Intravitreal Aflibercept 8 mg Injection in Patients With Neovascular Age-Related Macular Degeneration: 60-Week and 96-Week Results from the Phase 3 PULSAR Trial

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Disclosures

- **PL**: Consultant for Aerie, Allergan, Apellis, Bausch + Lomb, Bayer, Biogen, Boehringer Ingelheim, I-Care, Genentech, Novartis, Ocular Therapeutix, Outlook Therapeutics, 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
- The 48-week 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; ARVO Annual Meeting, April 23–27, 2023; ASRS Annual Meeting, July 28–August 1, 2023
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PULSAR Study Design

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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

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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 dosing intervals extended by 4-week increments. Patients on 8q16 can be extended to a maximum of Q20 and Q24 through Weeks 60 and 96 respectively

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

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	2q8	8q12	8q16	Total
Randomized, n	337	336	338	1011
Patient disposition				
Completed Week 48, %	91.7	94.0	92.3	92.7
Completed Week 60,[a] %	90.5	92.6	91.4	91.5
Discontinued before Week 60, %	8.9	6.5	8.3	7.9
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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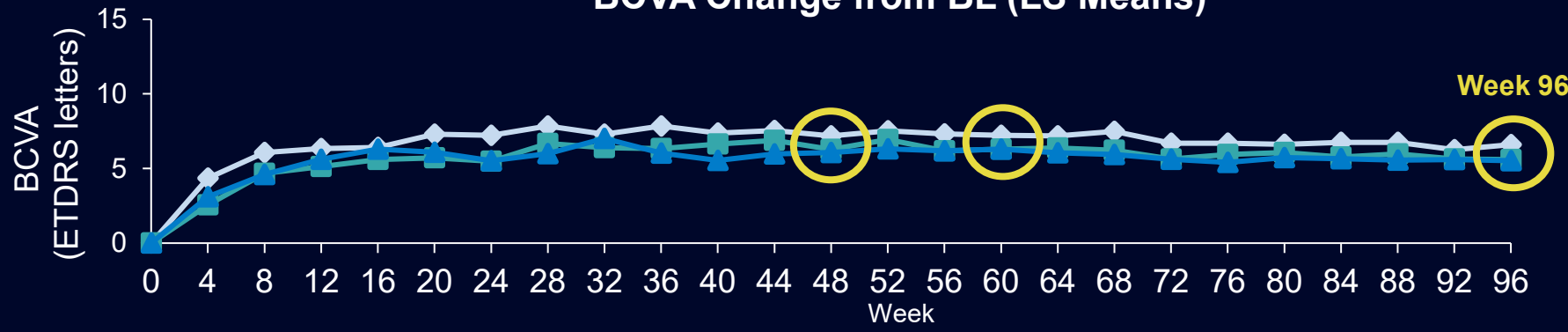
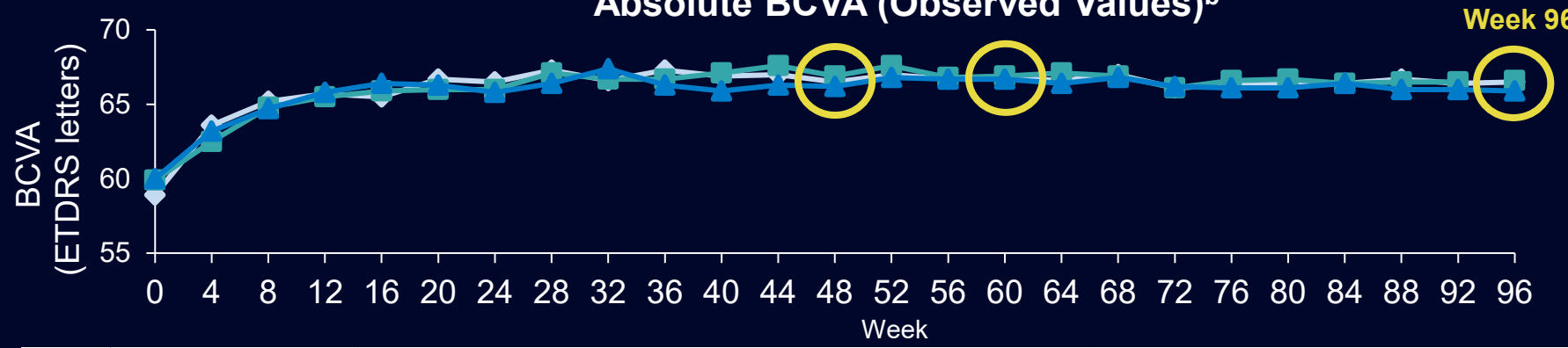
BCVA Change from BL (LS Means)[a]



	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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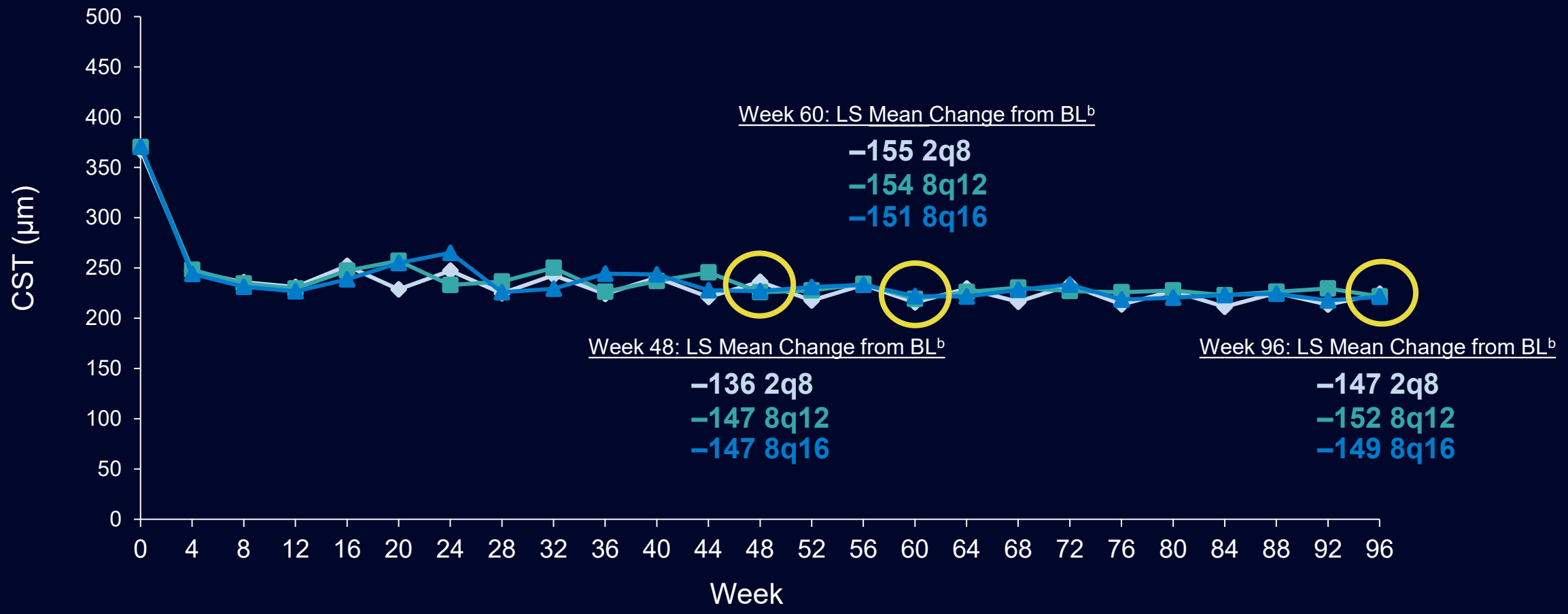
Absolute CST (Observed Values)[a]



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.

Last Assigned Dosing Interval at Week 60 and Week 96[a]

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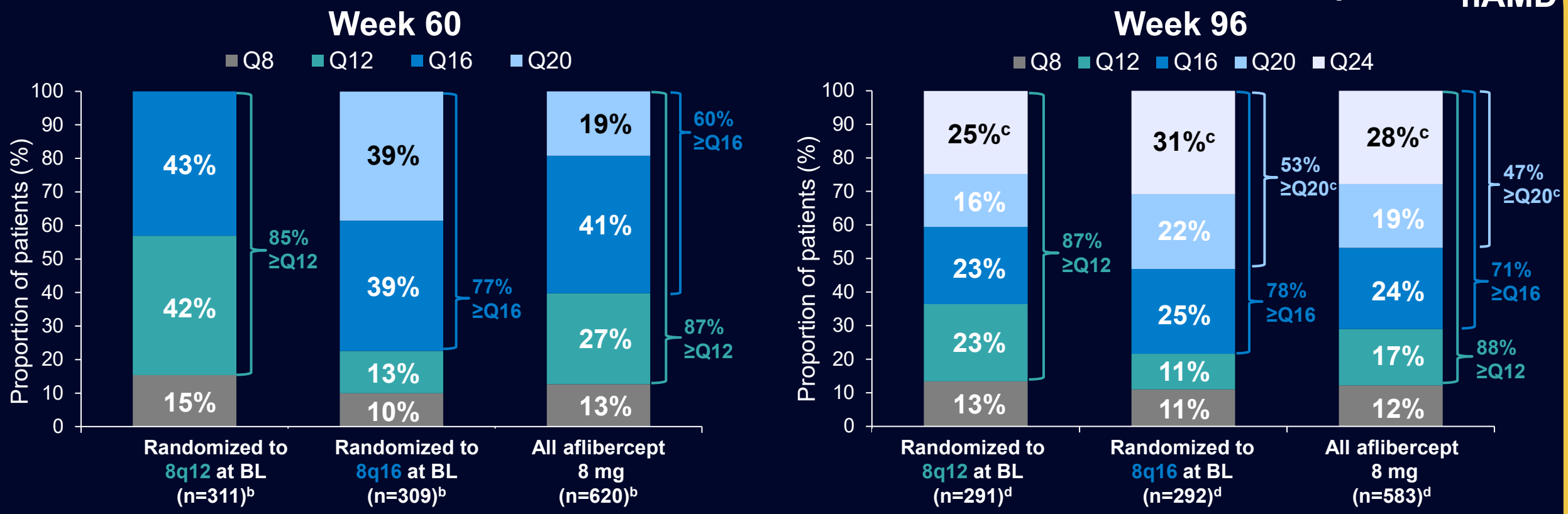

Mean number of active injections

	2q8	8q12	8q16
Week 48[e]	6.9	6.1	5.2
Week 60[b]	8.8	7.1	6.2
Week 96[d]	12.8	9.7	8.2

[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 60. [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. [d]Patients completing Week 96. [e]Patients completing Week 48. Values may not add up to 100% due to rounding. **Q16**, every 16 weeks.

Safety Through Week 60

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	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: 60- and 96-Week Results

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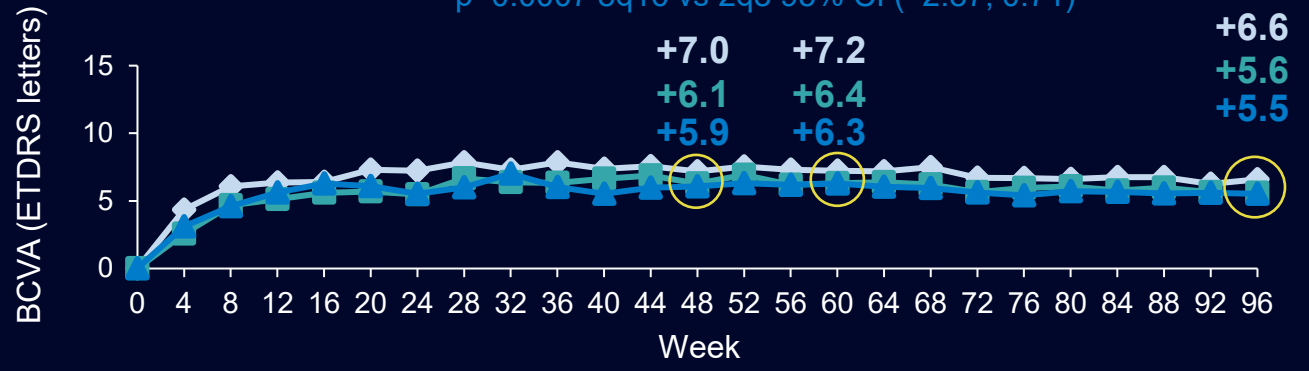
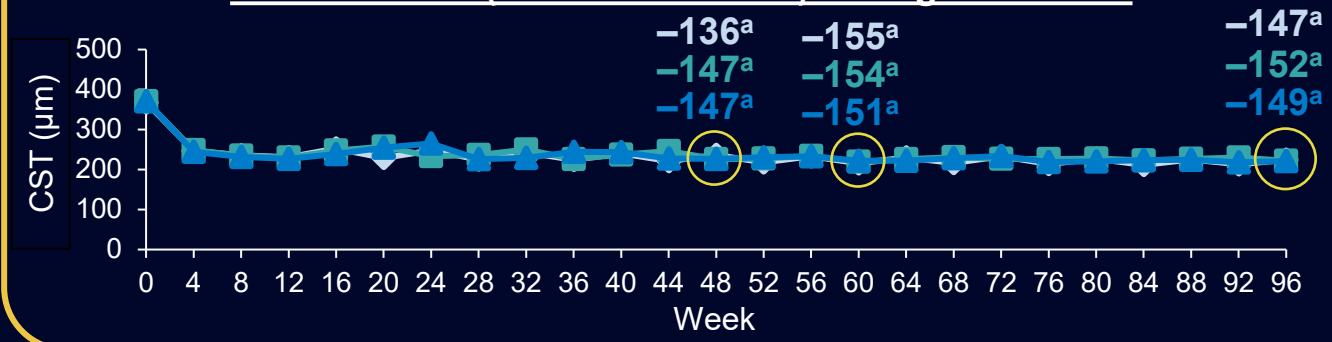
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Weeks 60 and 96
- Anatomic improvement in PULSAR for aflibercept 8 mg was generally maintained over time at Weeks 60 and 96
- At Weeks 60 and 96 respectively, **91% and 89%** of patients receiving aflibercept 8q16 achieved ≥Q12 dosing intervals and **77% and 78%** achieved ≥Q16 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]

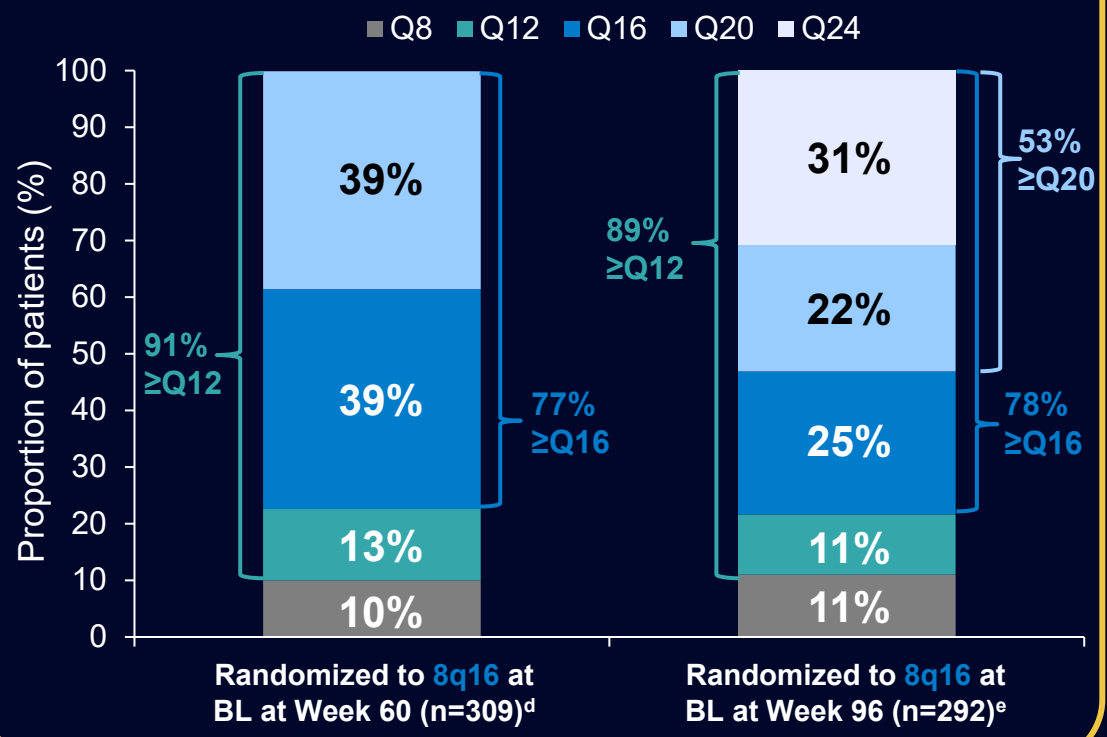
Week 60: p=0.0006 8q12 vs 2q8 95% CI (–2.28, 0.80)[b]
p=0.0007 8q16 vs 2q8 95% CI (–2.87, 0.71)[b]



Absolute CST (Observed Values) through Week 96[c]



Aflibercept 8q16: Last Assigned Dosing Interval at Week 60 and Week 96



[a]LS mean values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [b]p values for the one-sided non-inferiority test at a margin of four letters (based on adjusted means derived using an MMRM). [c]Observed values (censoring data post-ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [d]Patients completing Week 60. [e]Patients completing Week 96.
Values may not add up to 100% due to rounding.