Aflibercept 8 mg for PCV Subgroup in the PULSAR Study

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Disclosures

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Current Evidence in PCV Management

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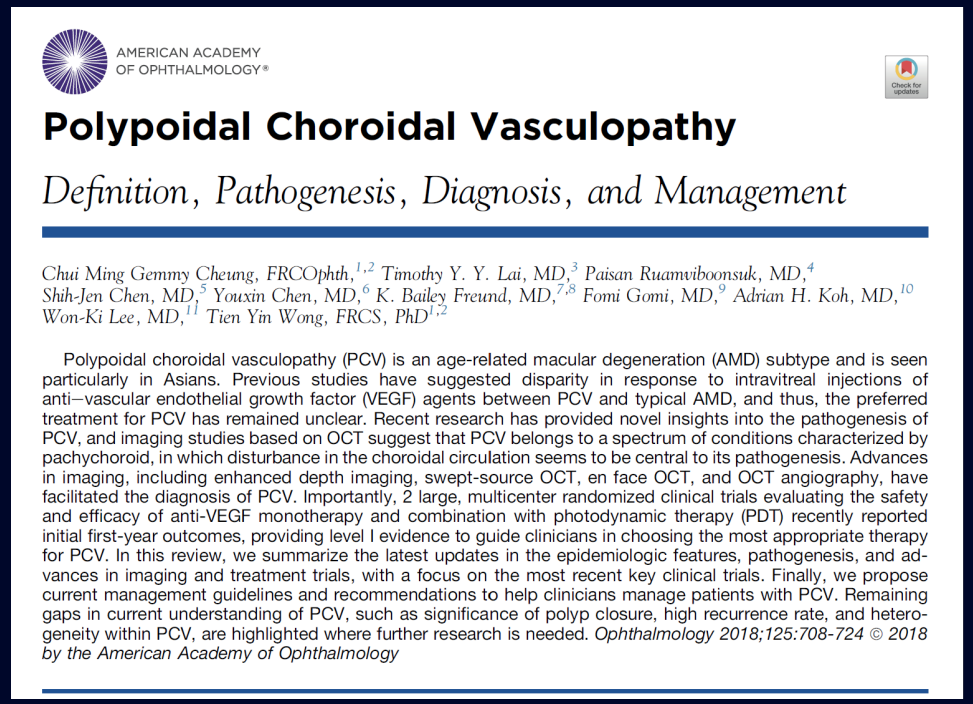
- **Anti-VEGF therapy** forms the backbone of **standard of care** for patients with PCV, whereas PDT may be used as adjunctive therapy
- Efficacy and safety of **aflibercept 2 mg monotherapy**, using 3 initial monthly doses, followed by injections every 2 months or a treat-and-extend (T&E) regimen, is well established[1,2]



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Polypoidal Choroidal Vasculopathy

Definition, Pathogenesis, Diagnosis, and Management

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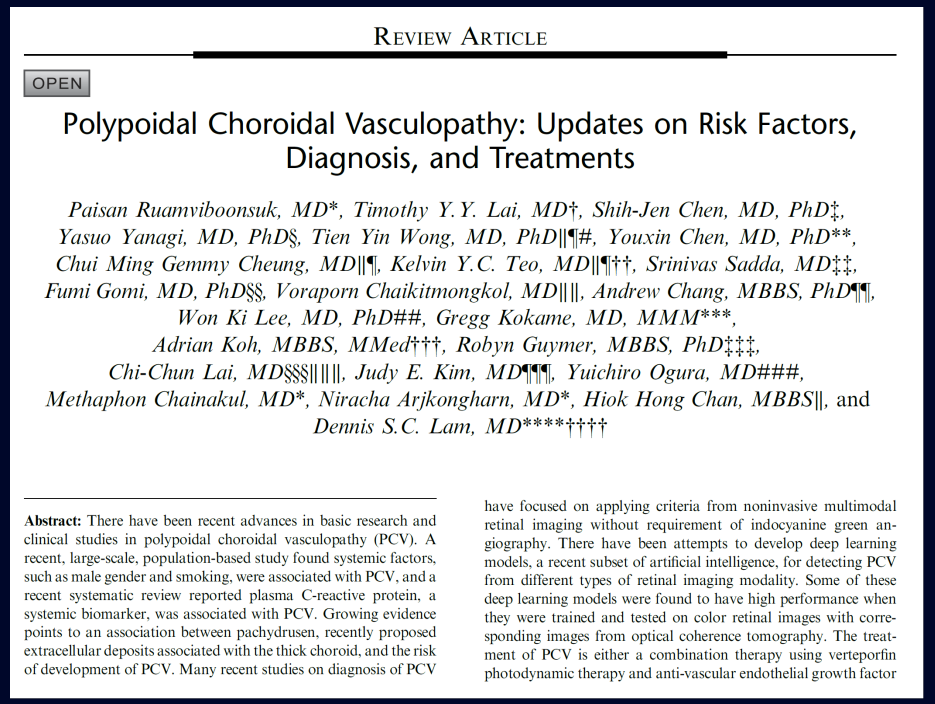
Polypoidal choroidal vasculopathy (PCV) is an age-related macular degeneration (AMD) subtype and is seen particularly in Asians. Previous studies have suggested disparity in response to intravitreal injections of anti–vascular endothelial growth factor (VEGF) agents between PCV and typical AMD, and thus, the preferred treatment for PCV has remained unclear. Recent research has provided novel insights into the pathogenesis of PCV, and imaging studies based on OCT suggest that PCV belongs to a spectrum of conditions characterized by pachychoroid, in which disturbance in the choroidal circulation seems to be central to its pathogenesis. Advances in imaging, including enhanced depth imaging, swept-source OCT, en face OCT, and OCT angiography, have facilitated the diagnosis of PCV. Importantly, 2 large, multicenter randomized clinical trials evaluating the safety and efficacy of anti-VEGF monotherapy and combination with photodynamic therapy (PDT) recently reported initial first-year outcomes, providing level I evidence to guide clinicians in choosing the most appropriate therapy for PCV. In this review, we summarize the latest updates in the epidemiologic features, pathogenesis, and advances in imaging and treatment trials, with a focus on the most recent key clinical trials. Finally, we propose current management guidelines and recommendations to help clinicians manage patients with PCV. Remaining gaps in current understanding of PCV, such as significance of polyp closure, high recurrence rate, and heterogeneity within PCV, are highlighted where further research is needed. *Ophthalmology 2018;125:708-724* © *2018 by the American Academy of Ophthalmology*



REVIEW ARTICLE

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Polypoidal Choroidal Vasculopathy: Updates on Risk Factors, Diagnosis, and Treatments

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Abstract: There have been recent advances in basic research and clinical studies in polypoidal choroidal vasculopathy (PCV). A recent, large-scale, population-based study found systemic factors, such as male gender and smoking, were associated with PCV, and a recent systematic review reported plasma C-reactive protein, a systemic biomarker, was associated with PCV. Growing evidence points to an association between pachydrusen, recently proposed extracellular deposits associated with the thick choroid, and the risk of development of PCV. Many recent studies on diagnosis of PCV have focused on applying criteria from noninvasive multimodal retinal imaging without requirement of indocyanine green angiography. There have been attempts to develop deep learning models, a recent subset of artificial intelligence, for detecting PCV from different types of retinal imaging modality. Some of these deep learning models were found to have high performance when they were trained and tested on color retinal images with corresponding images from optical coherence tomography. The treatment of PCV is either a combination therapy using verteporfin photodynamic therapy and anti-vascular endothelial growth factor

1. Cheung CMG, Lai TYY, Ruamviboonsuk P, et al. *Ophthalmology*. 2018;125(5):708–724. **2.** Ruamviboonsuk P, Lai TYY, Chen SJ, et al. *Asia Pac J Ophthalmol (Phila)*. 2023;12(2):184–195.

PCV, polypoidal choroidal vasculopathy; **PDT**, photodynamic therapy; **VEGF**, vascular endothelial growth factor.

PULSAR: A 3-Arm Randomized, Double-Masked, Phase 3 Study

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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)

↓

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

2q8, aflibercept 2 mg every 8 weeks; **8q12**, aflibercept 8 mg every 12 weeks; **8q16**, aflibercept 8 mg every 16 weeks; **BCVA**, best-corrected visual acuity; **nAMD**, neovascular age-related macular degeneration.

PULSAR: Dosing Schedule and Regimen Modification

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Primary Endpoint

YEAR 1	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	o	X	o	X	o	X	o	X
8q12	X	X	X		o[a]	X[a]	o	o	X[a]	o	o	X[a]	o
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o

YEAR 2	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96
2q8	o	X	o	X	o	X	o	X	o	X	o	–
8q12	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	o	o	X[a,b]	–
8q16	o	X[a,b]	o	o	o	X[a,b]	o	o	o	X[a,b]	o	–

[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; **CRT**, central retinal thickness; **DRM**, dose regimen modification; **OCT**, optical coherence tomography; **Wk**, week.

PULSAR: ICGA-Confirmed PCV in 139 Patients

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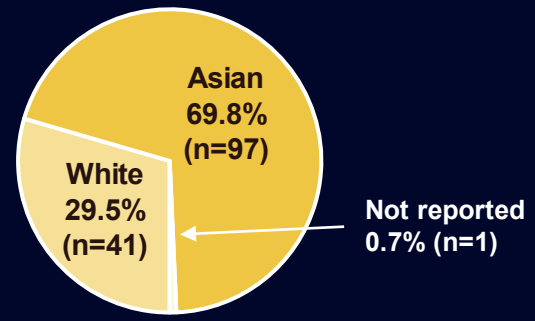
- PULSAR is a global study conducted across 223 sites in 27 countries
- **ICGA was optional** and **conducted in 296 patients in 13 countries**[a]
  - **PCV present, n=139; PCV absent, n=154**
  - PCV could not be graded in 3 patients

PCV Subgroup by Race[b]



BL demographics and disease characteristics	PCV Subgroup (ICGA-confirmed)				Overall Population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=44	n=41	n=85	n=336	n=335	n=338	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. ICGA images were graded by the reading center. [a]Australia (n=15); Austria (n=7); Estonia (n=1); France (n=2); Italy (n=22); Japan (n=70); South Korea (n=25); Latvia (n=2); Mainland China (n=65); Singapore (n=1); Spain (n=3); Switzerland (n=3); USA (n=77). [b]No patients were reported as Black or African American, or multi-racial.
BL, baseline; **CNV**, choroidal neovascularization; **CST**, central subfield thickness; **ETDRS,** Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **ICGA,** indocyanine green angiography.

Change in BCVA Through Week 96: Similar with 8q12 and 8q16 versus 2q8

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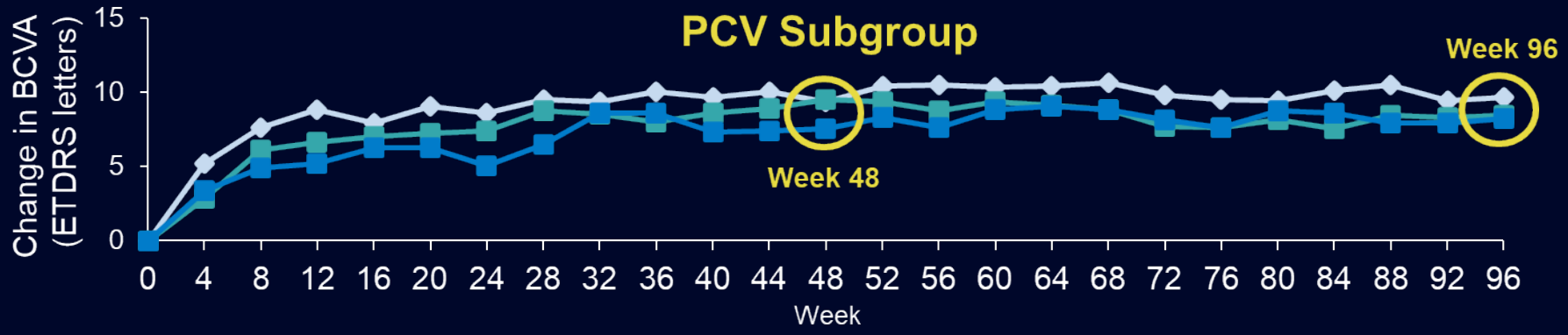
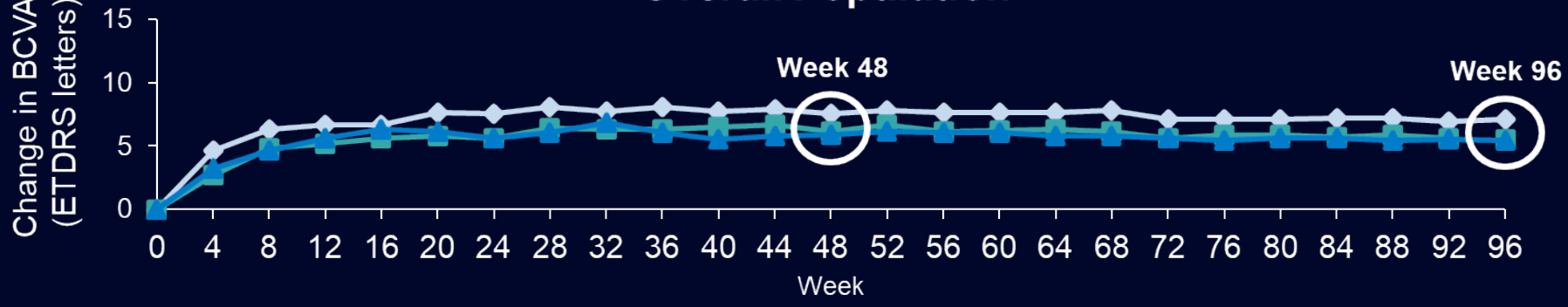
PCV Subgroup



	Week 48	Week 96
2q8 (n=54)	+9.3	+9.6
8q12 (n=44)	+9.5	+8.4
8q16 (n=41)	+7.5	+8.2

Overall Population



	Week 48	Week 96
2q8 (n=336)	+7.5	+7.1
8q12 (n=335)	+6.1	+5.5
8q16 (n=338)	+5.9	+5.4

PCV Subgroup	Mean ± SD change from BL to Week 96 (LOCF)	Two-sided 95% CI
2q8	+9.6 ± 12.1	6.3, 12.9
8q12	+8.4 ± 12.8	4.5, 12.3
8q16	+8.2 ± 9.0	5.4, 11.1

FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints as described). N values are number of patients with BCVA assessments at baseline.
ICE, intercurrent event; **LOCF,** last observation carried forward.

Absolute BCVA Through Week 96: Similar in PCV Subgroup and Overall Population

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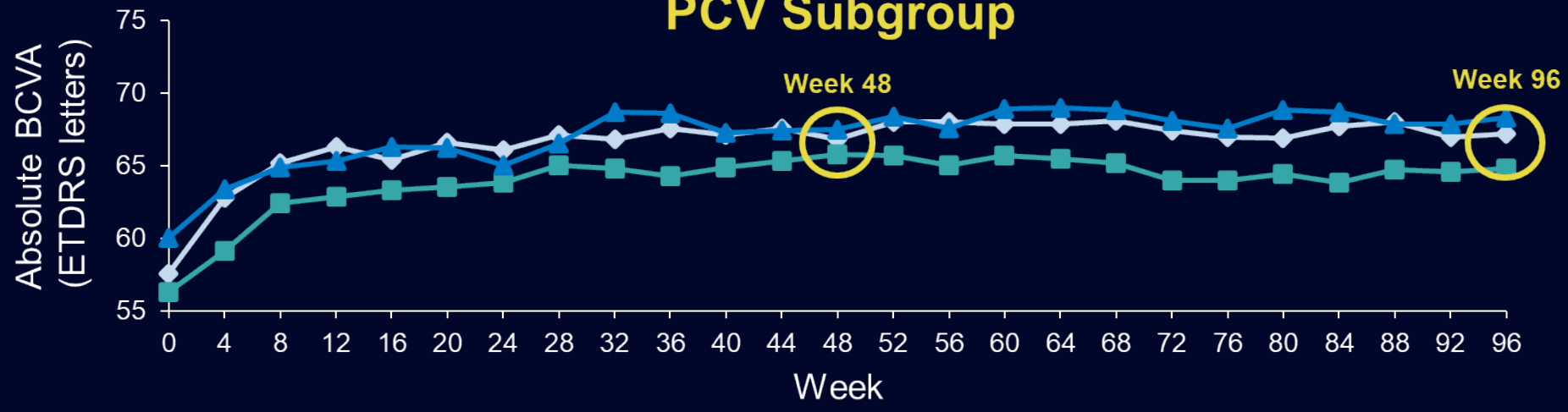
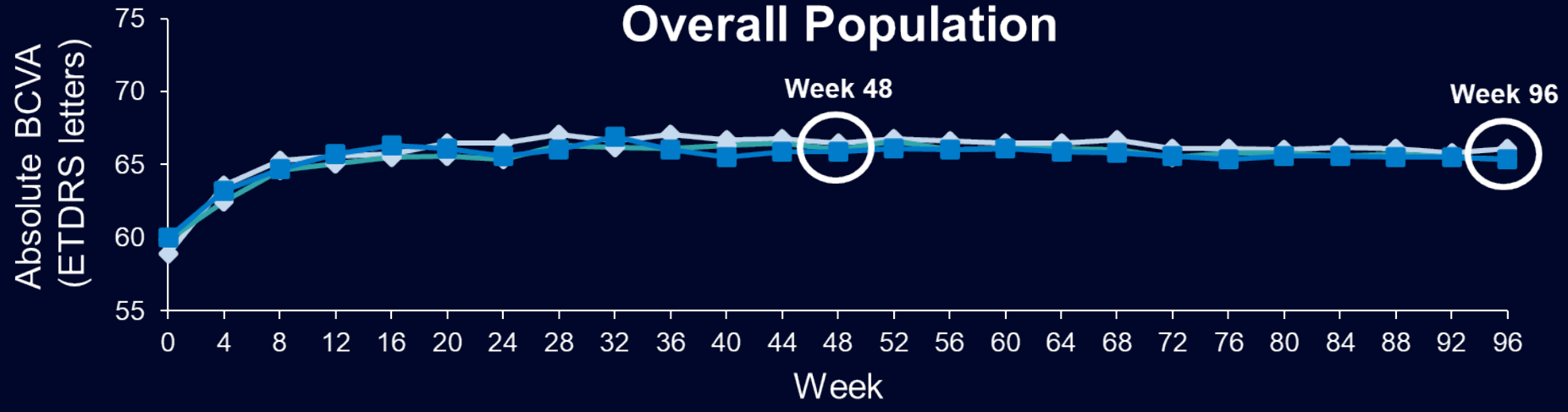
PCV Subgroup



	Week 48	Week 96
2q8 (n=54)	66.8	67.2
8q12 (n=44)	65.8	64.8
8q16 (n=41)	67.5	68.3

Overall Population



	Week 48	Week 96
2q8 (n=336)	66.5	66.1
8q12 (n=335)	66.0	65.4
8q16 (n=338)	65.9	65.4

FAS, LOCF (last available observed value prior to ICE was used to impute missing data; ICE were handled according to sensitivity estimand strategy for continuous endpoints as described). N values are number of patients with BCVA assessments at baseline.

CST Through Week 96: Similar with 8q12 and 8q16 versus 2q8

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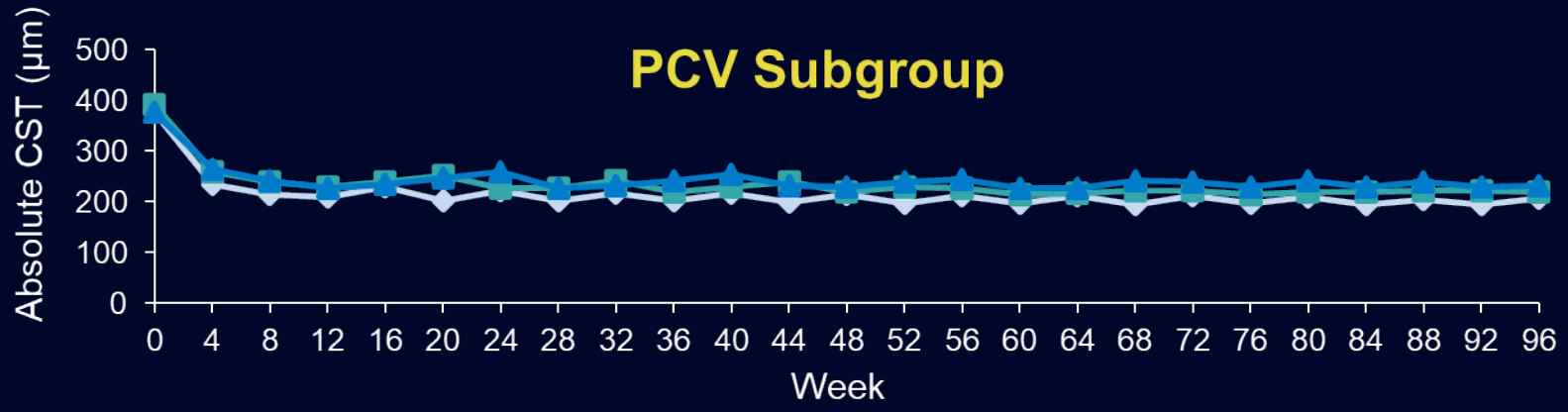
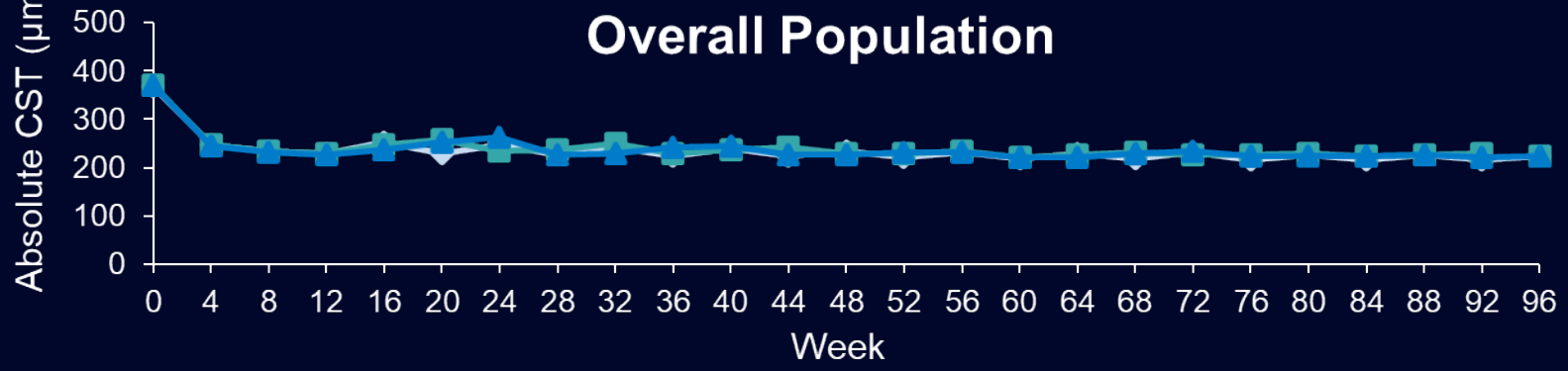
PCV Subgroup



	Week 48	Week 96
2q8 (n=54)	216	207
8q12 (n=44)	219	219
8q16 (n=41)	230	232

Overall Population



	Week 48	Week 96
2q8 (n=335)	236	225
8q12 (n=333)	228	223
8q16 (n=334)	227	225

PCV Subgroup	Mean ± SD change from BL to Week 96 (LOCF)	Two-sided 95% CI	Overall Population	Mean ± SD change from BL to Week 96 (LOCF)	Two-sided 95% CI
2q8	−157 ± 140	−195, −118	2q8	−141 ± 132	−155, −126
8q12	−172 ± 139	−215, −130	8q12	−147 ± 128	−161, −133
8q16	−145 ± 142	−190, −100	8q16	−145 ± 135	−160, −131

FAS, LOCF. N values are number of patients with CST assessments at baseline.

Retinal Fluid Through Week 96: Marked Increase in Proportion of Patients Without Retinal Fluid

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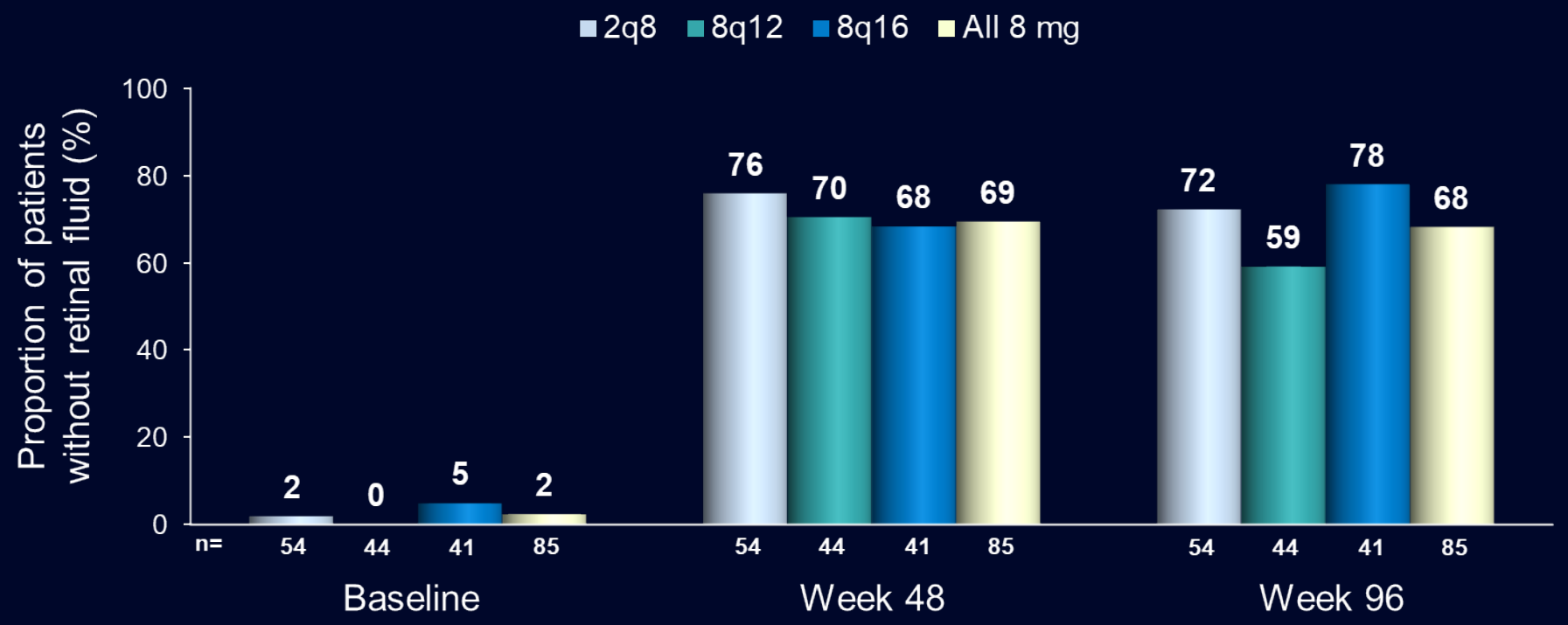
PCV Subgroup



FAS, LOCF (data post-ICE were censored). "Without retinal fluid" defined as absence of intraretinal and subretinal fluid in central subfield.

Mean Number of Injections Through Week 96: Similar in PCV Subgroup and Overall Population

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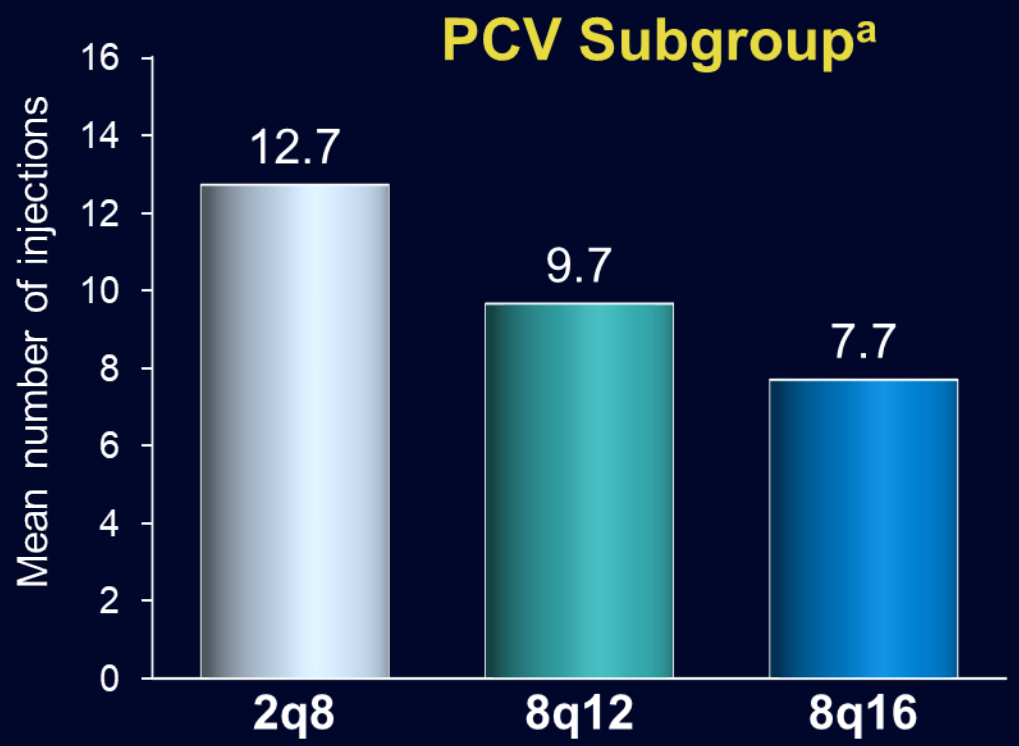
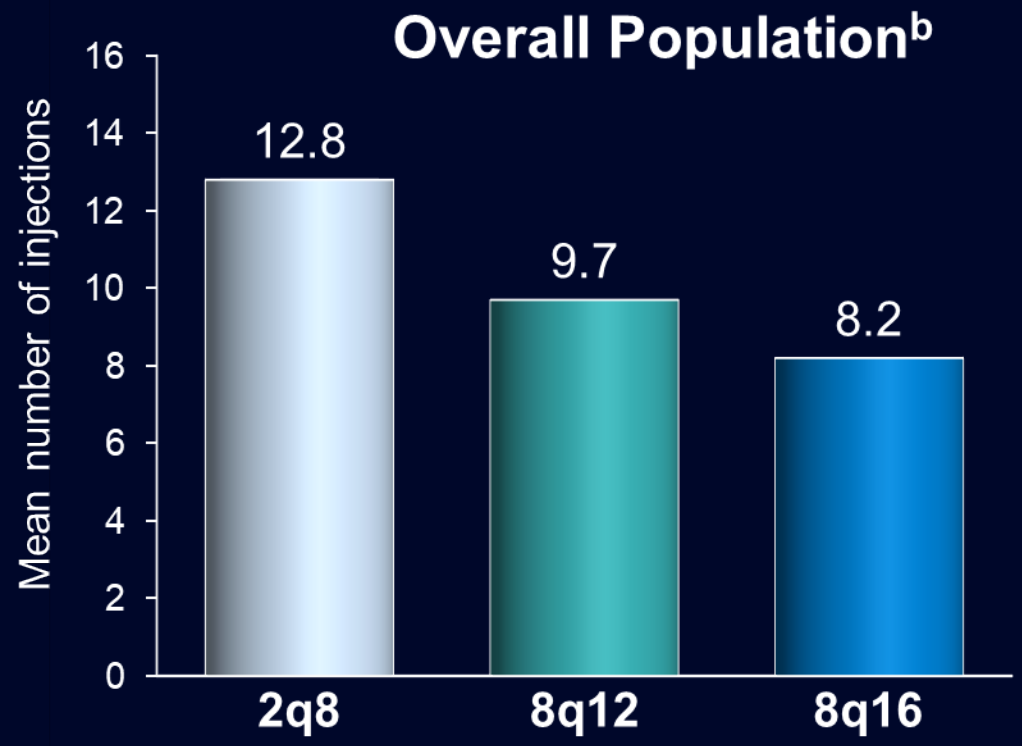


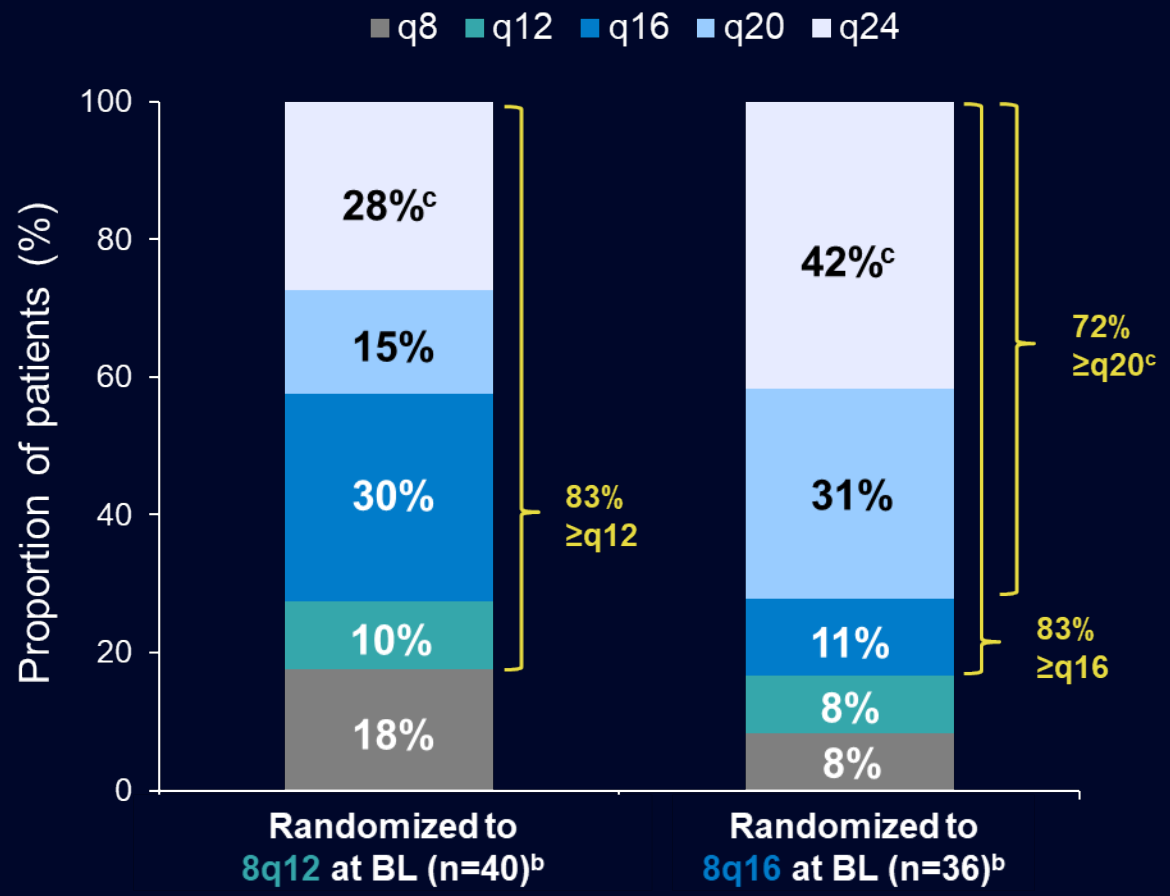


[a]FAS: Data are shown for patients who completed Week 96: 2q8, n=49; 8q12, n=40; 8q16, n=36. [b]Data are shown for patients who completed Week 96: 2q8, n=286; 8q12, n=291; 8q16, n=292.

Dosing Interval Extension in Year 2[a]: Most Patients with PCV Qualified for Extension

nAMD

Last Assigned Dosing Interval (PCV Subgroup)



[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 **AND** no fluid at the central subfield **AND** no new foveal hemorrhage or neovascularization.
[b]Patients completing Week 96. [c]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria; study duration did not allow enough time for patients to complete the interval within the 96-week study period. Values may not add up to 100% due to rounding.
q12, every 12 weeks; **q16**, every 16 weeks; **q20**, every 20 weeks.

Polypoidal Lesions Through Week 48

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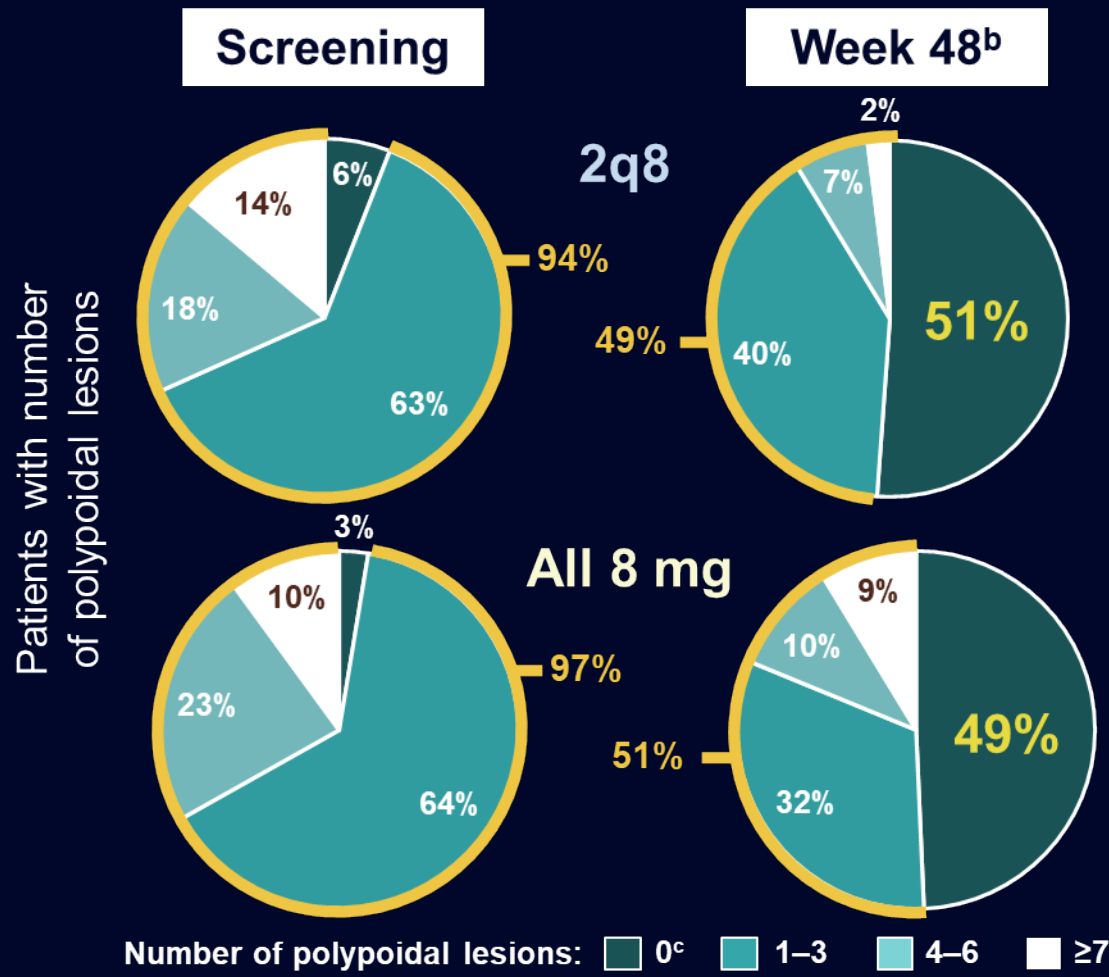
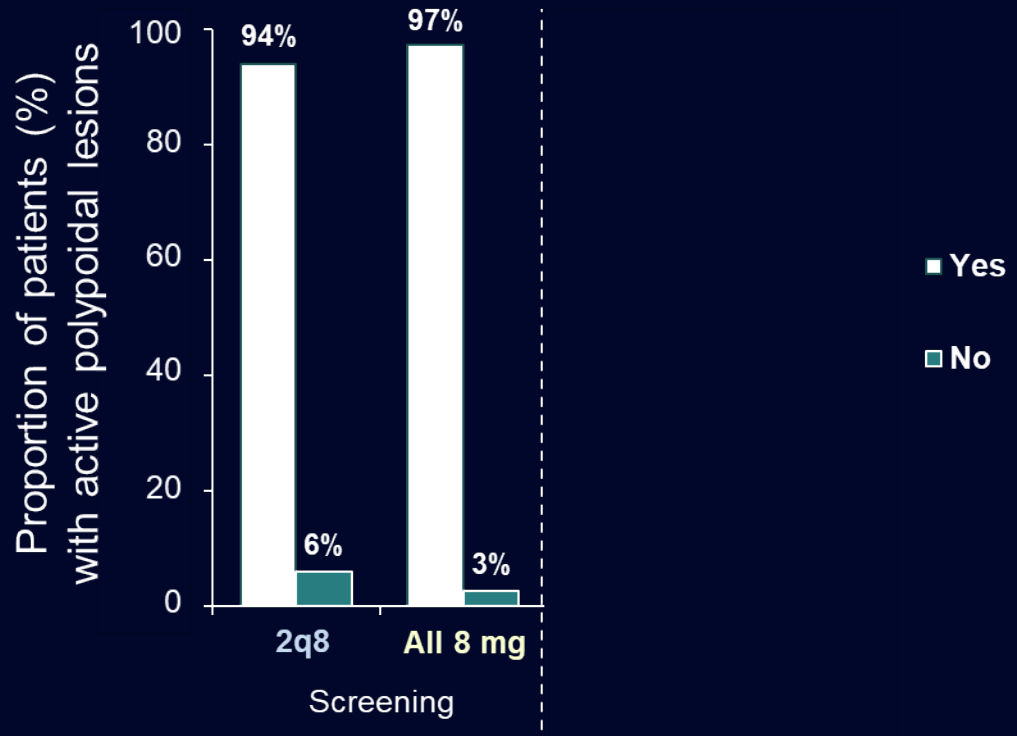
~50% of patients had no polypoidal lesions at Week 48[a]



≥78% of patients had no active polypoidal lesions[a,d] at Week 48



Data are for patients with PCV who completed Week 48. Screening (Visit 1) occurred before the baseline visit (Visit 2). [a]For polypoidal lesion data: 2q8, n=51; All 8 mg, n=78 (% calculated based on number of patients with known number of polypoidal lesions). [b]At Week 48, number of polypoidal lesions unknown for n=6 and n=9 in 2q8 and All 8 mg groups, respectively. [c]Patients shown here with no polypoidal lesions at screening were those who were first tested by ICGA at baseline. [d]"No" active polypoidal lesions defined as no polypoidal lesions present **OR** IRF and SRF are "absent" or "questionable". [e]At Week 48, n=2 unknown each for 2q8 and All 8 mg groups.

Total Area of Polypoidal Lesions: Similar Change From Baseline Through Week 96

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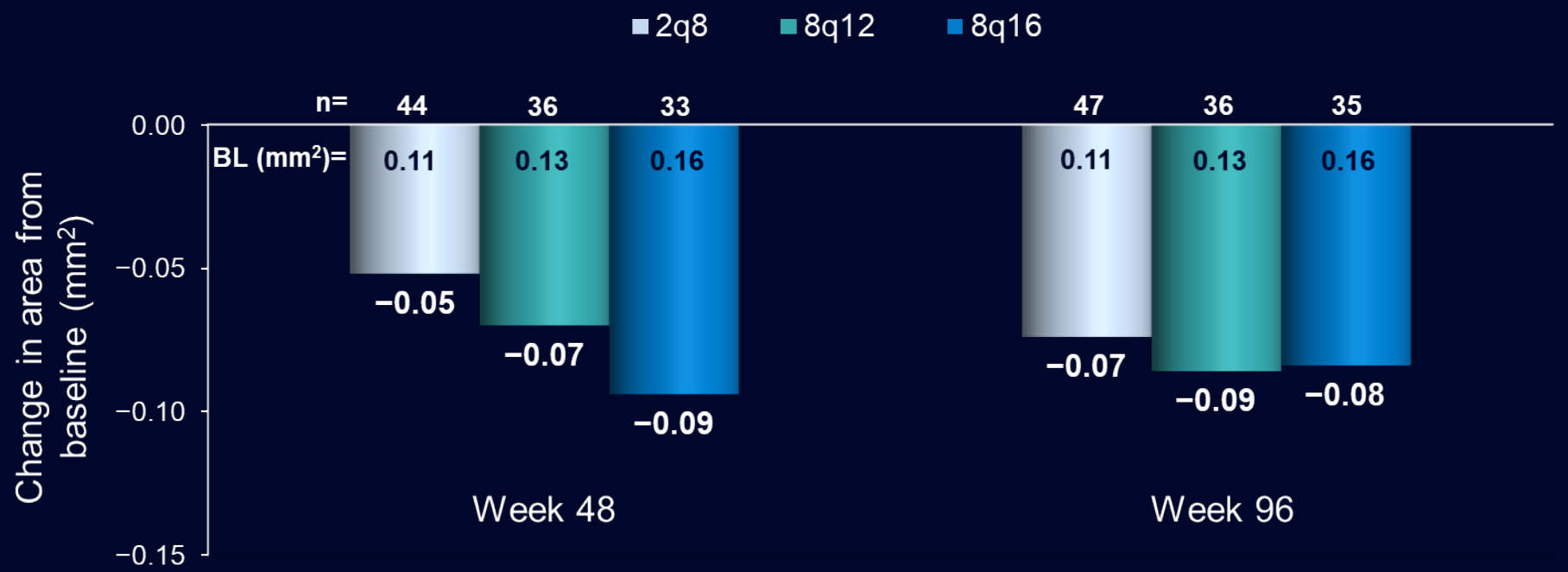
PCV Subgroup



Data are for patients with PCV who completed Week 96.

96-Week Ocular Safety Profile of Aflibercept 8 mg: Similar to 2 mg in PCV and Overall Populations

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TEAE, n (%) in study eye	PCV subgroup				Overall population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=44	n=41	n=85	n=336	n=335	n=338	n=673
Any ocular TEAE	21 (38.9)	20 (45.5)	20 (48.8)	40 (47.1)	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Any intraocular inflammation TEAE	1 (1.9)	1 (2.3)	0	1 (1.2)	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)

- Ocular TEAEs occurring in ≥5% of patients in any treatment arm in the PCV subgroup were retinal hemorrhage, conjunctival hemorrhage, reduced visual acuity, vitreous floaters, conjunctivitis, intraocular pressure increased, (worsening of) AMD, dry eye, and macular edema
- Two cases of intraocular inflammation occurred in the PCV subgroup: chorioretinitis (reported term: posterior uveitis)[a] and eye inflammation; both cases were mild in intensity and neither case was considered serious

Data are from the 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]The case of chorioretinitis was not considered related to the study drug.
AE, adverse event; **AMD**, age-related macular degeneration; **TEAE**, treatment-emergent adverse event; **SAF**, safety analysis set.

Conclusions: Aflibercept 8 mg Monotherapy in PCV

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Aflibercept 8 mg monotherapy[a] largely maintained efficacy in PCV over 2 years

- **Visual acuity gains** from baseline were **largely maintained from Week 48 to Week 96** in the aflibercept 8q12, 8q16, and 2q8 PCV subgroups, with gains of +8.4, +8.2, and +9.6 letters, respectively, from baseline to Week 96
- Through Week 96, the absolute and mean change in **CST** from baseline were numerically **similar** in the 3 treatment arms
- Both aflibercept 8 mg and 2 mg **markedly reduced the total polypoidal lesion area from baseline to Week 96**

Extended durability

- At Week 96, **72%** of patients with PCV treated with aflibercept 8q16 qualified for **extended dosing interval of ≥20 weeks**, suggesting **extended durability of aflibercept 8 mg** versus aflibercept 2 mg

Comparable safety profile for aflibercept 8 mg versus 2 mg

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

[a]Without active rescue photodynamic therapy.