Intravitreal Aflibercept 8 mg for Diabetic Macular Edema: Week 96 Efficacy Outcomes by Baseline Characteristics in the Phase 2/3 PHOTON Trial

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Disclosures

- Dr. Emanuelli is an investigator for Adverum Biotechnologies, Kodiak Sciences, Nanoscope Therapeutics, Novartis, Novartis Institute of Biomedical Research, Regeneron Pharmaceuticals, Inc., Roche/Genentech, Ophthea, and RegenXBio
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- Study disclosures: This study includes research conducted on human patients. Institutional review board approval was obtained prior to study initiation
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Background

- In the PHOTON trial, aflibercept 8 mg met the primary endpoint, demonstrating non-inferior BCVA gains versus aflibercept 2 mg at Week 48 with extended dosing intervals in patients with DME[1]
- At Week 96, both aflibercept 8-mg groups achieved similar BCVA gains versus aflibercept 2 mg, with no new safety signals observed through Week 96[2]
- The influence of baseline patient demographics and ocular characteristics on the treatment effects of aflibercept 8 mg in patients with DME at 96 weeks in the PHOTON trial have yet to be evaluated

This PHOTON analysis assessed whether visual improvements achieved with aflibercept 8 mg vs. 2 mg were comparable across patient subgroups

BCVA, best-corrected visual acuity; DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

1. Brown DM. *Lancet*. 2024:403:1153-1163. 2. Do DV. Presented at: American Society of Retina Specialists 2023 Meeting, July 28–August 1, 2023, Seattle, WA.

PHOTON Study Design

Multi-center, randomized, double-masked study in adult patients with center-involved DME[a]
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)

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 patients with DME.
2q8, 2 mg every 8 weeks; 8q12, 8 mg every 12 weeks; 8q16, 8 mg every 16 weeks; BCVA, best-corrected visual acuity.

PHOTON: Dosing Schedule and Dose Regimen Modification

Primary Endpoint

YEAR 1	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	X[a]	o	o

YEAR 2	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 beginning at **Week 52** 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, dosing regimen modification.

Patient Baseline Characteristics

	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)

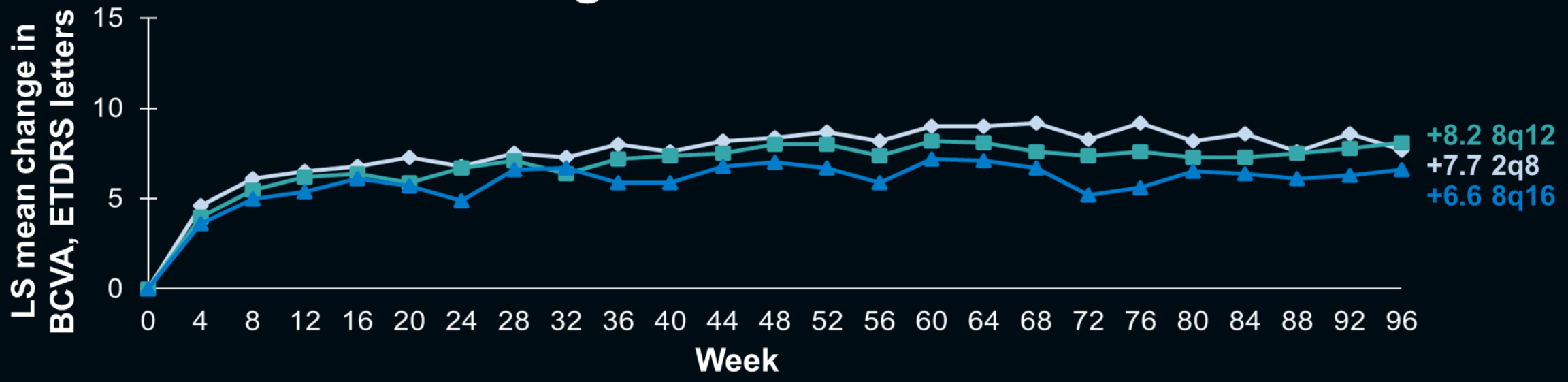
Data are mean (SD) unless otherwise indicated.
BMI, body mass index; FAS, full analysis set; SAF, safety analysis set; SD, standard deviation.

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 ETDRS letters)	12.0%	18.0%	14.1%	15.5%
20/40 or worse (≤73 ETDRS 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%

Data are mean (SD) unless otherwise indicated.
CRT, central retinal thickness; ETDRS, Early Treatment of Diabetic Retinopathy Study.

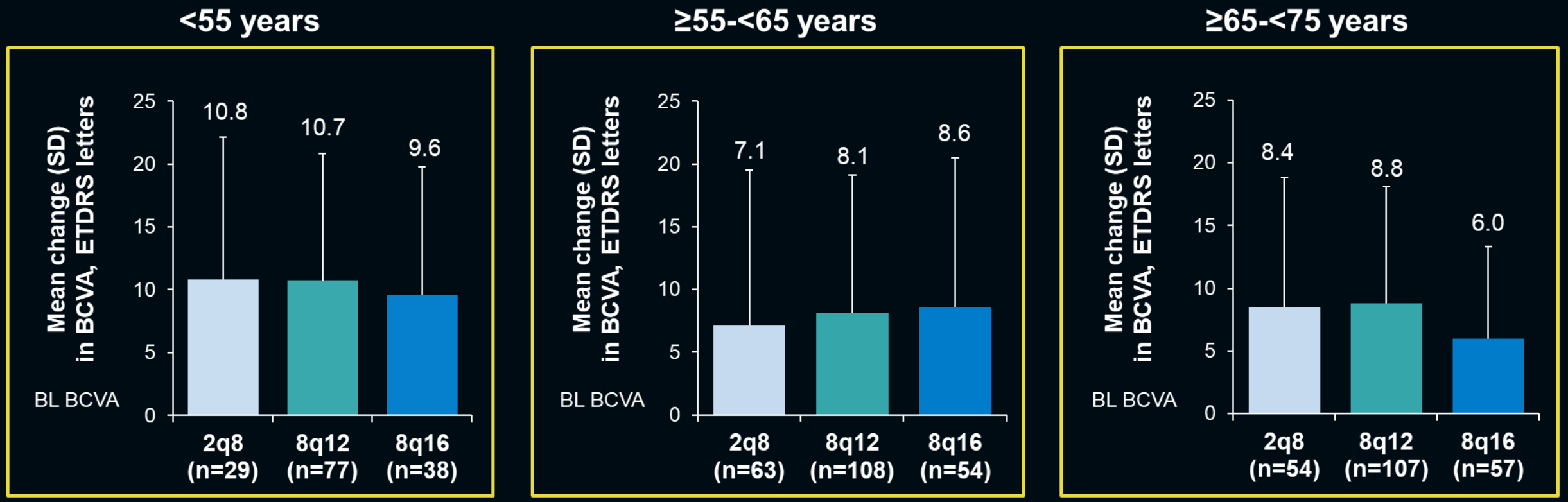
Mean Change in BCVA at Week 96



	Mean number of injections[a]	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	13.8	7.7			
8q12	9.5	8.2	**+0.45**	**–1.55, 2.45**	***P*<0.0001 (nominal)**
8q16	7.8	6.6	**–1.11**	**–3.27, 1.05**	***P*=0.0044 (nominal)**

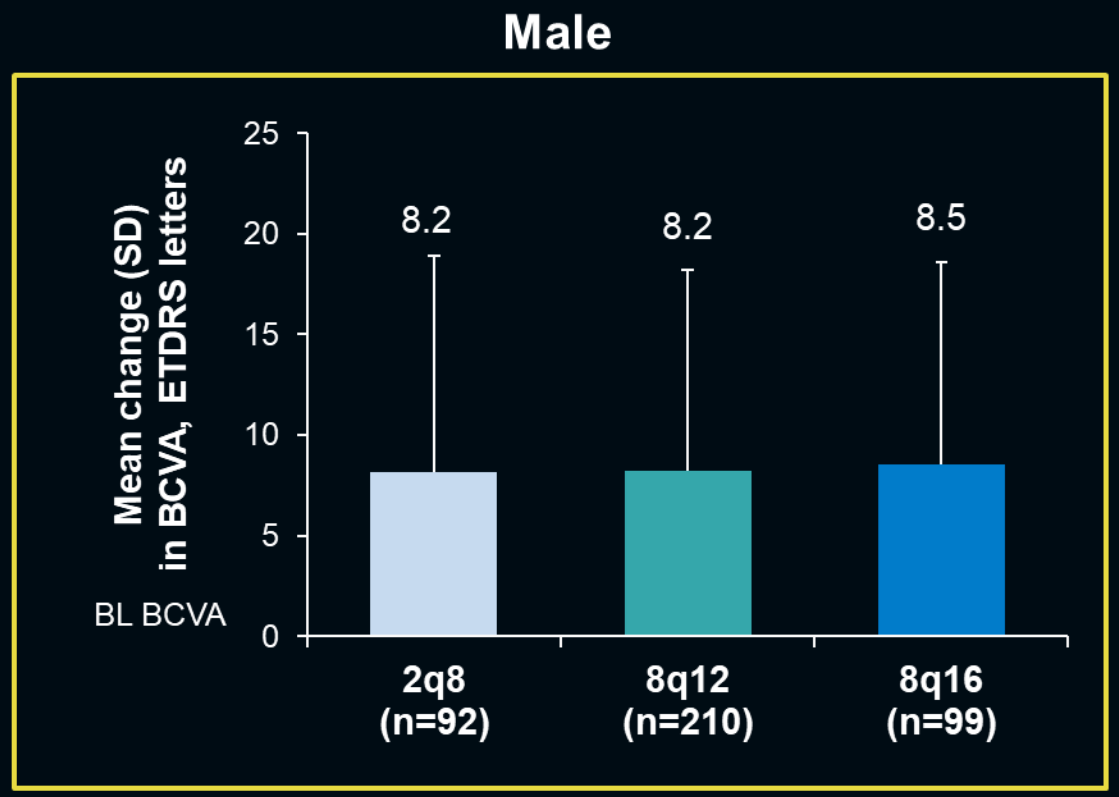
Data shown in the figure represent LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at BL).
LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for BL and visit and for treatment and visit.
[a]Patients completing Week 96: 2q8 n=139; 8q12 n=256; 8q16 n=139.
BL, baseline; CI, confidence interval; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

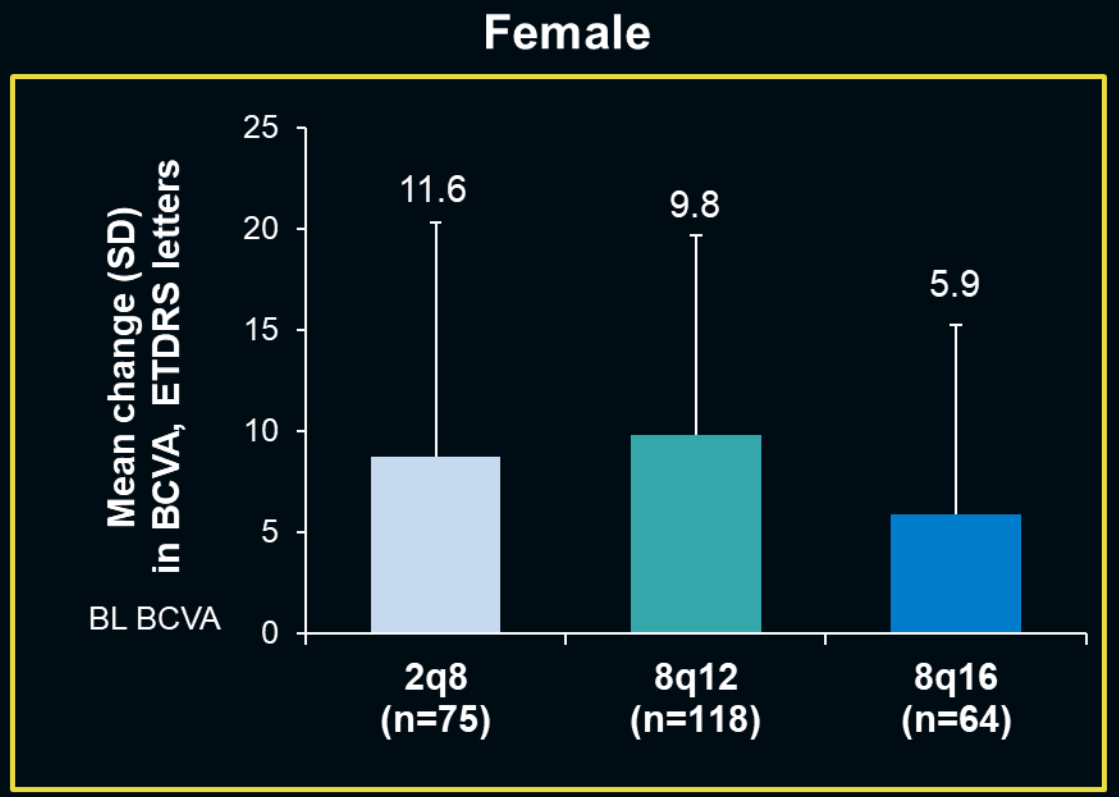
Mean Change in BCVA at Week 96 by Age[a]



Age was self-reported by patients.
FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.
[a]The subgroup age ≥75 years could not be evaluated due to the small sample size (<20 patients in the 2q8 and 8q16 treatment groups).

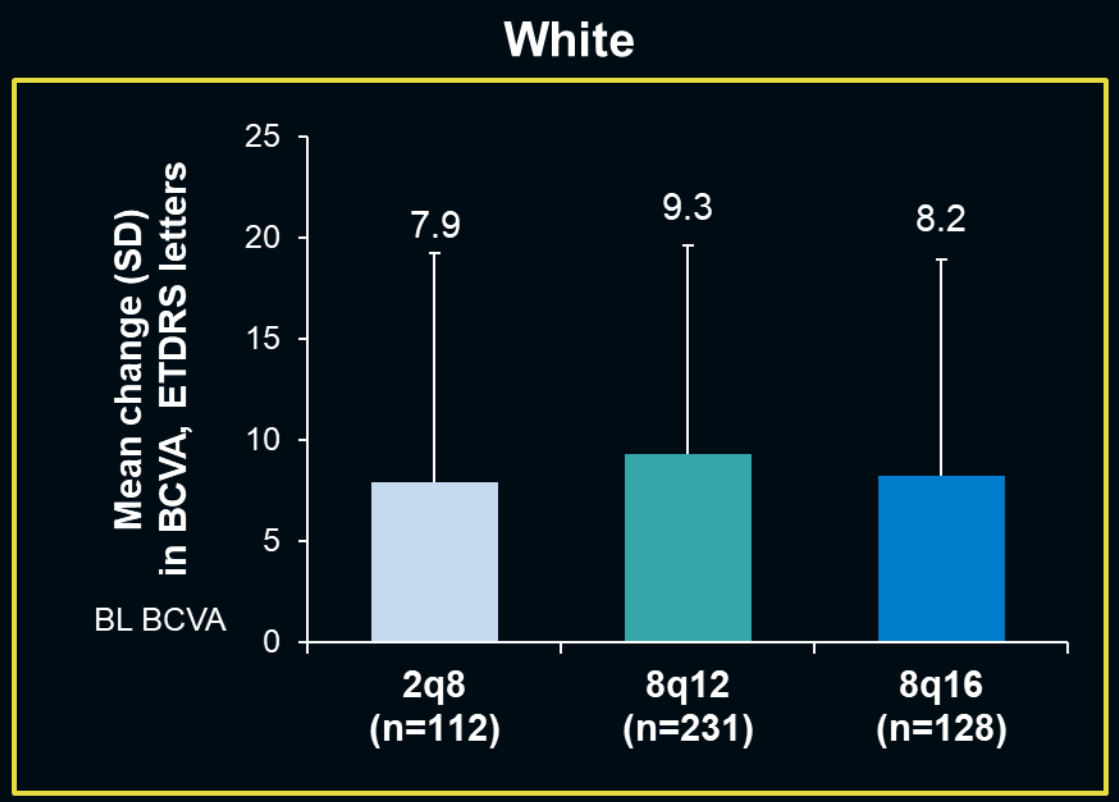
Mean Change in BCVA at Week 96 by Sex

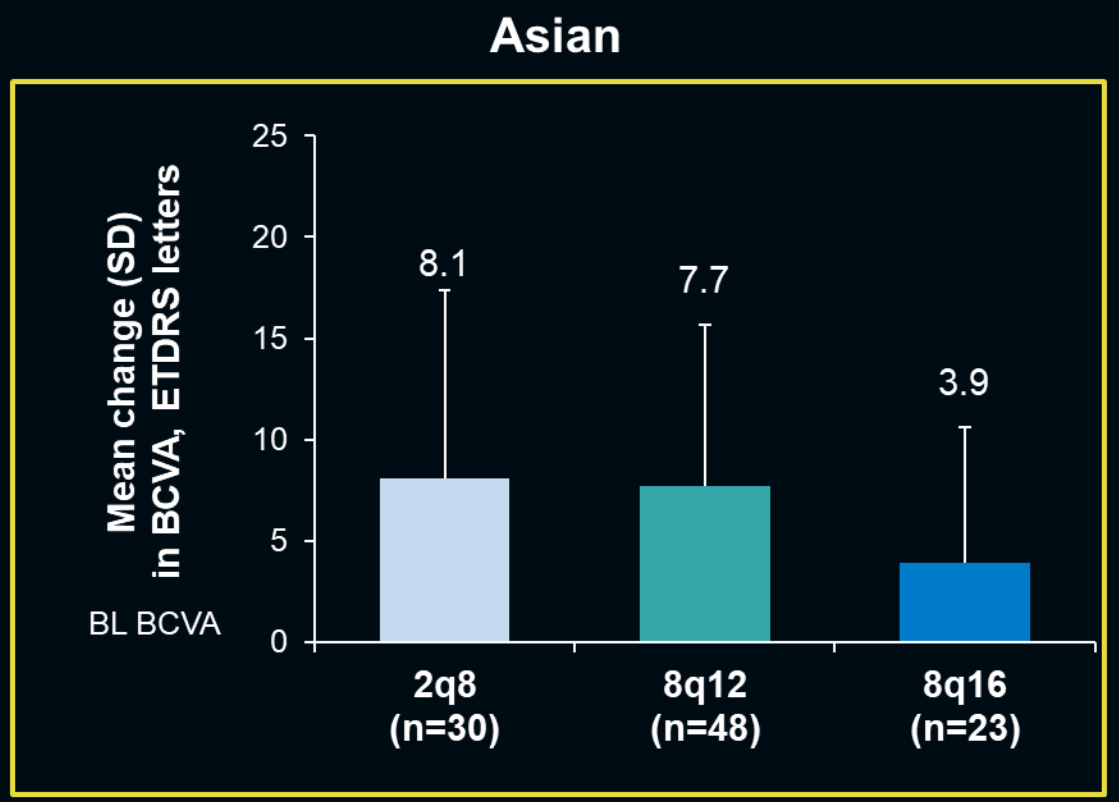




Sex was self-reported by patients.
FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.

Mean Change in BCVA at Week 96 by Race[a]

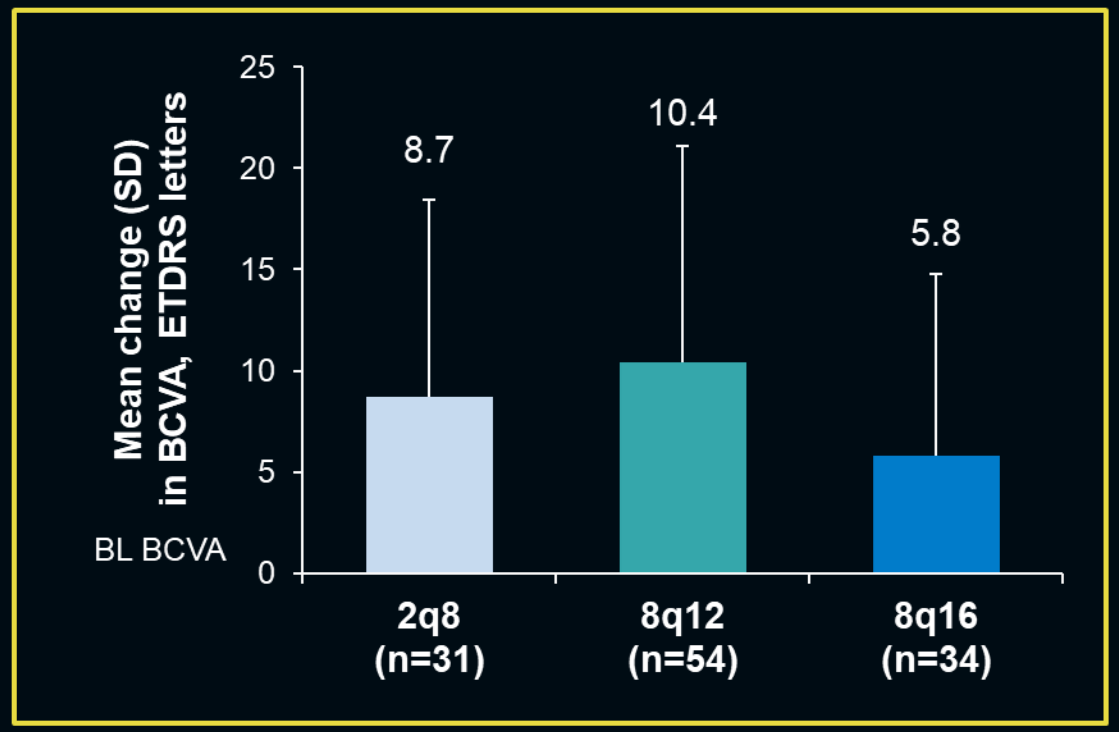




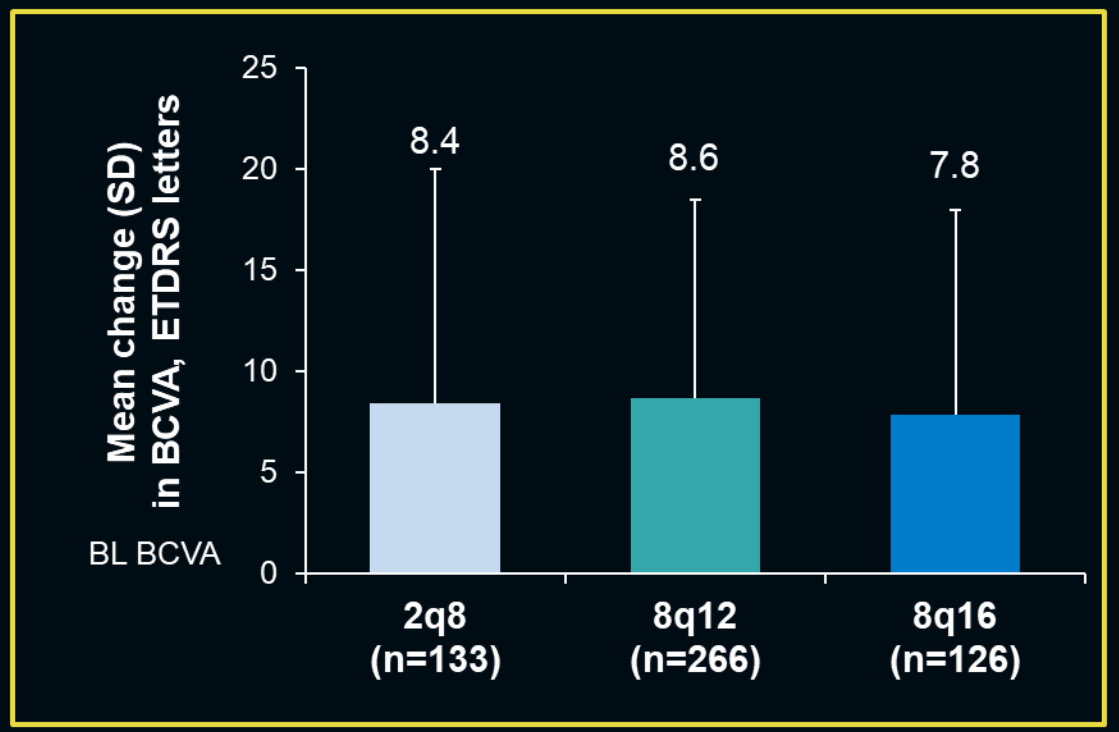
Race was self-reported by patients.
FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.
[a]The Black or African American race subgroup could not be evaluated due to the small sample size (<20 patients in the 2q8 and 8q16 groups).

Mean Change in BCVA at Week 96 by Ethnicity

Hispanic or Latino

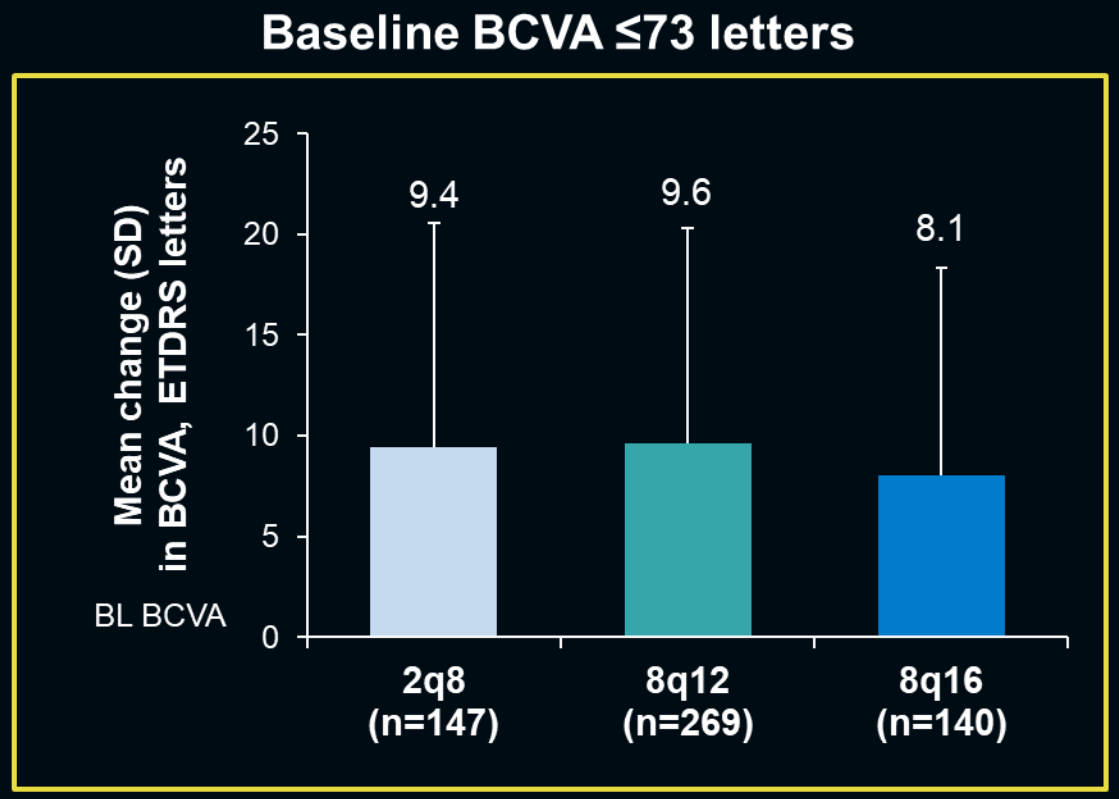


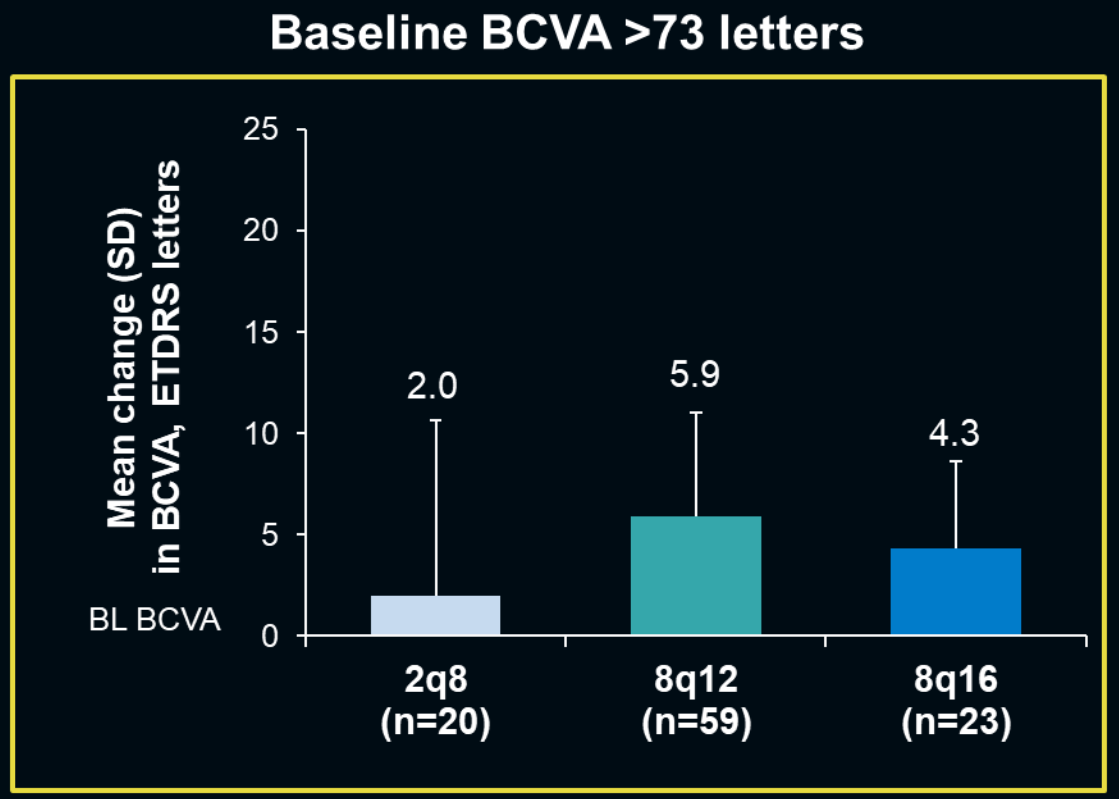
Not Hispanic or Latino



Ethnicity was self-reported by patients.
FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.

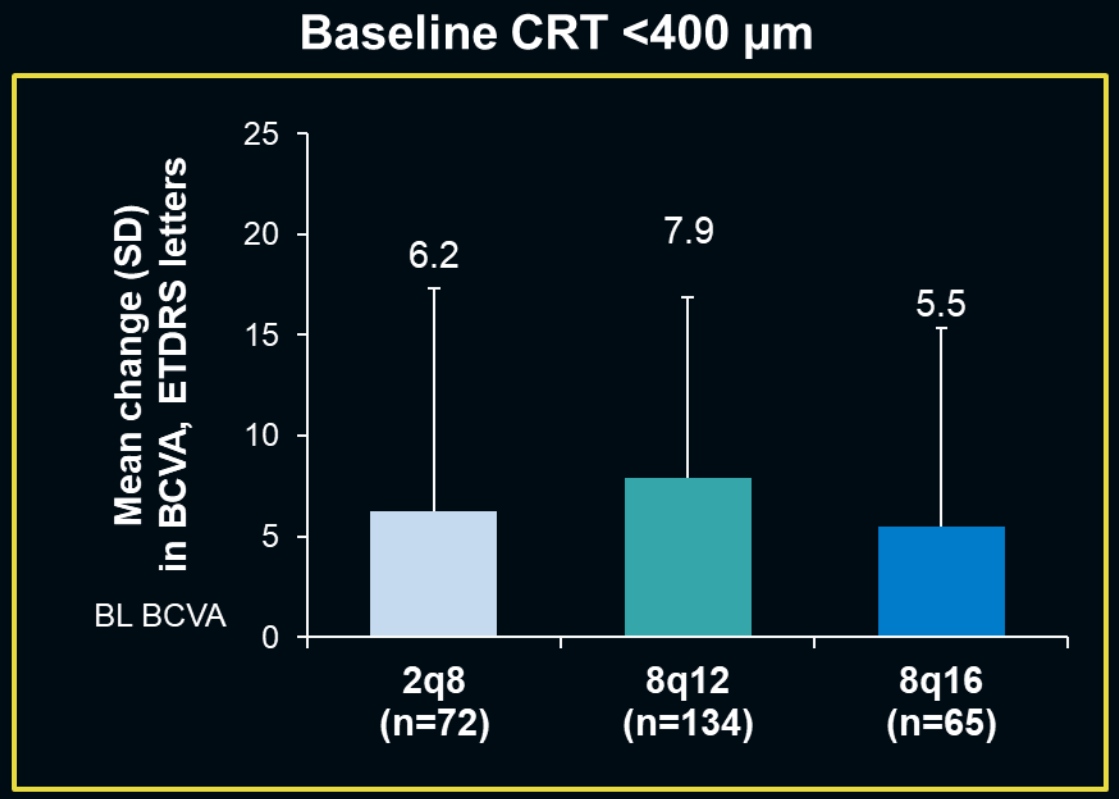
Mean Change in BCVA at Week 96 by Baseline BCVA

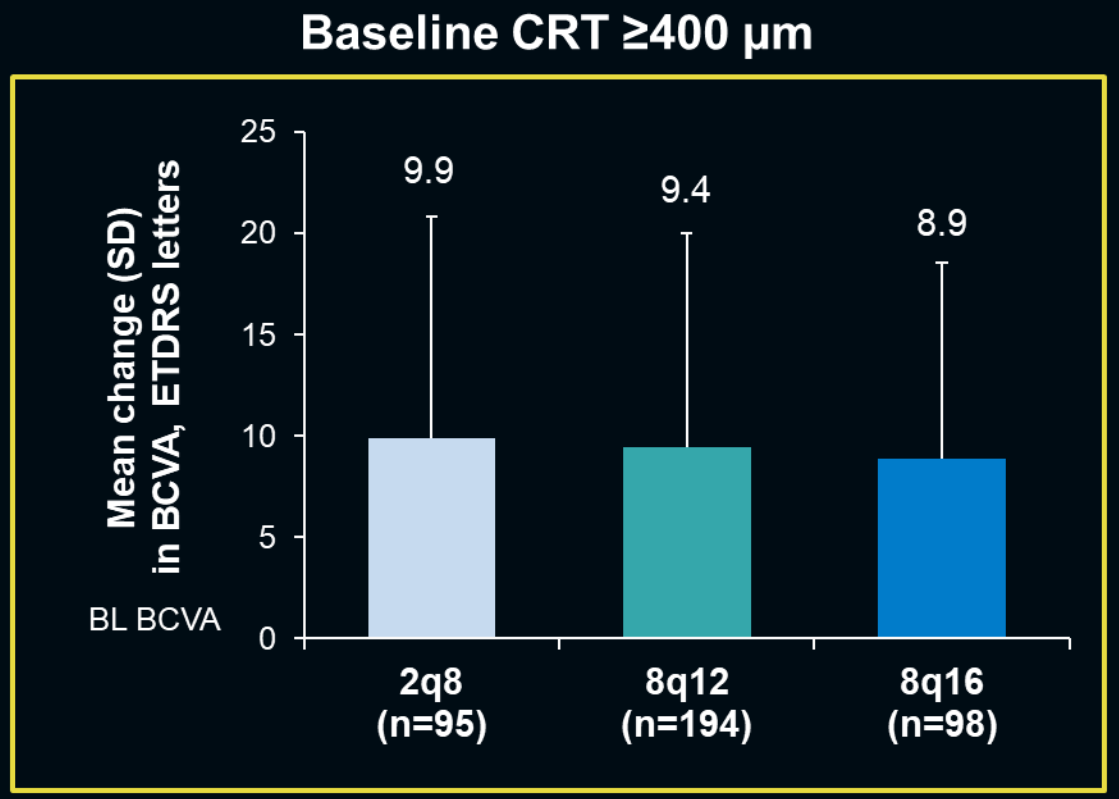




FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.

Mean Change in BCVA at Week 96 by Baseline CRT



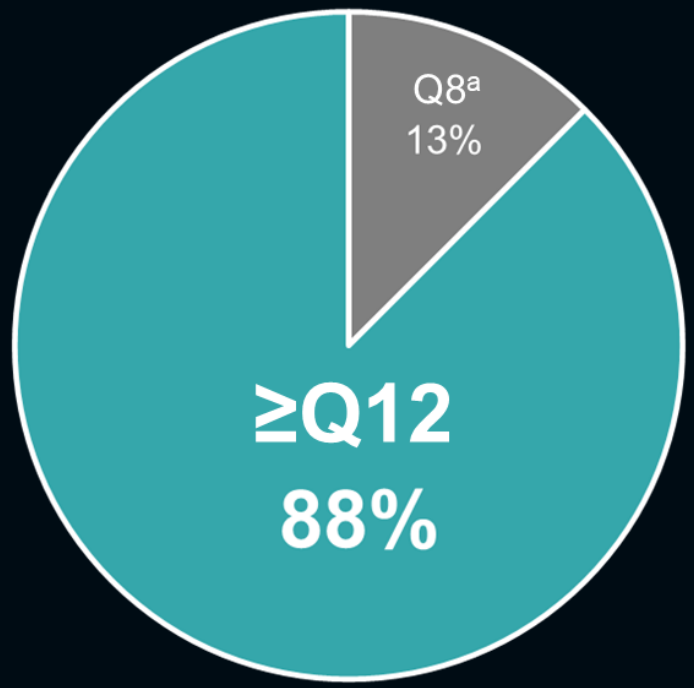


FAS, observed cases (censoring data post-ICE). At BL, 2q8: n=167; 8q12: n=328; 8q16: n=163.

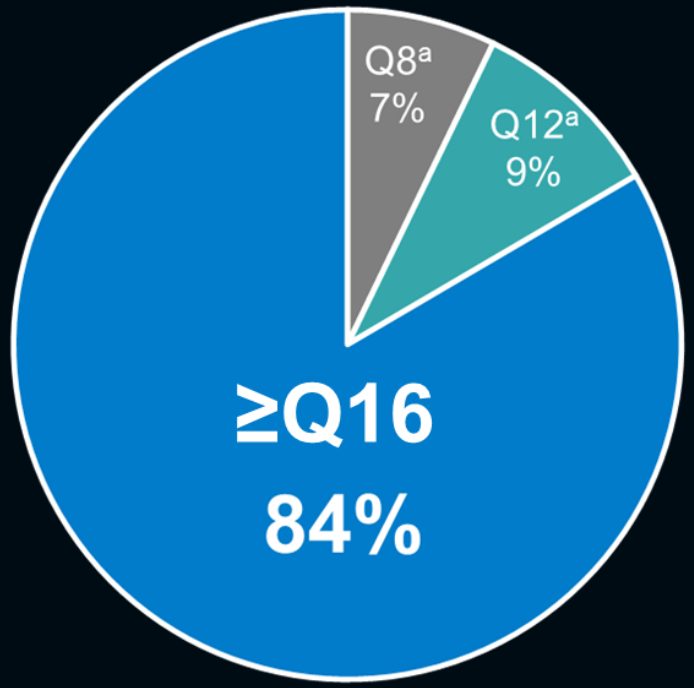
Large Majority of Aflibercept 8 mg Patients Maintained Randomized Intervals Through Week 96

88% of patients in the 8q12 group maintained ≥12-week intervals

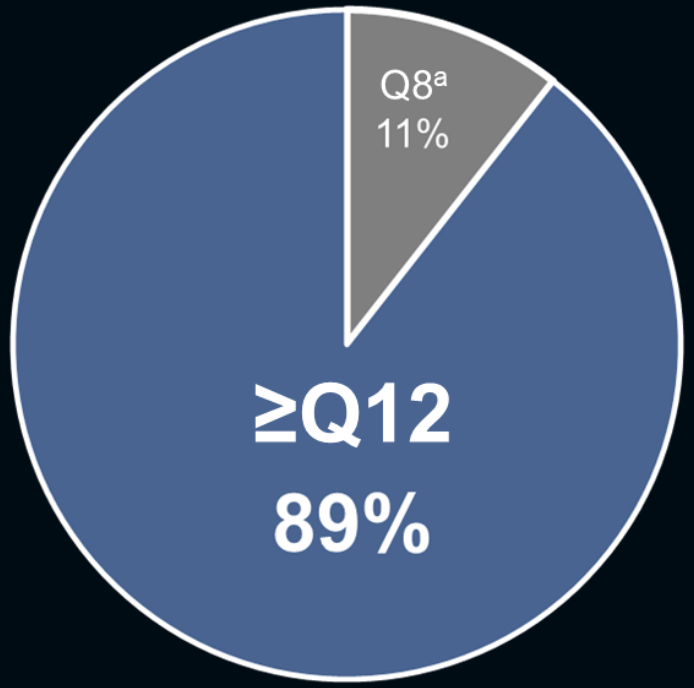
84% of patients in the 8q16 group maintained ≥16-week intervals



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



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

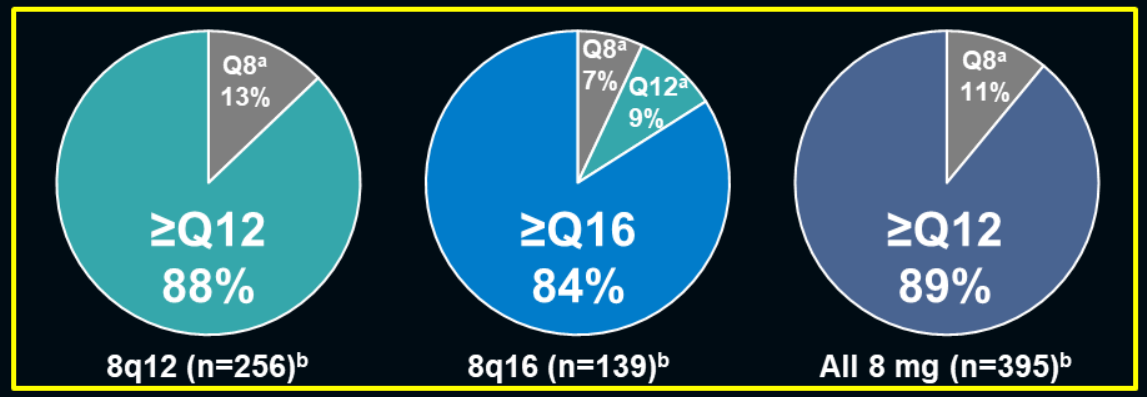


All 8 mg
(n=395)[b]

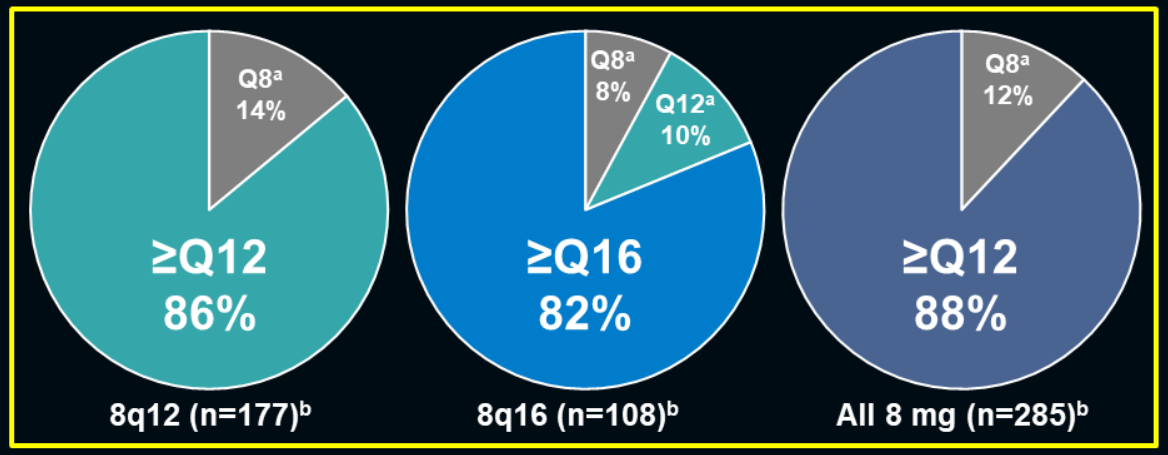
[a]Patients met DRM criteria for dosing interval shortening at some point through Week 96. [b]Patients completing Week 96.
Values may not add up to 100% due to rounding.
DRM, dose regimen modification.

Proportion of 8 mg Patients Who Maintained Randomized Dosing Interval Through Week 96 by Race

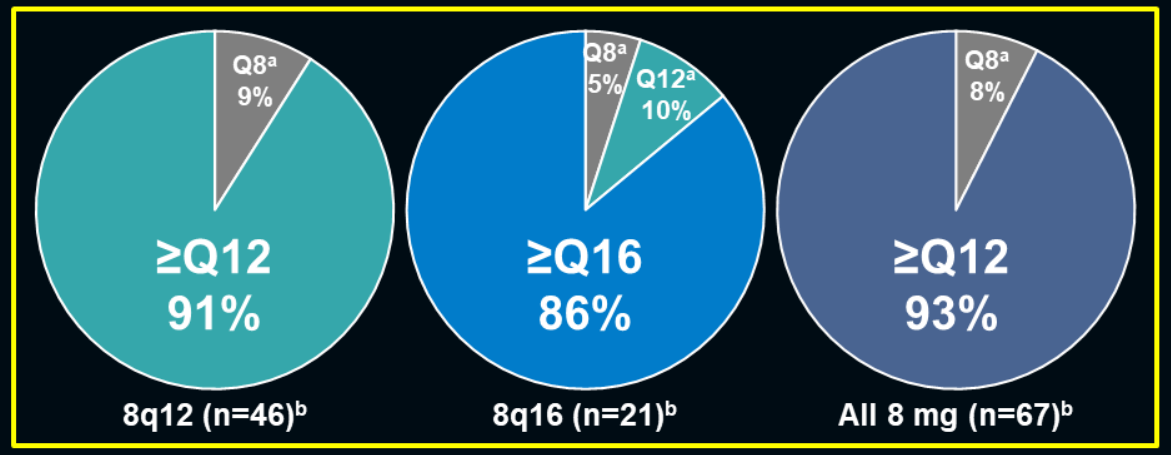
All Patients



White Patients



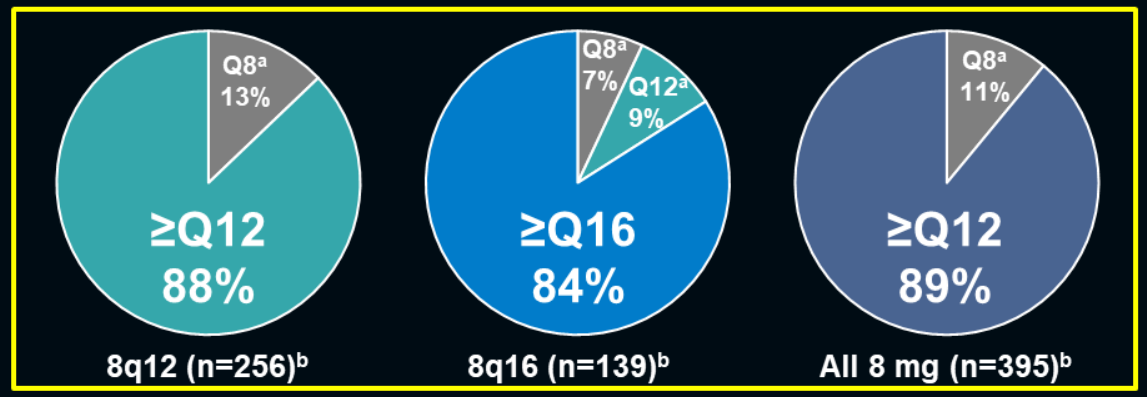
Asian Patients



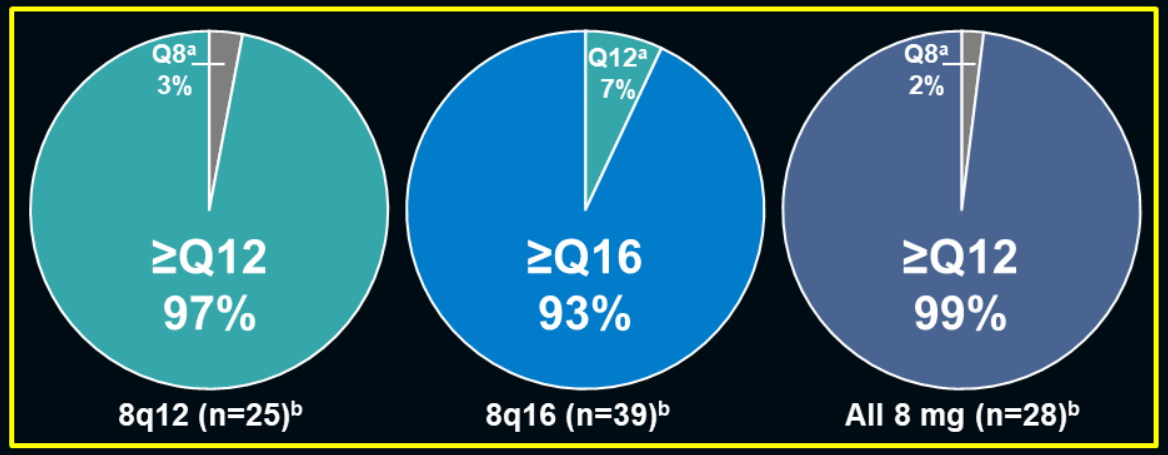
[a]Patients shortened based on DRM criteria through Week 96. [b]Patients completing Week 96.
Values may not add up to 100 due to rounding. Data are not reported for Black or African American patients due to the small sample size.

Proportion of 8 mg Patients Who Maintained Randomized Dosing Interval Through Week 96 by Ethnicity

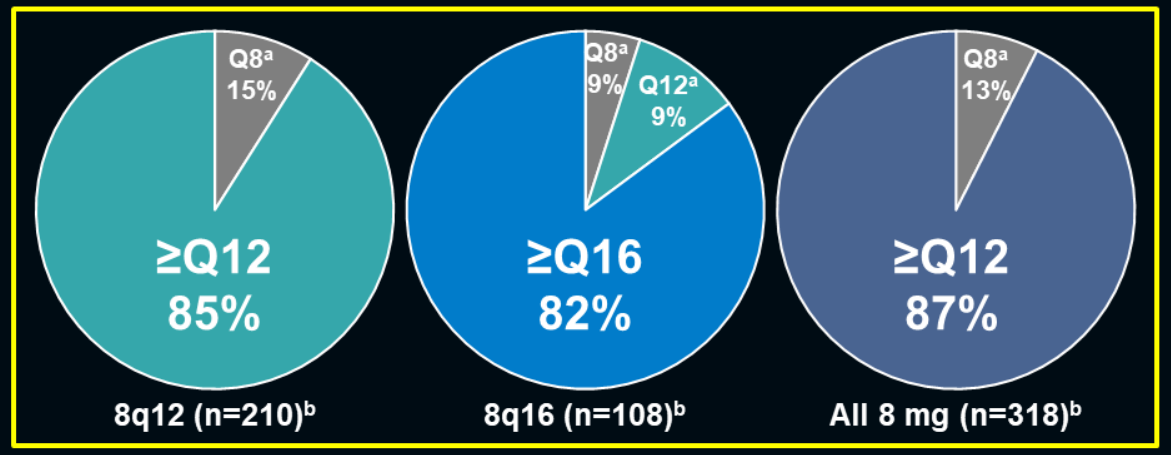
All Patients



Hispanic or Latino Patients



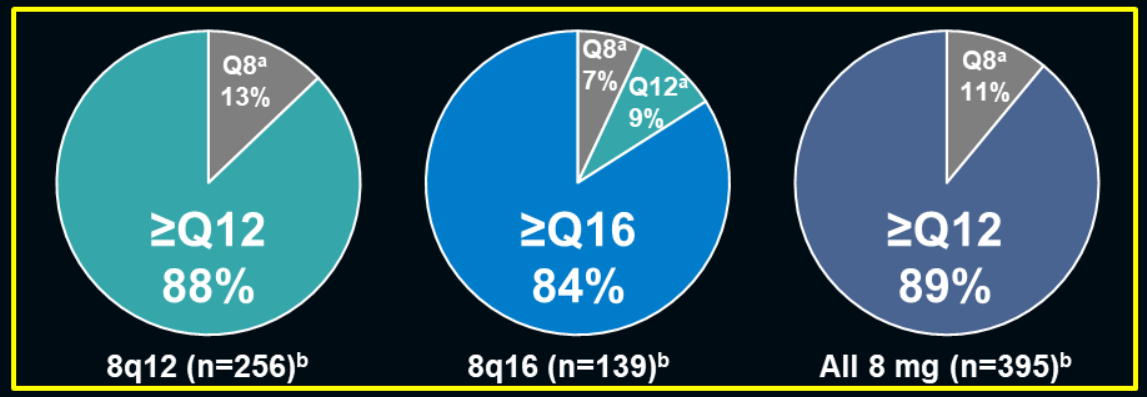
Not Hispanic or Latino Patients



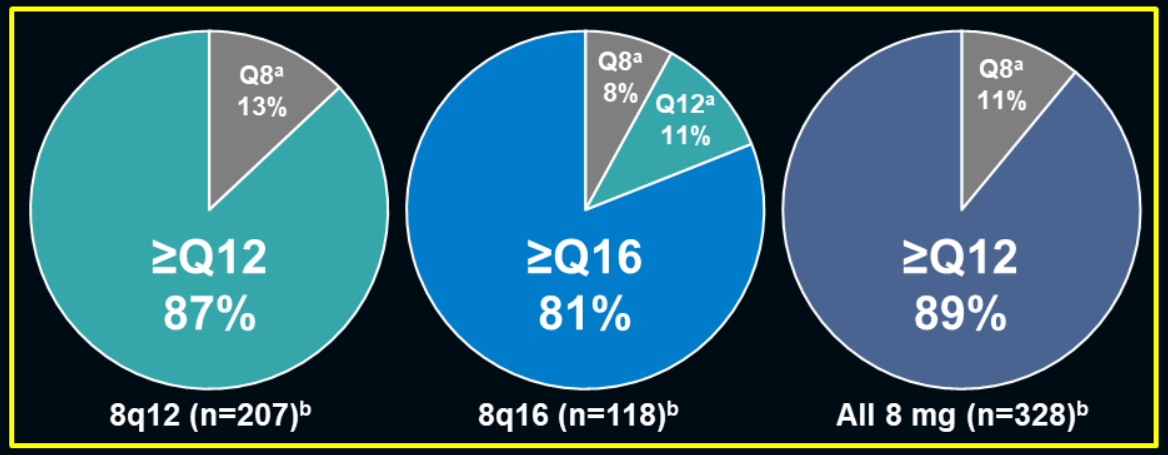
[a]Patients shortened based on DRM criteria through Week 96. [b]Patients completing Week 96.
Values may not add up to 100 due to rounding.

Proportion of 8 mg Patients Who Maintained Randomized Dosing Interval Through Week 96 by BL BCVA

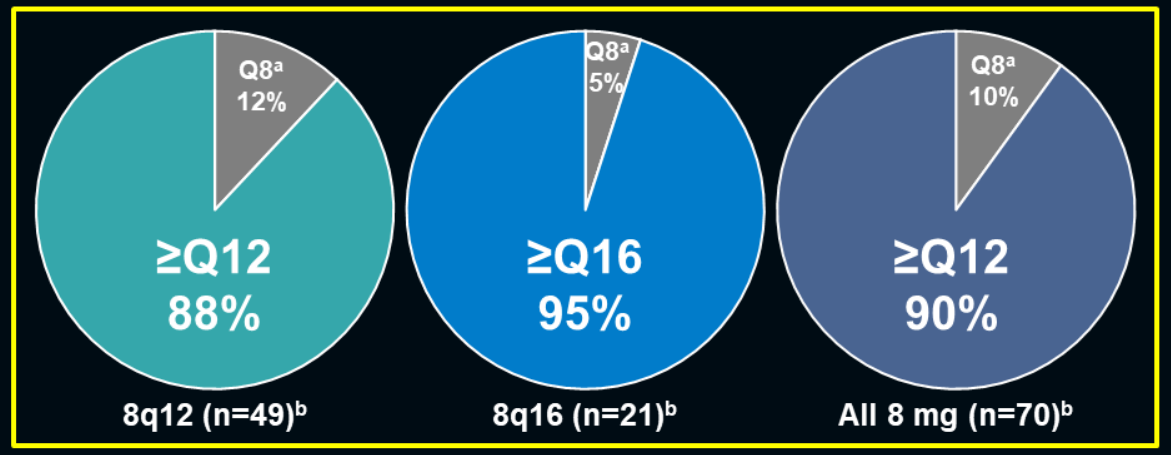
All Patients



BL BCVA ≤73 Letters



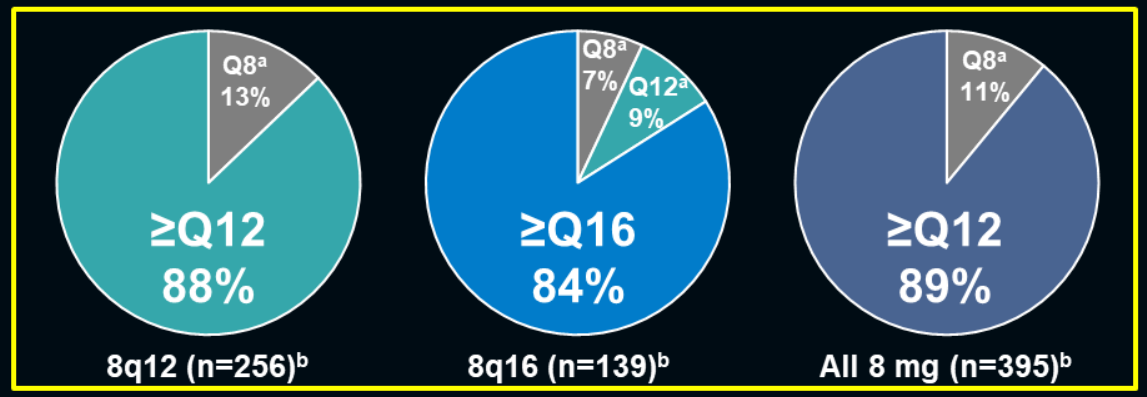
BL BCVA >73 Letters



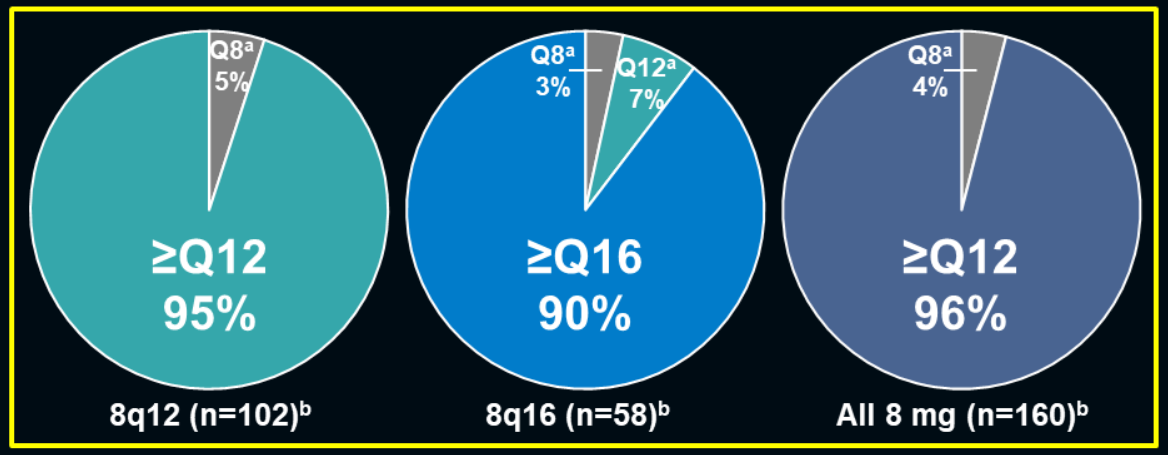
[a]Patients shortened based on DRM criteria through Week 96. [b]Patients completing Week 96.
Values may not add up to 100 due to rounding.

Proportion of 8 mg Patients Who Maintained Randomized Dosing Interval Through Week 96 by BL CRT

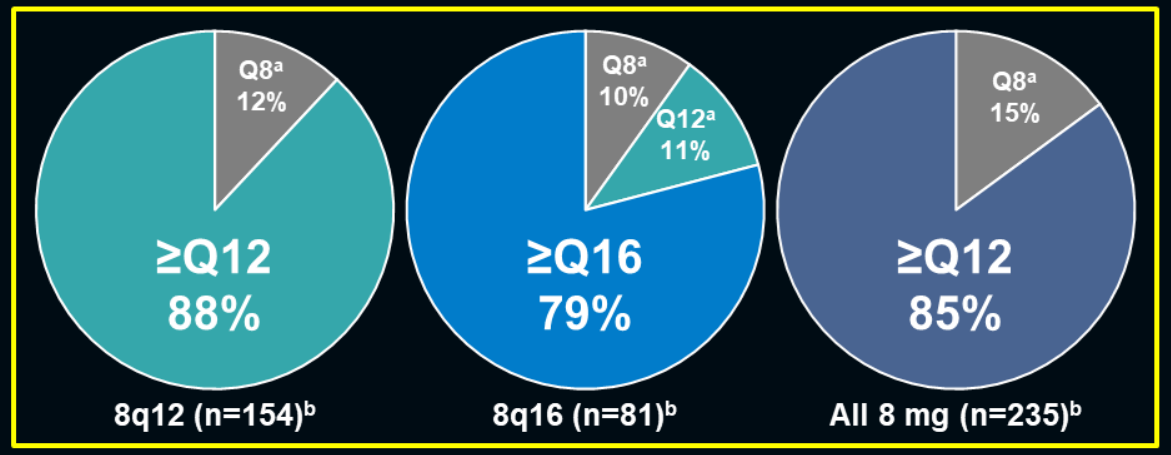
All Patients



BL CRT <400 µm



BL CRT ≥400 µm



[a]Patients shortened based on DRM criteria through Week 96. [b]Patients completing Week 96.
Values may not add up to 100 due to rounding.

Limitations

- This analysis was not designed to evaluate statistical differences within subgroups
- Select subgroups (age ≥75 years and Black or African American race) could not be evaluated due to the small sample size

Conclusions

- Aflibercept 8 mg achieved meaningful BCVA gains from baseline at Week 96 in patients with DME across evaluable subgroups of age, sex, race, ethnicity, baseline BCVA, and baseline CRT
- Similar proportions of patients across subgroups were able to achieve dosing intervals of 12 weeks or longer

For additional questions, please contact Andres Emanuelli, MD, at aemanuelli@gmail.com.