PULSAR subgroups defined by baseline BCVA, CRT, CNV and race: Similar Week 96 improvements with aflibercept 8 mg q12 weeks or longer vs 2 mg q8 weeks

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- **NM:** has no financial disclosure

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PULSAR: Multicenter, randomized, double-masked study

Patients with treatment-naïve nAMD, randomized at baseline

2q8
Aflibercept 2 mg every 8 weeks after 3 initial monthly injections
n=336

8q12
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections
n=335

8q16
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections
n=338

								YEAR 1												YEAR 2					
	Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
2q8	X	X	X		X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	–
8q12	X	X	X		o[a]	X[a]	o	o	X[a]	o	o	X[a]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	–
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	–

Primary endpoint at W48:
Mean change in BCVA (non-inferiority)

End of study at W96 with optional ~1-year extension through W156

[a]DRM: Interval Shortening During Years 1 and 2

Criteria for interval shortening
- \>5-letter loss in BCVA compared with Week 12 due to persistent or worsening nAMD **AND**
- \>25 μm increase in CRT compared with Week 12, **OR** new foveal neovascularization, **OR** new foveal hemorrhage

- 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 assigned dosing interval was q8

[b]DRM: Interval Extension During Year 2

Criteria for interval extension
- \<5-letter loss in BCVA compared with Week 12 **AND**
- No fluid at the central subfield on OCT **AND**
- No new foveal hemorrhage or foveal neovascularization

- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
    - The maximum assigned dosing interval was q24

Figure does not reflect all dosing options once a patient's dosing interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injections.
q8, every 8 weeks; **q24**, every 24 weeks; **BCVA**, best-corrected visual acuity; **CRT**, central retinal thickness; **DRM**, dose regimen modification; **nAMD**, neovascular age-related macular degeneration; **OCT**, optical coherence tomography; **W**, week.

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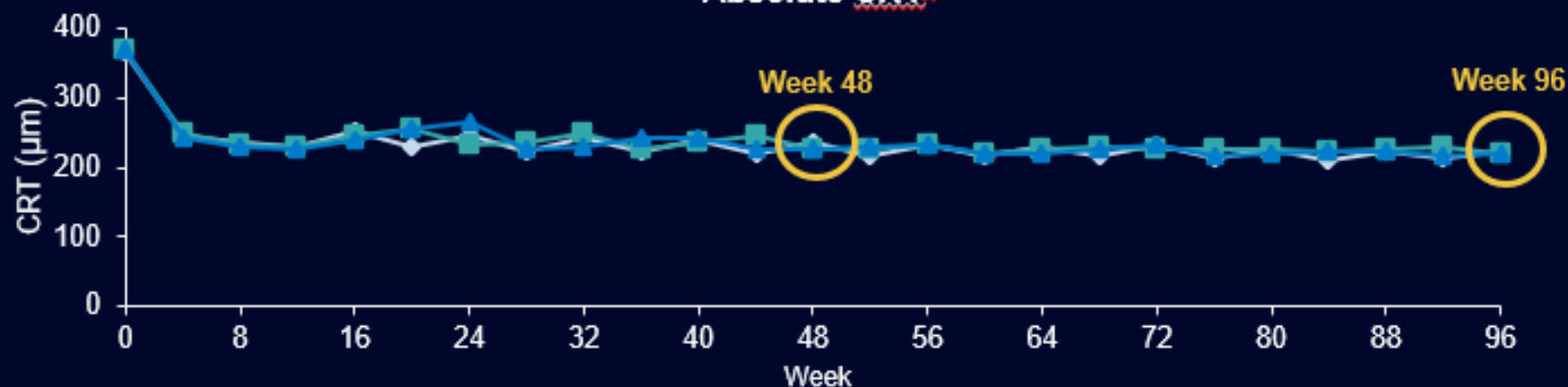# BCVA and CRT through Week 96: Comparable outcomes with aflibercept 8 mg and 2 mg overall

BCVA change from BL[a]

BCVA (ETDRS letters)
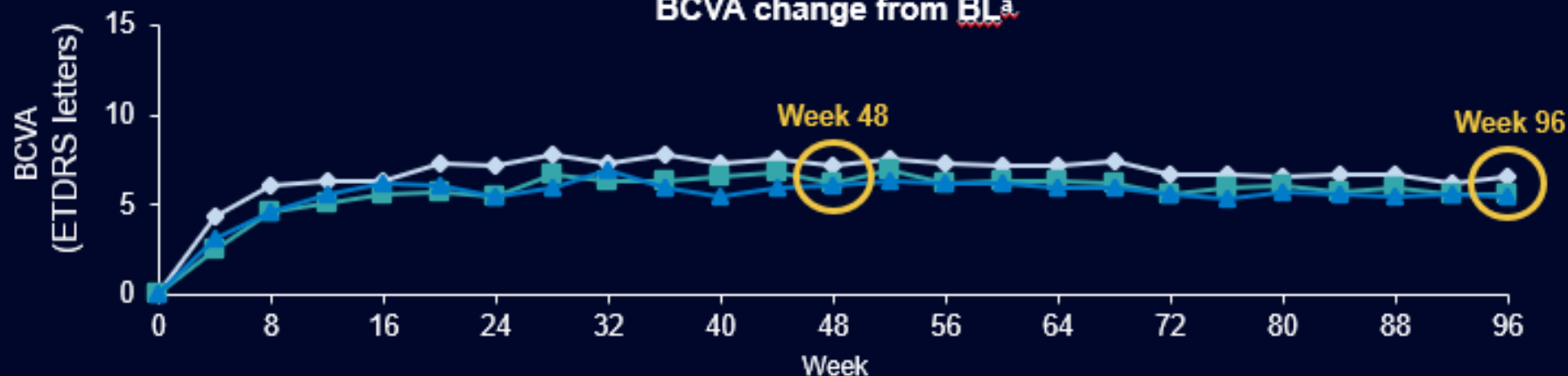
Week 48

Week 96

Week

LS means[a,b]	Week 48	Week 96
2q8	+7.0	+6.6
8q12	+6.1	+5.6
8q16	+5.9	+5.5

Absolute CRT[c]

CRT (µm)

Week 48

Week 96

Week

LS means[a,b]	Week 48	Week 96
2q8	−136	−147
8q12	−147	−152
8q16	−147	−149

FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [a]LS mean values (data post-ICE were censored); [b]LS means were generated using MMRM, with baseline BCVA measurement (for BCVA analysis) or BL CRT measurement (for CRT analysis) as a covariate, and treatment group (aflibercept 2q8, 8q12, 8q16), visit, and stratification variables (geographic region [Japan vs. Rest of World] and BL BCVA [<60 vs. ≥60]) as fixed factors, and interaction terms for BL and visit and for treatment and visit. [c]Observed values.
BL, baseline; ETDRS, Early Treatment of Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

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Baseline characteristics

	2q8	8q12	8q16	All 8mg	Total
Randomized, n	336	335	338	673	1009
Age, years	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.6 (8.2)	74.5 (8.4)
Female, %	56.0	54.3	53.3	53.8	54.5
Race, %					
Asian	24.7	22.1	22.8	22.4	23.2
Black or African American	0.6	0.6	0	0.3	0.4
White	74.1	76.4	76.9	76.7	75.8
Not reported	0.6	0.6	0.3	0.4	0.5
BCVA, ETDRS letters	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.9 (12.9)	59.6 (13.3)
CRT, µm	367 (134)	370 (124)	371 (133)	371 (128)	370 (130)
CNV size, mm²	6.4 (5.0)	6.0 (4.8)	6.5 (5.5)	6.3 (5.2)	6.3 (5.1)
CNV type, %					
Minimally classic CNV	18.2	16.7	20.1	18.4	18.3
Occult-only CNV	57.1	58.8	55.0	56.9	57.0
Predominantly classic CNV	21.1	21.2	19.8	20.5	20.7

FAS. Data are mean (SD) unless otherwise indicated.
CNV, choroidal neovascularization; SD, standard deviation.

BCVA outcomes with aflibercept 8 mg and 2 mg at Week 96 are independent of BL BCVA

	BL BCVA ≤54	BL BCVA 55–73	BL BCVA ≥74
Mean (95% CI) BCVA (ETDRS letters) change from BL at Week 96	+11.7 (8.8, 14.7) +10.4 (7.0, 13.7) +6.5 (2.9, 10.0)	+5.9 (4.2, 7.6) +4.1 (2.1, 6.1) +5.9 (4.4, 7.5)	+1.5 (−0.8, 3.9) +0.9 (−2.6, 4.3) +1.1 (−2.1, 4.4)
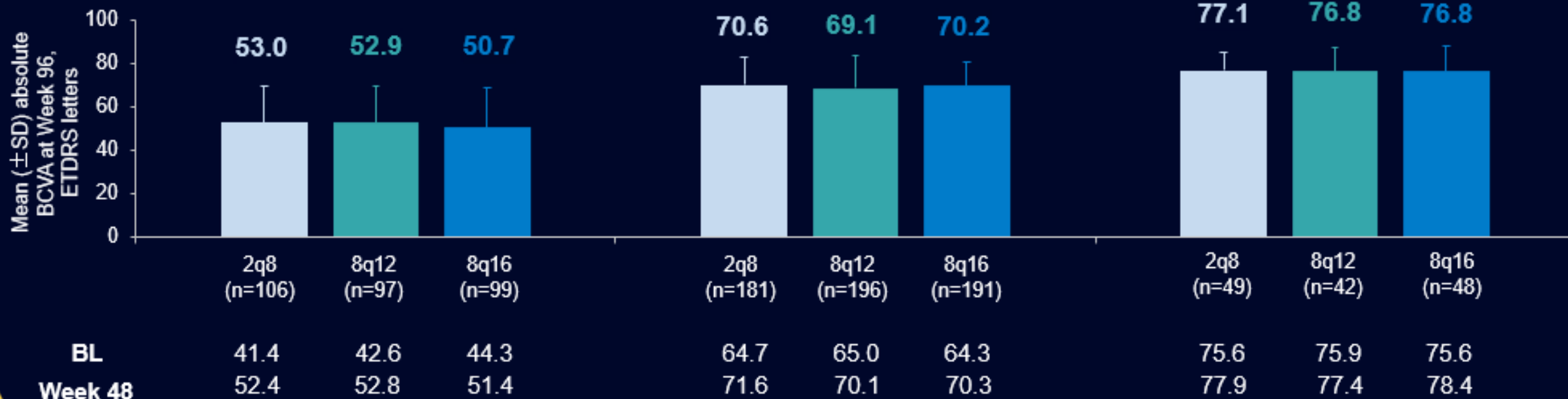
Mean (±SD) absolute BCVA at Week 96, ETDRS letters

BL BCVA ≤54
- 2q8 (n=106): 53.0
- 8q12 (n=97): 52.9
- 8q16 (n=99): 50.7

BL BCVA 55–73
- 2q8 (n=181): 70.6
- 8q12 (n=196): 69.1
- 8q16 (n=191): 70.2

BL BCVA ≥74
- 2q8 (n=49): 77.1
- 8q12 (n=42): 76.8
- 8q16 (n=48): 76.8

	2q8	8q12	8q16		2q8	8q12	8q16		2q8	8q12	8q16
BL	41.4	42.6	44.3		64.7	65.0	64.3		75.6	75.9	75.6
Week 48	52.4	52.8	51.4		71.6	70.1	70.3		77.9	77.4	78.4

CRT improvements with aflibercept 8 mg and 2 mg at Week 96 are independent of BL BCVA

	BL BCVA ≤54	BL BCVA 55—73	BL BCVA ≥74
Mean CRT (µm) change (95% CI) from BL at Week 96	−224 (−255, −193) −254 (−283, −224) −237 (−270, −205)	−115 (−129, −100) −109 (−121, −96) −112 (−126, −97)	−58 (−75, −42) −76 (−101, −51) −82 (−107, −58)

Mean (±SD) absolute CRT at Week 96, µm

	BL BCVA ≤54			BL BCVA 55—73			BL BCVA ≥74		
	2q8 (n=106)	8q12 (n=97)	8q16 (n=99)	2q8 (n=181)	8q12 (n=196)	8q16 (n=190)	2q8 (n=48)	8q12 (n=42)	8q16 (n=47)
(bar value)	211	201	220	230	231	225	236	240	238
BL	439	454	457	344	339	338	294	322	322
Week 48	227	217	226	239	232	225	243	236	237

FAS, LOCF. N values for BL. Analyses were not adjusted for multiplicity or to allow for differences in BL CRT.
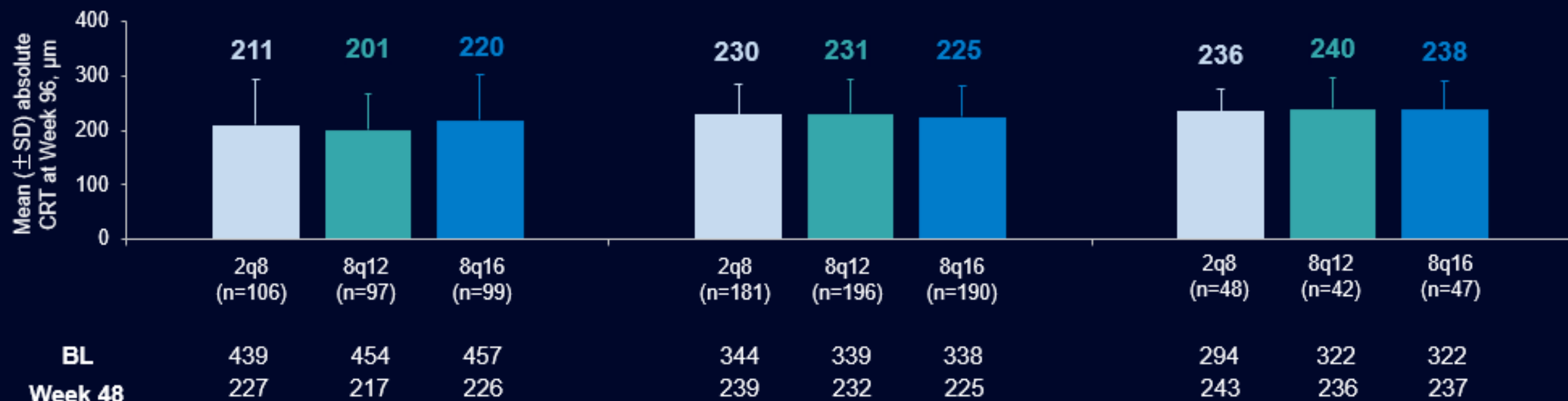
Last assigned treatment intervals at Week 96 categorized by BL BCVA

BL BCVA categories

≤54 ETDRS letters
(n=166)

11%
20%
20%
20%
29%
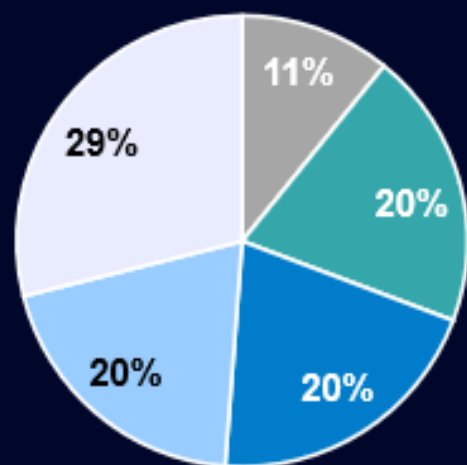
55–73 ETDRS letters
(n=338)

14%
15%
26%
18%
27%
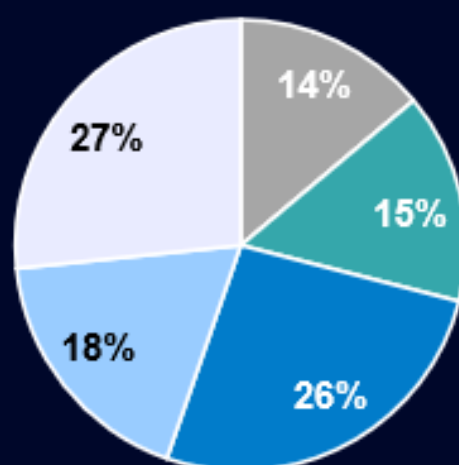
≥74 ETDRS letters
(n=79)
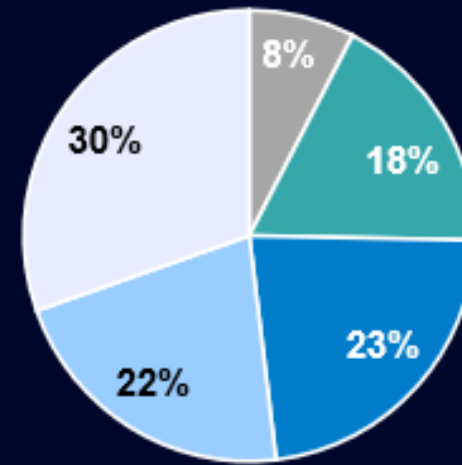
8%
18%
23%
22%
30%

All patients receiving aflibercept 8 mg

Last assigned treatment interval:　■ q8　■ q12　■ q16　■ q20　■ q24[a]

Data shown for patients who completed 96 weeks of treatment.
Values may not add up to 100% due to rounding.
[a]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period.

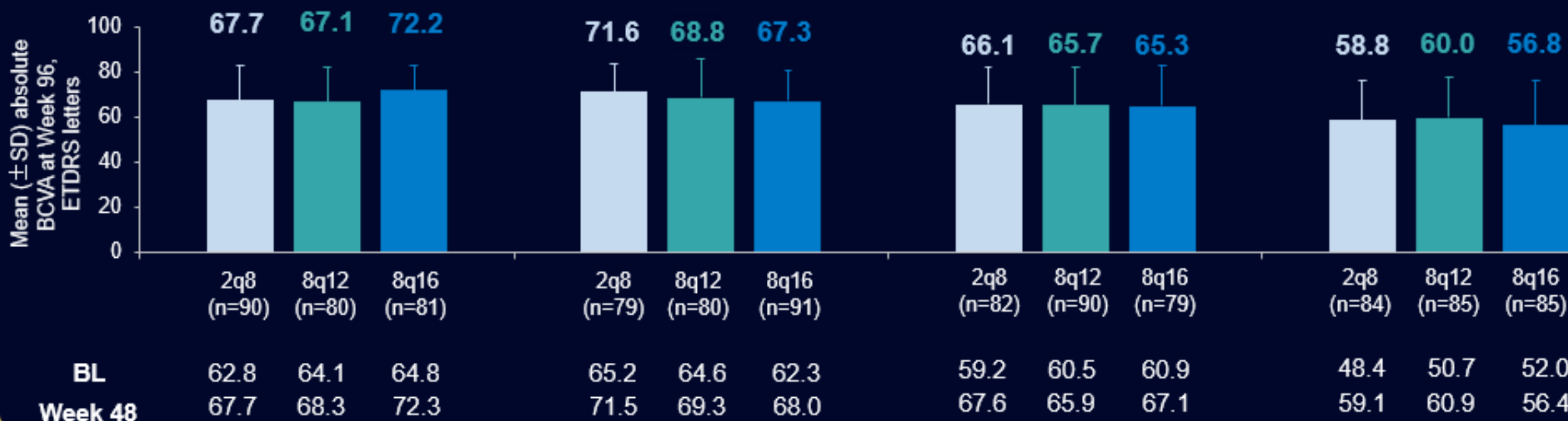# BCVA outcomes with aflibercept 8 mg and 2 mg at Week 96 are independent of BL CRT

	≤278 μm	279–343 μm	344–422 μm	≥423 μm
Mean (95% CI) BCVA (ETDRS letters) change from BL at Week 96	+4.8 (2.2, 7.4)	+6.3 (3.8, 8.8)	+6.9 (4.1, 9.7)	+10.4 (7.2, 13.6)
	+3.1 (0.7, 5.4)	+4.2 (0.3, 8.0)	+5.2 (2.4, 8.1)	+9.3 (5.7, 12.9)
	+7.4 (5.3, 9.5)	+5.0 (2.6, 7.4)	+4.3 (0.9, 7.7)	+4.8 (1.2, 8.3)

Bar chart — Mean (±SD) absolute BCVA at Week 96, ETDRS letters:

	≤278 μm			279–343 μm			344–422 μm			≥423 μm		
	2q8 (n=90)	8q12 (n=80)	8q16 (n=81)	2q8 (n=79)	8q12 (n=80)	8q16 (n=91)	2q8 (n=82)	8q12 (n=90)	8q16 (n=79)	2q8 (n=84)	8q12 (n=85)	8q16 (n=85)
Week 96	67.7	67.1	72.2	71.6	68.8	67.3	66.1	65.7	65.3	58.8	60.0	56.8
BL	62.8	64.1	64.8	65.2	64.6	62.3	59.2	60.5	60.9	48.4	50.7	52.0
Week 48	67.7	68.3	72.3	71.5	69.3	68.0	67.6	65.9	67.1	59.1	60.9	56.4

FAS, LOCF. N values for BL. Analyses were not adjusted for multiplicity or to allow for differences in BL BCVA.

CRT improvements with aflibercept 8 mg and 2 mg at Week 96 are independent of BL CRT

Mean (95% CI) CRT (µm) change from BL at Week 96	≤278 µm	279–343 µm	344–422 µm	≥423 µm
	−32 (−45, −19)	−79 (−91, −66)	−146 (−161, −132)	−310 (−335, −285)
	−49 (−58, −40)	−80 (−94, −67)	−143 (−157, −128)	−308 (−335, −280)
	−41 (−50, −33)	−82 (−94, −69)	−142 (−156, −128)	−317 (−347, −288)

Mean (±SD) absolute CRT at Week 96, µm

	≤278 µm			279–343 µm			344–422 µm			≥423 µm		
Week 96	207	193	198	234	228	227	230	236	239	232	234	236
	2q8 (n=90)	8q12 (n=80)	8q16 (n=81)	2q8 (n=79)	8q12 (n=80)	8q16 (n=91)	2q8 (n=82)	8q12 (n=90)	8q16 (n=79)	2q8 (n=84)	8q12 (n=85)	8q16 (n=85)
BL	239	242	239	312	309	309	376	379	381	547	541	553
Week 48	210	194	198	246	231	225	240	238	238	250	249	247

FAS, LOCF. N values for BL. Analyses were not adjusted for multiplicity or to allow for differences in BL CRT.

Last assigned treatment intervals at Week 96 categorized by BL CRT

BL CRT categories
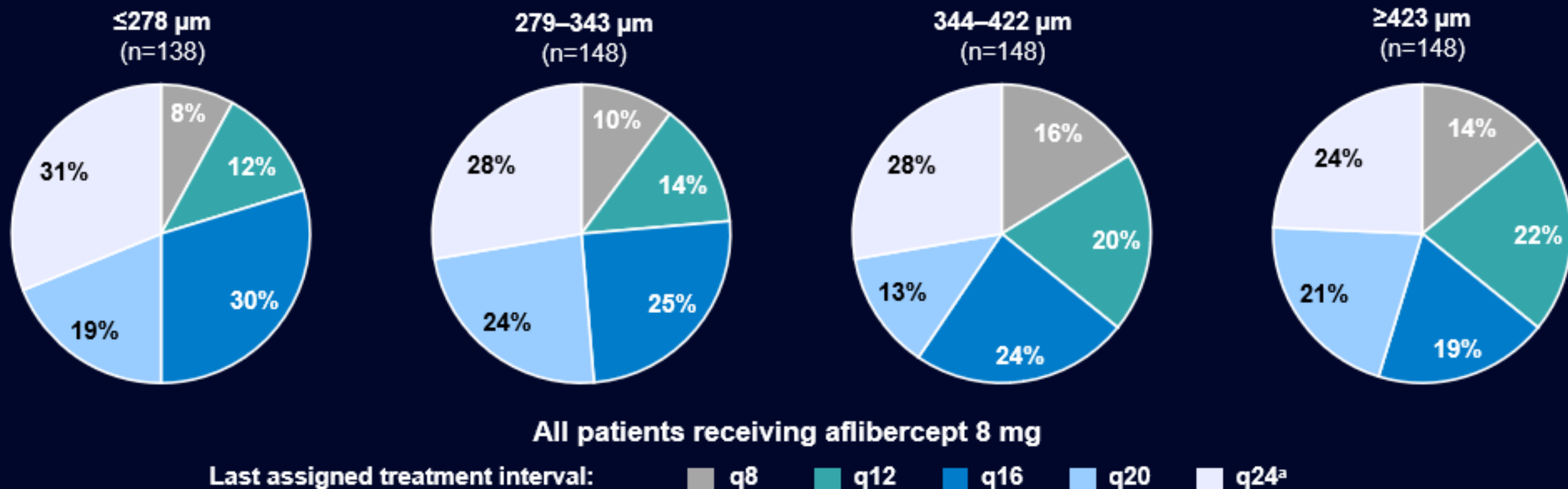
≤278 μm
(n=138)

279–343 μm
(n=148)

344–422 μm
(n=148)

≥423 μm
(n=148)

≤278 μm	279–343 μm	344–422 μm	≥423 μm
8%	10%	16%	14%
12%	14%	20%	22%
30%	25%	24%	19%
19%	24%	13%	21%
31%	28%	28%	24%

All patients receiving aflibercept 8 mg

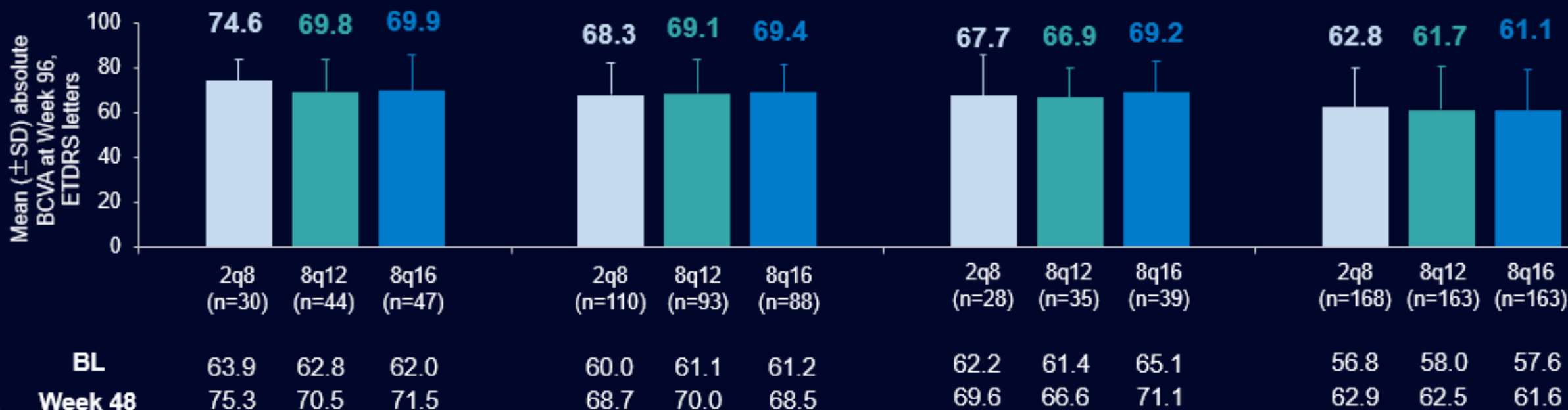Last assigned treatment interval: ▮ q8 ▮ q12 ▮ q16 ▮ q20 ▮ q24[a]

Data shown for patients who completed 96 weeks of treatment. Values may not add up to 100% due to rounding.
[a]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period.

BCVA outcomes with aflibercept 8 mg and 2 mg at Week 96 are independent of BL CNV size

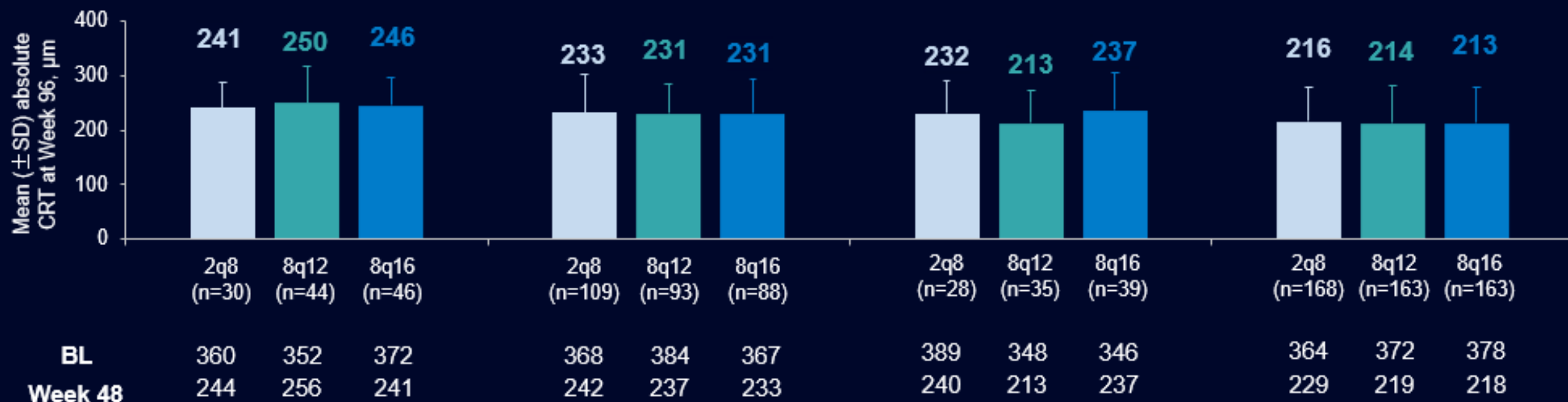**Mean (95% CI) BCVA (ETDRS letters) change from BL at Week 96**

	<1.3 mm²	1.3–<4 mm²	4–<5 mm²	≥5 mm²
	+10.7 (6.3, 15.2)	+8.2 (5.8, 10.6)	+5.5 (1.2, 9.8)	+6.0 (3.9, 8.1)
	+7.0 (2.8, 11.2)	+7.9 (5.1, 10.7)	+5.5 (1.1, 9.8)	+3.7 (1.2, 6.3)
	+7.8 (3.9, 11.7)	+8.2 (5.9, 10.5)	+4.2 (1.1, 7.3)	+3.5 (1.2, 5.8)

Mean (±SD) absolute BCVA at Week 96, ETDRS letters

	<1.3 mm²			1.3–<4 mm²			4–<5 mm²			≥5 mm²		
	74.6	69.8	69.9	68.3	69.1	69.4	67.7	66.9	69.2	62.8	61.7	61.1
	2q8 (n=30)	8q12 (n=44)	8q16 (n=47)	2q8 (n=110)	8q12 (n=93)	8q16 (n=88)	2q8 (n=28)	8q12 (n=35)	8q16 (n=39)	2q8 (n=168)	8q12 (n=163)	8q16 (n=163)
BL	63.9	62.8	62.0	60.0	61.1	61.2	62.2	61.4	65.1	56.8	58.0	57.6
Week 48	75.3	70.5	71.5	68.7	70.0	68.5	69.6	66.6	71.1	62.9	62.5	61.6

FAS, LOCF. N values for BL. Analyses were not adjusted for multiplicity or to allow for differences in BL BCVA.

CRT improvements with aflibercept 8 mg and 2 mg at Week 96 are independent of BL CNV size

Mean (95% CI) CRT (µm) change from BL at Week 96	<1.3 mm^2	1.3–<4 mm^2	4–<5 mm^2	≥5 mm^2
	−119 (−158, −80)	−138 (−164, −111)	−157 (−205, −109)	−144 (−164, −123)
	−102 (−133, −71)	−155 (−184, −126)	−135 (−173, −97)	−157 (−177, −137)
	−126 (−165, −86)	−135 (−164, −106)	−109 (−144, −75)	−165 (−186, −144)

Mean (±SD) absolute CRT at Week 96, µm

	<1.3 mm^2			1.3–<4 mm^2			4–<5 mm^2			≥5 mm^2		
	2q8 (n=30)	8q12 (n=44)	8q16 (n=46)	2q8 (n=109)	8q12 (n=93)	8q16 (n=88)	2q8 (n=28)	8q12 (n=35)	8q16 (n=39)	2q8 (n=168)	8q12 (n=163)	8q16 (n=163)
Week 96	241	250	246	233	231	231	232	213	237	216	214	213
BL	360	352	372	368	384	367	389	348	346	364	372	378
Week 48	244	256	241	242	237	233	240	213	237	229	219	218

FAS, LOCF. N values for BL. Analyses were not adjusted for multiplicity or to allow for differences in BL CRT.

Last assigned treatment intervals at Week 96 categorized by BL CNV size

Baseline CNV size
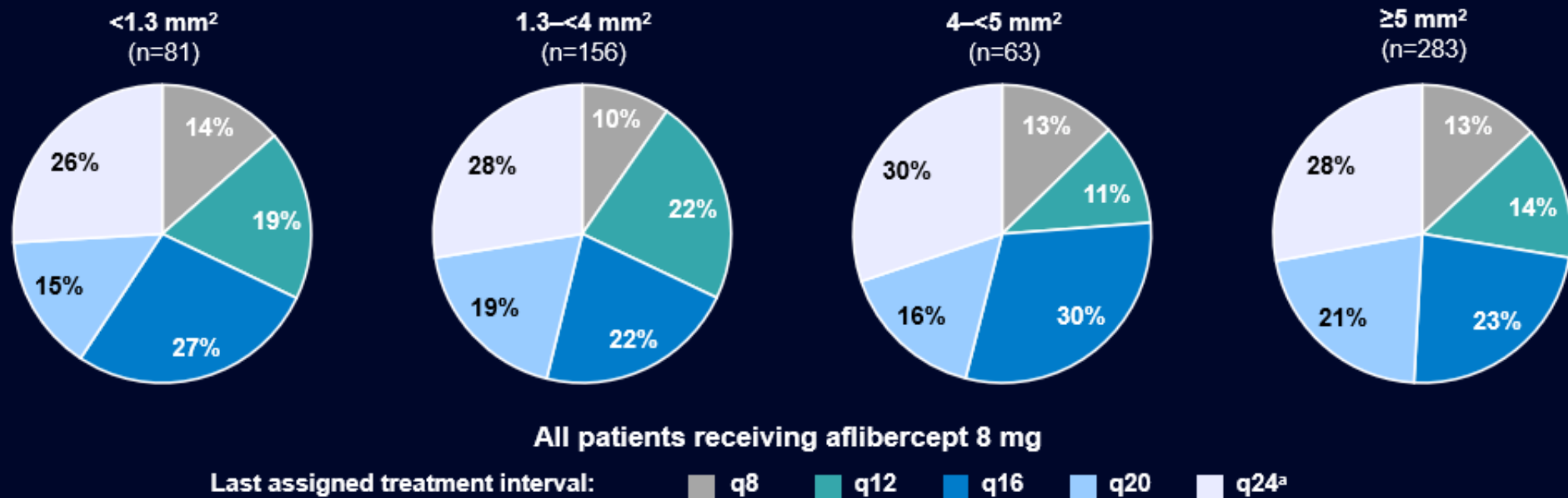
<1.3 mm² (n=81)

1.3–<4 mm² (n=156)

4–<5 mm² (n=63)

≥5 mm² (n=283)

All patients receiving aflibercept 8 mg

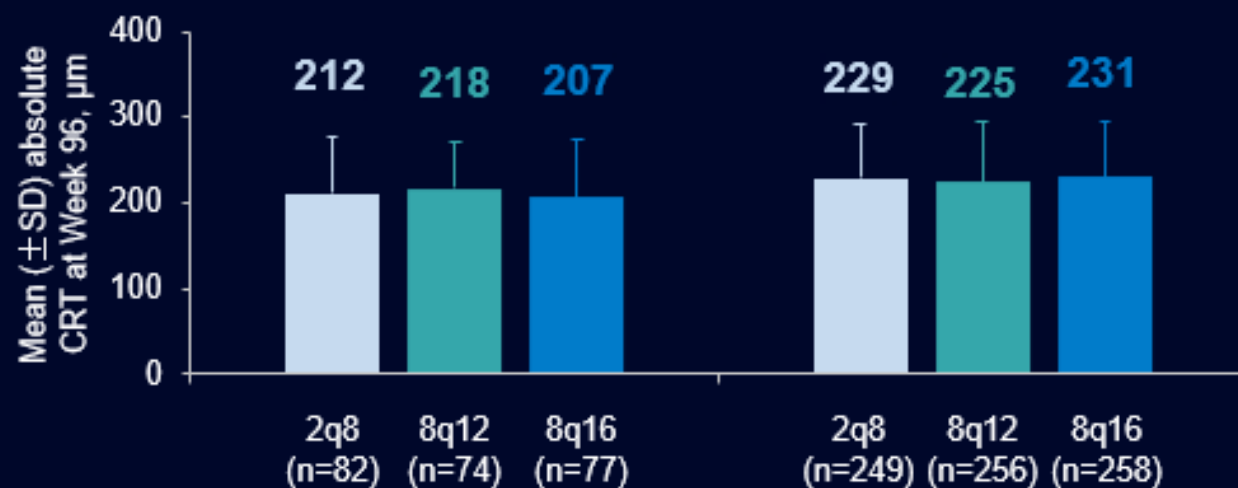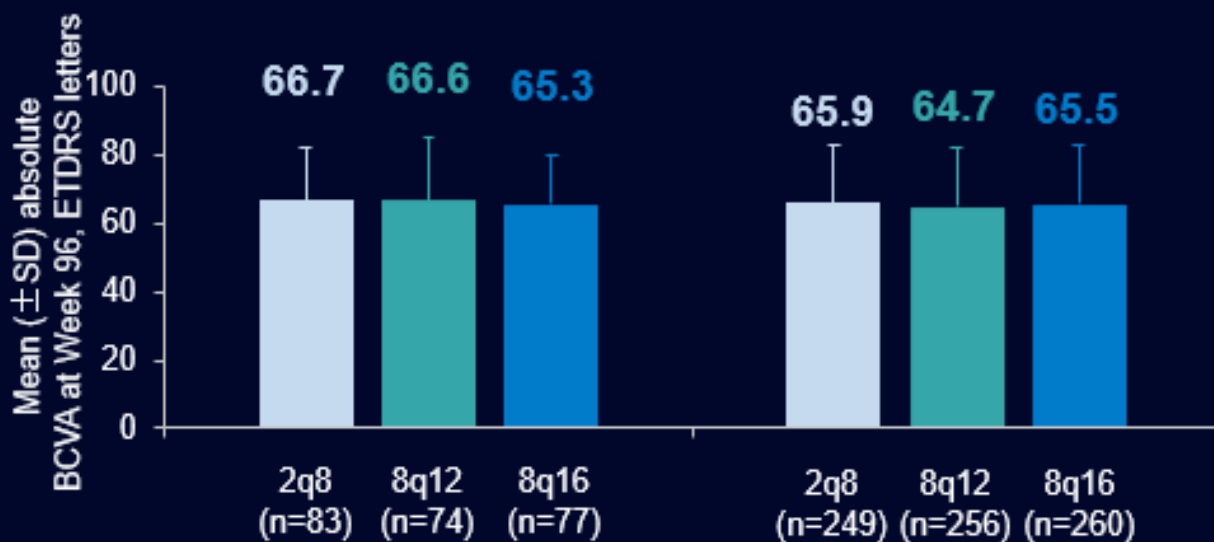Last assigned treatment interval: q8 q12 q16 q20 q24[a]

Data shown for patients who completed 96 weeks of treatment. Values may not add up to 100% due to rounding.
[a]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period.

Visual and anatomic outcomes with aflibercept 8 mg and 2 mg at Week 96 are independent of race

Mean (95% CI) BCVA (ETDRS letters) and CRT (µm) change from BL at Week 96

Asian	White	Asian	White
+7.5 (4.8, 10.3)	+6.9 (5.3, 8.6)	−144 (−176, −111)	−138 (−154, −123)
+8.9 (5.1, 12.8)	+4.4 (2.6, 6.1)	−147 (−179, −115)	−147 (−163, −132)
+7.2 (4.8, 9.6)	+4.8 (3.1, 6.5)	−140 (−169, −112)	−146 (−163, −129)

	Asian			White			Asian			White		
	2q8 (n=83)	8q12 (n=74)	8q16 (n=77)	2q8 (n=249)	8q12 (n=256)	8q16 (n=260)	2q8 (n=82)	8q12 (n=74)	8q16 (n=77)	2q8 (n=249)	8q12 (n=256)	8q16 (n=258)
BL	59.2	57.7	58.1	59.0	60.3	60.7	365	366	347	366	373	377
Week 48	66.7	67.0	66.8	66.5	65.5	65.7	216	217	201	242	232	235

FAS, LOCF. Analyses were not adjusted for multiplicity or to allow for differences in BL BCVA or CRT. Data are not reported for Black or African American patients due to small sample size (n=2).
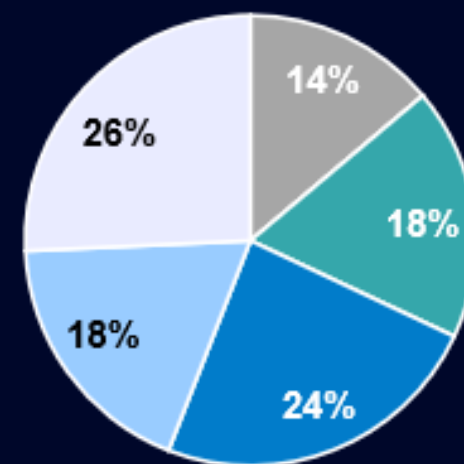
Last assigned treatment intervals at Week 96 categorized by race

Race

Asian
(n=130)
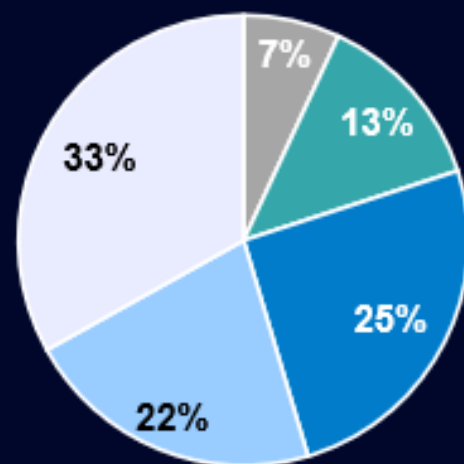
White
(n=447)

All patients receiving aflibercept 8 mg

Last assigned treatment interval: ■ q8 ■ q12 ■ q16 ■ q20 ■ q24[a]

Data shown for patients who completed 96 weeks of treatment. Values may not add up to 100% due to rounding.
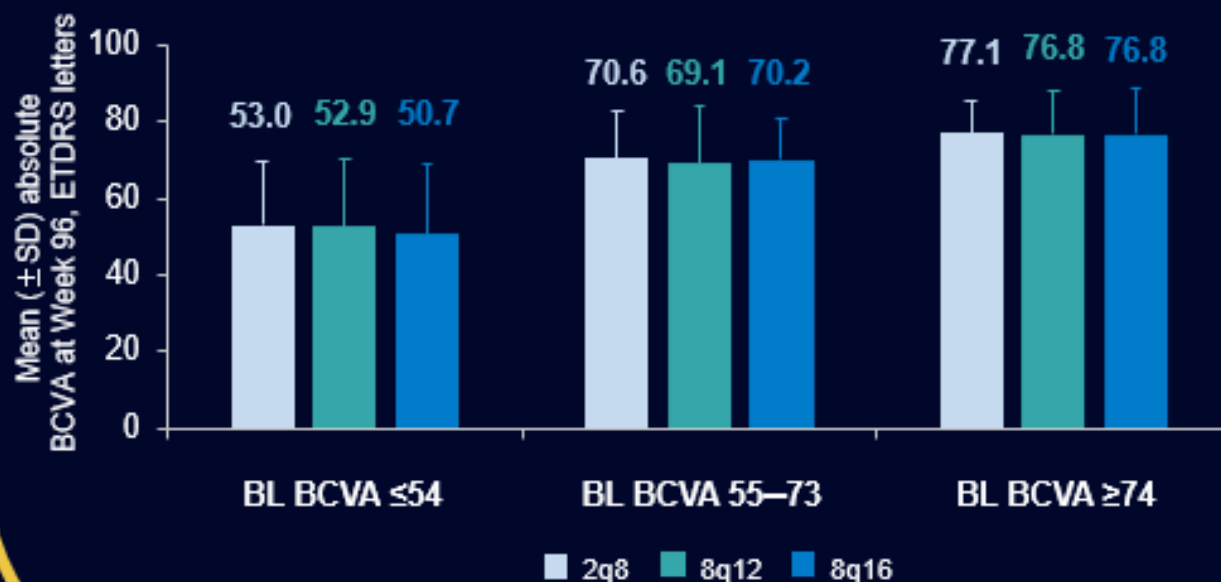Data are not reported for Black or African American patients due to small sample size (n=2).
[a]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period.
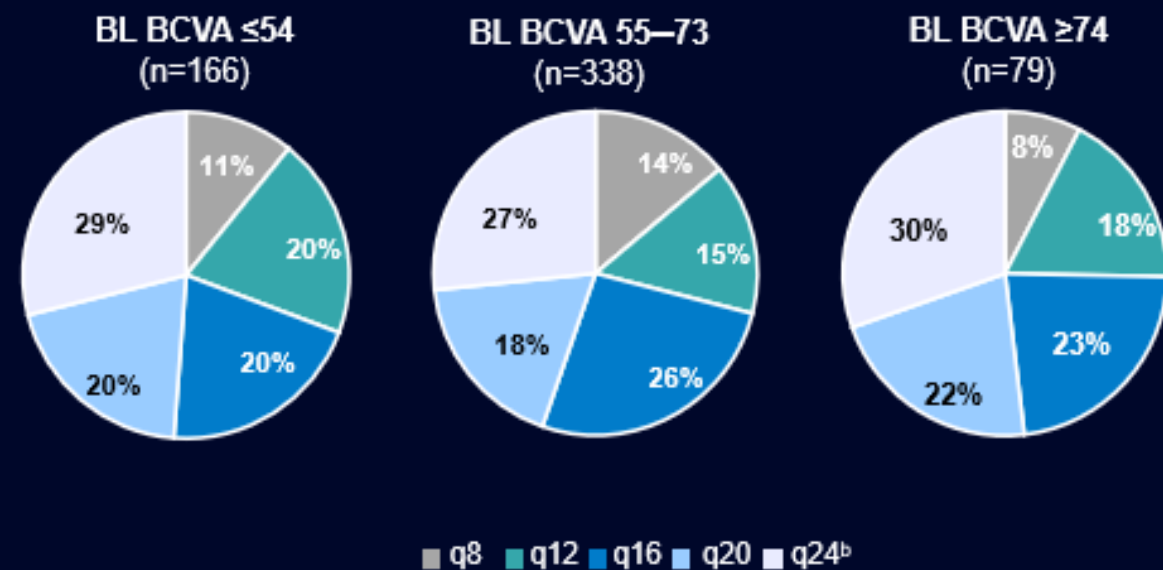
Conclusions

- At Week 96, mean absolute and change in BCVA and CRT values were similar after treatment with aflibercept 8 mg with extended treatment intervals compared with 2 mg every 8 weeks **across all subgroups based on** baseline BCVA, CRT, CNV size, and race.

- Proportion of patients with maintained, extended, or shortened **treatment intervals** through Week 96 was **also independent of baseline characteristics**

Week 96 BCVA outcomes according to BL BCVA

Mean (±SD) absolute BCVA at Week 96, ETDRS letters

BL BCVA ≤54: 53.0, 52.9, 50.7
BL BCVA 55–73: 70.6, 69.1, 70.2
BL BCVA ≥74: 77.1, 76.8, 76.8

■ 2q8 ■ 8q12 ■ 8q16

Last assigned treatment interval according to BL BCVA[a]

BL BCVA ≤54 (n=166): 11%, 20%, 20%, 20%, 29%
BL BCVA 55–73 (n=338): 14%, 15%, 26%, 18%, 27%
BL BCVA ≥74 (n=79): 8%, 18%, 23%, 22%, 30%

■ q8 ■ q12 ■ q16 ■ q20 ■ q24[b]

[a]Values may not add up to 100% due to rounding. [b]Patients assigned to a 24-week dosing interval did not have enough time to complete the interval within the 96-week study period.