Differential Anatomic Response to Aflibercept 8 mg Versus 2 mg in DME Patients Who Met Shortening Criteria in the Phase 2/3 PHOTON Trial

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Key Takeaways

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DME

The PHOTON trial showed that:

- ~90% of patients treated with aflibercept 8 mg **did not meet shortening criteria** and maintained their randomized dosing intervals through week 48
    - In this subgroup of patients, aflibercept 8 mg achieved similar visual and anatomic outcomes compared to aflibercept 2 mg during the matched dosing phase and afterwards with extended dosing intervals
- ~10% of patients treated with aflibercept 8 mg **met shortening criteria**
    - The current subanalysis in this subgroup of patients shows that, during the matched dosing phase, aflibercept 8 mg provided relatively greater anatomic benefit (greater CRT improvement, more patients with no retinal fluid, and shorter time to CRT <300 µm) than aflibercept 2 mg, with similar BCVA gains

These findings collectively suggest that aflibercept 8 mg may provide additional anatomic benefits over aflibercept 2 mg in patients with DME who need more frequent dosing (~10%) while it may decrease treatment burden in those who do not require more frequent dosing (~90%) when compared with aflibercept 2 mg

PHOTON Study Design

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DME

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)

Key secondary endpoint:
Proportion of patients with ≥2-step improvement in DRSS at Week 48

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

[a]Treatment naive and previously treated.
2q8, aflibercept 2 mg every 8 weeks after 5 initial monthly doses; 8q12 and 8q16, aflibercept 8 mg every 12 or 16 weeks after 3 initial monthly doses; BCVA, best-corrected visual acuity; DME, diabetic macular edema; DRSS, Diabetic Retinopathy Severity Scale.

PHOTON: Dosing Schedule and Dose Regimen Modifications in Year 1

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	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*

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

AND

- >50-micron increase in CRT

*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

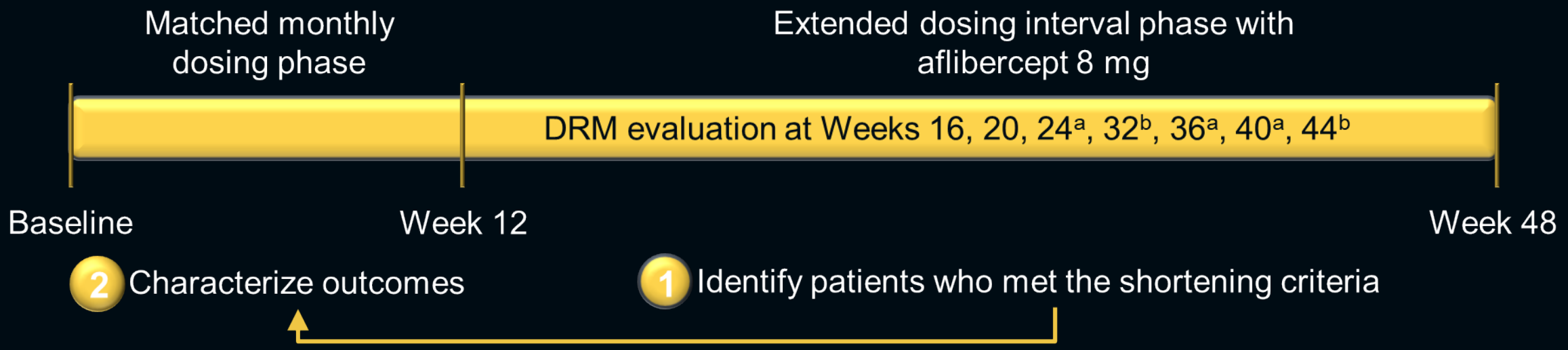
Week 32 and 44 for 8q12 and Week 36[a] and 40 for 8q16: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

Stippled boxes = initial treatment phase; X = active injection; o = sham injections. Note: Figure does not reflect all dosing options once a patient is shortened.
[a]At Week 36, patients on 8q16 who were previously shortened to Q12 could have been shortened to Q8.
CRT, central retinal thickness; DRM, dose regimen modification; Q8, every 8 weeks, Q12, every 12 weeks; Wk, Week.

Objective

DME

- This post hoc analysis aimed to characterize visual and anatomic outcomes of patients with DME over the matched dosing phase through Week 12 among patients who did or did not meet the dosing interval shortening criteria any time from Week 16 through Week 48



[a]For patients only in the 8q16 group.
[b]For patients only in the 8q12 group.

Methods

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- Patients in the **8q12** and **8q16** groups who met the shortening criteria in any DRM evaluation visit from Week 16 through Week 48 had their dosing intervals shortened
  - Patients in the **2q8** group who hypothetically met shortening criteria from Week 16 to Week 48 continued with every 8-week dosing
- Patients who did not meet the shortening criteria any time continued with their randomized dosing intervals through Week 48, but were included in this analysis
- Key outcomes were assessed in both subgroups of patients as follows:
  - Mean change in BCVA and CRT from baseline through Week 12
  - Proportion of patients with no retinal fluid (IRF, SRF) at Week 12
  - Time to and proportion of patients who achieved CRT <300 µm through Week 48
- The hazard ratio for the time to first CRT <300 µm was calculated using a Cox model, with stratification for geographic region (Japan vs rest of world), baseline CRT category (<400 µm vs ≥400 µm), and prior DME treatment
  - *P* values were calculated via stratified log-rank test comparing 2q8 versus 8q12 and 8q16
  - All analyses were descriptive, and *P* values were considered nominal

IRF, intraretinal fluid; SRF, subretinal fluid.

Proportion of Patients Who Did Versus Did Not Meet Shortening Criteria

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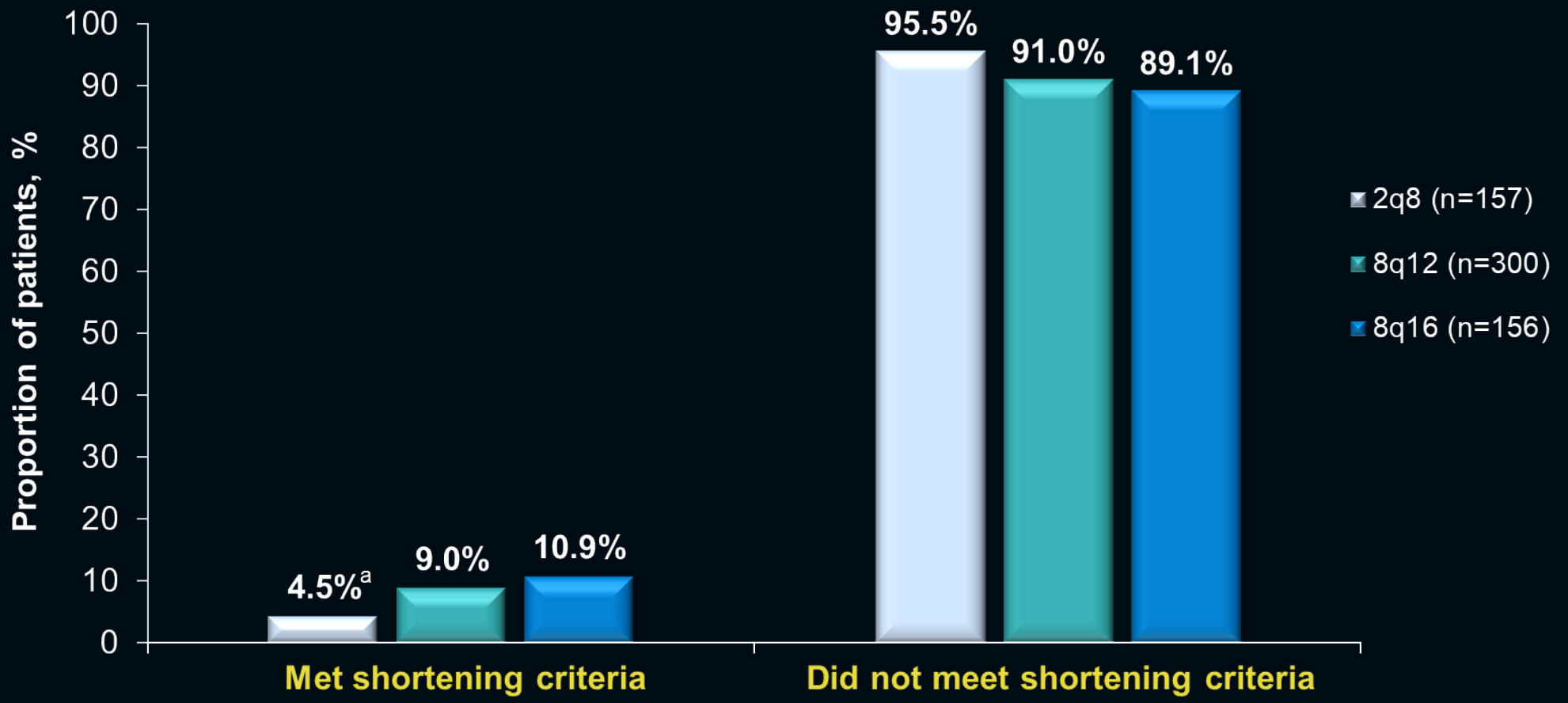


FAS, patients who completed Week 48 visit.
FAS, full analysis set
[a]Hypothetically shortened.

Demographics

DME

	Met shortening criteria			Did not meet shortening criteria		
	2q8 (n=7)	8q12 (n=27)	8q16 (n=17)	2q8 (n=150)	8q12 (n=273)	8q16 (n=139)
Age, years, mean (SD)	57.4 (10.7)	59.1 (13.9)	60.1 (9.9)	63.2 (9.6)	62.2 (10.9)	62.0 (9.6)
Female, n (%)	1 (14.3)	7 (25.9)	5 (29.4)	69 (46.0)	99 (36.3)	57 (41.0)
Hispanic or Latino, n (%)	1 (14.3)	1 (3.7)	1 (5.9)	29 (19.3)	44 (16.1)	32 (23.0)
Race, n (%)						
White	6 (85.7)	19 (70.4)	15 (88.2)	99 (66.0)	190 (69.6)	107 (77.0)
Asian	1 (14.3)	4 (14.8)	2 (11.8)	29 (19.3)	43 (15.8)	20 (14.4)
Black or African American	0 (0.0)	4 (14.8)	0 (0.0)	15 (10.0)	28 (10.3)	9 (6.5)

FAS, patients who completed Week 48 visit.
SD, standard deviation.

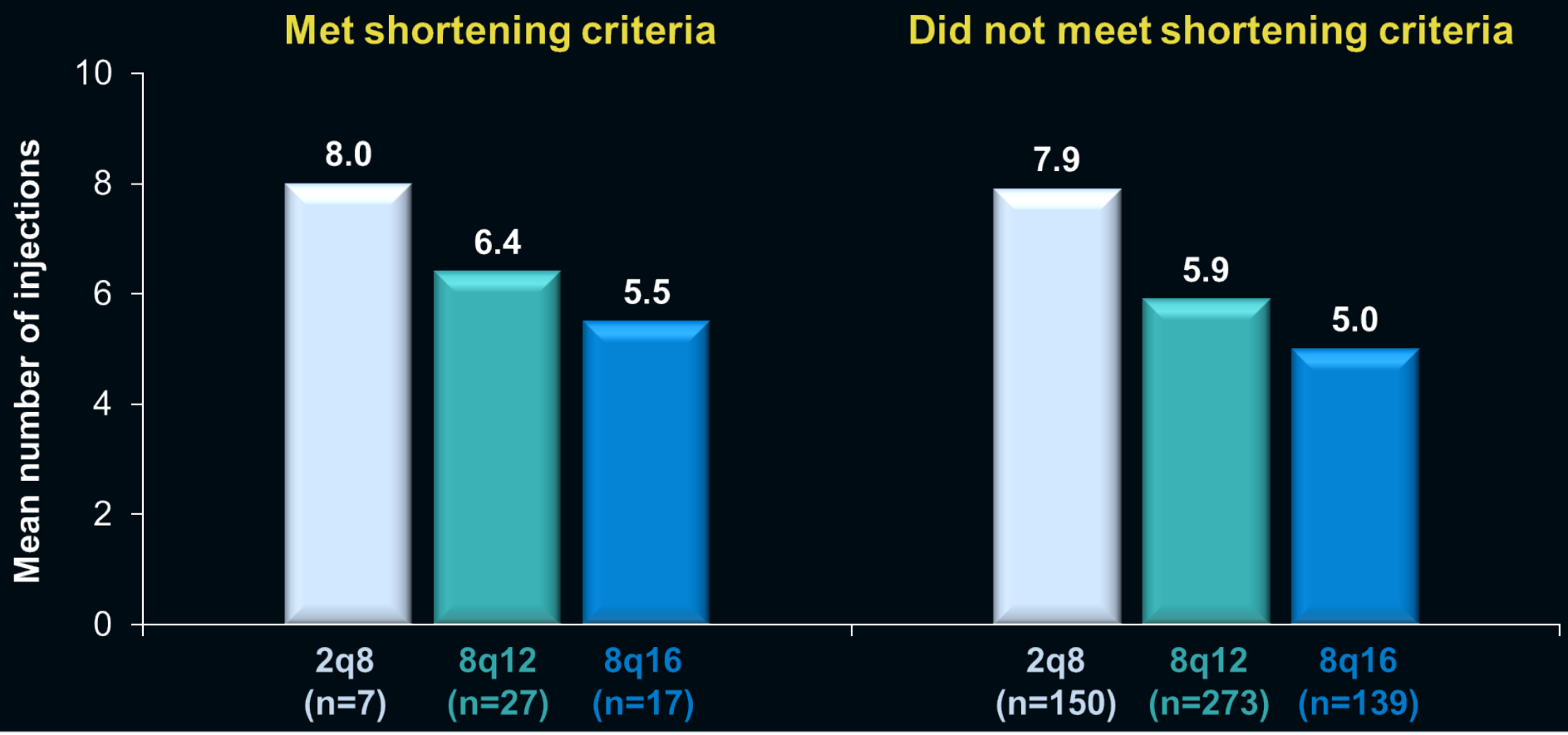
Baseline Characteristics

DME

	Met shortening criteria			Did not meet shortening criteria		
	2q8 (n=7)	8q12 (n=27)	8q16 (n=17)	2q8 (n=150)	8q12 (n=273)	8q16 (n=139)
BMI, kg/m^2, mean (SD)	31.1 (4.2)	29.3 (6.6)	30.5 (4.8)	29.8 (6.7)	30.3 (6.1)	31.1 (6.3)
Duration of diabetes, years, mean (SD)	19.9 (11.8)	11.1 (9.7)	15.8 (11.0)	15.6 (10.0)	15.5 (10.1)	15.6 (10.5)
HbA1c, %, mean (SD)	8.4 (1.1)	7.8 (1.4)	7.8 (1.9)	8.1 (1.5)	8.0 (1.5)	7.9 (1.5)
Prior DME treatment, n (%)	5 (71.4)	15 (55.6)	8 (47.1)	66 (44.0)	116 (42.5)	62 (44.6)
BCVA, ETDRS letters, mean (SD)	61.0 (7.9)	59.4 (10.0)	53.7 (12.8)	61.7 (11.3)	63.9 (10.1)	62.7 (11.2)
CRT, µm, mean (SD)	558.0 (149.4)	511.4 (117.5)	534.8 (134.3)	450.9 (137.2)	444.9 (129.8)	447.1 (112.5)

FAS, patients who completed Week 48 visit.
BMI, body mass index; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, hemoglobin A1c.M

Treatment Exposure Through Week 48



- Through Week 48, aflibercept 8 mg patients who met shortening criteria on average received more injections versus those who did not
- Aflibercept 2 mg patients could not be shortened and received the same mean number of injections regardless of whether they met shortening criteria

FAS, patients who completed Week 48 visit.

Mean Change in BCVA and CRT Through Week 12 in Patients Who Met Shortening Criteria

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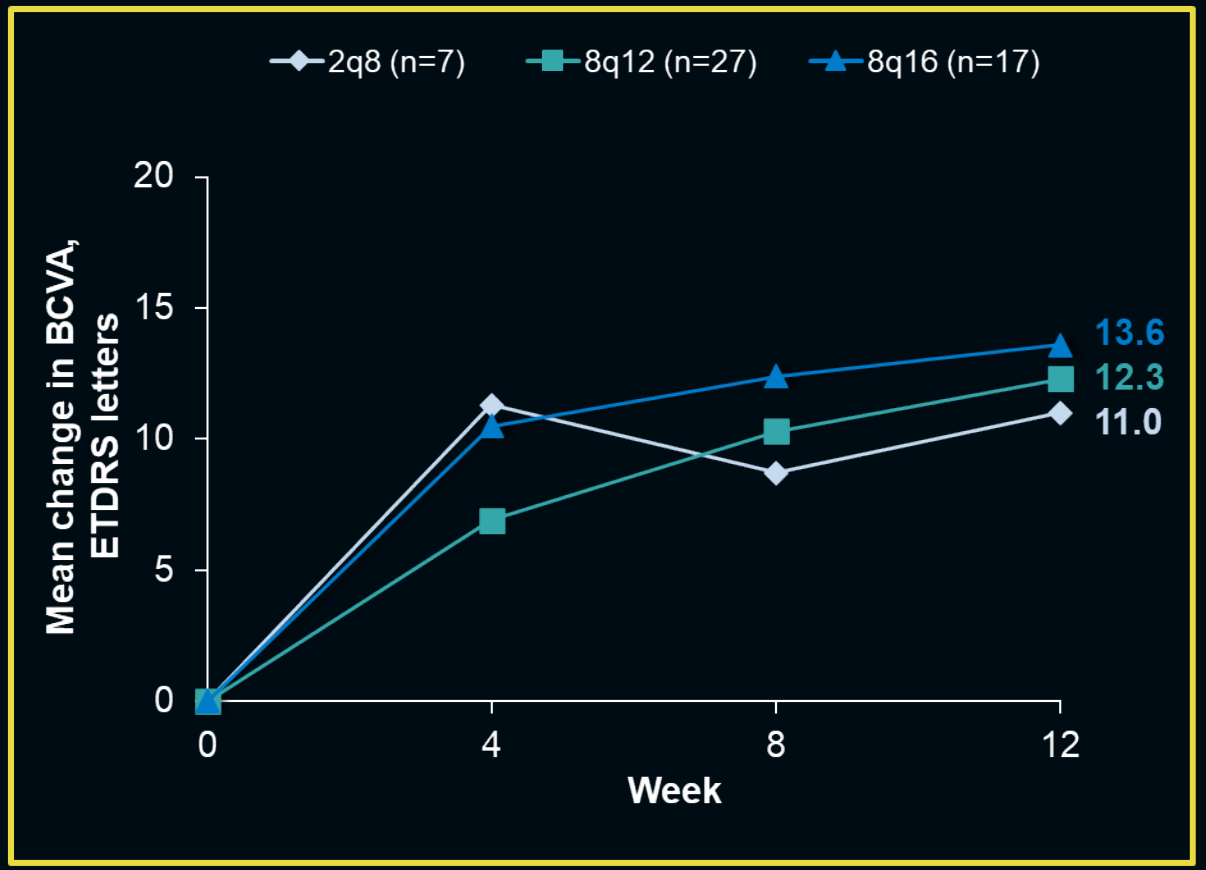
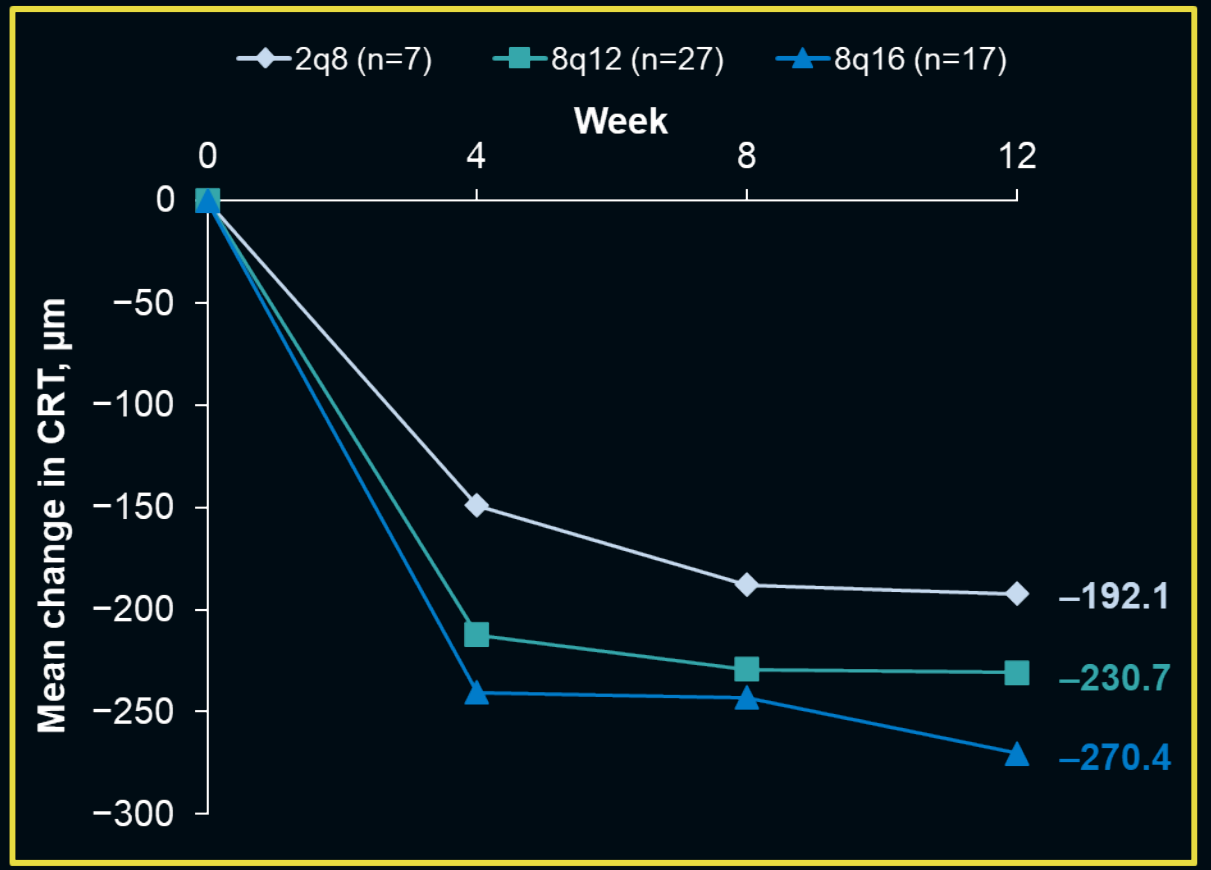
DME

BCVA



CRT



In patients who met shortening criteria, CRT improvements were relatively greater with aflibercept 8 mg than aflibercept 2 mg, with similar BCVA gains across treatment groups

FAS, patients who completed Week 48 visit, observed cases (data post-ICE were excluded).
ICE, intercurrent events.

Mean Change in BCVA and CRT Through Week 12 in Patients who Did Not Meet Shortening Criteria

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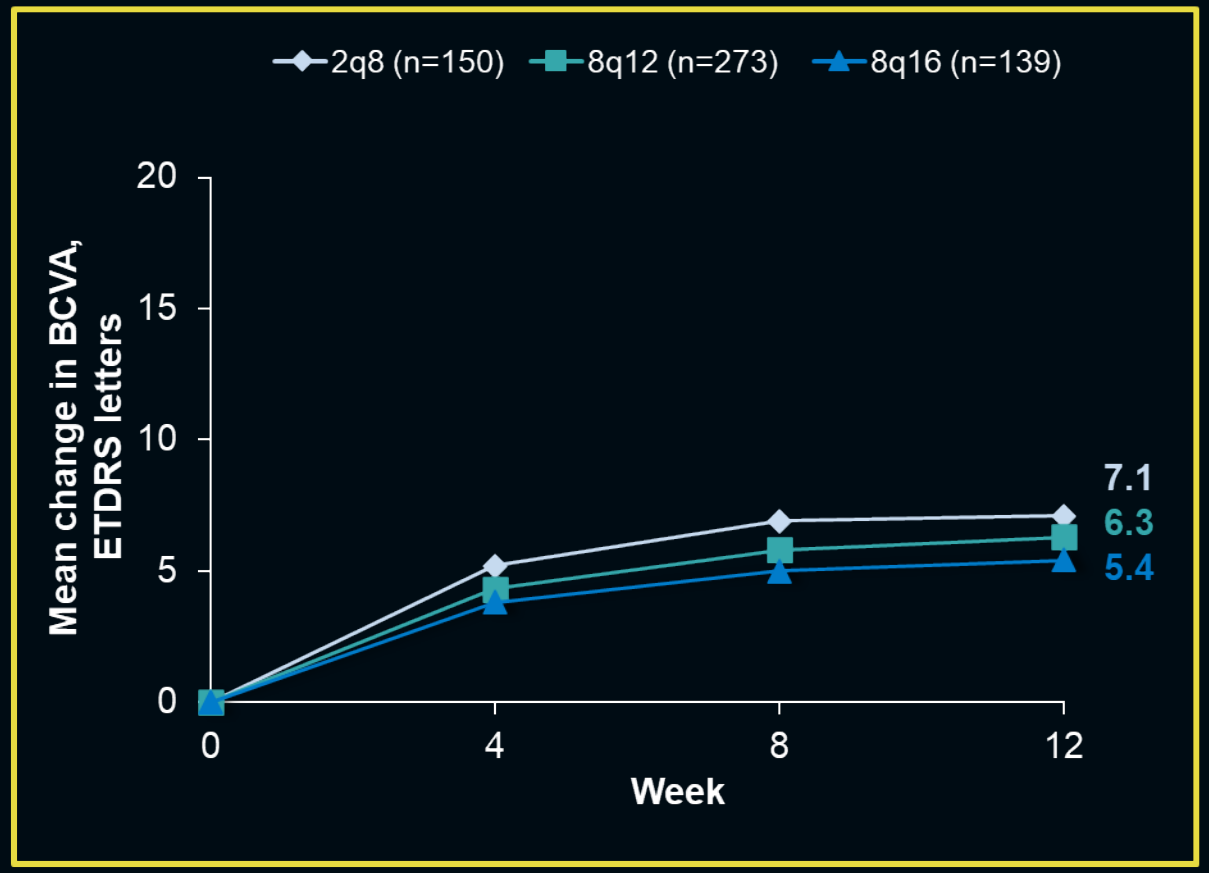
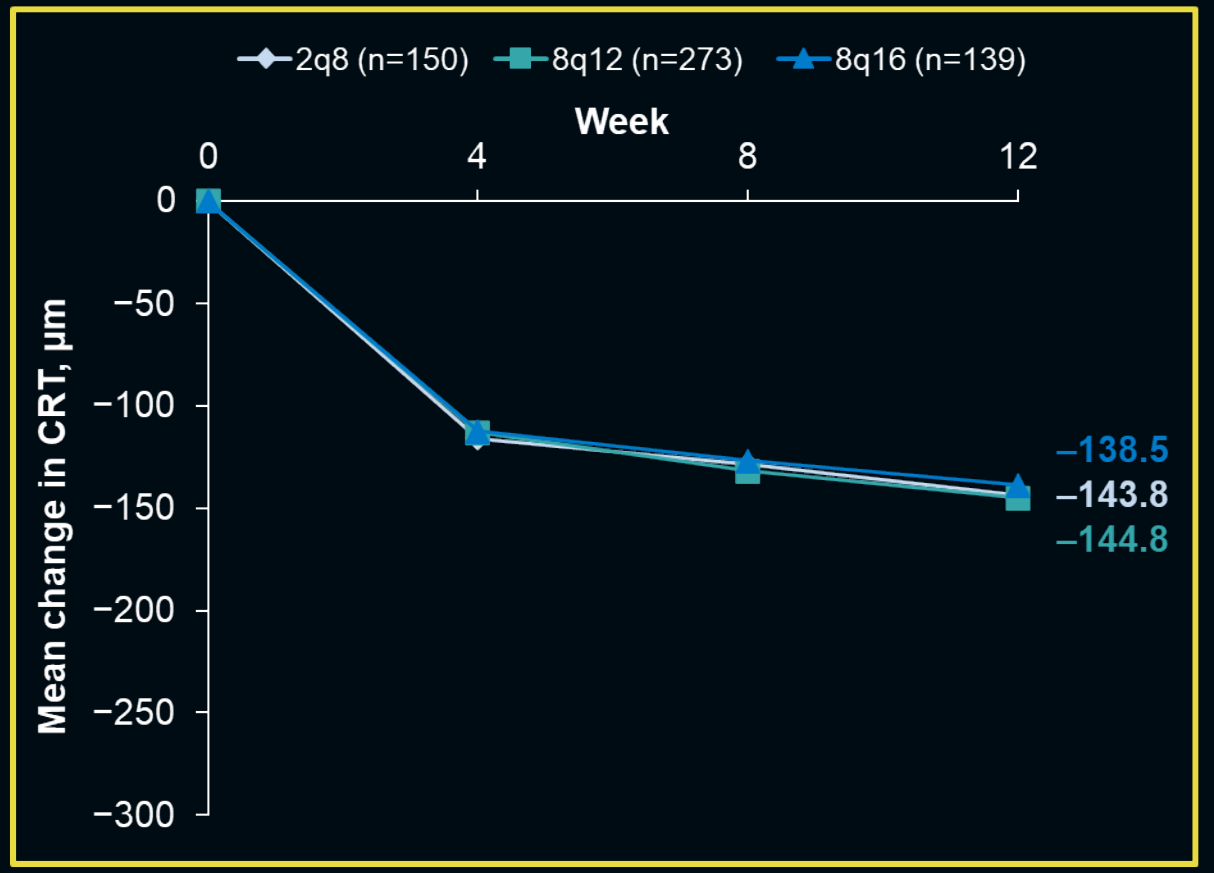
DME

BCVA



CRT



In patients who did not meet shortening criteria, BCVA and CRT improvements were comparable across all treatment groups

FAS completing Week 48, observed cases (data post-ICE were excluded).

Proportion of Patients With no IRF and SRF in the Center Subfield at Baseline and Week 12

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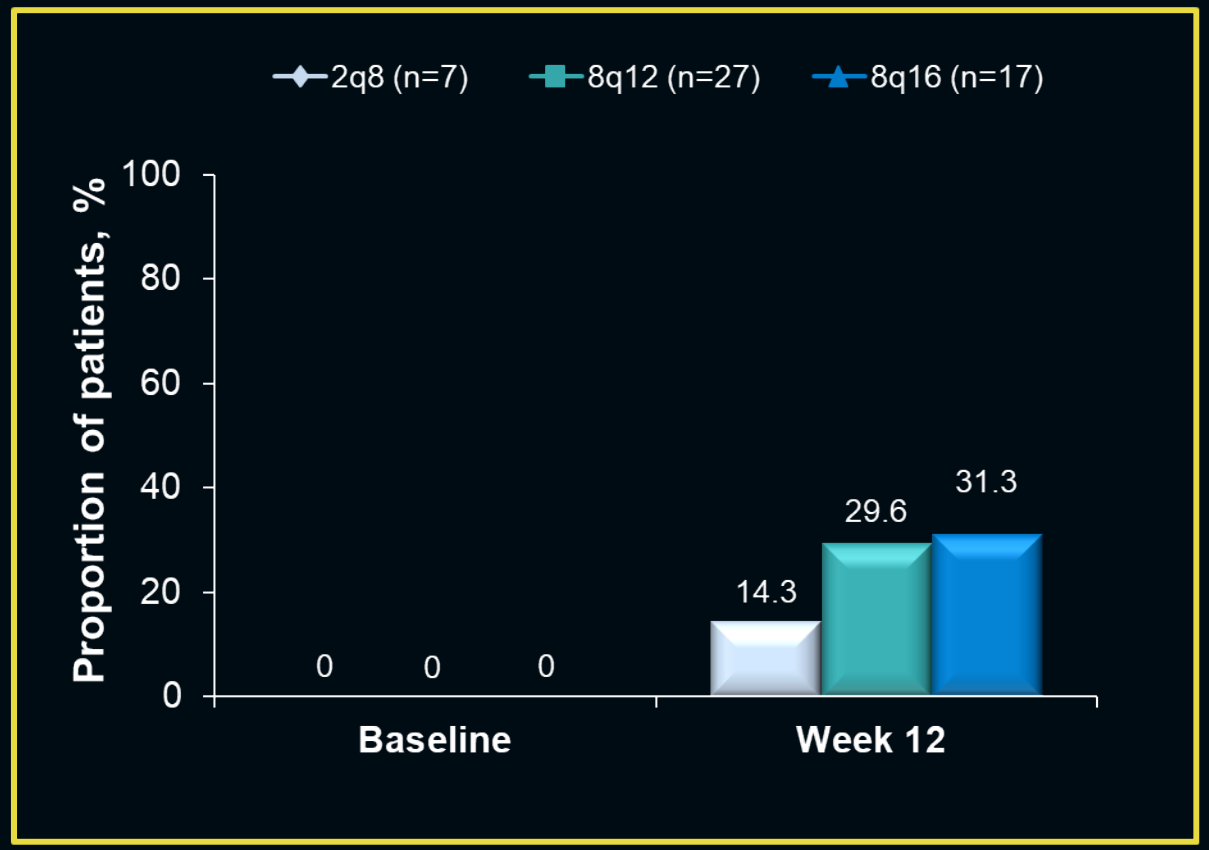
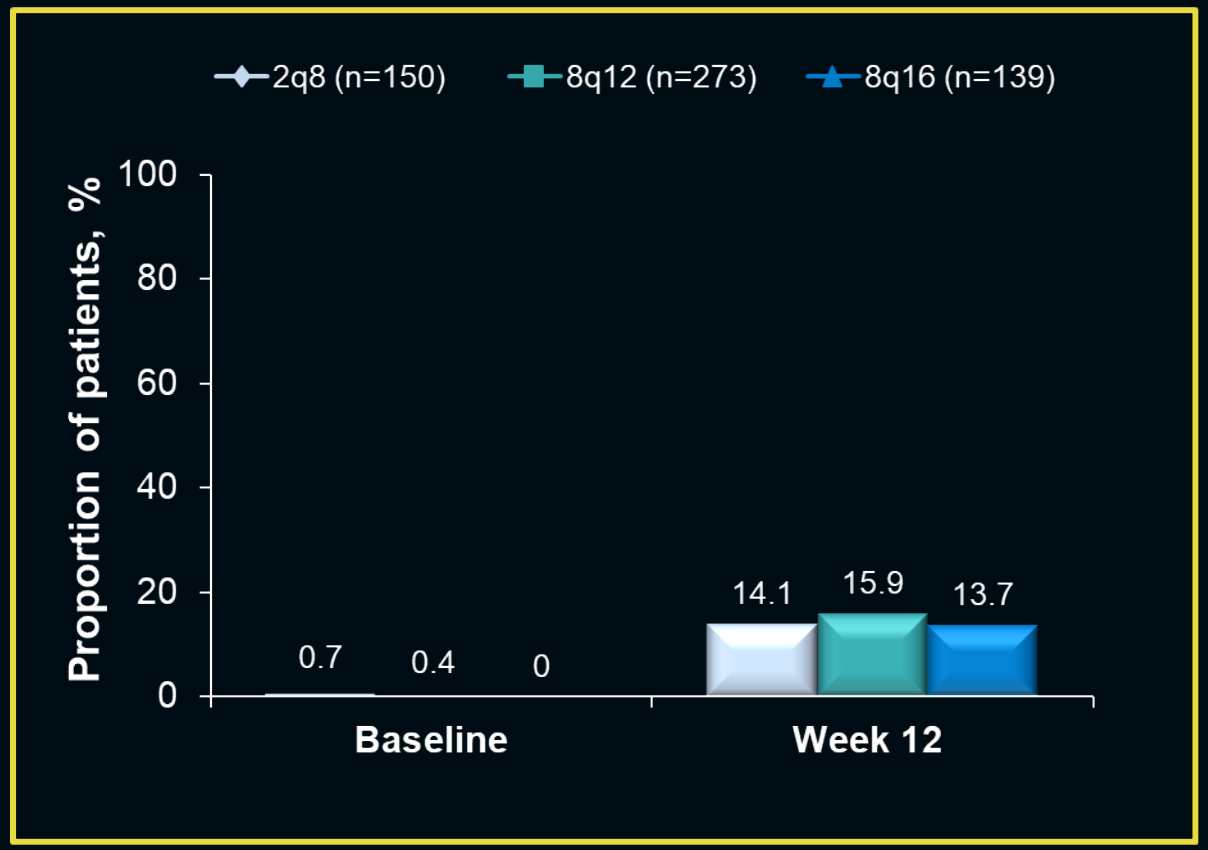
DME

Met shortening criteria



Did not meet shortening criteria



In patients who met shortening criteria, a relatively greater proportion of patients treated with aflibercept 8 mg had no retinal fluid at Week 12

FAS, patients who completed Week 48 visit, observed cases (data post-ICE were excluded).

Proportion of Patients With no IRF in the Center Subfield at Baseline and Week 12

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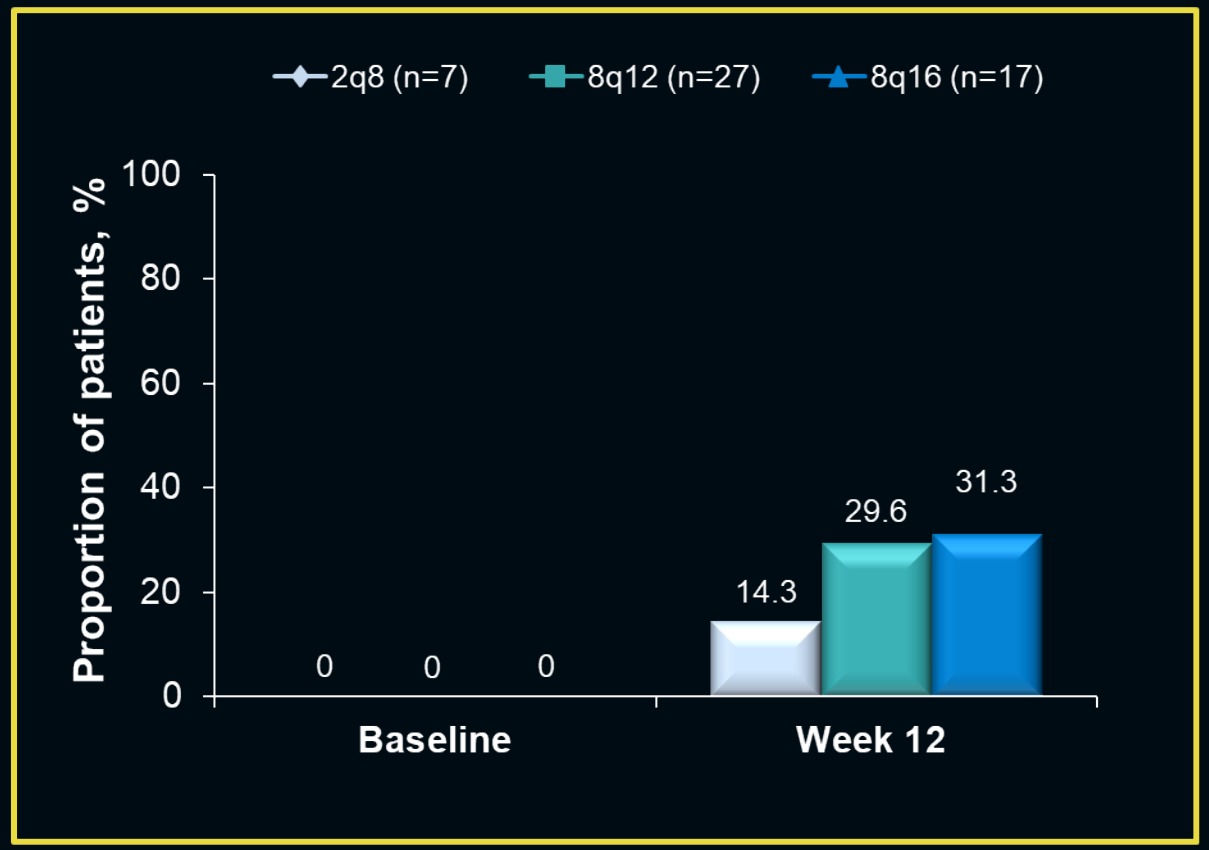
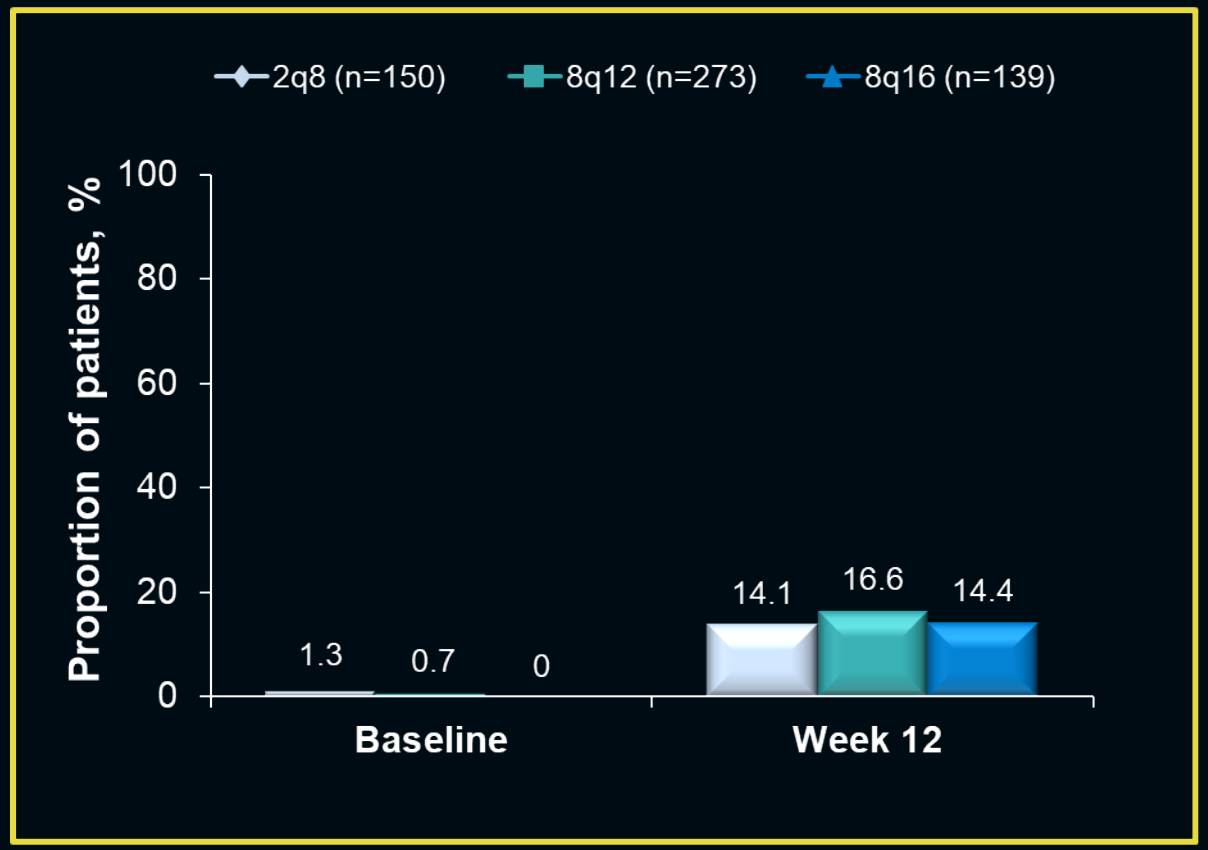
DME

Met shortening criteria



Did not meet shortening criteria



In patients who met shortening criteria, a relatively greater proportion of patients treated with aflibercept 8 mg had no intraretinal fluid at Week 12

FAS, patients who completed Week 48 visit, observed cases (data post-ICE were excluded).

Proportion of Patients With no SRF in the Center Subfield at Baseline and Week 12

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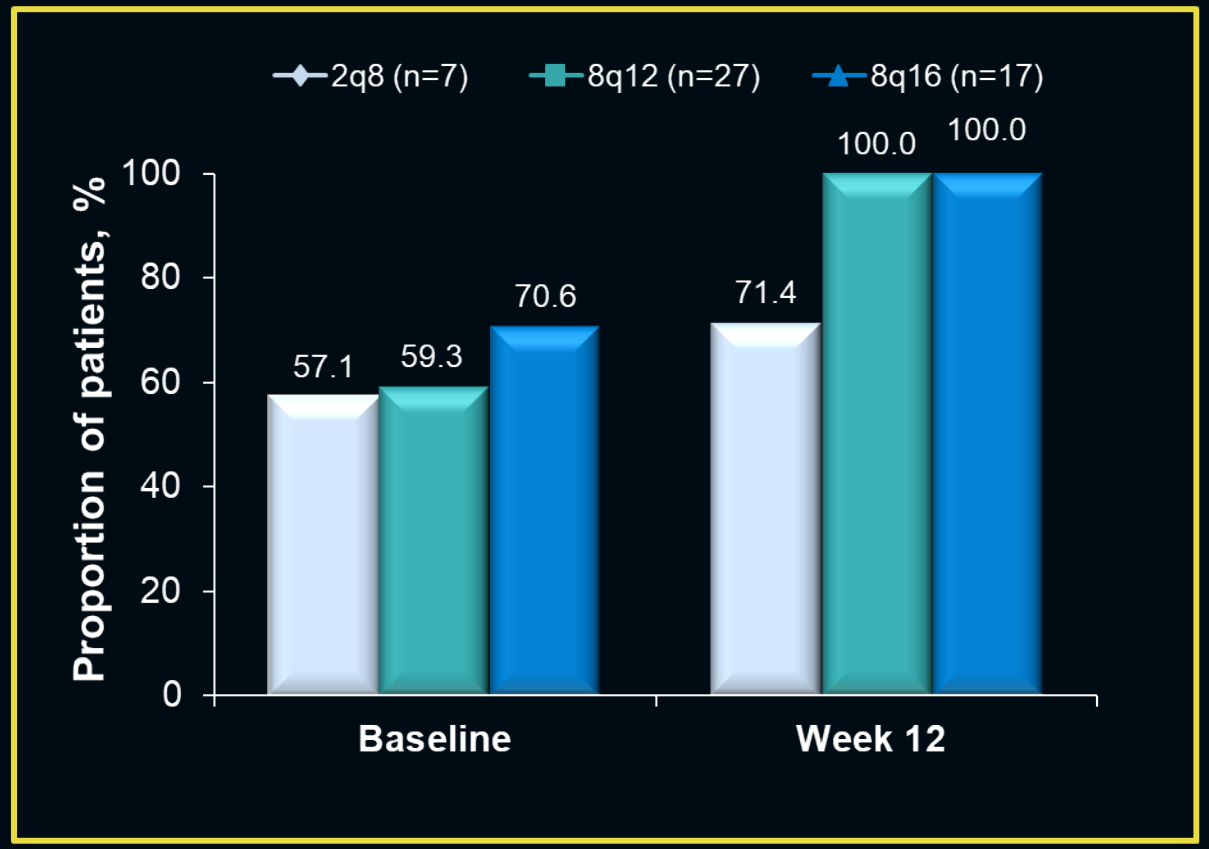
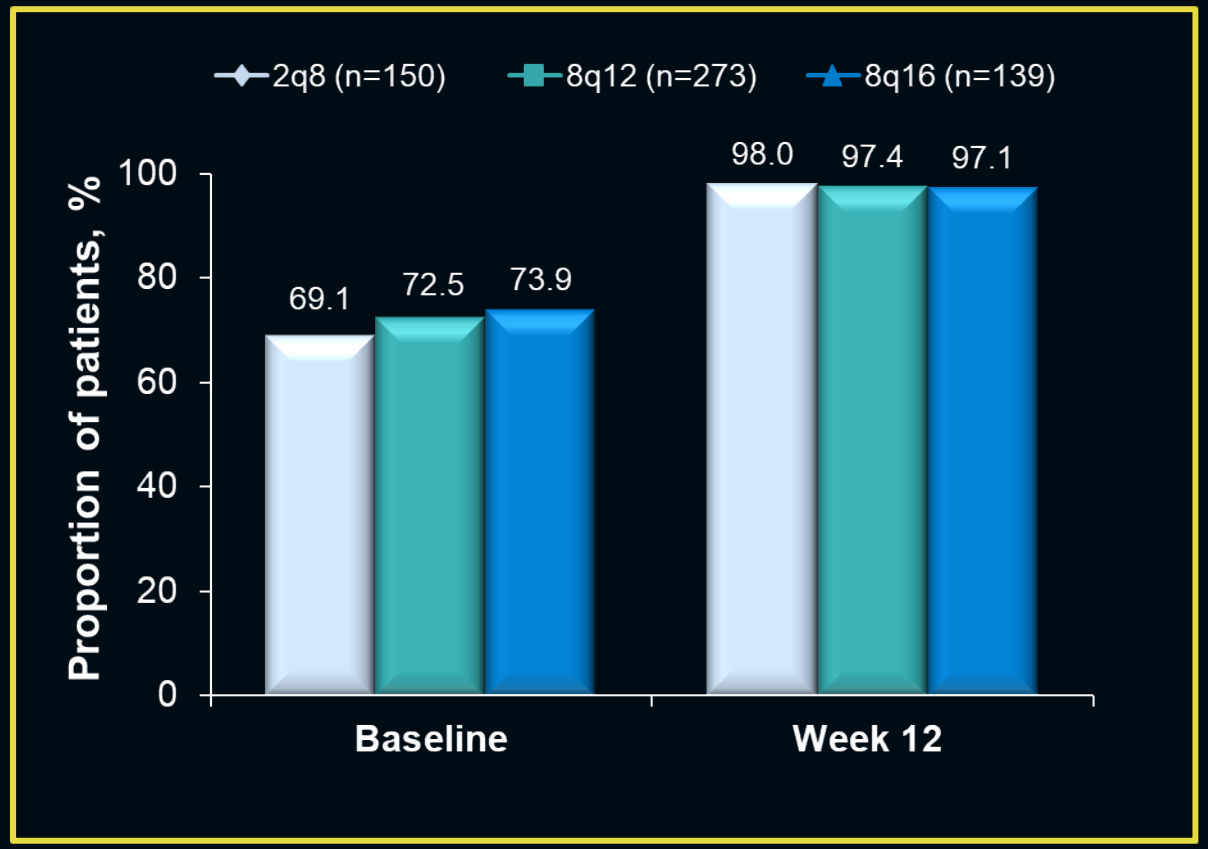
DME

Met shortening criteria



Did not meet shortening criteria

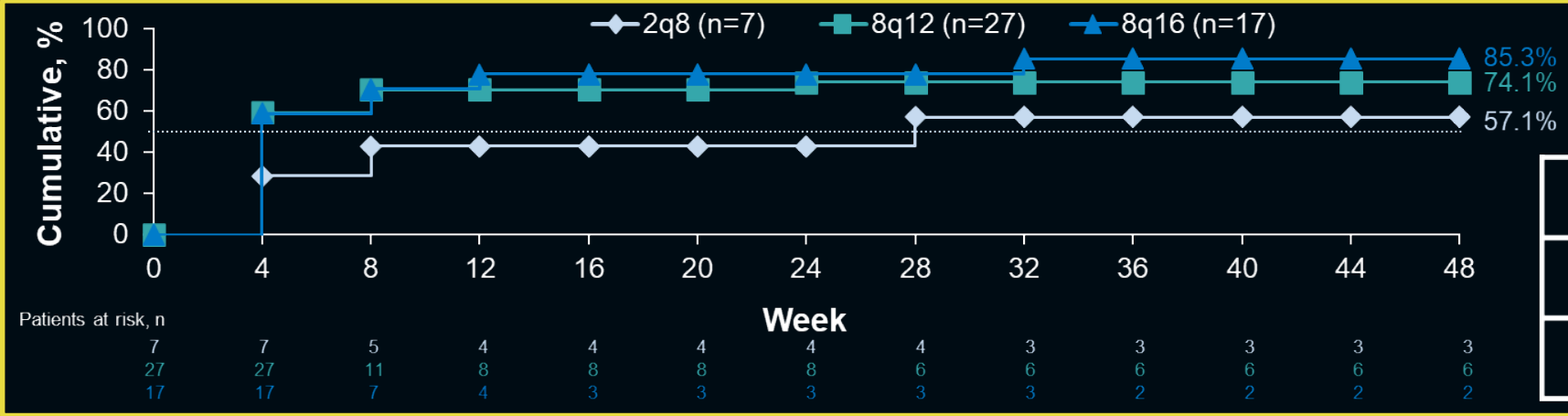


In patients who met shortening criteria, a relatively greater proportion of patients treated with aflibercept 8 mg had no subretinal fluid at week 12

FAS, patients who completed Week 48 visit, observed cases (data post-ICE were excluded).

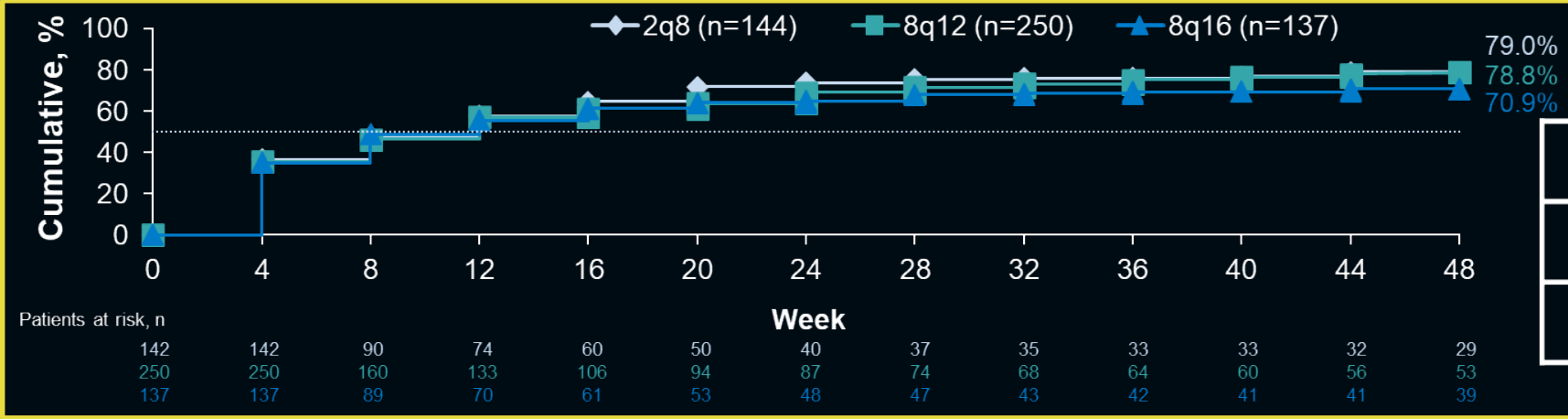
Time to CRT <300 µm Through Week 48[a]

Met shortening criteria



	2q8 (n=7)	8q12 (n=27)	8q16 (n=17)
Median time, weeks	28	4	4
Hazard ratio (95% CI)	-	1.71 (0.56, 5.18)	1.86 (0.58, 5.94)
Nominal *P*-value	-	0.3436	0.2938

Did not meet shortening criteria

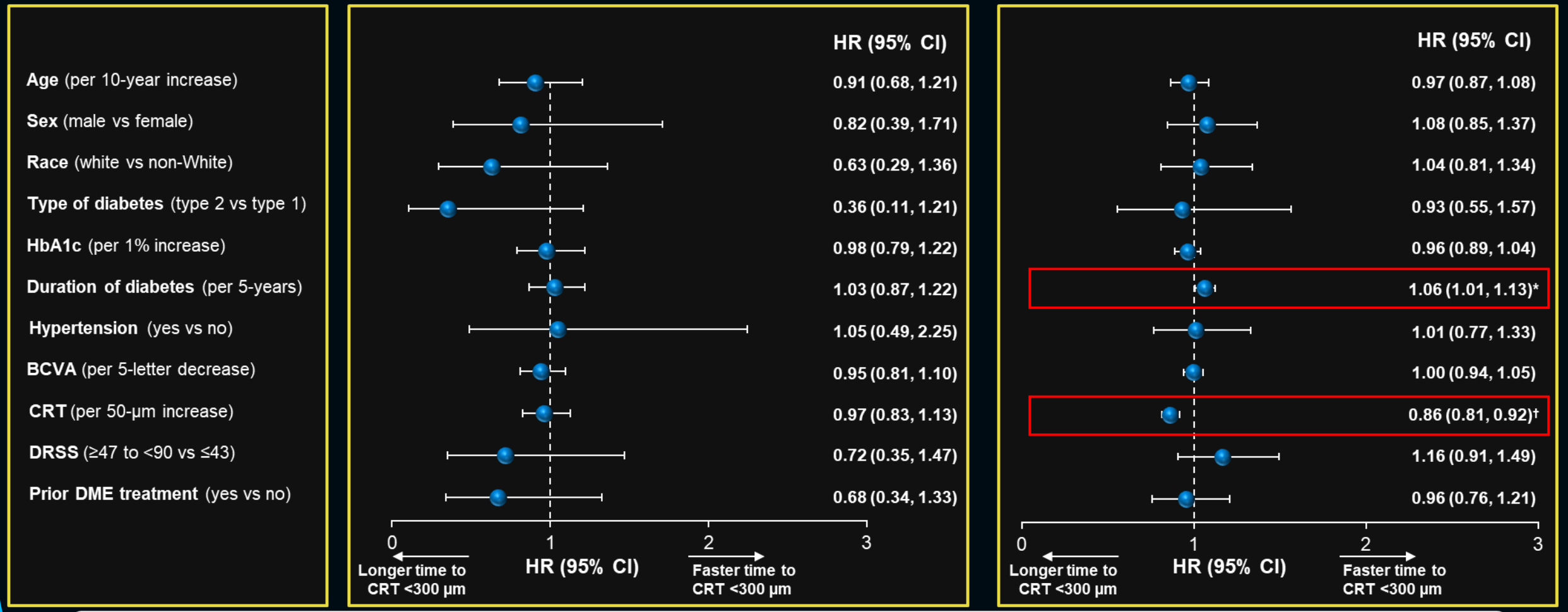


	2q8 (n=144)	8q12 (n=250)	8q16 (n=137)
Median time, weeks	12	12	12
Hazard ratio (95% CI)	-	0.99 (0.78, 1.25)	0.86 (0.65, 1.13)
Nominal *P*-value	-	0.9022	0.2654

Patients treated with aflibercept 8 mg who met shortening criteria achieved CRT <300 µm relatively faster than those treated with aflibercept 2 mg in the same subgroup

FAS, patients who completed Week 48 visit. [a]Patients with baseline CRT ≥300 µm.

Univariate Analysis of Baseline Factors Associated With Time to CRT <300 µm



Greater CRT at baseline was associated with longer time to CRT <300 µm, while longer duration of diabetes was associated with faster time to CRT <300 µm in the subgroup of 8-mg treated patients who did not meet shortening criteria

FAS, patients who completed the Week 48 visit. Data for patients in the 8q12 and 8q16 groups were pooled. Inferential statistics were estimated using Cox regression model with the specified baseline variable as the covariate stratified by study.

Multivariate Analysis of Baseline Factors Associated With Time to CRT <300 µm

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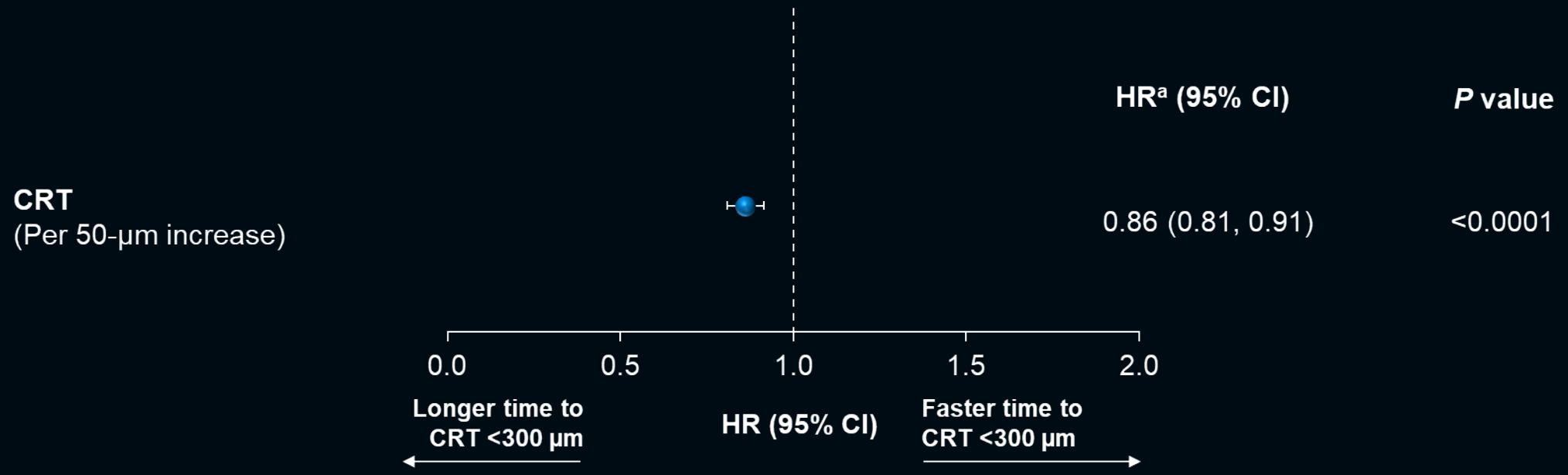
DME

Did not meet shortening criteria



Higher baseline CRT was associated with longer time to CRT <300 µm in the subgroup of patients who did not meet the shortening criteria

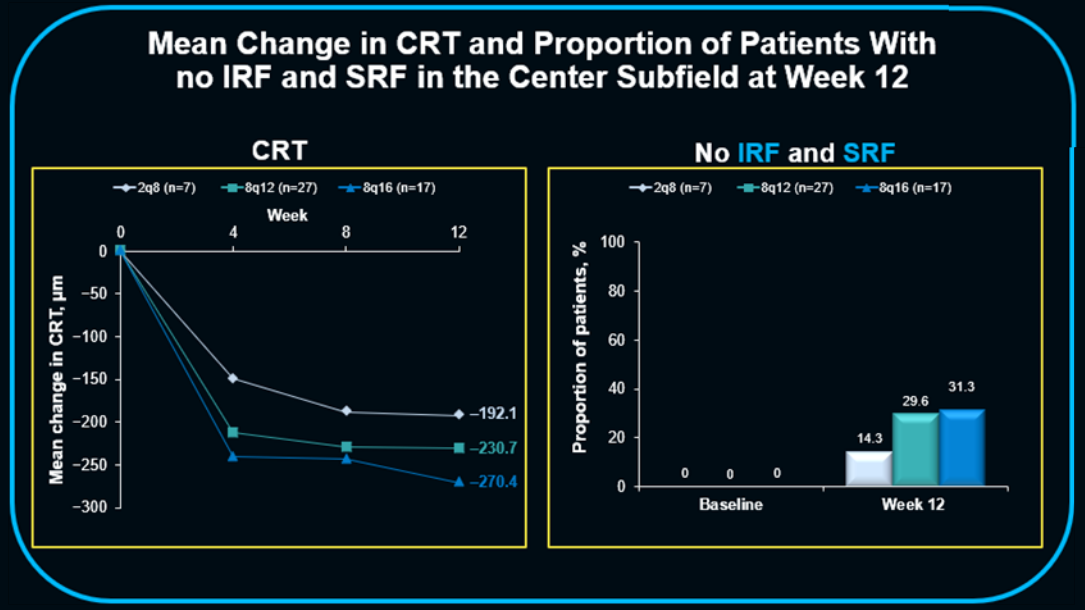
FAS, patients who completed the Week 48 visit. Data for patients in the 8q12 and 8q16 groups were pooled.
[a]The HR was estimated using a Cox regression model with duration of diabetes (per 5-year increase), BMI (per 5-kg/m^2 increase), and CRT (per 50-µm increase) as the covariates.

Limitations

- This was a post hoc analysis with no adjustment for multiplicity, and findings should be considered hypothesis-forming only
- The number of patients who met shortening criteria was low, limiting the interpretation of the results

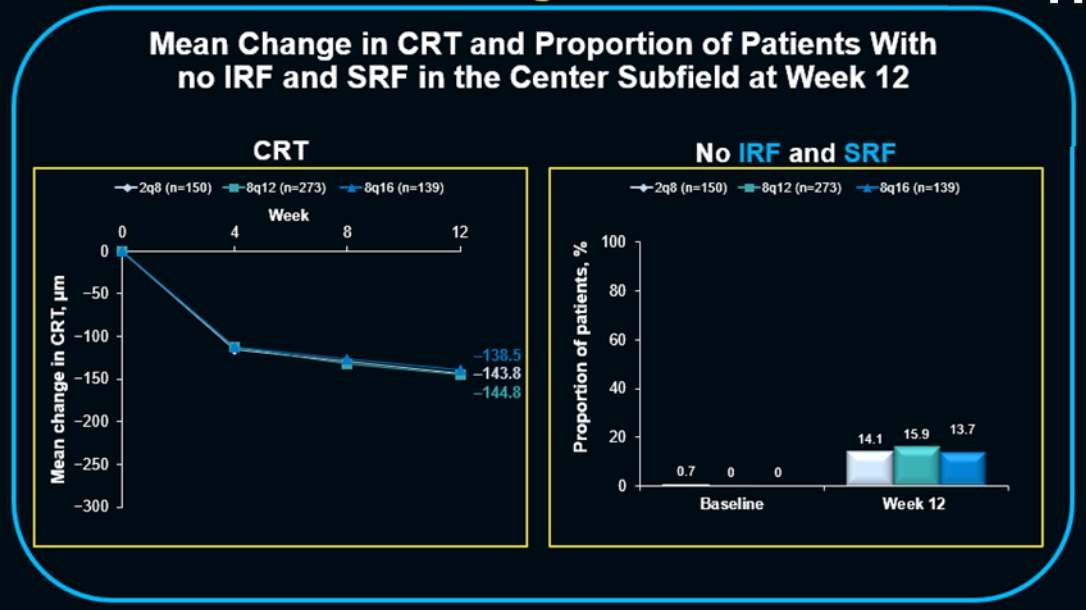
Conclusions

In patients who met shortening criteria:



- Aflibercept 8 mg provided relatively greater anatomic benefit (greater CRT improvement, more patients with no retinal fluid, and shorter time to CRT <300 µm) than aflibercept 2 mg, with similar BCVA gains

In patients who did not meet shortening criteria:



- Aflibercept 8 mg and 2 mg provided similar CRT reductions and BCVA gains, proportions with no retinal fluid, and time to CRT <300 µm

- **These findings suggest that aflibercept 8 mg may provide additional anatomic benefits over aflibercept 2 mg in patients with DME who need more frequent dosing (~10%) while it may decrease treatment burden in those who do not require more frequent dosing (~90%), when compared with aflibercept 2 mg**