Intravitreal Aflibercept 8 mg in Patients with Polypoidal Choroidal Vasculopathy (PCV): A Phase 3 PULSAR Trial Subgroup Analysis

Michael Singer,[1] on behalf of the PULSAR study investigators

[1]Medical Center of Ophthalmology, University of Texas Health Science Center, San Antonio, Texas, USA

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Disclosures

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- Michael Singer reports consulting fees for Aerie, Biogen Bausch, Alimera, Adverum, Allergan, Eyepoint, Genentech, Novartis, Ocular Therapeutics, Regeneron Pharmaceuticals, Inc., and Eyepoint; has served on speakers bureau for Allergan, Eyepoint, Genentech, Eyepoint, Regeneron Pharmaceuticals, Inc., Apellis, and Biogen; contracted research: Aerie, Adverum, Allergan, Alimera, Ashvanta, Clearside, DRCR, Genentech, Icon, Ionis, Kalvista, Kodiak, Jansen, Novartis, ,Ocuterra Opthea, Optos, Oysterpoint, Regeneron, Recens, Rezolute Medical, Santen, Senju, Sydnexis, and Ribomic; and holds equityin Aviceda, Nanoscope, Olives and Inflammasome

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- This study includes research conducted with human patients. Institutional Review Board approval was obtained prior to study initiation

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PULSAR Study Design

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Multicenter, randomized, double-masked study in patients with treatment-naïve nAMD
Randomized at baseline 1 (2q8) : 1 (8q12) : 1 (8q16)

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

Primary endpoint at Week 48:
Mean change in BCVA (non-inferiority)

Key secondary endpoint at Week 16:
Proportion of patients without IRF and SRF in the center subfield

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

BCVA, best corrected visual acuity; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid.

PULSAR: Dosing Schedule and Regimen Modification in Year 1

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Primary Endpoint

	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	o	X	o	X	o	X	o	X
8q12	X	X	X		o	X	o	o	X	o	o	X	o
8q16	X	X	X		o	o	X	o	o	o	X	o	o

DRM criteria for shortening dosing interval[a]

- >5-letter loss in BCVA due to persistent or worsening nAMD

AND

- >25-µm increase in CST, or new-onset foveal neovascularization, or foveal hemorrhage

[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**

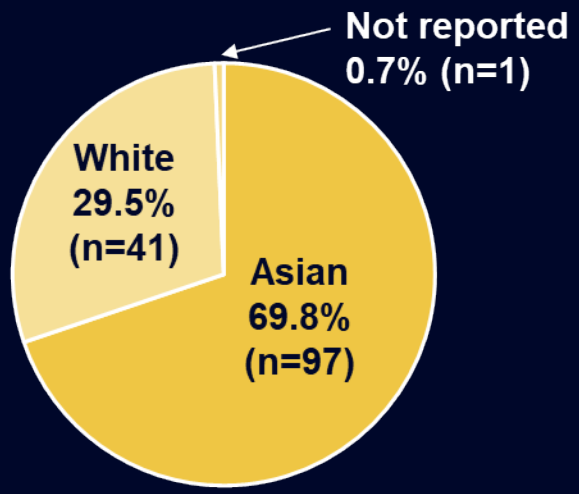
- **Week 16 and 20:** Patients on 8q12 and 8q16 meeting DRM criteria shortened to q8
- **Week 24:** Patients on 8q16 meeting DRM criteria shortened to q12
- **Week 32 and 44 for 8q12 and Week 40 for 8q16:** Treatment interval shortened by 4 weeks for patients meeting DRM criteria

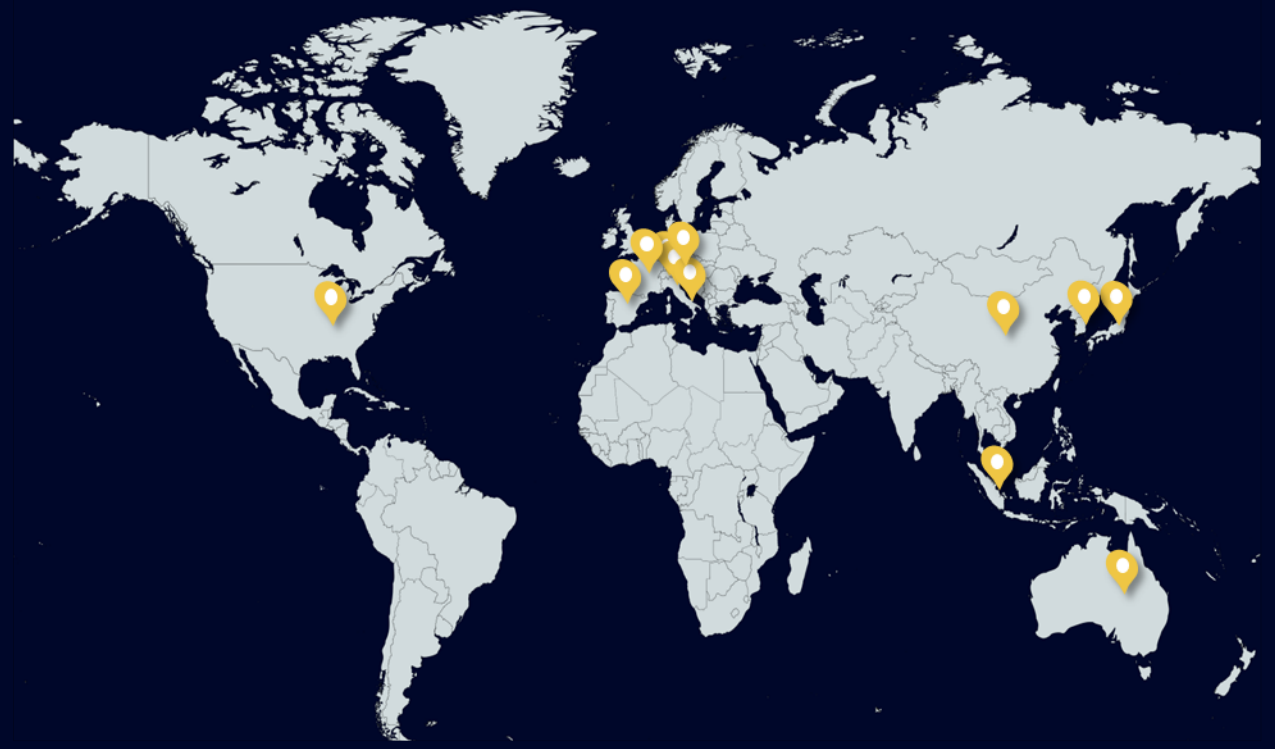
Stippled boxes = initial treatment phase; X = active injection; o = sham injections. Note: Table does not reflect all dosing options once a patient is shortened.
CST, central subfield thickness; DRM, dose regimen modification; Wk, week.

PCV in PULSAR

- PULSAR is a global study conducted across 223 sites in 27 countries
- **ICGA** was optional and **conducted in 295 patients in 12 countries**[a]
  - PCV present: n=139
  - PCV absent: n=153
  - Data missing: n=3

Race of PCV subgroup[b]





ICGA images were graded by the reading center.
[a]Australia (n=15); Austria (n=7); France (n=2); Italy (n=22); Japan (n=72); Korea (n=26); Latvia (n=2); mainland China (n=67); Singapore (n=1); Spain (n=3); Switzerland (n=3); USA (n=77).
[b]No patients were reported as Black or African American, or as being of multiple ethnicity.
APAC, Asia Pacific; ICGA, indocyanine green angiography; PCV, polypoidal choroidal vasculopathy.

Baseline Demographics and Disease Characteristics

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	PCV Subgroup				Overall Population			
	2q8 (n=54)	8q12 (n=44)	8q16 (n=41)	All 8 mg (n=85)	2q8 (n=336)	8q12 (n=335)	8q16 (n=338)	All 8 mg (n=673)
Age, years	72.6 (8.2)	72.2 (8.1)	73.2 (8.7)	72.7 (8.3)	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.6 (8.2)
Female, %	31.5	50.0	36.6	43.5	56.0	54.3	53.3	53.8
BCVA, ETDRS letters	57.6 (15.5)	56.3 (13.3)	60.1 (11.5)	58.1 (12.5)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.9 (12.9)
CST, µm	378 (163)	392 (129)	377 (139)	384 (134)	367 (134)	370 (124)	371 (133)	371 (128)
CNV size, mm^2	5.8 (4.7)	5.1 (3.8)	5.2 (4.5)	5.1 (4.2)	6.4 (5.0)	6.0 (4.8)	6.5 (5.5)	6.3 (5.2)

FAS.
Data are mean (SD) unless otherwise indicated.
CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.

Absolute BCVA and Change from Baseline in BCVA Through Week 48

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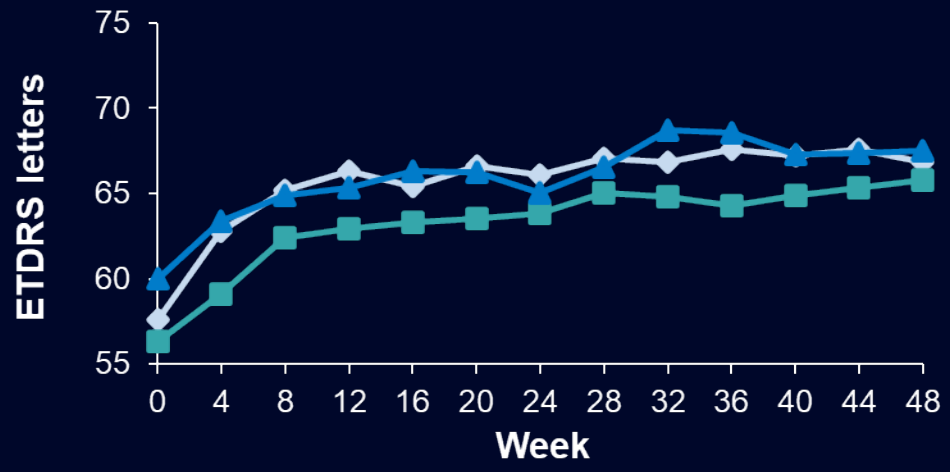
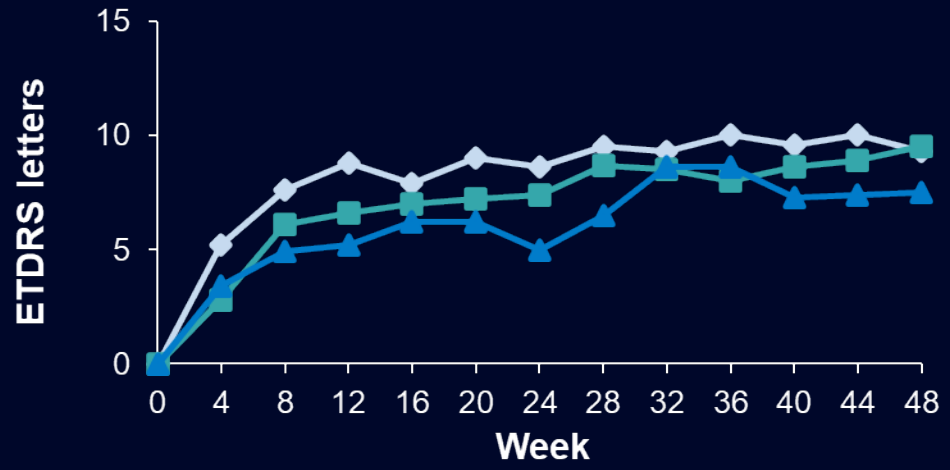
PCV subgroup

Absolute BCVA (LOCF)

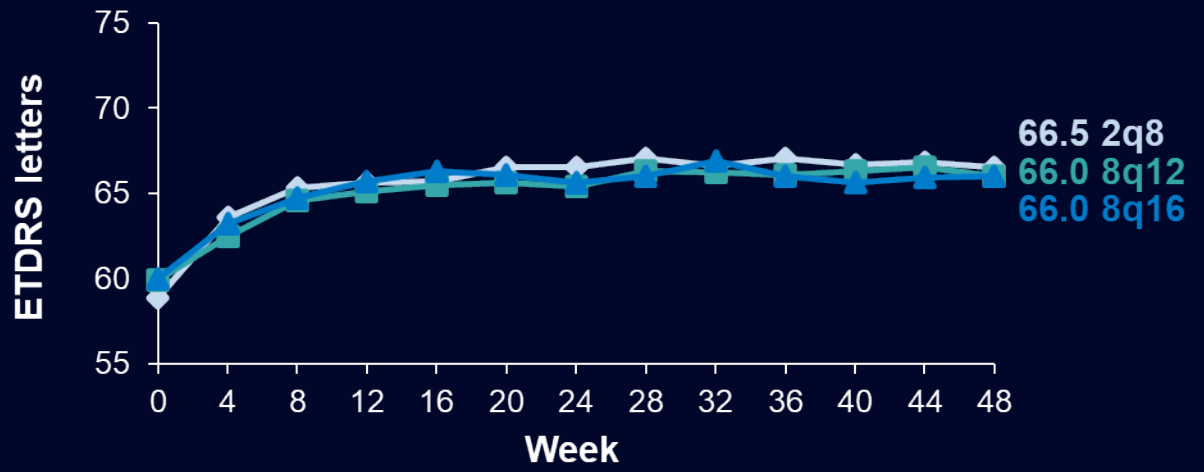


BCVA change from Baseline (LOCF)

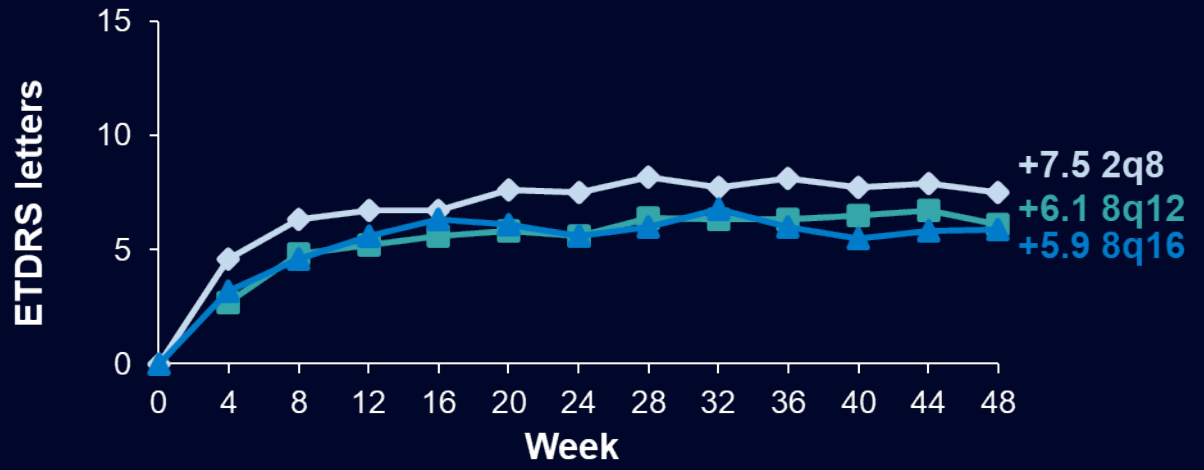


Overall population

Absolute BCVA (LOCF)



BCVA change from Baseline (LOCF)



FAS, LOCF. PCV subgroup: 2q8 n=54; 8q12 n=44; 8q16 n=41 (at baseline). Overall population: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
LOCF: last available observed value prior to ICE will be used to impute missing data. ICE was handled according to sensitivity estimand strategy for continuous endpoints as described.
ICE, intercurrent event; LOCF, last observation carried forward.

Proportions of Patients Maintained on Q12 and Q16 Dosing Intervals Through Week 48

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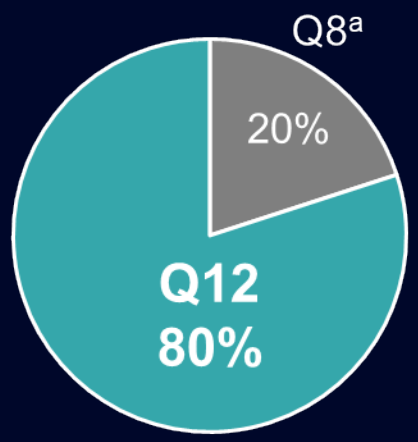
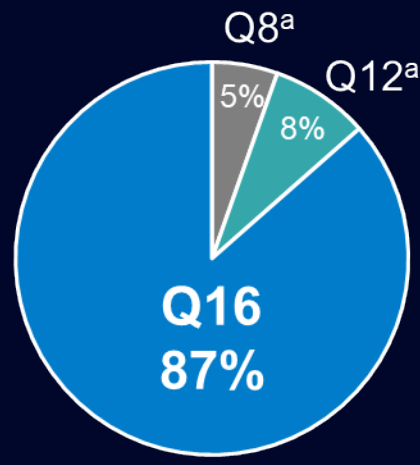
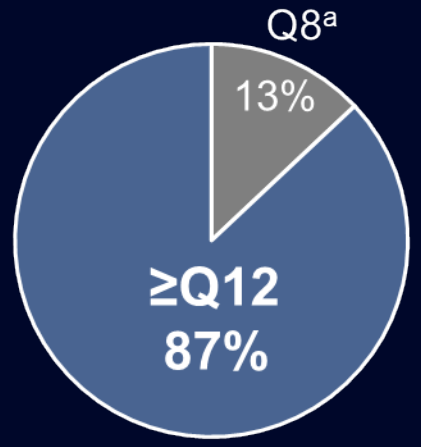
PCV subgroup



8q12
(n=41)[b]



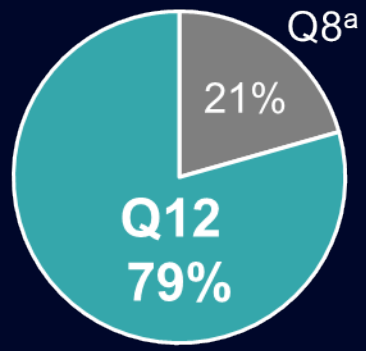
8q16
(n=37)[b]



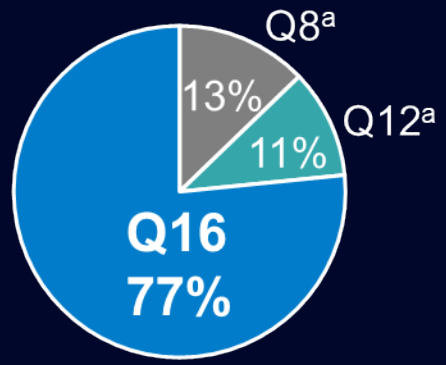
All aflibercept 8 mg
(n=78)[b]

87% of patients receiving aflibercept 8 mg maintained dosing intervals ≥12 weeks

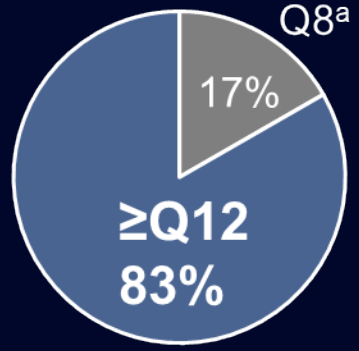
Overall population



8q12
(n=316)[b]



8q16
(n=312)[b]



All aflibercept 8 mg
(n=628)[b]

83% of patients receiving aflibercept 8 mg maintained dosing intervals ≥12 weeks

Values may not add up to 100% due to rounding.
[a]Patients shortened based on DRM assessments at some point through Week 48. [b]Patients completing Week 48.

Proportion of Patients Without Retinal Fluid in the Center Subfield At Week 16

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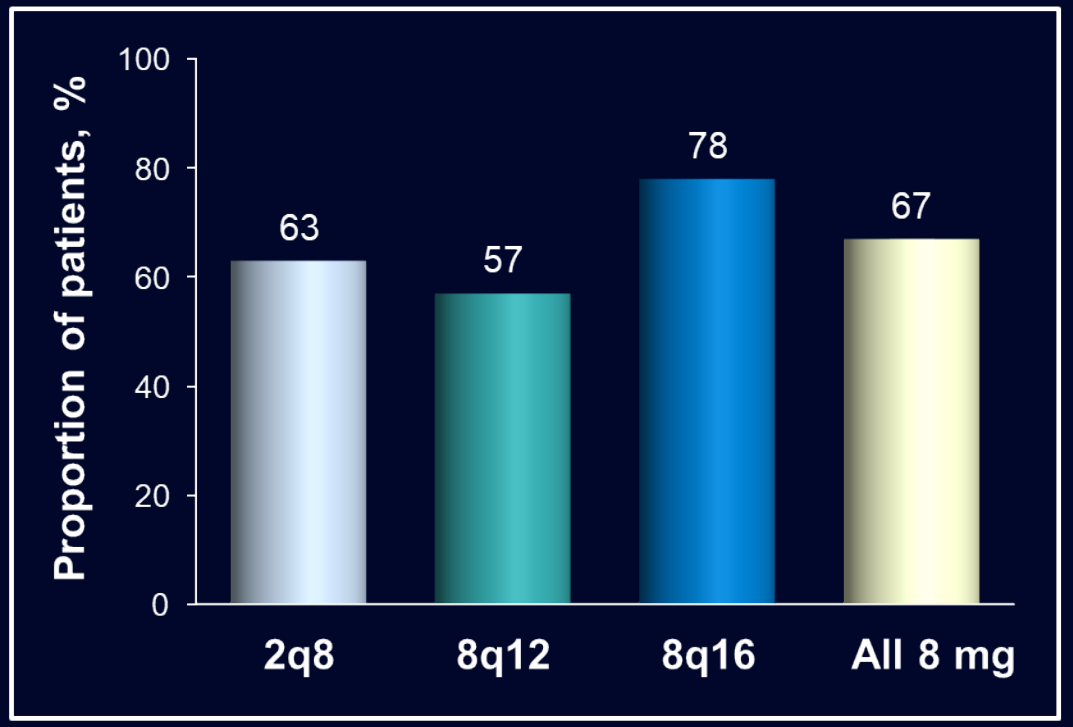
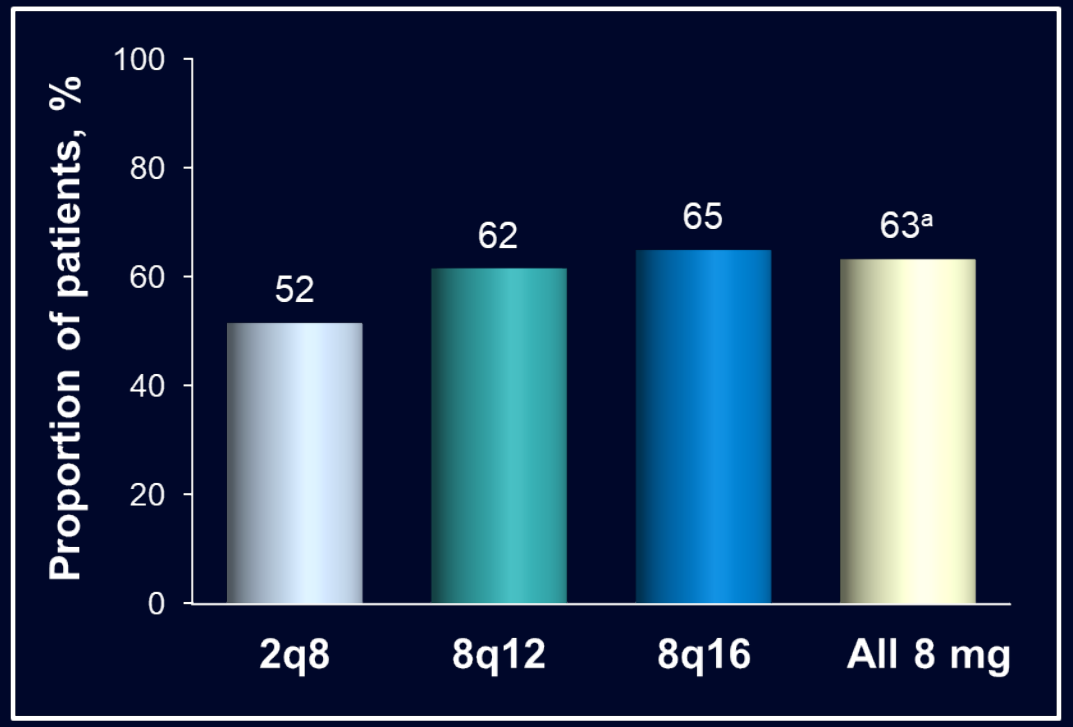
PCV Subgroup



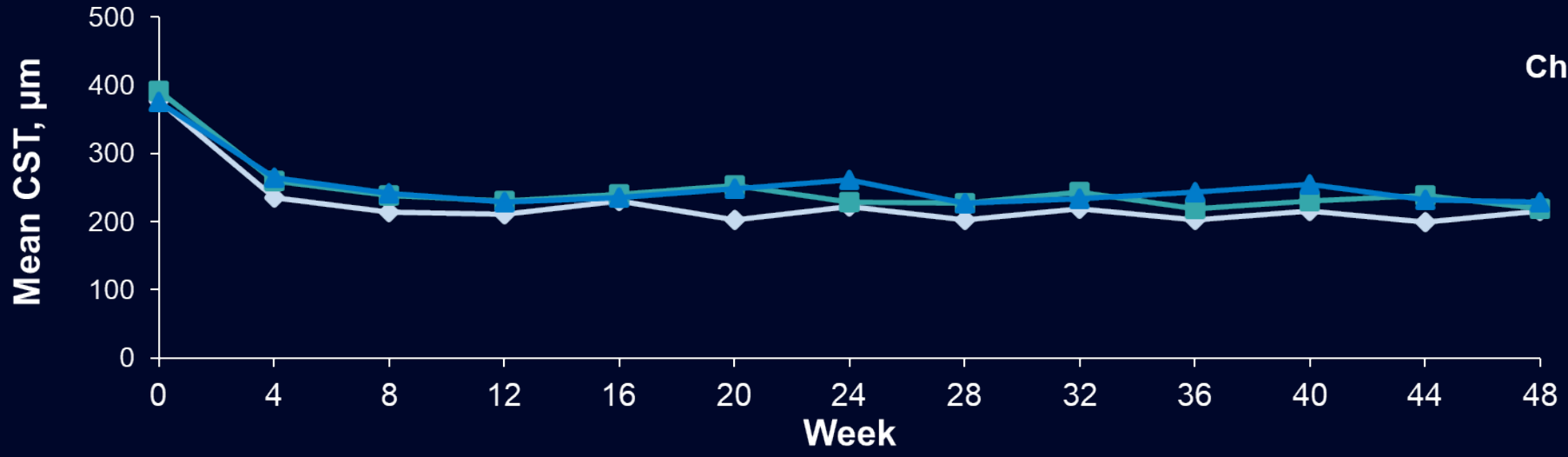
Overall Population



LOCF (censoring data post ICEs); FAS (PCV subgroup).
'Without retinal fluid' defined as absence of IRF and SRF in center subfield.
[a]Key secondary endpoint; 1-sided superiority p-value: p = 0.0002 for all 8 mg vs 2q8.

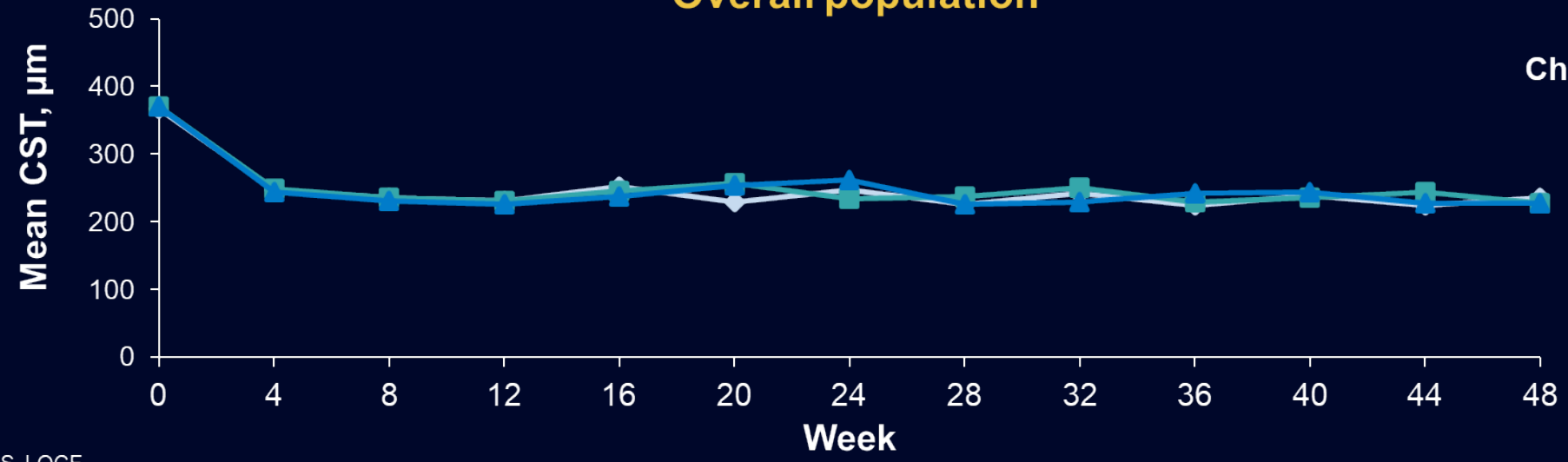
Absolute CST Through Week 48

PCV subgroup



Change from baseline at Week 48
–147 µm 8q16
–148 µm 2q8
–172 µm 8q12

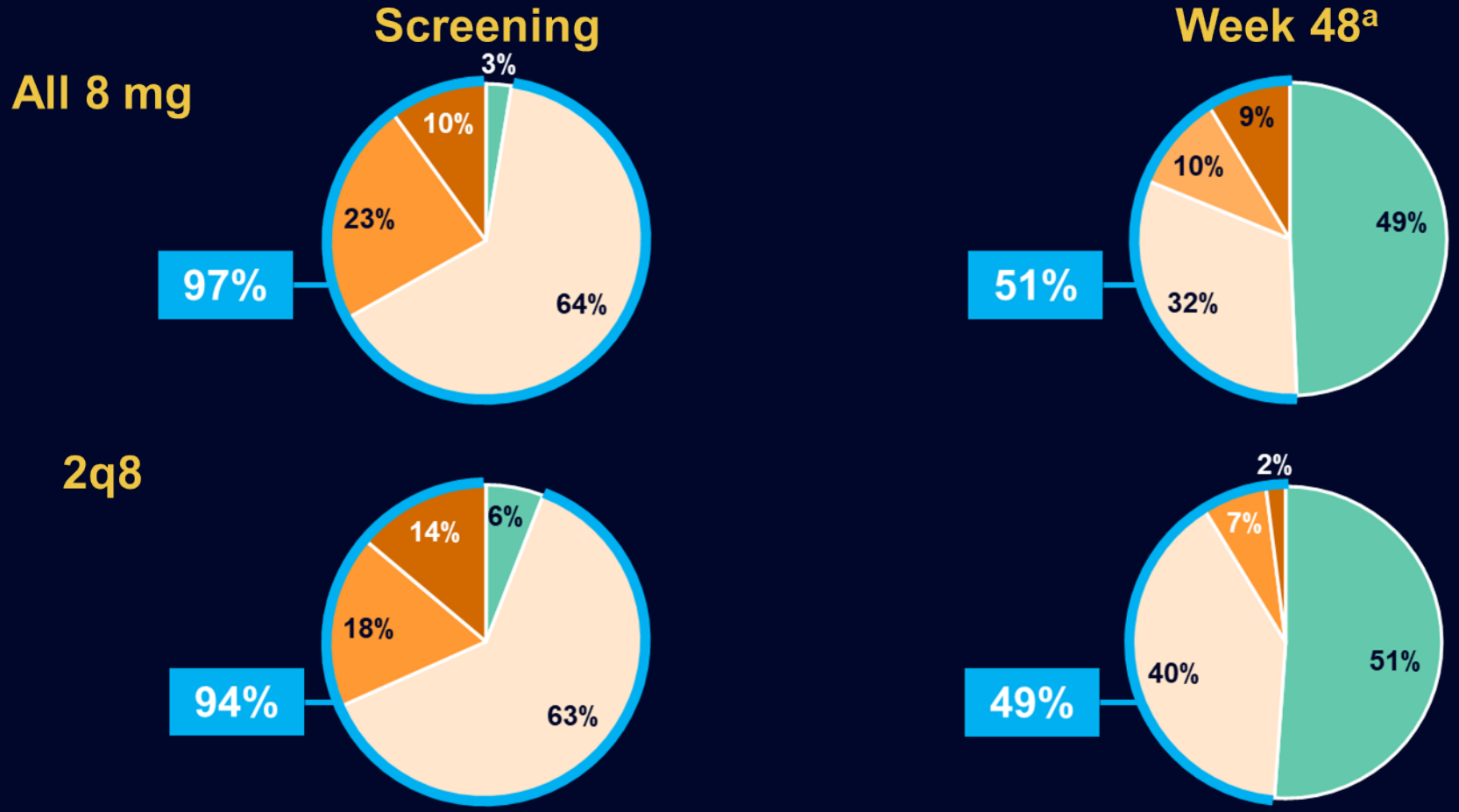
Overall population



Change from baseline at Week 48
–130 µm 2q8
–141 µm 8q12
–143 µm 8q16

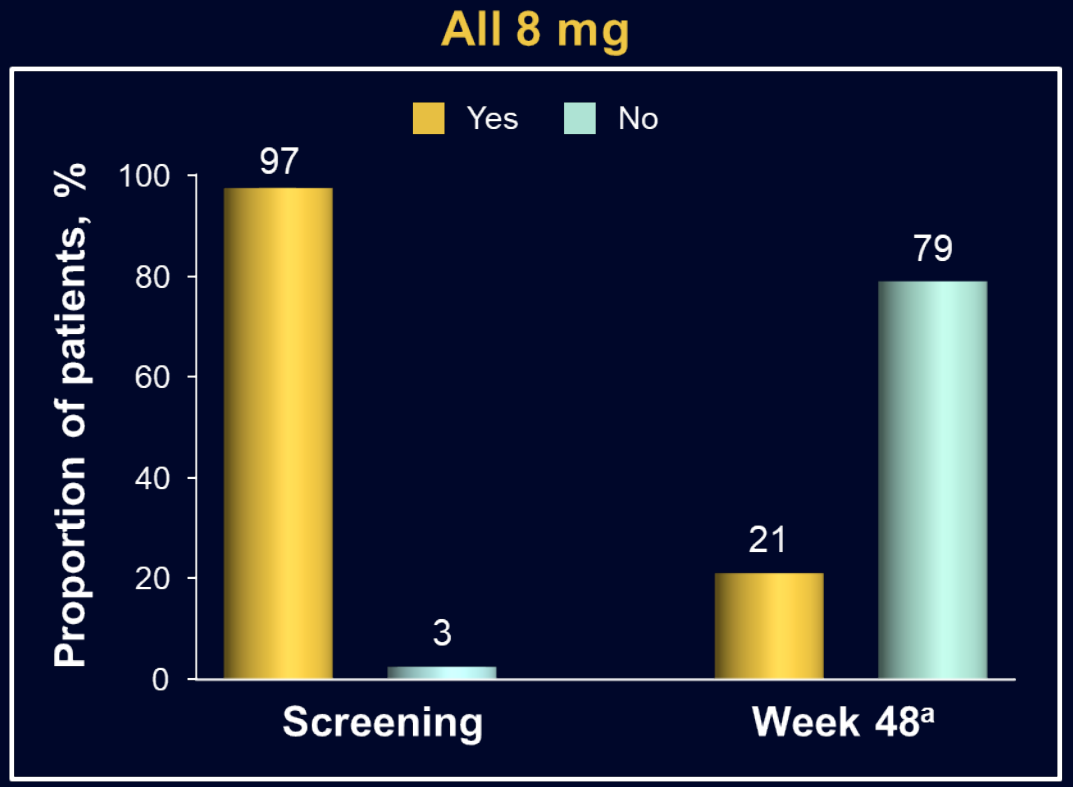
FAS, LOCF.
PCV subgroup: 2q8 n=54; 8q12 n=44; 8q16 n=41. Overall population: 2q8 n=335; 8q12 n=333; 8q16 n=334.

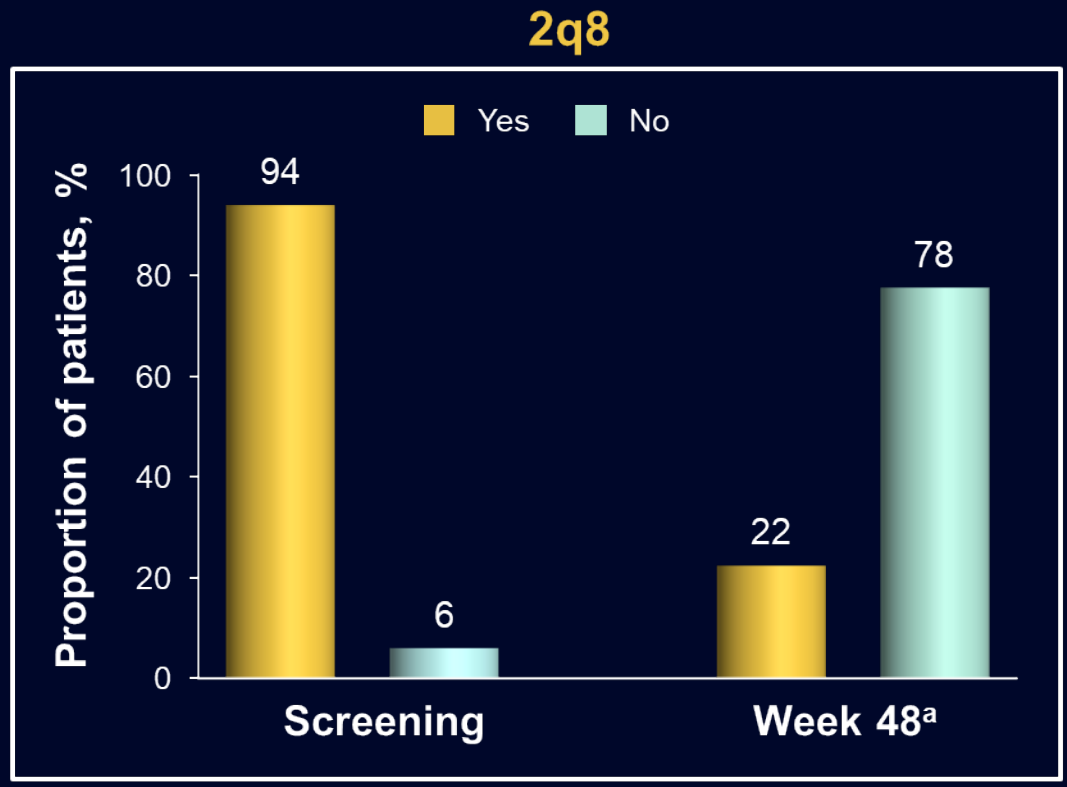
PCV Subgroup: Proportion of Patients with Polyps



Data are for patients with PCV who completed Week 48. Screening (Visit 1) occurred before the baseline visit (Visit 2). For polyp data: 2q8, n=51; All 8 mg, n=78.
Percentage calculated based on number of patients with known number of polyps. Values may not add up to 100% due to rounding.
[a]At Week 48, number of polyps unknown for n=6 and n=9 in 2q8 and All 8 mg groups, respectively.

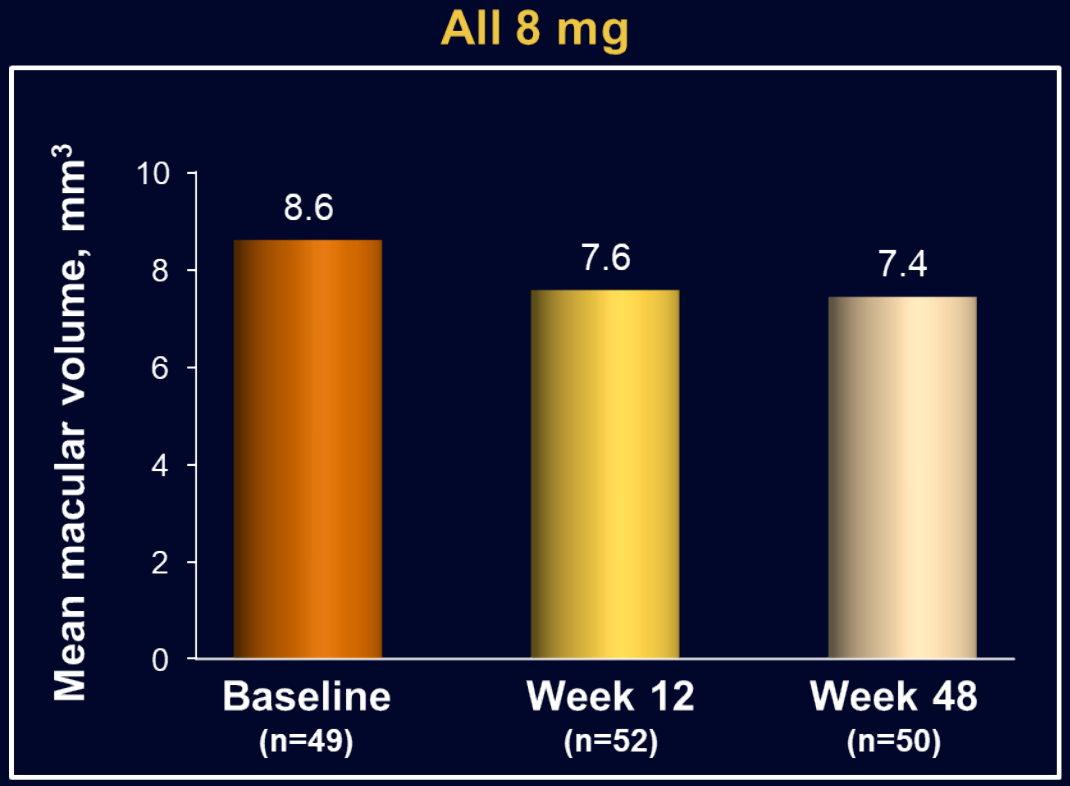
PCV Subgroup: Proportion of Patients with Active Polyps

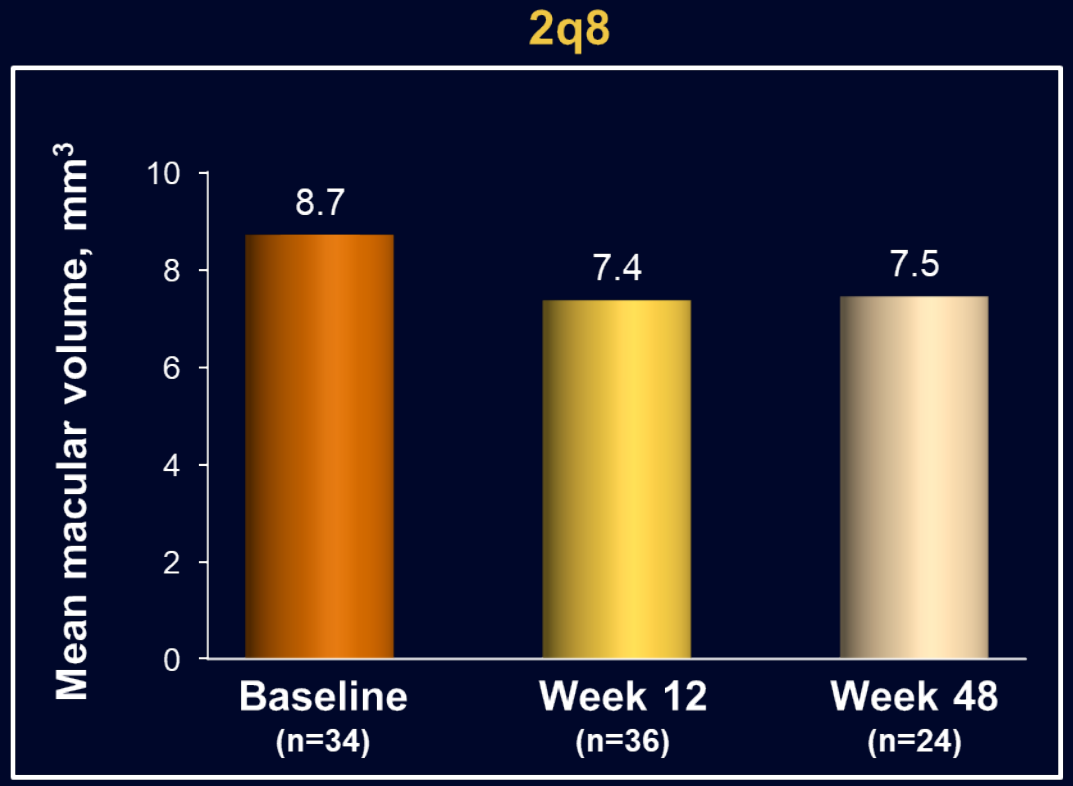




Data are for patients with PCV who completed Week 48. Screening (Visit 1) occurred before the baseline visit (Visit 2). For polyp data: 2q8, n=51; All 8 mg, n=78.
Percentage calculated based on number of patients with known number of polyps.
No' active polyps defined as no polyps present OR (IRF and SRF are 'absent' or 'questionable').
[a]At Week 48, n=2 unknown each for 2q8 and All 8 mg groups.

PCV Subgroup: Absolute Macular Volume





Safety Through Week 48

	PCV Subgroup				Overall Population			
	2q8 (n=54)	8q12 (n=44)	8q16 (n=41)	All 8 mg (n=85)	2q8 (n=336)	8q12 (n=335)	8q16 (n=338)	All 8 mg (n=673)
Any ocular TEAE, n (%)	14 (25.9)	17 (38.6)	13 (31.7)	30 (35.3)	130 (38.7)	129 (38.5)	127 (37.6)	256 (38.0)
Reduced visual acuity	3 (5.6)	2 (4.5)	0	2 (2.4)	20 (6.0)	12 (3.6)	18 (5.3)	30 (4.5)
Cataract	2 cases of cataracts[a]				10 (3.0)	12 (3.6)	12 (3.6)	24 (3.6)
Retinal hemorrhage	2 (3.7)	3 (6.8)	1 (2.4)	4 (4.7)	14 (4.2)	11 (3.3)	10 (3.0)	21 (3.1)
Intraocular pressure increased	1 (1.9)	2 (4.5)	3 (7.3)	5 (5.9)	7 (2.1)	11 (3.3)	9 (2.7)	20 (3.0)
Vitreous floaters	2 (3.7)	0	3 (7.3)	3 (3.5)	11 (3.3)	4 (1.2)	12 (3.6)	16 (2.4)
Subretinal fluid	0	0	0	0	11 (3.3)	10 (3.0)	5 (1.5)	15 (2.2)
Intraocular inflammation	1 mild case[a]				2 (0.6)	4 (1.2)	1 (0.3)	5 (0.7)
Endophthalmitis	0	0	0	0	0	0	0	0
Occlusive retinal vasculitis	0	0	0	0	0	0	0	0

- No APTC events, hypertension events, and non-ocular SAEs were reported in the PCV subgroup
- The safety profile of aflibercept 8 mg in nAMD was comparable with that of aflibercept 2 mg, both in the PCV subgroup and overall population of patients with nAMD

SAF.
TEAEs are AEs occurring from the first injection to 30 days after the last injection (active or sham); ocular TEAEs are those occurring in the study eye.
[a]Data presented in this way to avoid unintentional patient unmasking.
AE, adverse event; TEAE, treatment-emergent adverse event; SAF, safety analysis set.

Conclusions: Aflibercept 8 mg Monotherapy in PCV

Aflibercept 8 mg monotherapy[a] showed robust efficacy benefits

Robust improvements in BCVA from baseline to Week 48 were observed in the aflibercept 8q12, 8q16, and 2q8 PCV subgroups (+9.5, +7.5, and +9.3 letters, respectively)

At **Week 16, fluid was absent** in 67% and 63% of patients with PCV in the pooled aflibercept 8 mg group and aflibercept 2 mg group, respectively

Aflibercept 8 mg and aflibercept 2 mg **markedly reduced** the proportion of patients with PCV with **active polyps** from baseline (97% and 94%) to Week 48 (21% and 22%), respectively

Extended durability

In total, **87%** of patients with PCV treated with aflibercept 8 mg were maintained on dosing intervals **≥12 weeks**, suggesting extended durability compared with aflibercept 2 mg

Comparable safety profile with aflibercept 2 mg

In the PULSAR study, the **safety profile** of aflibercept 8 mg was **similar** in the PCV subgroup and the overall study population, and the safety profile was comparable to that of aflibercept 2 mg[1,2]

[a]Without active rescue photodynamic therapy.

1. Heier et al. *Ophthalmology* 2012;119(12):2537-48.; 2. Schmidt-Erfurth et al. *Ophthalmology* 2014;121(1):193-201.

PULSAR: 96-week Results

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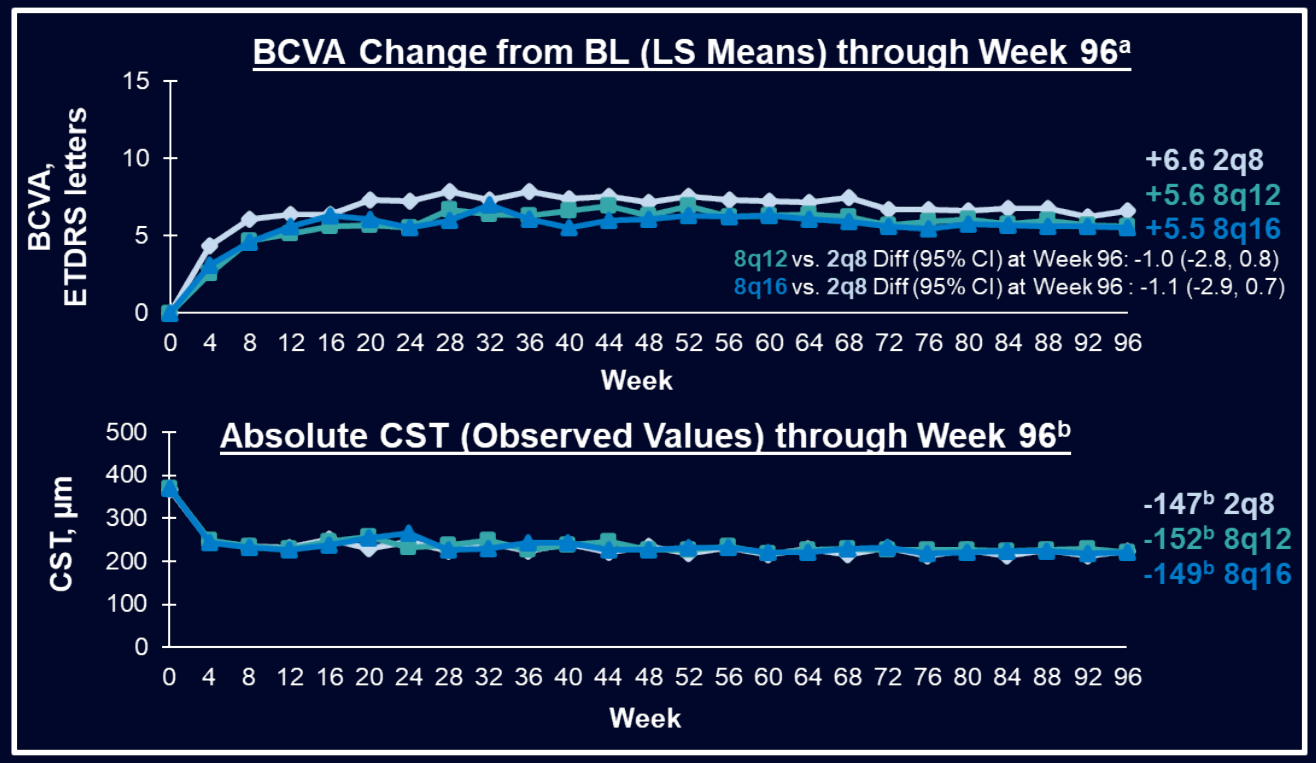
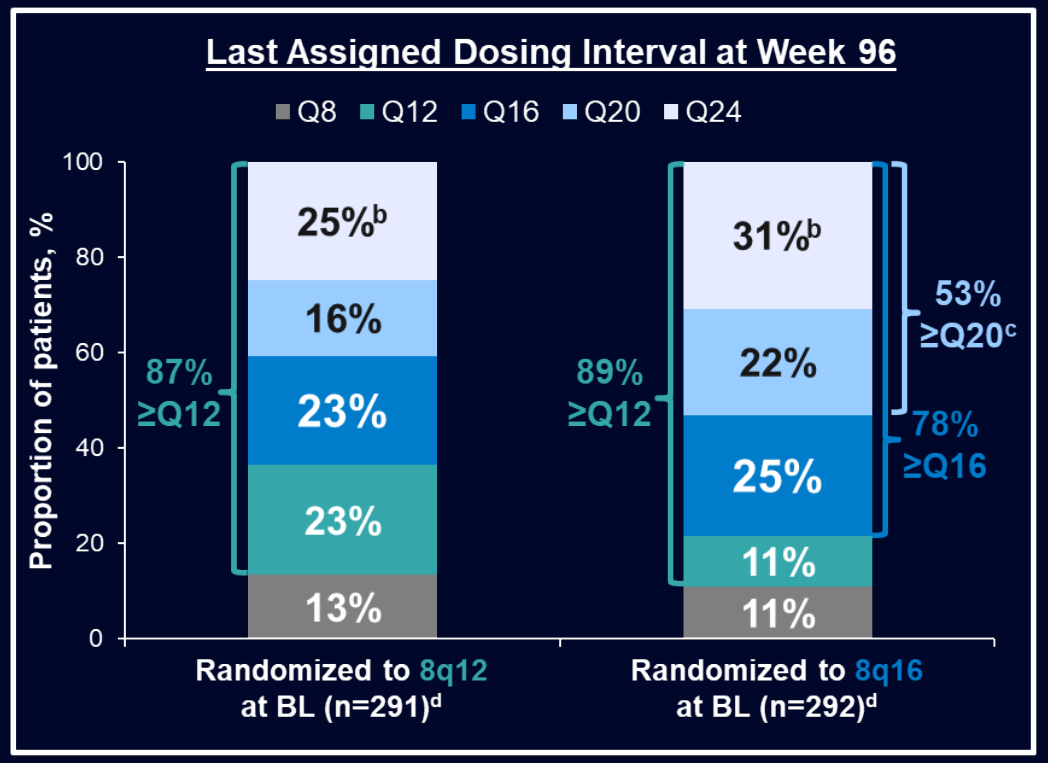
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic improvement in PULSAR for aflibercept 8 mg was generally maintained over time at Week 96
- At Week 96, 89% of patients receiving aflibercept 8q16 achieved ≥Q12 dosing intervals and 78% achieved ≥Q16 intervals
- The safety profile of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks





[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (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) as fixed factors, and interaction terms for baseline and visit and for treatment and visit. [b]Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [c]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within the 96-week study period. [d]Patients completing Week 96.