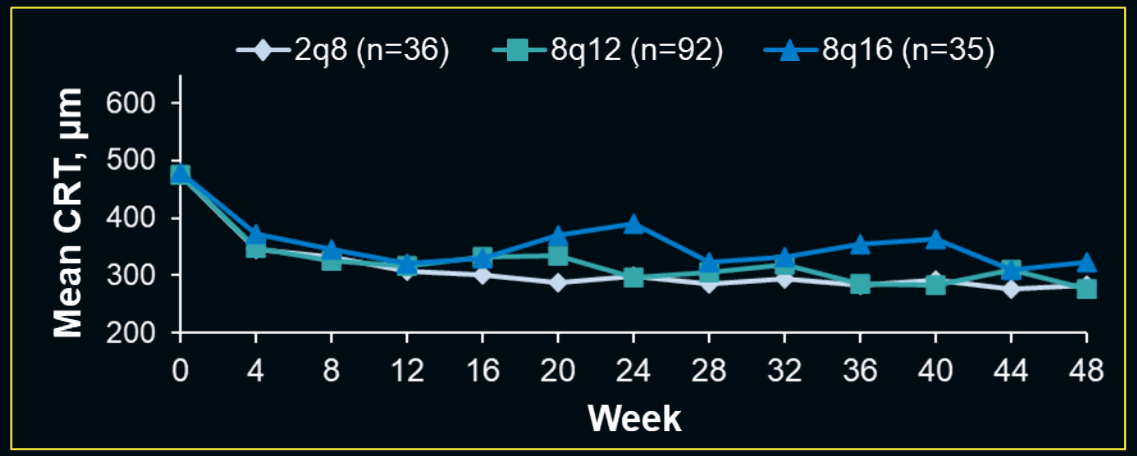
Q3: ≥431 to ≤528 µm

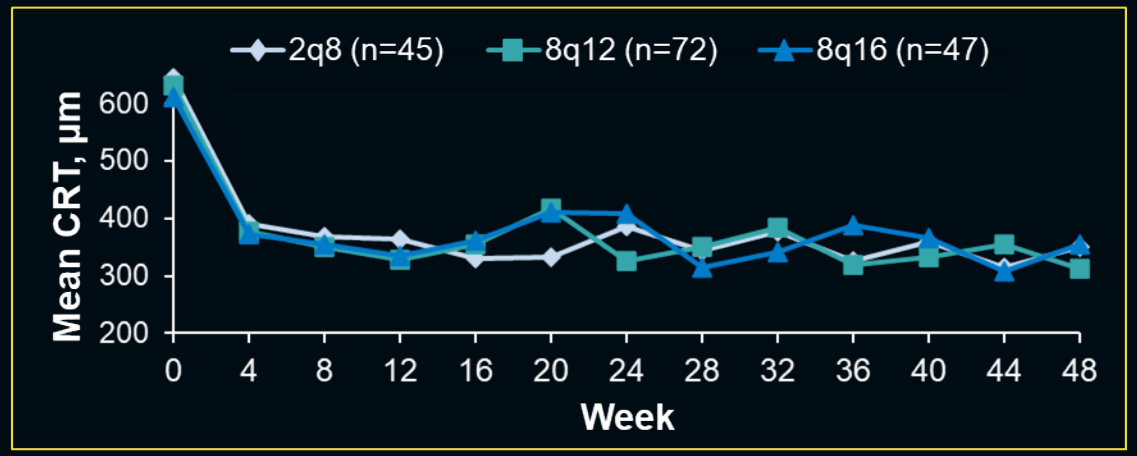


Q4: >528 µm



CRT





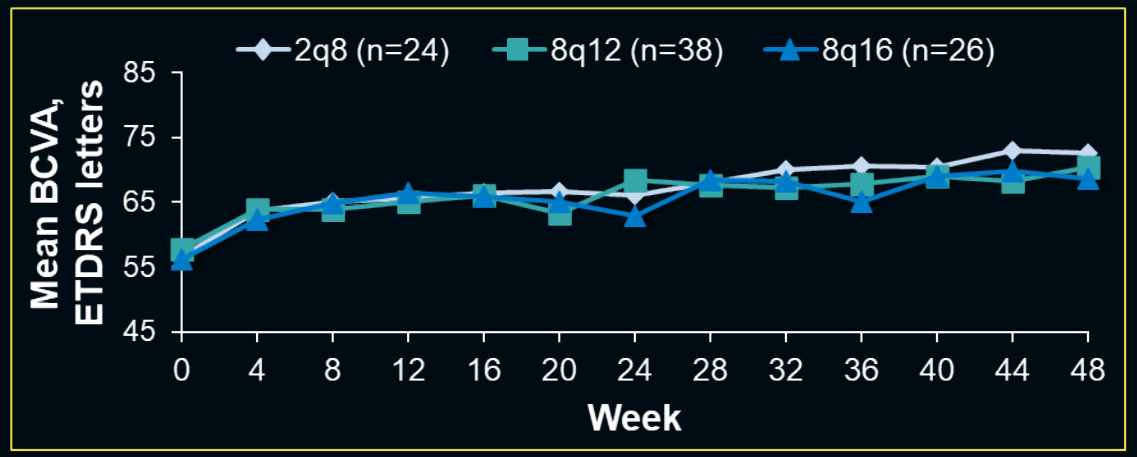
FAS, observed cases.

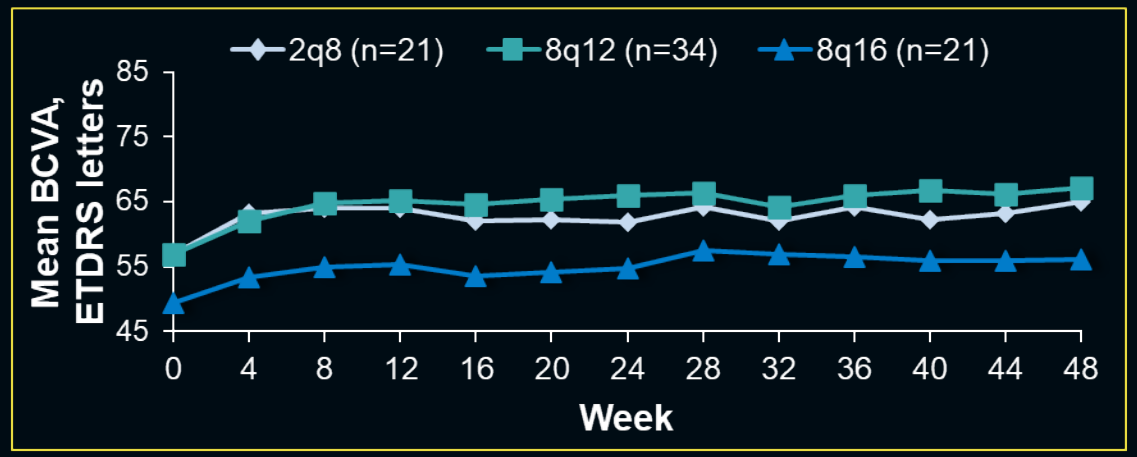
Mean BCVA and CRT Through Week 48 for Patients Without and With Prior DME Treatment in Q4

Without Prior Treatment

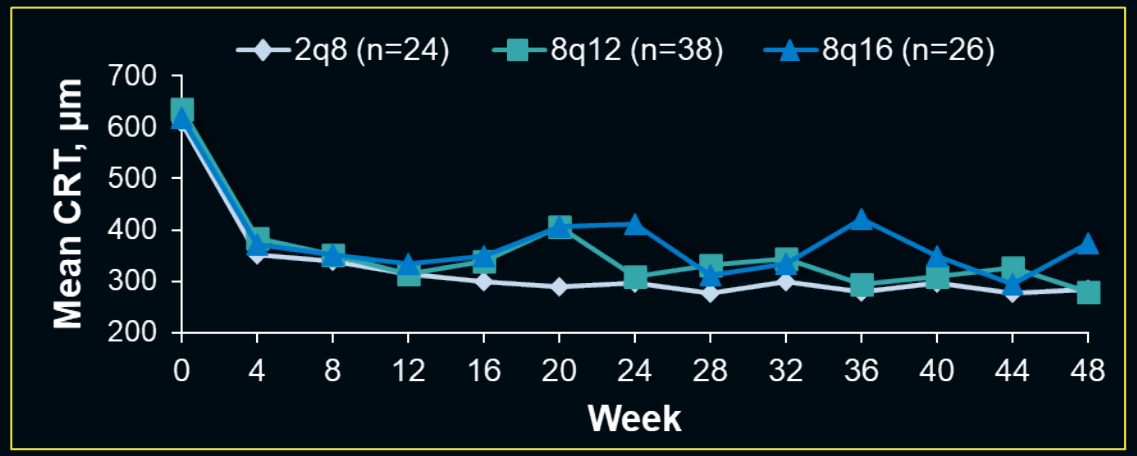
With Prior Treatment

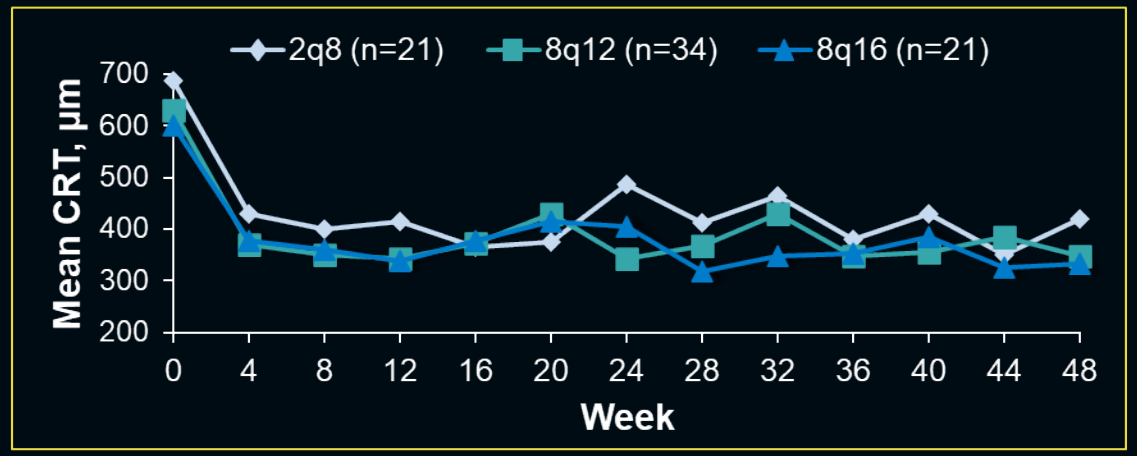
BCVA





CRT





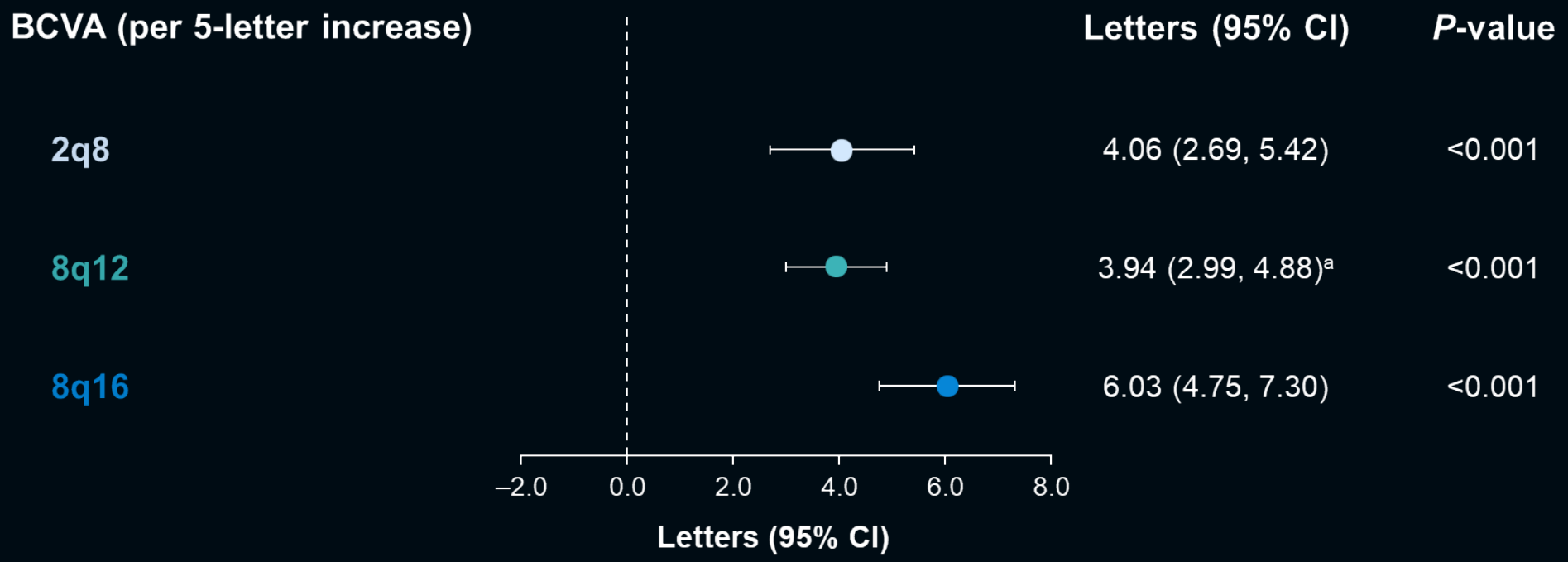
FAS, observed cases.

Univariate Analysis: Impact of Baseline Characteristics on BCVA at Week 48 in Q4

	2q8		8q12		8q16	
	Letters (95% CI)	*P*-value	Letters (95% CI)	*P*-value	Letters (95% CI)	*P*-value
Age (per 10-year increase)	–3.45 (–7.98, 1.09)	0.1322	–1.81 (–4.15, 0.53)	0.1266	**–6.52 (–11.24, –1.80)**	**0.0081**
HbA1c (per 1% increase)	–1.23 (–4.64, 2.18)	0.1685	–1.12 (–3.12, 0.88)	0.2671	–0.72 (–3.88, 2.43)	0.6455
Duration of diabetes (per 5-year increase)	–0.81 (–3.57, 1.94)	0.5541	–1.29 (–2.89, 0.31)	0.1109	–0.70 (–3.07, 1.68)	0.5554
BMI (per 5-kg/m^2 increase)	2.96 (–1.00, 6.92)	0.1381	–0.32 (–2.75, 2.12)	0.7960	1.55 (–2.84, 5.93)	0.4790
BCVA (per 5-letter increase)	**4.06 (2.69, 5.42)**	**<0.0001**	**3.94 (2.99, 4.88)**	**<0.0001**	**6.36 (5.11, 7.60)**	**<0.0001**
CRT (per 50-µm increase)	**–2.34 (–4.08, –0.60)**	**0.0096**	–0.43 (–1.77, 0.91)	0.5213	–0.64 (–3.99, 2.70)	0.6992
DRSS (≥47 to 90 vs ≤43)	–0.36 (–10.46, 9.74)	0.9433	1.22 (–5.42, 7.87)	0.7141	12.81 (1.99, 23.63)	0.0216
Prior DME treatment status (yes or no)	–7.67 (–16.54, 1.20)	0.0882	–3.17 (–9.53, 3.19)	0.3224	–12.60 (–22.34, –2.86)	0.0126
HbA1c (>8% vs ≤8%)	–5.20 (–14.58, 4.18)	0.2685	–4.68 (–11.19, 1.83)	0.1553	–7.77 (–18.95, 3.42)	0.1677

P-values were not adjusted for multiplicity.
BMI, body mass index; DRSS, Diabetic Retinopathy Severity Scale; HbA1c, hemoglobin A1c.

Multivariable Analysis: Impact of Baseline Characteristics on BCVA at Week 48 in Q4

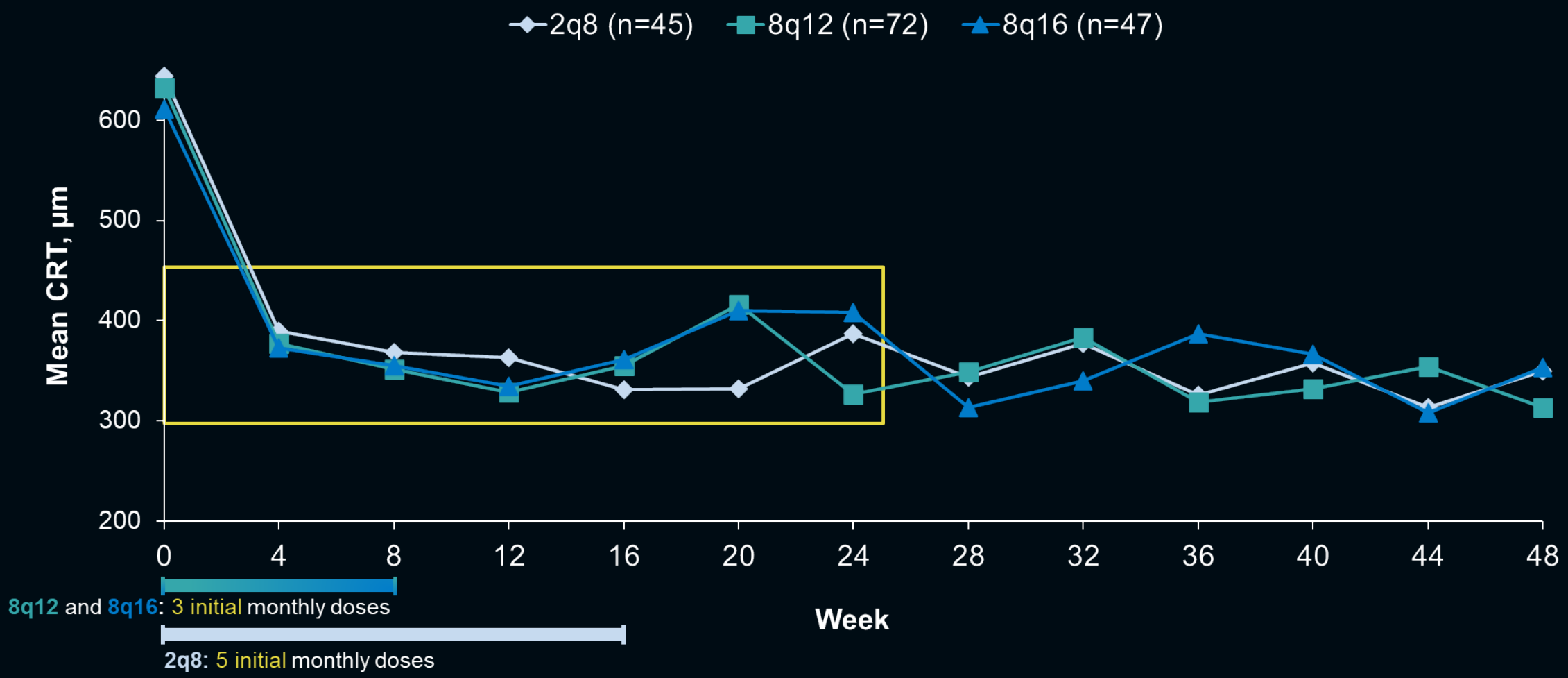


For every 5-letter increase in BCVA at baseline, there was a 4- to 6-letter increase in BCVA at Week 48

Univariate analysis included age, HbA1c, duration of diabetes, BMI, BCVA, CRT, DRSS ≤43 vs ≥47, prior DME treatment, and HbA1c >8% vs ≤8%. If more than 1 factor was significant (P<0.05) in univariate analysis, factors were then tested in multivariate analysis. P-values were not adjusted for multiplicity.

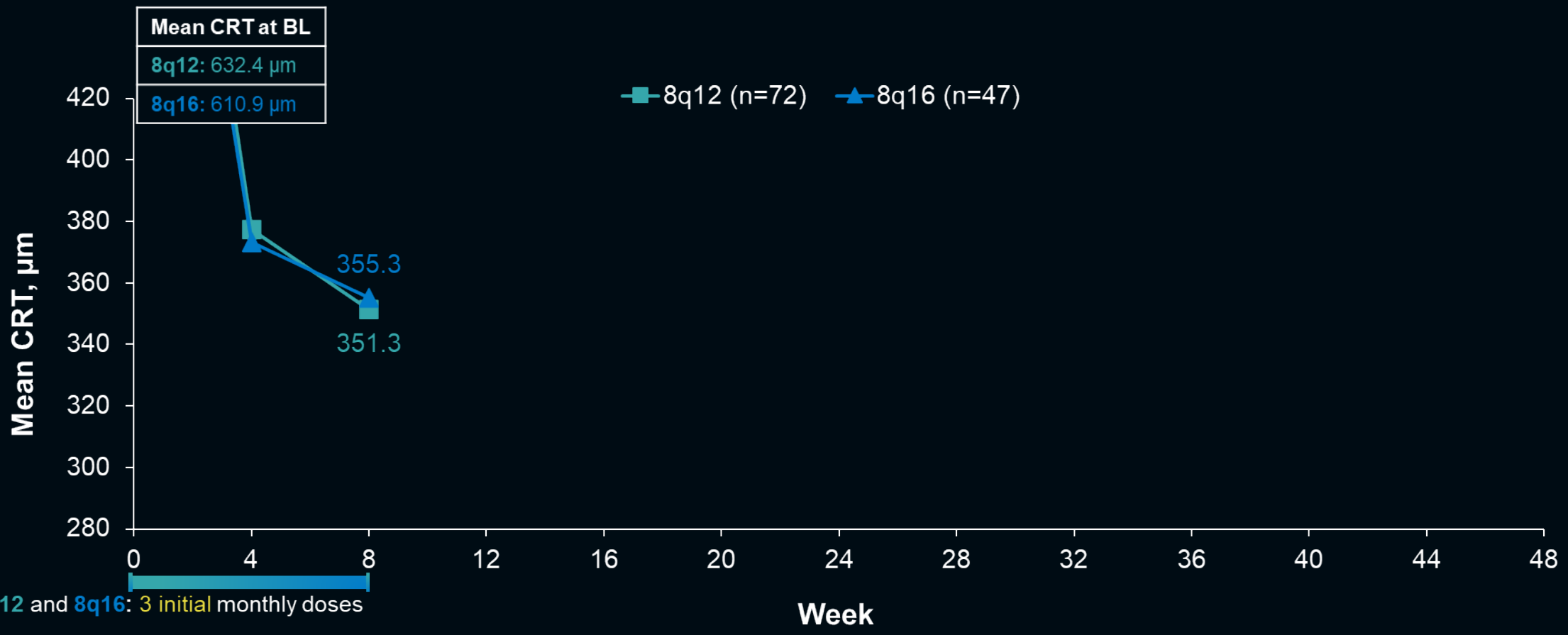
[a]Univariate analysis result. Only baseline BCVA was significantly associated with the BCVA outcome in the univariate analysis for 8q12, hence no multivariate analysis performed.

Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg Versus 2 mg Among Eyes in Q4



Q4 baseline CRT: >528 µm.
FAS, observed cases.

Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg Versus 2 mg Among Eyes in Q4



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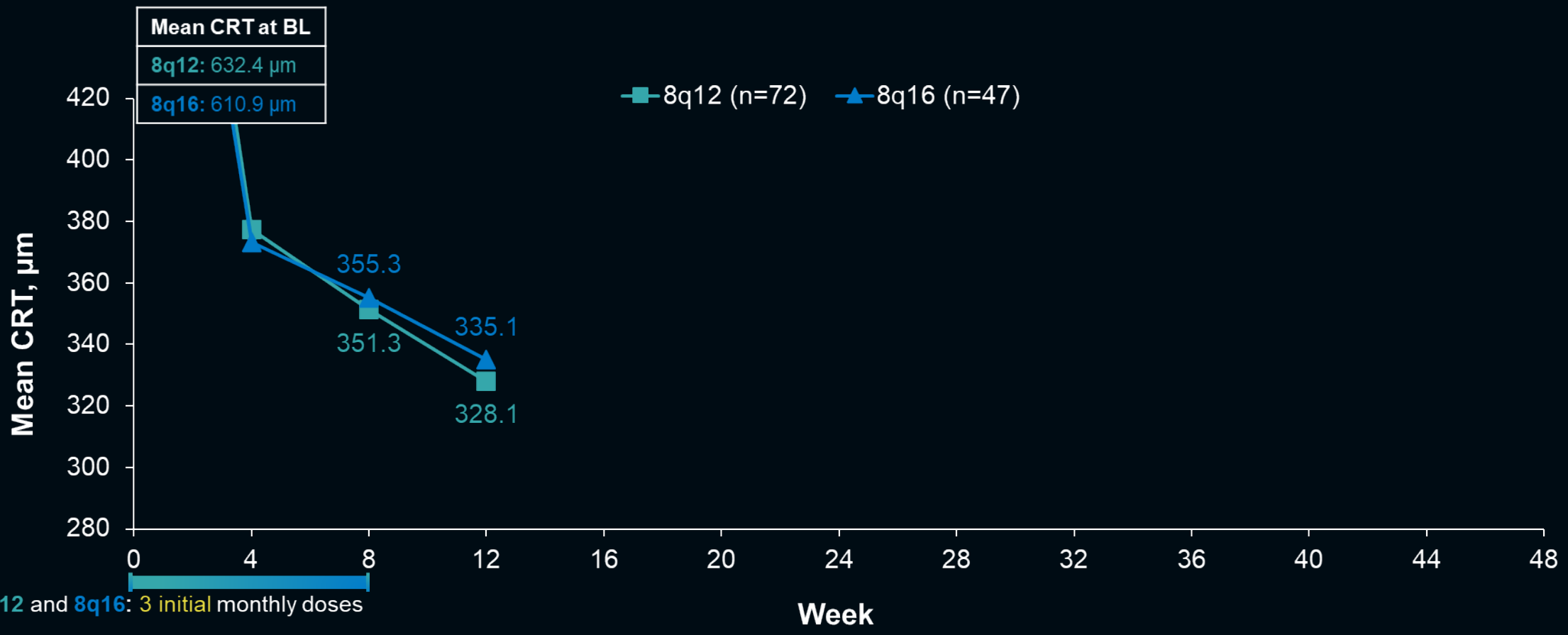

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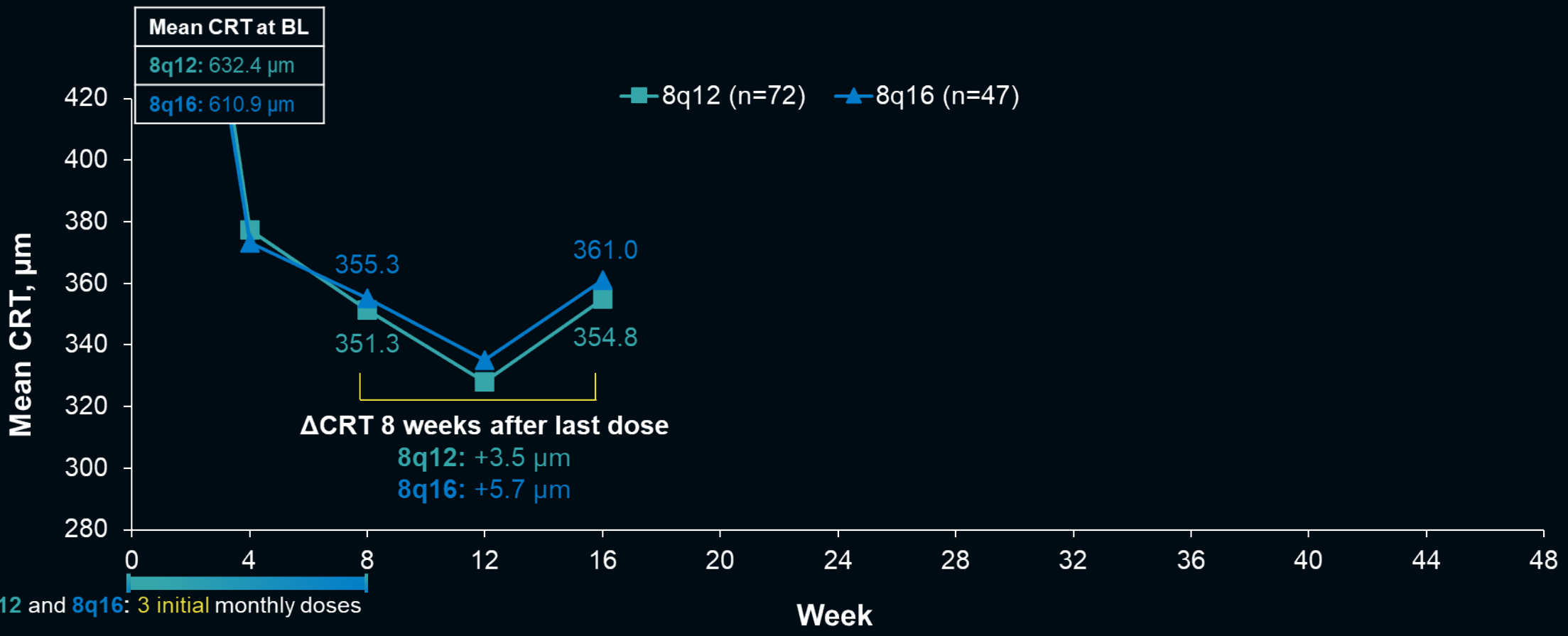
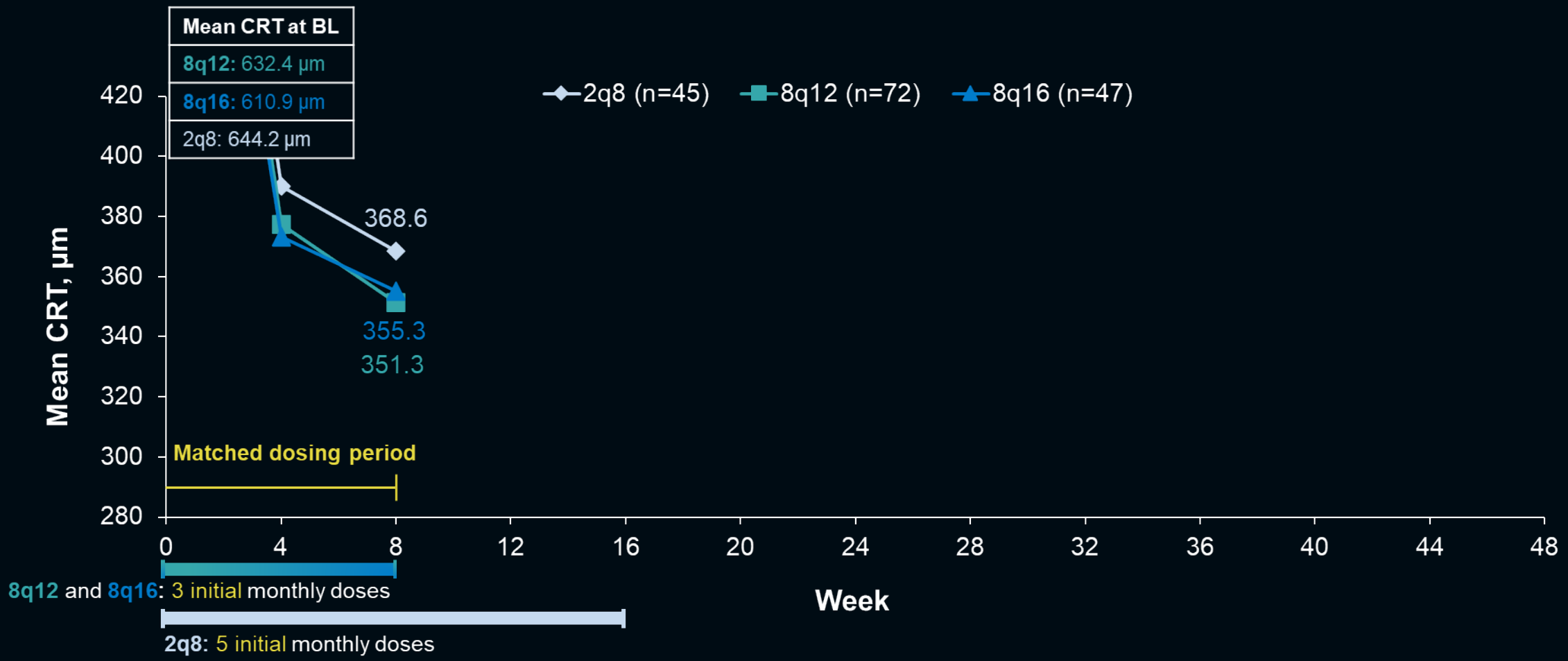


CRT for 8q12 and 8q16 groups was similar 8 weeks after the third monthly dose

Q4 baseline CRT: >528 µm.
FAS, observed cases.

Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg Versus 2 mg Among Eyes in Q4



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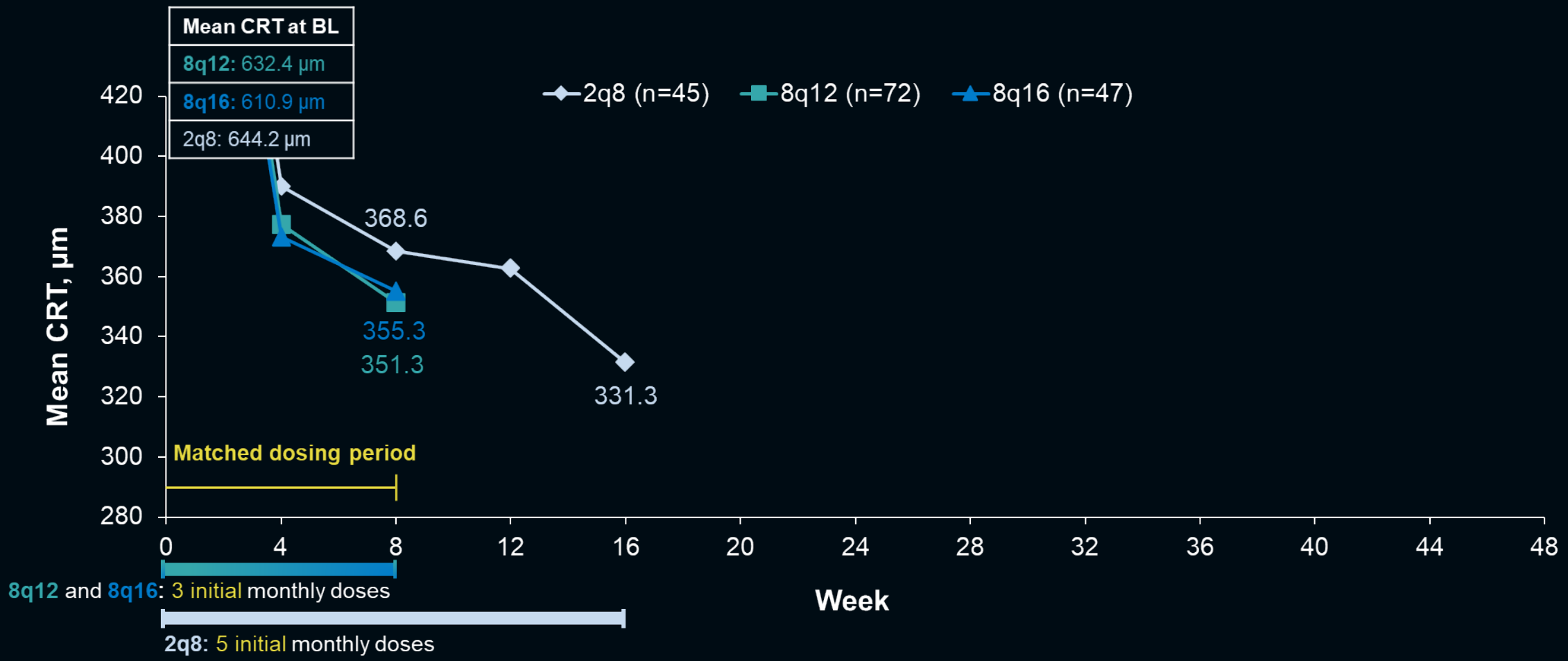
Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg Versus 2 mg Among Eyes in Q4



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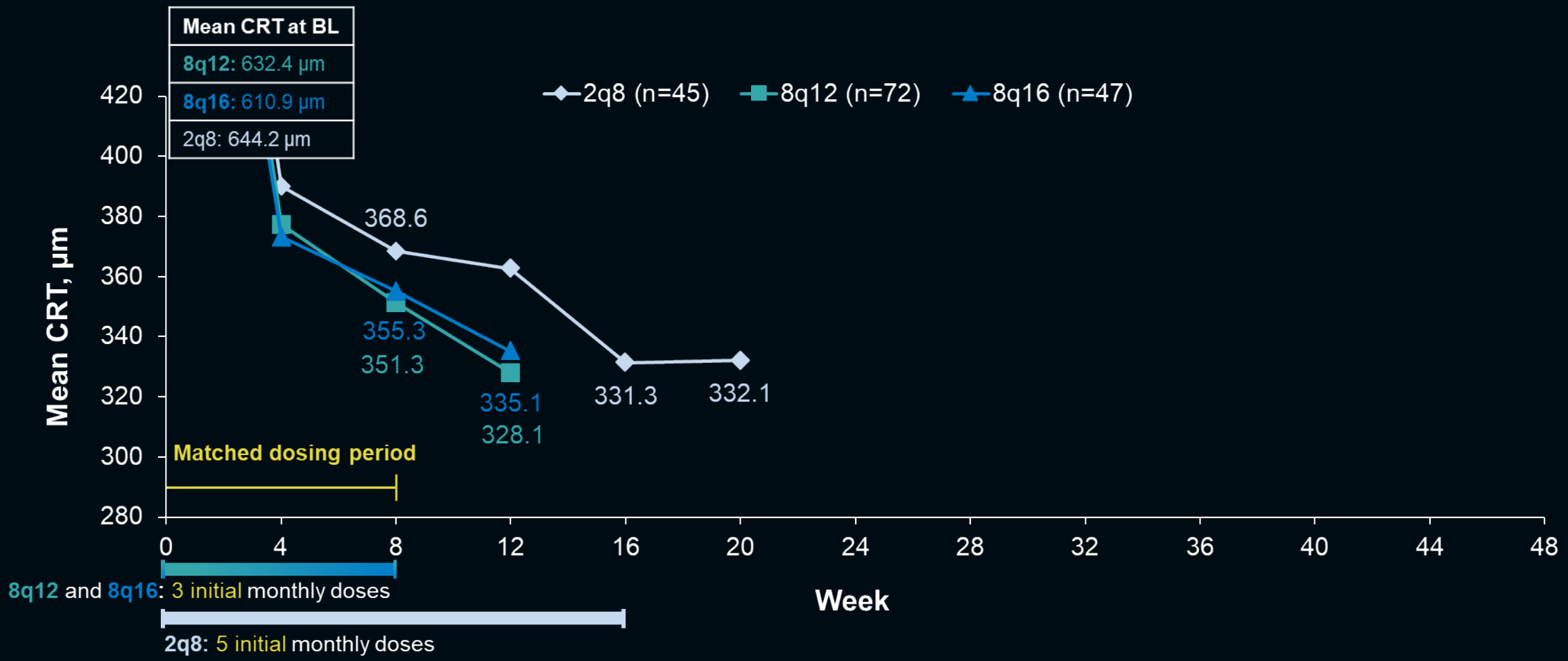

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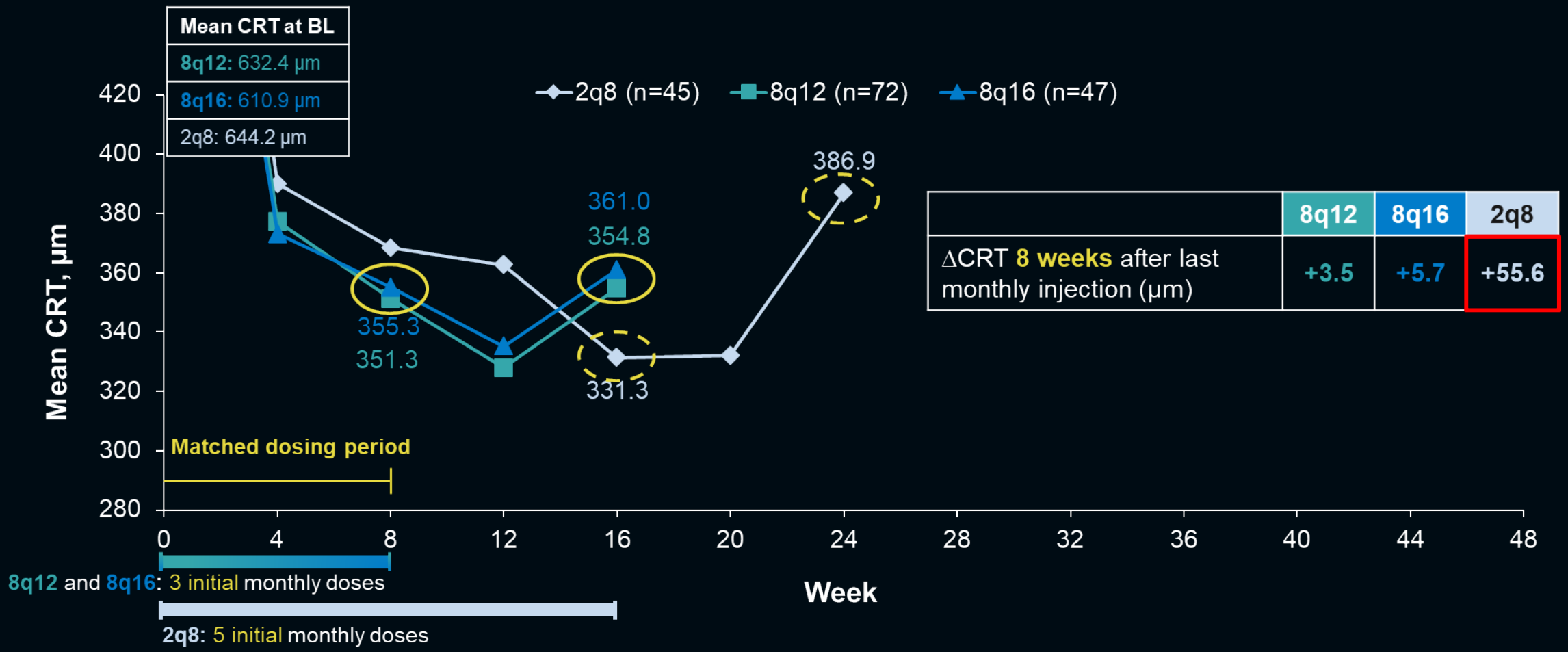
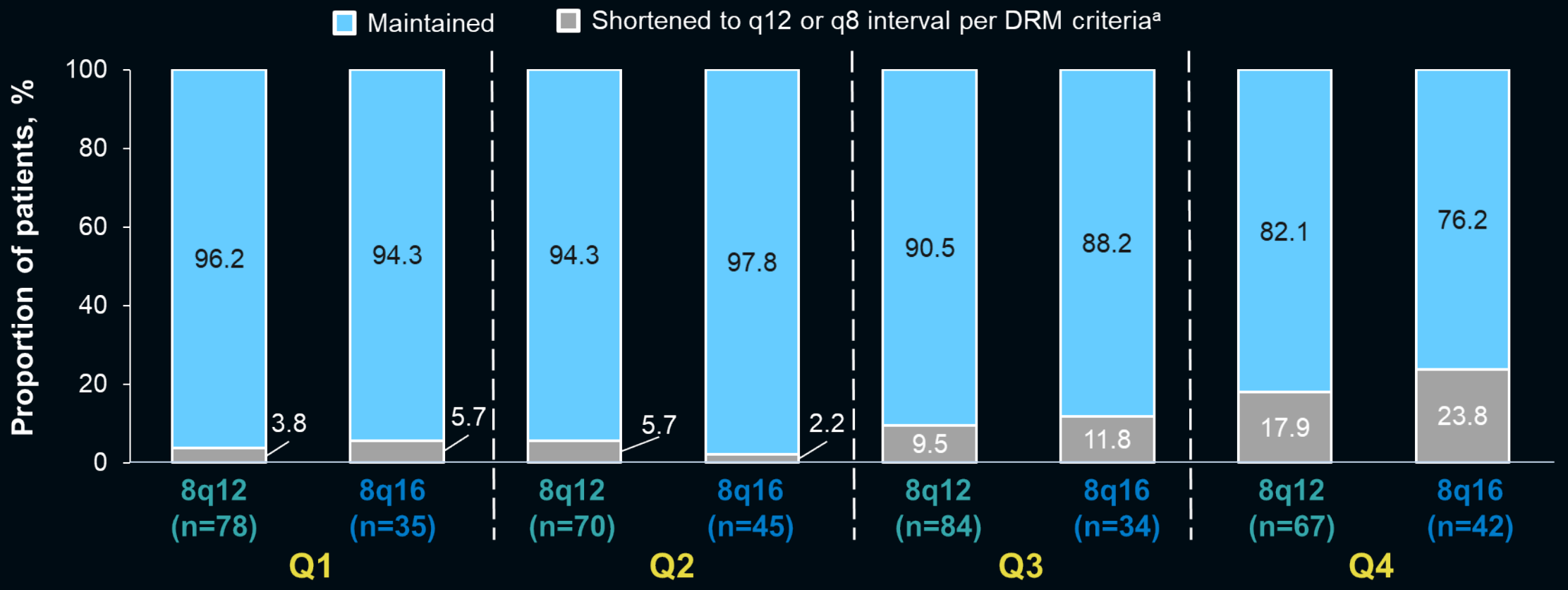


	8q12	8q16	2q8
ΔCRT 8 weeks after last monthly injection (µm)	+3.5	+5.7	+55.6

Q4 baseline CRT: >528 µm.
FAS, observed cases.

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



Relatively more patients in Q4 had intervals shortened through Week 48 versus Q1, Q2, and Q3

Q1: ≤360 µm; Q2: ≥361 to ≤430 µm; Q3: ≥431 to ≤528 µm; Q4: >528 µm.
FAS, patients who completed Week 48.
[a]Dosing intervals of patients who met study-specified DRM criteria for interval shortening (loss of >10 letters from Week 12 due to persistent or worsening DME and >50-µm increase in CRT from Week 12) at prespecified timepoints were shortened to either q12 or q8 weeks through Week 48.
DRM, dose regimen modification.

Conclusions

- Aflibercept 8 mg demonstrated meaningful visual and anatomic improvements in patients with DME at Week 48 across a wide range of baseline CRT values, with up to an average of 3 fewer injections compared with aflibercept 2 mg
- In eyes with baseline CRT >528 µm (Q4), fluid reaccumulation was numerically less 8 weeks after the third initial monthly dose with aflibercept 8 mg versus 8 weeks after the fifth initial monthly dose with aflibercept 2 mg, suggesting a more durable treatment effect