Intravitreal Aflibercept Injection 8mg for DME: 48-Week Results From the Phase 2/3 PHOTON Trial

Taiji Sakamoto[1] on behalf of the PHOTON study investigators

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Disclosures

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DME

- Taiji Sakamoto has received consulting fees from Bayer, Boehringer Ingelheim, Chugai/Roche, Novartis, and Senju
- The PHOTON study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors 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
- 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)

PHOTON Study Design

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DME

Multi-center, randomized, double-masked study in patients with DME*
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)
Note: 2mg arm received 5 initial monthly injections versus 8mg arms, which received only 3 initial monthly injections

2q8
Aflibercept 2mg every 8 weeks after 5 initial monthly injections
n=167

8q12
8mg every 12 weeks after 3 initial monthly injections
n=328

8q16
8mg every 16 weeks after 3 initial monthly injections
n=163

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

Key secondary endpoint:
Proportion of patients with ≥2-step improvement in DRSS at Week 48

↓

End of study at Week 96
with optional 1-year extension through Week 156

*Treatment naïve and previously treated.

PHOTON: Dosing Schedule and Regimen Modification in Year 1

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DME
Primary Endpoint

	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	X	o	X	o	X	o	X	o	X
8q12	X	X	X	o	o	X	o	o	X	o	o	X	o
8q16	X	X	X	o	o	o	X	o	o	o	X	o	o

Note: 2mg arm received 5 initial monthly injections versus 8mg arms, which received only 3 initial monthly injections

DRM Criteria for Shortening Dosing Interval*

- >10-letter loss in BCVA due to persistent or worsening DME

AND

- >50-micron increase in CRT

*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: Figure 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.
DRM, dose regimen modification.

Patient Disposition at Week 48

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DME

	2q8	8q12	8q16	Total
# Randomized	167	329	164	660
# Completing Week 48	94.0%	91.2%	95.1%	92.9%
# Discontinued before Week 48	6.0%	8.8%	4.9%	7.1%
Reasons for discontinuation				
Adverse event	0	1.2%	0.6%	0.8%
Investigator decision/ noncompliance[a]	0.6%	1.2%	0.6%	0.9%
Consent withdrawal	2.4%	2.1%	1.2%	2.0%
Lost to follow-up	0.6%	1.5%	0.6%	1.1%
Death	2.4%	2.7%	1.8%	2.4%

[a]Categories were combined to maintain masking of individual patients.

Baseline Characteristics of the Study Eye

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DME

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
BCVA (ETDRS letters)	61.5 (11.2)	63.6 (10.1)	61.4 (11.8)	62.5 (10.9)
Snellen equivalent	20/63	20/50	20/63	20/63
20/32 (>73 to 78 letters)	12.0%	18.0%	14.1%	15.5%
20/40 or worse (≤73 letters)	88.0%	82.0%	85.9%	84.5%
CRT (μm)	457.2 (144.0)	449.1 (127.4)	460.3 (117.8)	454.0 (129.5)
Prior treatment for DME (%)	44.3%	43.6%	43.6%	43.8%

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

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

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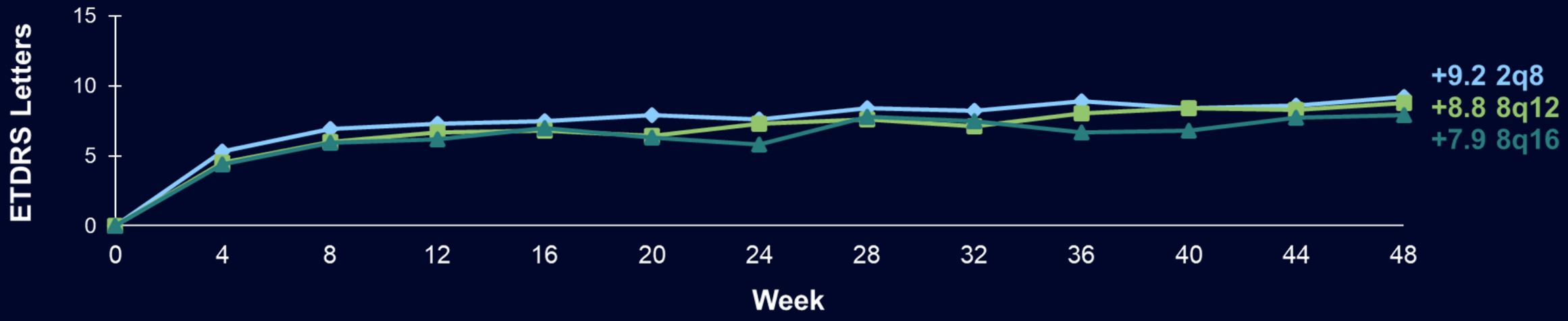
DME

BCVA Change from Baseline



	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	8.7			
8q12	8.1	-0.57	-2.26, 1.13	p < 0.0001
8q16	7.2	-1.44	-3.27, 0.39	p = 0.0031

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

Proportion of Patients With ≥2-step DRSS Improvement at Weeks 12 and 48

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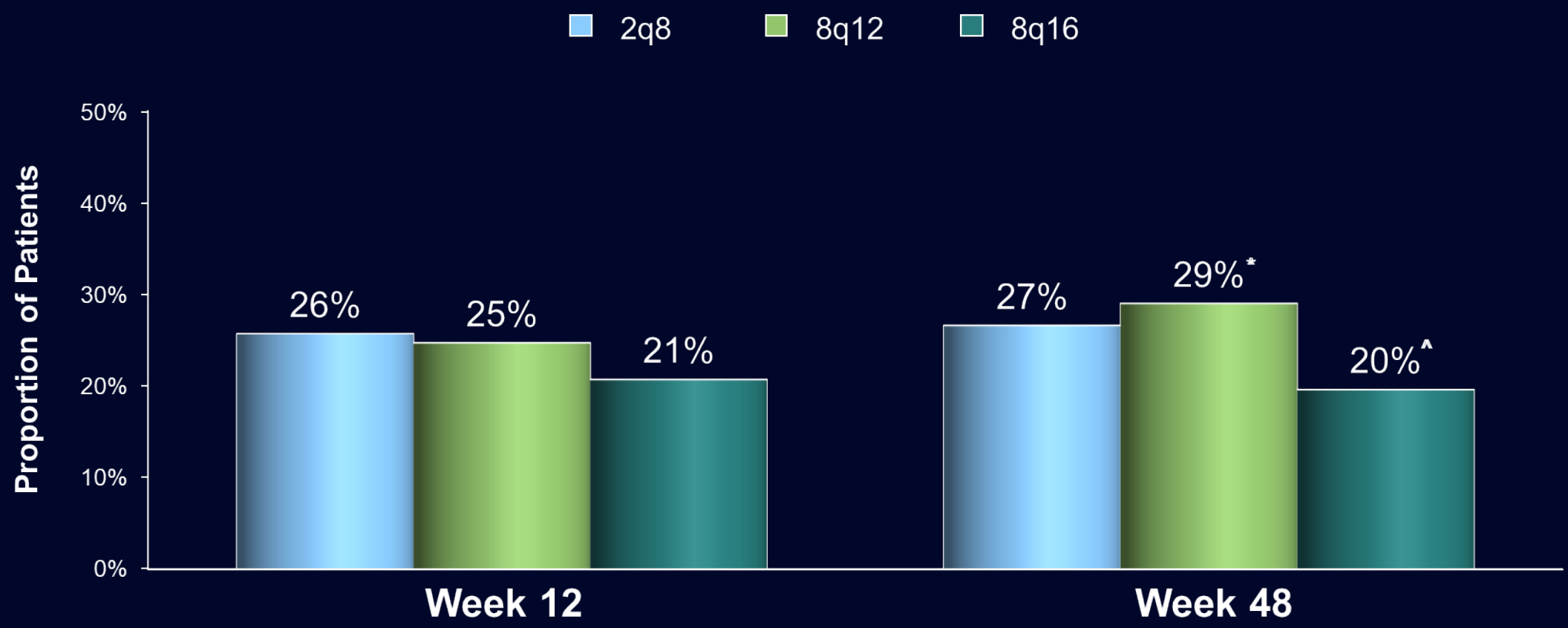
DME



Key secondary endpoint

**8q12 vs. 2q8 Diff (95% CI): 1.98 (-6.61, 10.57)*
^8q16 vs. 2q8 Diff (95% CI): -7.52 (-16.88, 1.84)
(NI margin set at 15%)

LOCF (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163.
LOCF, last observation carried forward; NI, non-inferiority.

Proportion of 8mg Patients Maintaining Q12- and Q16-Week Intervals Through Week 48

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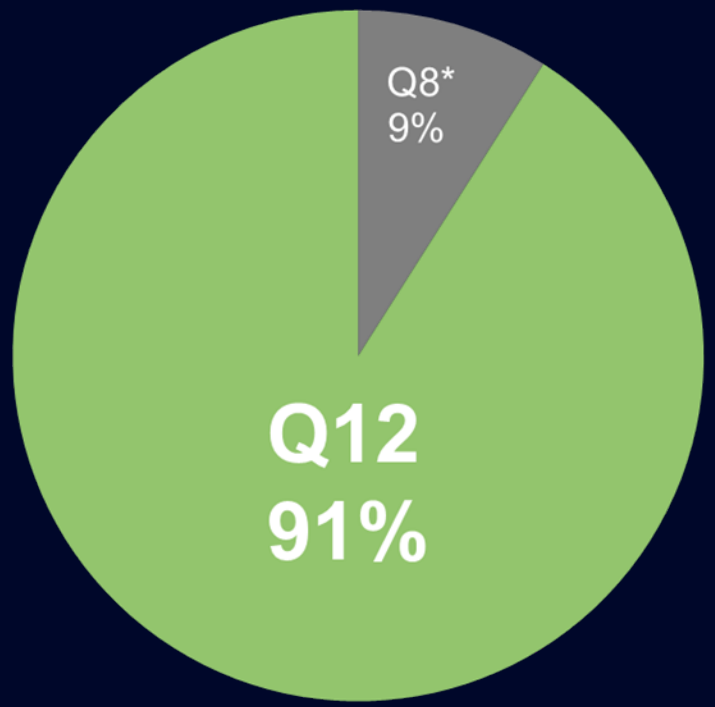
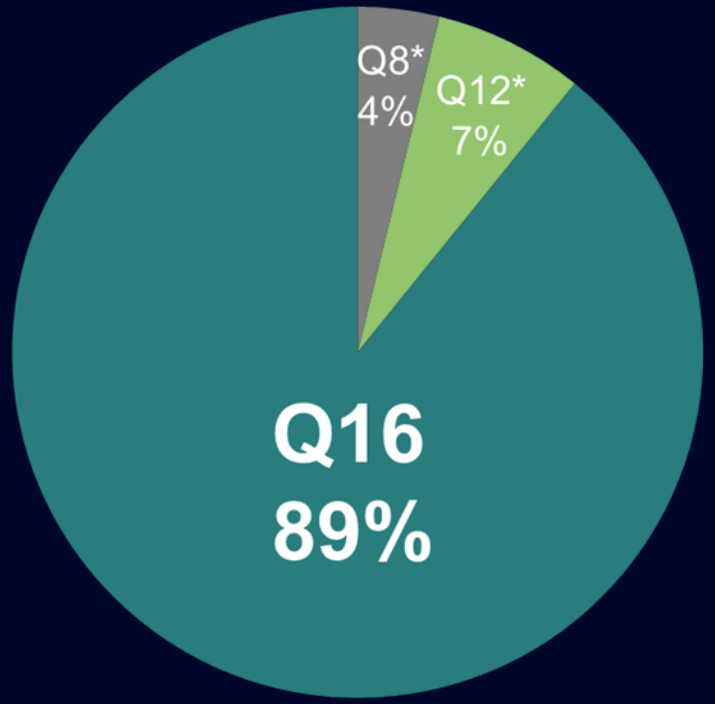
DME

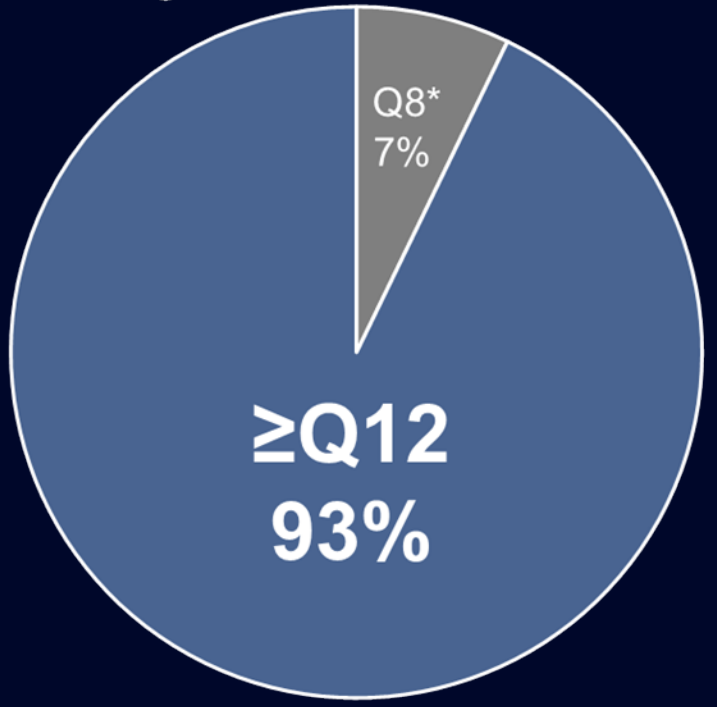
93% of 8mg patients maintained dosing intervals ≥12 weeks



8q12 (n=300)^



8q16 (n=156)^



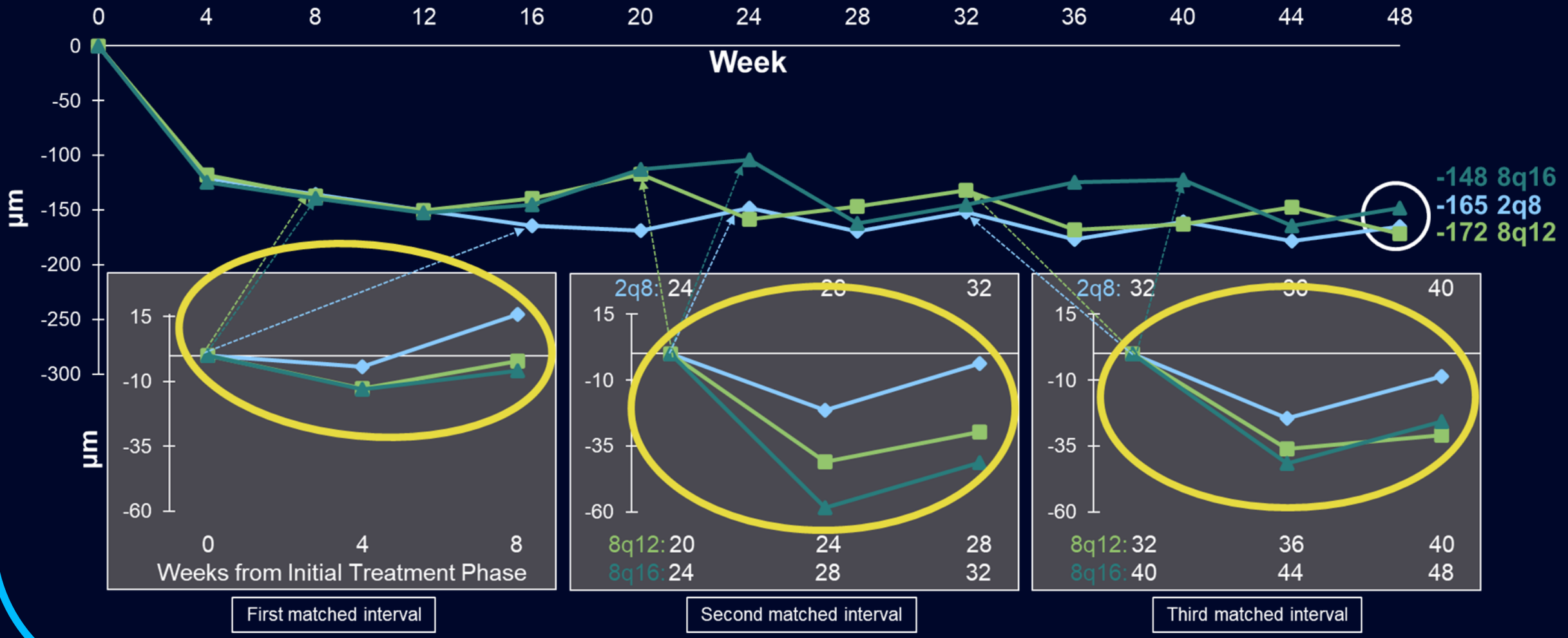
All 8mg (n=456)^

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

Mean Change in Central Retinal Thickness

Note: 2mg arm received 5 initial monthly injections versus 8mg arms, which received only 3 initial monthly injections

Despite fewer initial monthly doses, 8mg exhibited longer duration at each matched interval, thus achieving similar retinal thickness to 2mg by Week 48



Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

Most Frequent Ocular AEs Through Week 48

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DME

	2q8	8q12	8q16	All 8mg
N (SAF)	167	328	163	491
Patients with ≥ 1 AE (%)*	27.5%	31.7%	29.4%	31.0%
Cataract	1.2%	1.5%	4.9%	2.6%
Conjunctival hemorrhage	3.6%	4.3%	3.7%	4.1%
Intraocular pressure increased	3.6%	2.1%	0.6%	1.6%
Punctate keratitis	0.6%	1.5%	3.7%	2.2%
Retinal hemorrhage	0.6%	0	3.7%	1.2%
Vitreous floaters	2.4%	4.9%	1.8%	3.9%

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

Intraocular Inflammation Through Week 48

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DME

	2q8	8q12	8q16	All 8mg
N (SAF)	167	328	163	491
Patients with ≥ 1 IOI AE (%)*	0.6%	1.2%	0	0.8%

- No cases of endophthalmitis or occlusive retinal vasculitis

Reported IOI terms: iridocyclitis, iritis, uveitis, vitreal cells, vitritis.
*Treatment-emergent events.
IOI, intraocular inflammation.

Intraocular Pressure Through Week 48

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DME

	2q8	8q12	8q16	All 8mg
N (SAF)	167	328	163	491
Patients with IOP ≥ 35 mmHg pre- or post-injection (%)	1.2%	0.3%	0	0.2%

- Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 48

IOP, intraocular pressure.

Non-Ocular Safety Through Week 48

photon

DME

	2q8	8q12	8q16	All 8mg
N (SAF)	167	328	163	491
Patients (%):				
APTC events*	3.6%	2.4%	4.3%	3.1%
Hypertension events*	12.0%	11.0%	14.1%	12.0%
Non-ocular SAEs*	15.6%	15.9%	13.5%	15.1%
Deaths^	2.4%	2.7%	1.8%	2.4%

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

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

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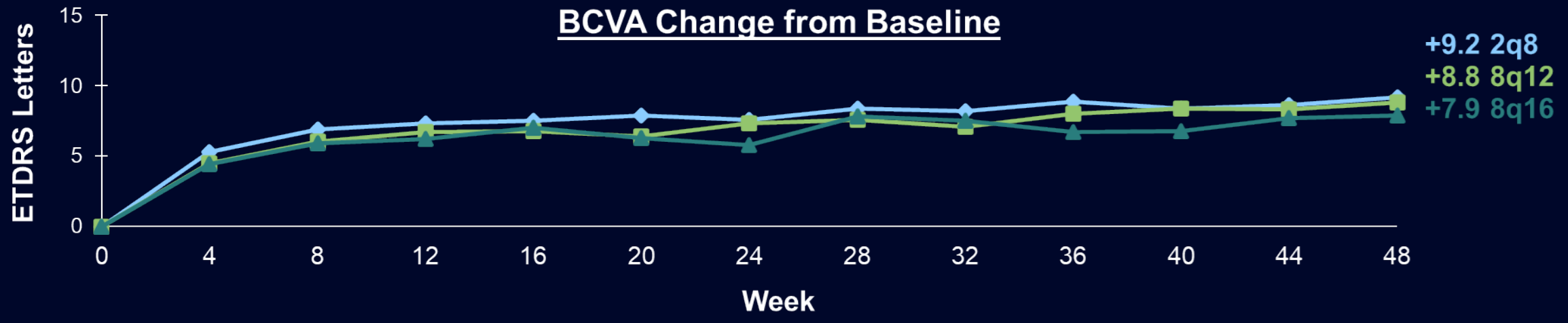
DME

- 8q12 and 8q16 groups had non-inferior BCVA compared to 2q8 at Week 48
- 8q12 met the non-inferiority margin of 15% in the proportion of patients with ≥2-step improvement in DRSS at Week 48



	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	8.7			
8q12	8.1	-0.57	-2.26, 1.13	p < 0.0001
8q16	7.2	-1.44	-3.27, 0.39	p = 0.0031

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).

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

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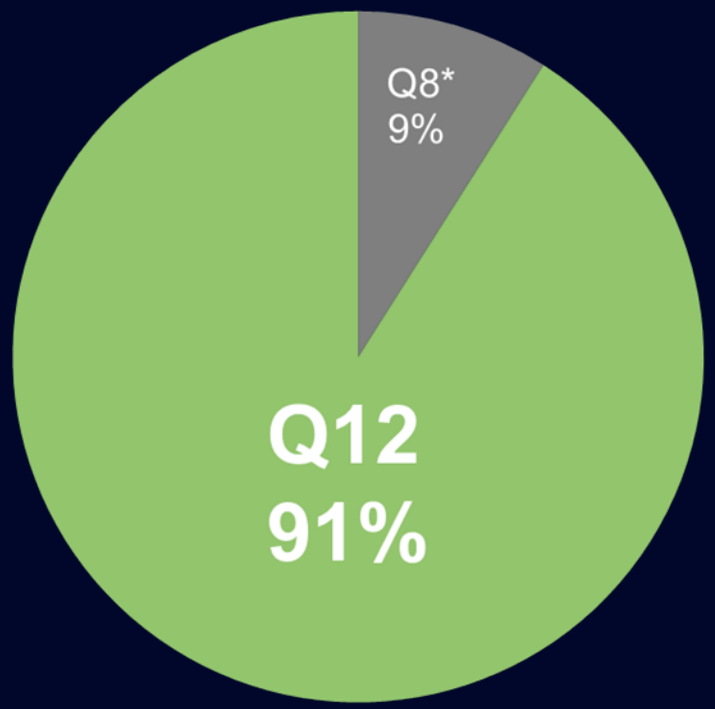
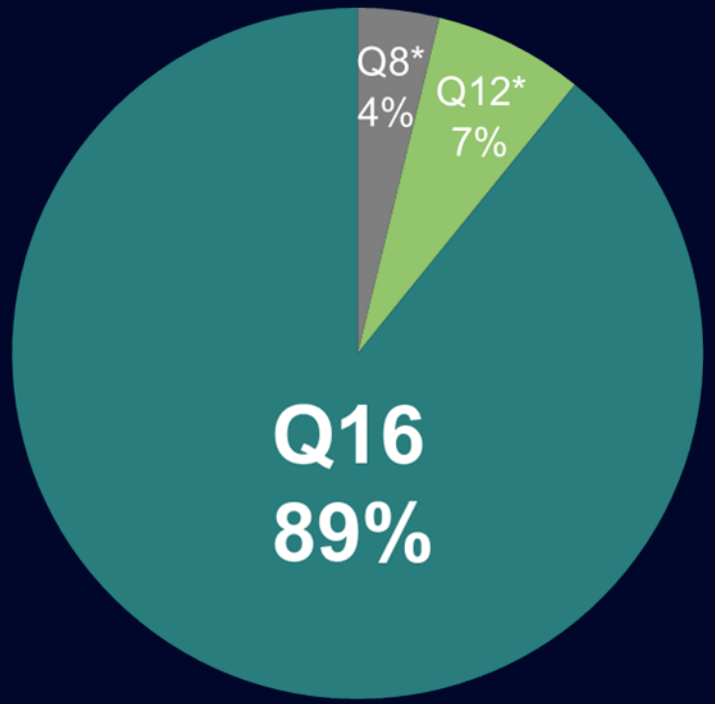
DME

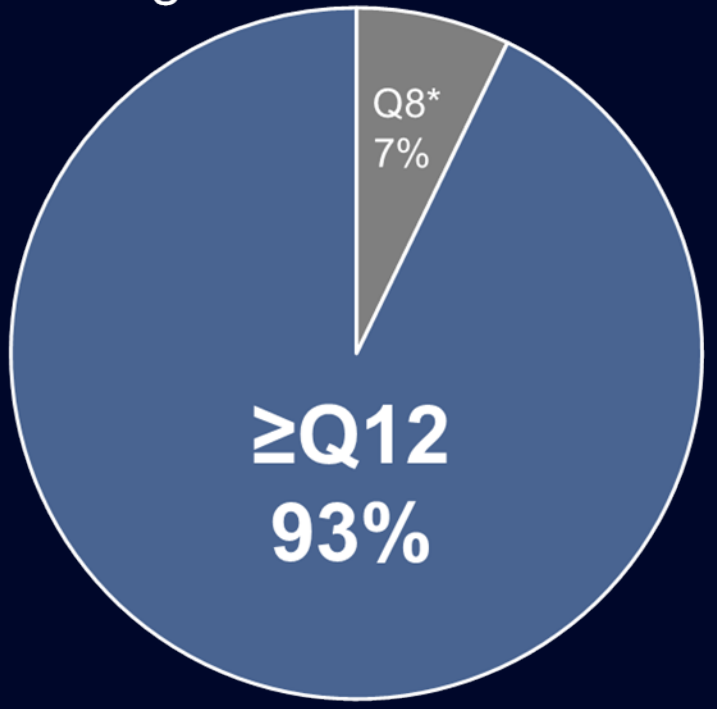
93% of 8mg patients maintained dosing intervals ≥12 weeks



8q12 (n=300)^



8q16 (n=156)^



All 8mg (n=456)^

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

Aflibercept 8 mg in Patients with nAMD: 48-Week Results from the Phase 3 PULSAR Trial

Andrew Chang,[1] on behalf of the PULSAR study investigators

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Presented at the 38th Asia-Pacific Academy of Ophthalmology (APAO) Congress, Kuala Lumpur, Malaysia, February 23–26, 2023

Disclosures

pulsar
nAMD

- Andrew Chang has received consulting fees from Alcon, Allergan, Bayer, Novartis, 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
- 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

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; **SRF**, subretinal fluid.

PULSAR: Dosing Schedule and Regimen Modification in Year 1

pulsar nAMD

	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[a]

- >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

[a]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[b] 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.
[b]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

pulsar
nAMD

	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 subject	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 Characteristics of the Study Eye

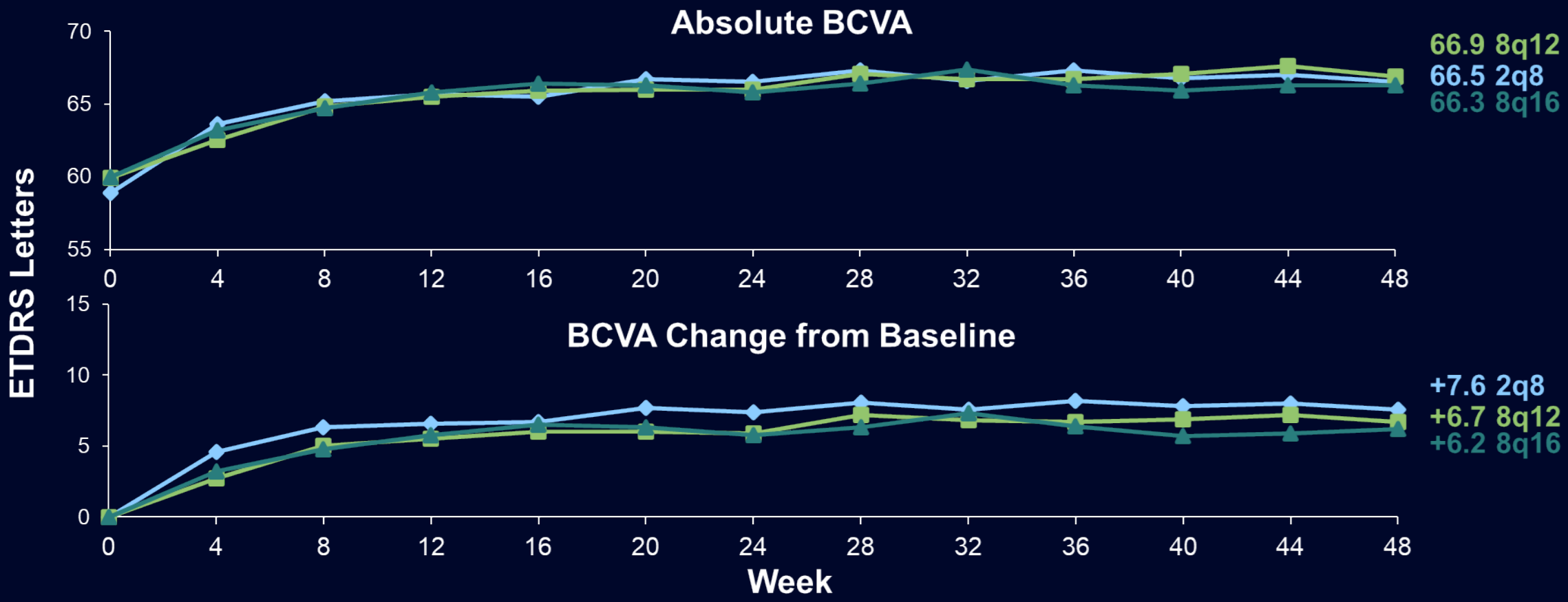
pulsar nAMD

	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

pulsar nAMD



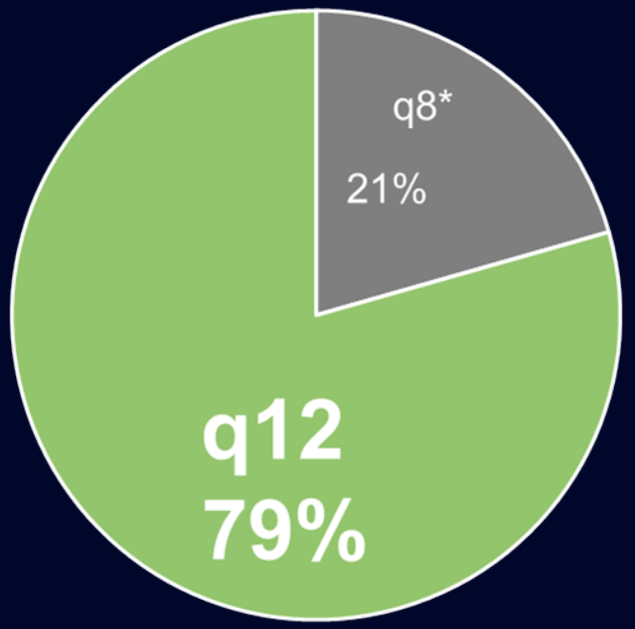
	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

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.

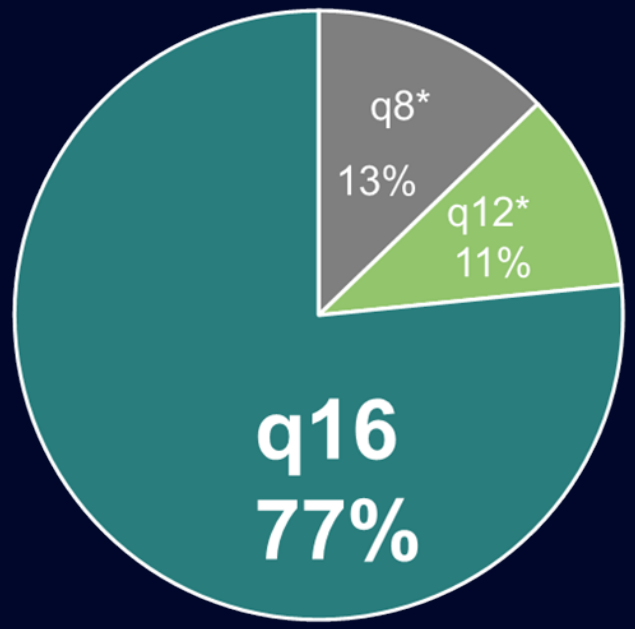
Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48

pulsar nAMD

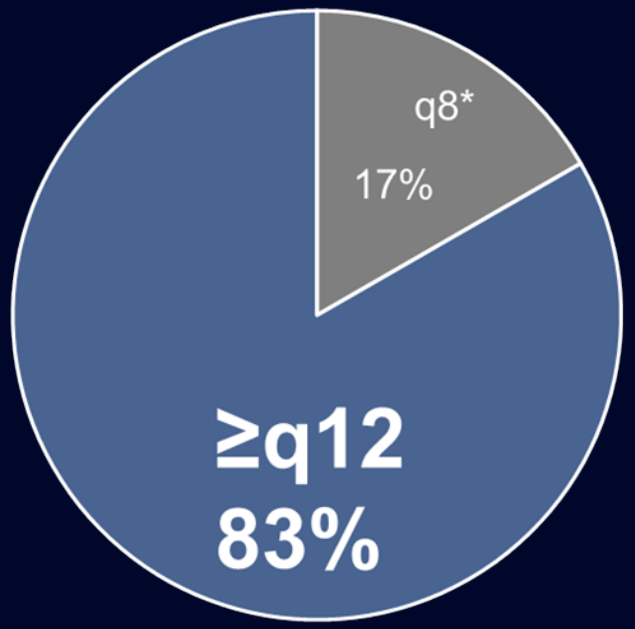
83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 n=316^



8q16 n=312^

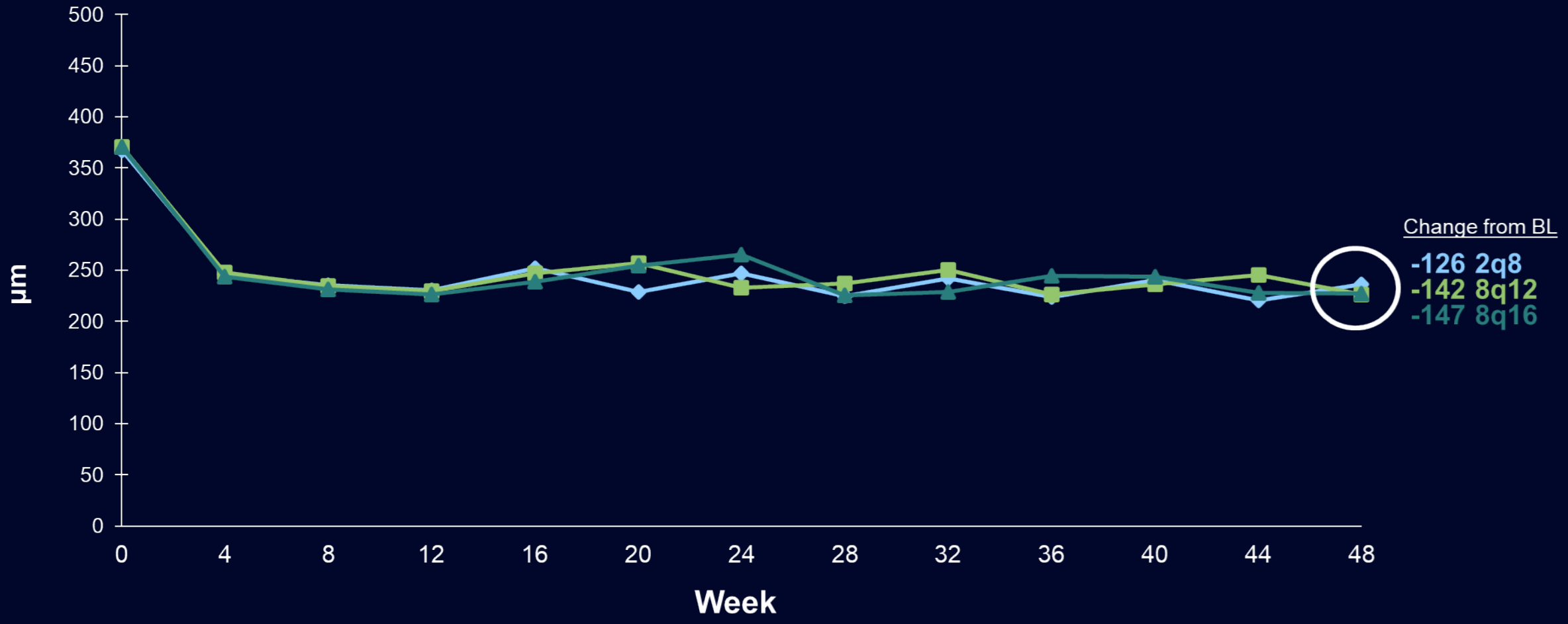


All 8 mg n=628^

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.

Central Retinal Thickness

pulsar
nAMD



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

pulsar nAMD

	2q8	8q12	8q16	All 8 mg
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 event in the study eye.
AE, adverse event; **SAE**, serious adverse event; **SAF**, safety analysis set.

Intraocular Inflammation Through Week 48

pulsar nAMD

	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.

Intraocular Pressure Through Week 48

pulsar
nAMD

	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

Non-Ocular Safety Through Week 48

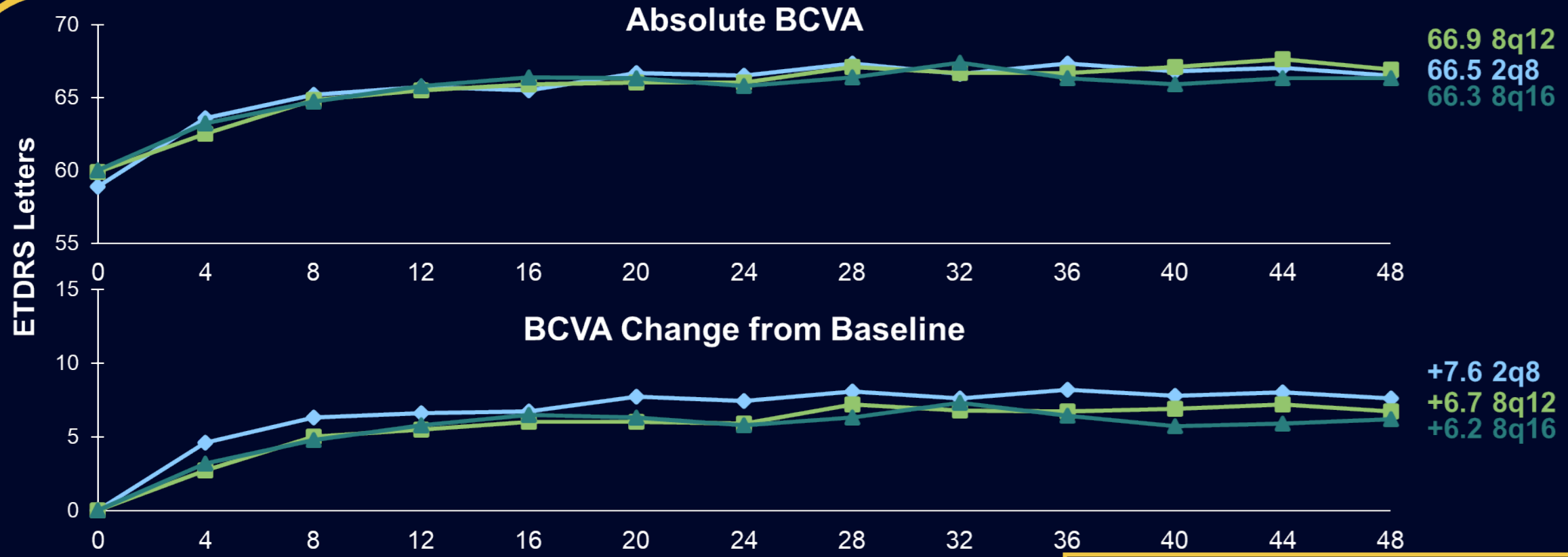
	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)				
APTC events*	1.5%	0.3%	0.6%	0.4%
Hypertension events*	3.6%	4.8%	4.7%	4.8%
Non-ocular SAEs*	13.7%	10.1%	9.5%	9.8%
Deaths^	1.5%	0.9%	0.3%	0.6%

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

PULSAR Summary: Primary and Key Secondary Endpoints Met

pulsar nAMD

- 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)

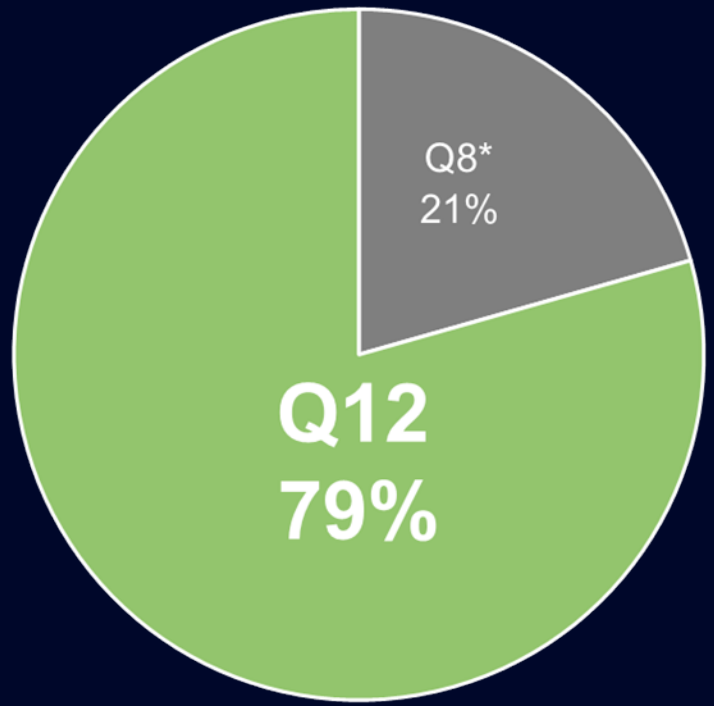
NOTE: p-values for the one-sided non-inferiority test at a margin of 4 letters (based on adjusted means derived using an MMRM).

PULSAR: 48-Week Results

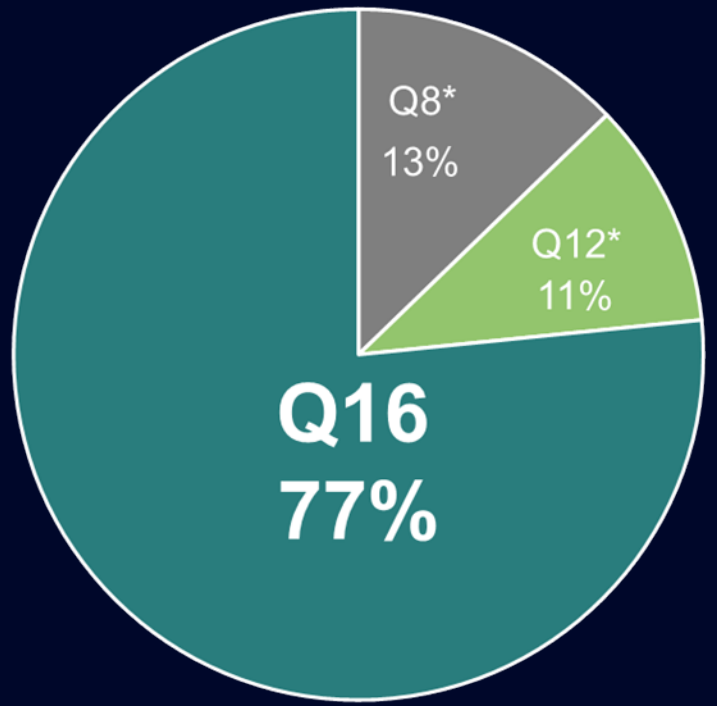
Majority of 8 mg Patients Maintained Randomized Intervals

pulsar nAMD

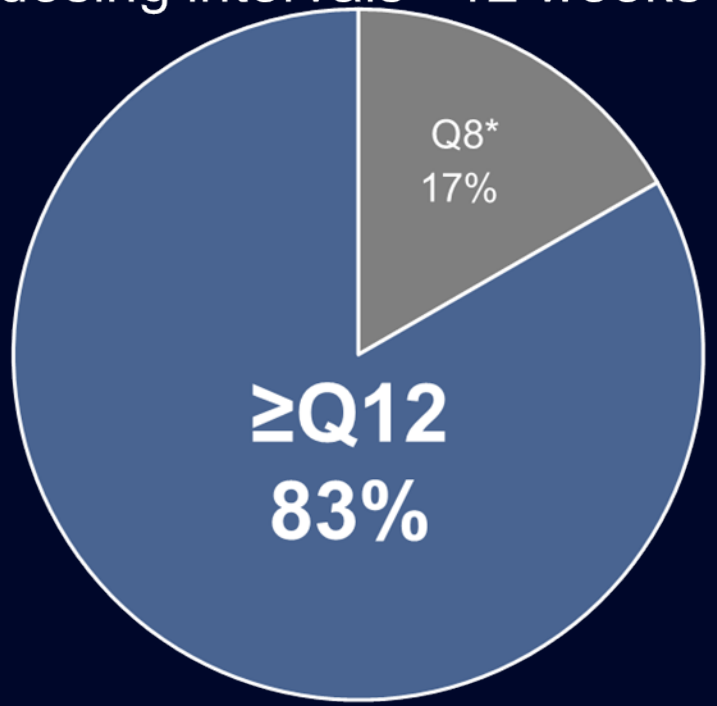
83% of 8 mg patients maintained dosing intervals ≥12 weeks



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.