# Aflibercept 8 mg for Diabetic Macular Edema: 96-Week Results From the Phase 2/3 PHOTON Trial

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# Disclosures

- Diana V. Do is a consultant to Boehringer Ingelheim, Genentech, Kodiak Sciences, Kriya, and Regeneron Pharmaceuticals, Inc.; has received research funding from Boehringer Ingelheim, Genentech, Kriya, and Regeneron Pharmaceuticals, Inc.; and has stock options from Kodiak Sciences
- This study was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA) 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

# PHOTON Study Design

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DME

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

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

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

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

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

↓

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

[a]Treatment-naïve and previously treated patients aged ≥18 years with type 1 or type 2 diabetes, DME with central involvement with CRT ≥300 µm in the study eye, and BCVA of 78-24 letters (Snellen equivalent of 20/32-20/320) with decreased vision due to DME.
BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema.

# PHOTON: Dosing Schedule and Dose Regimen Modification

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DME
Primary Endpoint

| YEAR 1 | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 28 | Week 32 | Week 36 | Week 40 | Week 44 | Week 48 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | X | X | o | X | o | X | o | X | o | X |
| 8q12 | X | X | X | o | o[a] | X[a] | o | o | X[a] | o | o | X[a] | o |
| 8q16 | X | X | X | o | o[a] | o[a] | X[a] | o | o | o | X[a] | o | o |

| YEAR 2 | Week 52 | Week 56 | Week 60 | Week 64 | Week 68 | Week 72 | Week 76 | Week 80 | Week 84 | Week 88 | Week 92 | Week 96 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | o | X | o | X | o | X | o | X | o | X | o | o |
| 8q12 | o | X[a, b] | o | o | X[a, b] | o | o | X[a, b] | o | o | X[a, b] | o |
| 8q16 | o | X[a, b] | o | o | o | X[a, b] | o | o | o | X[a, b] | o | o |

**[a]DRM: Interval Shortening During Years 1 and 2**

- **Criteria for interval shortening:**
  - >10-letter loss in BCVA from Week 12 due to persistent or worsening DME **AND**
  - >50-µm increase in CRT from Week 12
- Patients who met DRM criteria had dosing intervals shortened to Q8 at **Weeks 16** and **20** or by 4-week increments from **Week 24**
  - The minimum interval was Q8

**[b]DRM: Interval Extension During Year 2**

- **Criteria for interval extension:**
  - <5-letter loss in BCVA from Week 12 **AND**
  - CRT <300 µm (or <320 µm on Spectralis)
- Patients who met DRM criteria beginning at **Week 52** had dosing intervals extended by 4-week increments
  - The maximum assigned interval was Q24

Figure does not reflect all dosing options once a patient's interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injection.
DRM, dose regimen modification.

# Patient Disposition

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DME

| | 2q8 | 8q12 | 8q16 | Total |
|---|---|---|---|---|
| N (FAS/SAF) | 167 | 328 | 163 | 658 |
| Completion rate at Week 48 (%) | 94.0% | 91.2% | 95.1% | 92.9% |
| Completion rate at Week 96 (%) | 83.2% | 77.8% | 84.8% | 80.9% |
| | | | | |
| Reasons for discontinuation through Week 96 (%) | | | | |
| Consent withdrawal | 5.4% | 5.2% | 4.9% | 5.2% |
| Death | 5.4% | 5.5% | 3.0% | 4.8% |
| Lost to follow-up | 3.0% | 5.8% | 4.3% | 4.7% |
| Decision by the investigator | 1.2% | 2.7% | 1.8% | 2.1% |
| Adverse event | 0.6% | 2.7% | 1.2% | 1.8% |
| Noncompliance with protocol | 1.2% | 0.3% | 0 | 0.5% |

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

# Patient Baseline Characteristics

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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) |
| History of 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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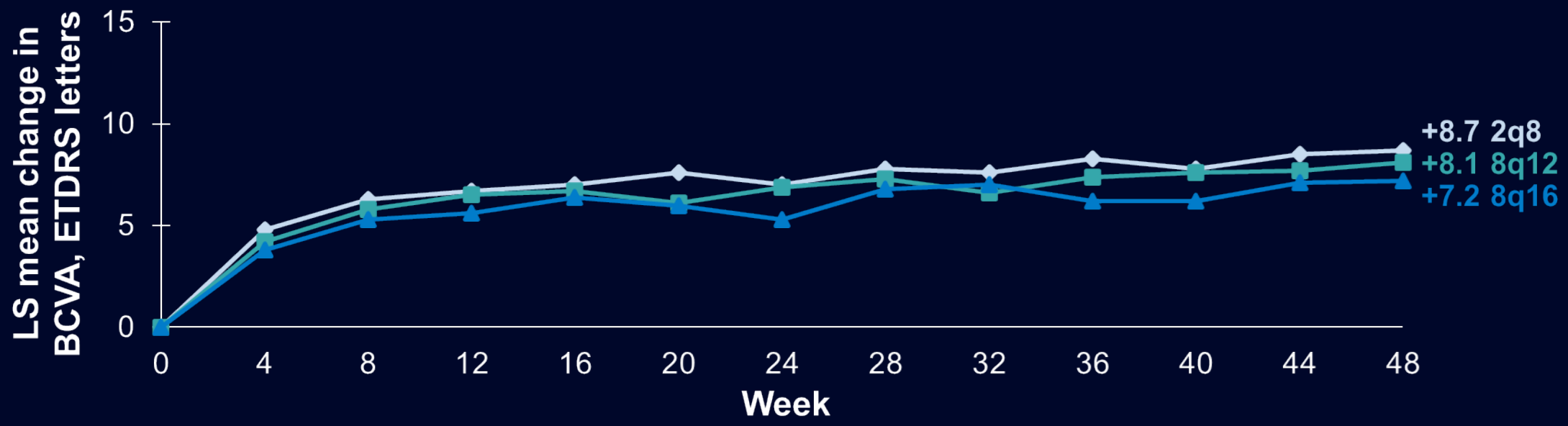
DME

| | 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% |

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

# Primary Endpoint: Mean Change in BCVA at Week 48

DME



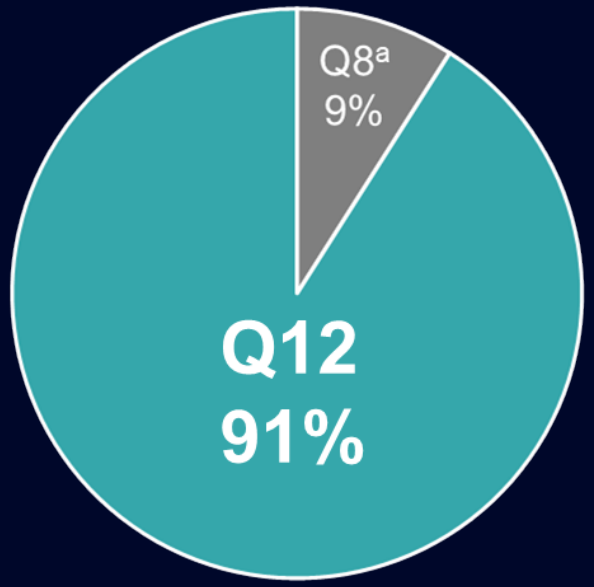

| | Mean number of injections[a] | LS mean change from BL at Week 48 (MMRM) | Diff. in LS means vs. 2q8 | 2-sided 95% CI | 1-sided test for non-inferiority at 4-letter margin |
|---|---|---|---|---|---|
| **2q8** | 7.9 | 8.7 | | | |
| **8q12** | 6.0 | 8.1 | **-0.57** | **-2.26, 1.13** | **p < 0.0001** |
| **8q16** | 5.0 | 7.2 | **-1.44** | **-3.27, 0.39** | **p = 0.0031** |

Data shown in the figure represent LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit.
[a]Patients completing Week 48: 2q8 n=157; 8q12 n=300; 8q16 n=156.
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

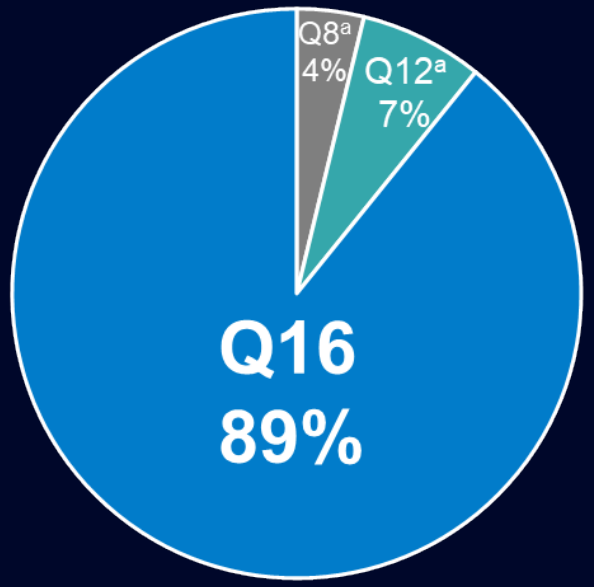
# Large Majority of Aflibercept 8 mg Patients Maintained Randomized Intervals Through Week 48

photon

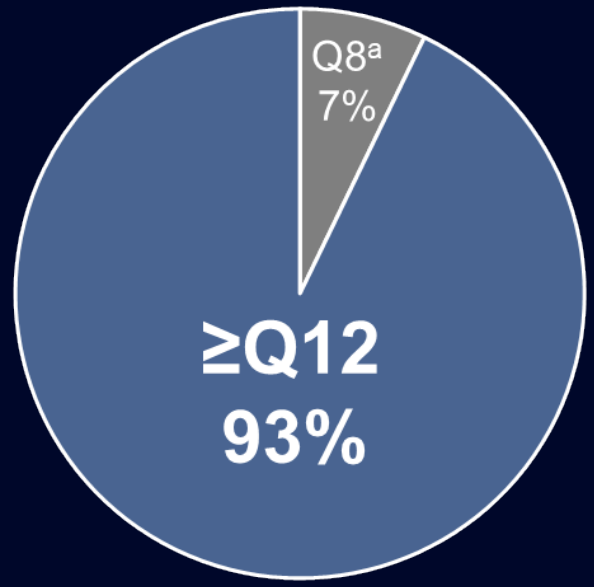
DME




**8q12**
**(n=300)[b]**




**8q16**
**(n=156)[b]**




**All 8 mg**
**(n=456)[b]**

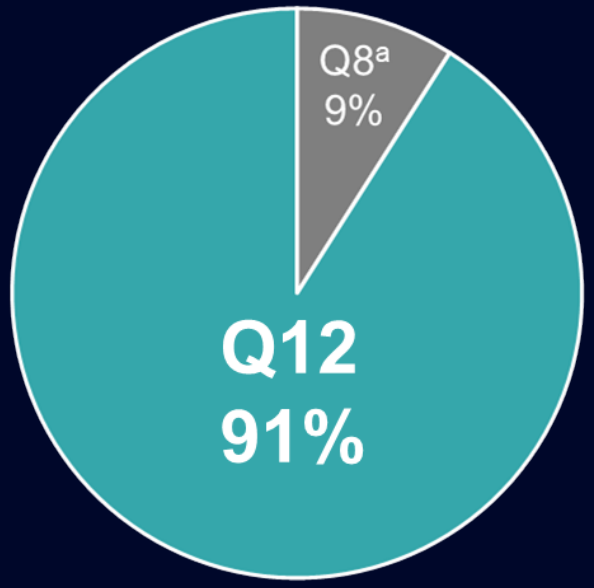
[a]Patients whose dosing intervals were shortened based on DRM assessments at some point through Week 48.
[b]Patients completing Week 48.

# Exploratory Analysis of Patients Who Would Hypothetically Meet DRM Criteria for Additional Interval Shortening Through Week 48

photon

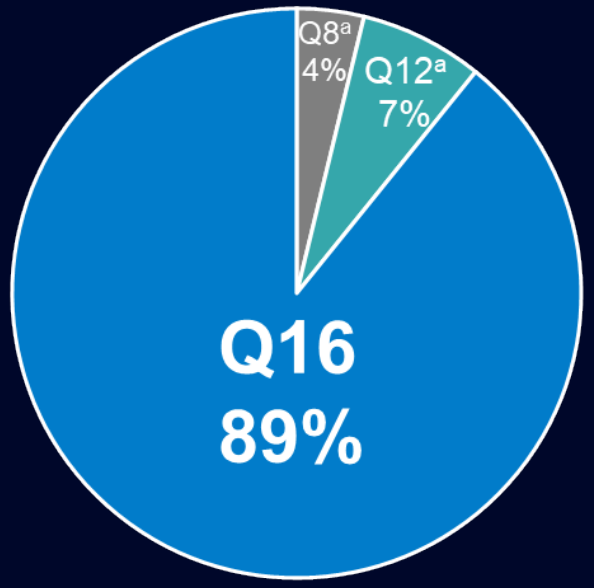
DME

**1.7%** of patients in the **8q12** group would have met DRM criteria for shortening to Q4



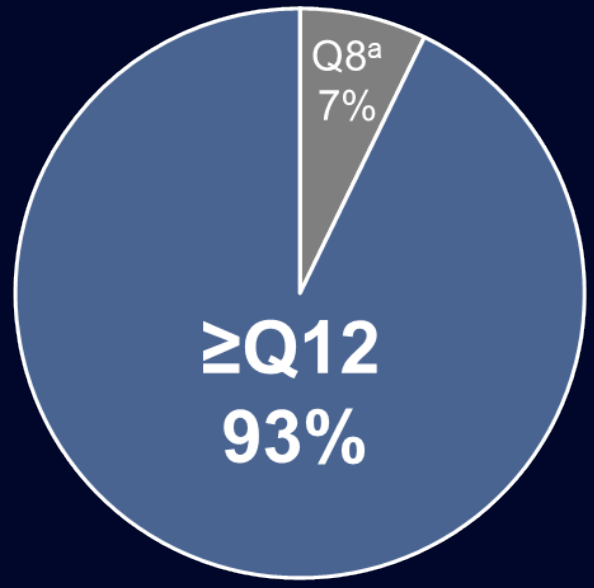

**8q12**
**(n=300)[b]**

**1.3%** of patients in the **8q16** group would have met DRM criteria for shortening to Q4




**8q16**
**(n=156)[b]**

**1.5%** of all 8 mg patients would have met DRM criteria for shortening to Q4




**All 8 mg**
**(n=456)[b]**

In this exploratory analysis, eyes that were shortened to a Q8 dosing interval through Week 48 were further evaluated to determine if the study-specified DRM criteria would have been met for shortening to a Q4 interval. DRM criteria for interval shortening were defined as >10-letter loss in BCVA from Week 12 due to persistent or worsening DME and >50-µm increase in CRT from Week 12 (assessed using OCT data from the central reading center).

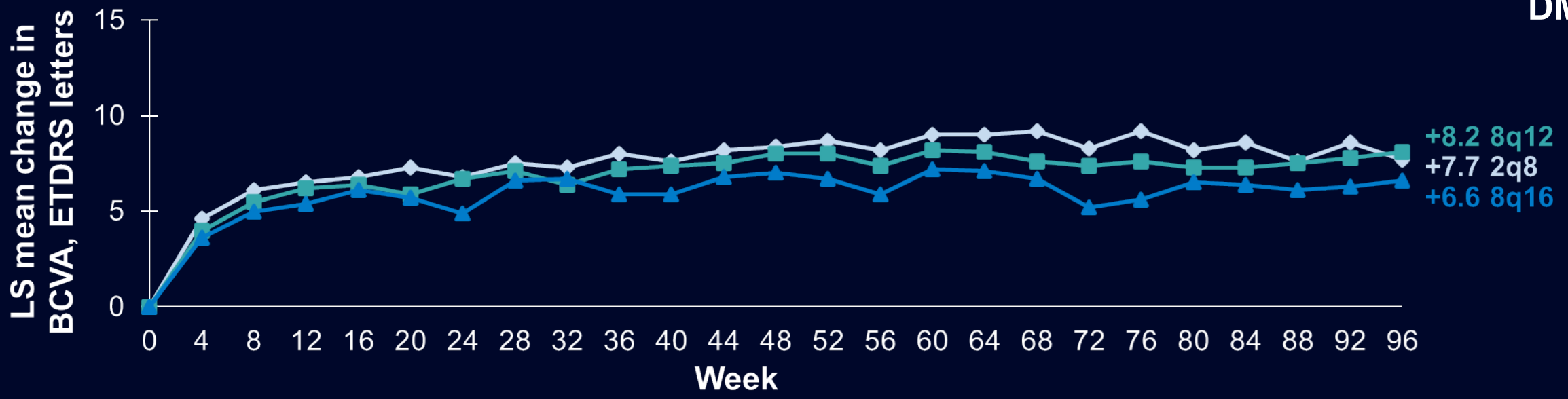
[a]Patients whose dosing intervals were shortened based on DRM assessments at some point through Week 48.

[b]Patients completing Week 48.

OCT, optical coherence tomography.

# Mean Change in BCVA at Week 96

DME




| | Mean number of injections[a] | LS mean change from BL at **Week 96** (MMRM) | Diff. in LS means vs. 2q8 | 2-sided 95% CI | 1-sided test for non-inferiority at 4-letter margin |
|---|---|---|---|---|---|
| **2q8** | 13.8 | 7.7 | | | |
| **8q12** | 9.5 | 8.2 | **+0.45** | **-1.55, 2.45** | **p < 0.0001 (nominal)** |
| **8q16** | 7.8 | 6.6 | **-1.11** | **-3.27, 1.05** | **p = 0.0044 (nominal)** |

Data shown in the figure represent LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit.
[a]Patients completing Week 96: 2q8 n=139; 8q12 n=256; 8q16 n=139.
BL, baseline; ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

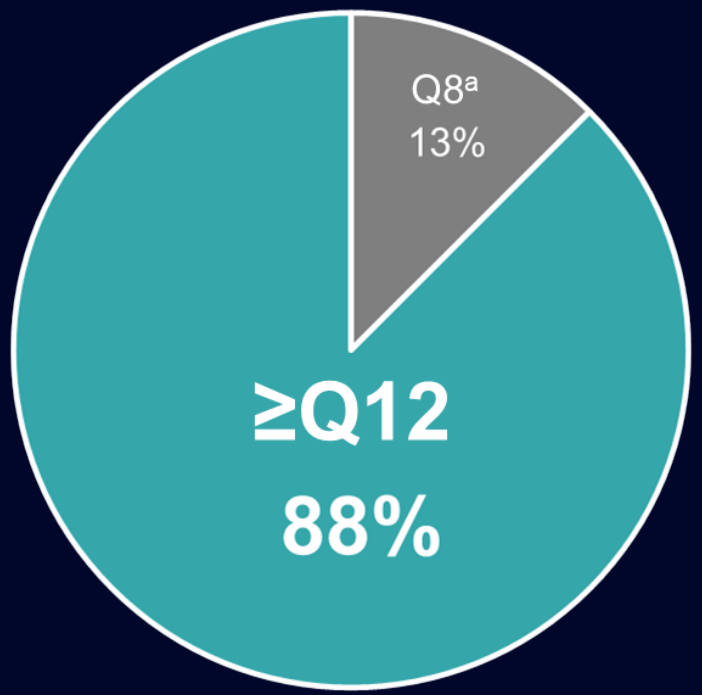
# Large Majority of Aflibercept 8 mg Patients Maintained Randomized Intervals Through Week 96

photon

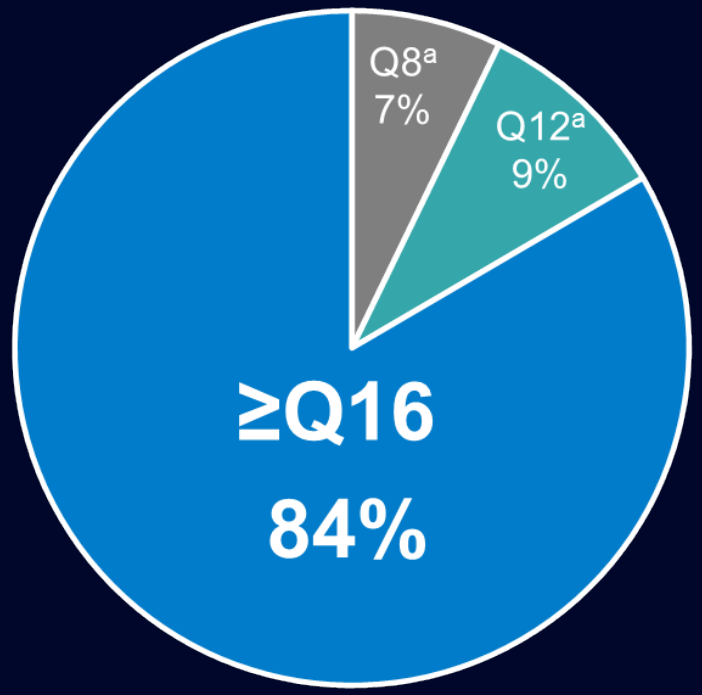
DME

**88%** of patients in the 8q12 group maintained ≥12-week intervals

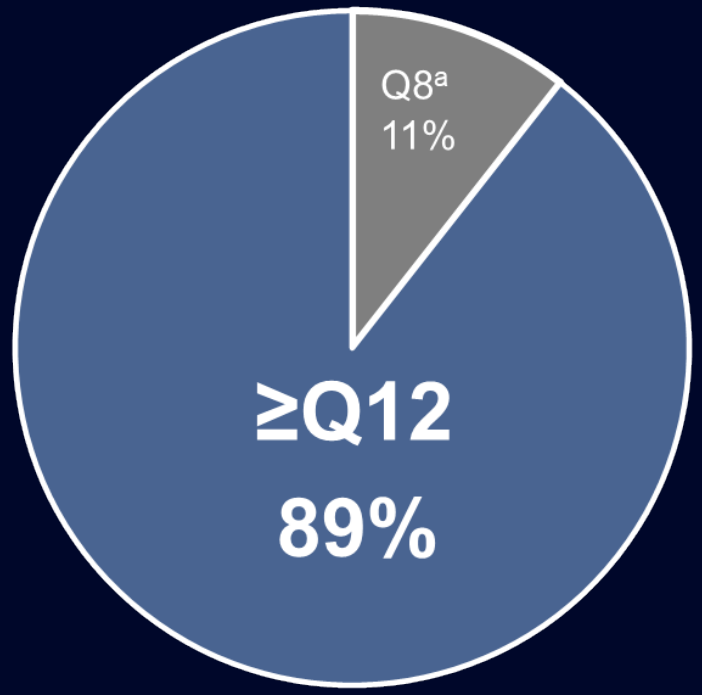
**84%** of patients in the 8q16 group maintained ≥16-week intervals




Randomized to **8q12** at BL
(n=256)[b]




Randomized to **8q16** at BL
(n=139)[b]




All 8 mg
(n=395)[b]

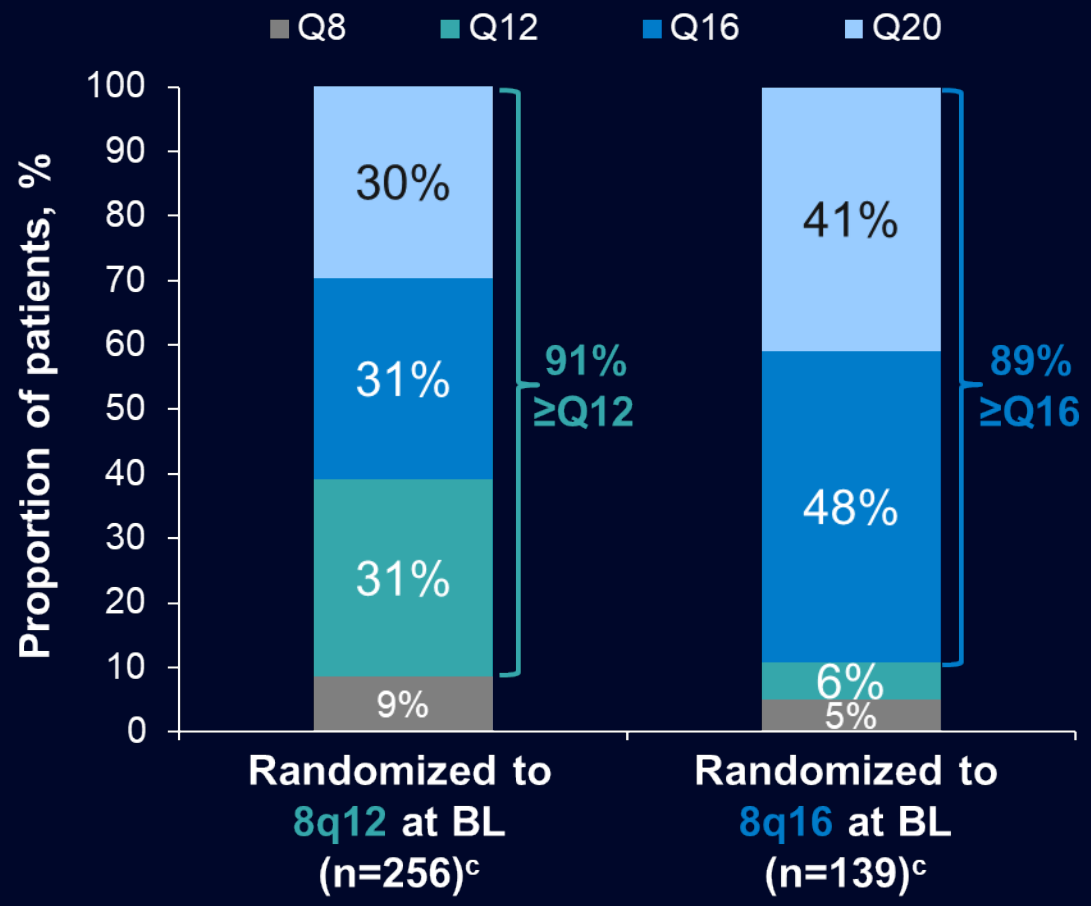
[a]Patients met DRM criteria for dosing interval shortening at some point through Week 96. [b]Patients completing Week 96.
Values may not add up to 100% due to rounding.

# Large Proportion of Patients Qualified for Interval Extension in Year 2[a]

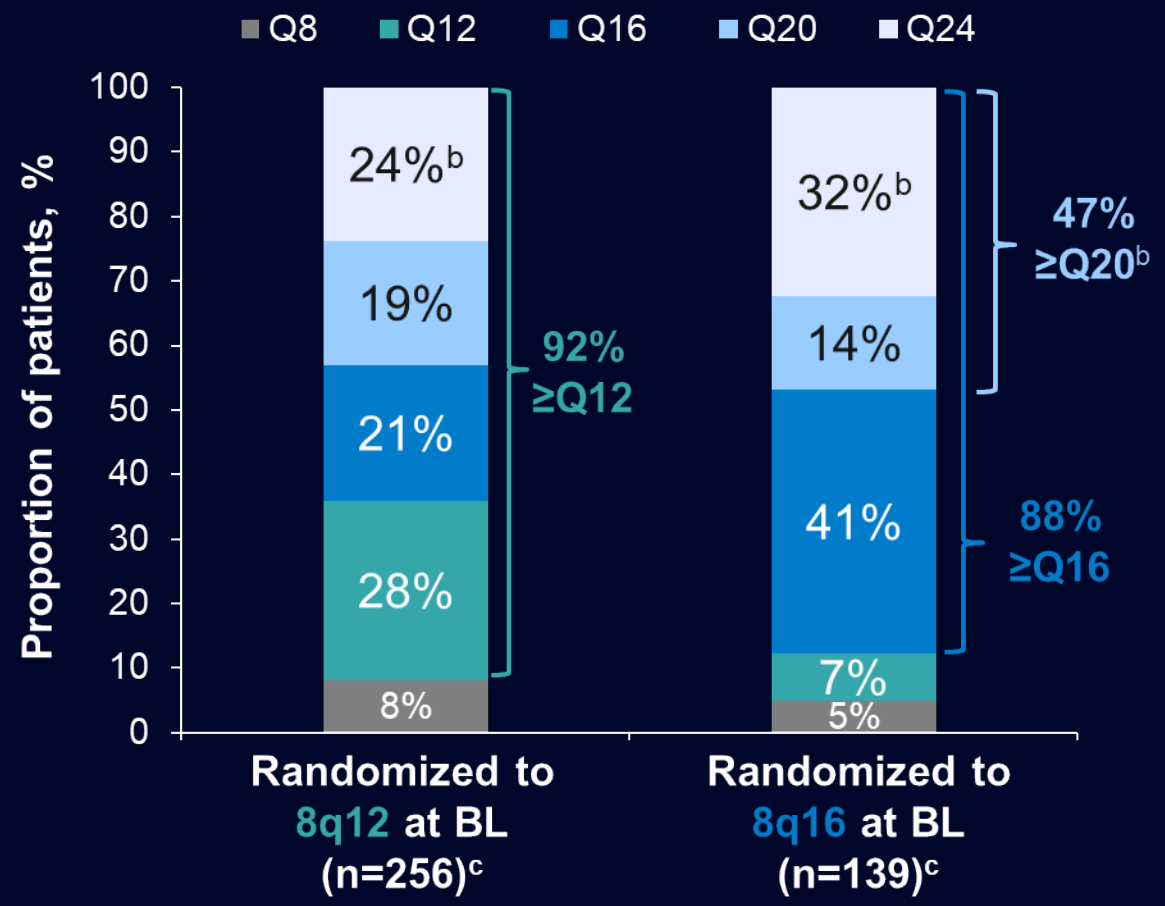
photon

DME

## Last Completed




## Last Assigned

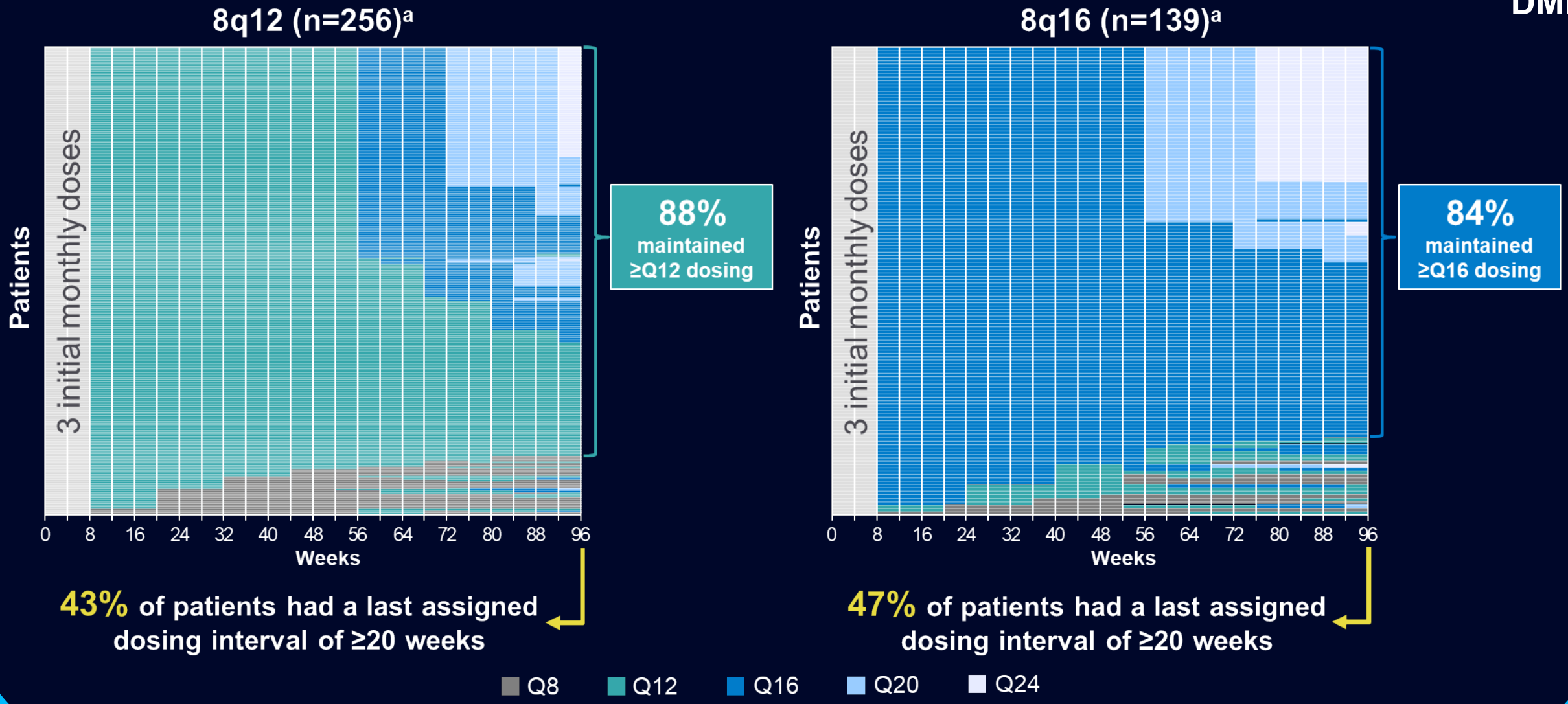



[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 and CRT <300 µm (or <320 µm on Spectralis). [b]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within the 96-week study period. [c]Patients completing Week 96.
Values may not add up to 100% due to rounding.

# Dosing Interval for Majority of 8 mg Patients Was Maintained or Extended Through Week 96

photon

DME

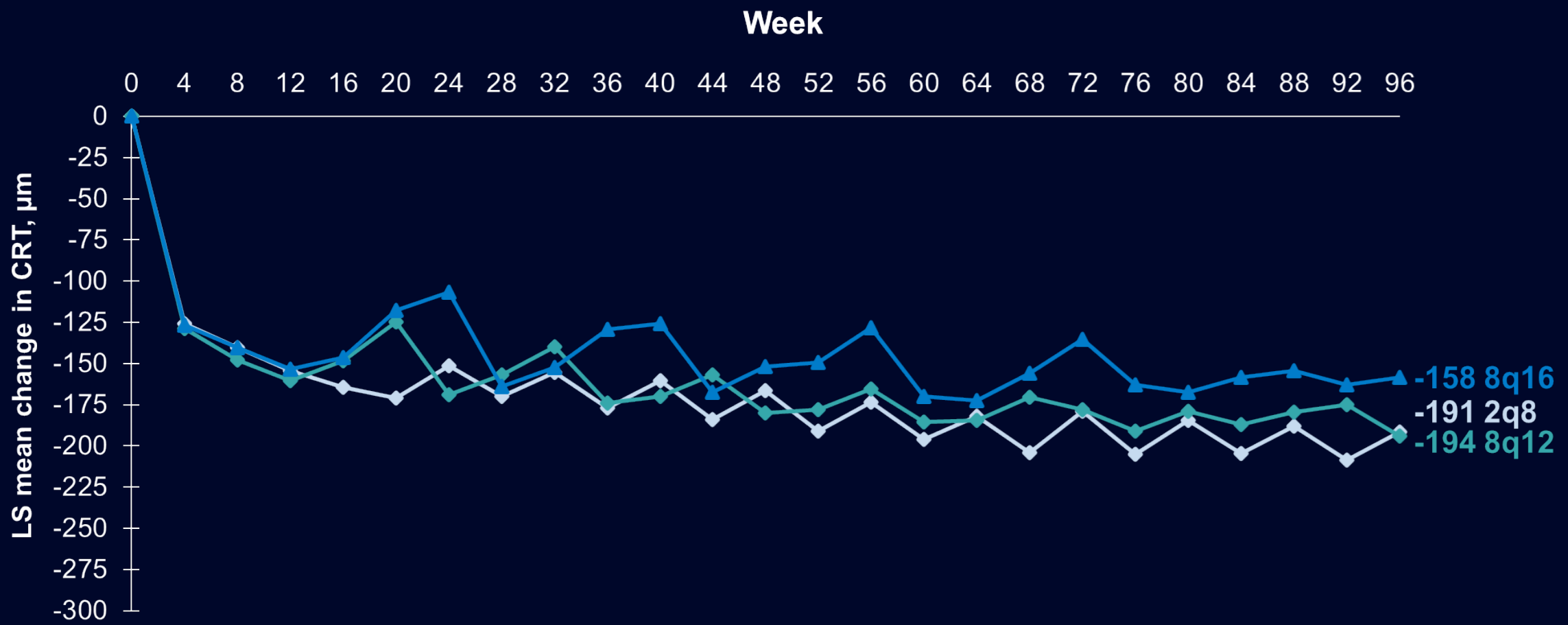



[a]Patients completing Week 96.

# Mean Change in Central Retinal Thickness

photon

DME




LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).
LS mean values were generated using MMRM, with baseline CRT as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit.

# Safety Through Week 96

photon

DME

| | 2q8 | 8q12 | 8q16 | All 8 mg |
|---|---|---|---|---|
| N (SAF) | 167 | 328 | 163 | 491 |
| **Ocular safety** | | | | |
| Patients with ≥1 ocular AE (%)[a] | 37.1% | 43.9% | 45.4% | 44.4% |
| Patients with ≥1 IOI AE (%)[a] | 1.2% | 1.5% | 0.6% | 1.2% |
| Patients with IOP ≥35 mmHg pre- or post-injection (%)[b] | 1.2% | 0.6% | 0 | 0.4% |
| **Non-ocular safety** | | | | |
| APTC events (%)[a] | 7.2% | 6.7% | 6.7% | 6.7% |
| Hypertension events (%)[a] | 16.2% | 15.5% | 20.9% | 17.3% |
| Non-ocular SAEs (%)[a] | 25.1% | 22.9% | 23.9% | 23.2% |
| Deaths (%)[c] | 5.4% | 5.5% | 3.1% | 4.7% |

- Ocular AEs occurring in ≥5% of patients in any treatment group were cataract, vitreous floaters, and conjunctival hemorrhage
- No cases of ischemic optic neuropathy, retinal vasculitis, or occlusive retinitis were reported through Week 96
- Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 96 in any treatment group

[a]Treatment emergent. [b]IOP was measured in the study eye. [c]All events.
AE, adverse event; APTC, Anti-Platelet Trialists' Collaboration; IOI, intraocular inflammation; SAE, serious adverse event.

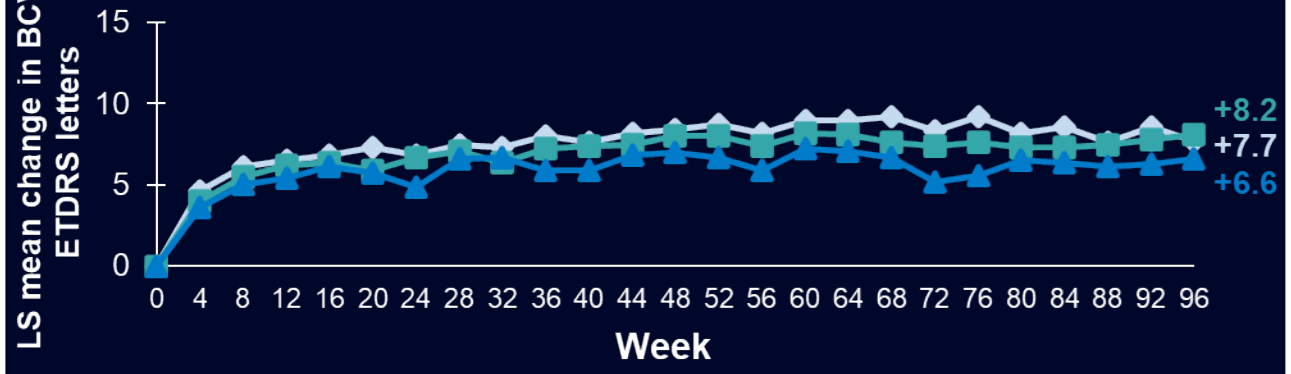
# PHOTON: 96-week Results

photon

DME

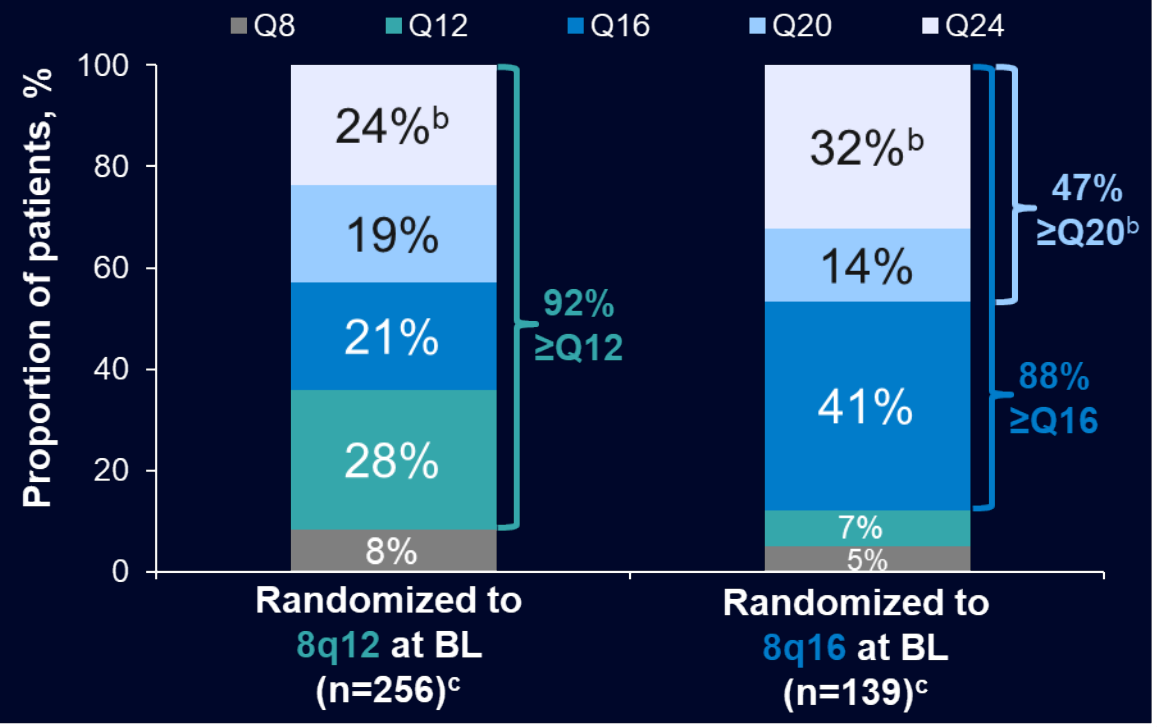
- 8q12 and 8q16 groups achieved similar BCVA gains compared to 2q8 at Week 96, with up to 6 fewer injections
- Through Week 96, 88% of 8q12 patients and 84% of 8q16 patients maintained ≥12- and ≥16-week dosing intervals, respectively
  - At Week 96, 43% of 8q12 patients and 47% of 8q16 patients had a last assigned dosing interval of ≥20 weeks
- Safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks

## Mean Change From Baseline in BCVA[a]



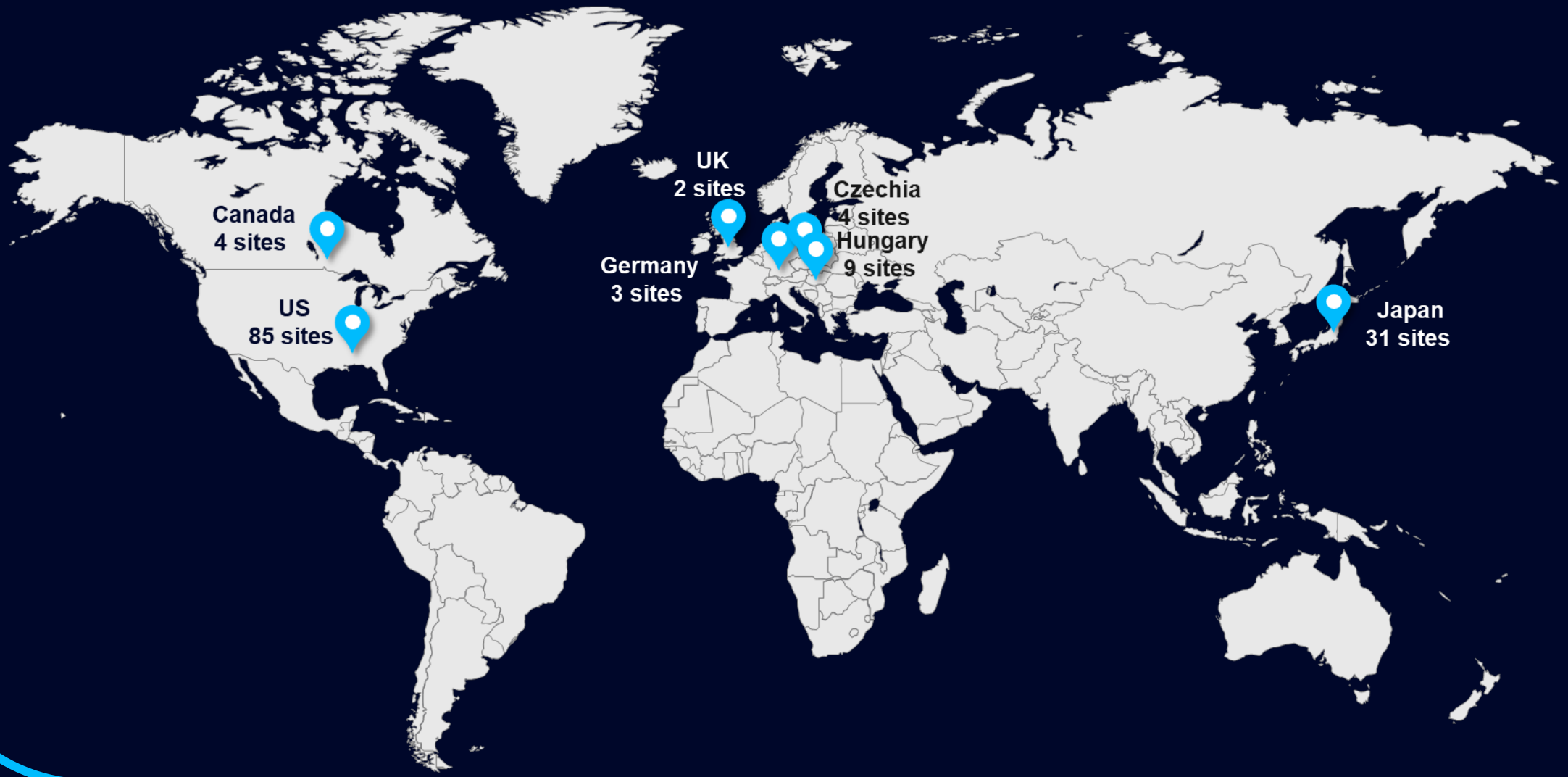

| | LS mean change from BL at Week 96 (MMRM) | Diff. in LS means vs. 2q8 | 2-sided 95% CI | 1-sided test for NI at 4-letter margin |
|---|---|---|---|---|
| 2q8 | 7.7 | | | |
| 8q12 | 8.2 | +0.45 | -1.55, 2.45 | p < 0.0001 (nominal) |
| 8q16 | 6.6 | -1.11 | -3.27, 1.05 | p = 0.0044 (nominal) |

## Last Assigned Dosing Interval at Week 96




[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline). LS mean values were generated using MMRM, with baseline BCVA as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16) and stratification variables (geographic region [Japan vs rest of the world], baseline CRT [<400 µm vs ≥400 µm], prior treatment for DME [yes vs no]) as fixed factors, and interaction terms for baseline and visit and for treatment and visit. [b]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria but there was not sufficient time to complete the interval within the 96-week study period. [c]Patients completing Week 96.

# Thank you to all co-investigators and patients who participated in the PHOTON trial

photon

DME