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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- 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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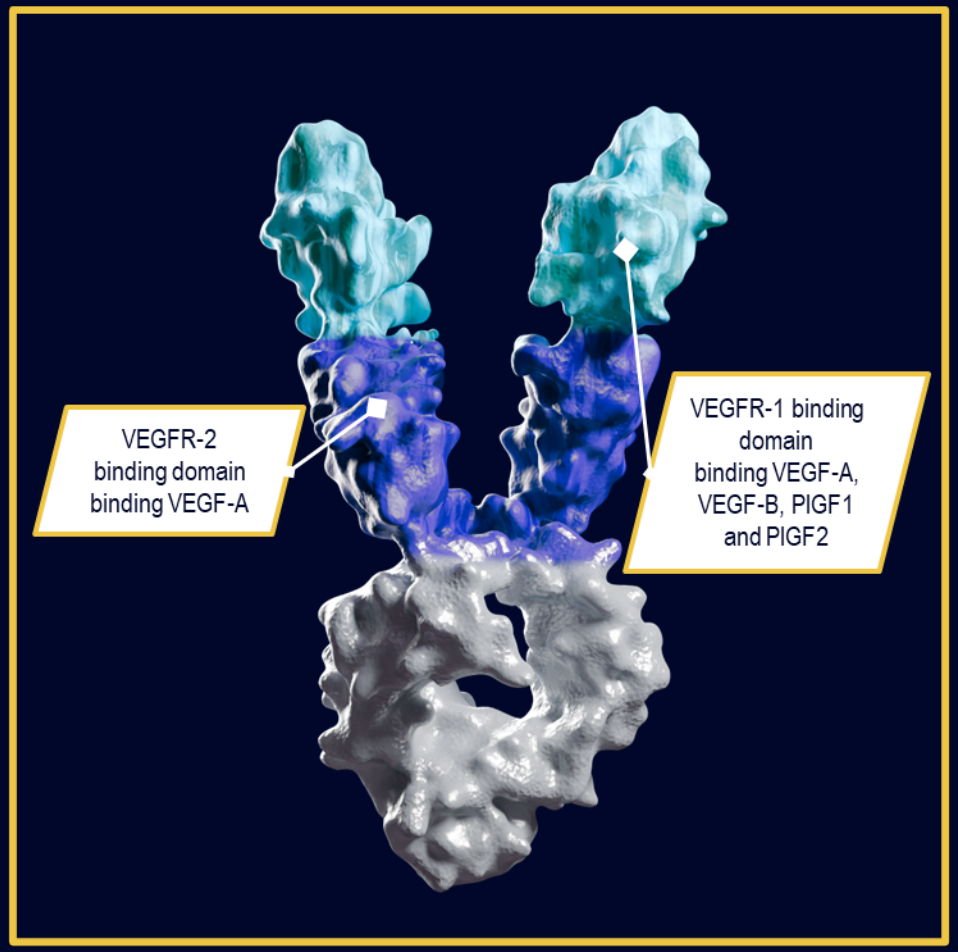

- Novel intravitreal formulation delivers 8 mg in 70 µL injection (114.3 mg/mL)
- 4-times higher molar dose compared with aflibercept 2 mg is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on VEGF signaling

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; **PIGF**, 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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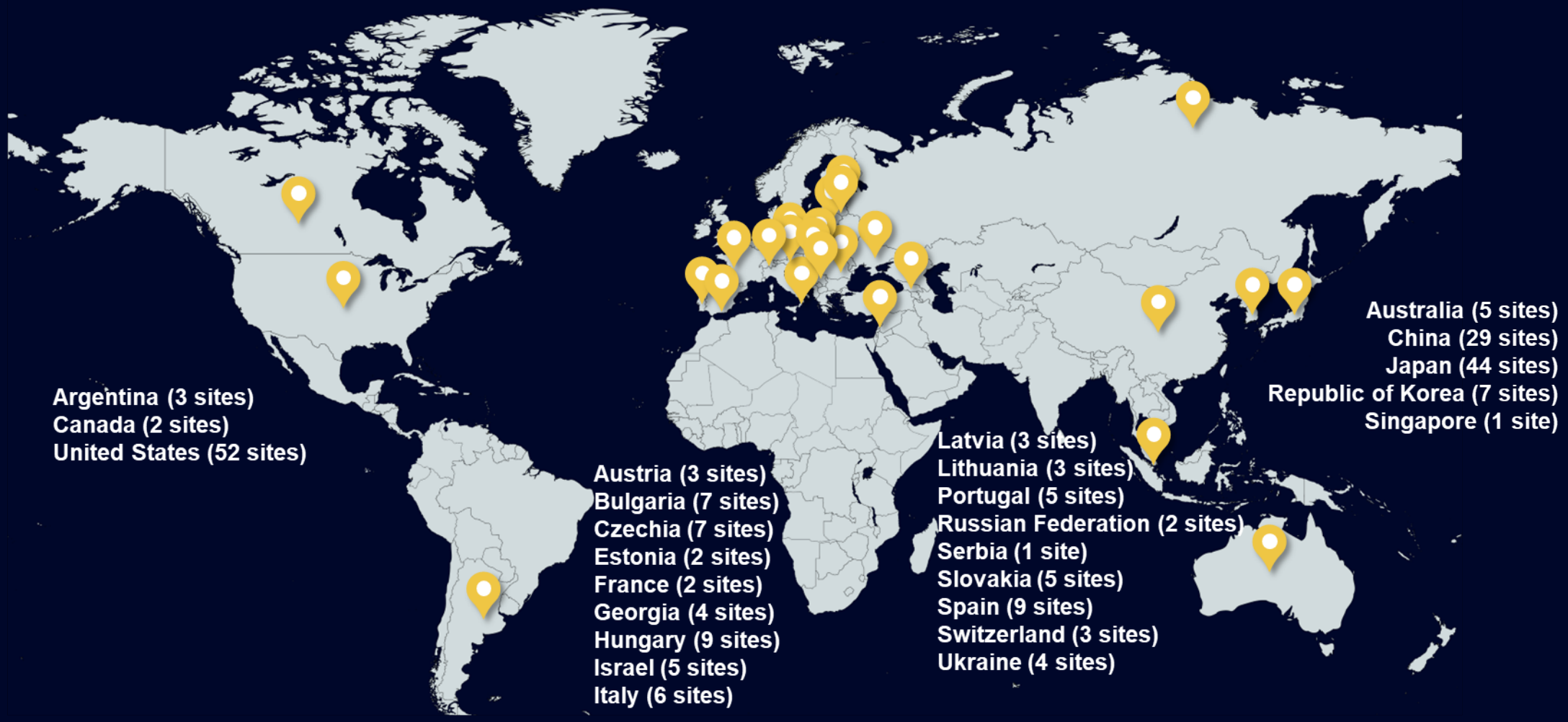
Global study conducted in 223 sites in 26 countries



Key Inclusion/Exclusion Criteria

pulsar 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)

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

	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

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	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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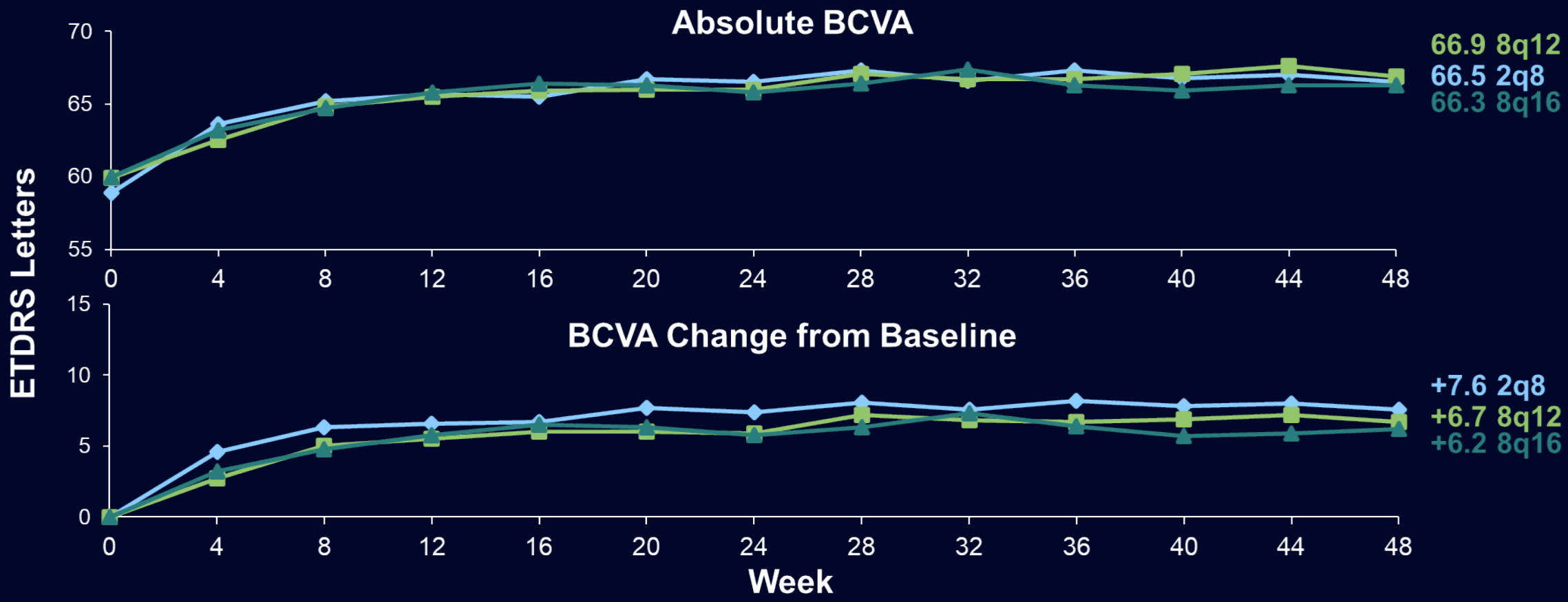


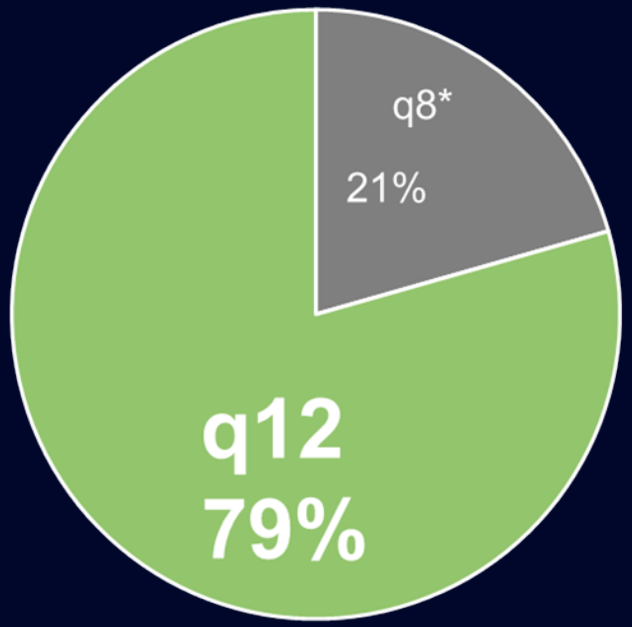
	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

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.

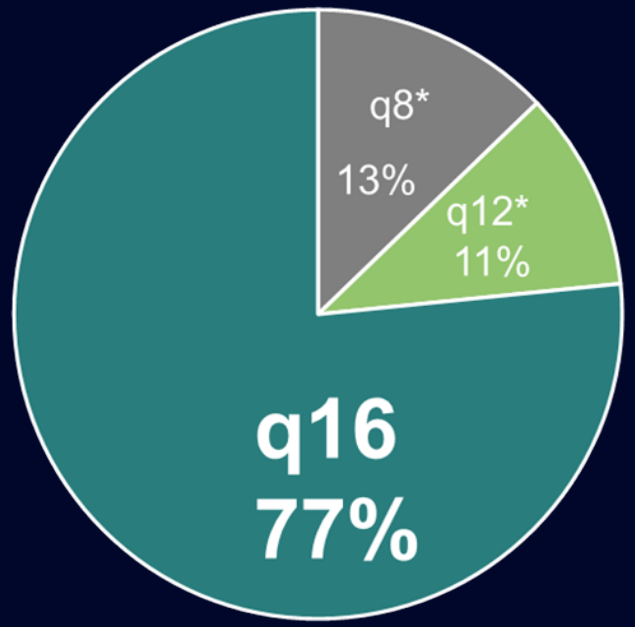
Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48

pulsar nAMD

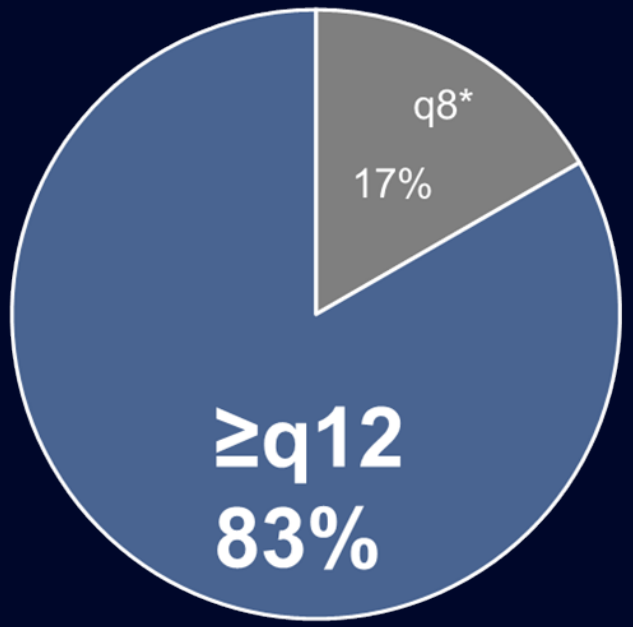
83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 n=316^



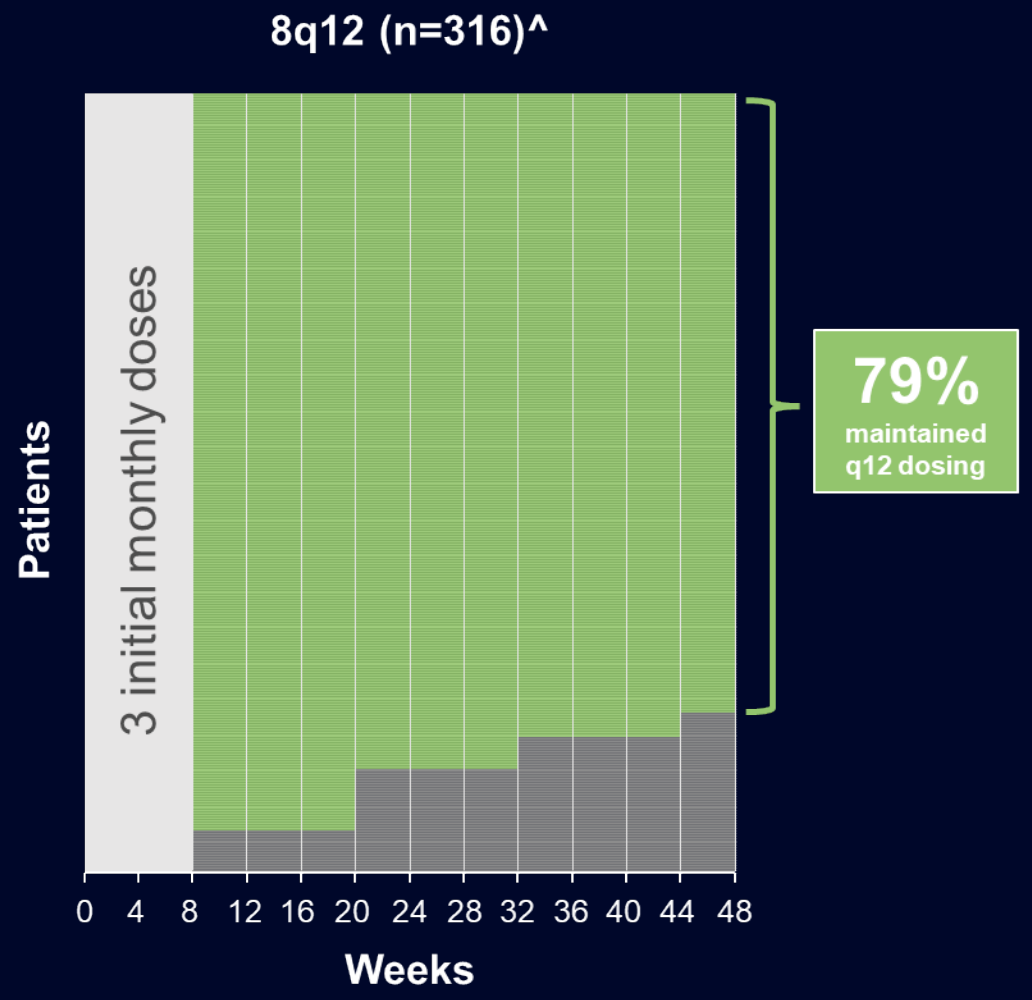
8q16 n=312^

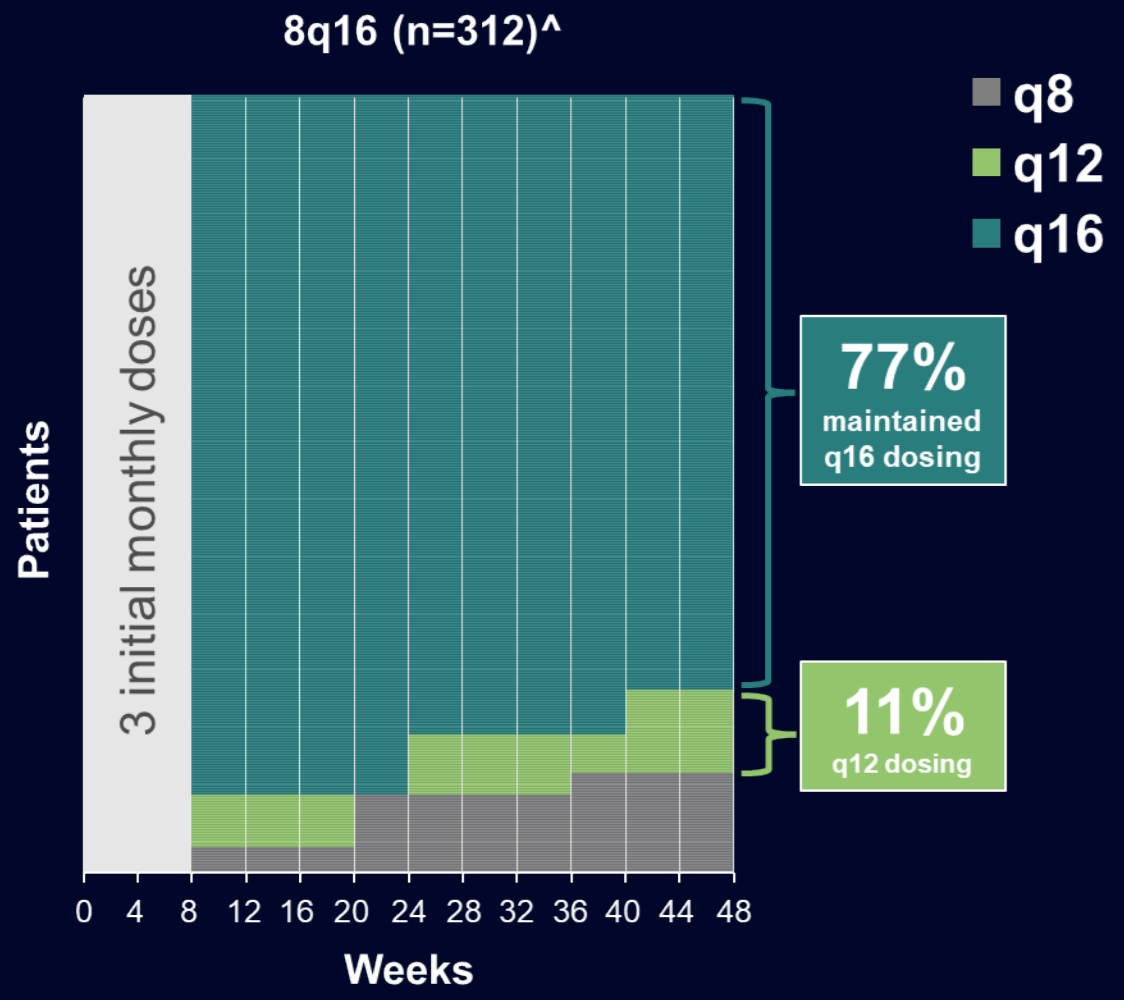


All 8 mg n=628^

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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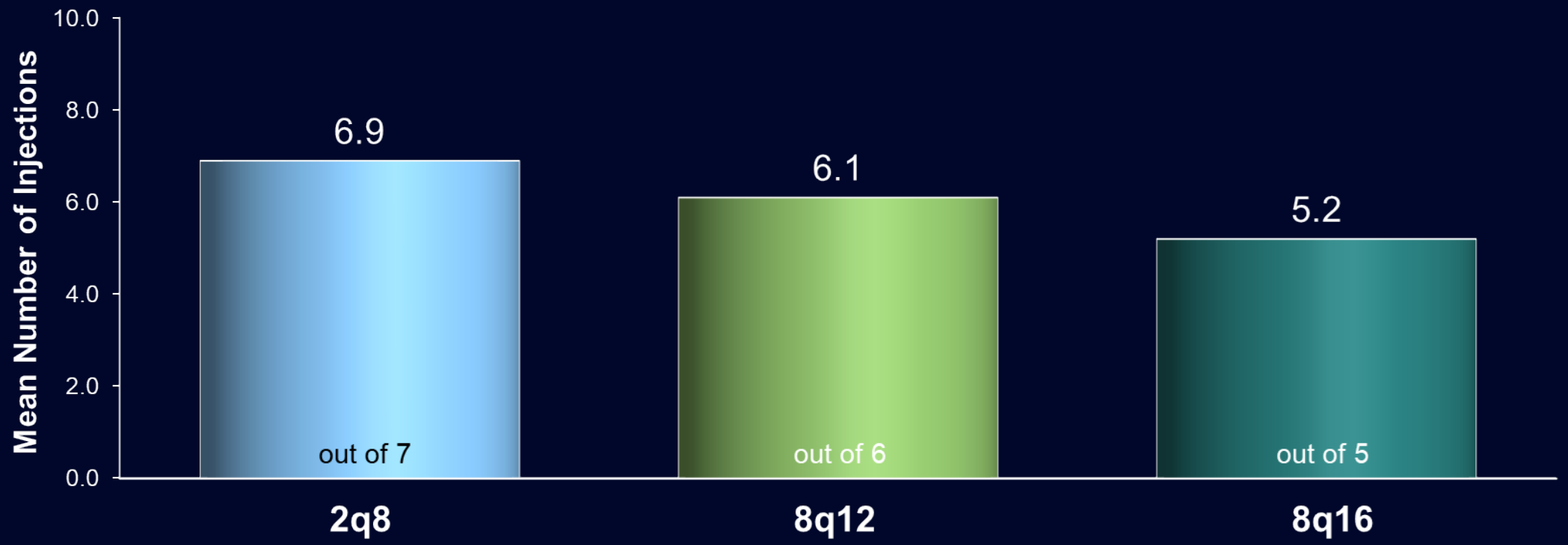

Patients completing Week 48; 2q8 n=309; 8q12 n=316; 8q16 n=312.

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

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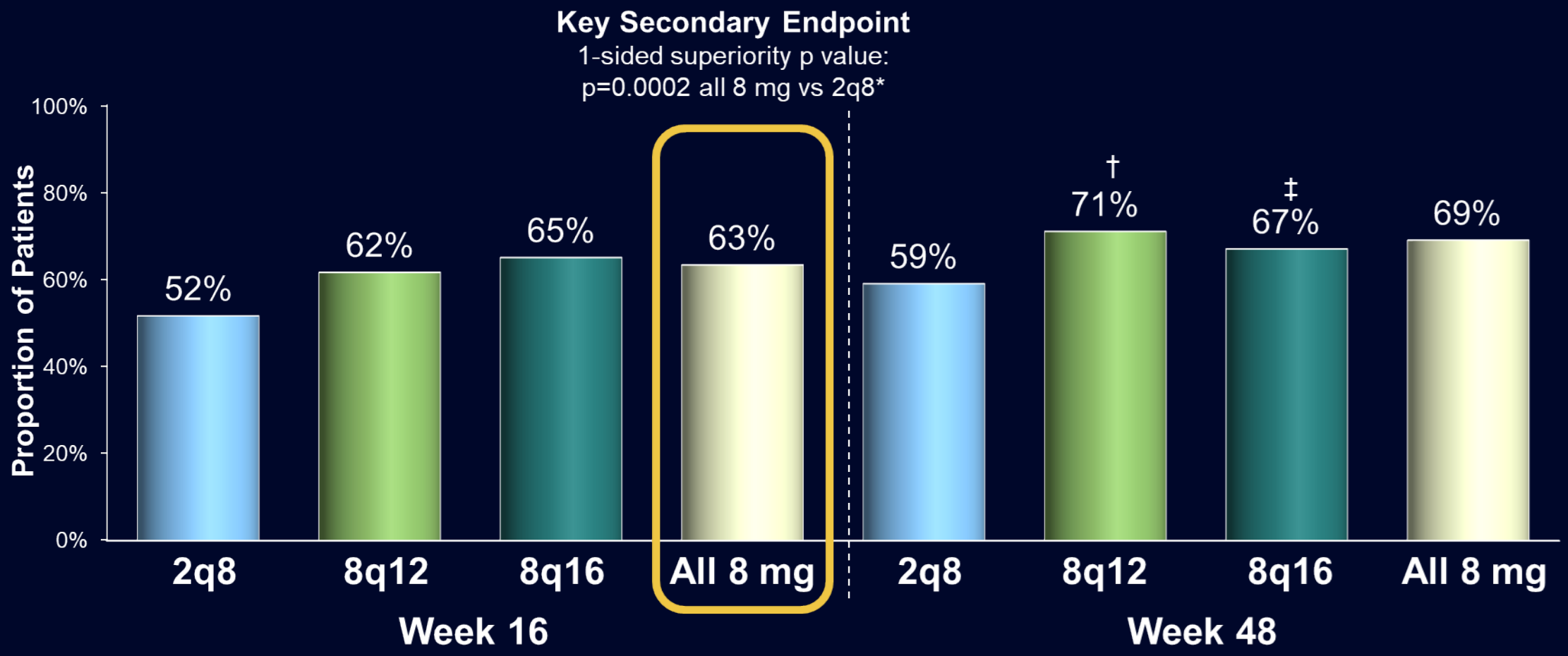

Without retinal fluid defined as absence of IRF and SRF in center subfield.
LOCF (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
*P value: one-sided Cochran-Mantel-Haenszel (CMH); weighting scheme adjusted by geographical region and baseline BCVA (<60 vs ≥60).
†nominal p=0.0015 8q12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

Time to a Fluid-Free Center Subfield

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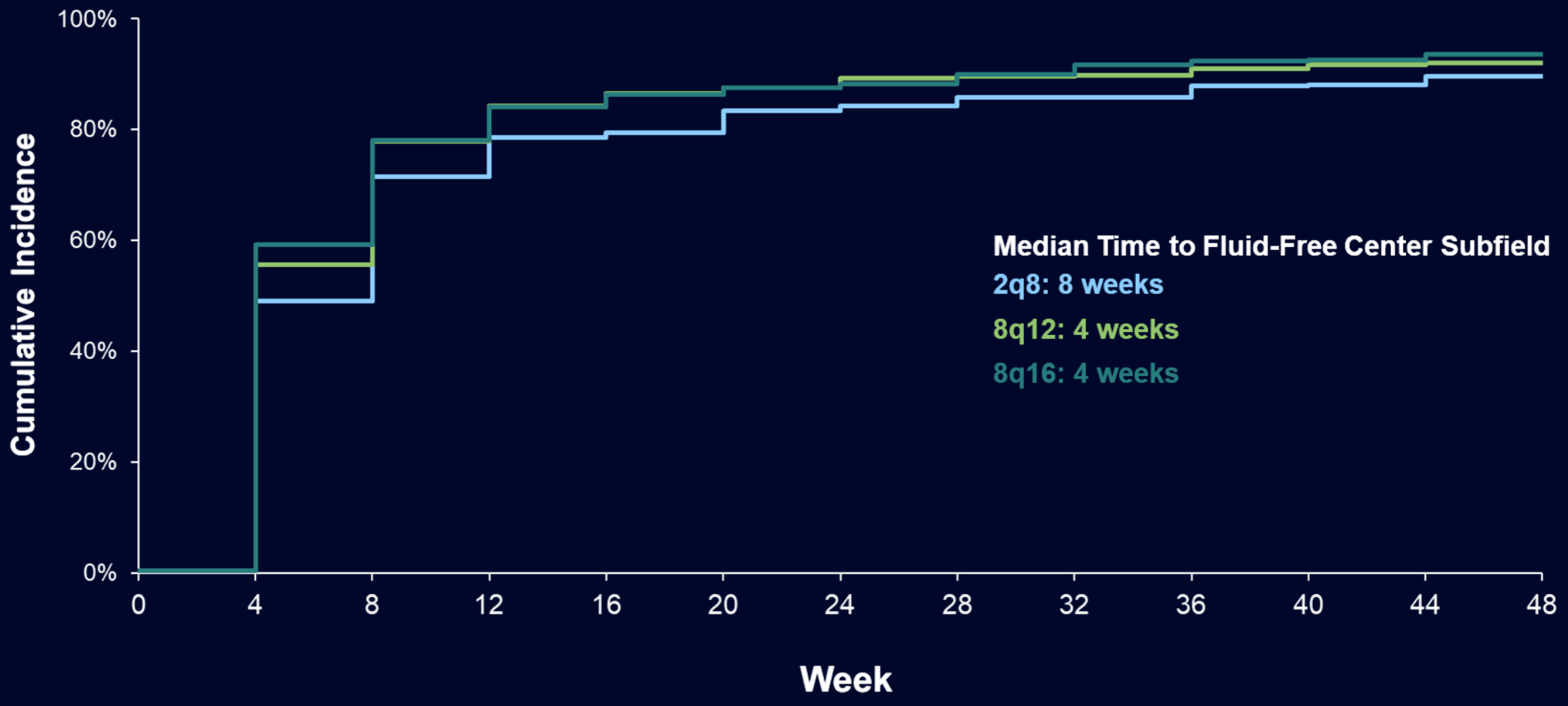

Time to fluid-free retina is defined as the time of first injection until the time where a patient did not have any IRF or SRF in the central subfield for the first time (regardless of whether any retinal fluid was found again after that).
FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.

Central Retinal Thickness

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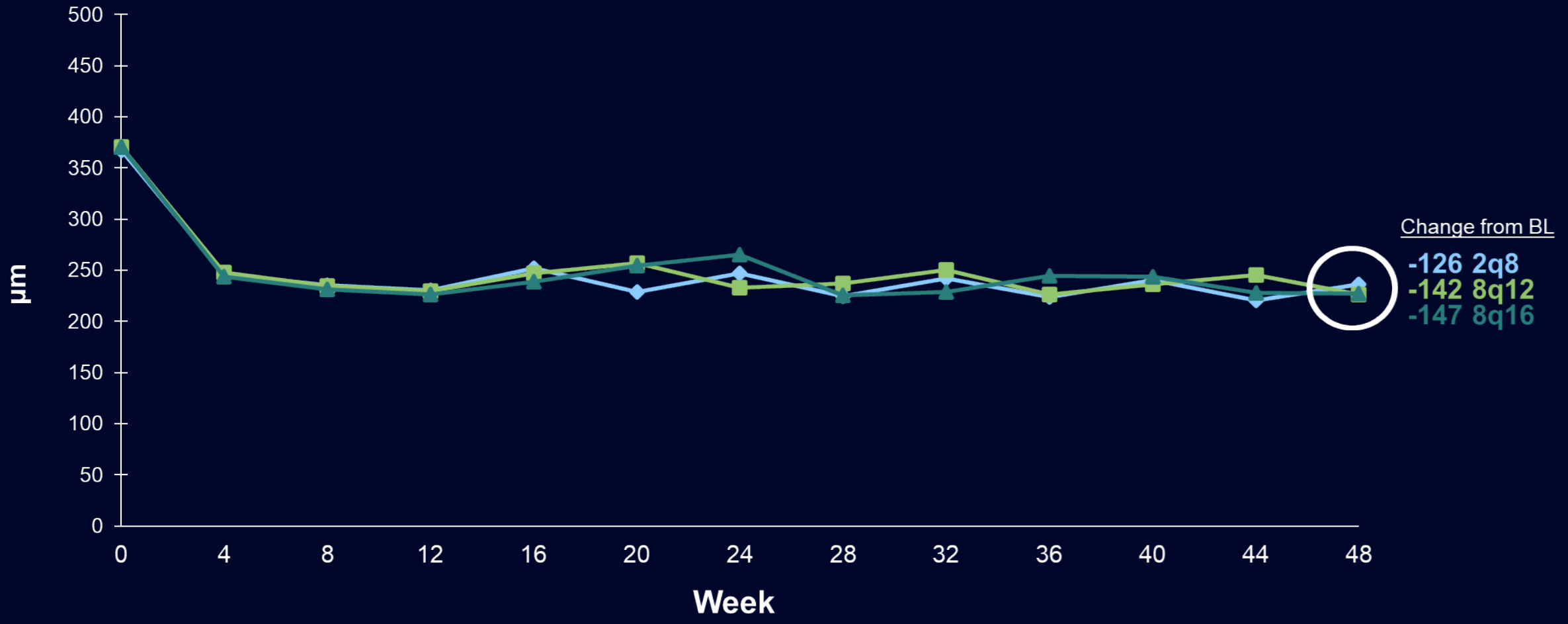

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

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

	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

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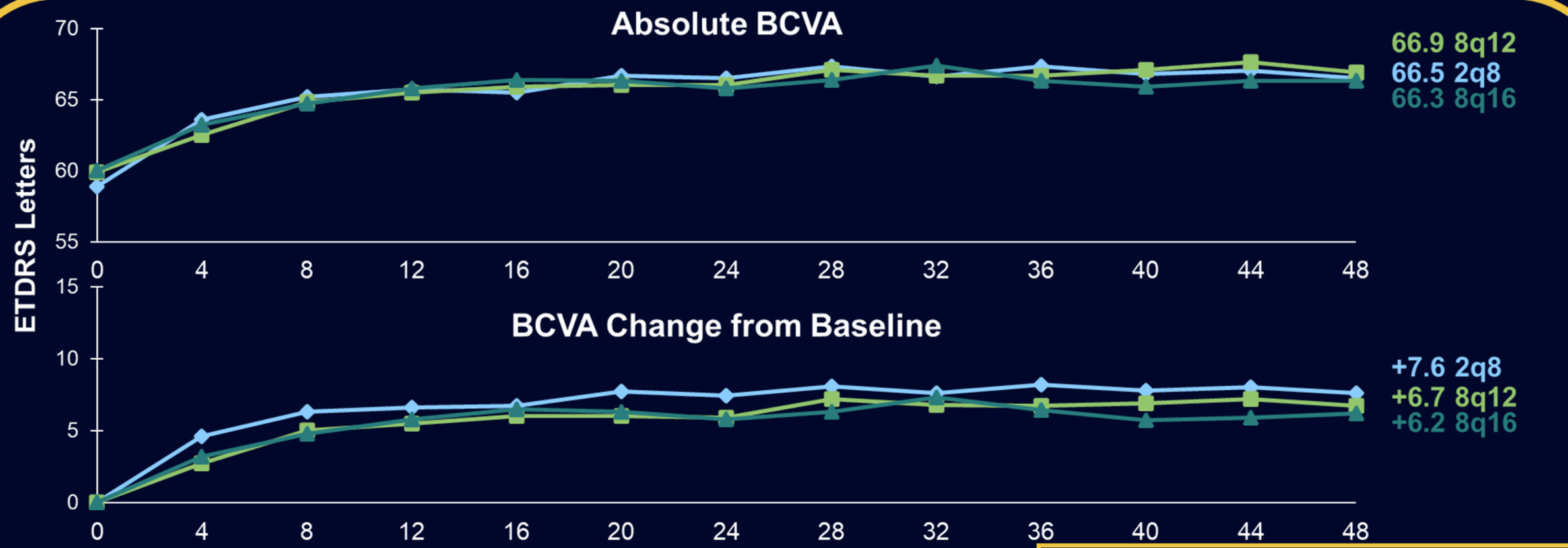
- 8q12 and 8q16 groups had non-inferior BCVA compared to 2q8 at Week 48
- 8q12 and 8q16 combined had superior drying compared to 2q8 at Week 16



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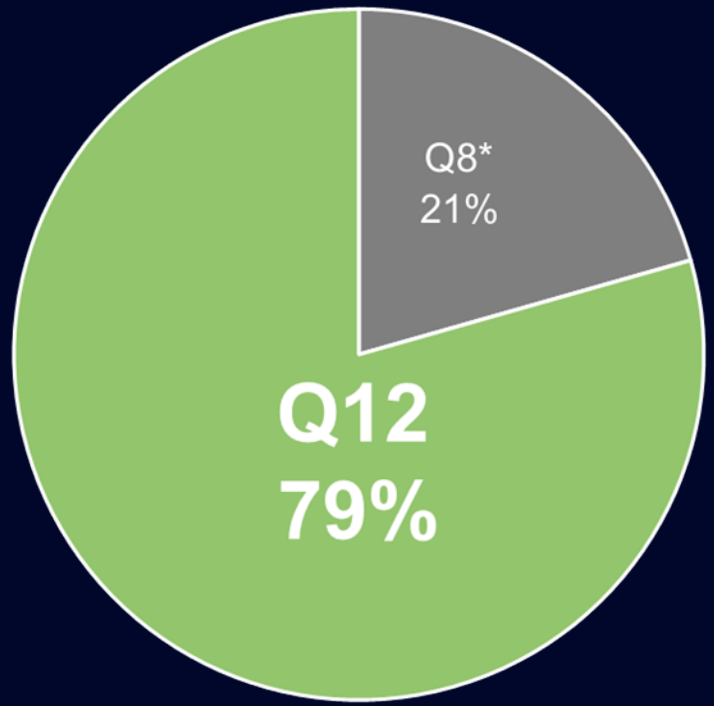
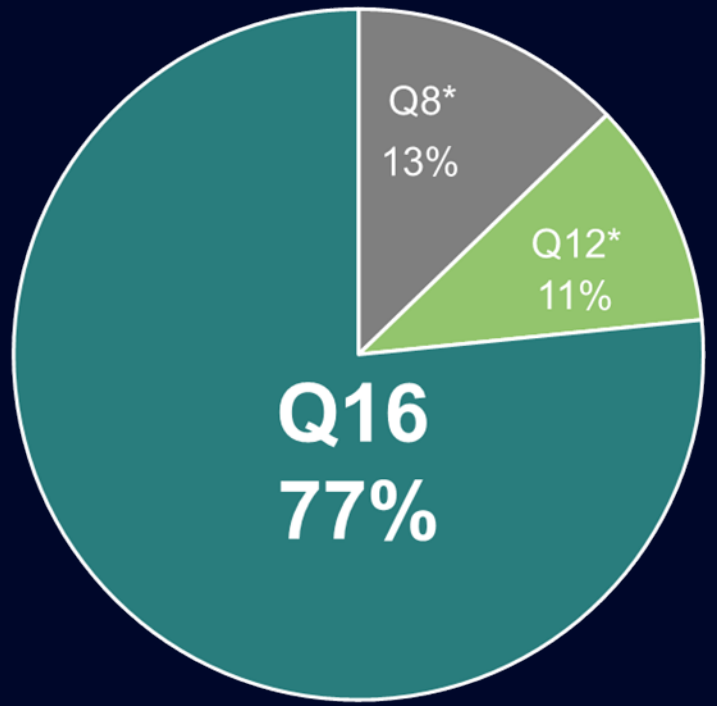
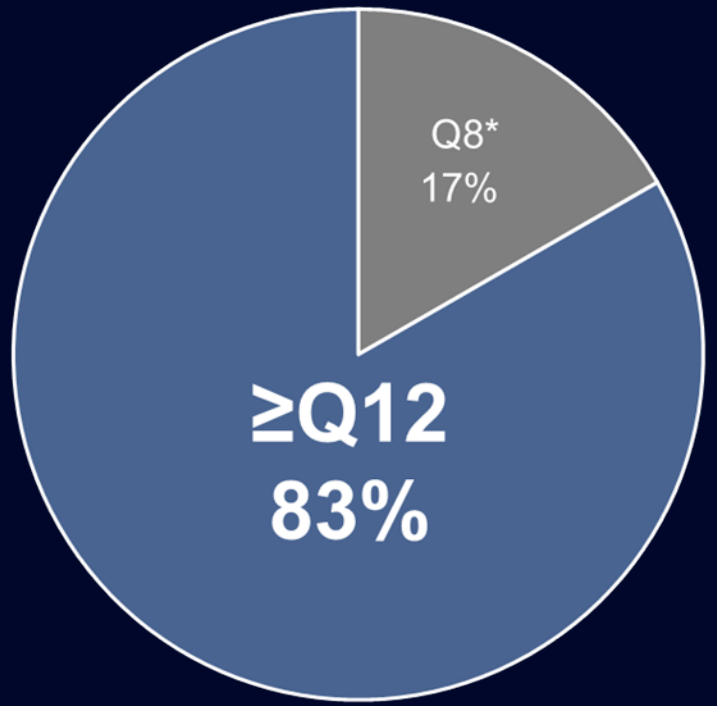
83% of 8 mg patients maintained dosing intervals ≥12 weeks



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.