Impact of Baseline Central Retinal Thickness on Visual and Anatomic Outcomes in Patients With Diabetic Macular Edema: Post Hoc Analysis of the Phase 2/3 PHOTON Trial

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Disclosures

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- Dr. Khurana serves on the Advisory Board to Arrowhead Pharmaceuticals, Bausch + Lomb, Genentech, Inc., NGM Biopharmaceuticals, Opthea and Regeneron; and has received research funding from Annexion, Apellis, Chengdu Kanghong, Clearside Biomedical, EyePoint, Genentech, NGM Biopharmaceuticals, Opthea, Oxurion, and RegenxBio
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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

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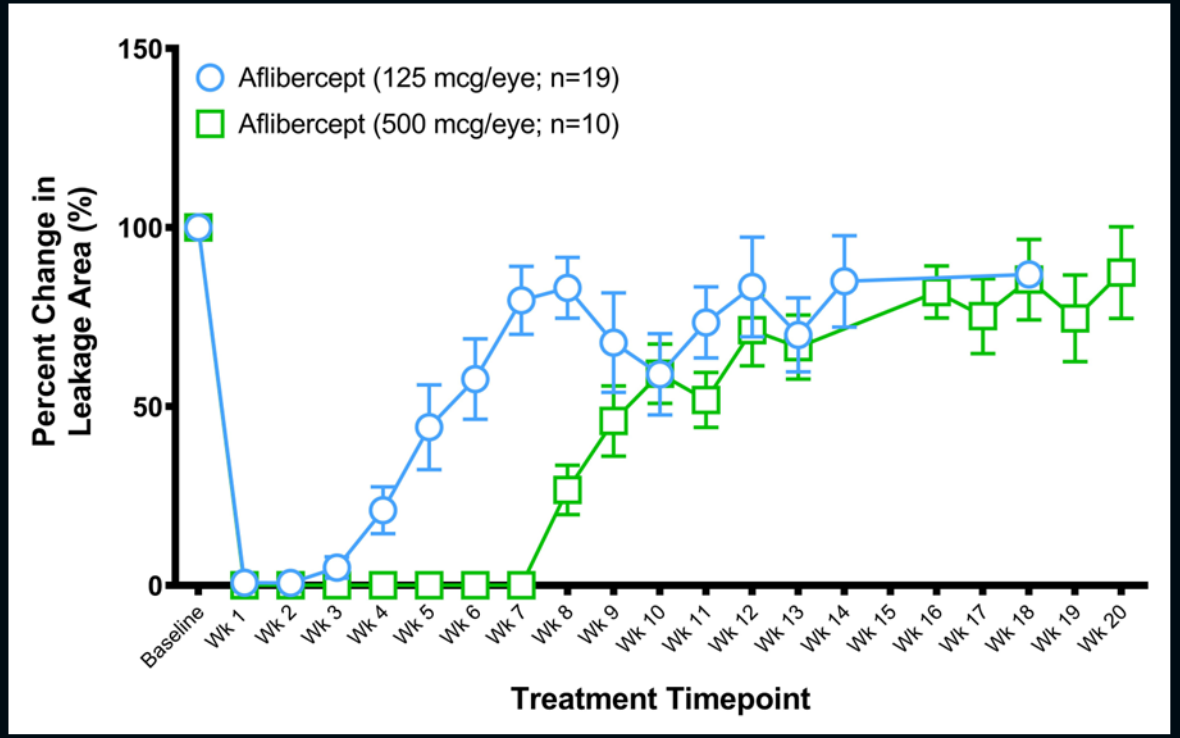
- Aflibercept is a fully human recombinant fusion protein that binds VEGF-A, VEGF-B, and PIGF, thereby inhibiting the activation of cognate VEGF receptors[1,2]

- 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.

PIGF, placental growth factor.

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

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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 macular edema.

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

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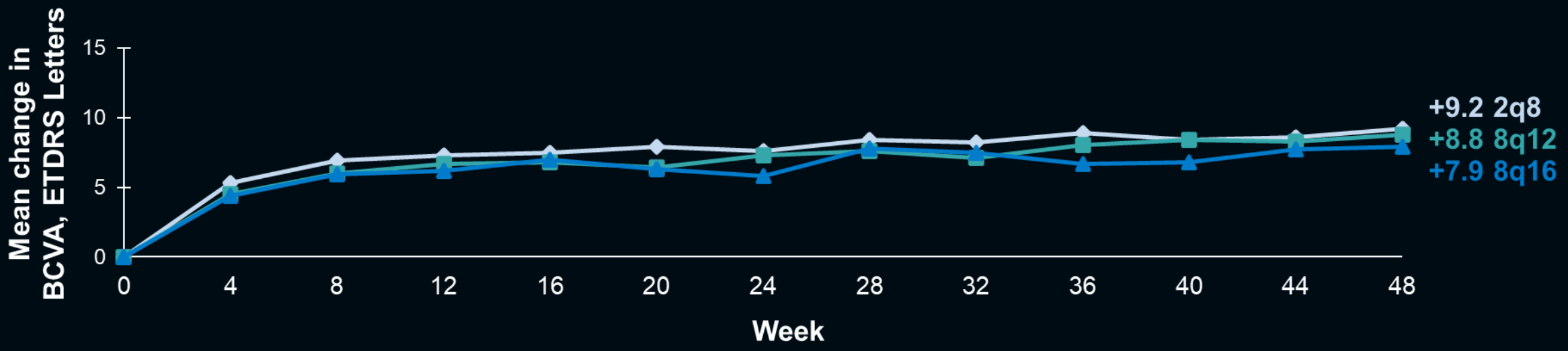
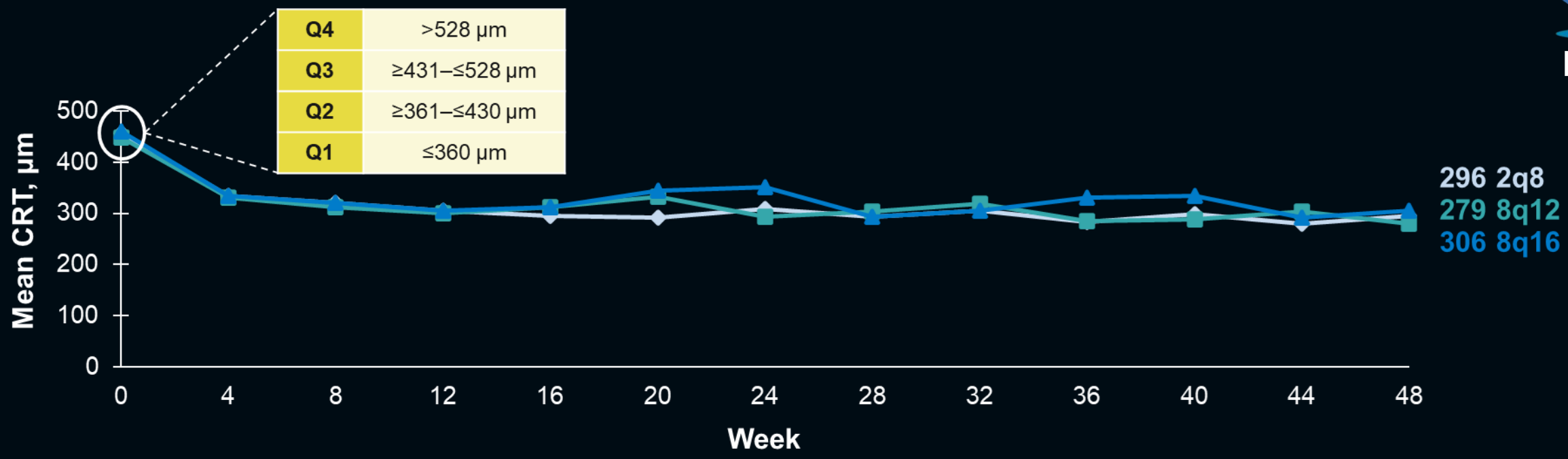
BCVA Change from Baseline[a]



	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	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).
ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

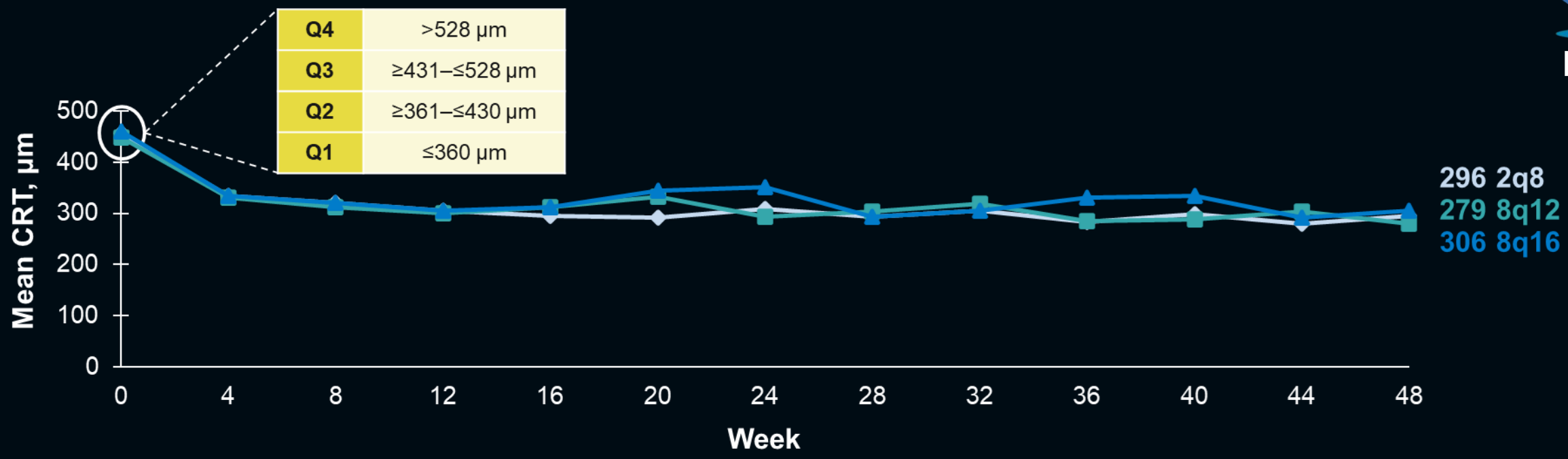
Mean CRT Through Week 48



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.

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.

Baseline Characteristics by Baseline CRT Quartiles

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	Q1: ≤360 µm (n=167)			Q2: ≥361–≤430 µm (n=163)			Q3: ≥431–≤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).
ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.

Treatment Exposure to Week 48 by Baseline CRT Quartiles

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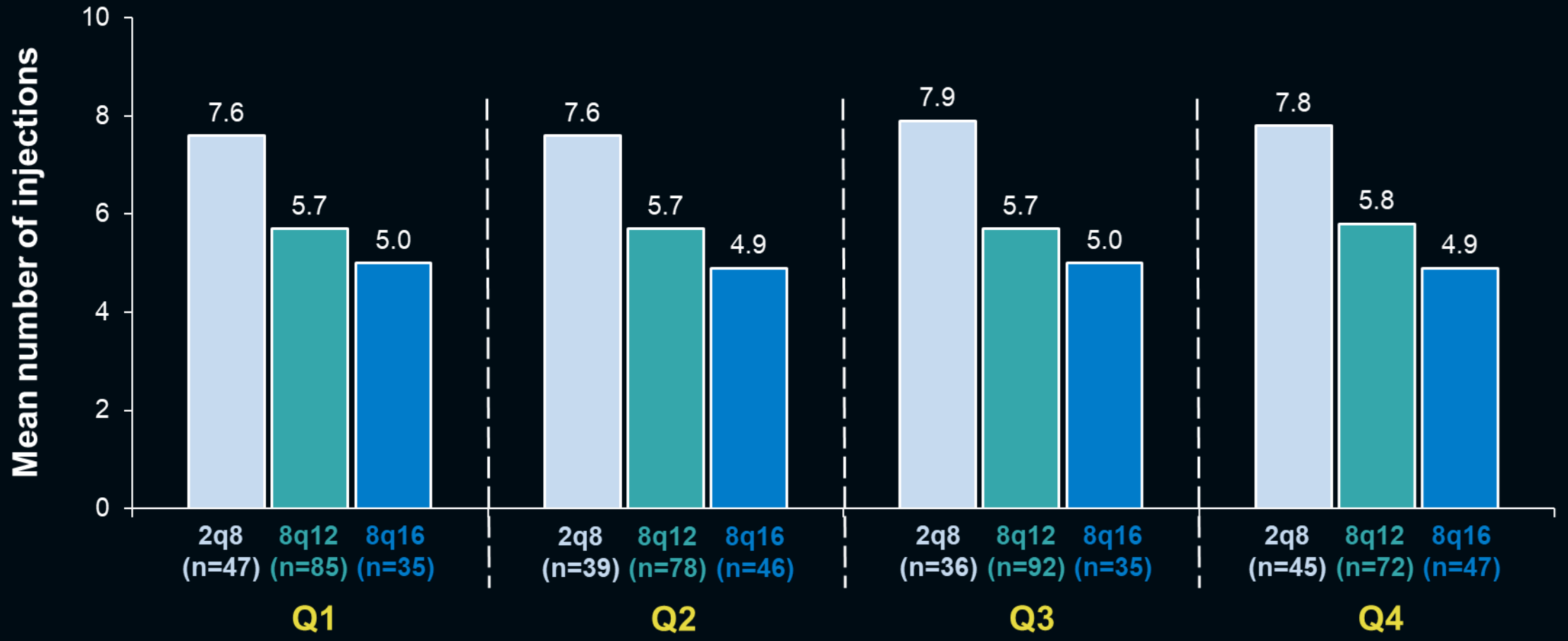


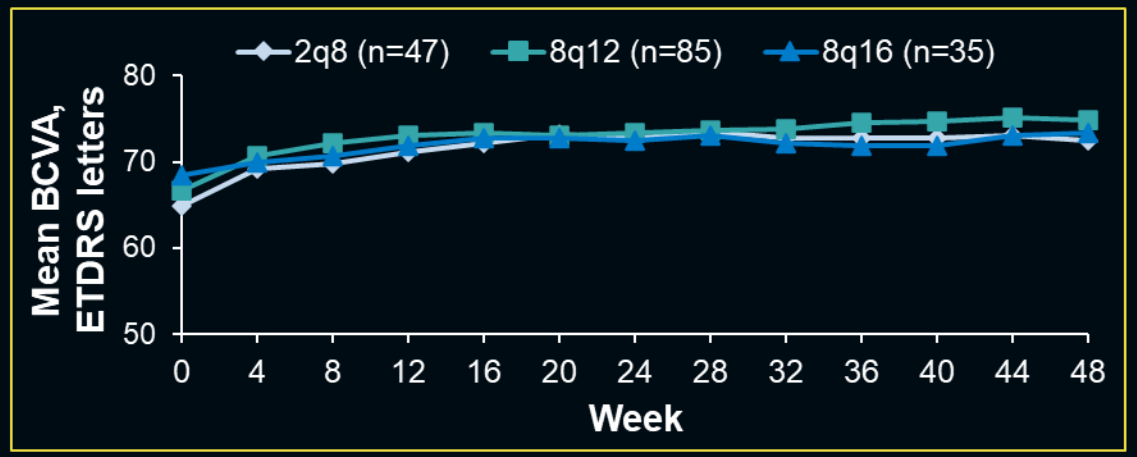
FAS, observed cases.
Q1: ≤360 µm; Q2: ≥361–≤430 µm; Q3: ≥431–≤528 µm; Q4: >528 µm.

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

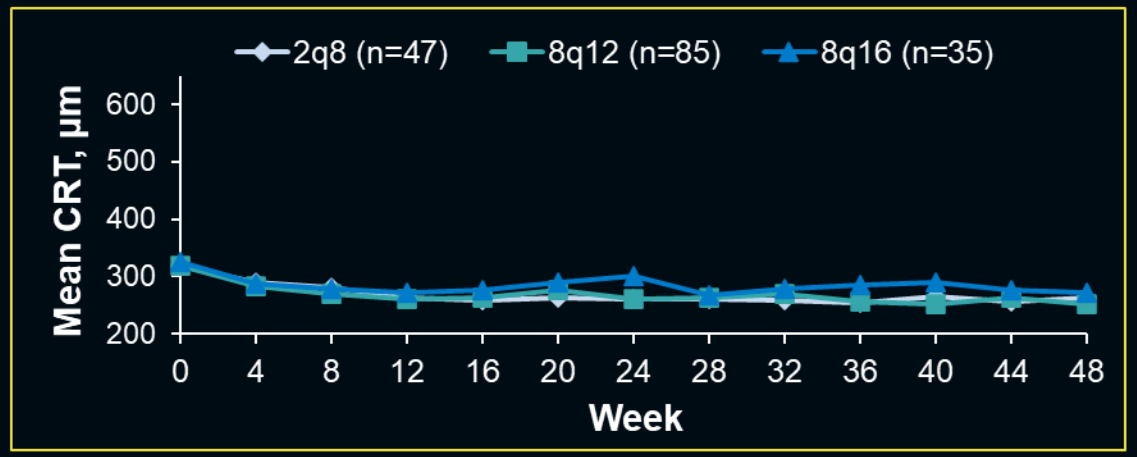
DME

Q1: ≤360 µm

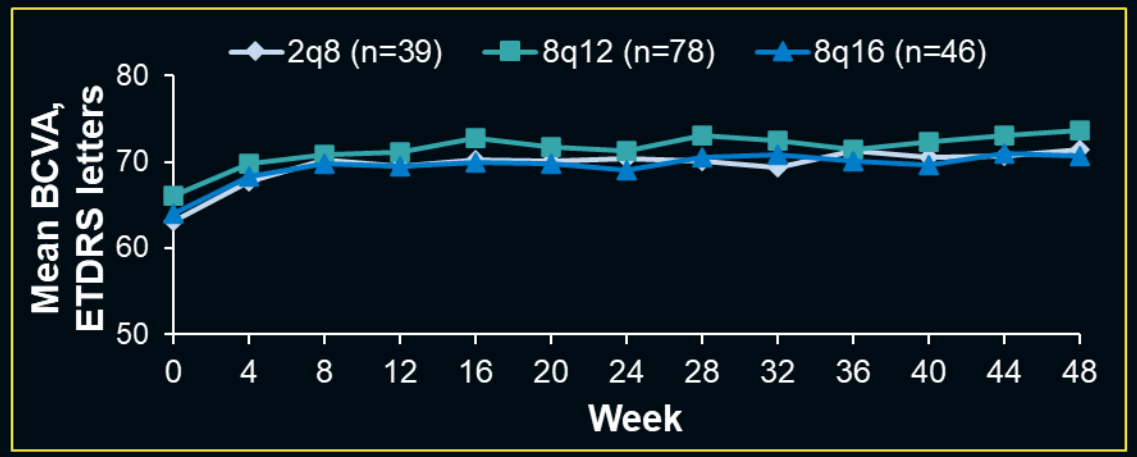
BCVA

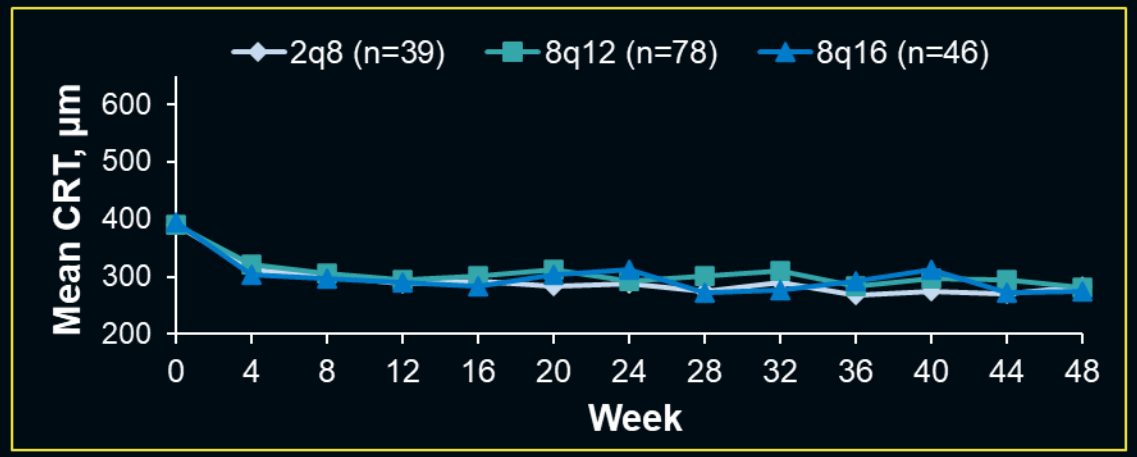


CRT



Q2: ≥361–≤430 µm





FAS, observed cases.

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

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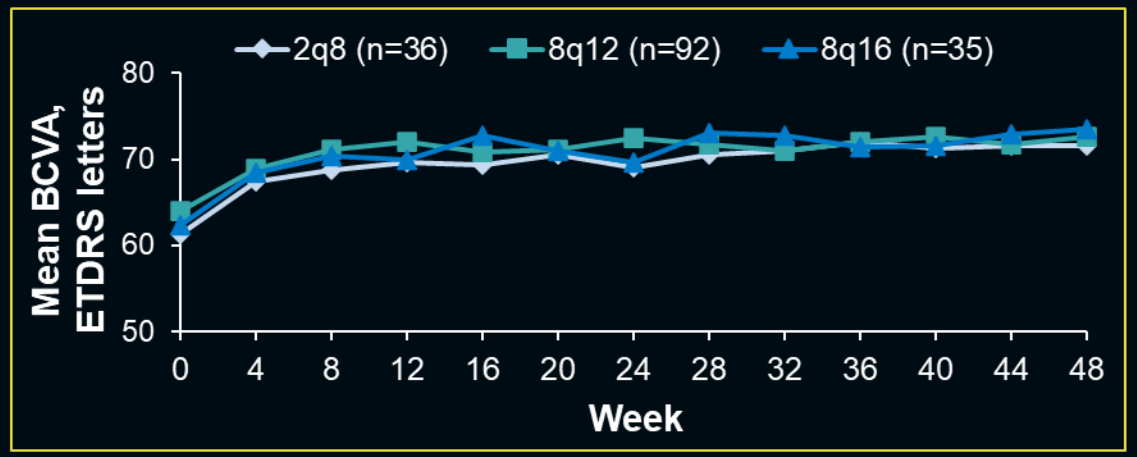
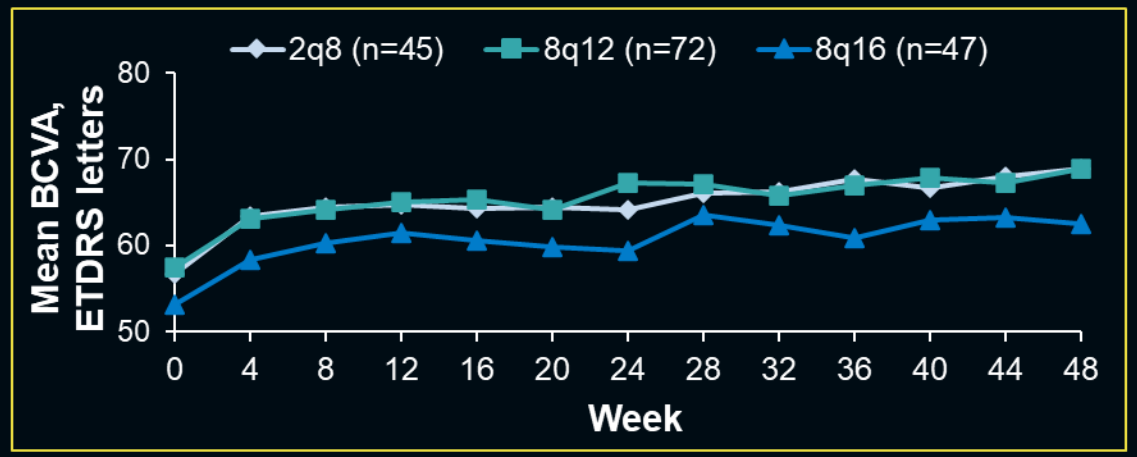
DME

Q3: ≥431–≤528 µm

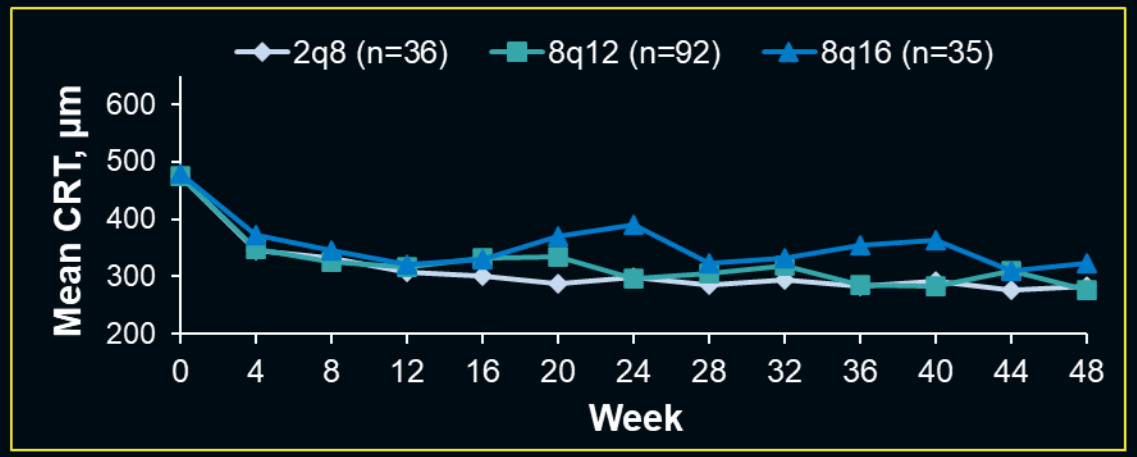
Q4: >528 µm

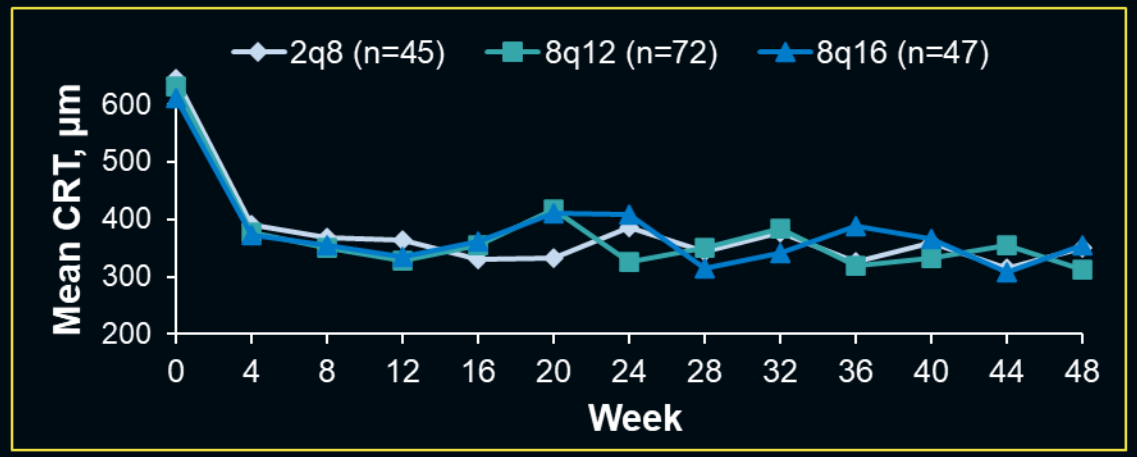
BCVA





CRT





FAS, observed cases.

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

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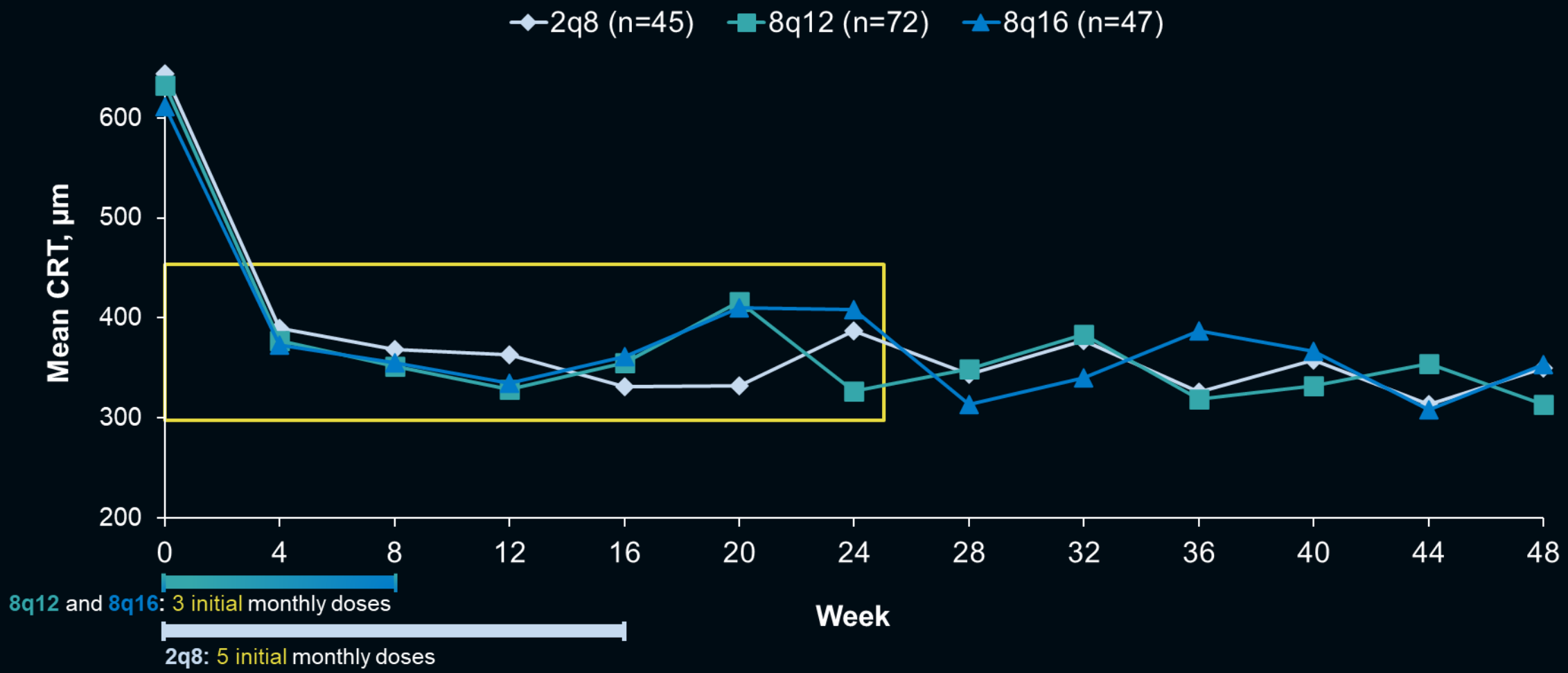
DME



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

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

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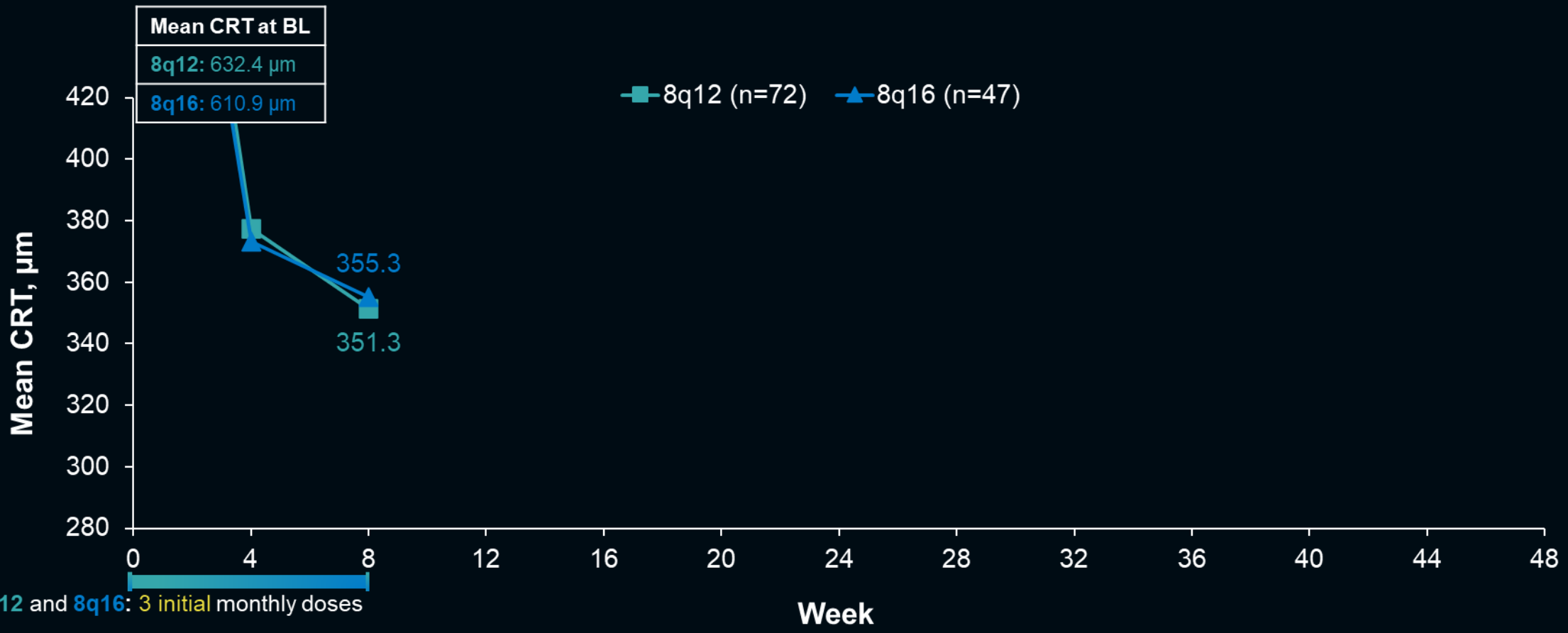
DME



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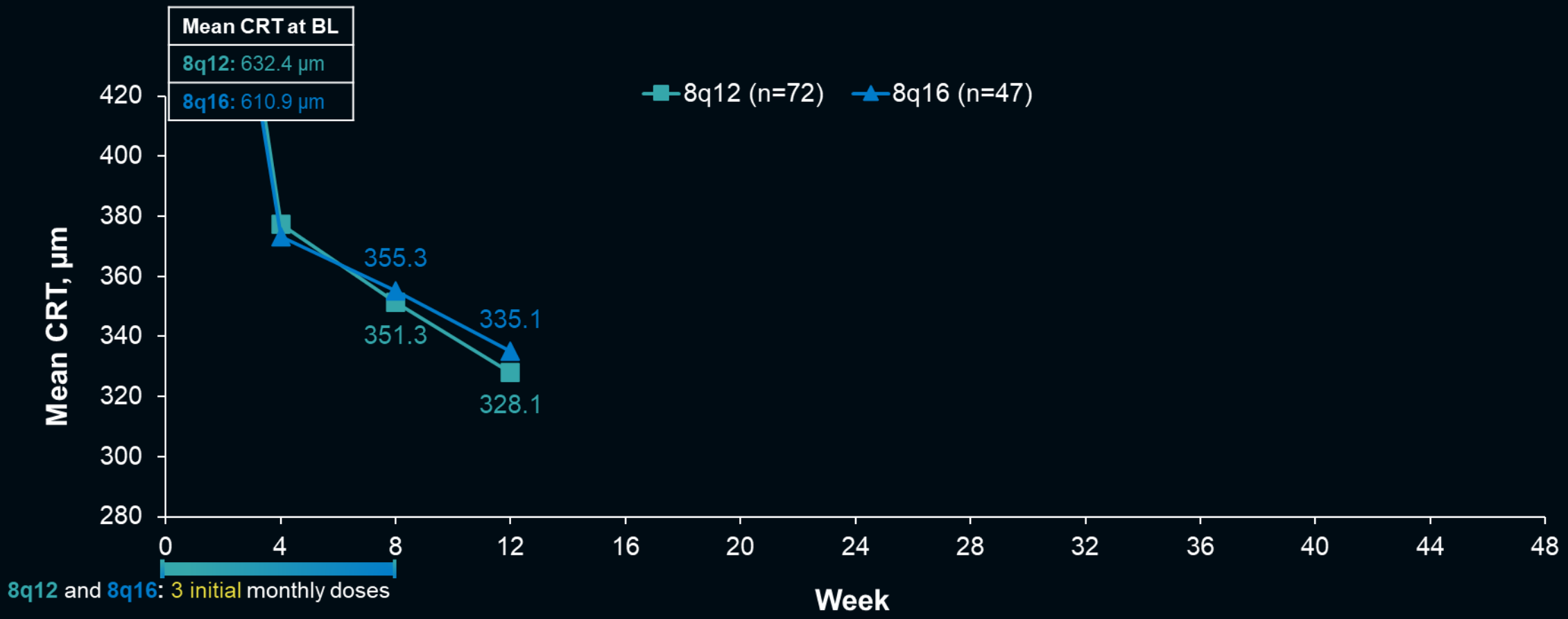
DME



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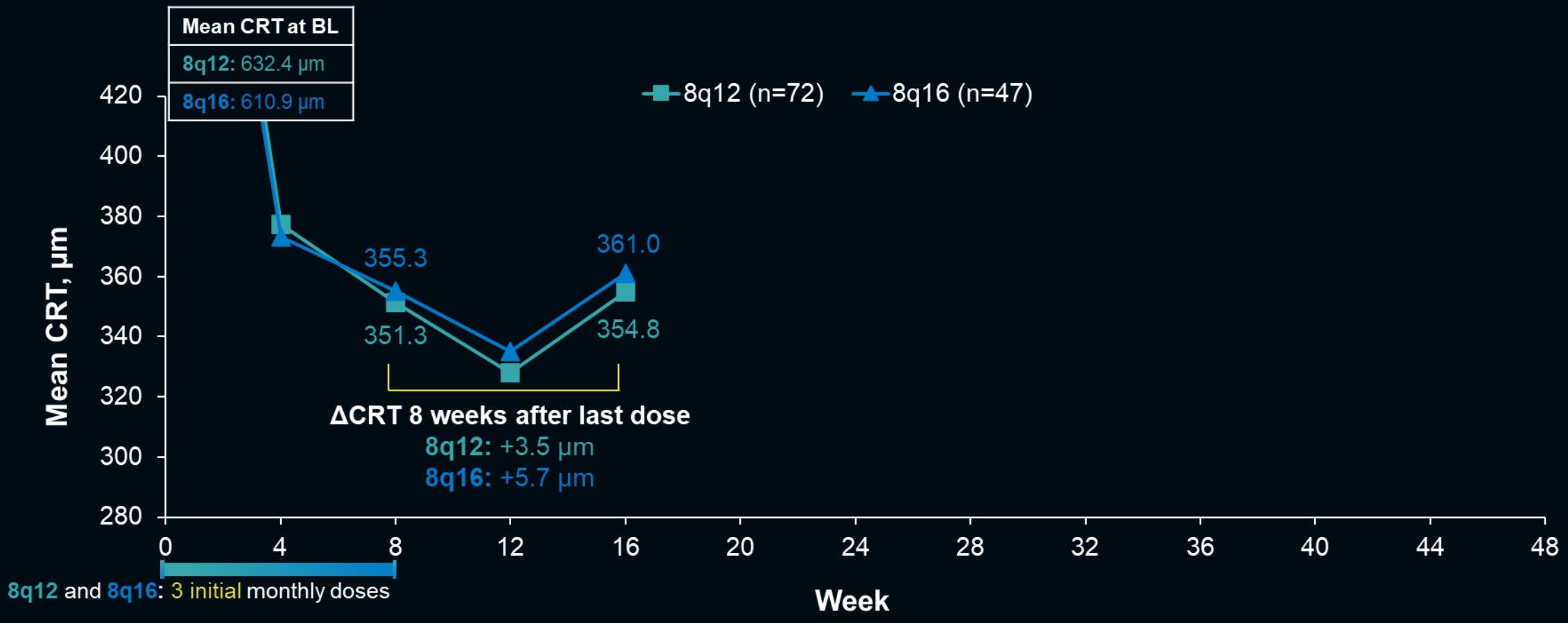
DME



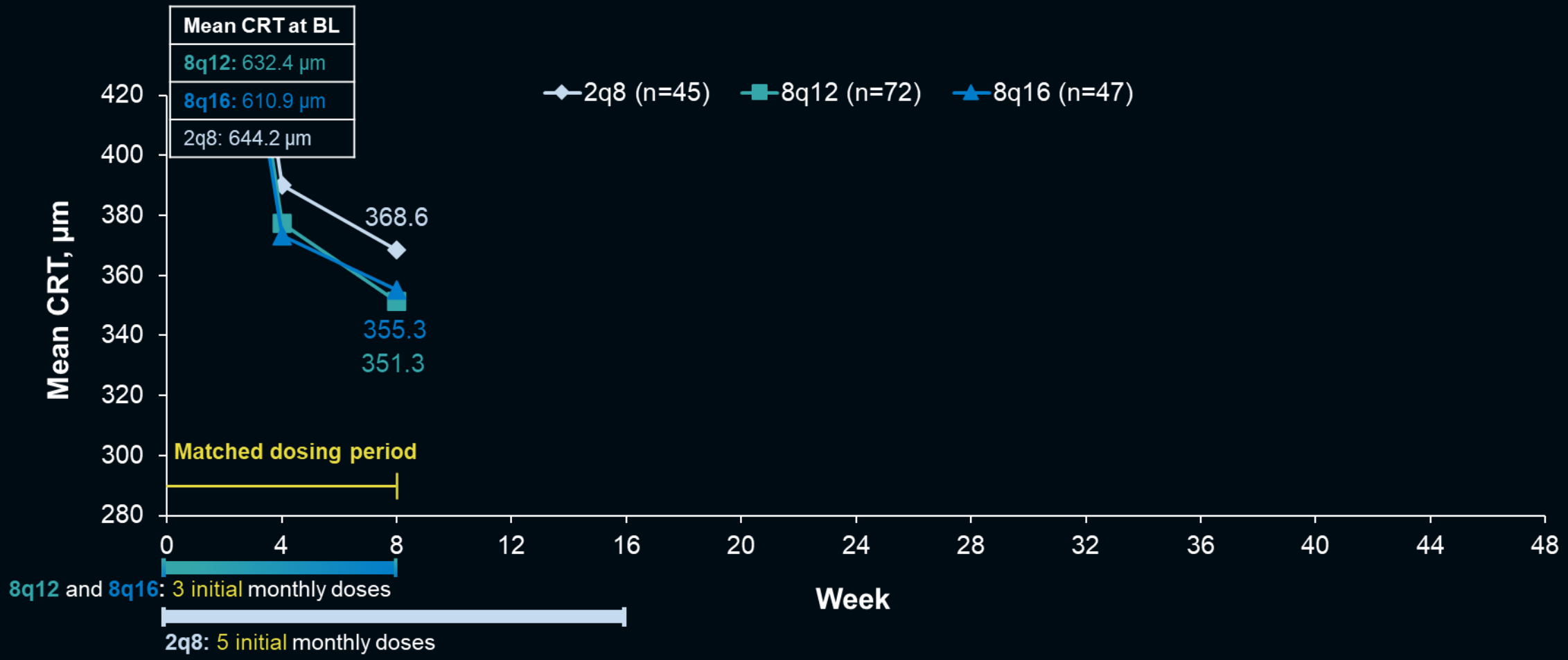
CRT for 8q12 and 8q16 groups was similar 8 weeks after the third monthly dose

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

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

photon

DME



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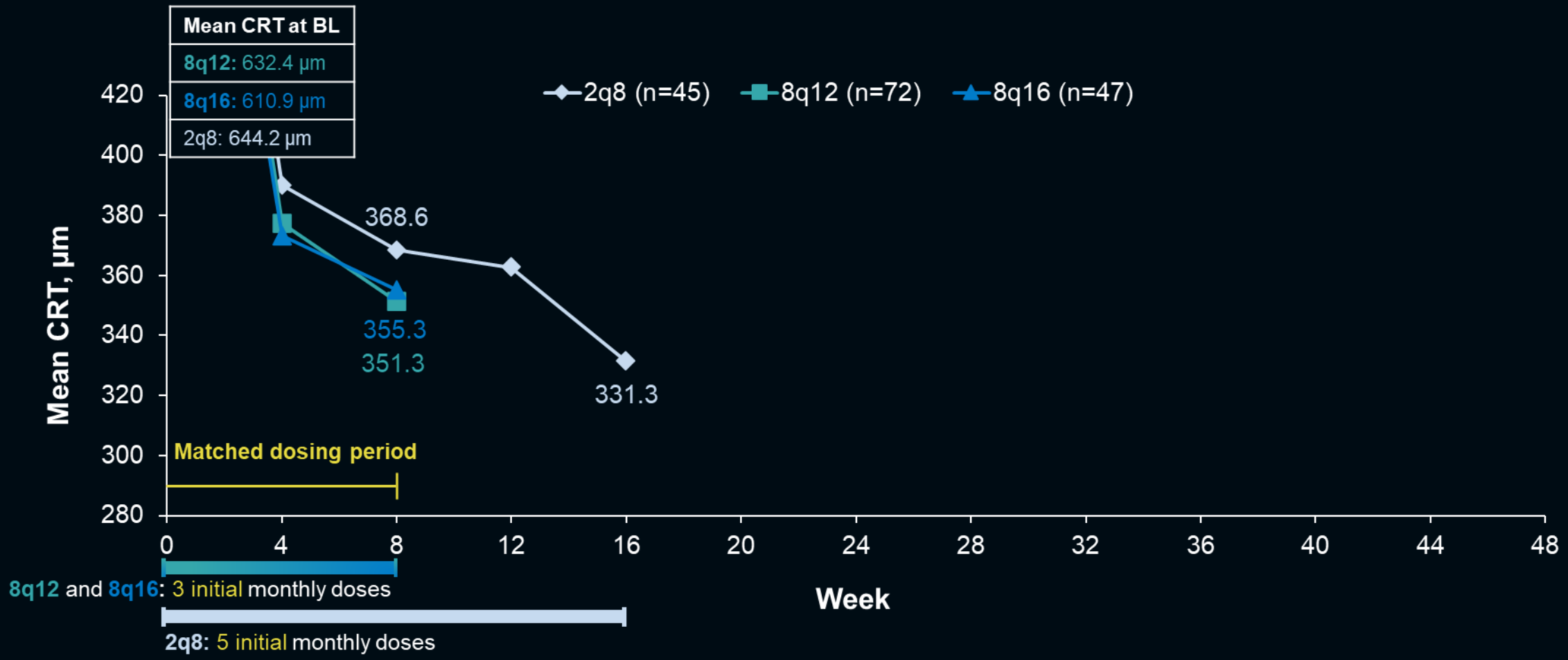
FAS, observed cases.

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

photon

DME



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

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

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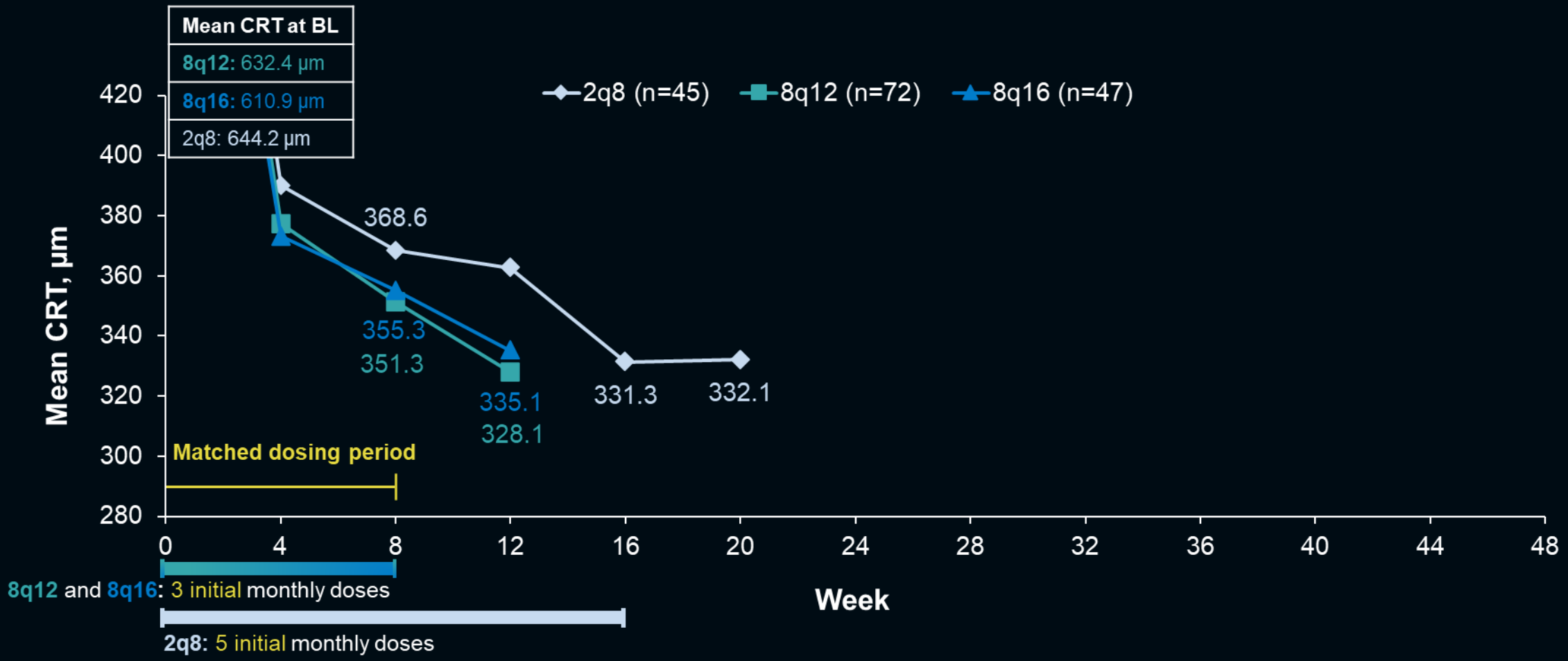
DME



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

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

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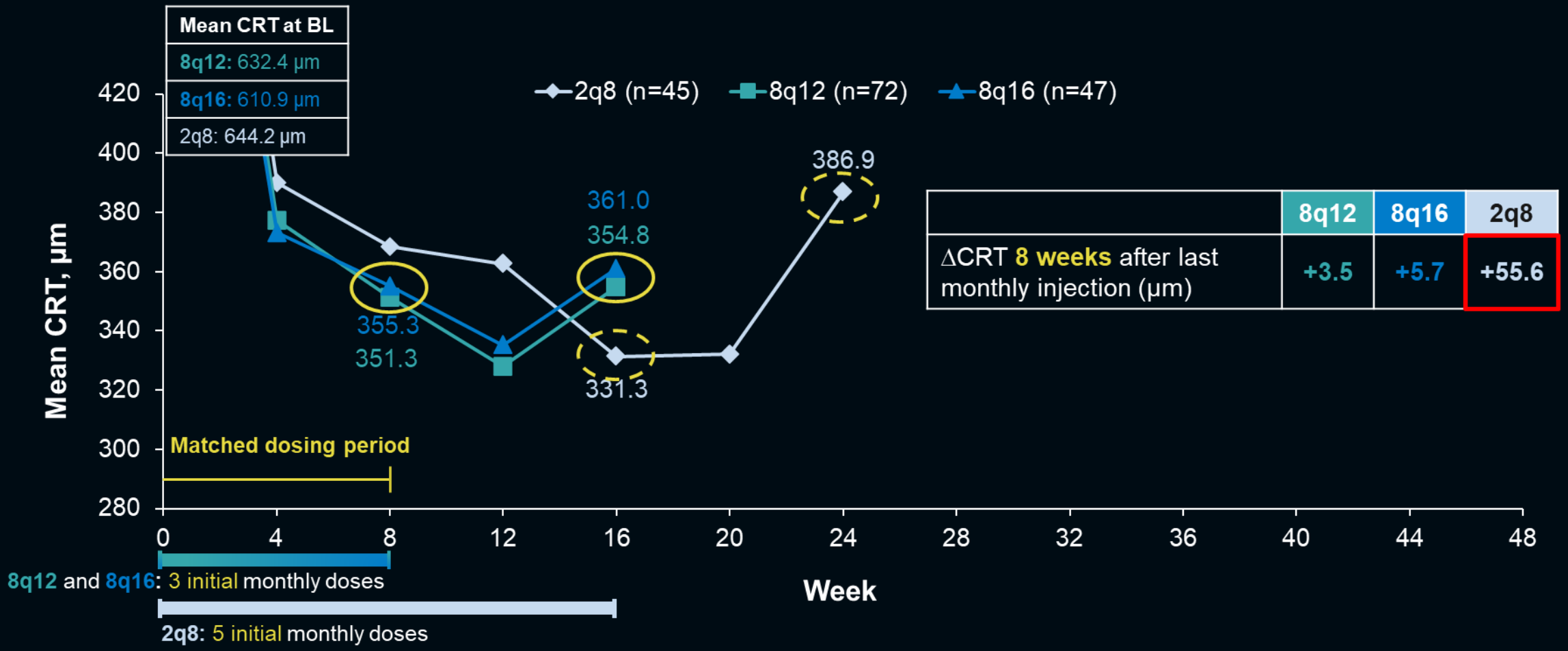
DME



	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

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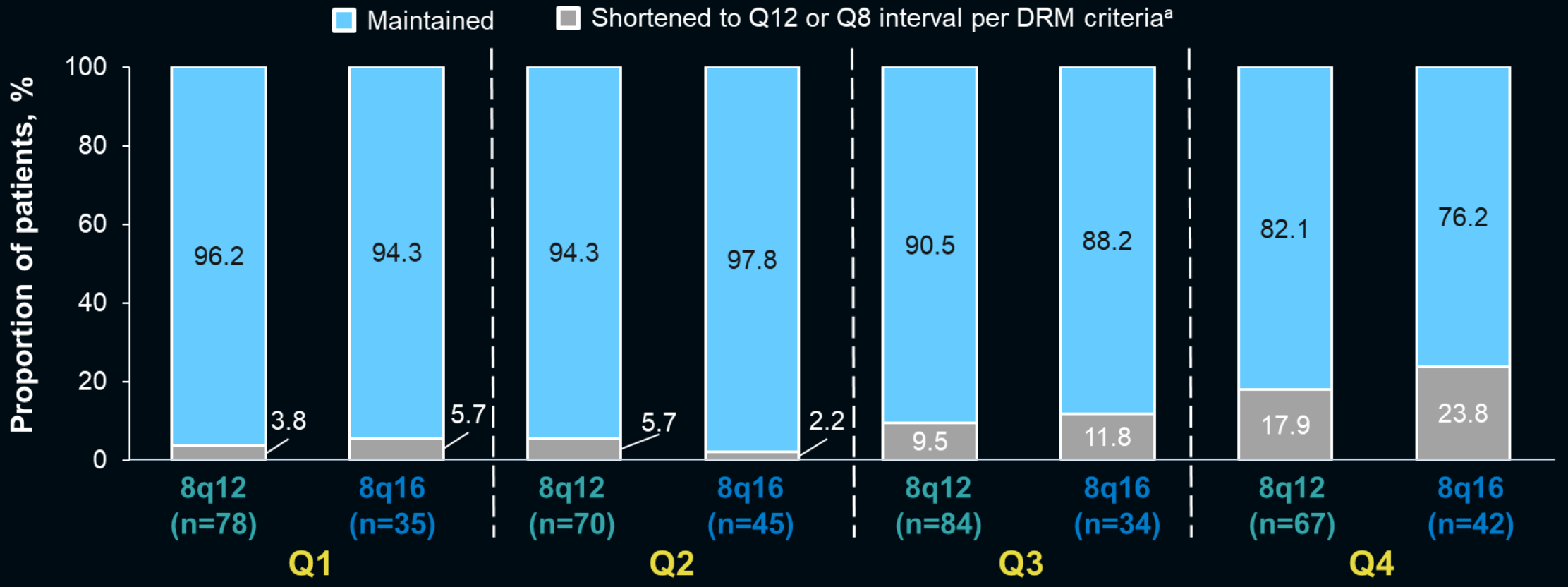

Relatively more patients in Q4 had intervals shortened through Week 48 versus Q1, Q2, and Q3

[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 12 or 8 weeks through Week 48.
Q1: ≤360 µm; Q2: ≥361—≤430 µm; Q3: ≥431—≤528 µm; Q4: >528 µm.
FAS, patients who completed Week 48.
DRM, dose regimen modification.

Conclusions

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- 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, fluid reaccumulation was numerically less 8 weeks after the third initial monthly dose with aflibercept 8 mg versus 2 mg after 5 initial monthly doses, suggesting a more durable treatment effect

DME

BACKUP

Dosing Schedule and DRM Criteria in Year 1

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Primary Endpoint

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X	X	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections

DRM Criteria for Shortening Dosing Interval[a]

- >10-letter loss in BCVA due to persistent or worsening DME

AND

- >50-micron increase in CRT

[a]All assessments compared to Week 12

DRM in Year 1

- Intervals can only be **shortened**
- **Multiple opportunities** to shorten interval
- Minimum interval for all patients was **Q8**

Week 16 and 20: Patients on 8q12 and 8q16 meeting DRM criteria shortened to Q8

Week 24: Patients on 8q16 meeting DRM criteria shortened to Q12

Week 32 and 44 for 8q12 and Week 40 for 8q16: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

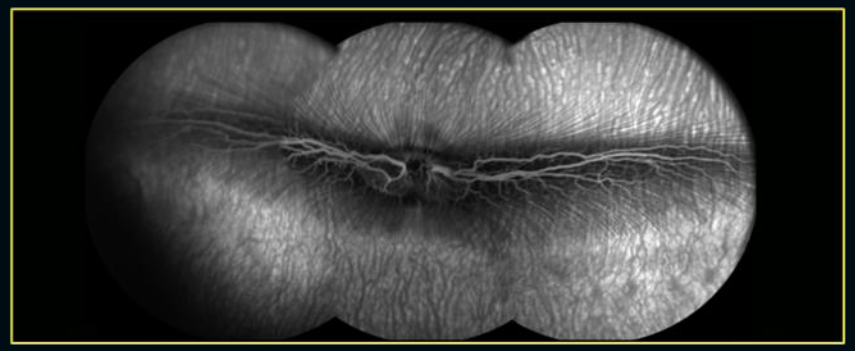
Stippled boxes = initial treatment phase; X=active injection; o=sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
DRM, dose regimen modification; Wk, week.

Background

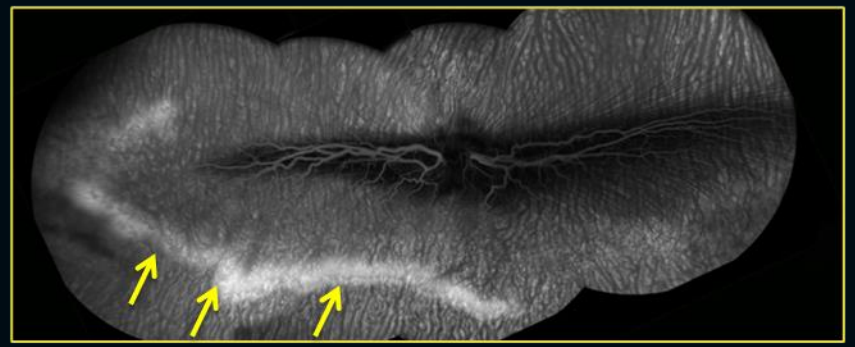
- The DL-AAA rabbit model of chronic retinal neovascularization has been commonly used to evaluate the efficacy and duration of action of intravitreal anti-VEGF agents in exudative retinal disease[1,2]

- In rabbits, subretinal injection of DL-AAA induces extensive vascular leakage as observed on FA and promotes vessel tortuosity[1]

Normal rabbit FA[1]



8 weeks post DL-AAA FA[1]



Yellow arrows indicate fluorescein leakage from neovasculature.

DL-AAA, DL-α-aminoadipic acid; FA, fluorescein angiogram; VEGF, vascular endothelial growth factor.

1. Cao J et al. *Invest Ophthalmol Vis Sci.* 2018;59(2):1033-1044. 2. Kumar S et al. *Int J Ophthalmol.* 2022;15(1):15-22.