Intravitreal Aflibercept 8 mg Injection in Patients with Neovascular Age-Related Macular Degeneration: 48-Week Results from the Phase 3 PULSAR Trial

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Disclosures

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nAMD

- Martin Spitzer receives consultancy fees from Allergan/AbbVie, Apellis, Bayer, Biogen, Boehringer Ingelheim, Gensight Biologics, Iveric Bio, Neurogene, Novartis, Roche, Stada, and Zeiss
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- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- The results of the PULSAR study were previously presented at The Retina Society 55th Annual Scientific Meeting, November 2–5, 2022; Angiogenesis, February 10–11, 2023; The 46th Annual Macular Society Meeting, February 15–18, 2023, and FujiRetina, March 23–25, 2023
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Characteristics of Aflibercept 8 mg

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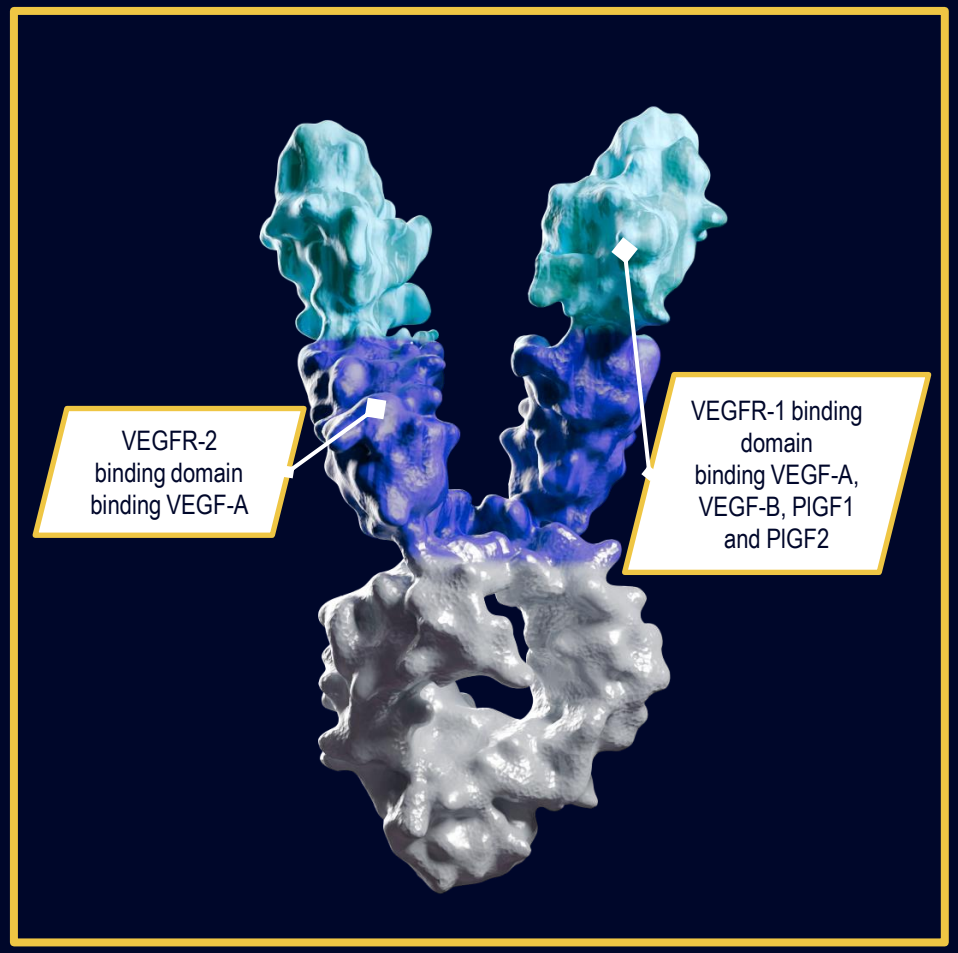

- Novel intravitreal formulation delivers 8 mg in 70 µL injection (114.3 mg/mL)
- 4-times higher molar dose compared with aflibercept 2 mg is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on VEGF signaling

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

nAMD, neovascular age-related macular degeneration; **PlGF**, placental growth factor; **VEGF**, vascular endothelial growth factor.

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; **SRF**, subretinal fluid.

PULSAR Study Sites

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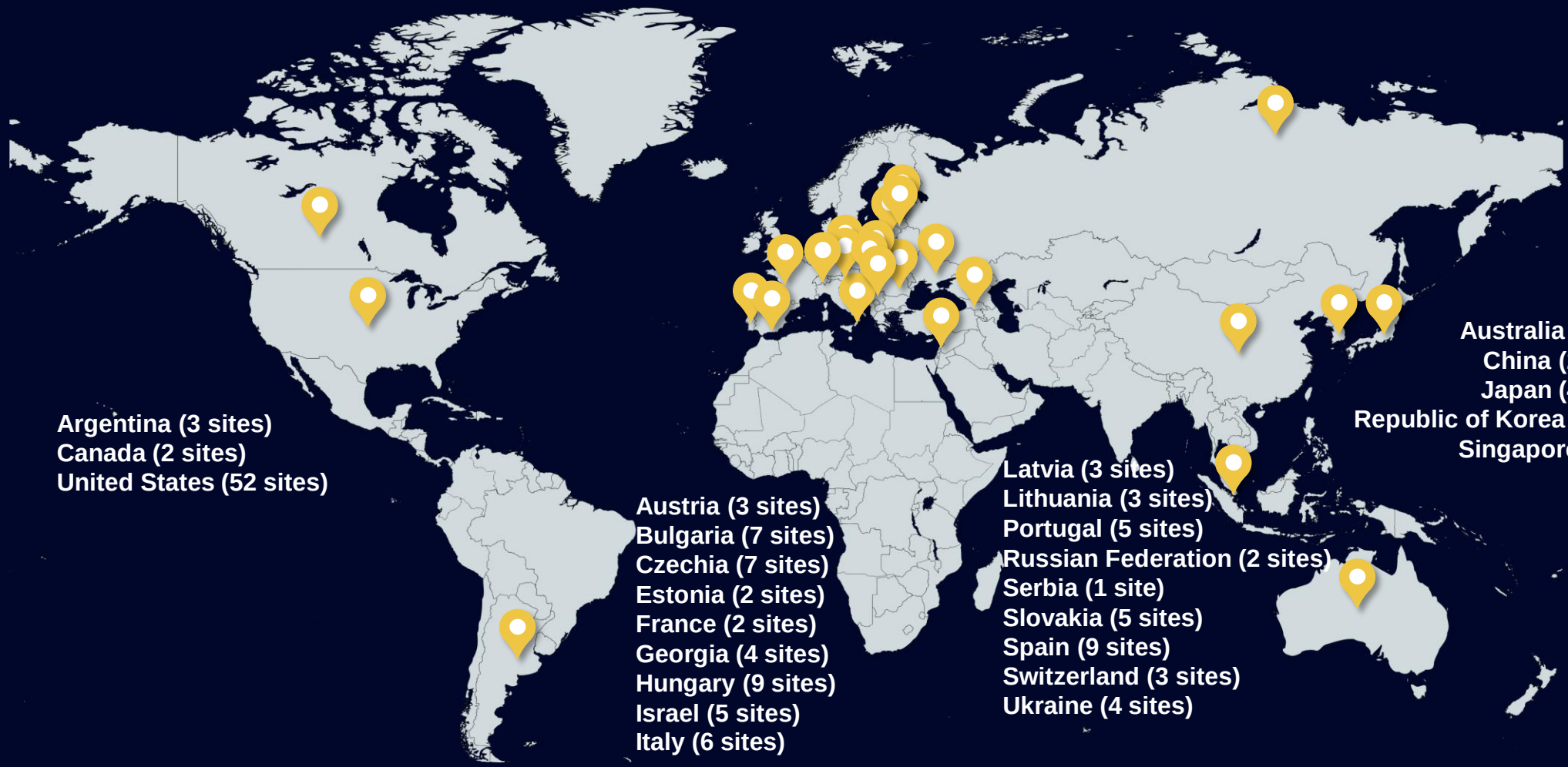
Global study conducted in 223 sites in 26 countries



Argentina (3 sites)
Canada (2 sites)
United States (52 sites)

Austria (3 sites)
Bulgaria (7 sites)
Czechia (7 sites)
Estonia (2 sites)
France (2 sites)
Georgia (4 sites)
Hungary (9 sites)
Israel (5 sites)
Italy (6 sites)

Latvia (3 sites)
Lithuania (3 sites)
Portugal (5 sites)
Russian Federation (2 sites)
Serbia (1 site)
Slovakia (5 sites)
Spain (9 sites)
Switzerland (3 sites)
Ukraine (4 sites)

Australia (5 sites)
China (29 sites)
Japan (44 sites)
Republic of Korea (7 sites)
Singapore (1 site)

Key Inclusion/Exclusion Criteria

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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)

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

PULSAR: Dosing Schedule and Regimen Modification in Year 1

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	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.

Patient Disposition at Week 48

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	2q8	8q12	8q16	Total
# Randomized	337	336	338	1011
# Treated	99.7%	99.7%	100%	99.8%
# Completing Week 48	92.3%	94.6%	92.9%	93.3%
# Discontinued before Week 48	7.4%	5.1%	7.1%	6.5%
Reasons for discontinuation				
Withdrawal by patient	1.8%	1.5%	3.8%	2.4%
Adverse events	1.5%	0.6%	1.2%	1.1%
Death	1.5%	0.9%	0.3%	0.9%
COVID-19 related	0.6%	0.6%	0.6%	0.6%
Physician decision	0.3%	0.6%	0.6%	0.5%
Other[a]	1.8%	0.9%	0.6%	1.1%

[a]Includes 'lost to follow-up', 'lack of efficacy', and 'protocol deviation'. Categories were combined to maintain masking of individual patients.

Baseline Demographics

nAMD

	2q8	8q12	8q16	Total
N (FAS)	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%
Hypertension (%)	60.7%	66.3%	64.8%	63.9%

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

Baseline Characteristics of the Study Eye

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	2q8	8q12	8q16	Total
N (FAS)	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 (134)	371 (124)	371 (133)	370 (130)
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
ETDRS, Early Treatment of Diabetic Retinopathy Study.

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

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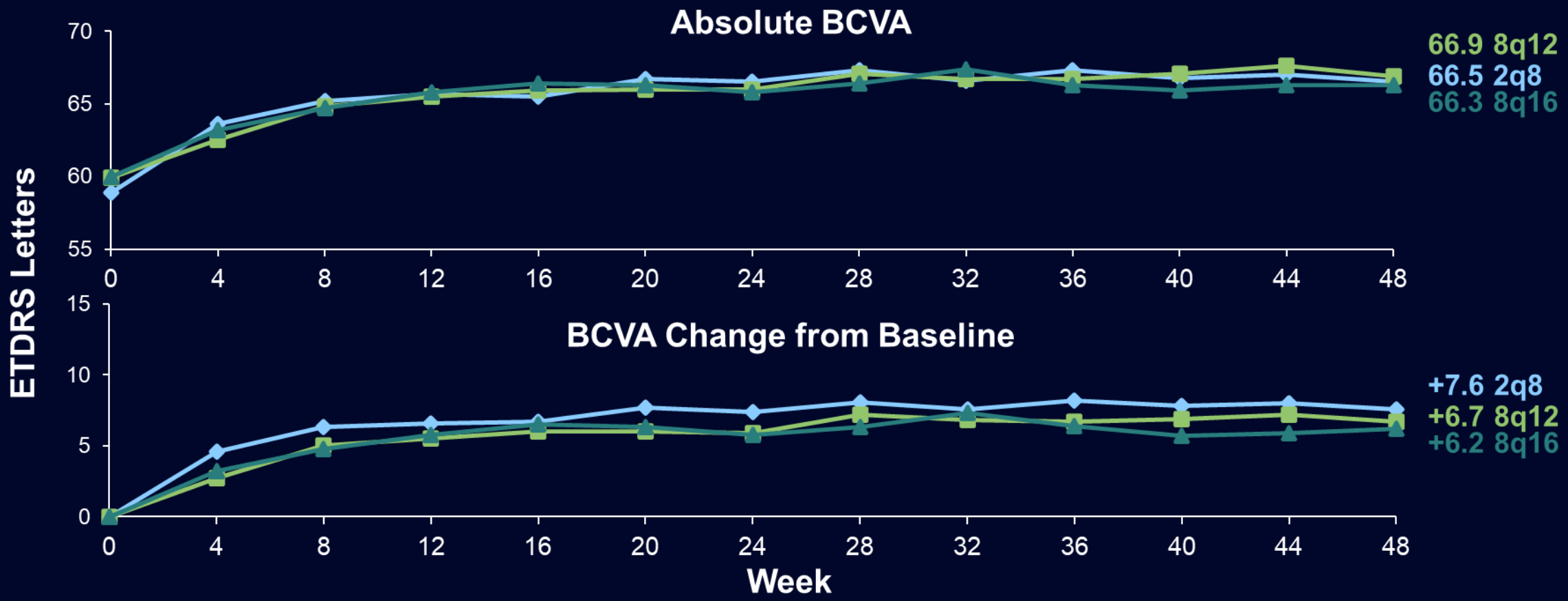


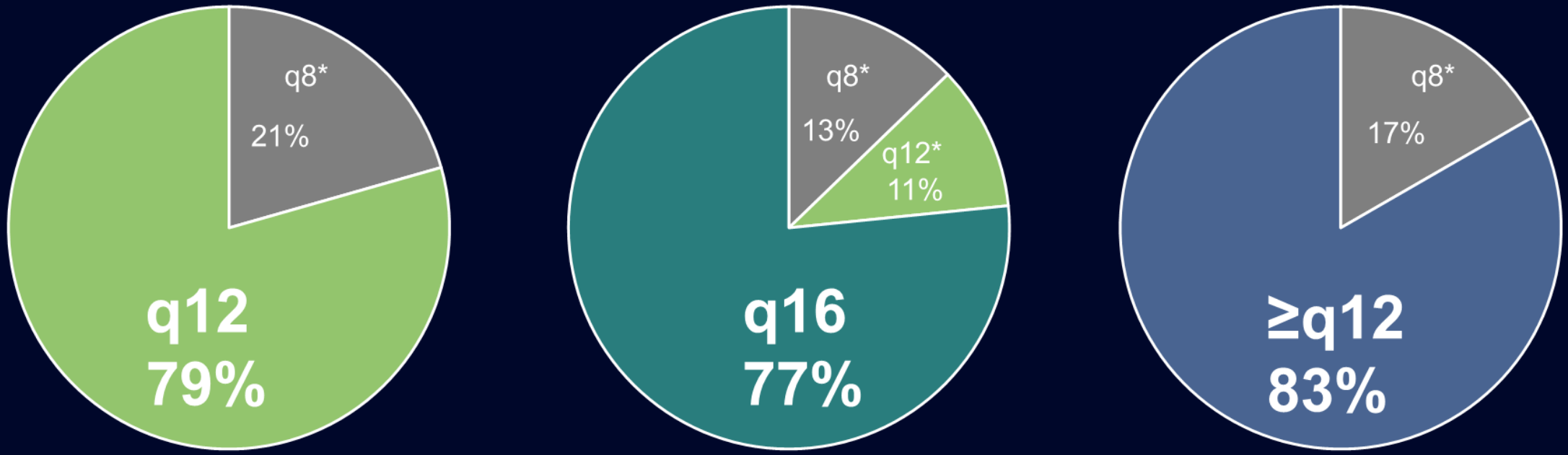
	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
ICE, intercurrent events; **MMRM**, mixed model for repeated measurements.

Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48

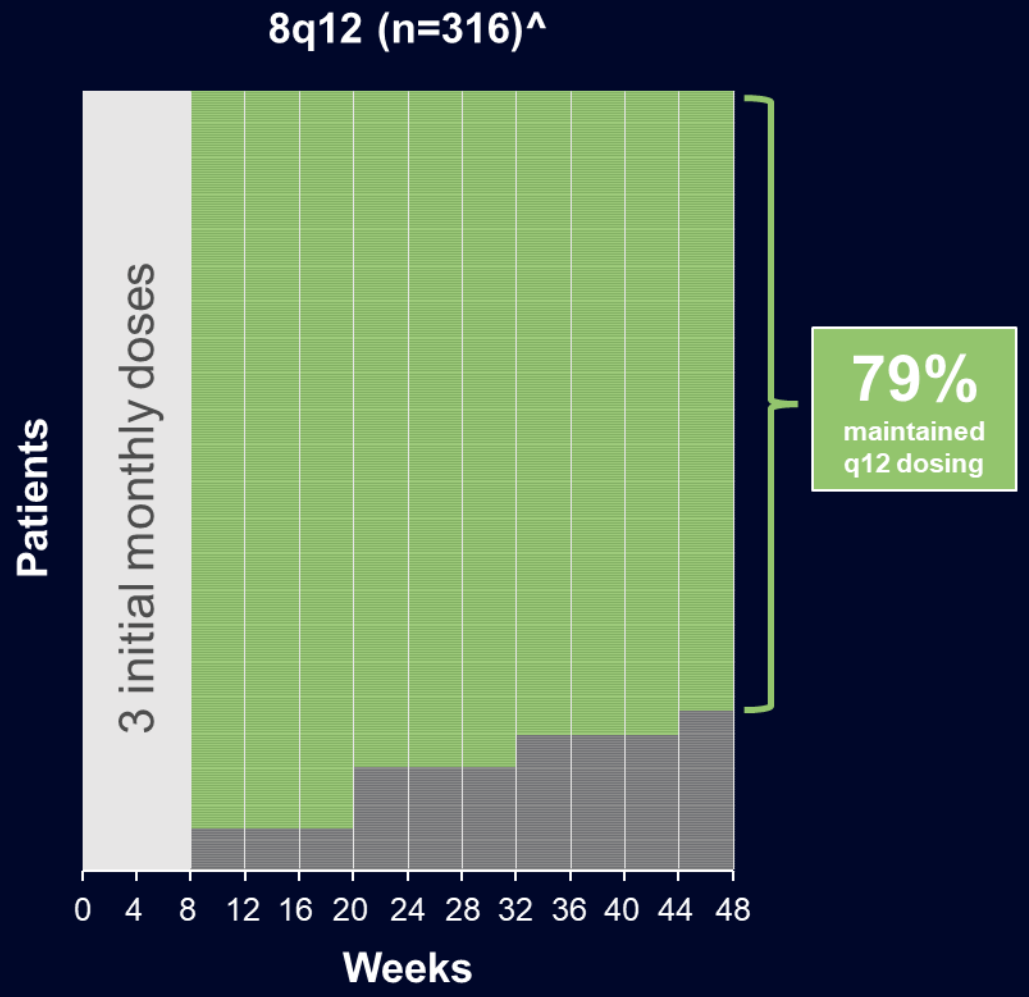
pulsar nAMD

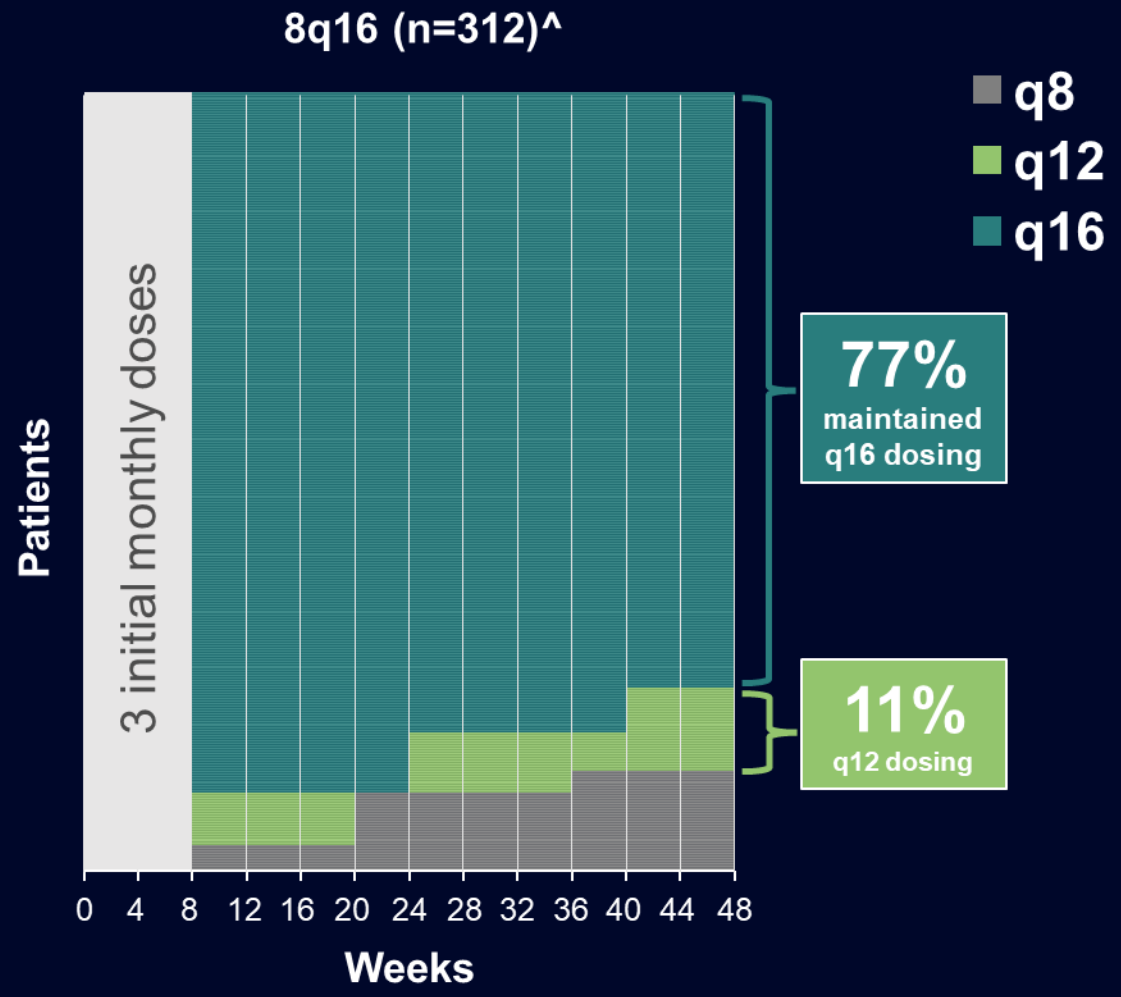
83% of 8 mg patients maintained dosing intervals ≥12 weeks



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.

Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48





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

Mean Number of Injections through Week 48

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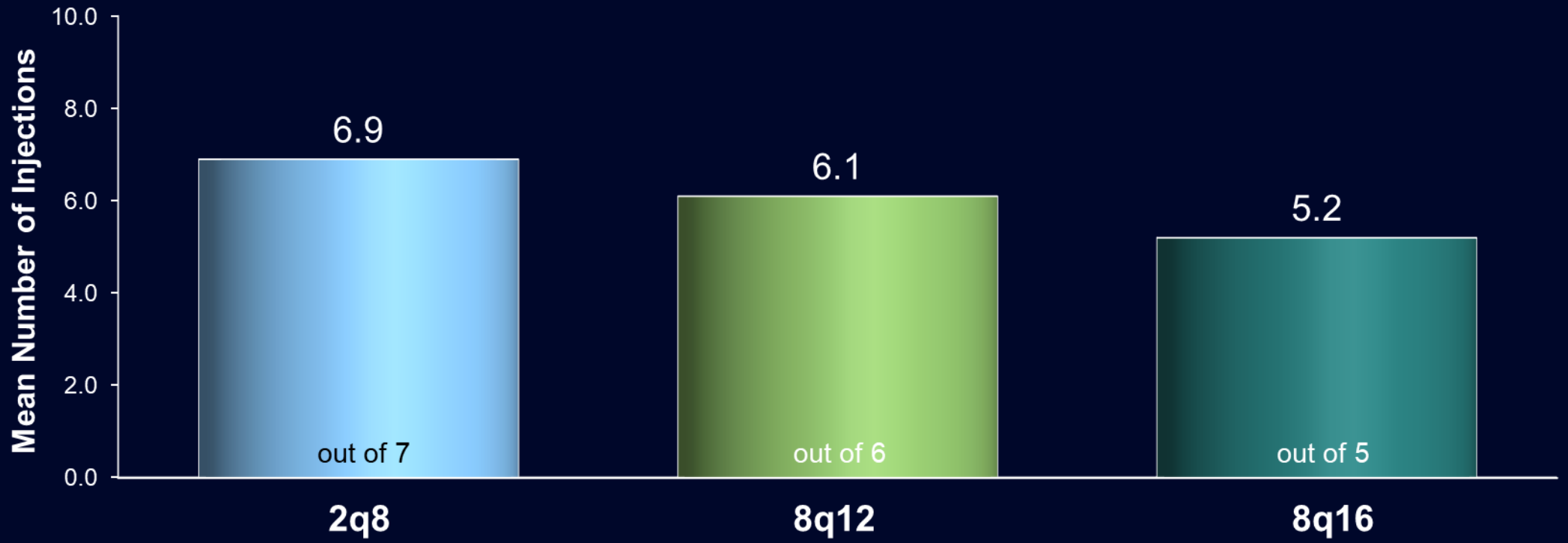

Patients completing Week 48; 2q8 n=309; 8q12 n=316; 8q16 n=312.

Proportion of Patients Without Retinal Fluid in Center Subfield at Weeks 16 and 48

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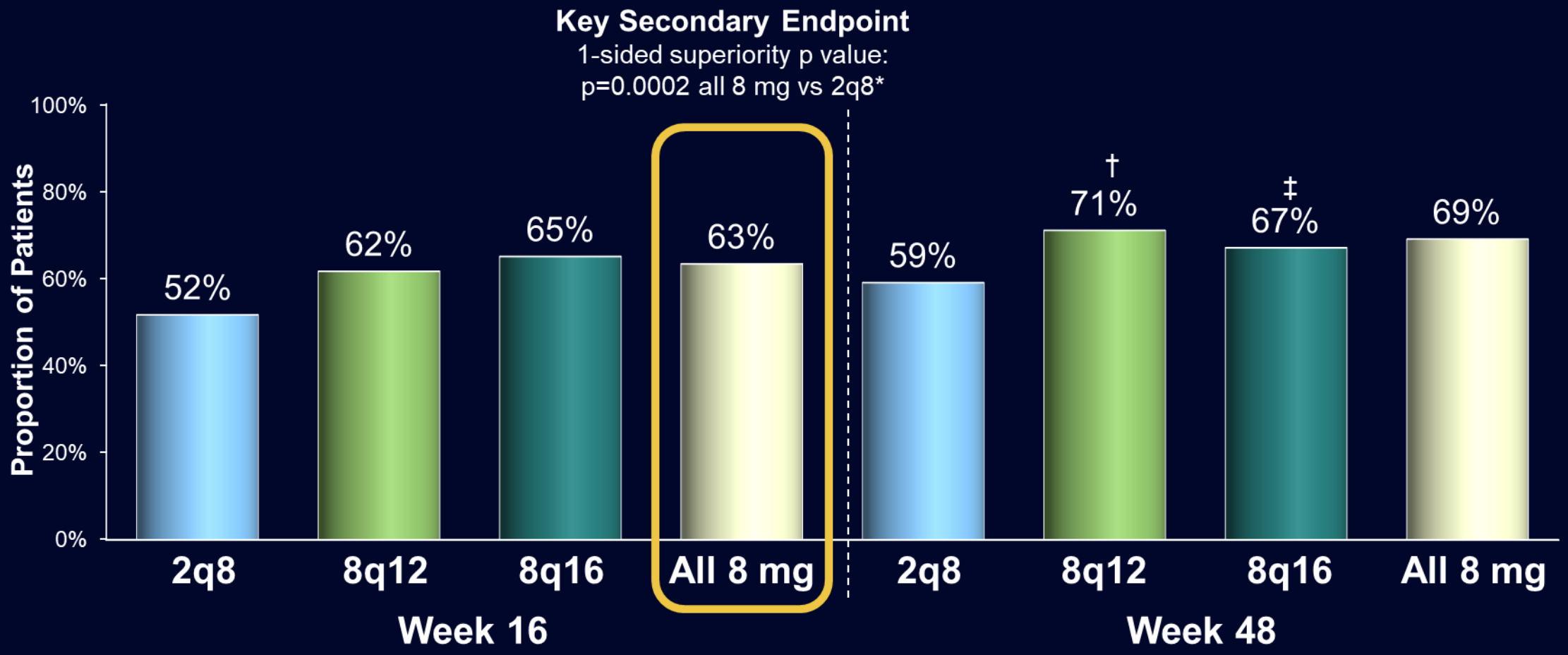

Without retinal fluid defined as absence of IRF and SRF in center subfield.
LOCF (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
*P value: one-sided Cochran-Mantel-Haenszel (CMH); weighting scheme adjusted by geographical region and baseline BCVA (<60 vs ≥60).
†nominal p=0.0015 8q12 vs 2q8; ‡nominal p=0.0458 8q16 vs 2q8.

Time to a Fluid-Free Center Subfield

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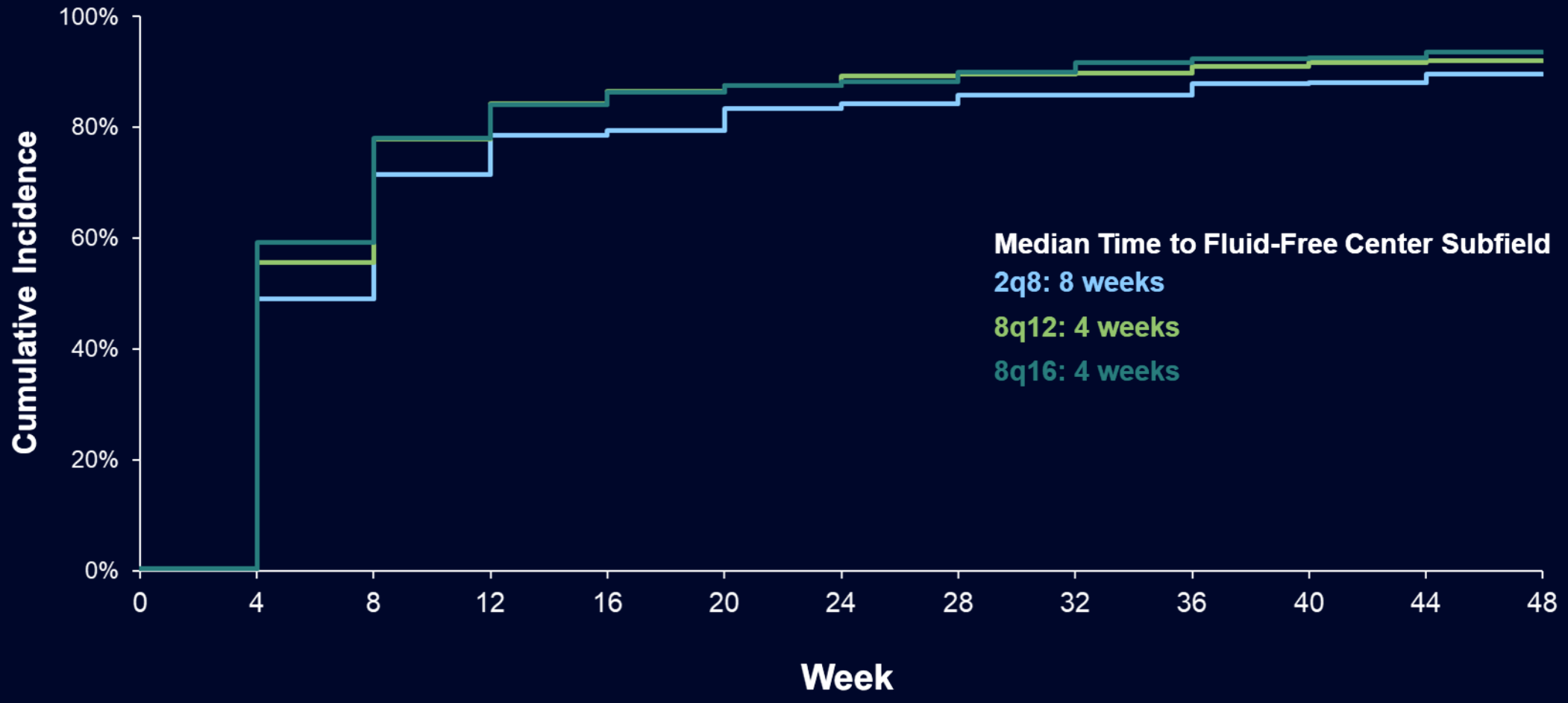
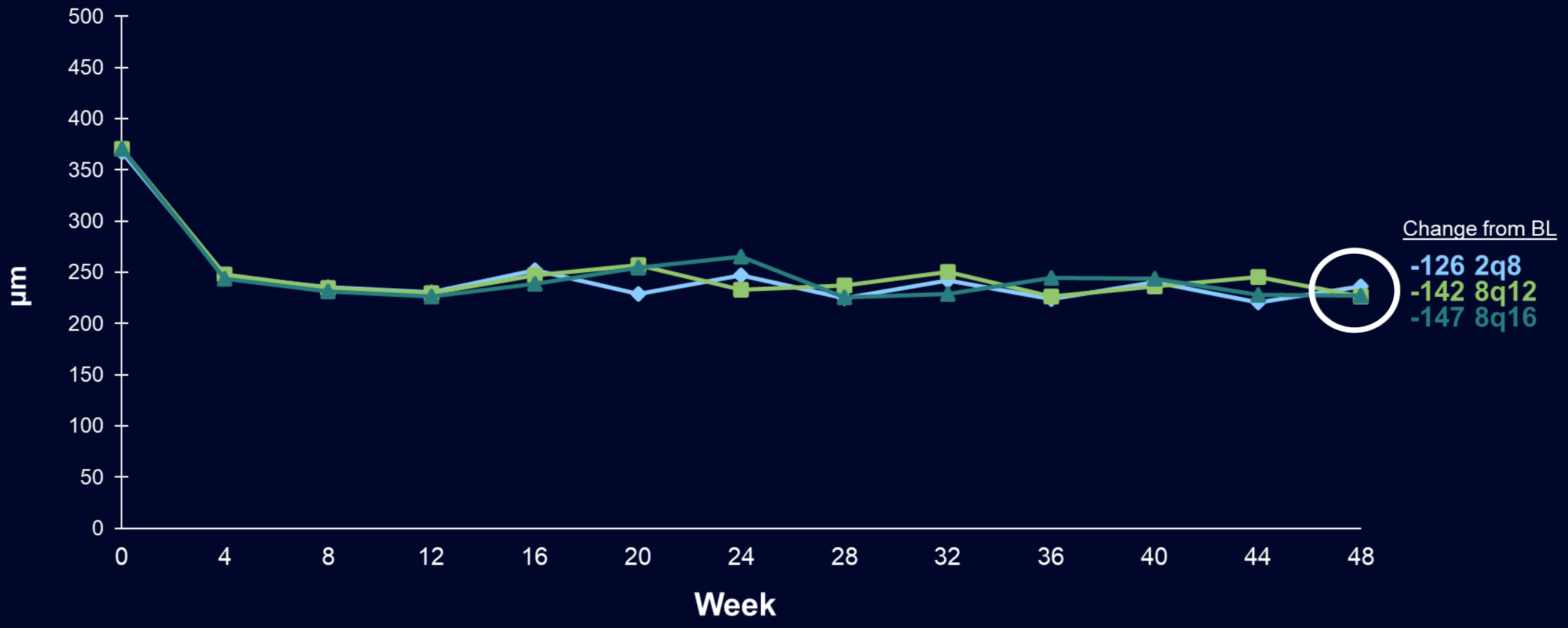


Time to fluid-free retina is defined as the time of first injection until the time where a patient did not have any IRF or SRF in the central subfield for the first time (regardless of whether any retinal fluid was found again after that).
FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.

Central Retinal Thickness

nAMD



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

Ocular AEs Through Week 48

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	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)*	38.7%	38.5%	37.6%	38.0%
AEs occurring in ≥2% of patients in any group				
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%

No cases of ischemic optic neuropathy were reported through Week 48

*Any ocular treatment-emergent event in the study eye.
AE, adverse event; **SAE**, serious adverse event; **SAF**, safety analysis set.

Intraocular Pressure Through Week 48

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	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with IOP ≥ 35 mmHg pre- or post-injection (%)	0.3%	0.9%	0.3%	0.6%

Pre-injection IOP values were similar to baseline values at all timepoints through Week 48

Intraocular Inflammation Through Week 48

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	2q8	8q12	8q16	All 8 mg
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 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)				
APTC events*	1.5%	0.3%	0.6%	0.4%
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: 48-Week Safety Results

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- Safety of aflibercept 8 mg consistent with the established safety profile of aflibercept 2 mg
- There were no new safety signals for aflibercept 8 mg or 2 mg and no cases of retinal vasculitis, occlusive retinitis or endophthalmitis
- The incidence of patients with increased IOP were similar in the aflibercept 8 mg and aflibercept 2 mg groups
- The incidence of APTC events was similar with aflibercept 8 mg and 2 mg

PULSAR Summary: Primary and Key Secondary Endpoints Met

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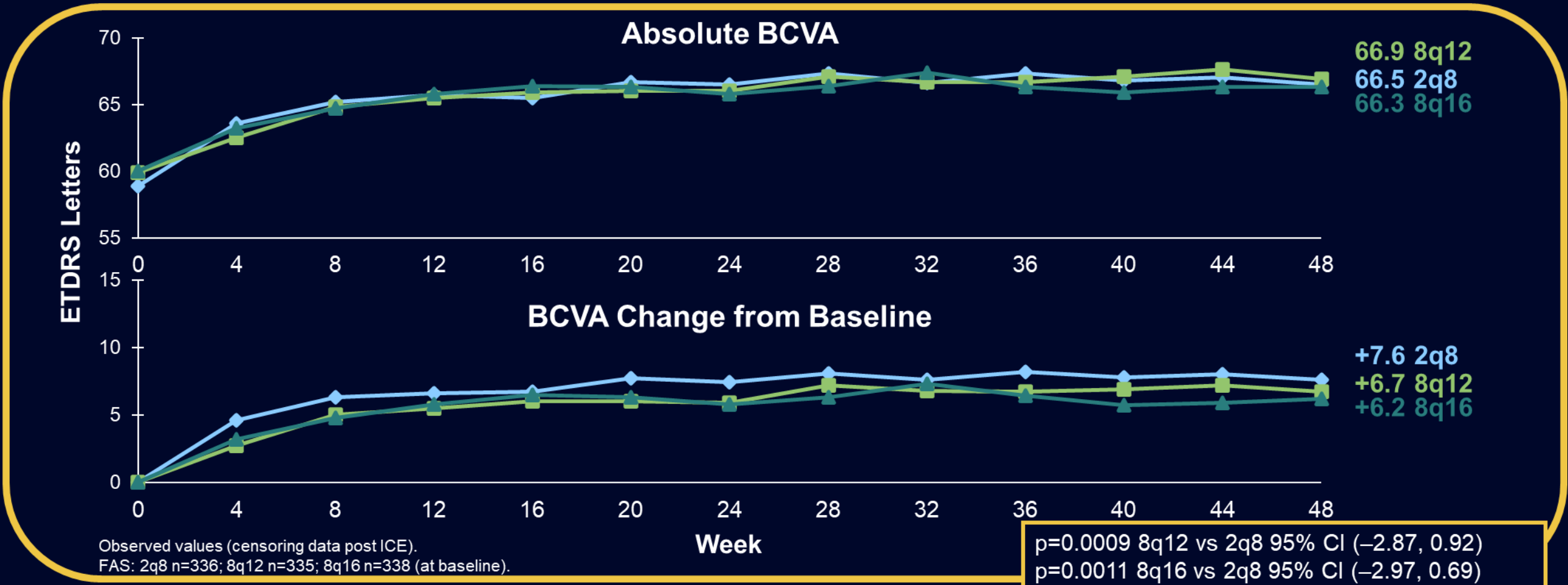
- 8q12 and 8q16 groups had non-inferior BCVA compared to 2q8 at Week 48
- 8q12 and 8q16 combined had superior drying compared to 2q8 at Week 16



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 8 mg Patients Maintained Randomized Intervals

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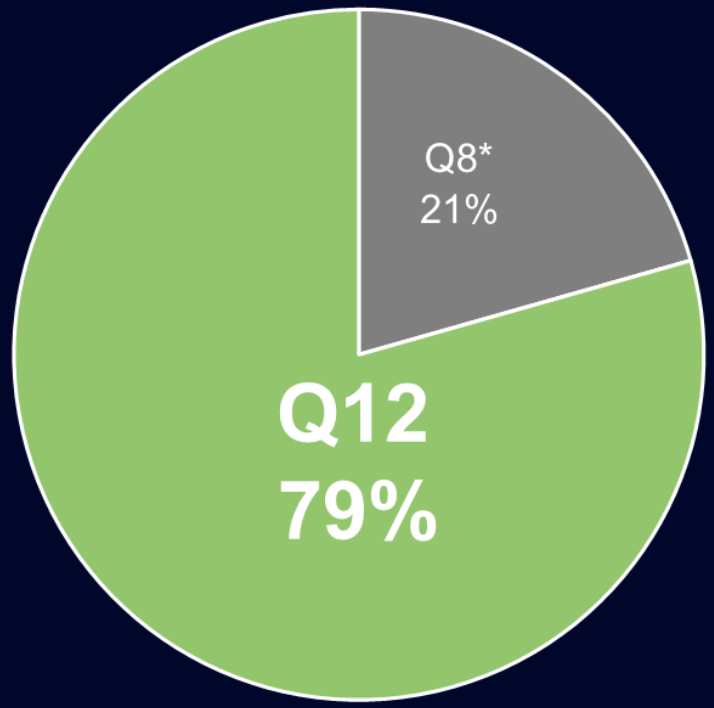
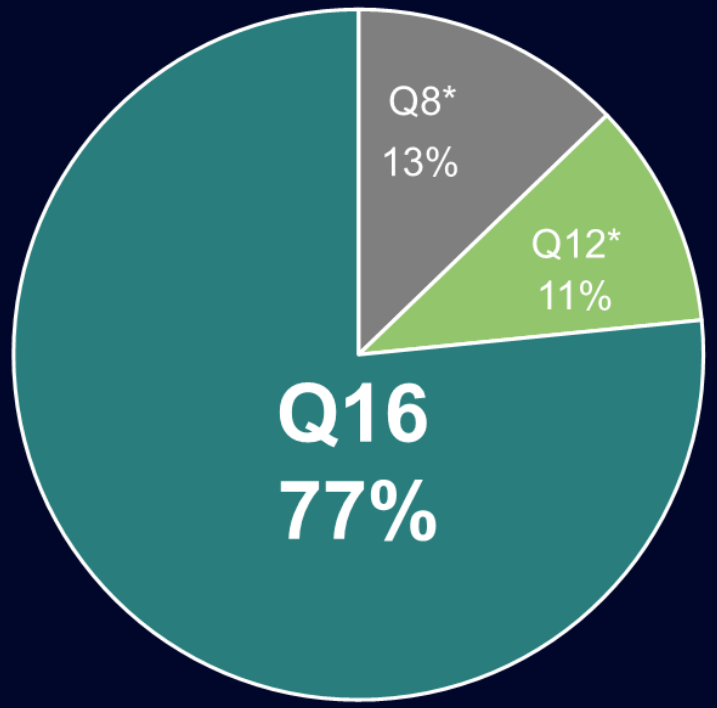
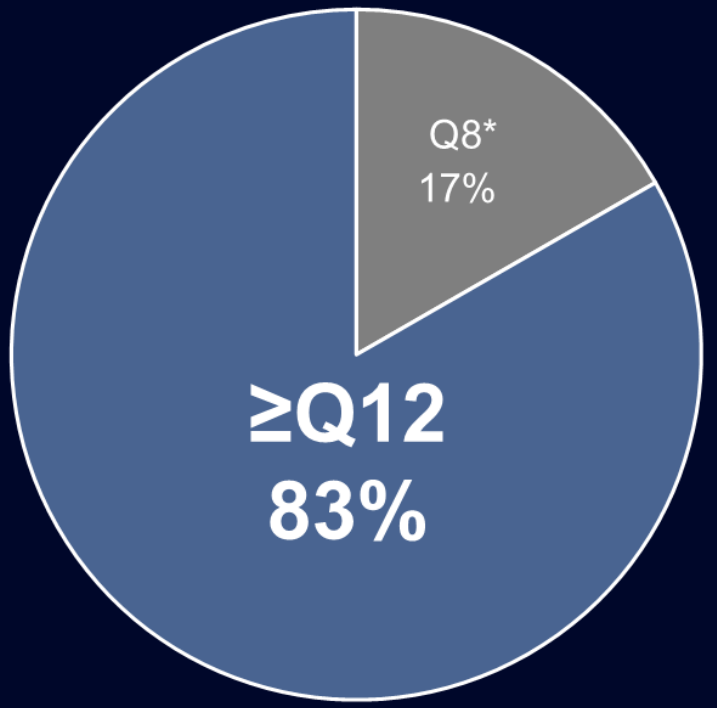
83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 (n=316^)
Mean 6.1 injections



8q16 (n=312^)
Mean 5.2 injections



All 8 mg (n=628^)
Mean 5.6 injections

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.