Intravitreal Aflibercept Injection 8 mg for nAMD: 48-Week Results From the Phase 3 PULSAR Trial

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Disclosures

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- Paolo Lanzetta is a consultant for Aerie, Allergan, Apellis, Bausch & Lomb, Bayer, Biogen, Boehringer Ingelheim, I-Care, Genentech, Novartis, Outlook Therapeutics, and Roche
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- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation

PULSAR Study Design

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

2q8
Aflibercept 2mg every 8 weeks after 3 initial monthly injections
n=336

8q12
8mg every 12 weeks after 3 initial monthly injections
n=335

8q16
8mg every 16 weeks after 3 initial monthly injections
n=338

Primary EP at Week 48
Mean change in BCVA (Non-inferiority)

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

BCVA, best corrected visual acuity; **EP**, endpoint; **IRF**, intraretinal fluid; **SRF**, subretinal fluid.

PULSAR: Dosing Schedule

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

Dose Regimen Modifications (DRM) in Year 1

- At Weeks 16 or 20, 8q12 and 8q16 patients meeting DRM criteria will be shortened to Q8
- At Week 24, 8q16 patients meeting DRM criteria will be shortened to Q12
- At subsequent dosing visits, 8mg patients meeting DRM criteria will be shortened by 4 weeks
- Minimum interval for all patients is Q8

DRM Criteria for Shortening Dosing Interval:

>5-letter loss in BCVA from Week 12 BCVA due to persistent or worsening AMD

AND

>25-micron increase in CRT from Week 12 OR new onset foveal neovascularization or foveal hemorrhage

Stippled boxes = initial treatment phase; X=active injection; o=sham injections
Note: Table does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in the first year
DRM criteria for shortening: >5-letter loss in BCVA from Week 12 BCVA due to persistent or worsening AMD in conjunction with >25-micron increase in CRT from Week 12 or new onset foveal neovascularization or foveal hemorrhage

Patient Disposition at Week 48

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	2q8	8q12	8q16	Total
# Randomized	337	336	338	1011
# Completing Week 48	92.3%	94.6%	92.9%	93.3%
# Discontinued before Week 48	7.4%	5.1%	7.1%	6.5%

Baseline Demographics

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	2q8	8q12	8q16	Total
N (FAS/SAF)	336	335	338	1009
Age (years)	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.5 (8.4)
Female (%)	56.0%	54.3%	53.3%	54.5%
Race (%)				
Asian	24.7%	22.1%	22.8%	23.2%
Black or African American	0.6%	0.6%	0	0.4%
White	74.1%	76.4%	76.9%	75.8%
Not reported	0.6%	0.6%	0.3%	0.5%
Hispanic or Latino (%)	3.6%	2.1%	2.7%	2.8%

Data are mean (SD) unless otherwise indicated
FAS, full analysis set; **SAF**, safety analysis set; **SD**, standard deviation.

Baseline Characteristics of the Study Eye

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	2q8	8q12	8q16	Total
N (FAS/SAF)	336	335	338	1009
BCVA (ETDRS letters)	58.9 (14.0)	59.9 (13.4)	60.0 (12.4)	59.6 (13.3)
Snellen Equivalent	20/63	20/63	20/63	20/63
20/32 (73 to 78 letters)	14.6%	12.5%	14.2%	13.8%
20/40 or worse (<73 letters)	85.4%	87.5%	85.8%	86.2%
CRT (µm)	367.1 (133.6)	370.6 (123.8)	370.7 (132.7)	369.4 (130.0)
Total lesion area (mm^2)	6.9 (5.4)	6.4 (5.1)	6.9 (5.7)	6.7 (5.4)
Lesion type (%)				
Occult	57.1%	58.8%	55.0%	57.0%
Predominantly classic	21.1%	21.2%	19.8%	20.7%
Minimally classic	18.2%	16.7%	20.1%	18.3%

Data are mean (SD) unless otherwise indicated
CRT, central retinal thickness; **ETDRS**, Early Treatment of Diabetic Retinopathy Study.

PULSAR: 48-Week BCVA Results
Primary Endpoint Met in Both 8mg Groups

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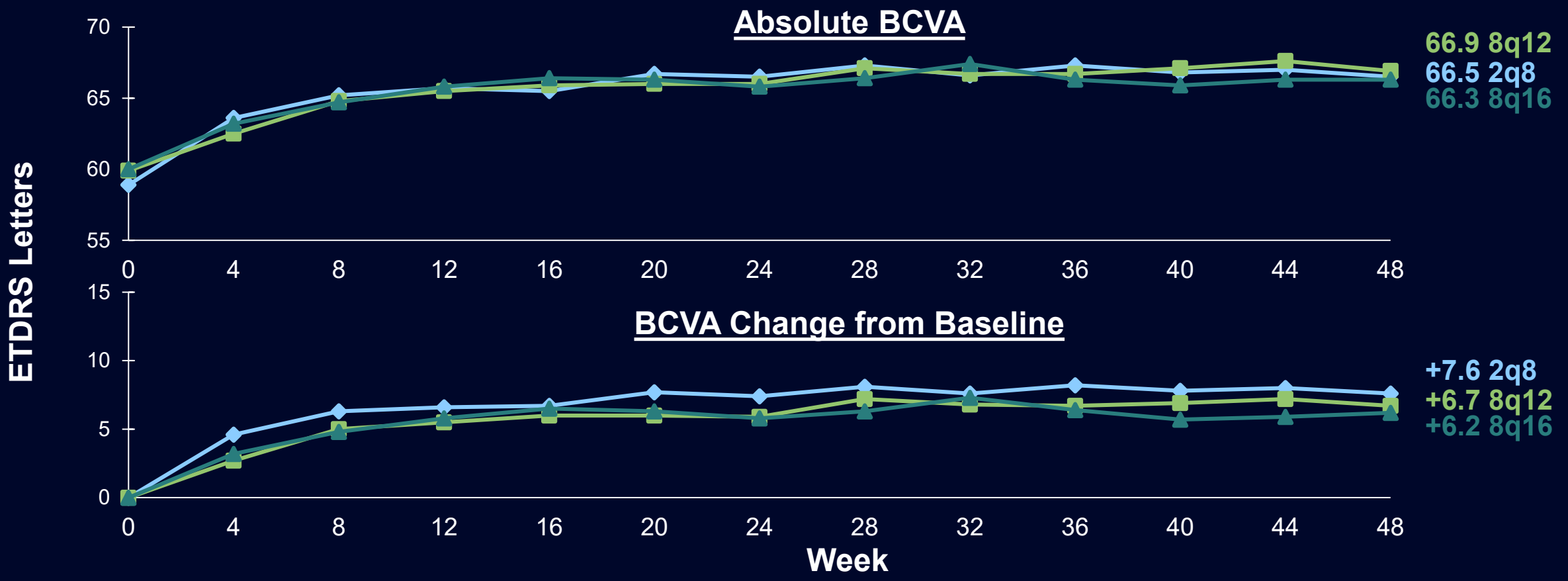

	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	-0.97	-2.87, 0.92	p = 0.0009
8q16	5.9	-1.14	-2.97, 0.69	p = 0.0011

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

Key Secondary Endpoint: Proportion of Patients Without Retinal Fluid in Center Subfield at Week 16

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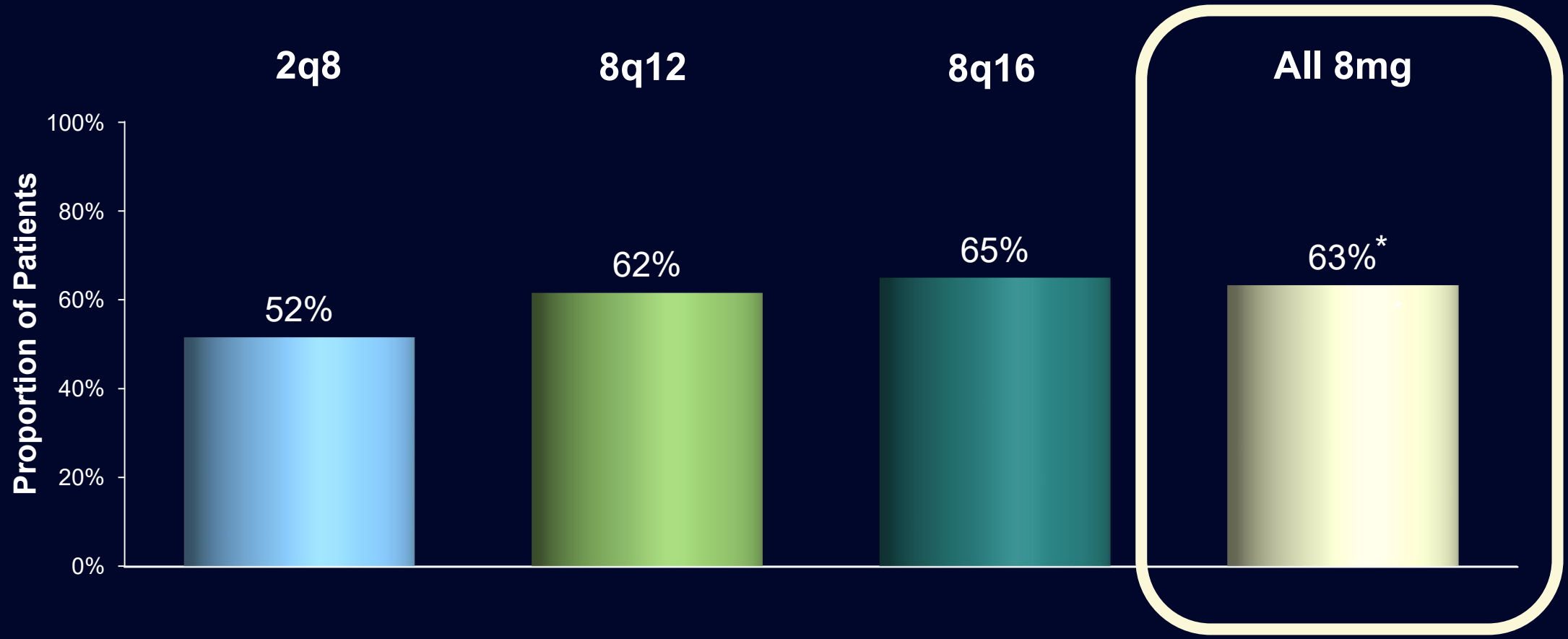

1-sided superiority p-value:
**p = 0.0002 All 8mg vs. 2q8*

Without Retinal Fluid defined as absence of IRF and SRF in center subfield
LOCF (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338

Proportion of Patients Maintaining Q12- and Q16-Week Intervals Through Week 48

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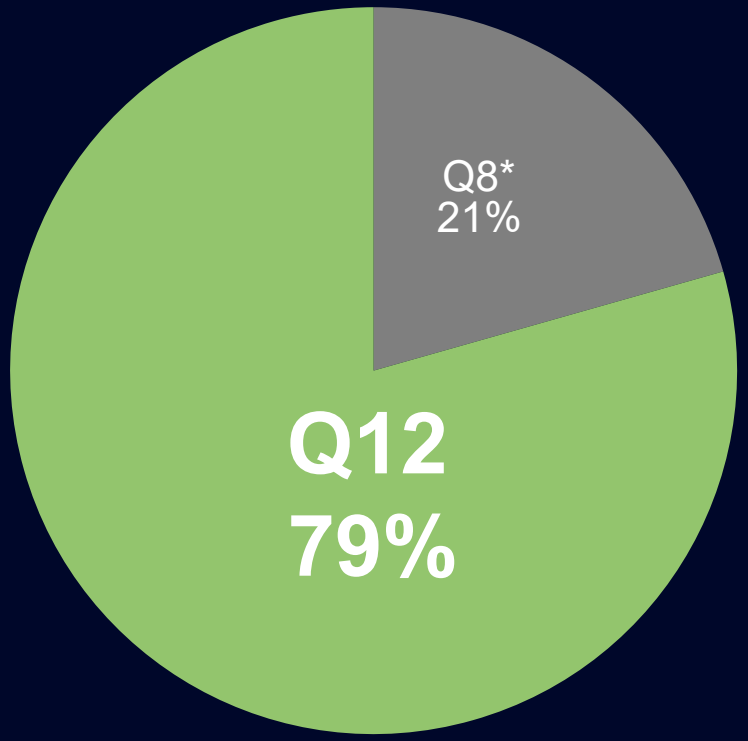
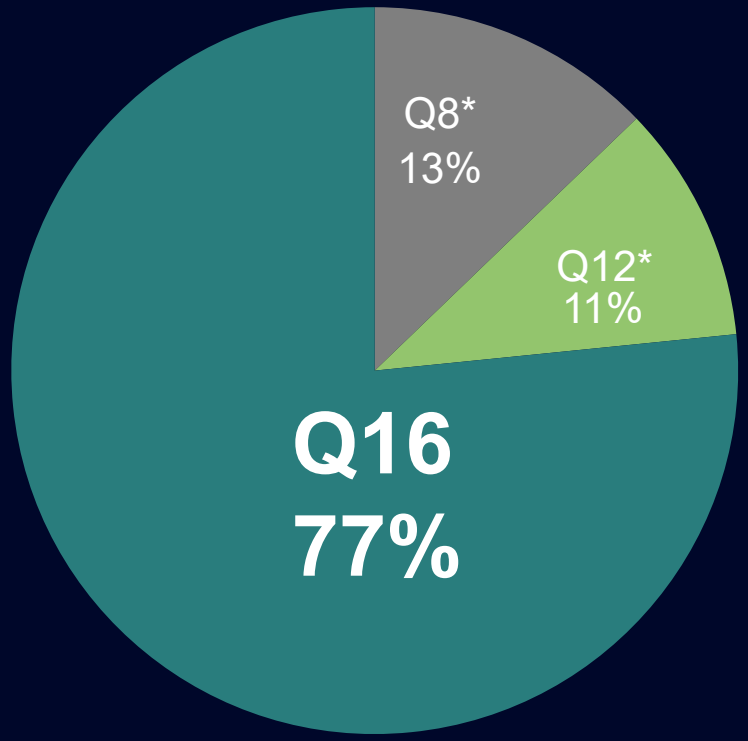
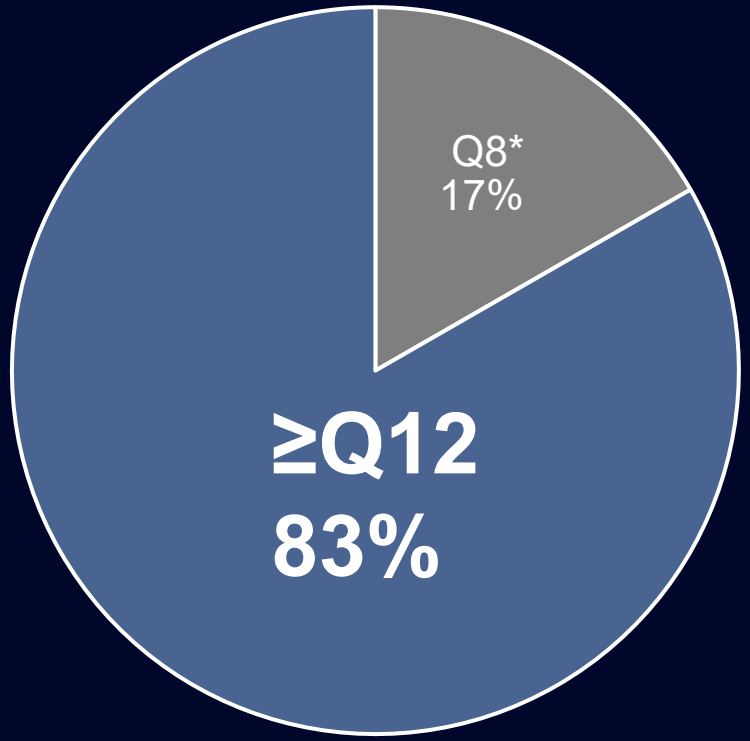
83% of 8mg patients maintained dosing intervals ≥12 weeks



8q12 n=316^



8q16 n=312^



All 8mg n=628^

*Patients shortened based on DRM assessments at some point through Week 48
^Patients completing Week 48

Central Retinal Thickness

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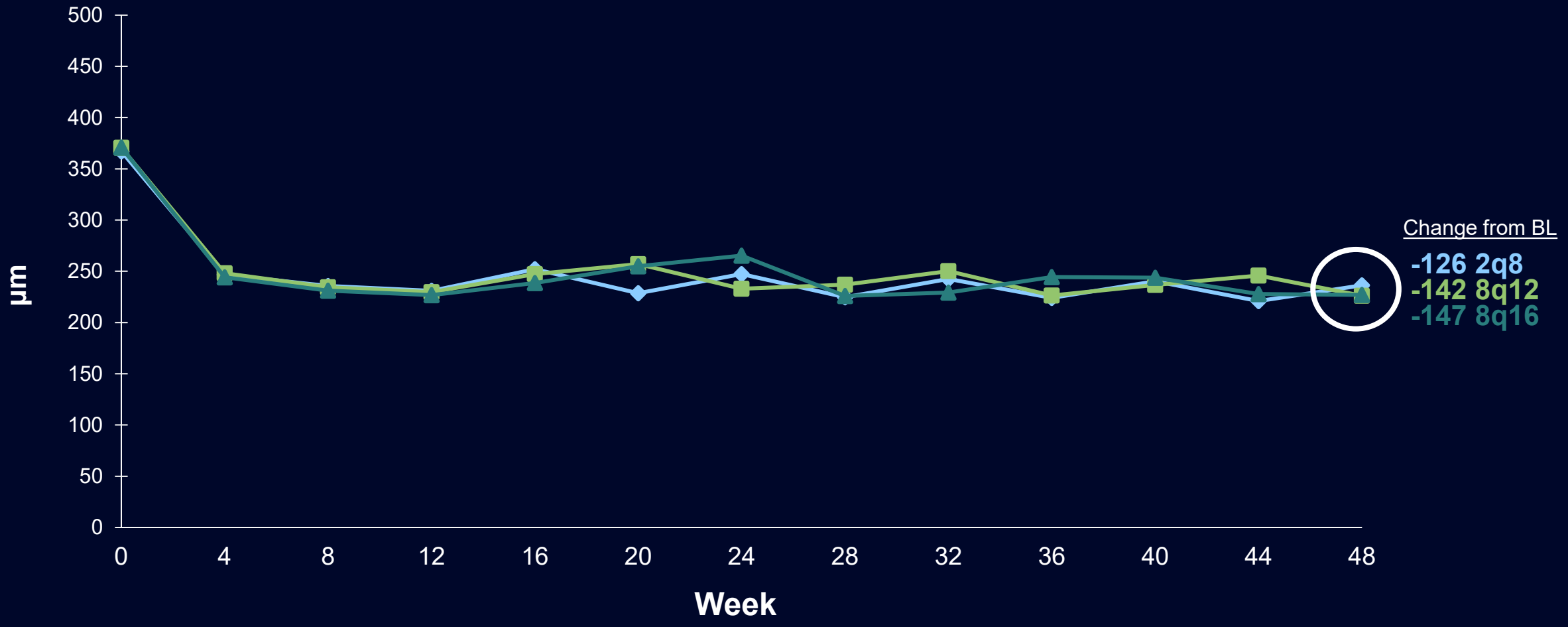

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

Most Frequent Ocular AEs Through Week 48

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	2q8	8q12	8q16	All 8mg
N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)*	38.7%	38.5%	37.6%	38.0%
Cataract	3.0%	3.6%	3.6%	3.6%
Intraocular pressure increased	2.1%	3.3%	2.7%	3.0%
Retinal hemorrhage	4.2%	3.3%	3.0%	3.1%
Subretinal fluid	3.3%	3.0%	1.5%	2.2%
Visual acuity reduced	6.0%	3.6%	5.3%	4.5%
Vitreous floaters	3.3%	1.2%	3.6%	2.4%

*Any ocular treatment-emergent AE in the study eye

AE, adverse event; SAF, safety analysis set.

Intraocular Inflammation Through Week 48

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	2q8	8q12	8q16	All 8mg
N (SAF)	336	335	338	673
Patients with ≥ 1 IOI AE (%)*	0.6%	1.2%	0.3%	0.7%

- No cases of endophthalmitis or occlusive retinal vasculitis

Reported IOI terms: chorioretinitis, iridocyclitis, iritis, vitreal cells, vitritis
*Treatment-emergent events

Non-Ocular Safety Through Week 48

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	2q8	8q12	8q16	All 8mg
N (SAF)	336	335	338	673
Patients (%):				
APTC events*	1.5%	0.3%	0.3%	0.3%
Hypertension events*	3.6%	4.8%	4.7%	4.8%
Non-ocular SAEs*	13.7%	10.1%	9.5%	9.8%
Deaths^	1.5%	0.9%	0.3%	0.6%

*Treatment-emergent events; ^All events
APTC, Anti-Platelet Trialists' Collaboration; **SAE**, serious adverse events.

PULSAR:
Primary and Key Secondary Endpoints Met

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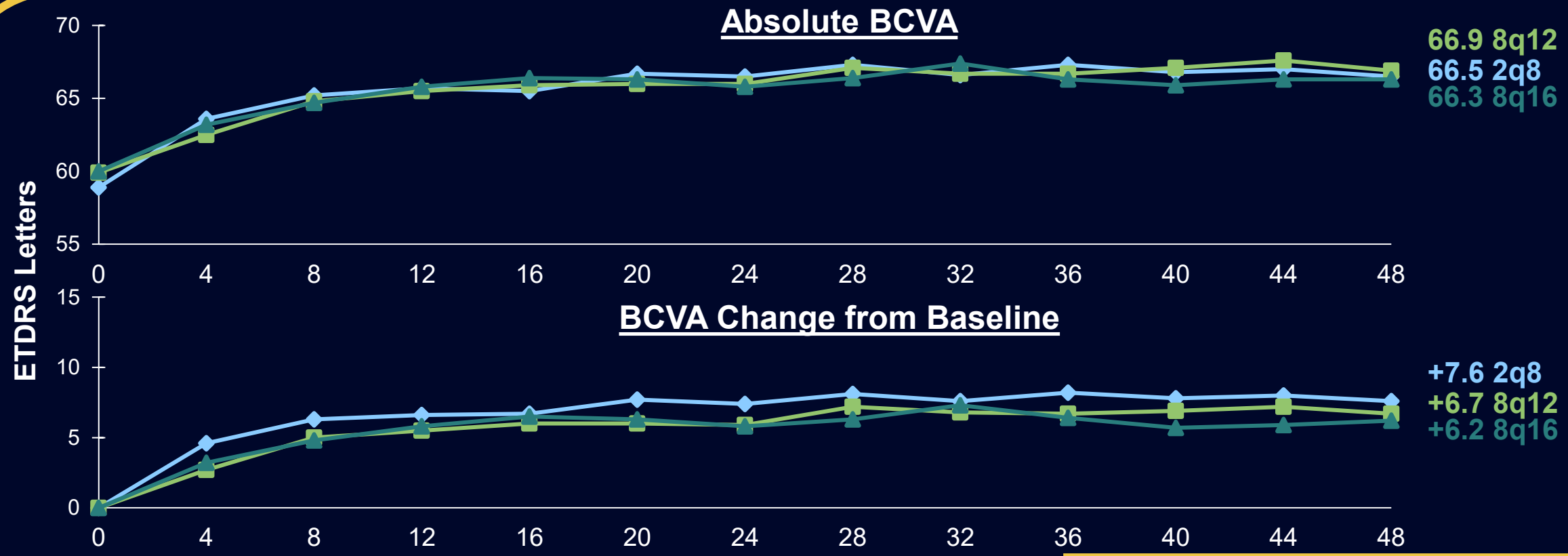
- 8q12 and 8q16 groups had non-inferior BCVA compared to 2q8 at Week 48
- 8q12 and 8q16 combined had superior drying compared to 2q8 at Week 16
- Ocular and non-ocular safety comparable to 2mg



Observed values (censoring data post ICE);
FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

p = 0.0009 8q12 vs. 2q8 95% CI (-2.87, 0.92)
p = 0.0011 8q16 vs. 2q8 95% CI (-2.97, 0.69)

NOTE: p-values for the one-sided non-inferiority test at a margin of 4 letters (based on adjusted means derived using an MMRM)

PULSAR: 48-Week Results
Majority of 8mg Patients Maintained Randomized Intervals

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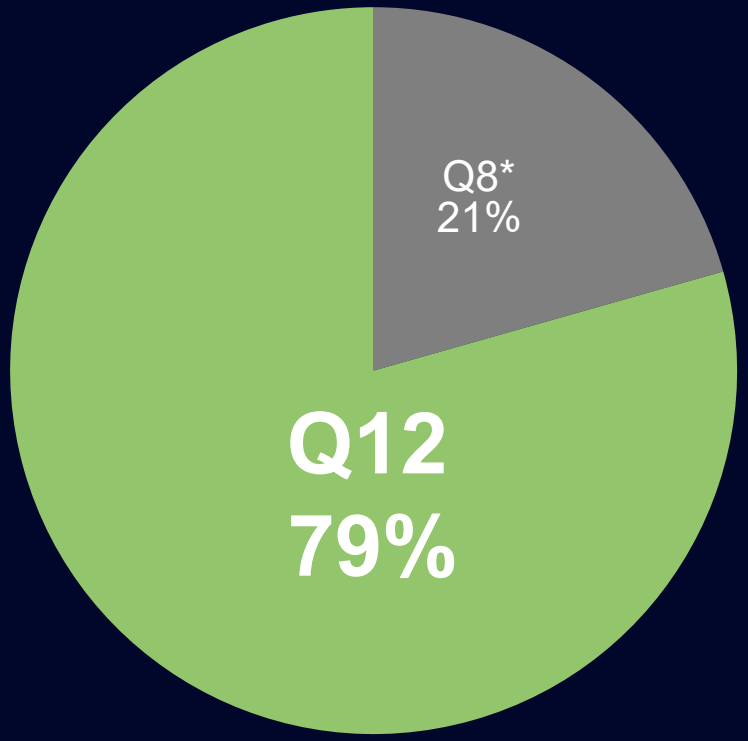
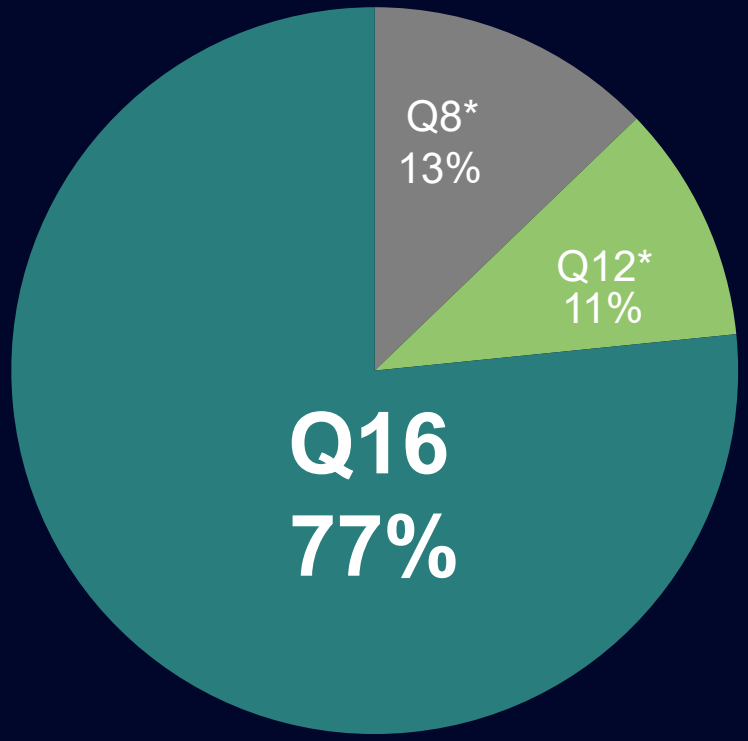
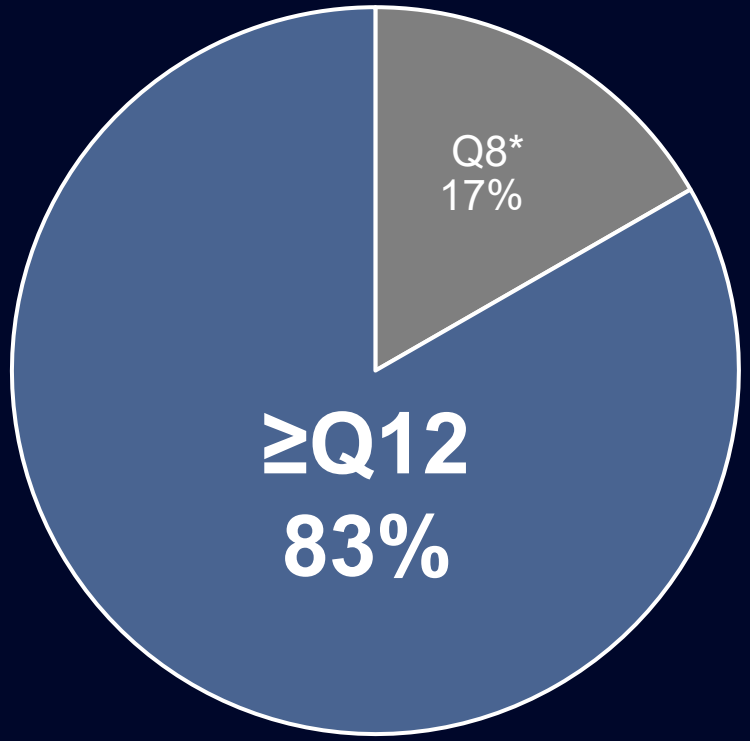
83% of 8mg patients maintained dosing intervals ≥12 weeks



8q12 (n=316^)



8q16 (n=312^)



All 8mg (n=628^)

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