Aflibercept 8 mg in Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion: Primary Endpoint Results from the QUASAR Study

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Disclosures

- **Seenu M. Hariprasad** reports being a consultant or a member of the Speakers Bureau for AbbVie, Alimera Sciences/ANI, Astellas, Bayer, Harrow, Regeneron Pharmaceuticals, Inc., and Sun Pharma
    - **VC** receives grants from Bayer, Novartis, and Roche; and serves on advisory boards for Alcon, Apellis, Bayer, Boehringer Ingelheim, Novartis, and Roche. **YC** serves as a speaker for AbbVie, Bayer, Chengdu Kanghong, Novartis, and Roche. **AC** receives consultant fees from Alcon, Apellis, Astellis, Bayer, Novartis, Opthea, Roche, and Zeiss; and grant funding from Bayer, Novartis, and Roche. **MK** receives financial support from Alcon Japan, Hoya Surgical Optics, Otsuka Pharmaceutical, Santen, and Senju; compensation or travel expenses from Alcon Japan, Bayer, Chugai, Hoya Surgical Optics, Kowa, Santen, Senju, and Wakamoto Pharma; and consultant fees from Chugai, Daisel, Hoya Surgical Optics, Senju, and SONY. **SL** is an employee, investor, and patent holder of Bayer Consumer Care AG. **LB** was an employee of Bayer Consumer Care AG at the time of analysis. **RG** and **ZH** are employees of Bayer Consumer Care AG. **TN**, **SS**, and **FM** are employees of Bayer AG. **AJB** and **AA** are employees of Regeneron Pharmaceuticals, Inc. **RK** receives research funding from Alimera, Bayer, Chengdu Kanghong, Novartis, Opthea, and Roche; and serves as a speaker for AbbVie, Alimera, Apellis, Bayer, Heidelberg Engineering, Novartis, and Roche
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- This study included research conducted on human patients. Institutional Review Board/Institutional Ethics Committee approval was obtained prior to study initiation
- Medical writing support, under the direction of the author, was provided by ApotheCom and funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med.* 2022;175:1298–1304)
- Aflibercept 8 mg is currently not on label for treating macular edema due to retinal vein occlusion; however, applications seeking approval of aflibercept 8 mg for macular edema due to retinal vein occlusion, including central, branch, and hemiretinal vein occlusion, have been submitted to the FDA and the EMA

QUASAR: Study Design

A multi-center, randomized, double-masked, Phase 3 study in patients with treatment-naïve macular edema secondary to RVO
Randomized at baseline 1 (2q4) : 1 (8q8/3) : 1 (8q8/5)

2q4
Aflibercept 2 mg every 4 weeks[a]
n=301

8q8/3
Aflibercept 8 mg every 8 weeks, after 3 initial monthly injections[a]
n=293

8q8/5
Aflibercept 8 mg every 8 weeks, after 5 initial monthly injections[a]
n=298

Primary endpoint
Mean change in BCVA (non-inferiority)

	Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36
2q4	X	X	X	X	X	X	X	X	X	T&E
8q8/3	X	X	X	o	X	o[b]	X	o[c]	X	T&E
8q8/5	X	X	X	X	X	o	X	o[c]	X	o[d]

DRM for interval shortening

Dosing interval shortened by 4 weeks if the last dosing interval was >4 weeks and both the following criteria are met at a dosing visit:

- BCVA loss of >5 letters from reference visit, AND
- >50 µm increase in CRT from reference visit[e]

DRM for interval extension

Dosing interval extended by 4 weeks starting at Week 32 for 8q8/3 and 2q4 and at Week 40 for 8q8/5 if both the following criteria are met at a dosing visit:

- BCVA loss of <5 letters from reference visit[e], AND
- CRT <320 µm Heidelberg/<300 µm Cirrus or Topcon SD-OCT

The primary efficacy endpoint was change from baseline in BCVA at Week 36, with a non-inferiority margin of 4 letters. Stippled boxes = initial treatment phase; X = active injection; o = sham injection. Note: Table does not reflect all dosing options once a patient's dosing interval is shortened. [a]With opportunity for extension per DRM. [b]Active injection for participants meeting DRM criteria at Week 16. [c]Active injection for participants meeting DRM criteria at Week 16 or 24. [d]Active injection for participants meeting DRM at Weeks 16, 24, or 32. [e]Reference is Week 12 for 8q8/3 and Week 20 for 8q8/5 and 2q4 (denoted by green boxes on table). **2q4**, aflibercept 2 mg administered every 4 weeks; **8q8/3**, aflibercept 8 mg administered every 8 weeks, after 3 initial injections at 4-week intervals; **8q8/5**, aflibercept 8 mg administered every 8 weeks, after 5 initial injections at 4-week intervals; **BCVA**, best-corrected visual acuity; **CRT**, central subfield retinal thickness; **DRM**, dose-regimen modification; **RVO**, retinal vein occlusion; **SD-OCT**, spectral domain-optical coherence tomography; **T&E**, treat and extend; **W**, week.

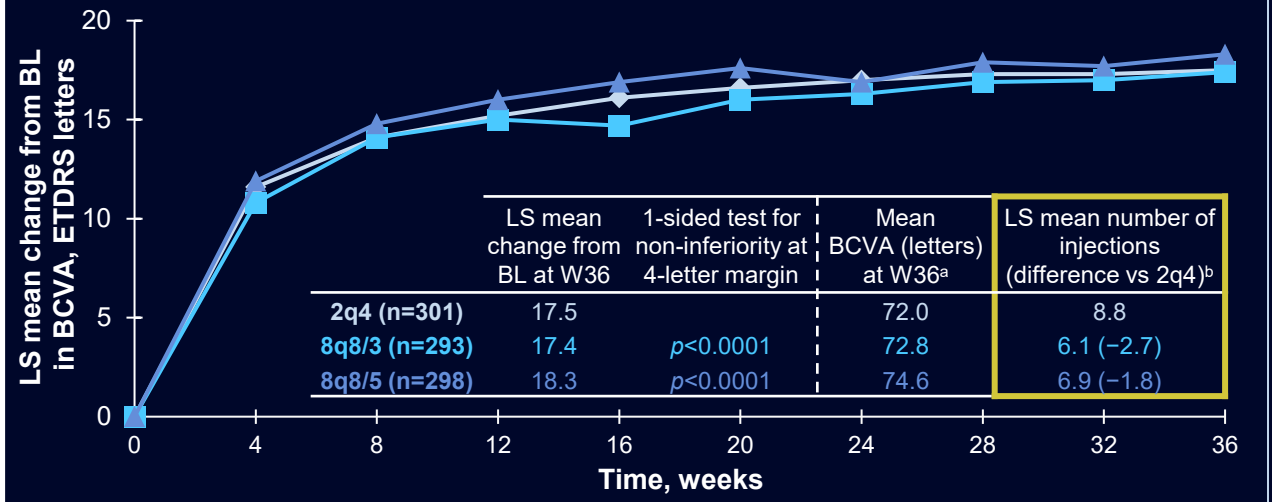
Baseline Demographics and Disease Characteristics

	2q4 (n=301)	8q8/3 (n=293)	8q8/5 (n=298)	Total (n=892)
Age, years	65.9 (11.7)	65.8 (11.5)	65.8 (11.5)	65.9 (11.6)
Female, n (%)	144 (47.8)	136 (46.4)	146 (49.0)	426 (47.8)
Race, n (%)				
Asian	101 (33.6)	91 (31.1)	97 (32.6)	289 (32.4)
Black or African American	8 (2.7)	7 (2.4)	9 (3.0)	24 (2.7)
White	178 (59.1)	173 (59.0)	177 (59.4)	528 (59.2)
Other[a]	1 (0.3)	0	4 (1.3)	5 (0.6)
Not reported	13 (4.3)	22 (7.5)	11 (3.7)	46 (5.2)
Hispanic or Latino, n (%)	22 (7.3)	25 (8.5)	14 (4.7)	61 (6.8)
Medical history of hypertension, n (%)	187 (62.1)	192 (65.5)	196 (65.8)	575 (64.5)
RVO type, n (%)[b]				
BRVO	149 (49.5)	159 (54.3)	159 (53.4)	467 (52.4)
CRVO	117 (38.9)	99 (33.8)	102 (34.2)	318 (35.7)
HRVO	35 (11.6)	35 (11.9)	37 (12.4)	107 (12.0)
BCVA, ETDRS letters	54.1 (14.3)	55.2 (13.6)	55.4 (13.4)	54.9 (13.8)
CRT, µm[c]	651 (240)	626 (230)	609 (213)	629 (229)

Full analysis set. Data are mean (SD) unless otherwise indicated. [a]Includes American Indian or Alaskan native, native Hawaiian or other Pacific Islander, and Multiple. [b]Reading center assessed [c]2q4, n=300; Total, n=891. **BRVO**, branch retinal vein occlusion; **CRVO**, central retinal vein occlusion; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **HRVO**, hemiretinal vein occlusion; **SD,** standard deviation.

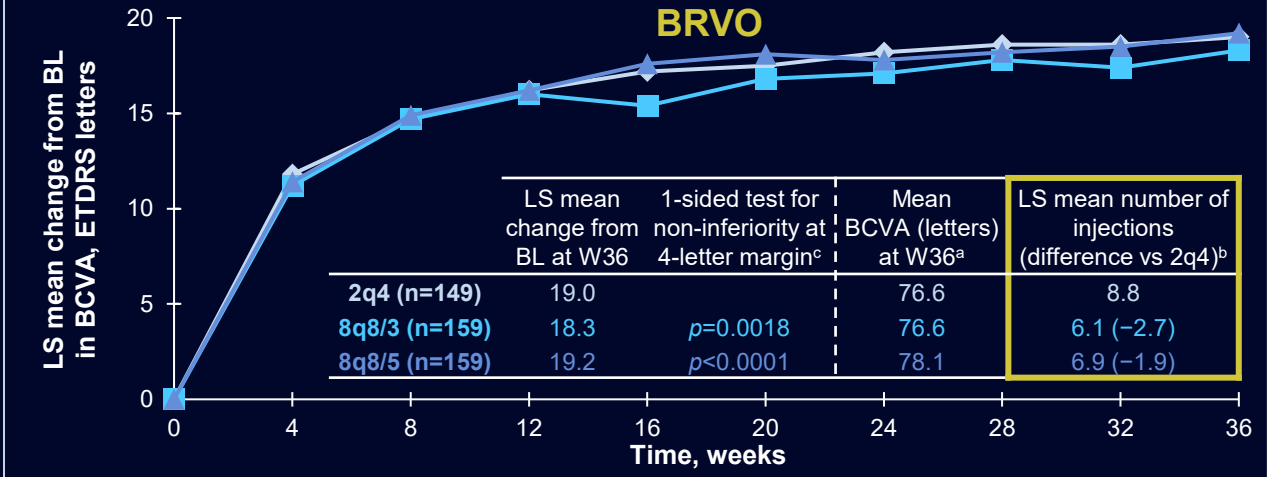
Both Aflibercept 8 mg Groups Achieved Non-inferior BCVA Gains Compared to Aflibercept 2 mg at Week 36, with Fewer Injections Overall and Across RVO Subtypes

Overall RVO Population



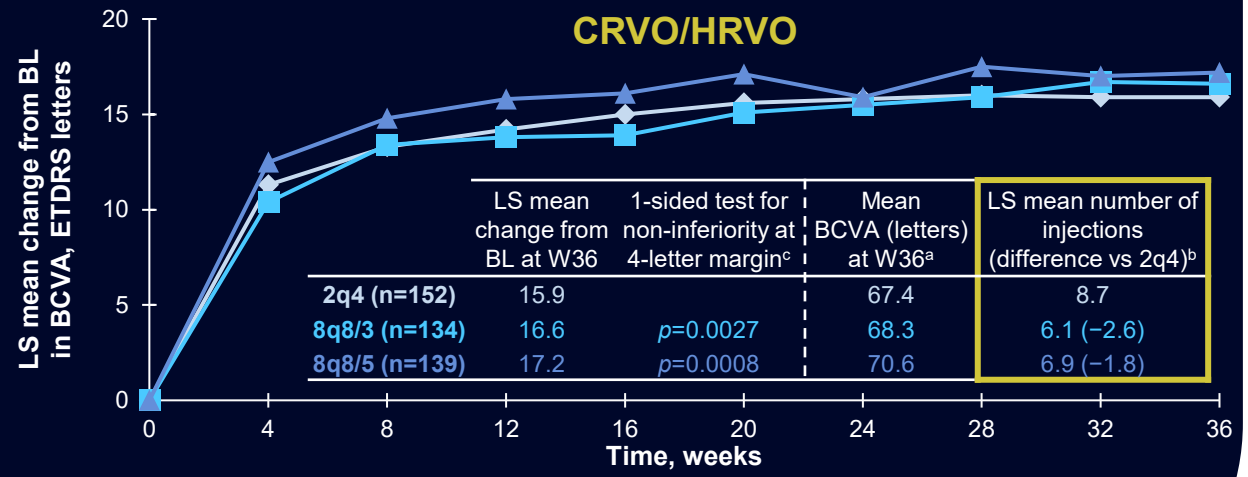
	LS mean change from BL at W36	1-sided test for non-inferiority at 4-letter margin	Mean BCVA (letters) at W36[a]	LS mean number of injections (difference vs 2q4)[b]
2q4 (n=301)	17.5		72.0	8.8
8q8/3 (n=293)	17.4	*p*<0.0001	72.8	6.1 (−2.7)
8q8/5 (n=298)	18.3	*p*<0.0001	74.6	6.9 (−1.8)

BRVO



	LS mean change from BL at W36	1-sided test for non-inferiority at 4-letter margin[c]	Mean BCVA (letters) at W36[a]	LS mean number of injections (difference vs 2q4)[b]
2q4 (n=149)	19.0		76.6	8.8
8q8/3 (n=159)	18.3	*p*=0.0018	76.6	6.1 (−2.7)
8q8/5 (n=159)	19.2	*p*<0.0001	78.1	6.9 (−1.9)

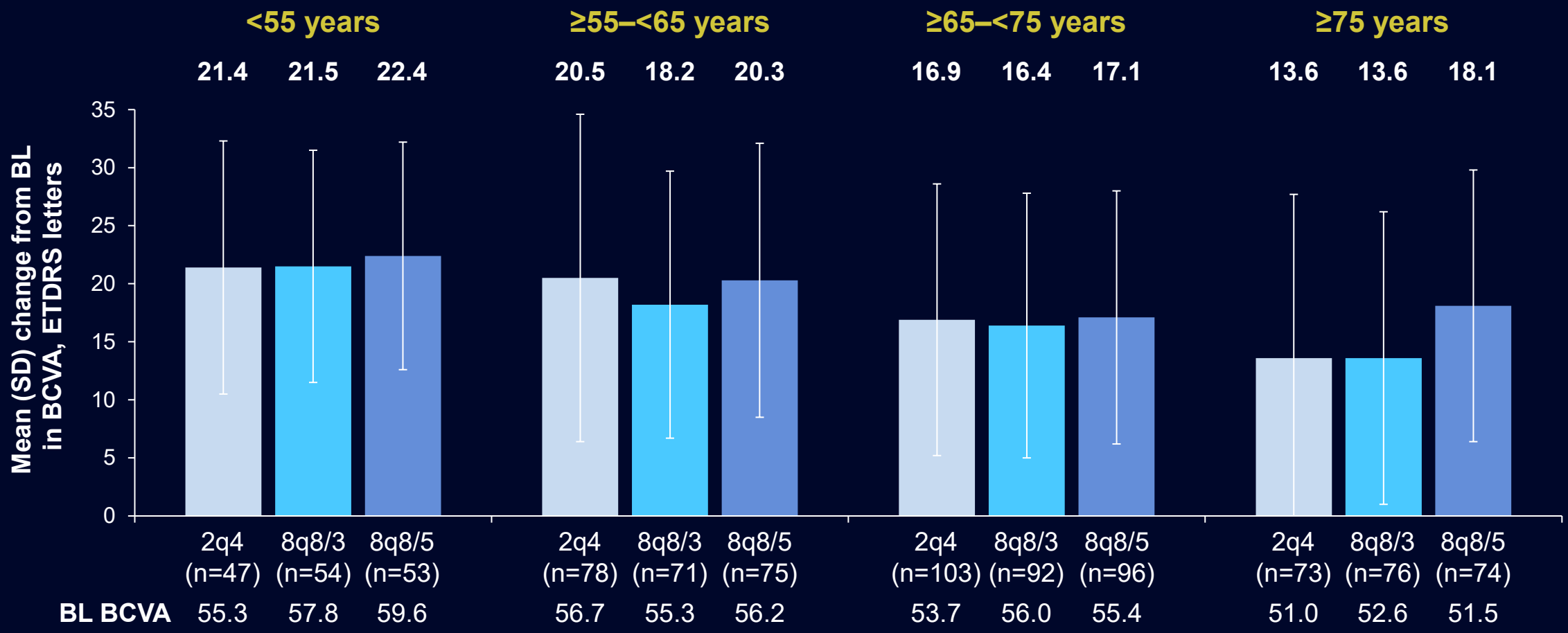
CRVO/HRVO



	LS mean change from BL at W36	1-sided test for non-inferiority at 4-letter margin[c]	Mean BCVA (letters) at W36[a]	LS mean number of injections (difference vs 2q4)[b]
2q4 (n=152)	15.9		67.4	8.7
8q8/3 (n=134)	16.6	*p*=0.0027	68.3	6.1 (−2.6)
8q8/5 (n=139)	17.2	*p*=0.0008	70.6	6.9 (−1.8)

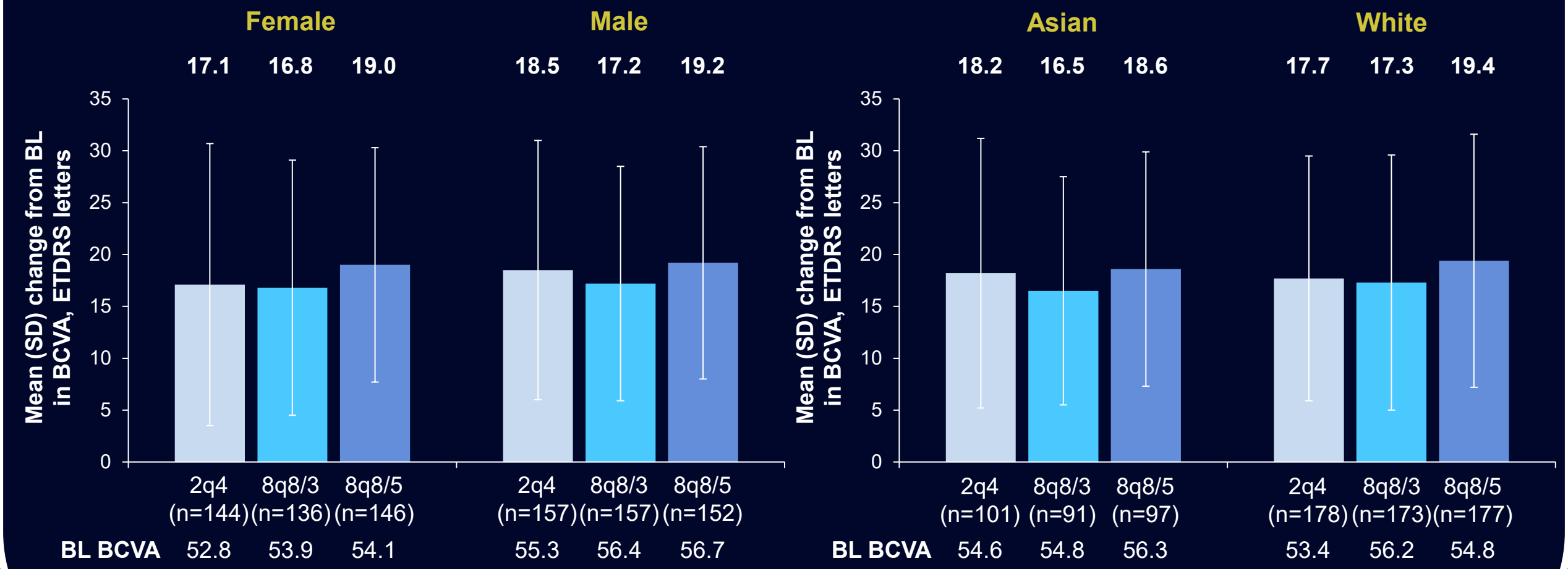
Full analysis set. LS means were generated using a mixed model for repeated measures with baseline BCVA as a covariate. The fixed factors were treatment group (aflibercept 8q8/3, 8q8/5, 2q4); visit; and stratification variables: geographic region (Japan, Asia-Pacific, Europe, America), BL BCVA (<60 vs ≥60 letters), and, for the overall RVO population analysis only, RVO type (CRVO/HRVO vs BRVO). The model also included terms for the interactions between baseline BCVA and visit, and between treatment and visit. [a]Observed values (censoring data post intercurrent event). [b]Missing endpoint values imputed using a multiple imputation procedure. Estimates based on a linear regression model, within the multiple imputation procedure, adjusted for BL BCVA, BL CRT, and stratification variables (geographic region [Japan vs Asia-Pacific vs Europe vs America], BCVA score [>60 vs ≥60], RVO type [CRVO/HRVO vs BRVO]). [c]Nominal *p*-values. **BL**, baseline; **CI**, confidence interval; **LS**, least squares.

Mean Change in BCVA at Week 36 by Age



Full analysis set. Observed values (censoring data post intercurrent event).

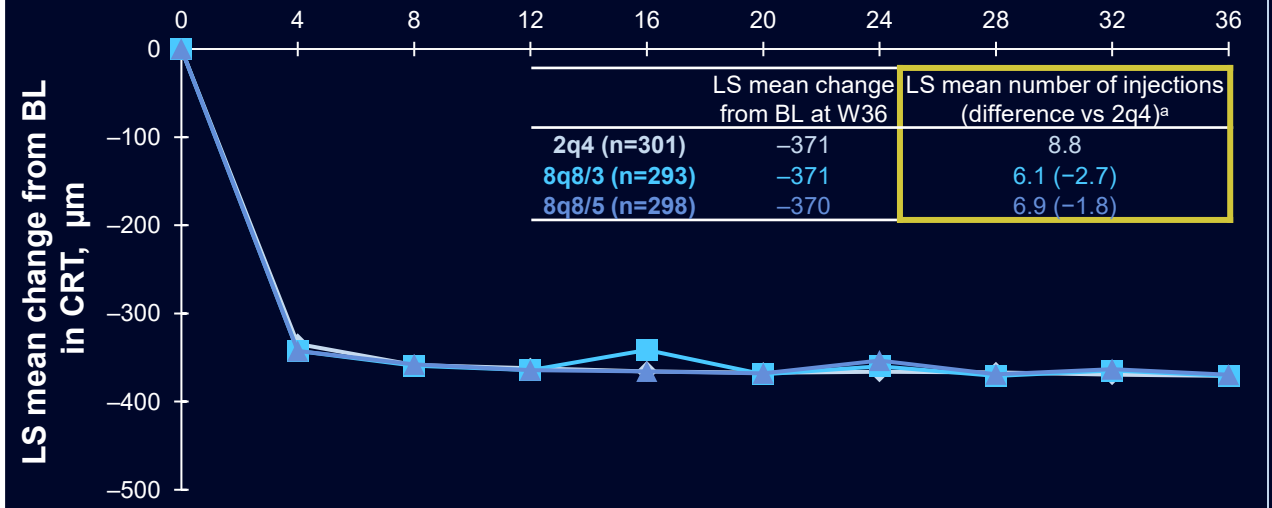
Mean Change in BCVA at Week 36 by Sex and Race[a]



Full analysis set. Observed values (censoring data post intercurrent event). [a]The subgroup Black or African American race could not be evaluated due to small sample size (8, 7, and 9 patients in the 2q4, 8q8/3 and 8q8/5 groups, respectively).

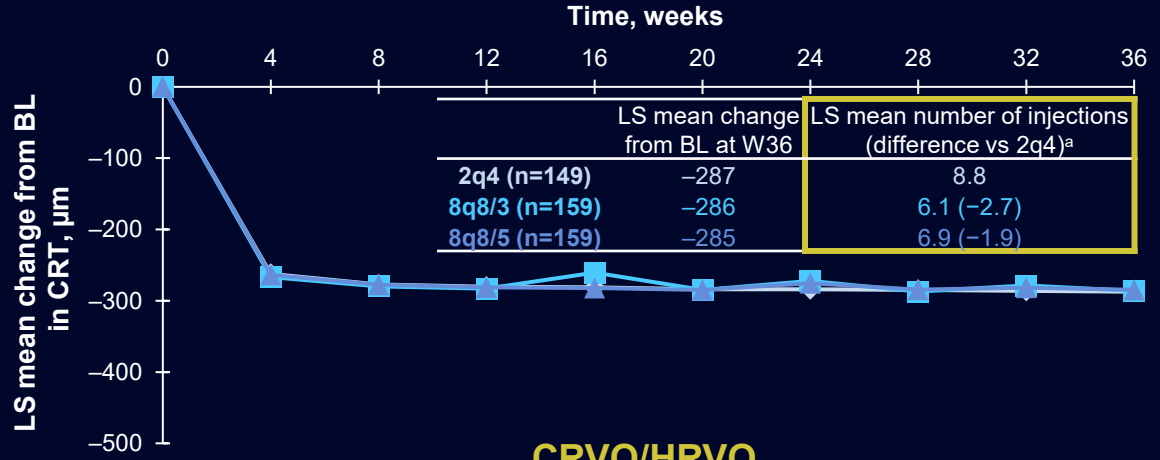
Both Aflibercept 8 mg Groups Achieved Robust CRT Reductions Compared to Aflibercept 2 mg at Week 36, with Fewer Injections Overall and Across RVO Subtypes

Overall RVO Population



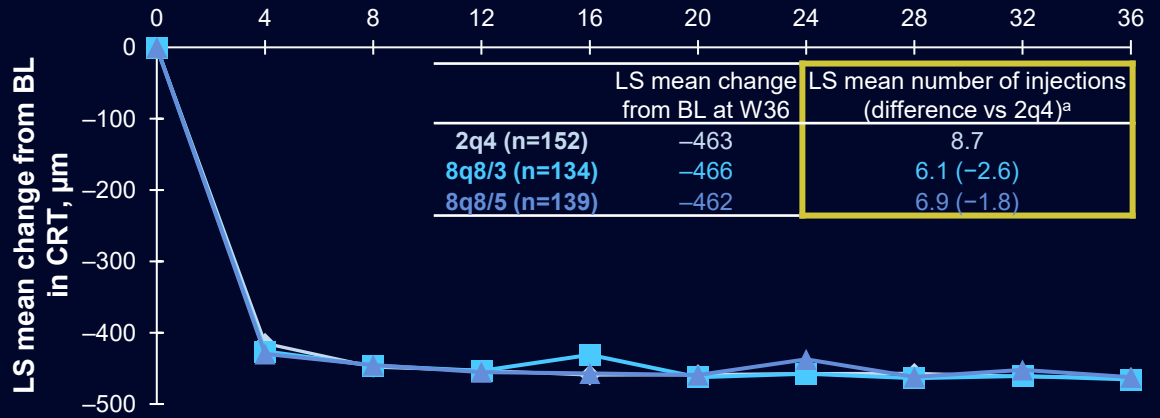
	LS mean change from BL at W36	LS mean number of injections (difference vs 2q4)[a]
2q4 (n=301)	–371	8.8
8q8/3 (n=293)	–371	6.1 (−2.7)
8q8/5 (n=298)	–370	6.9 (−1.8)

BRVO



	LS mean change from BL at W36	LS mean number of injections (difference vs 2q4)[a]
2q4 (n=149)	–287	8.8
8q8/3 (n=159)	–286	6.1 (−2.7)
8q8/5 (n=159)	–285	6.9 (−1.9)

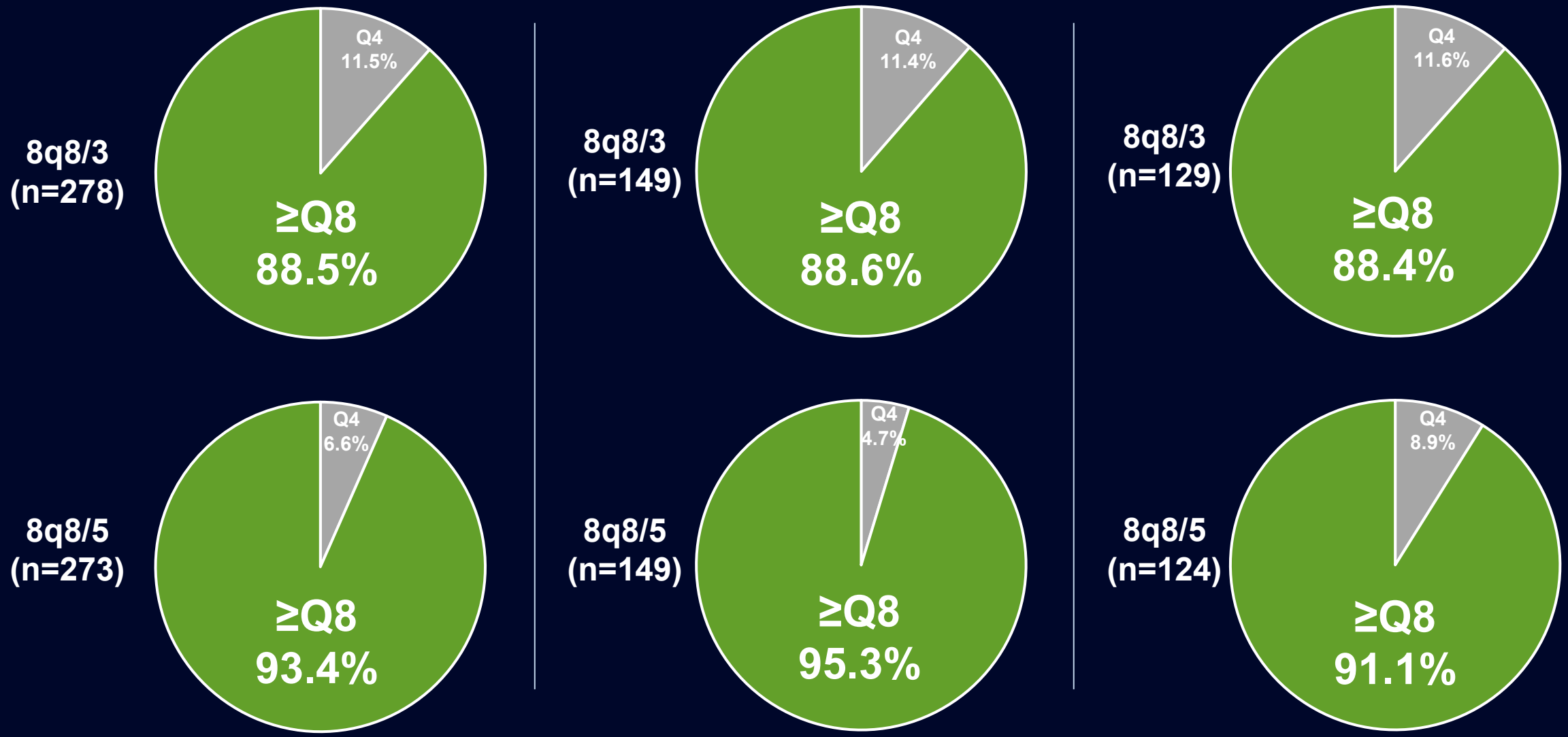
CRVO/HRVO



	LS mean change from BL at W36	LS mean number of injections (difference vs 2q4)[a]
2q4 (n=152)	–463	8.7
8q8/3 (n=134)	–466	6.1 (−2.6)
8q8/5 (n=139)	–462	6.9 (−1.8)

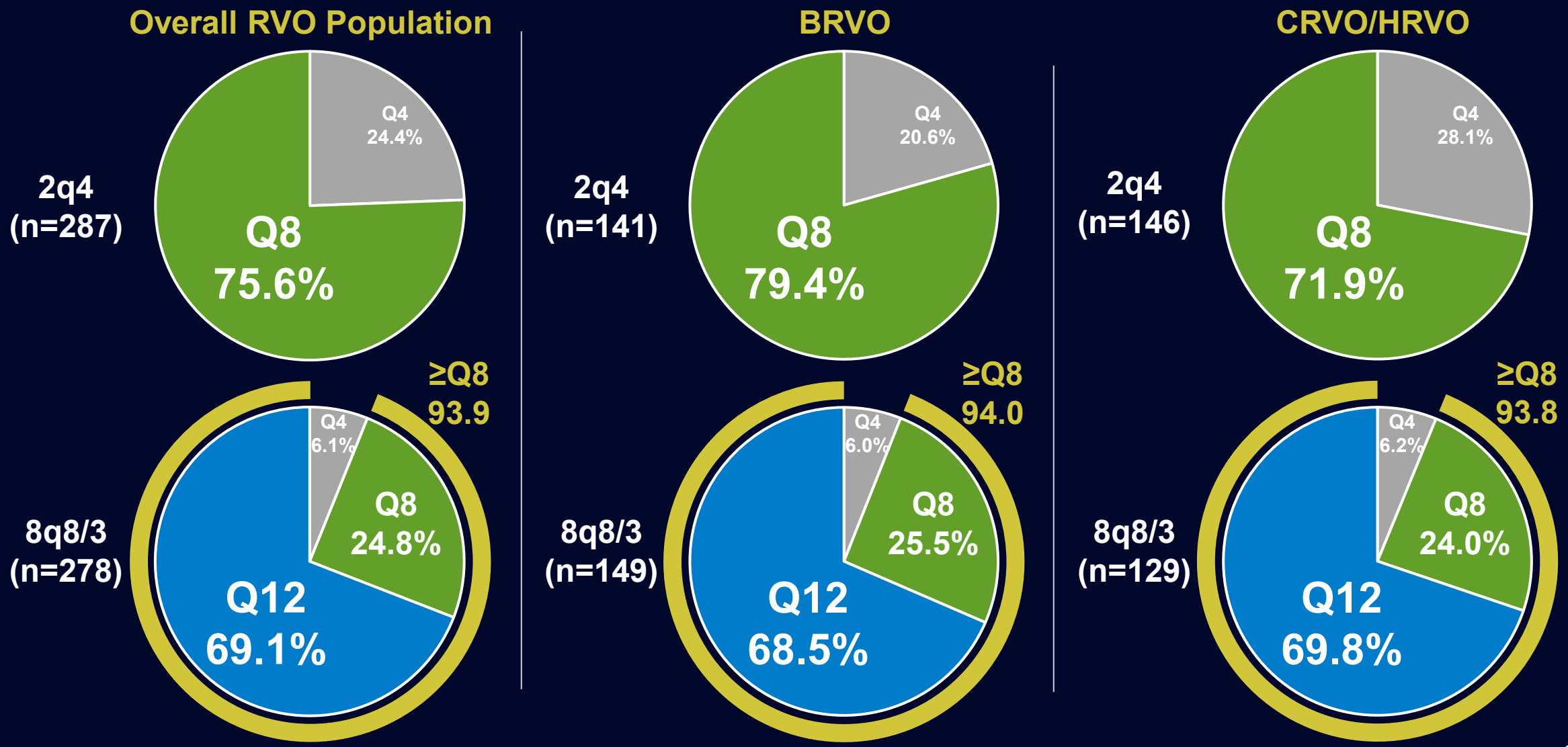
Full analysis set. LS means were generated using a mixed model for repeated measures with baseline CRT as a covariate. The fixed factors were treatment group (aflibercept 8q8/3, 8q8/5, 2q4); visit; and stratification variables: geographic region (Japan, Asia-Pacific, Europe, America), BL BCVA (<60 vs ≥60 letters), and, for the overall RVO population analysis only, RVO type (CRVO/HRVO vs BRVO). The model also included terms for the interaction between baseline CRT and visit, and treatment and visit. [a]Missing endpoint values imputed using a multiple imputation procedure. Estimates based on a linear regression model, within the multiple imputation procedure, adjusted for BL BCVA, BL CRT, and stratification variables (geographic region [Japan vs Asia-Pacific vs Europe vs America], BCVA score [>60 vs ≥60], RVO type [CRVO/HRVO vs BRVO]).

Participants with ≥Q8 Dosing Intervals for the Overall Population, BRVO, and CRVO/HRVO Subtypes at Week 36



Safety analysis set. Patients completing Week 36. **Q4**, every 4 weeks; **Q8**, every 8 weeks.

Last Assigned Dosing Interval at Week 36 for Patients Eligible for Interval Extension: Overall Population, BRVO, and CRVO/HRVO Subtypes



Safety analysis set. Patients completing Week 36. Per study design, dosing interval extension was not possible in the 8q8/5 group until Week 40. **Q12**, every 12 weeks.

Ocular and Non-ocular Safety Through Week 36

	2q4 (n=301)	8q8/3 (n=293)	8q8/5 (n=298)	All 8 mg (n=591)
Ocular TEAEs in the study eye, n (%)	85 (28.2)	103 (35.2)	86 (28.9)	189 (32.0)
Ocular SAEs in the study eye, n (%)	8 (2.7)	3 (1.0)	4 (1.3)	7 (1.2)
Intraocular inflammation in the study eye, n (%)	4 (1.3)	2 (0.7)	1 (0.3)	3 (0.5)
Anterior chamber cell	1 (0.3)	0	0	0
Eye inflammation	1 (0.3)	0	0	0
Iritis	0	1 (0.3)	0	1 (0.2)
Uveitis	0	0	1 (0.3)	1 (0.2)
Endophthalmitis	2 (0.7)	1 (0.3)	0	1 (0.2)
Non-ocular SAEs, n (%)	26 (8.6)	22 (7.5)	28 (9.4)	50 (8.5)
APTC events, n (%)	5 (1.7)	0	3 (1.0)	3 (0.5)
Deaths, n (%)	2 (0.7)	2 (0.7)	3 (1.0)	5 (0.8)

No cases of occlusive retinal vasculitis were reported

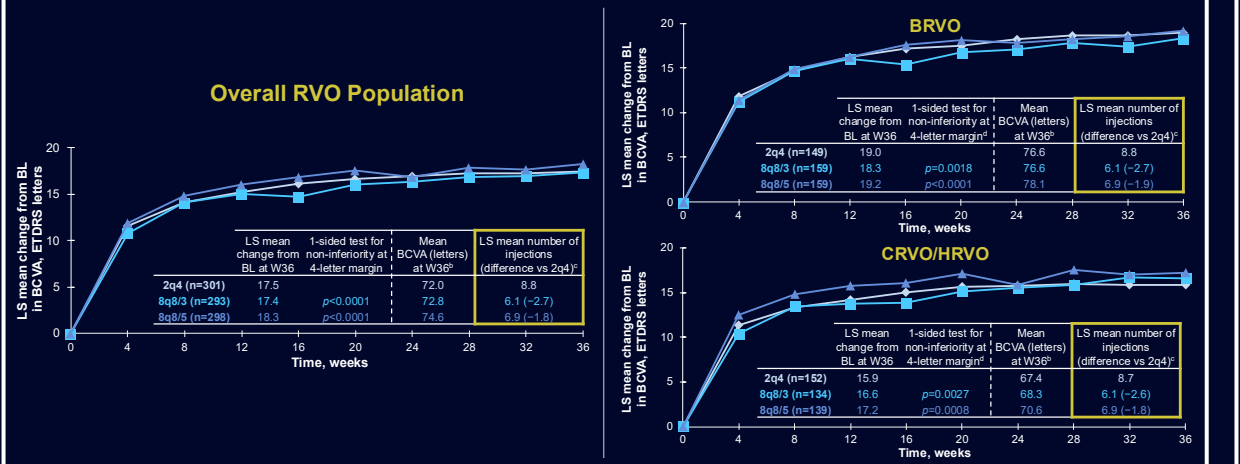
Aflibercept 8 mg had a safety profile consistent with the established safety profile of aflibercept 2 mg and 8 mg

Safety analysis set. **APTC**, Anti-Platelet Trialists' Collaboration; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

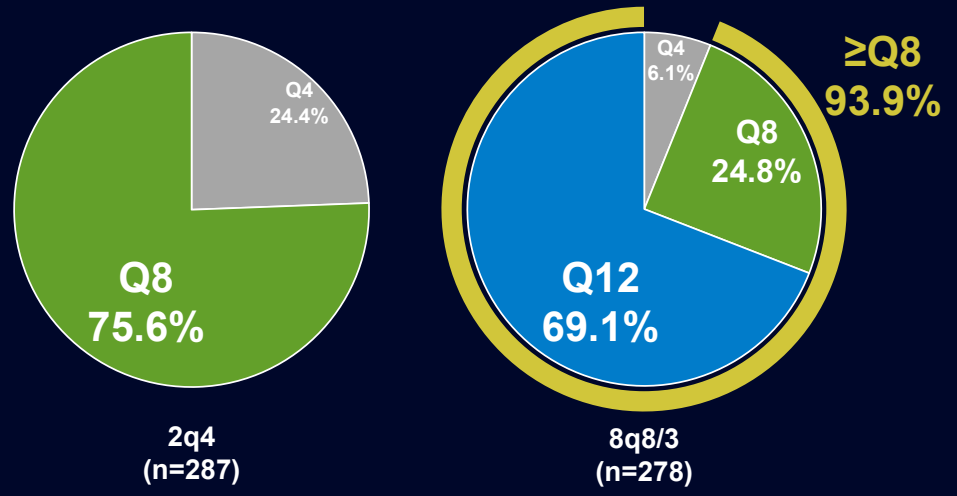
QUASAR: Paradigm Shift in the Treatment of RVO with Aflibercept 8 mg

- Aflibercept 8q8/3 and 8q8/5 groups achieved **non-inferior BCVA gains and robust reductions in CRT,** with fewer injections than in the aflibercept 2q4 group at Week 36
- Aflibercept 8 mg **achieved clinically meaningful BCVA gains from baseline** at Week 36 in patients with macular edema secondary to RVO **across evaluable subgroups of age, sex, and race** with fewer injections than in the aflibercept 2q4 group
- Approximately **94% of patients in the aflibercept 8q8/3 group achieved a last assigned dosing interval of ≥8 weeks**
- The safety profile of aflibercept 8 mg in patients with macular edema secondary to RVO was **consistent with the established safety profile of aflibercept 2 mg and 8 mg**

Primary Endpoint at Week 36: Both Aflibercept 8 mg Groups Achieved Non-inferior BCVA Gains Compared to 2q4 at Week 36,[a] with Fewer Injections



Last Assigned Dosing Interval at Week 36 for Patients Eligible for Interval Extension[e]



[a]Full analysis set. LS means were generated using a mixed model for repeated measures with baseline BCVA as a covariate. The fixed factors were treatment group (aflibercept 8q8/3, 8q8/5, 2q4); visit; and stratification variables: geographic region (Japan, Asia-Pacific, Europe, America), BL BCVA (<60 vs ≥60 letters), and RVO type (CRVO/HRVO vs BRVO). The model also included terms for the interactions between baseline BCVA and visit, and between treatment and visit. [b]Observed values (censoring data post intercurrent event). [c]Missing endpoint values imputed using a multiple imputation procedure. Estimates based on a linear regression model, within the multiple imputation procedure, adjusted for BL BCVA, BL CRT, and stratification variables (geographic region [Japan vs Asia-Pacific vs Europe vs America], BCVA score [>60 vs ≥60], RVO type [CRVO/HRVO vs BRVO]). [d]Nominal *p*-values. [e]Safety analysis set. Patients completing Week 36.