Intravitreal aflibercept 8 mg in patients with polypoidal choroidal vasculopathy (PCV): A subgroup analysis from the Phase 3 PULSAR trial

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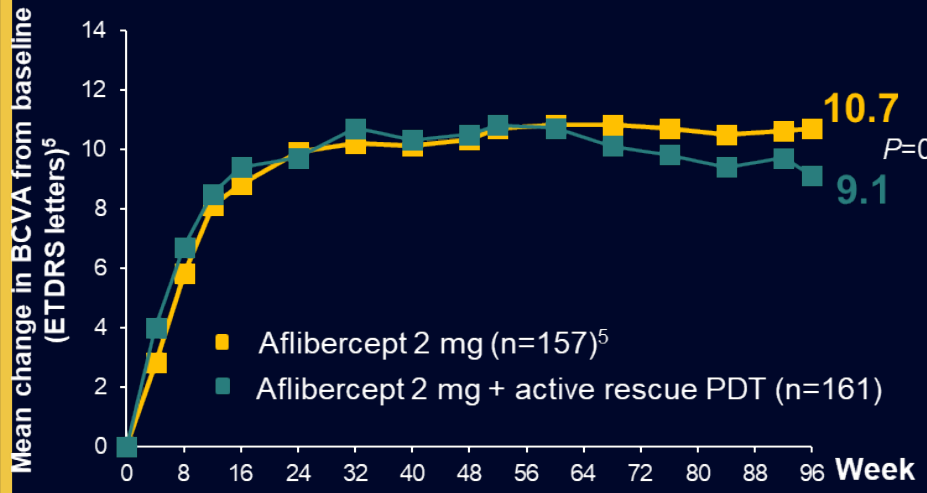
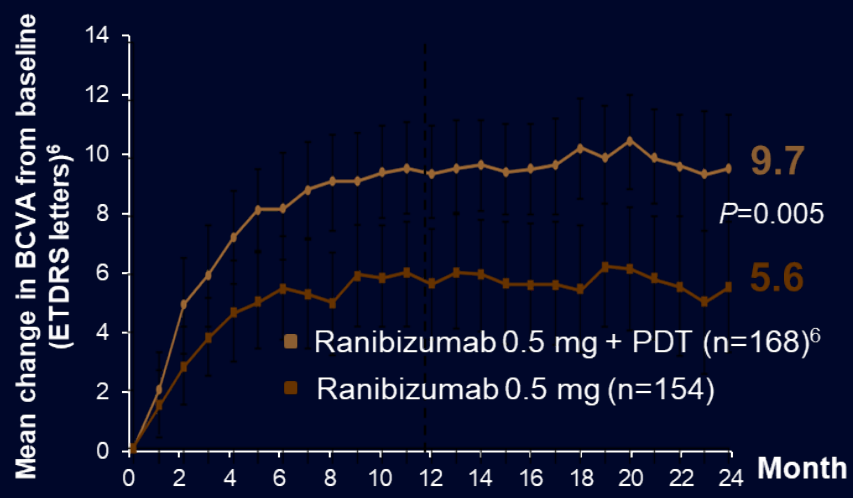
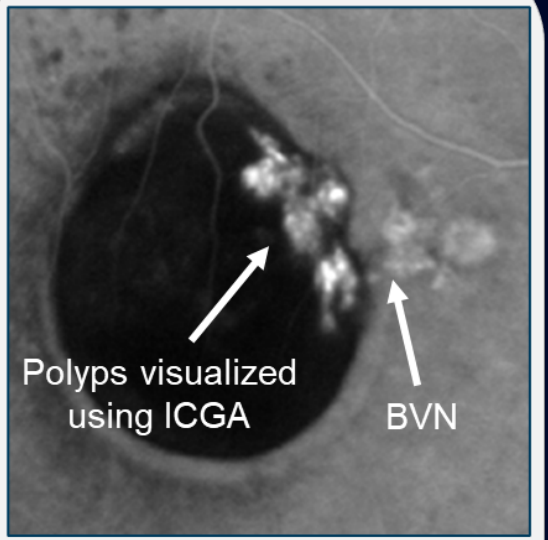
Polypoidal choroidal vasculopathy

pulsar nAMD

- PCV presents as serosanguinous exudative maculopathy characterized by retinal PED, serous exudation, and hemorrhage in multiple retinal layers[1,2]
- PCV is particularly prevalent among Asian populations (25–50% of Asian patients with nAMD have PCV)[1,3]
- The most reliable method of diagnosing PCV is ICGA; however, ICGA is not routinely performed, particularly in areas where the disease is uncommon[4]





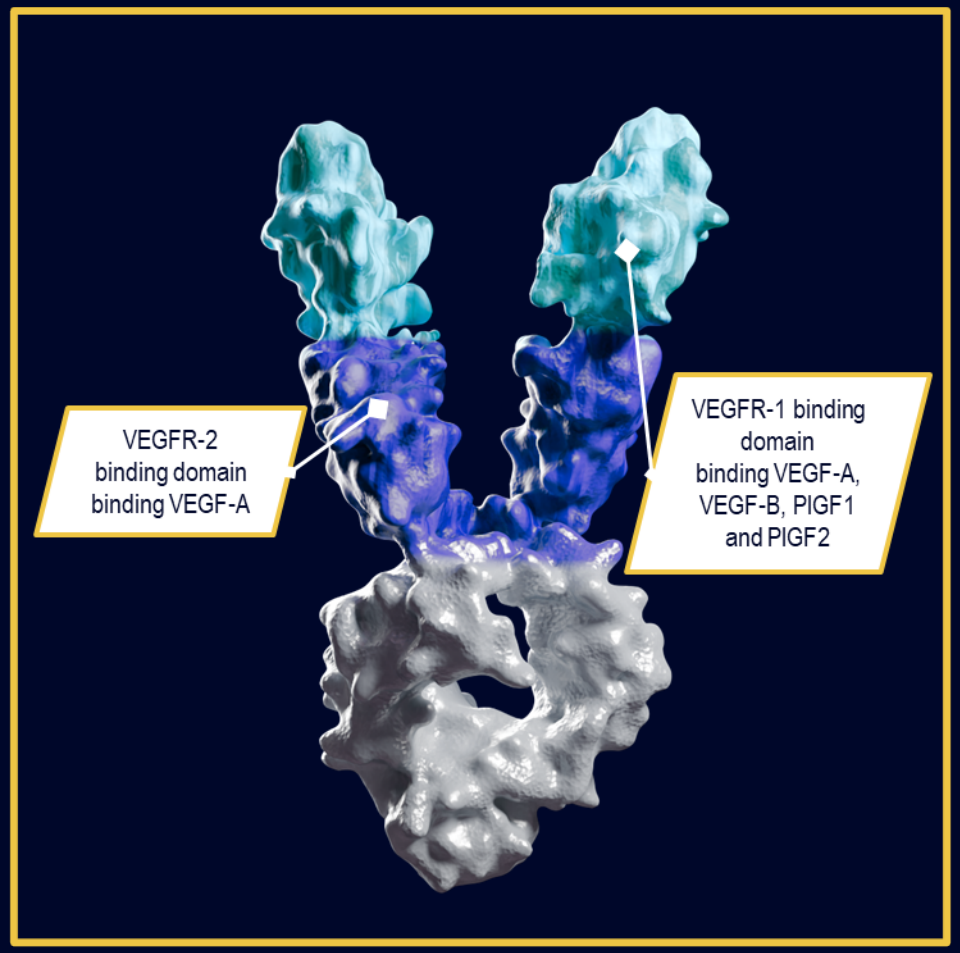


PCV is characterized by abnormal choroidal vascular networks ending in polyps and is considered a variant of type 1 CNV[7]

BVN, branching vascular network; **BCVA**, best-corrected visual acuity; **CNV**, choroidal neovascularization; **ICGA,** indocyanine green angiography; **nAMD**, neovascular age-related macular degeneration; **PCV**, polypoidal choroidal vasculopathy; **PDT,** photodynamic therapy; **PED**, pigment epithelial detachment.

1. Wong et al. J Ophthalmic Vis Res 2013;8:359–71; **2.** Yannuzzi et al. Retina 1990;10:1–8; **3.** Byeon et al. Jpn J Ophthalmol 2008;52:57–62; **4.** Zhalka et al. Int J Retina Vitreous 2022; 8(1):82 **5.** Wong et al. Am J Ophthalmol 2019;204:80–9; **6.** Lim et al. JAMA Ophthalmol 2020;138:935–42; **7.** Cheung et al. Ophthalmology 2018;125:708–724.

Characteristics of aflibercept 8 mg



- Novel intravitreal formulation delivers 8 mg in 70 µL injection (114.3 mg/mL)
- 4-times higher molar dose compared with aflibercept 2 mg is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on VEGF signaling

Here, we present the **PCV subgroup** results of the ongoing, randomized, double-masked, 96-week, **Phase 3 PULSAR trial in patients with treatment-naïve nAMD**

PIGF, placental growth factor; **VEGF**, vascular endothelial growth factor.

PULSAR study design

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nAMD

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

IRF, intraretinal fluid; **SRF**, subretinal fluid.

Key inclusion/exclusion criteria

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nAMD

Inclusion Criteria

- Men or women ≥50 years of age with treatment-naïve nAMD
- Active subfoveal CNV, with a total area >50% of the total lesion area in the study eye
- Presence of IRF and/or SRF fluid in the central subfield on OCT
- BCVA of 78–24 letters (Snellen equivalent 20/32–20/320) with decreased vision due to nAMD

Exclusion Criteria

- Diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye
- Retinal pigment epithelial tears or rips, scar, fibrosis, or atrophy involving the central subfield in the study eye
- Total lesion size >12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) as assessed by FA in the study eye
- Uncontrolled glaucoma (IOP >25 mmHg despite anti-glaucoma medication) in the study eye
- Extra/periocular infection or inflammation in either eye at screening/randomization
- Uncontrolled blood pressure (SBP >160 mmHg or DBP >95 mmHg)

DBP, diastolic blood pressure; **FA**, fluorescein angiography; **IOP**, intraocular pressure; **SBP**, systolic blood pressure.

PULSAR: Dosing Schedule and Regimen Modification in Year 1

pulsar nAMD

	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	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*

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

AND

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

*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

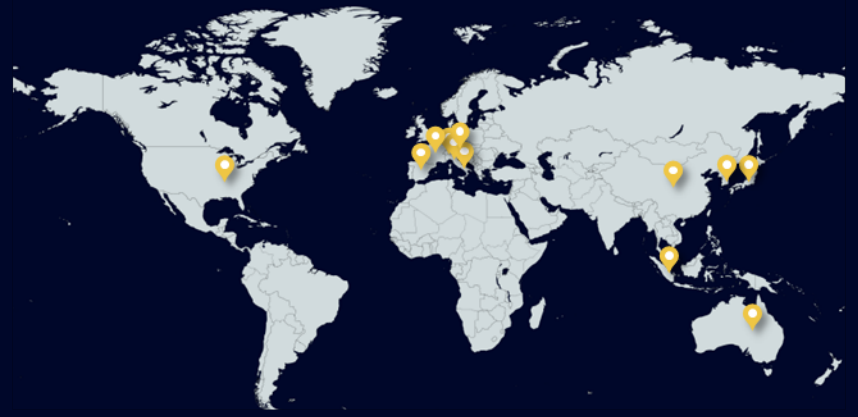
Week 32 and 44 for 8q12 and Week 36[a] and 40 for 8q16: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

Stippled boxes = initial treatment phase; X=active injection; o=sham injections. Note: Table does not reflect all dosing options once a patient is shortened.
[a]At Week 36, patients on 8q16 who were previously shortened to q12 could have been shortened to q8.
CRT, central retinal thickness; **DRM**, dose regimen modification; **Wk**, week.

PCV in PULSAR

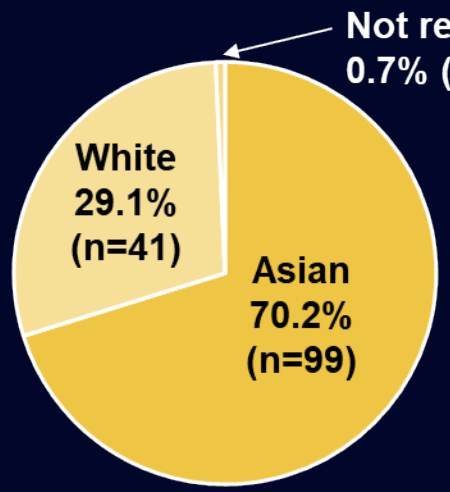
pulsar nAMD

- PULSAR is a global study conducted across 223 sites in 26 countries
- **ICGA** was optional and **conducted in 297 patients in 12 countries***
  - 141 patients – PCV present
  - 153 patients – PCV absent
  - 3 patients – data missing



Patients with PCV present (n=141)					
Europe	**18**	**APAC**	**102**	**Americas**	**21**
Austria	3	Australia	5	USA	21
Italy	12	Japan	43		
Latvia	1	Korea	18		
Spain	1	Mainland China	36		
Switzerland	1				

Ethnicity of PCV subgroup^



*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). ICGA images were graded by the reading center. ^No patients were reported as Black or African American, or multiple ethnicity.
APAC, Asia Pacific; **USA**, United States of America.

PCV subgroup: Baseline demographics and disease characteristics

pulsar nAMD

	PCV subgroup				Overall population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=45	n=42	n=87	n=336	n=335	n=338	n=673
Age, years	72.6 (8.2)	72.2 (8.0)	73.0 (8.6)	72.6 (8.2)	74.2 (8.8)	74.7 (7.9)	74.5(8.5)	74.6 (8.2)
Female, %	31.5%	48.9%	38.1%	43.7%	56.0%	54.3%	53.3%	53.8%
BCVA, EDTRS letters	57.6 (15.5)	56.7 (13.4)	60.1 (11.3)	58.3 (12.5)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.9 (12.9)
CRT, µm	378 (163)	390 (128)	375 (138)	383 (132)	367 (134)	371 (124)	371 (133)	369 (130)
CNV size, mm^2	5.8 (4.7)	5.0 (3.9)	5.1 (4.5)	5.1 (4.1)	6.9 (5.4)	6.4 (5.1)	6.9 (5.7)	6.6 (5.4)

FAS, data are mean (SD) unless otherwise indicated.
FAS, full analysis set.

PCV subgroup: Absolute and change from baseline in BCVA through Week 48

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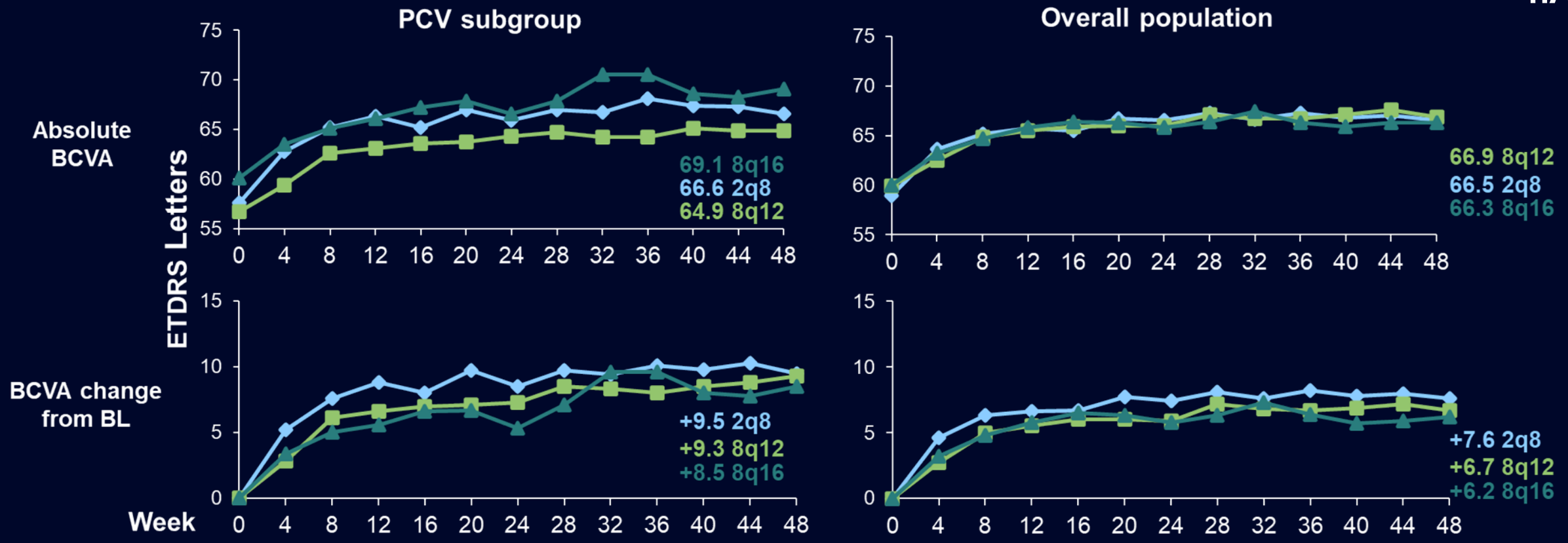


	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI
2q8	+9.3		
8q12	+9.5	0.23	–4.53, 5.00
8q16	+8.9	–0.45	–4.30, 3.39

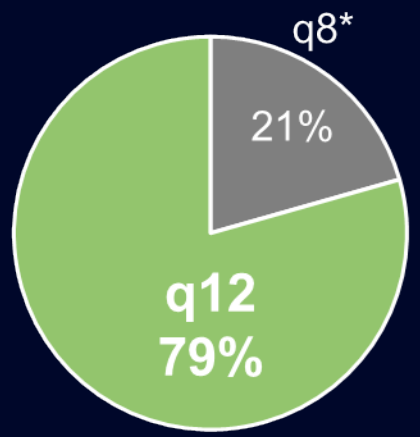
	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI
2q8	7.0		
8q12	6.1	–0.97	–2.87, 0.92
8q16	5.9	–1.14	–2.97, 0.69

Observed values (censoring data post ICE); FAS (PCV subgroup): 2q8 n=54; 8q12 n=45; 8q16 n=42 (at baseline), (overall population): 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
BL, baseline; **ICE**, intercurrent events; **MMRM**, mixed models for repeated measurements.

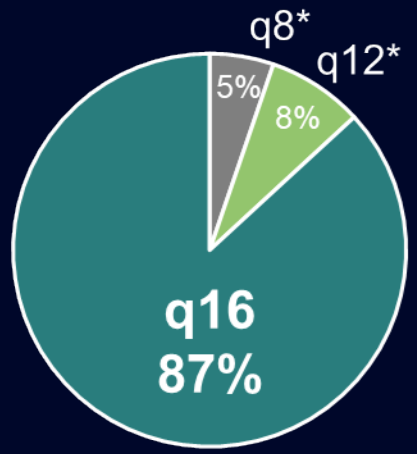
PCV subgroup: Proportions of patients maintained on q12- and q16-week intervals through Week 48

pulsar nAMD

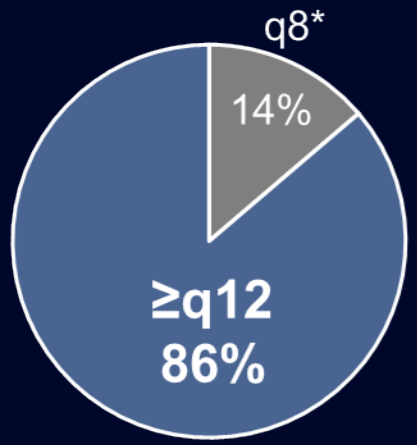
PCV subgroup



8q12 n=42^



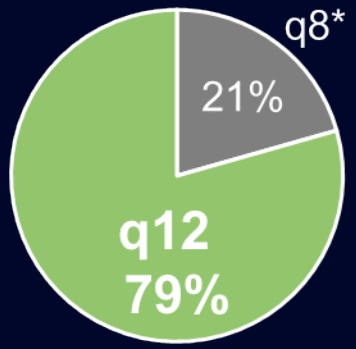
8q16 n=38^



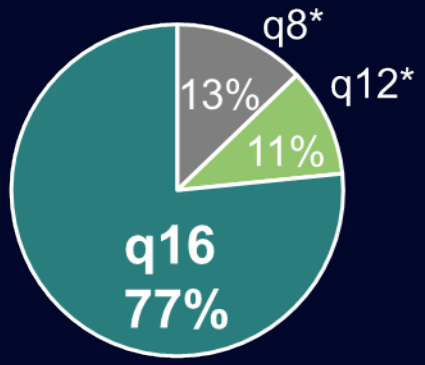
All 8 mg n=80^

86% of 8 mg patients maintained dosing intervals ≥12 weeks

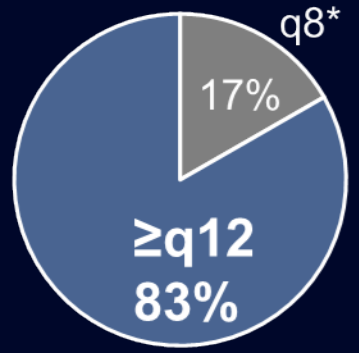
Overall population



8q12 n=316^



8q16 n=312^



All 8 mg n=628^

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

Values may not add to 100% due to rounding.*Patients shortened based on DRM assessments at some point through Week 48. ^Patients completing Week 48.

PCV subgroup: Proportions of patients without retinal fluid in the center subfield at Week 16

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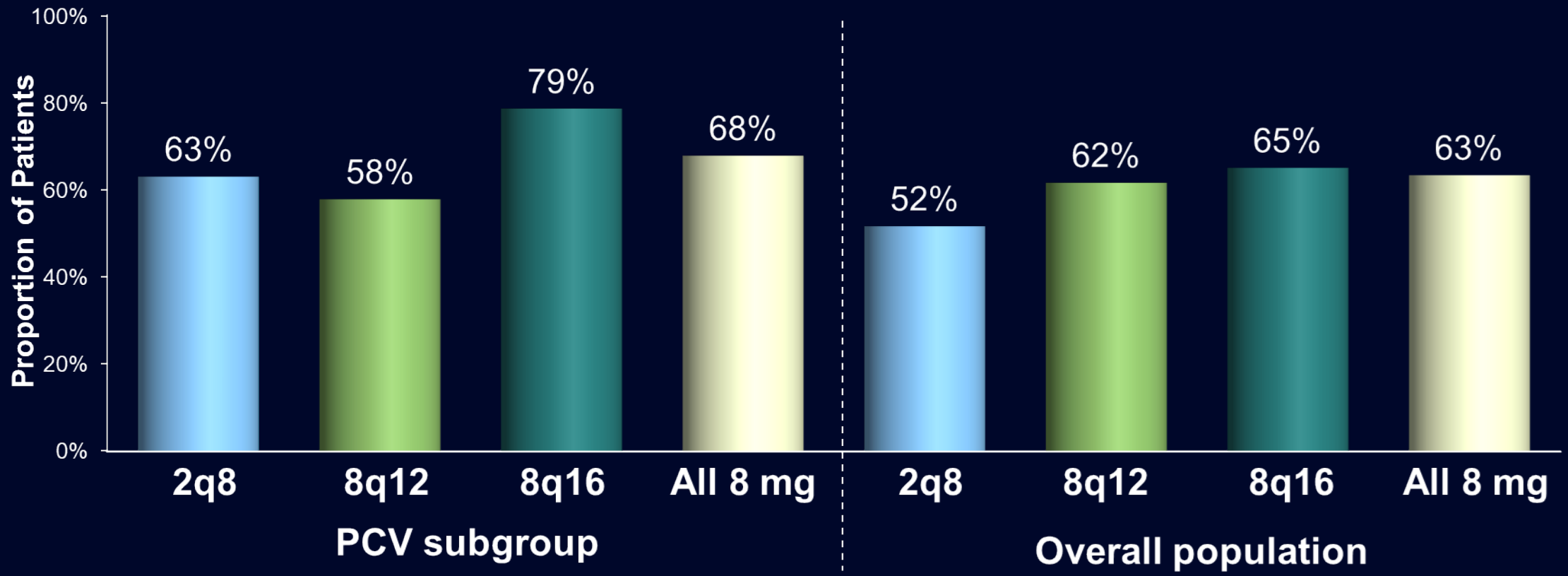
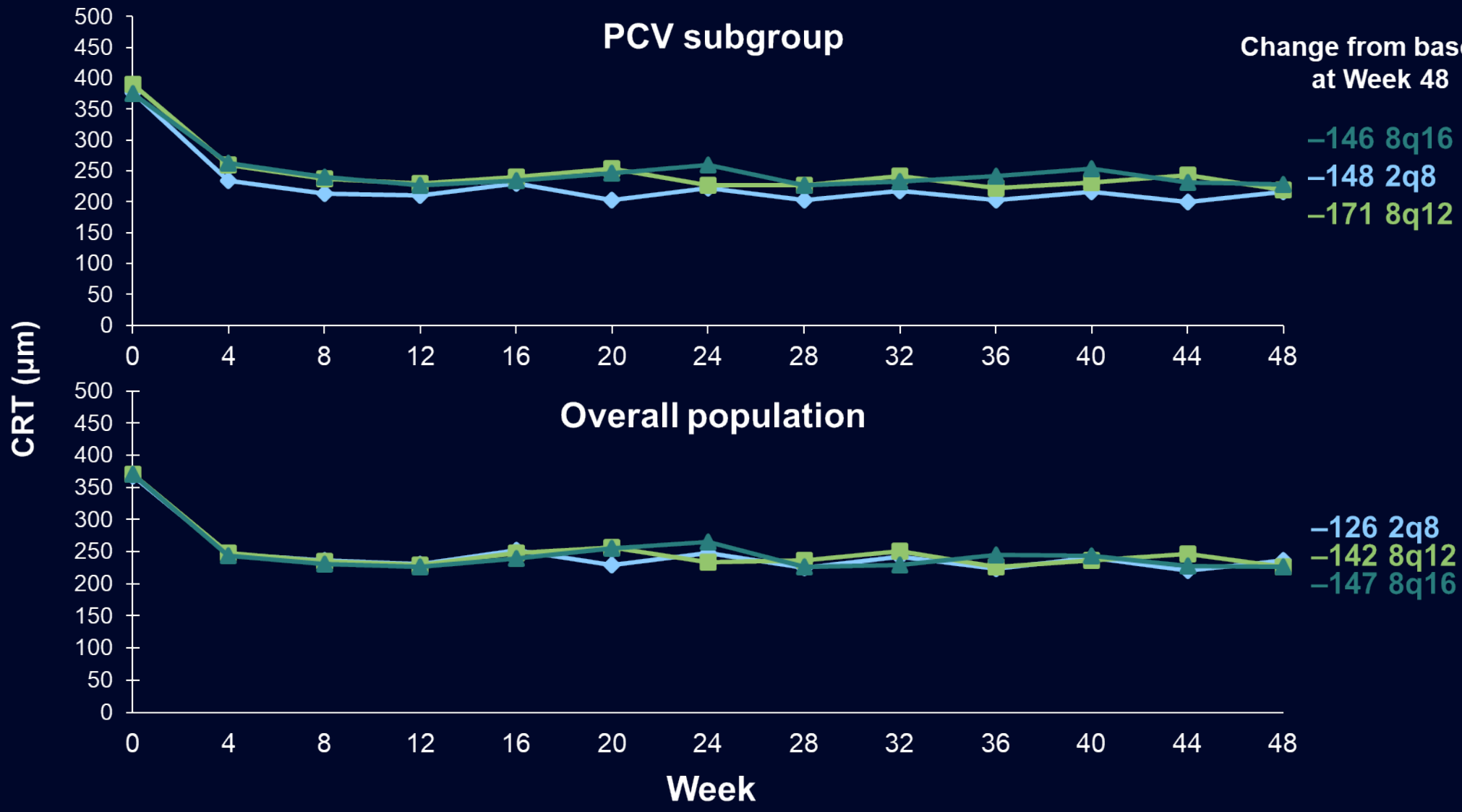


Without retinal fluid defined as absence of IRF and SRF in center subfield.
LOCF (censoring data post ICE); FAS (PCV subgroup).

PCV subgroup: Absolute and change from baseline in CRT through Week 48



LOCF; FAS: PCV subgroup, 2q8 n=54; 8q12 n=45; 8q16 n=42; overall population, 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).

Ocular AEs (%)* through Week 48

pulsar nAMD

	PCV subgroup				Overall population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=45	n=42	n=87	n=336	n=335	n=338	n=673
Any ocular AE^	25.9%	37.8%	31.0%	34.5%	38.7%	38.5%	37.6%	38.0%
Reduced visual acuity (n, %)	3 (5.6%)	2 (4.4%)	0	2 (2.3%)	20 (6.0%)	12 (3.6%)	18 (5.3%)	30 (4.5%)
Cataract	2 cases of cataracts‡				10 (3.0%)	12 (3.6%)	12 (3.6%)	24 (3.6%)
Retinal hemorrhage	2 (3.7%)	3 (6.7%)	1 (2.4%)	4 (4.6%)	14 (4.2%)	11 (3.3%)	10 (3.0%)	21 (3.1%)
Intraocular pressure increased	1 (1.9%)	2 (4.4%)	3 (7.1%)	5 (5.7%)	7 (2.1%)	11 (3.3%)	9 (2.7%)	20 (3.0%)
Vitreous floaters	2 (3.7%)	0	3 (7.1%)	3 (3.4%)	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‡				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

SAF. *AEs and SAEs are those occurring from first injection to 30 days after the last injection (active or sham); ocular AEs and SAEs are those occurring in the study eye. ^Most commonly reported AEs occurring in ≥3% in any treatment arm in the overall study population. ‡Data presented in this way to avoid unintentional patient unmasking.
AE, adverse event; **SAE**, serious adverse event; **SAF**, safety analysis set.

Non-Ocular safety through Week 48

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	PCV subgroup				Overall population			
	2q8	8q12	8q16	All 8 mg	2q8	8q12	8q16	All 8 mg
	n=54	n=45	n=42	n=87	n=336	n=335	n=338	n=673
Patients with ≥ 1 TEAE (%)	44.4	53.5	57.1	55.2	69.9	71.3	73.7	72.5
Non-ocular serious TEAEs (%)	11.1%	11.1%	11.9%	11.5%	13.7	10.1	9.5	9.8
Deaths (%)	0	0	0	0	0	0	0.3	0.1

SAF. No cases of APTC, hypertension events, and non-ocular SAEs were reported in the PCV subgroup.
SAF, safety analysis set; **TEAE**, treatment-emergent adverse events.

Conclusions – Aflibercept 8 mg monotherapy in PCV

pulsar nAMD

Aflibercept 8 mg monotherapy* showed robust efficacy benefits

Robust increases in BCVA from baseline at Week 48 were observed in the 8q12, 8q16, and 2q8 groups (+8.5, +9.3, and +9.5 ETDRS letters, respectively)

At Week 16, **More patients** in the pooled 8 mg group had **absence of fluid** in the central subfield compared to the 2 mg group (68% vs 63%)

Extended durability

In total, **86.3%** (69/80) of patients with PCV receiving aflibercept 8 mg were maintained on treatment intervals **≥12 weeks**

Comparable safety profile with aflibercept 2 mg

The **safety profile** of aflibercept **8 mg was similar in** patients with **PCV** and the overall PULSAR nAMD population compared to the known safety profile of **2 mg**

*without active rescue PDT.