Aflibercept 8 mg in Polypoidal Choroidal Vasculopathy: PULSAR subgroup analysis

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【Conflict of Interest】

Tomohiro Iida: 【F】Nidec, Topcon, Santen

【P】

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PULSAR study design

pulsar
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

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

PULSAR Study Design and Dosing Schedule

pulsar nAMD

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

Key secondary endpoint:
Proportion of patients without IRF and SRF in the central subfield

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

	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 (n=336)	X	X	X		X	o	X	o	X	o	X	o	X
8q12 (n=335)	X	X	X		o	X	o	o	X	o	o	X	o
8q16 (n=338)	X	X	X		o	o	X	o	o	o	X	o	o

DRM Criteria for Shortening Dosing Interval

- >5-letter loss in BCVA compared with Week 12, due to persistent or worsening nAMD

AND

- >25 µm increase in CST compared with Week 12, or new-onset foveal neovascularization, or foveal hemorrhage

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

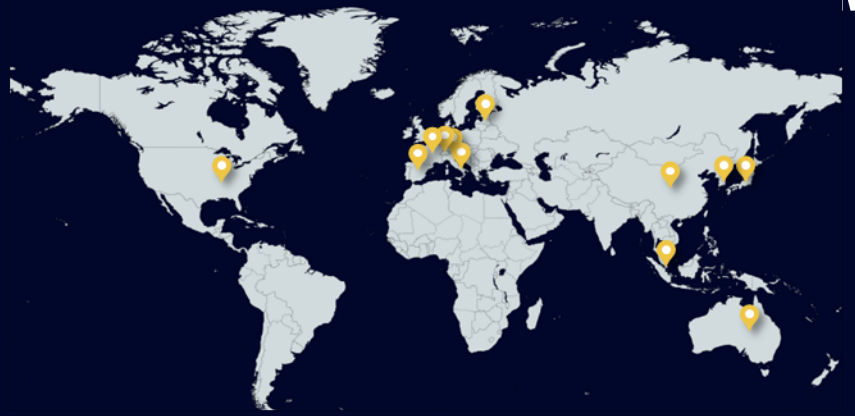
Week 24: Patients on 8q16 meeting DRM criteria shortened to Q12

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 injection. Note: Table does not reflect all dosing options once a patient's dosing interval is shortened.
2q8, aflibercept 2 mg every 8 weeks after 3 initial monthly injections; **8q12**, aflibercept 8 mg every 12 weeks after 3 initial monthly injections; **8q16**, aflibercept 8 mg every 16 weeks after 3 initial monthly injections; **CST**, central subfield thickness; **DRM**, dose regimen modification' **Q8**, every 8 weeks; **Q12**, every 12 weeks; **Wk**, week.

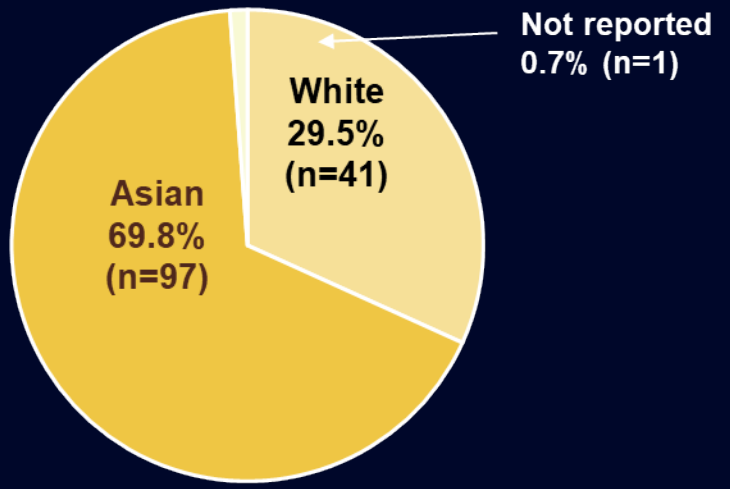
PCV in PULSAR

- 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



Patients with PCV present (ICGA-confirmed)					
Europe	**18**	**APAC**	**100**	**Americas**	**21**
Austria	3	Australia	5	USA	21
Italy	12	Japan	42		
Latvia	1	Korea	18		
Spain	1	Mainland China	35		
Switzerland	1				

PCV subgroup by race[b]



ICGA images were graded by the reading center.
[a]Australia (n=15); Austria (n=7); France (n=2); Italy (n=22); Japan (n=71); Korea (n=26); Latvia (n=2); mainland China (n=66); 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.
APAC, Asia Pacific; **ICGA,** indocyanine green angiography; **PCV**, polypoidal choroidal vasculopathy.

PCV subgroup: Baseline demographics and disease characteristics

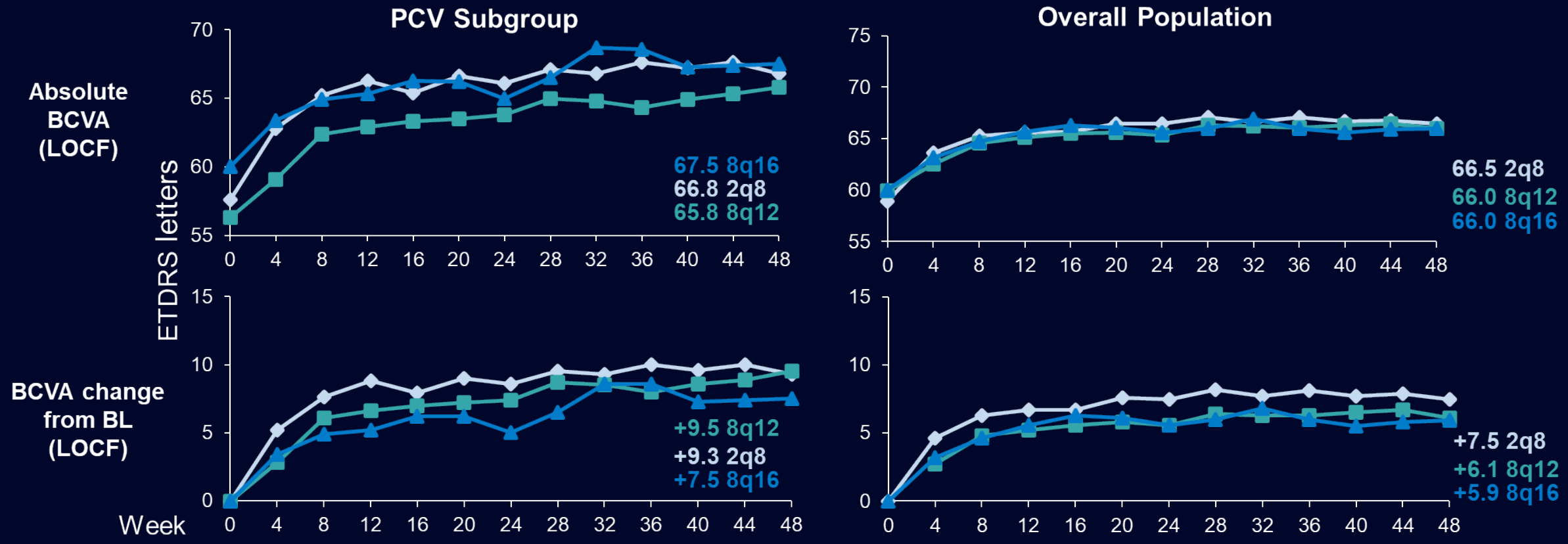
pulsar nAMD

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.
BL, baseline; **CNV**, choroidal neovascularization; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **ICGA**, indocyanine green angiography; **PCV**, polypoidal choroidal vasculopathy; **SD**, standard deviation.

PCV Subgroup: Absolute and Change from Baseline in BCVA through Week 48 (LOCF)

pulsar nAMD



	Mean ± SD change from BL to Week 48 (LOCF)	Two-sided 95% CI
2q8	+9.3 ± 11.1	6.2, 12.3
8q12	+9.5 ± 13.0	5.5, 13.4
8q16	+7.5 ± 7.6	5.1, 9.9

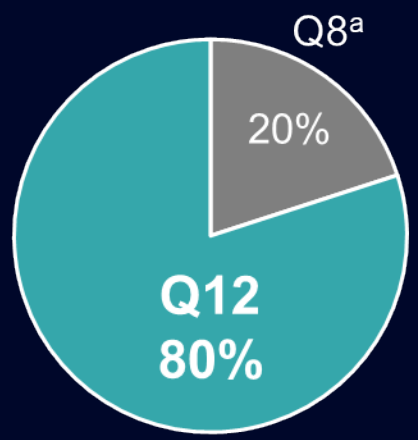
	Mean ± SD change from BL to Week 48 (LOCF)	Two-sided 95% CI
2q8	+7.5 ± 12.0	6.2, 8.8
8q12	+6.1 ± 13.2	4.7, 7.6
8q16	+5.9 ± 11.8	4.6, 7.2

LOCF: last available observed value prior to ICE will be used to impute missing data. ICE will be handled according to sensitivity estimand strategy for continuous endpoints as described; FAS (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).
CI, confidence interval; **ICE**, intercurrent event; **LOCF**, last observation carried forward.

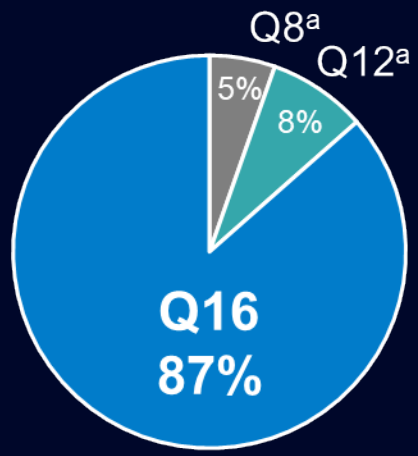
PCV Subgroup: Proportions of Patients Maintained on Q12 and Q16 Dosing Intervals through Week 48

pulsar nAMD

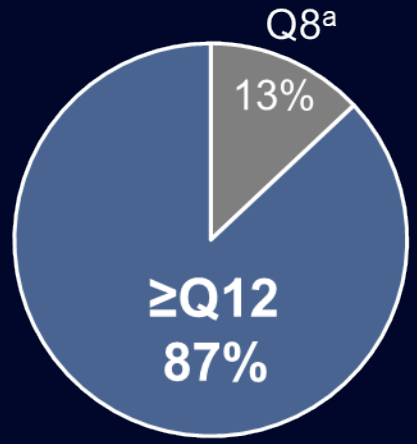
PCV subgroup



8q12 n=41[b]



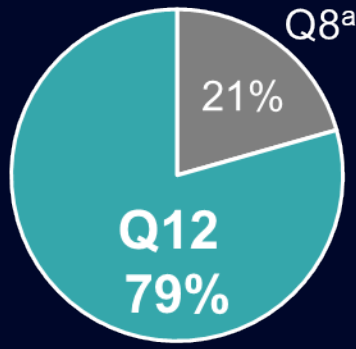
8q16 n=37[b]



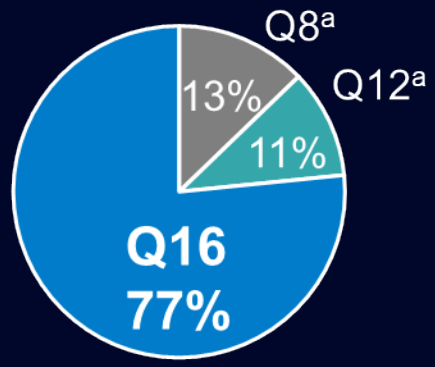
All aflibercept 8 mg n=78[b]

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

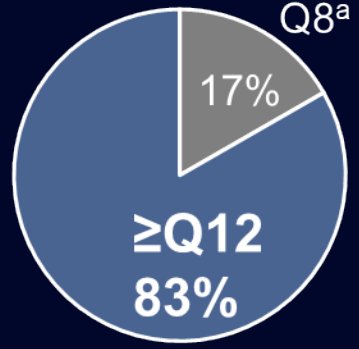
Overall population



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

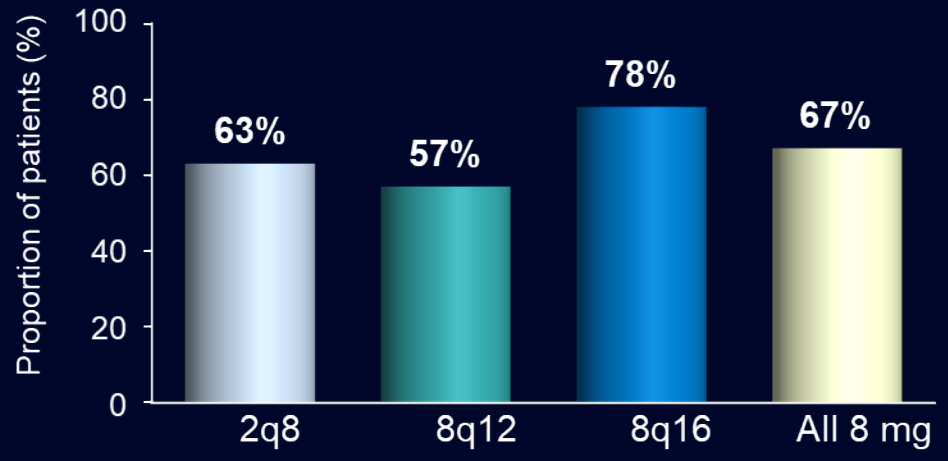
Values may not add up to 100% due to rounding.
[a]Patients shortened based on DRM assessments at some point through Week 48. [b]Patients completing Week 48.

PCV Subgroup: Anatomic Endpoints

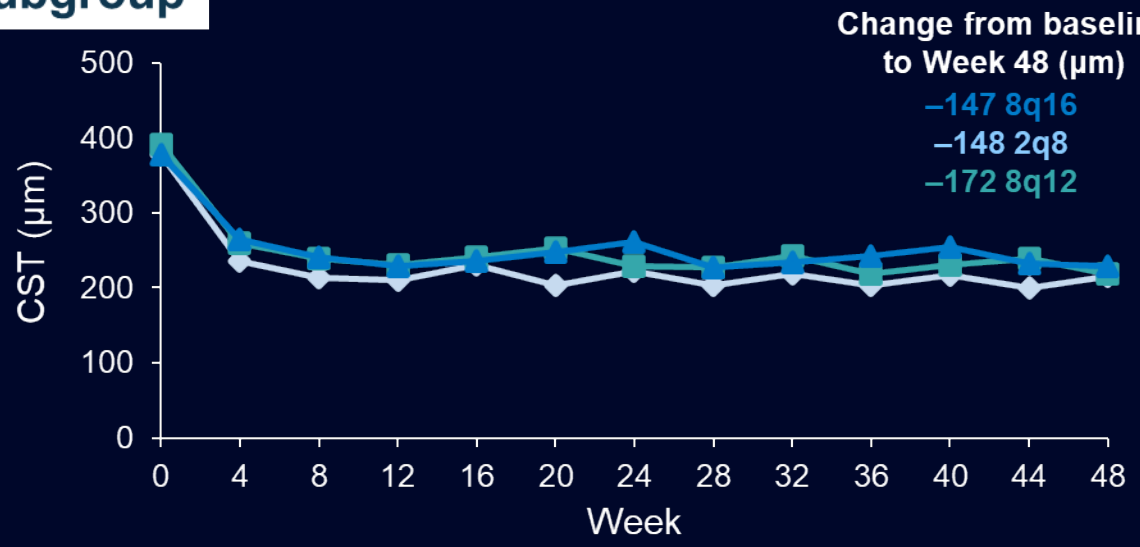
pulsar nAMD

Patients without retinal fluid in central subfield at Wk 16

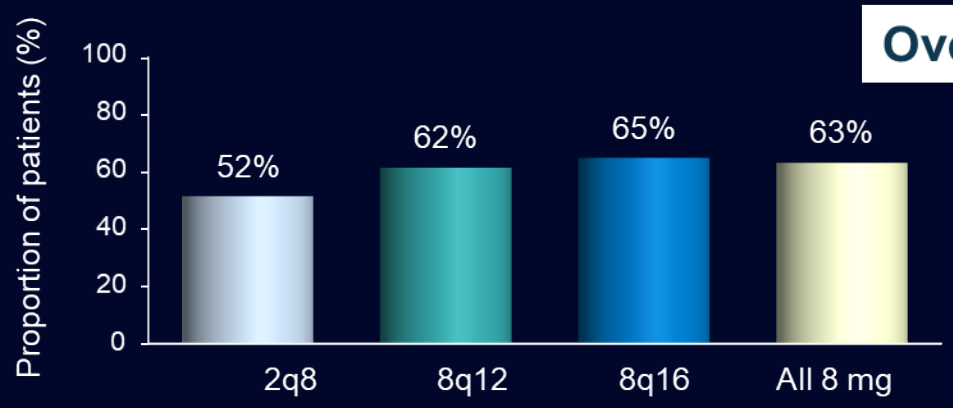
PCV subgroup

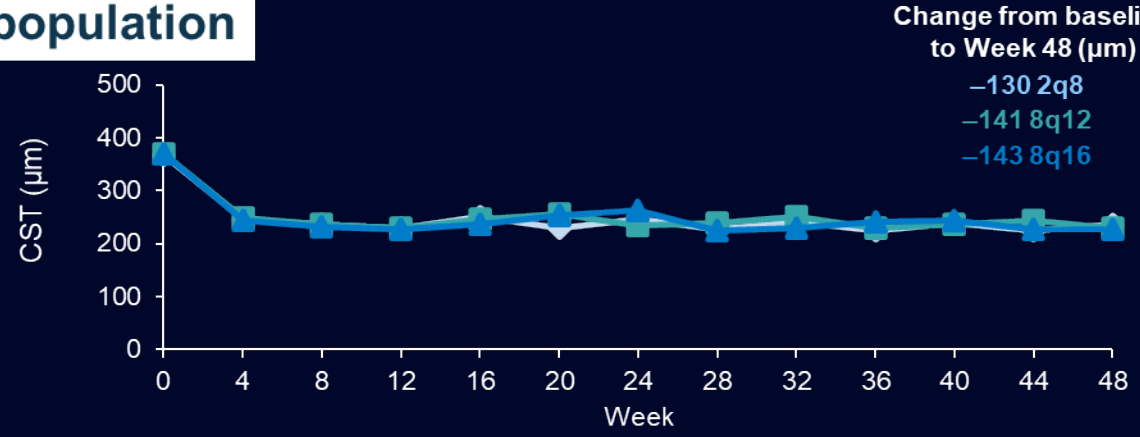


Absolute CST



Overall population



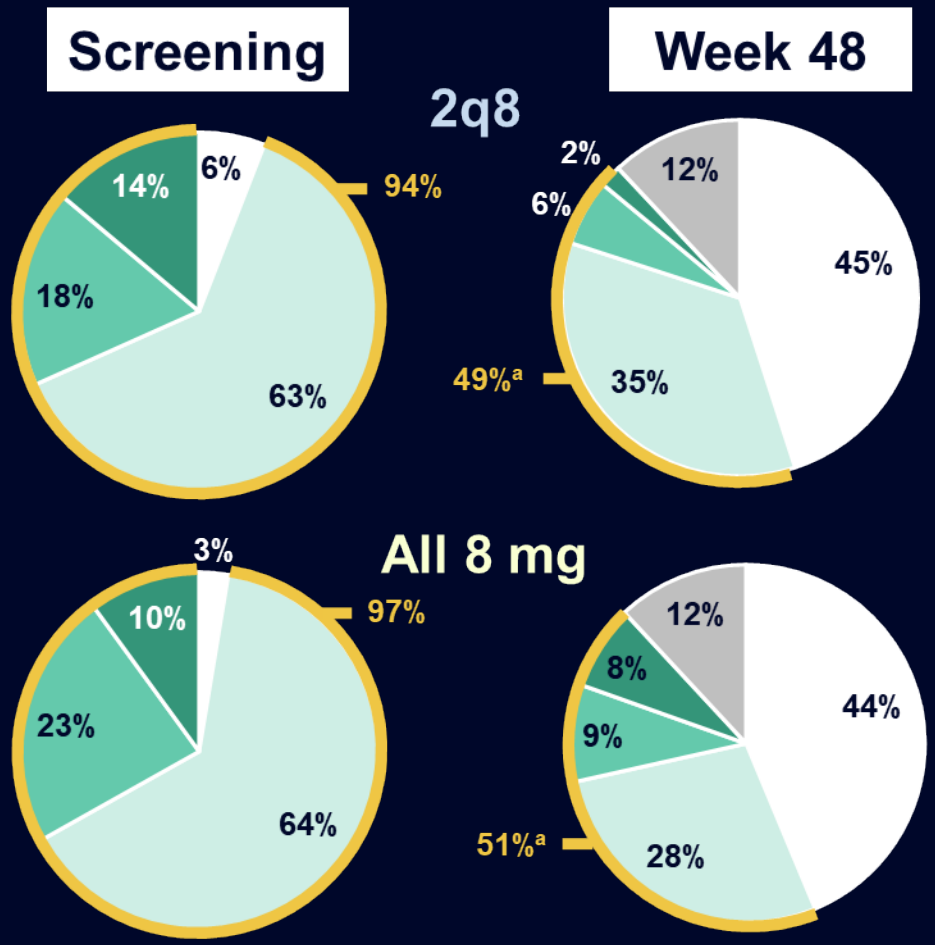


'Without retinal fluid' defined as absence of IRF and SRF in central subfield. For fluid: LOCF (censoring data post ICEs); FAS (PCV subgroup).
For CST: LOCF, FAS. PCV subgroup, 2q8 n=54; 8q12 n=44; 8q16 n=41; overall population, 2q8 n=335; 8q12 n=333; 8q16 n=334.

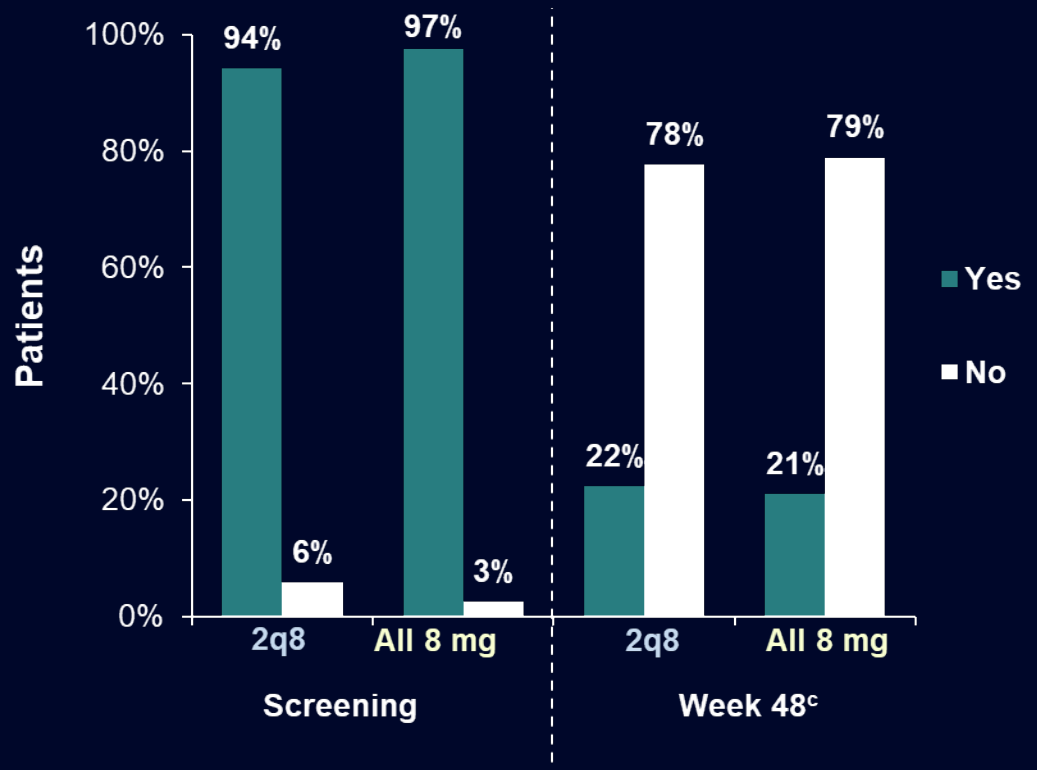
PCV subgroup: Additional analyses

pulsar nAMD

Patients with polyps



Patients with active polyps[a,b]



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. [a] % calculated based on number of patients with known number of polyps. [b] 'No' active polyps defined as no polyps present **OR** IRF and SRF are 'absent' or 'questionable'. [c] At Wk 48, n=2 unknown each for 2q8 and All 8 mg groups.

PCV subgroup: Safety – Week 48

pulsar nAMD

TEAE, n (%)	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	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

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

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]Data presented in this way to avoid unintentional patient unmasking.
AE, adverse event; **TEAE**, treatment-emergent adverse event; **SAF**, safety analysis set.

PCV subgroup: Non-Ocular safety through Week 48

pulsar nAMD

	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
Patients with ≥1 non-ocular TEAE (%)	44.4	52.3	56.1	54.1	53.0	52.2	53.8	53.0
Non-ocular serious TEAEs (%)	11.1	9.1	12.2	10.6	13.7	10.1	9.5	9.8

SAF. No cases of APTC events or hypertension events were reported in the PCV subgroup.
All events death: Overall population: 2q8, 1.5%; 8q12, 0.9%; 8q16, 0.3%; All 8mg, 0.6%.
APTC, Anti-Platelet Trialists' Collaboration.

Conclusions:
Aflibercept 8 mg monotherapy in PCV

pulsar nAMD

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%, respectively) 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.