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

David M. Brown,[1] on behalf of the PHOTON study investigators

[1]*Retina Consultants of Texas, Houston, TX, USA*

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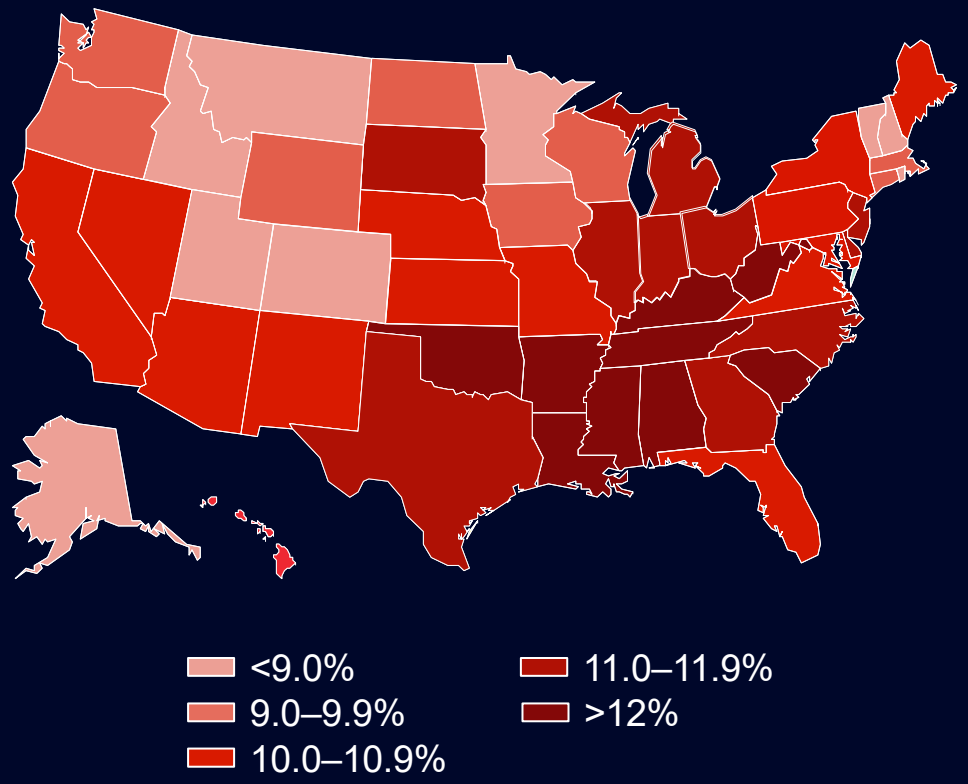
* This slide has been added for purposes of posting this presentation on Regeneron’s website.

Disclosures

- David M. Brown serves as a scientific advisor for Regeneron/Bayer and Genentech/Roche and as a member of the Regeneron Combination Products Steering Committee
- This 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

Background

Prevalence of Diabetes in the US (2017)[1,a]

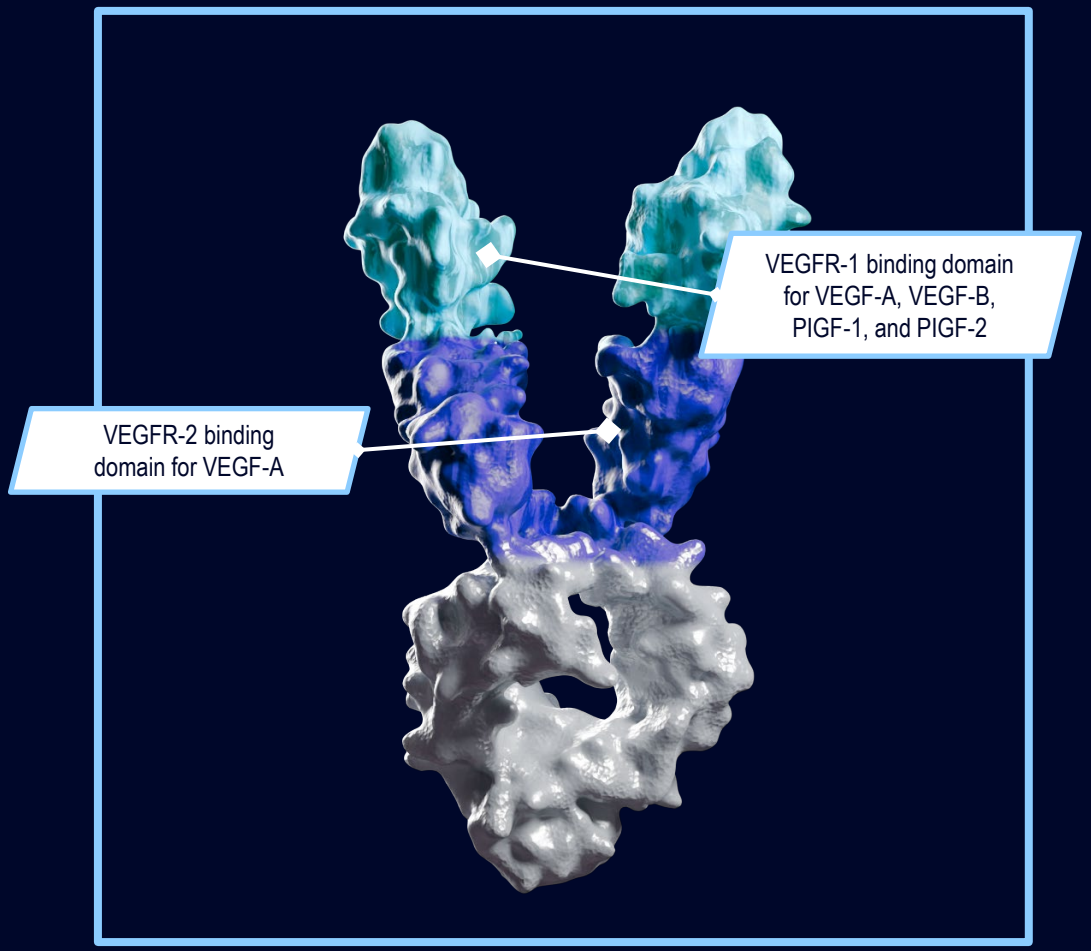


- Intravitreal anti-VEGF therapy is the current standard of care for CI-DME[2]; however, real-world effectiveness may be limited by the requirement for frequent monitoring and injections[3-6]
- Increasing the molar dose of an intravitreal anti-VEGF agent may provide clinical benefits, including reduced treatment burden through a longer duration of VEGF suppression[7,8]

[a]Includes pregnancy-related diabetes, percentages are weighted to reflect population characteristics (e.g., average age).
CI, center-involved; DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

1. Statista. Where Diabetes is Most Prevalent in the US. Available at: https://www.statista.com/chart/18160/us-states-with-highest-diabetes-rates/. Accessed October 21, 2022.
2. Flaxel CJ et al. *Ophthalmology*. 2020;127(1):P66-P145. 3. Ciulla TA et al. *Ophthalmol Retina*. 2018;2(12):1179-1187. 4. Ehlken C et al. *Clin Ophthalmol*. 2018;12:13-20.
5. Weiss M et al. *Retina*. 2018;38(12):2293-2300. 6. Lally DR et al. *Surv Ophthalmol*. 2016;61(6):759-768. 7. Brown DM. Do we need more VEGF blockade? The rationale for a clinical trial testing high-dose aflibercept. Presented at: Angiogenesis, Exudation, and Degeneration 2020; February 8, 2020; Miami, FL. 8. Do DV et al. *Retina*. 2020;40(4):643-647.

Characteristics of Aflibercept 8mg



- Novel intravitreal formulation delivers aflibercept 8mg in 70 µL injection (114.3 mg/mL)

- 4-times higher molar dose compared to aflibercept 2mg is hypothesized to provide longer effective vitreal concentration and enable more sustained effect on VEGF signaling

The ongoing pivotal PHOTON trial evaluates the efficacy and safety of aflibercept 8mg vs 2mg in patients with DME

PIGF, placental growth factor; VEGFR, vascular endothelial growth factor receptor.

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)

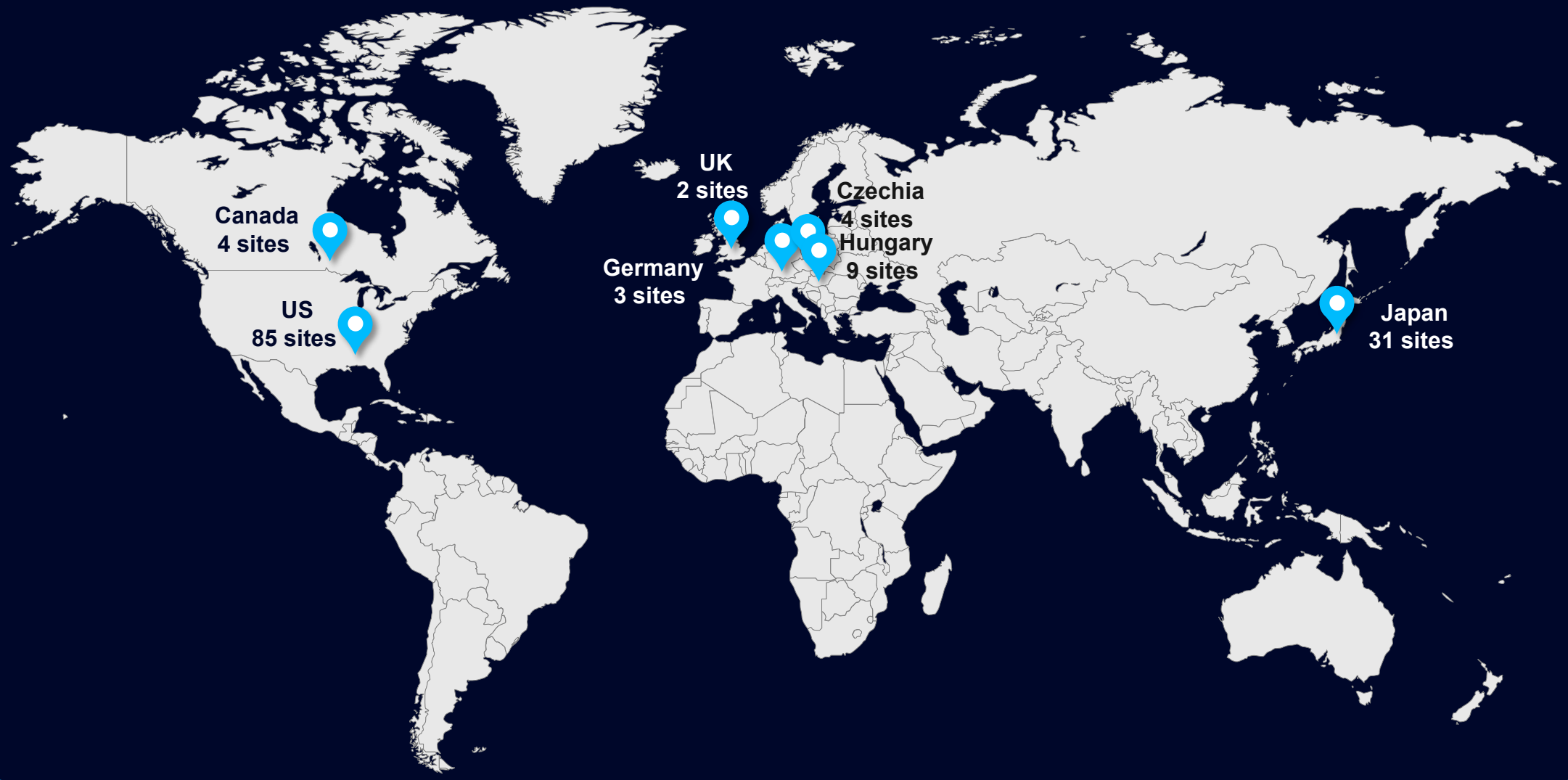
Key secondary endpoint:
Proportion of patients with ≥2-step improvement in DRSS at Week 48

End of study at Week 96

*Treatment naïve and previously treated.

PHOTON Study Sites

Global study conducted across 138 sites in 7 countries



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DME

Key Eligibility Criteria

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DME

Inclusion Criteria

- Adults (≥18 years of age) with type 1 or type 2 diabetes
- DME with central involvement with CRT ≥300 µm (or ≥320 µm on Spectralis) in the study eye as determined by the reading center
- BCVA of 78-24 letters (Snellen equivalent 20/32-20/320) with decreased vision due to DME

Exclusion Criteria

- Active PDR in the study eye
- PRP or laser photocoagulation in the study eye within 12 weeks of screening visit
- IVT anti-VEGF treatment in the study eye within 12 weeks of screening visit
- Intraocular or periocular steroids in the study eye within 16 weeks of the screening visit

CRT, central retinal thickness; IVT, intravitreal; PDR, proliferative diabetic retinopathy; PRP, panretinal photocoagulation.

PHOTON: Dosing Schedule 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

Dose Regimen Modifications (DRM) in Year 1

- **Weeks 16 or 20:** patients on 8q12 or 8q16 and meeting DRM criteria had treatment interval shortened to q8
- **Week 24:** patients on 8q16 and meeting DRM criteria had treatment interval shortened to q12
- **Subsequent dosing visits:** patients on 8mg and meeting DRM criteria had treatment interval shortened by 4 weeks
- Minimum interval for all patients was q8

DRM Criteria for Shortening Dosing Interval:

>10-letter loss in BCVA from Week 12 due to persistent or worsening DME

AND

>50-micron increase in CRT from Week 12

Stippled boxes = initial treatment phase; X=active injection; o=sham injections.
Note: Figure does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in the first year.

PHOTON: Dosing Schedule 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

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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 Demographics

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DME

	2q8	8q12	8q16	Total
N (FAS/SAF)	167	328	163	658
Age (years)	63.0 (9.8)	62.1 (11.1)	61.9 (9.5)	62.3 (10.4)
Female (%)	44.9%	36.0%	39.3%	39.1%
Race (%)				
White	67.1%	70.4%	78.5%	71.6%
Black or African American	10.8%	10.7%	5.5%	9.4%
Asian	18.0%	14.6%	14.1%	15.3%
Other	2.4%	3.0%	0.6%	2.4%
Not reported	1.8%	1.2%	1.2%	1.4%
Hispanic or Latino (%)	18.6%	16.5%	20.9%	18.1%
Duration of diabetes (years)	15.9 (10.0)	15.1 (10.0)	15.7 (10.7)	15.5 (10.2)
Hemoglobin A1c (%)	8.1 (1.5)	7.9 (1.5)	7.8 (1.5)	8.0 (1.5)
Hypertension (%)	77.8%	77.4%	79.8%	78.1%
BMI (kg/m^2)	29.9 (6.5)	30.4 (6.2)	31.0 (6.1)	30.5 (6.2)

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

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%
DRSS categories (%)				
Better or equal to level 43	62.9%	60.1%	65.6%	62.2%
Level 47 or worse	31.7%	34.5%	28.2%	32.4%
Missing/ungradable	5.4%	5.5%	6.1%	5.6%

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

Mean Number of Injections Through Week 48

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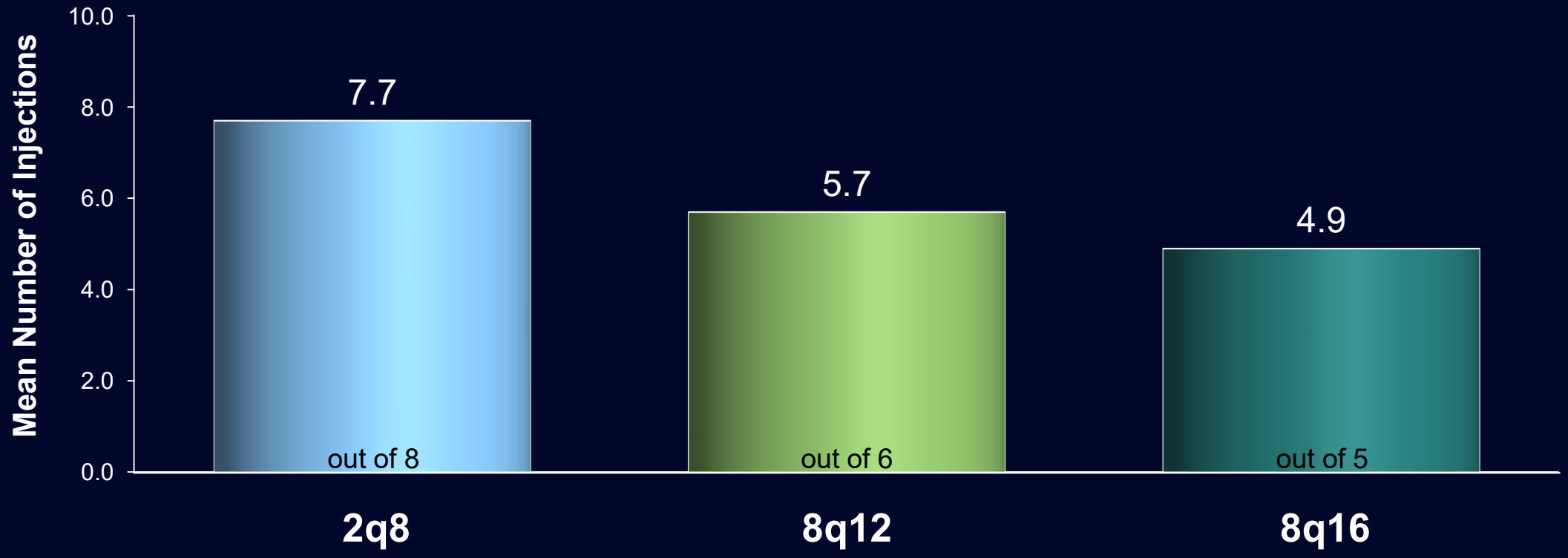
DME



SAF: 2q8 n=167; 8q12 n=328; 8q16 n=163.

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

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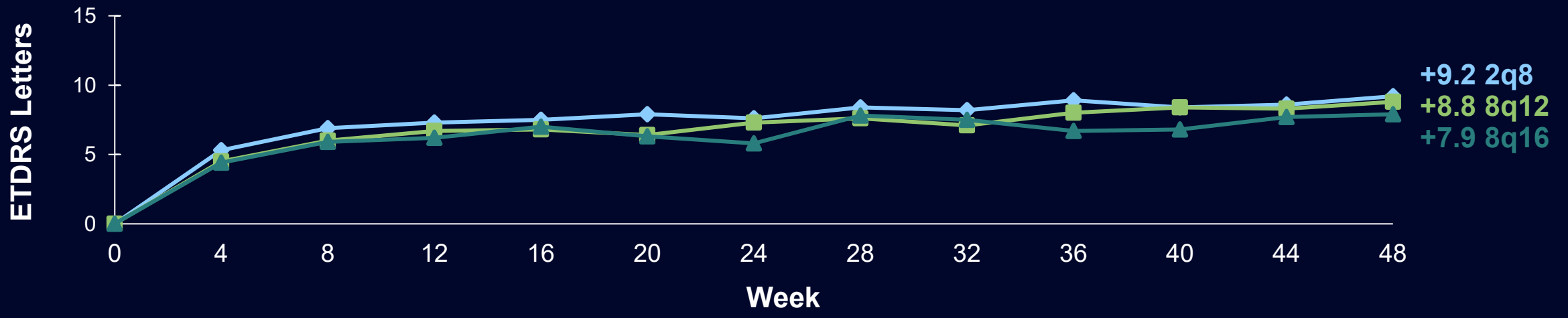
DME

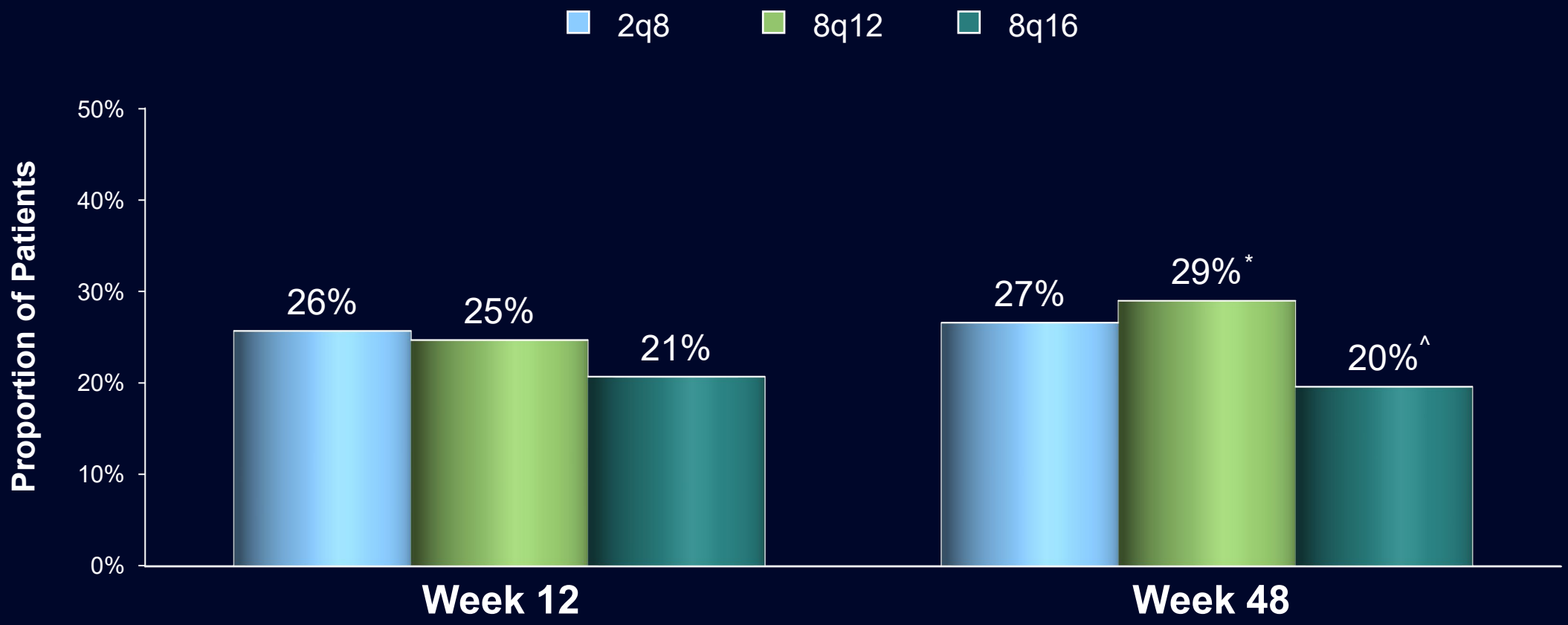
BCVA Change from Baseline



	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



Key secondary endpoint

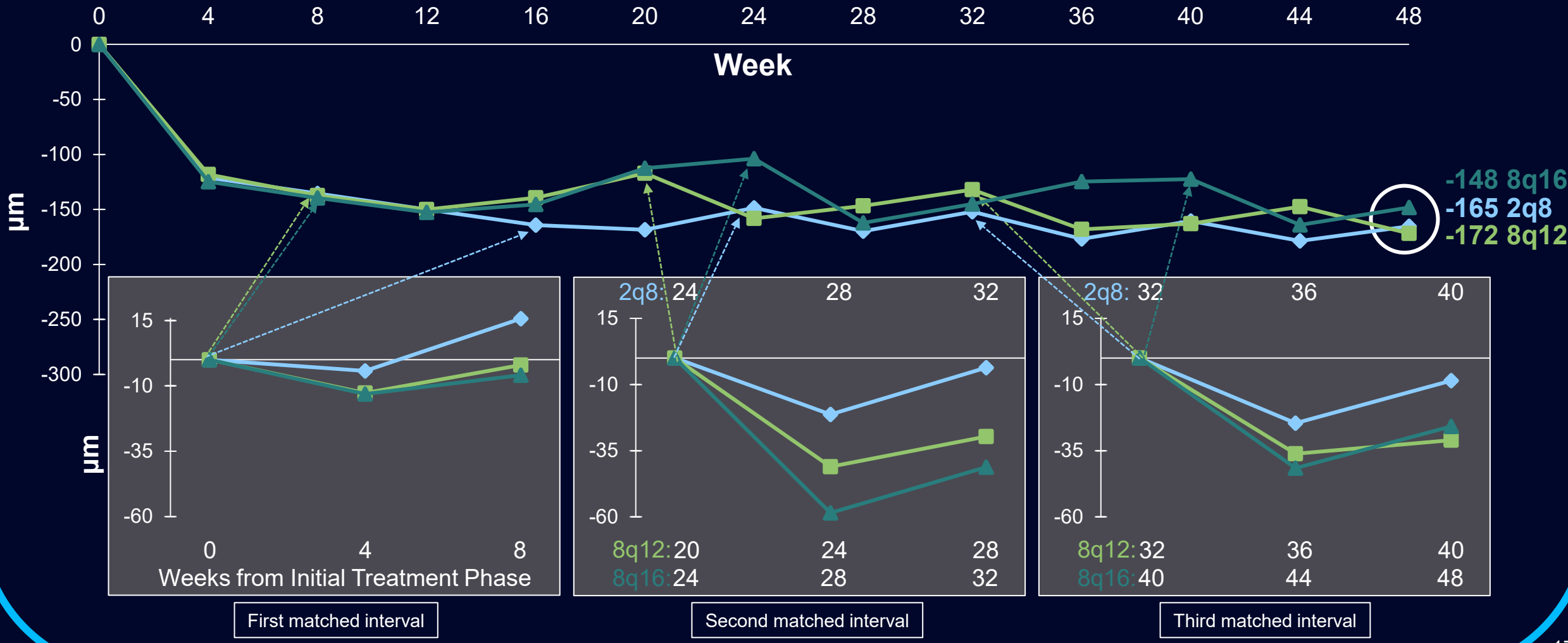
**8q12 vs. 2q8 Diff (95% CI): 1.98 (-6.61, 10.57)*
^8q16 vs. 2q8 Diff (95% CI): -7.52 (-16.88, 1.84)
(NI margin set at 15%)

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

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



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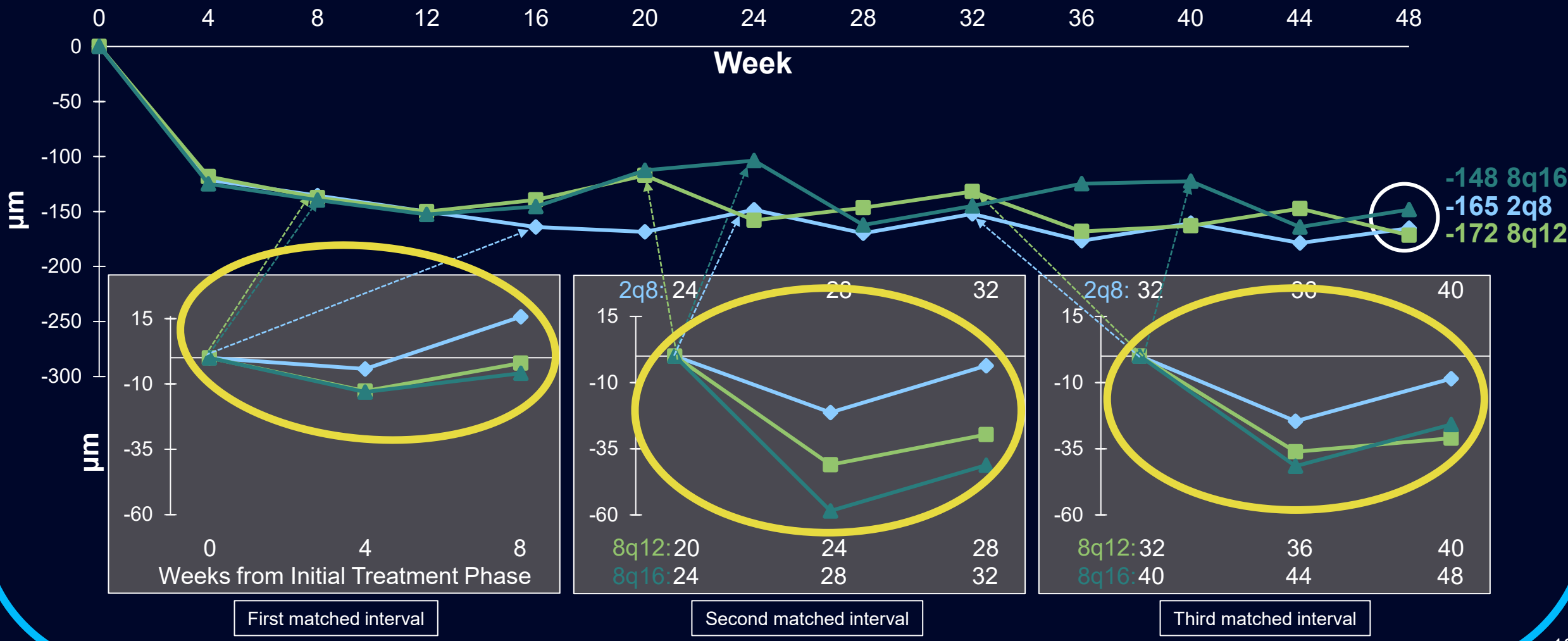


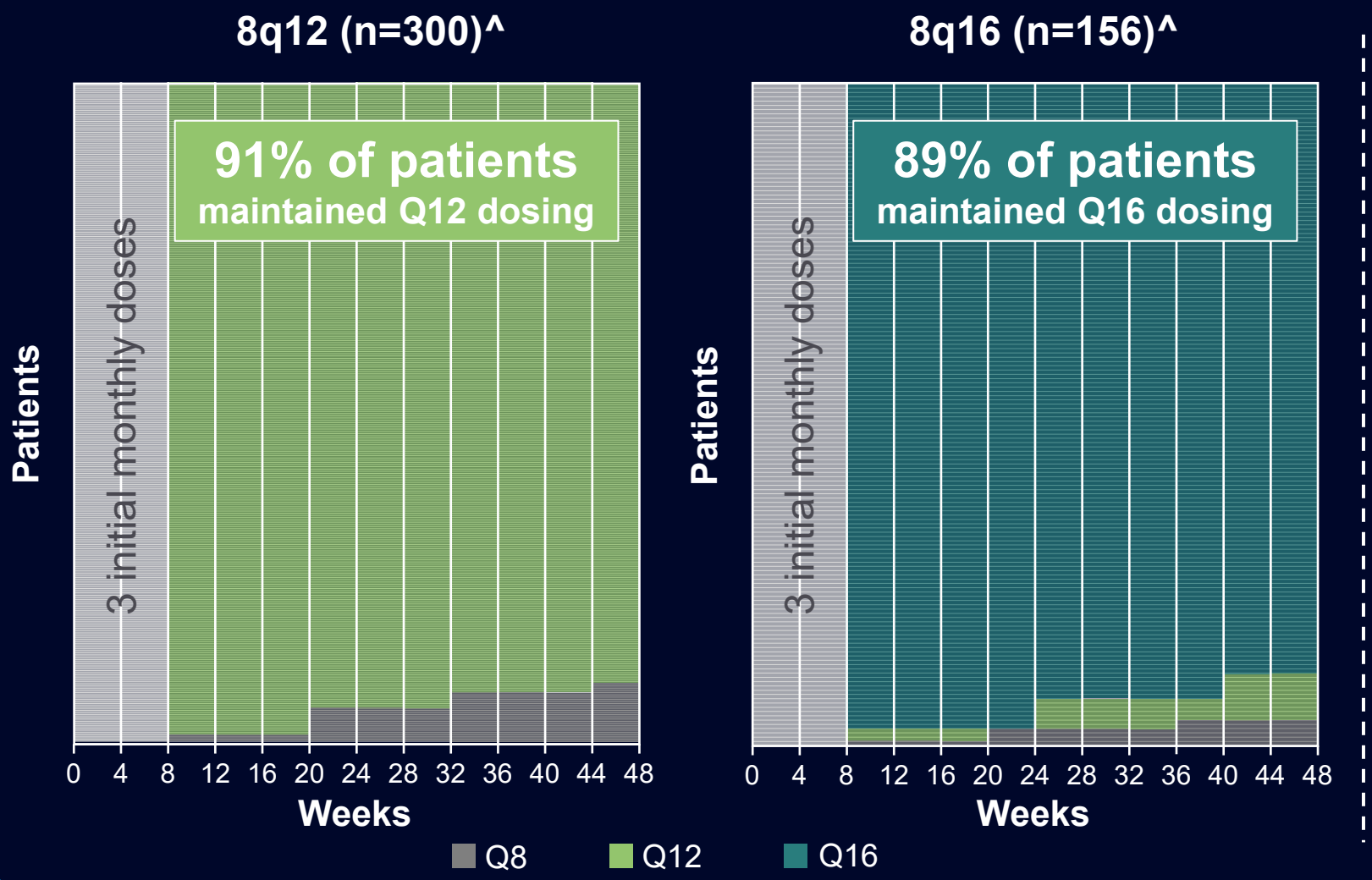
First matched interval | Second matched interval | Third matched interval

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

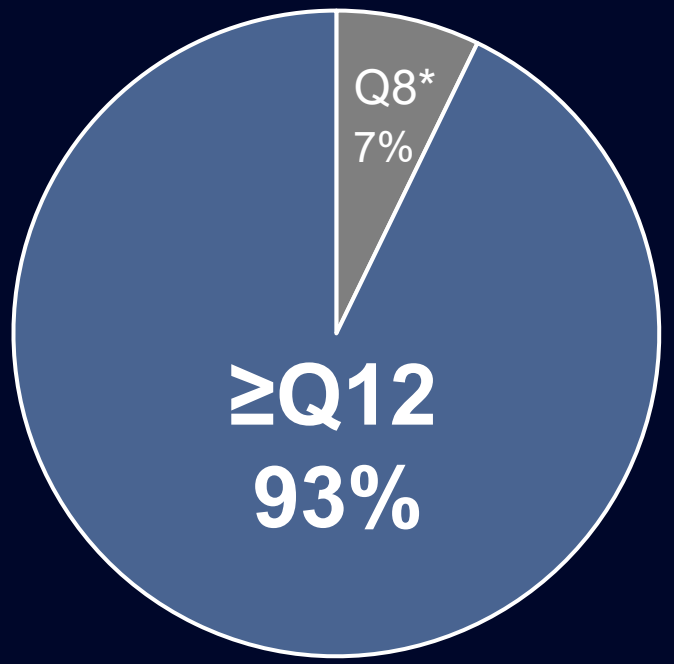
Large Majority of 8mg Patients Maintained Randomized Intervals Through Week 48

photon

DME



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



All 8mg
(n=456)^

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

Mean Change in Total Area of Fluorescein Leakage at Weeks 12 and 48

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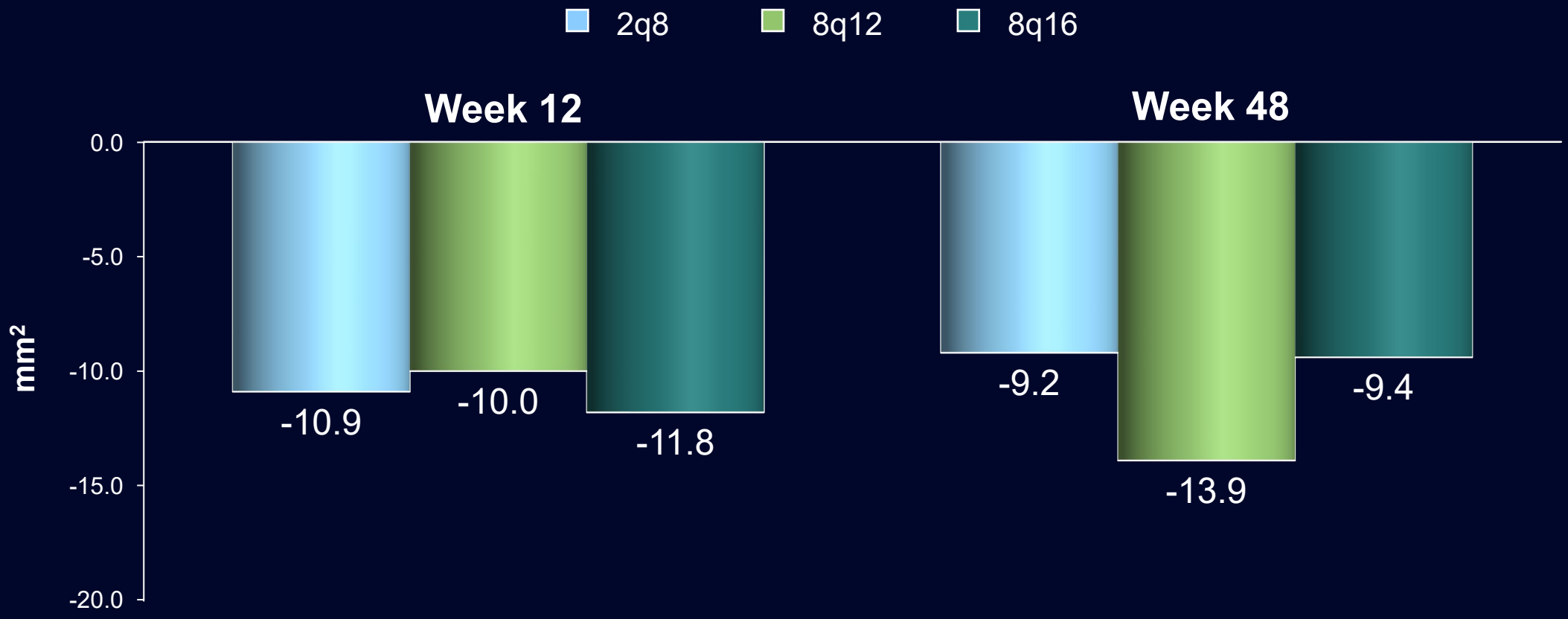
DME



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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 Safety Results

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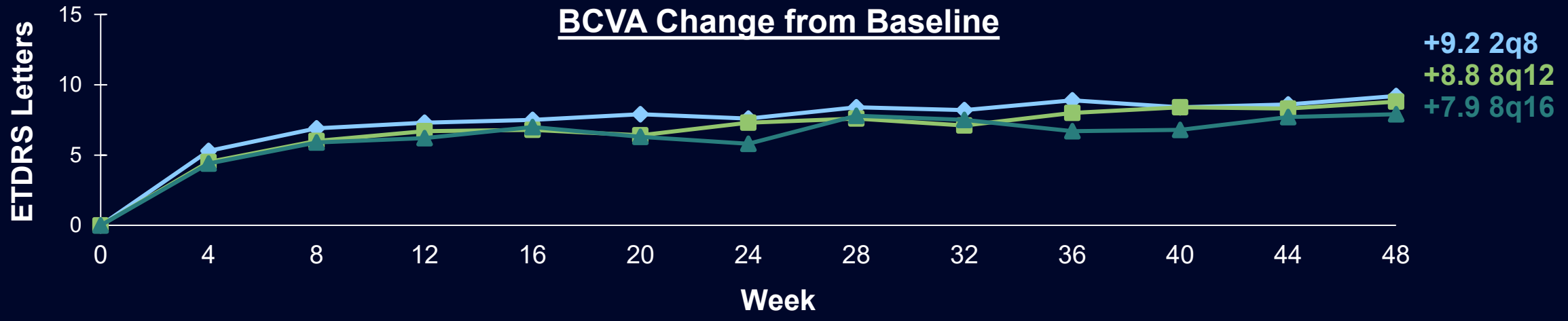
DME

- Safety of aflibercept 8mg comparable to that of aflibercept 2mg
- No cases of endophthalmitis or occlusive retinal vasculitis were reported
- No clinically relevant change was observed in IOP with aflibercept 8mg throughout the study
- Incidence of APTC events, hypertension events, and death was similar between aflibercept 8mg and 2mg

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

photon
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



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Large Majority of 8mg Patients Maintained Randomized Intervals

DME

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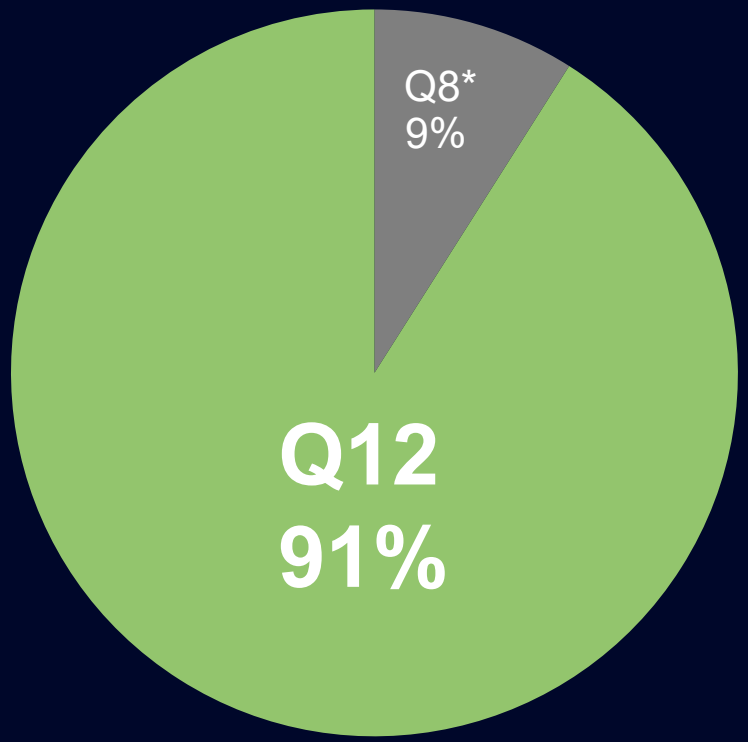
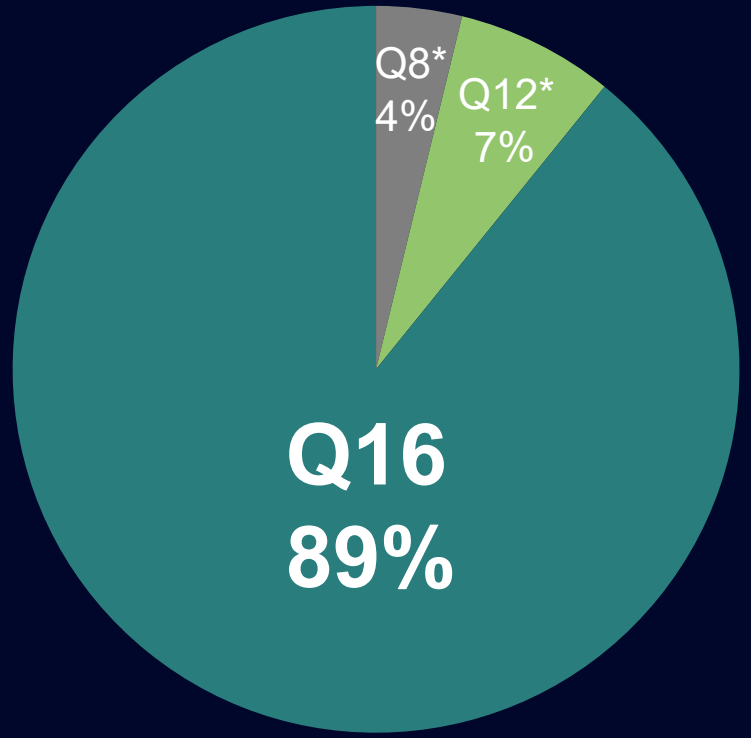
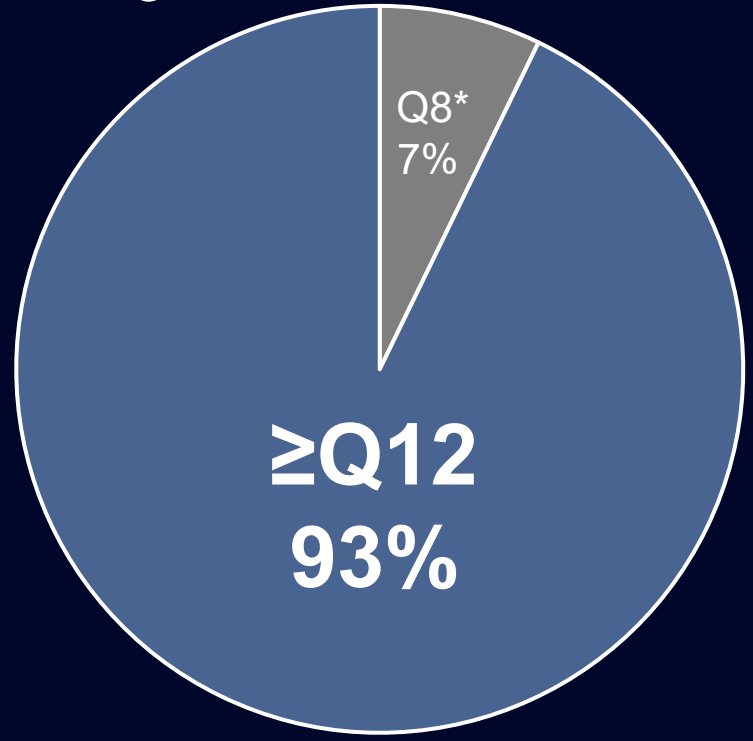


8q12 (n=300)^



8q16 (n=156)^



All 8mg (n=456)^

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