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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Presented at the American Society of Retina Specialists (ASRS) Annual Meeting, Seattle, Wa., USA, July 28–Aug 1, 2023

Disclosures

- Jignesh Patel receives travel bursaries from Bayer and speaker fees from Roche
- The PULSAR study was sponsored by Bayer AG (Leverkusen, Germany) and co-funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). The sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
- 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; FujiRetina, March 23–25, 2023, and ARVO Annual Meeting, April 23–27, 2023
- Medical writing support, under the direction of the author, was provided by ApotheCom and funded by Bayer Consumer Care AG, Basel, Switzerland, in accordance with Good Publication Practice (GPP) standards (*Ann Intern Med* 2022;175:1298–1304)

PULSAR Study Design

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: Dosing Schedule and Regimen Modification in 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

DRM criteria for shortening dosing interval*

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

AND

- >25-µm increase in CST, 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.

CST, central subfield 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*	1.8%	0.9%	0.6%	1.1%

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

Baseline Demographics

	2q8	8q12	8q16	Total
N	336	335	338	1009
Age, years (SD)	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

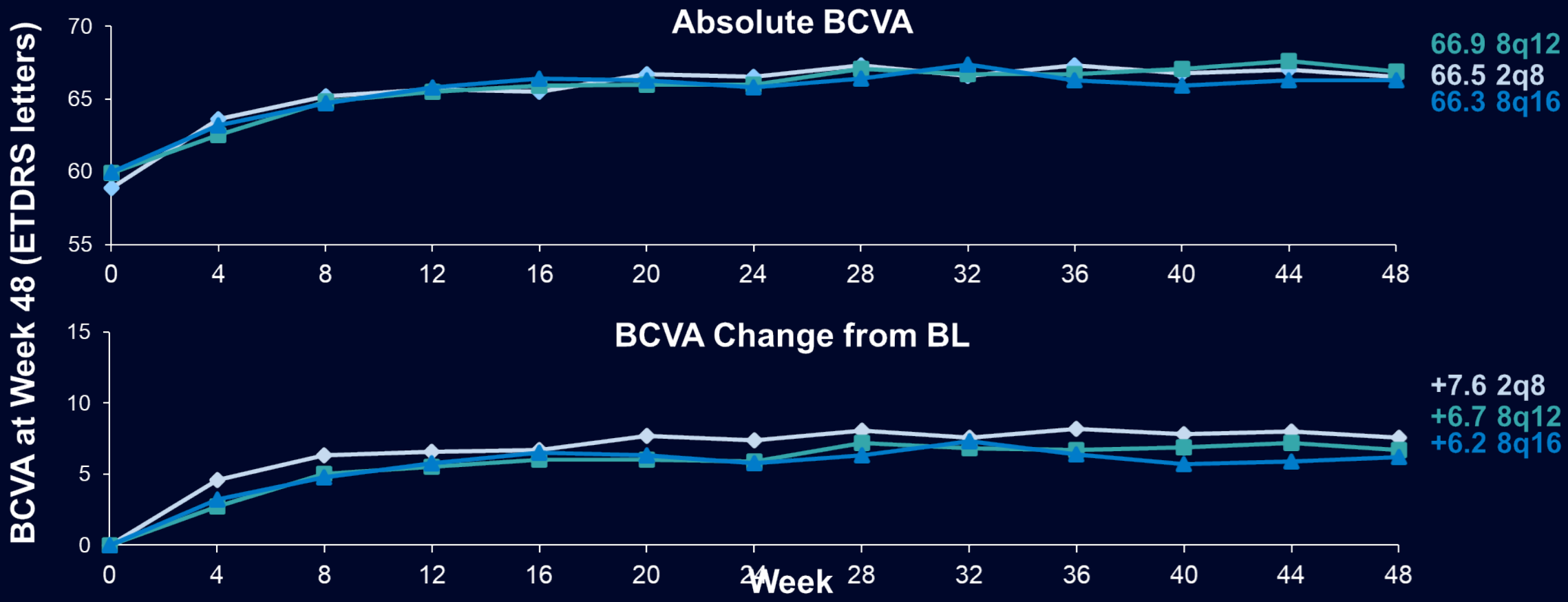
FAS
FAS, full analysis set.

Baseline Characteristics of the Study Eye

	2q8	8q12	8q16	Total
N	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%
CST, 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%

FAS, data are mean (SD) unless otherwise indicated
ETDRS, Early Treatment of Diabetic Retinopathy Study.

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

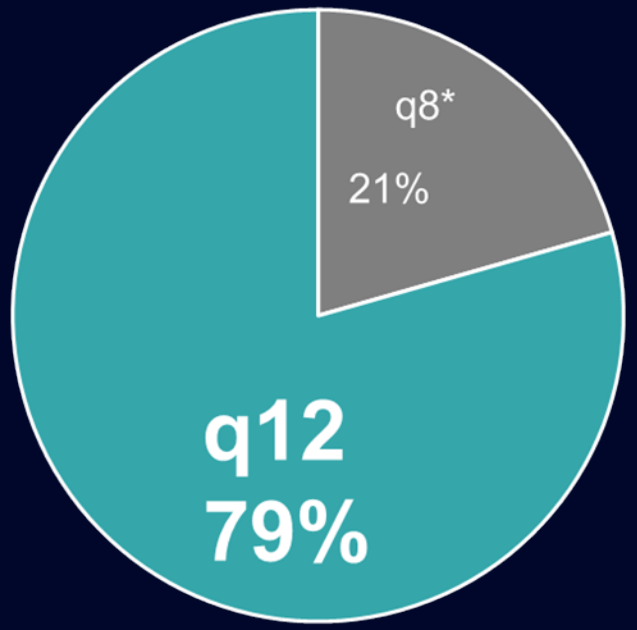


	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

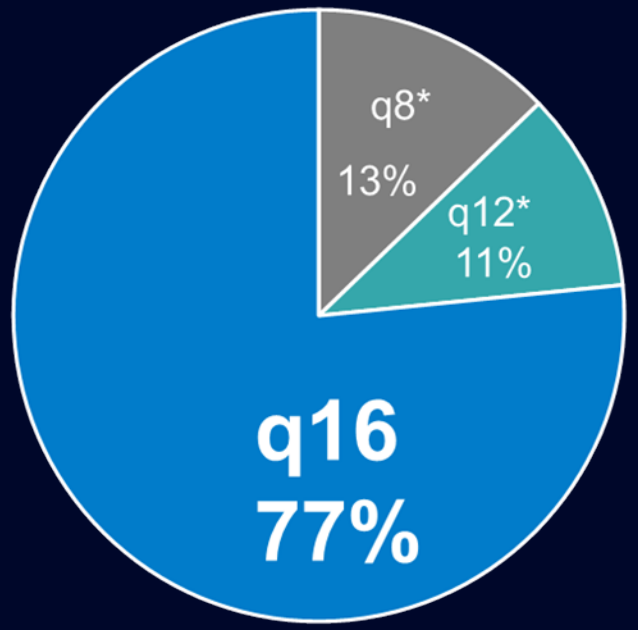
Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL).
BL, baseline; **ICE**, intercurrent events; **LS**, least squares; **MMRM**, mixed model for repeated measurements.

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

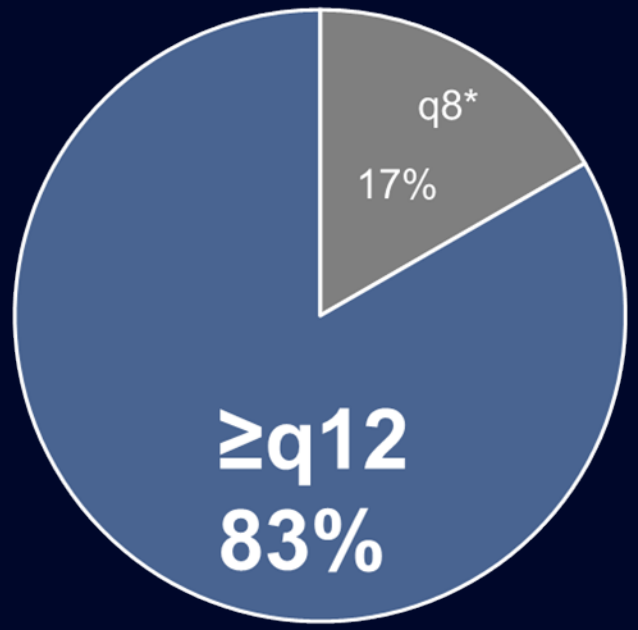
83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 n=316^



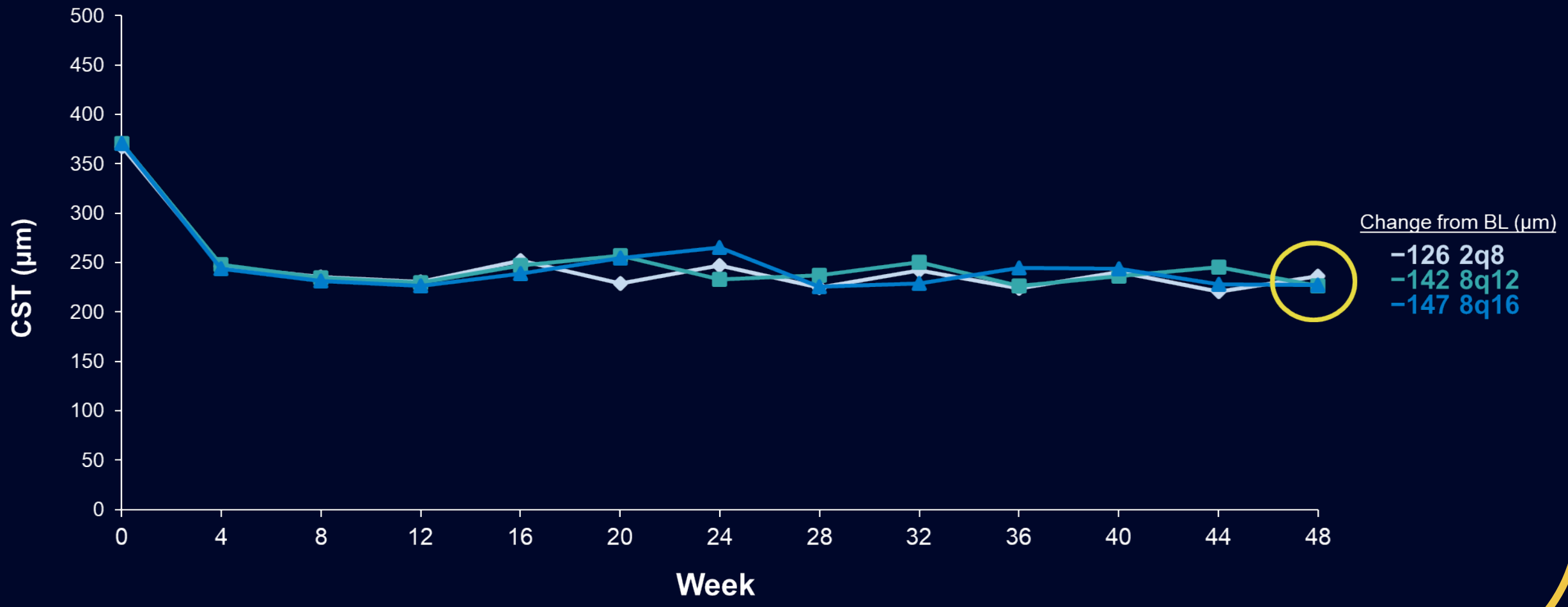
8q16 n=312^



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.

Central Subfield Thickness



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

Ocular AEs Through Week 48

	2q8	8q12	8q16	All 8mg
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 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. IOI, intraocular inflammation.

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

IOP, intraocular pressure.

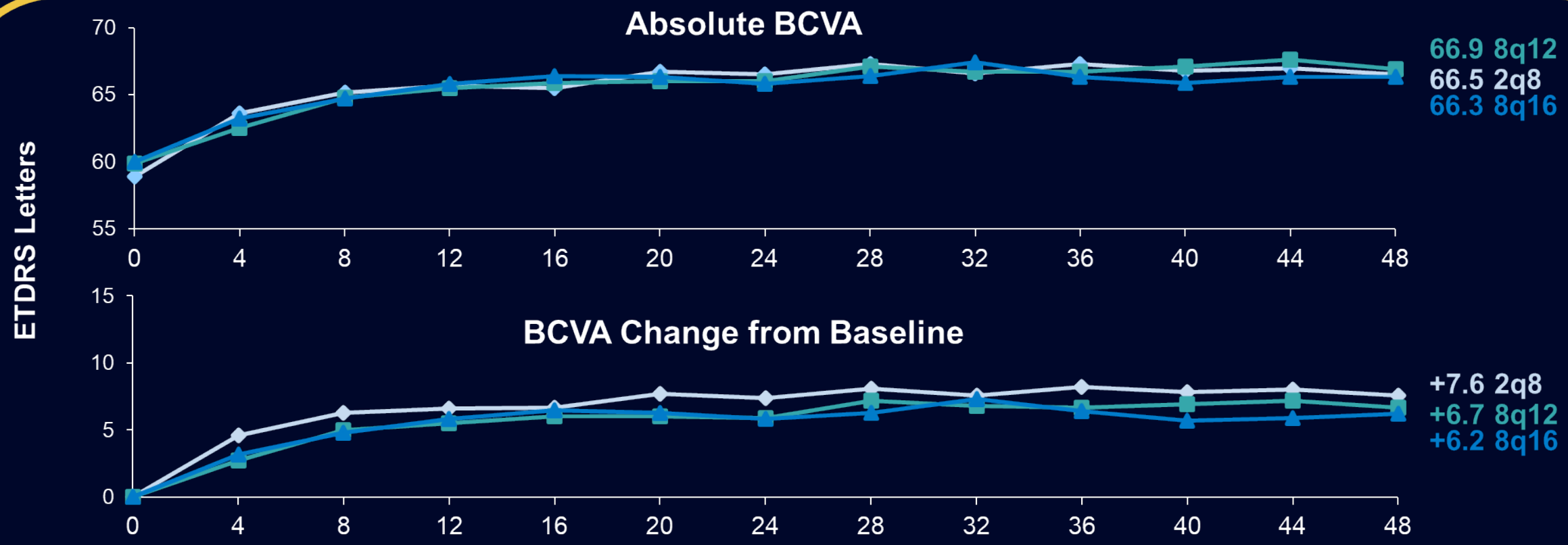
Non-Ocular Safety Through Week 48

	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 Summary: Primary and Key Secondary Endpoints Met

- 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).

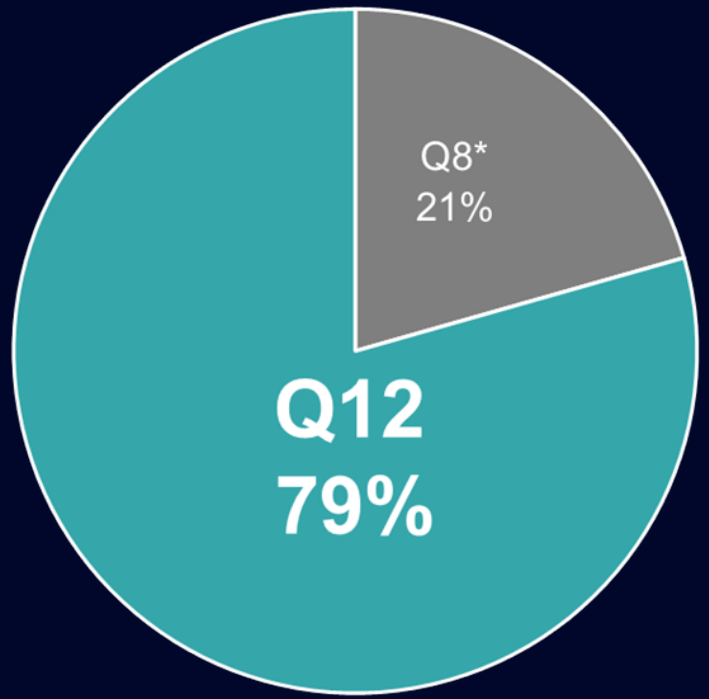
p=0.0009 8q12 vs 2q8 95% CI (–2.87, 0.92)
p=0.0011 8q16 vs 2q8 95% CI (–2.97, 0.69)

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

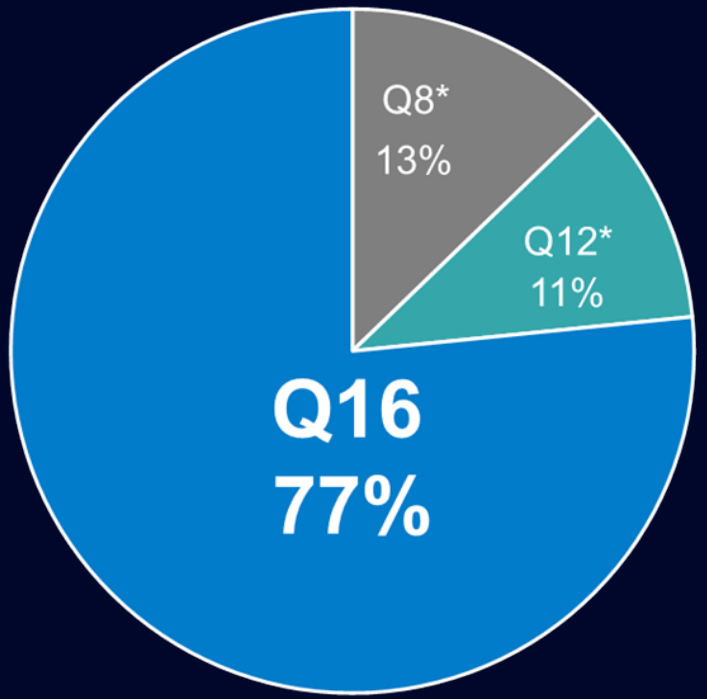
PULSAR: 48-Week Results

Majority of 8 mg Patients Maintained Randomized Intervals

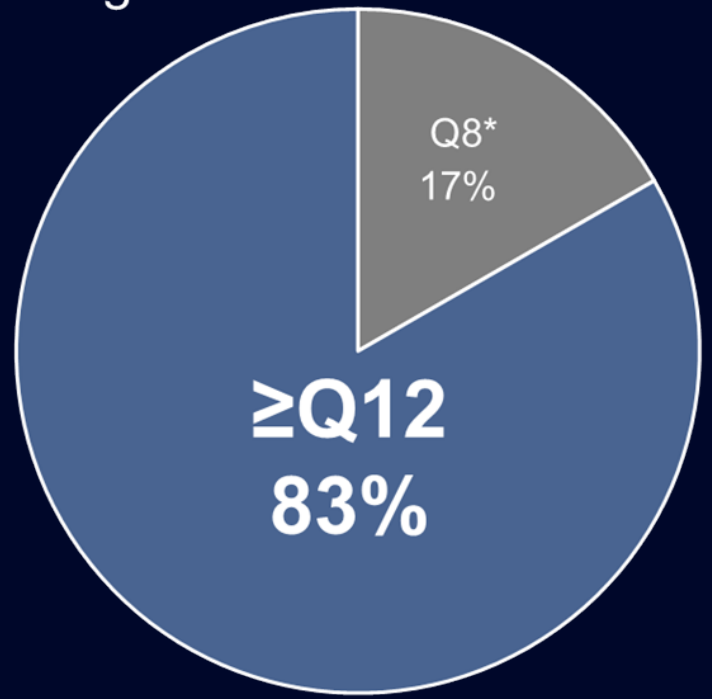
83% of 8 mg patients maintained dosing intervals ≥12 weeks



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.