# Intravitreal Aflibercept 8 mg Injection: Results From the PULSAR and PHOTON Trials

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# Disclosures

- **SS**: Receives funding/fees from Allergan, Apellis, Bayer, Biogen, Boehringer Ingelheim, EyeBiotech, Novartis, Optos, and 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.
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- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
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# 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 endpoints**
Mean change in BCVA from baseline to Week 60[a]
Proportion of patients without IRF and SRF in the center subfield at Week 16

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

[a]For European Medicines Agency/Pharmaceuticals and Medical Devices Agency regulatory approval only.
**2q8**, aflibercept 2 mg every 8 weeks; **8q12,** aflibercept 8 mg every 12 weeks; **8q16**, aflibercept 8 mg every 16 weeks; **BCVA**, best-corrected visual acuity; **IRF**, intraretinal fluid; **nAMD**, neovascular age-related macular degeneration; **SRF**, subretinal fluid.

# PULSAR: Dosing Schedule and Regimen Modification

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 | Wk 52 | Wk 56 | Wk 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2q8 | X | X | X | | X | o | X | o | X | o | X | o | X | o | X | o |
| 8q12 | X | X | X | | o | X | o | o | X | o | o | X | o | o | X | o |
| 8q16 | X | X | X | | o | o | X | o | o | o | X | o | o | o | X | o |

## DRM: Interval Shortening During Years 1 and 2

**Criteria for interval shortening**

- >5-letter loss in BCVA compared with Week 12 due to persistent or worsening nAMD **AND**
- >25 µm increase in CST compared with Week 12, **OR** new-onset foveal neovascularization, **OR** foveal hemorrhage

**Patients who met the DRM criteria could have their intervals shortened at:**

- **Weeks 16 and 20:** Patients on 8q12 and 8q16 to Q8
- **Week 24:** Patients on 8q16 to Q12
- **Weeks 32 and 44 for 8q12 and Week 40 for 8q16:** Intervals shortened by 4 weeks
- **Week 52 onward:** Patients on 8q12 and 8q16 will have dosing intervals shortened in 4-week intervals (to a minimum of Q8)

## DRM: Interval Extension During Year 2

**Criteria for interval extension**

- <5-letter loss in BCVA compared with Week 12 **AND**
- No fluid at the central subfield on OCT **AND**
- No new foveal hemorrhage or foveal neovascularization

**Patients who met the DRM criteria were able to extend at:**

- **Week 52 onward:** Patients on 8q12 and 8q16 will have dosinupdg intervals extended by 4-week increments. Patients on 8q16 can be extended to a maximum of Q20 and Q24 through Weeks 60 and 96

Stippled boxes = initial treatment phase; X = active injection; o = sham injection. Note: Table does not reflect all dosing options once a patient's dosing interval is shortened or extended.
**CST**, central subfield thickness; **DRM**, dose regimen modification; **OCT**, optical coherence tomography; **Q8**, every 8 weeks; **Q12,** every 12 weeks; **Q20**, every 20 weeks; **Q24**, every 24 weeks; **Wk**, week.

# Patient Disposition and Baseline Characteristics

pulsar nAMD

| | 2q8 | 8q12 | 8q16 | Total |
|---|---|---|---|---|
| **Randomized**, n | 337 | 336 | 338 | 1011 |
| **Patient disposition** | | | | |
| Completed Week 48, % | 91.7% | 94.0% | 92.3% | 92.7% |
| **Baseline characteristics** | | | | |
| 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 |
| BCVA, ETDRS letters | 58.9 (14.0) | 59.9 (13.4) | 60.0 (12.4) | 59.6 (13.3) |
| CST, µm | 367 (134) | 370 (124) | 371 (133) | 369 (130) |
| Total lesion area, $mm^2$ | 6.9 (5.4) | 6.4 (5.1) | 6.9 (5.7) | 6.7 (5.4) |

FAS. Data are mean (SD) unless stated otherwise. [a]The proportion of patients who completed and discontinued does not add up to 100% due to missing information from the study sites.
**ETDRS**, Early Treatment of Diabetic Retinopathy Study; **FAS**, full analysis set; **SD**, standard deviation.

# BCVA Outcomes

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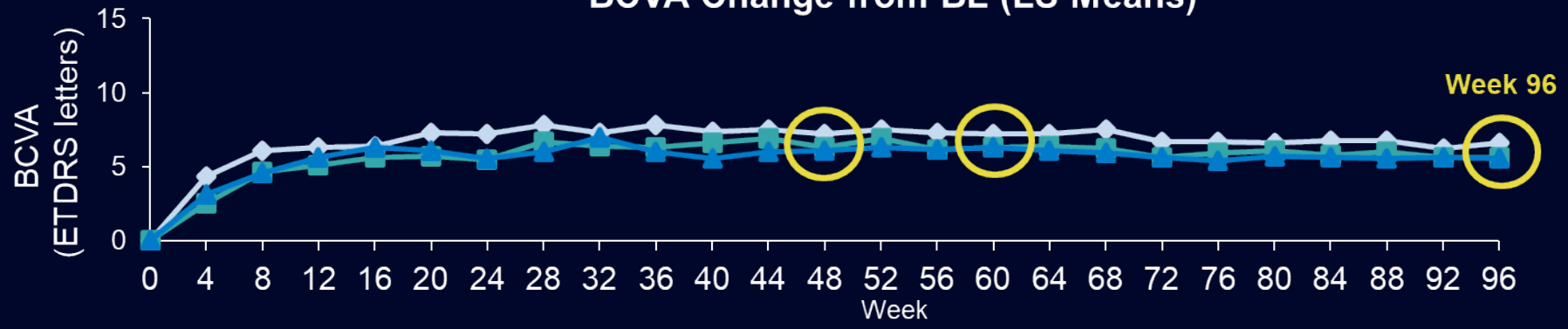
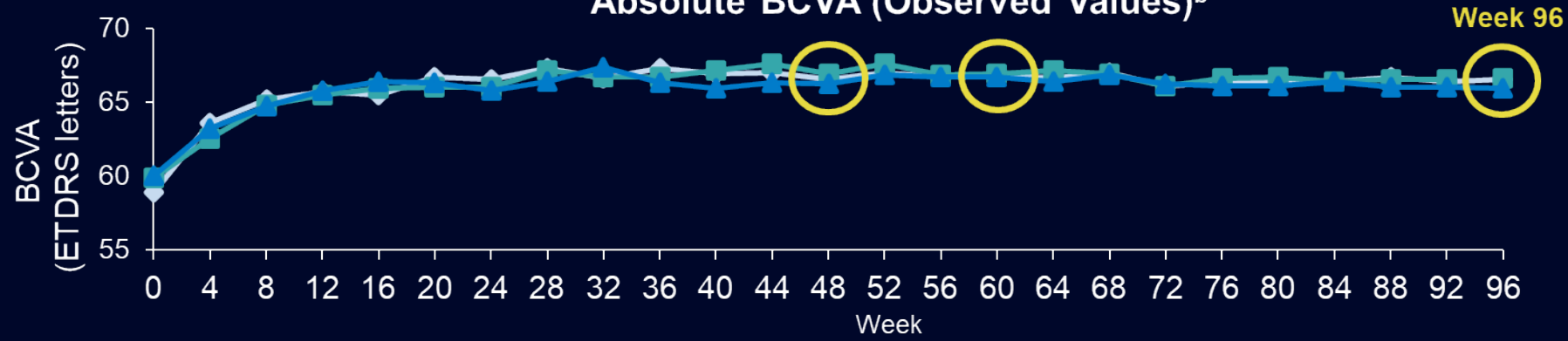
## BCVA Change from BL (LS Means)[a]




| | Week 48 | Week 60 | Week 96 |
|---|---|---|---|
| 2q8 | +7.0 | +7.2 | +6.6 |
| 8q12 | +6.1 | +6.4 | +5.6 |
| 8q16 | +5.9 | +6.3 | +5.5 |

## Absolute BCVA (Observed Values)[b]




| | Week 48 | Week 60 | Week 96 |
|---|---|---|---|
| 2q8 | 66.5 | 66.8 | 66.5 |
| 8q12 | 66.9 | 66.9 | 66.6 |
| 8q16 | 66.3 | 66.7 | 65.9 |

| | LS mean change from BL[a] at **Week 60** (MMRM) | Difference in LS means vs. 2q8 (95% CI) | One-sided test for non-inferiority at 4-letter margin | LS mean change from BL[a] at **Week 96** (MMRM) | Difference in LS means vs. 2q8 (95% CI) | One-sided test for non-inferiority at 4-letter margin |
|---|---|---|---|---|---|---|
| 2q8 | 7.2 | | | 6.6 | | |
| 8q12 | 6.4 | –0.86 (–2.57, 0.84) | p=0.0002 | 5.6 | –1.01 (–2.82, 0.80) | p=0.0006 (nominal) |
| 8q16 | 6.3 | –0.92 (–2.51, 0.66) | p<0.0001 | 5.5 | –1.08 (–2.87, 0.71) | p=0.0007 (nominal) |

[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). LS means were generated using MMRM, with baseline BCVA measurement as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16), visit, and stratification variables (geographic region [Japan vs. Rest of World] and BL BCVA [<60 vs. ≥60]) as fixed factors, and interaction terms for BL and visit and for treatment and visit. [b]Observed values (censoring data post-ICEs); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL).

**BL**, baseline; **CI**, confidence interval; **ICE**, intercurrent event; **LS**, least squares; **MMRM**, mixed model for repeated measures.

# Central Subfield Thickness

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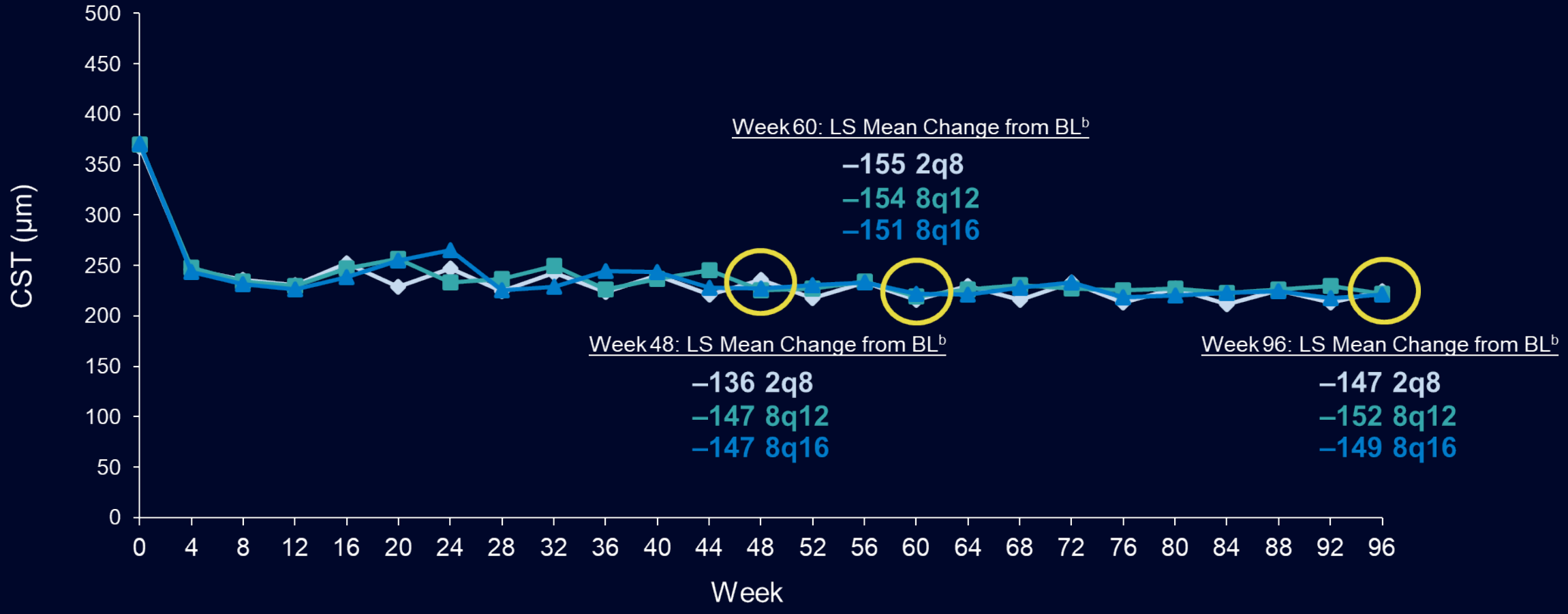
## Absolute CST (Observed Values)[a]

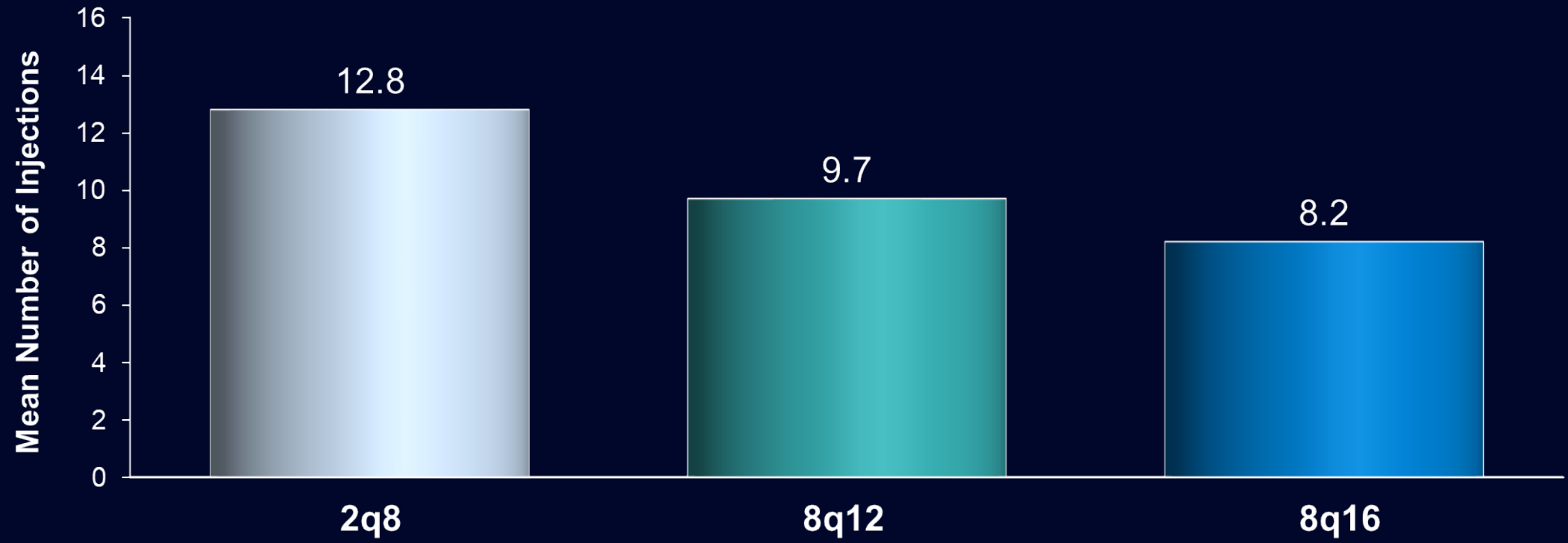



Change in CST was similar in the three treatment arms, with minimal fluctuations over the course of treatment

[a]Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [b]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). LS means were generated using MRMM, with BL CST measurement as a covariate, treatment group (aflibercept 2q8, 8q12, 8q16), visit and stratification variables (geographic region [Japan vs. Rest of World] and baseline BCVA [<60 vs. ≥60]) as fixed factors, and interaction terms for BL and visit and for treatment and visit.

# Mean Number of Injections through Week 96

pulsar
nAMD




Patients completing Week 96; 2q8 n=291; 8q12 n=292; 8q16 n=583.

# Last Assigned Dosing Interval at Week 96[a]

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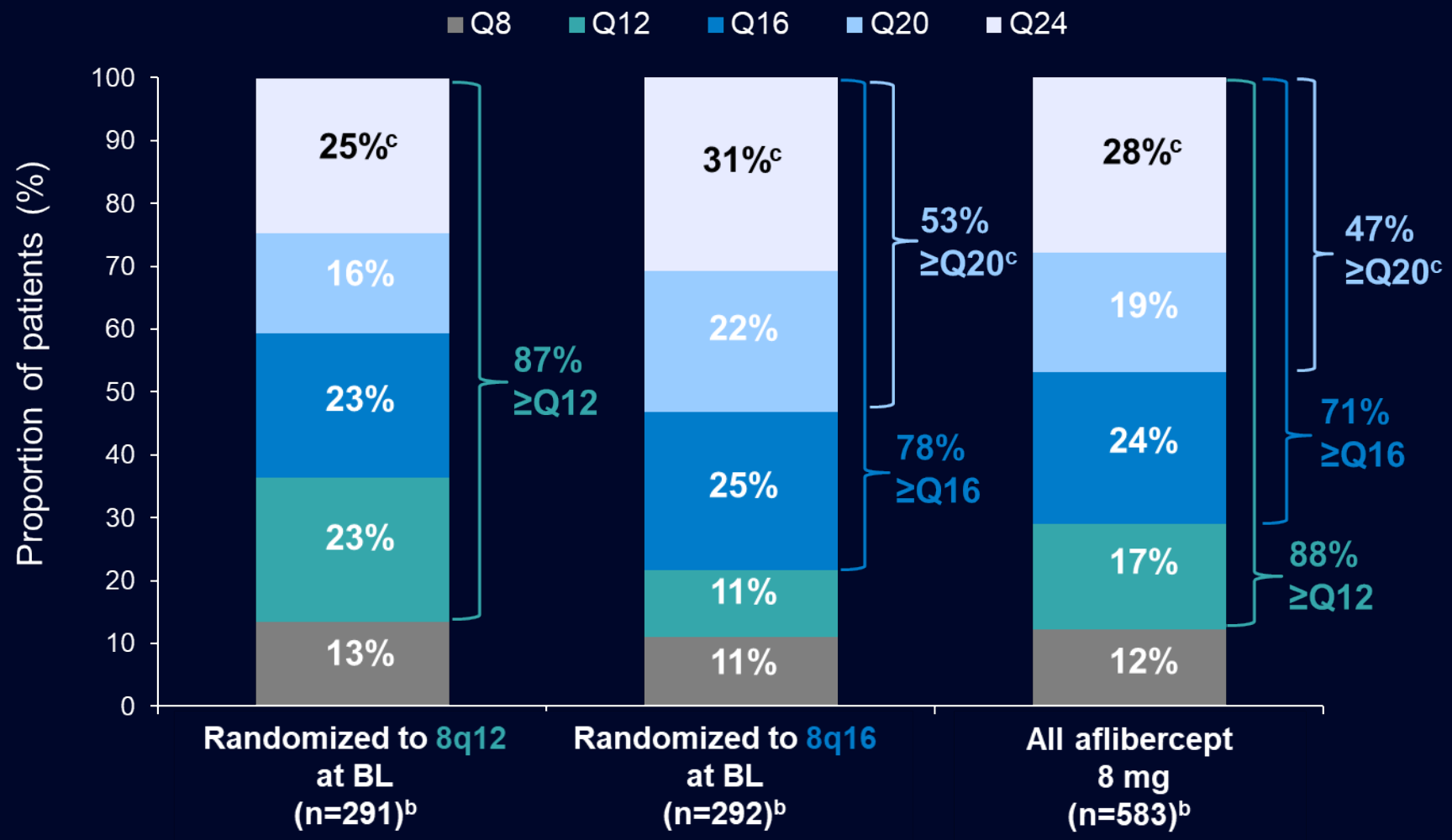



[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 **AND** no fluid at the center subfield **AND** no new foveal hemorrhage or neovascularization. [b]Patients completing Week 96. [c]Patients were assigned to 24-week dosing intervals if they continued to meet extension criteria, but did not have enough time to complete the interval within the 96-week study period. Values may not add up to 100% due to rounding.

# Safety Through Week 60

pulsar nAMD

| | 2q8 | 8q12 | 8q16 | All 8 mg |
|---|---|---|---|---|
| N (SAF) | 336 | 335 | 338 | 673 |
| **Ocular safety** | | | | |
| Patients with ≥1 ocular TEAE[a] | 45.2% | 42.4% | 42.3% | 42.3% |
| Patients with ≥1 IOI TEAE | 1.2% | 1.2% | 0.3% | 0.7% |
| Patients with IOP ≥35 mmHg pre- or post-injection | 0.3% | 0.9% | 0.3% | 0.6% |
| **Non-ocular safety** | | | | |
| APTC events[b] | 2.4% | 0.3% | 0.6% | 0.4% |
| Hypertension events[b] | 4.8% | 6.9% | 6.5% | 6.7% |
| Non-ocular SAEs[b] | 15.8% | 12.2% | 12.1% | 12.2% |
| Deaths[c] | 1.5% | 0.9% | 0.6% | 0.7% |

- Ocular TEAEs occurring in ≥3% of patients in any treatment group were cataract, IOP increased,[d] SRF, retinal hemorrhage, visual acuity reduced, and vitreous floaters
- The safety profile of aflibercept 8 mg at Week 96 is comparable to that at Week 60, and also with aflibercept 2 mg

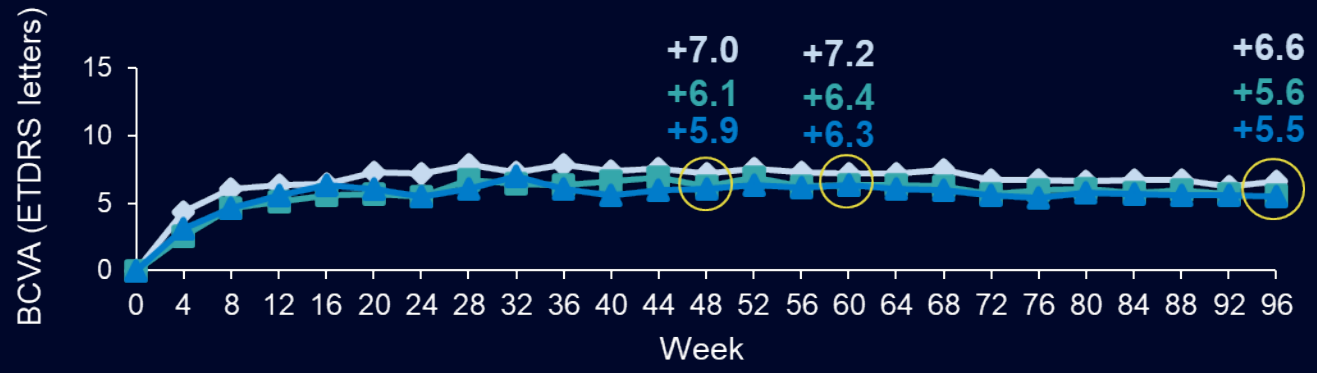
[a]In the study eye. [b]Treatment emergent. [c]All events. [d]Defined by preferred terms 'intraocular pressure increased' and 'ocular hypertension'.
**APTC**, Anti-Platelet Trialists' Collaboration; **IOI**, intraocular inflammation; **IOP**, intraocular pressure; **SAE**, serious adverse event; **SAF**, safety analysis set; **TEAE**, treatment-emergent adverse event.

# PULSAR: 96-Week Results

pulsar nAMD

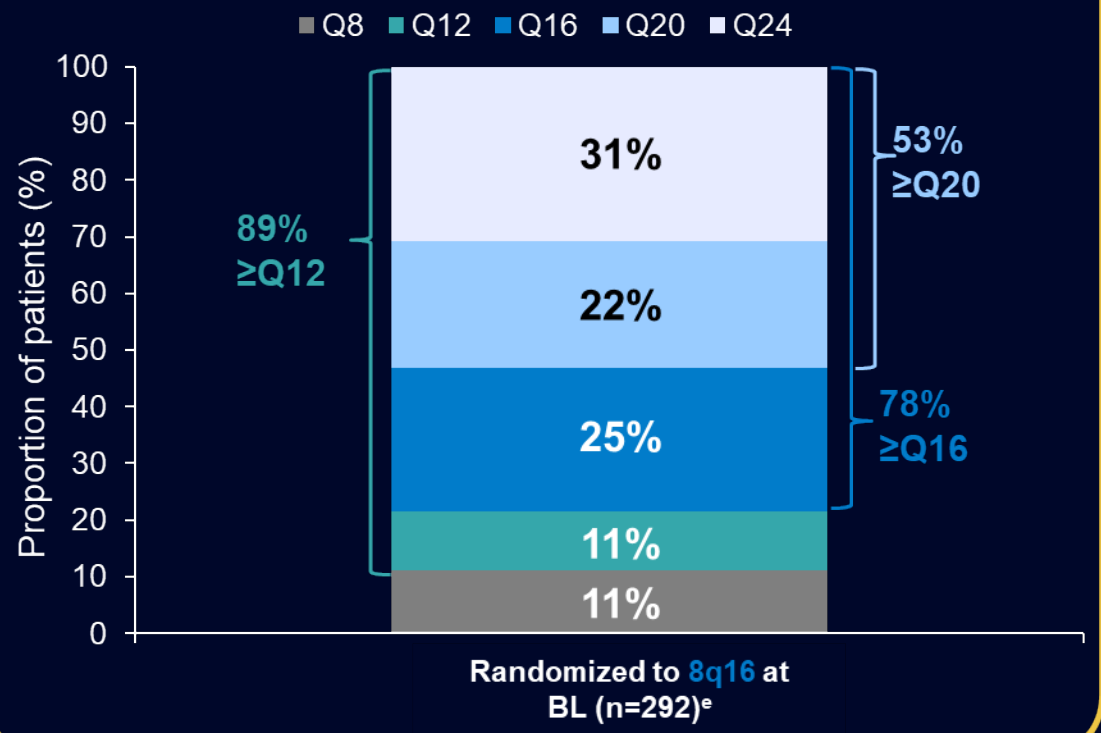
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic improvement in PULSAR for aflibercept 8 mg was generally maintained over time at Week 96
- At Week 96 respectively, **89%** of patients receiving aflibercept 8q16 achieved ≥Q12 dosing intervals and **78%** achieved ≥Q16 dosing intervals
- The safety profile of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks

## BCVA Change from BL (LS Means) through Week 96[a]




## Absolute CST (Observed Values) through Week 96[b]


## Aflibercept 8q16: Last Assigned Dosing Interval at Week 96




[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [b]Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [e]Patients completing Week 96. Values may not add up to 100% due to rounding.

# 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 CST ≥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.
DME, diabetic macular edema.

# PHOTON: Dosing Schedule and Dose Regimen Modification

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DME

Primary Endpoint

| | 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 |

| | 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 CST 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**
  - CST <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

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

# Patient Disposition and Baseline Characteristics

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DME

| | 2q8 | 8q12 | 8q16 | Total |
|---|---|---|---|---|
| N (FAS/SAF) | 167 | 328 | 163 | 658 |
| **Patient disposition** | | | | |
| Completed Week 48, % | 94.0% | 91.2% | 95.1% | 92.9% |
| **Baseline characteristics** | | | | |
| 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% |
| 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) |
| 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 |
| CST, 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.
BMI, body mass index.

# Mean Change in BCVA Through Week 48

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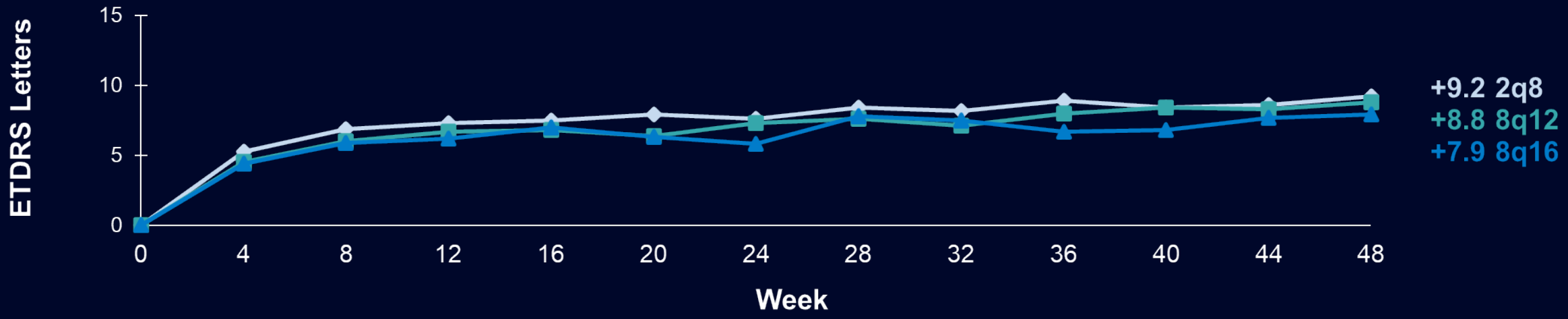
DME

## BCVA Change From Baseline[a]




| | LS mean change from baseline[b] | Difference in LS means vs aflibercept 2q8 | Two-sided 95% CI | One-sided test for non-inferiority at four-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 |

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

# Mean Number of Injections Through Week 48

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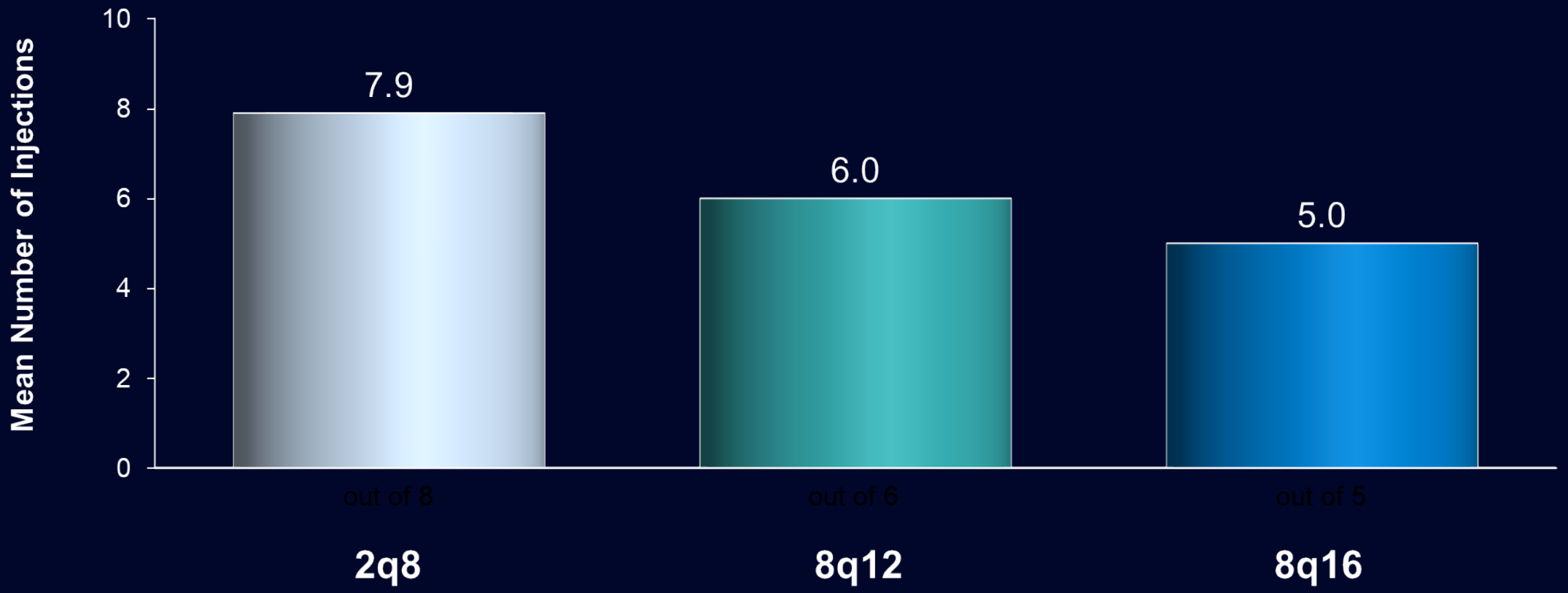
DME

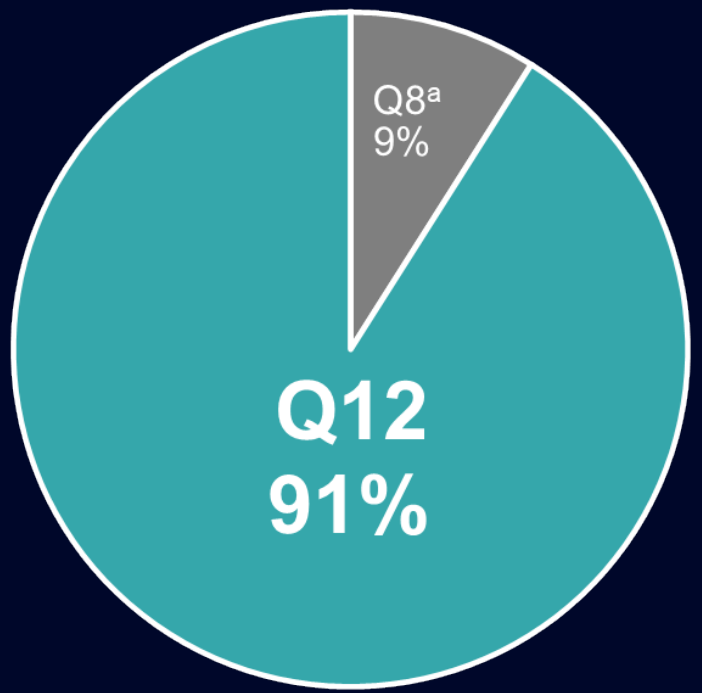



Patients completing Week 48: 2q8 n=157; 8q12 n=300; 8q16 n=156.

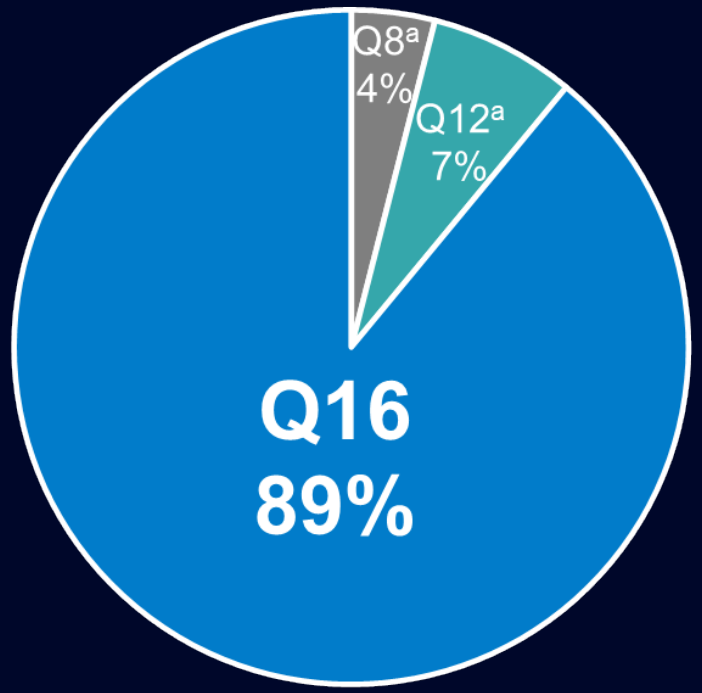
# Large Majority of Patients Receiving Aflibercept 8 mg Maintained Randomized Intervals Through Week 48

DME

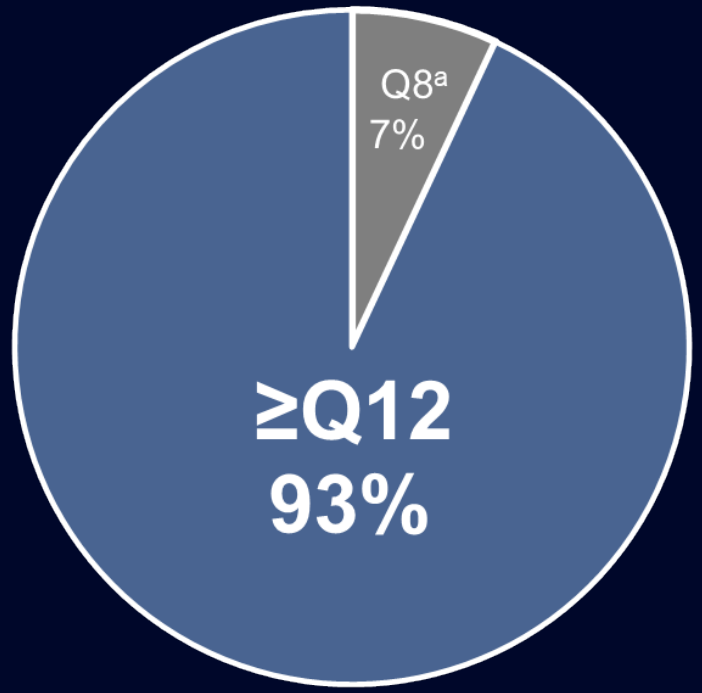
**93%** of 8 mg patients maintained dosing intervals ≥12 weeks




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




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




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

[a]Patients met DRM criteria for dosing interval shortening at some point through Week 48[6].
[b]Patients completing Week 48.
Values may not add up to 100% due to rounding.

# Safety Through Week 48

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DME

| | 2q8 | 8q12 | 8q16 | All 8 mg |
|---|---|---|---|---|
| N (SAF) | 167 | 328 | 163 | 491 |
| **Ocular safety** | | | | |
| Patients with ≥1 ocular AE[a] | 27.5% | 31.7% | 29.4% | 31.0% |
| Patients with ≥1 IOI TEAE | 0.6% | 1.2% | 0 | 0.8% |
| Patients with IOP ≥35 mmHg pre- or post-injection | 1.2% | 0.3% | 0 | 0.2% |
| **Non-ocular safety** | | | | |
| APTC events[b] | 3.6% | 2.4% | 4.3% | 3.1% |
| Hypertension events[b] | 12.0% | 11.0% | 14.1% | 12.0% |
| Non-ocular SAEs[b] | 15.6% | 15.9% | 13.5% | 15.1% |
| Deaths[c] | 2.4% | 2.7% | 1.8% | 2.4% |

- No cases of endophthalmitis, occlusive retinal vasculitis, or ischemic optic neuropathy were reported through Week 48
- Mean changes from baseline in pre-dose IOP did not exceed ±1 mmHg at any timepoint through Week 48

Reported IOI terms: iridocyclitis, iritis, uveitis, vitreal cells, vitritis
[a]In the study eye. [b]Treatment emergent. [c]All events.

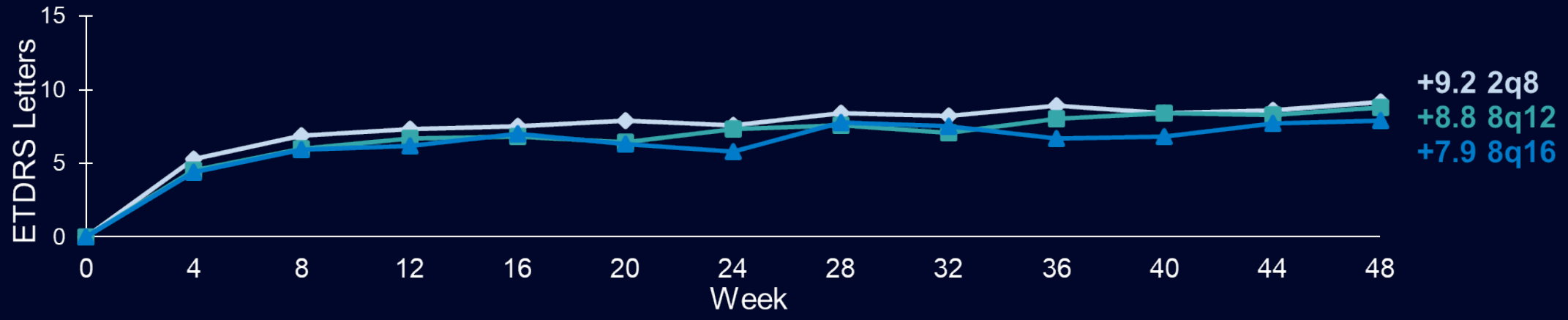
# PHOTON: 48-Week Results

photon

DME

- Aflibercept 8q12 and 8q16 groups had non-inferior BCVA compared to aflibercept 2q8 at Week 48
- The safety of aflibercept 8 mg was comparable to that of aflibercept 2 mg

## BCVA Change from Baseline[a]




| | LS mean change from baseline[b] | Difference in LS means vs aflibercept 2q8 | Two-sided 95% CI | One-sided test for non-inferiority at four-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 |

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