Aflibercept 8 mg in Patients with Neovascular Age-Related Macular Degeneration: Phase 3 PULSAR Trial 96-Week Results

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Disclosures

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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)

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

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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YEAR 1	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[a]	X[a]	o	o	X[a]	o	o	X[a]	o
8q16	X	X	X		o[a]	o[a]	X[a]	o	o	o	X[a]	o	o

YEAR 2	Wk 52	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 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

- >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 DRM criteria had dosing intervals shortened to q8 at **Weeks 16** and **20** or by 4-week increments from **Week 24**
  - The minimum assigned dosing interval was q8

[b]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-onset foveal hemorrhage or foveal neovascularization

- Patients who met DRM criteria from **Weeks 52 through 96** had dosing intervals extended by 4-week increments
  - The maximum assigned dosing interval was q24

Figure does not reflect all dosing options once a patient's dosing interval is shortened or extended. Stippled boxes = initial treatment phase; X = active injection; o = sham injections.
CST, central subfield thickness; **DRM**, dose regimen modification; **OCT**, optical coherence tomography; **Wk**, week.

Patient Disposition, Baseline Demographics, and Disease Characteristics

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	2q8	8q12	8q16	Total
Randomized, n	337	337	338	1012
Treated, n	336	335	338	1009
Completed Week 48, n (%)[a]	309 (91.7)	316 (94.0)	312 (92.3)	937 (92.7)
Completed Week 96, n (%)[a]	286 (84.9)	291 (86.4)	292 (86.4)	869 (85.9)
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, %[b]				
Asian	24.7	22.1	22.8	23.2
White	74.1	76.4	76.9	75.8
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)
Lesion type, %				
Occult	58.3	60.3	55.9	58.2
Predominantly classic	21.1	21.2	19.8	20.7
Minimally classic	18.5	17.0	20.4	18.6

FAS. Data are mean (SD) unless stated otherwise. [a]The proportions of patients who completed do not add up to 100% due to missing information from the study sites. [b]The proportions of patients with race reported as Black/African American, "Multiple," or "Not reported" were 1.2%, 1.5%, 0.3%, and 1.0% for the 2q8, 8q12, 8q16, and Total groups, respectively.
ETDRS, Early Treatment of Diabetic Retinopathy Study; **FAS**, full analysis set; **SD**, standard deviation.

BCVA Outcomes

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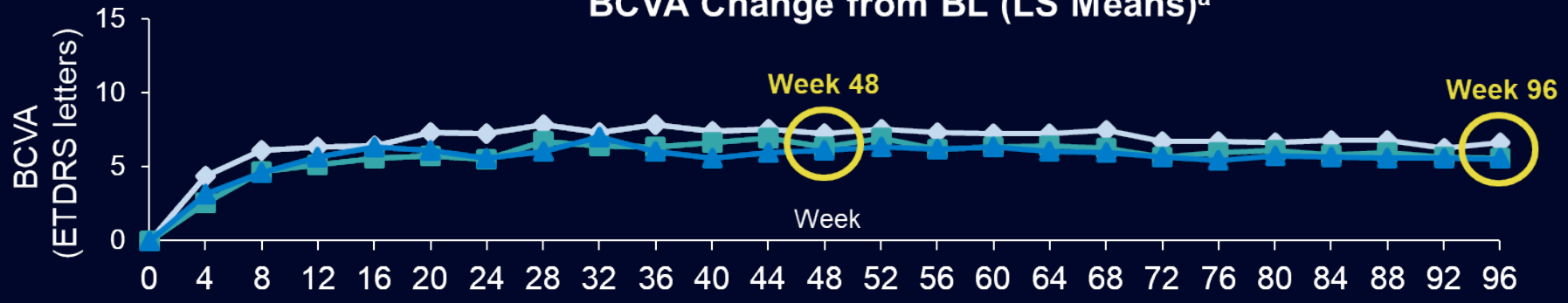
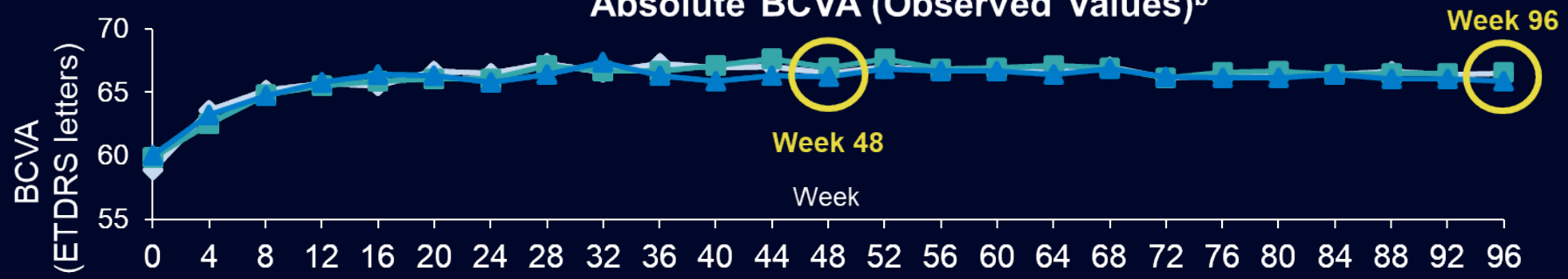
BCVA Change from BL (LS Means)[a]



	Week 48	Week 96
2q8	+7.0	+6.6
8q12	+6.1	+5.6
8q16	+5.9	+5.5

Absolute BCVA (Observed Values)[b]



	Week 48	Week 96
2q8	66.5	66.5
8q12	66.9	66.6
8q16	66.3	65.9

LS mean change from BL[a] at **Week 48** (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
7.0			6.6		
6.1	–0.97 (–2.87, 0.92)	p=0.0009	5.6	–1.01 (–2.82, 0.80)	p=0.0006 (nominal)
5.9	–1.14 (–2.97, 0.69)	p=0.0011	5.5	–1.08 (–2.87, 0.71)	p=0.0007 (nominal)

FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [a]LS mean values (data post-ICE were censored); LS means were generated using MMRM, with baseline BCVA measurement as a covariate, and 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 (data post-ICE were censored).

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

Central Subfield Thickness

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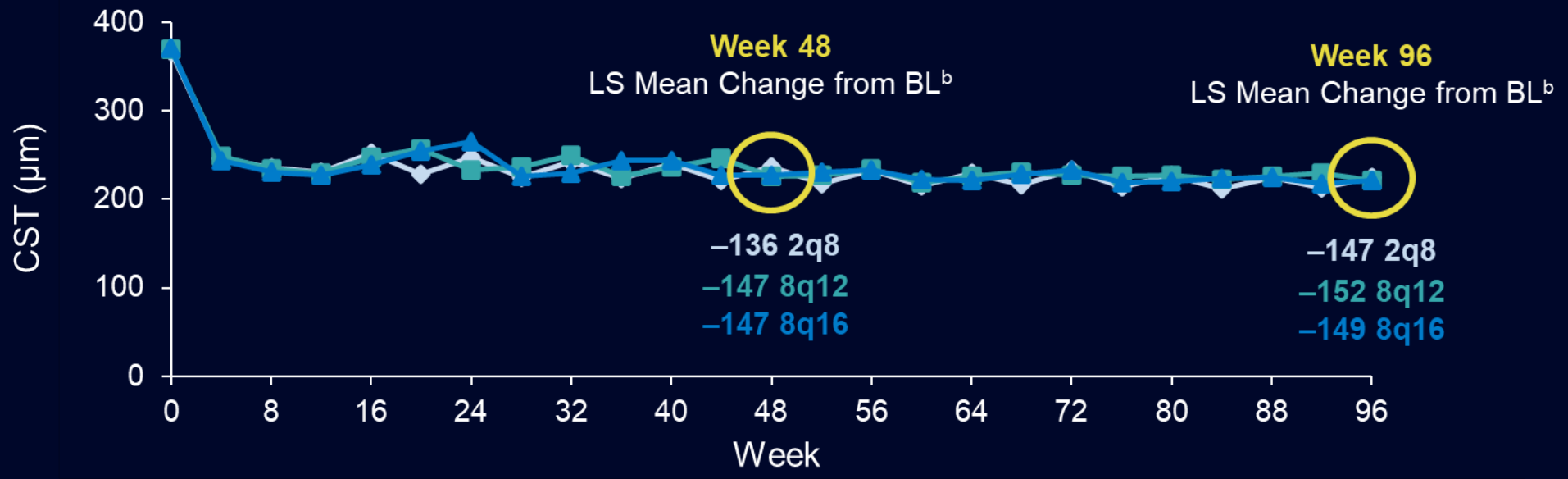
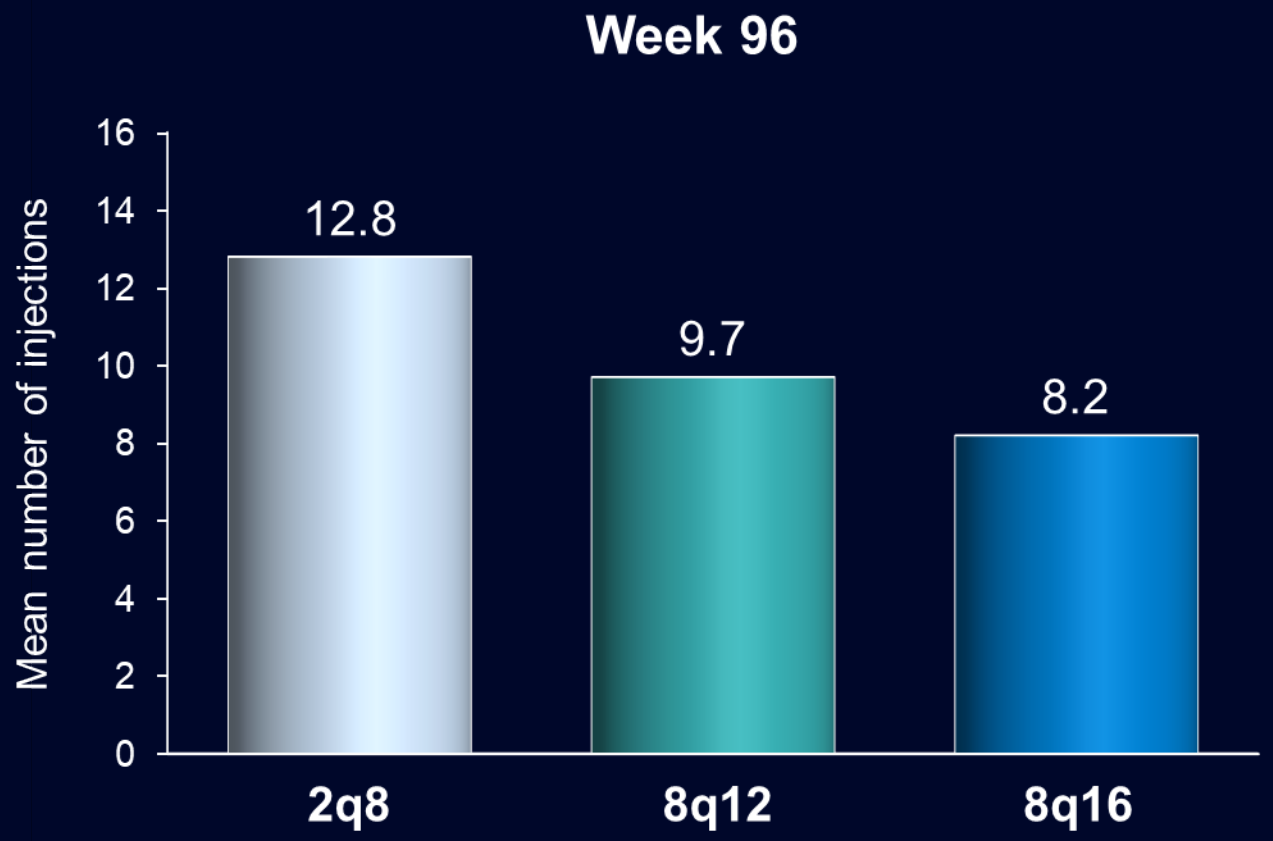
Absolute CST (Observed Values)[a]



FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [a]Observed values (data post-ICE were censored). [b]LS mean values (data post-ICE were censored); LS means were generated using MRMM, with BL CST measurement as a covariate, and 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

nAMD

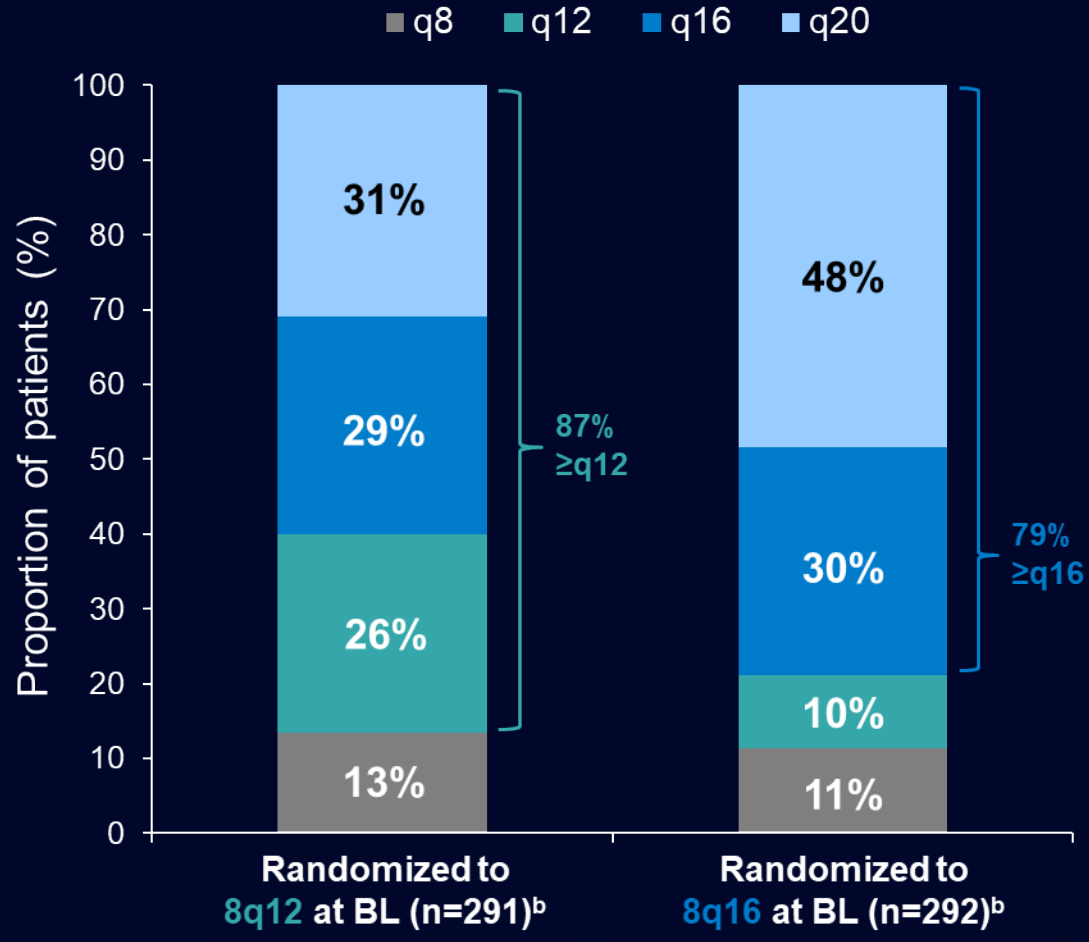


Data shown are for shown for patients who completed Week 48 (2q8 n=309, 8q12 n=316, 8q16 n=312) and Week 96 (2q8 n=286, 8q12 n=291, 8q16 n=292).

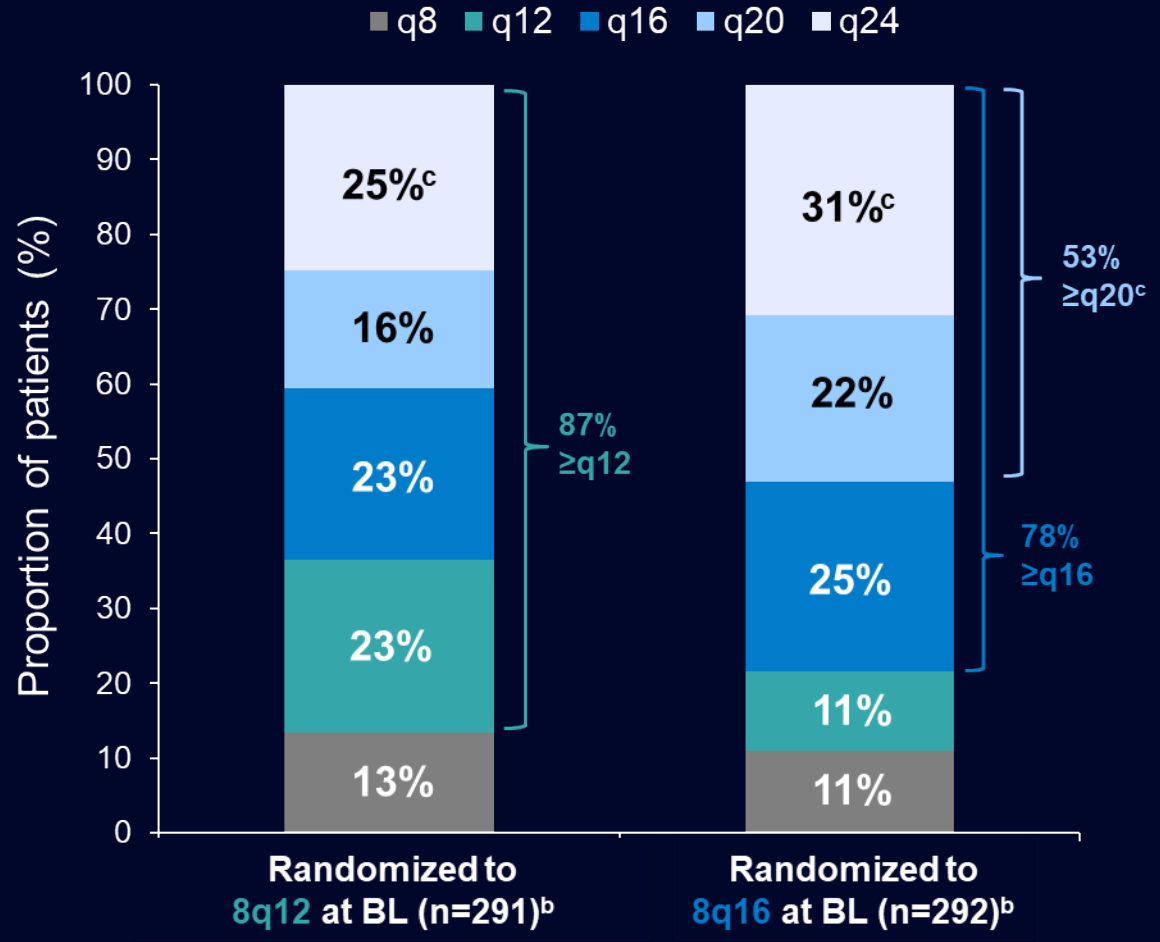
Dosing interval at Week 96[a]

nAMD

Last Completed



Last Assigned



[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 **AND** no fluid at the central 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.

Dosing Intervals ≥q20 were Assigned to ~50% of Patients on 8 mg by Week 96

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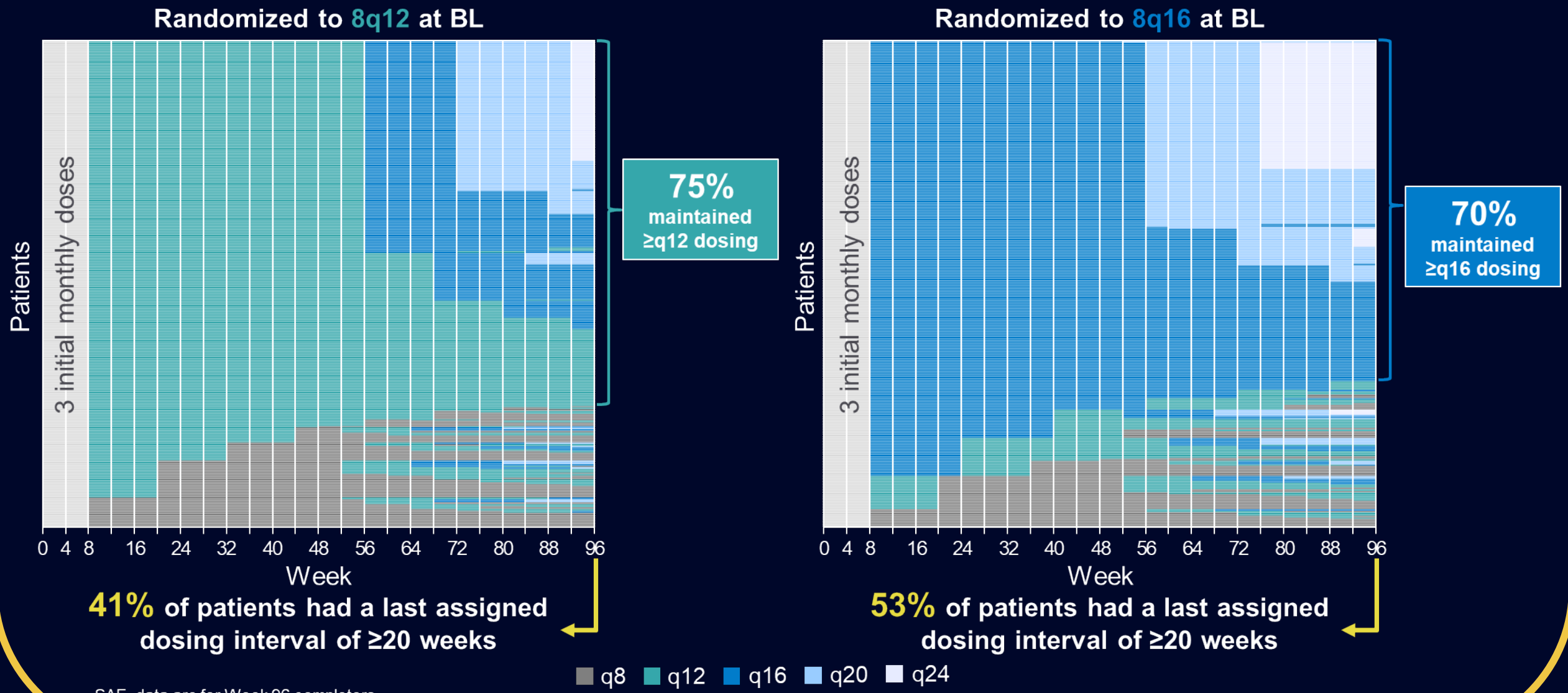

SAF, data are for Week 96 completers.
SAF, safety analysis set.

Most Frequent Ocular TEAEs Through Week 96 (Study Eye)

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Patients with ≥1 ocular TEAE, n (%)	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Patients with IOI, n (%)	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)

- Ocular TEAEs occurring in ≥5% of patients in any treatment group were cataract, retinal hemorrhage, visual acuity reduced, and vitreous floaters
- Reported IOI terms in the 8 mg arm were anterior chamber cell, chorioretinitis, iridocyclitis, iritis, uveitis, vitreal cells, and vitritis
- No cases of endophthalmitis, ischemic optic neuropathy, occlusive retinitis, or retinal vasculitis were reported for the 8 mg arm

IOI, intraocular inflammation; **TEAE**, treatment-emergent adverse event.

Non-Ocular Safety Through Week 96

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Patients, %				
APTC events[a]	3.3	1.5	2.1	1.8
Hypertension events[a]	8.0	8.1	8.3	8.2
Non-ocular serious TEAEs[a]	19.6	21.8	18.9	20.4
Deaths[b]	3.6	3.0	2.1	2.5

- The safety profile for aflibercept 8 mg was similar to that of aflibercept 2 mg

[a]Treatment-emergent events; [b]All events.
APTC, Anti-Platelet Trialists' Collaboration.

PULSAR: 96-Week Results

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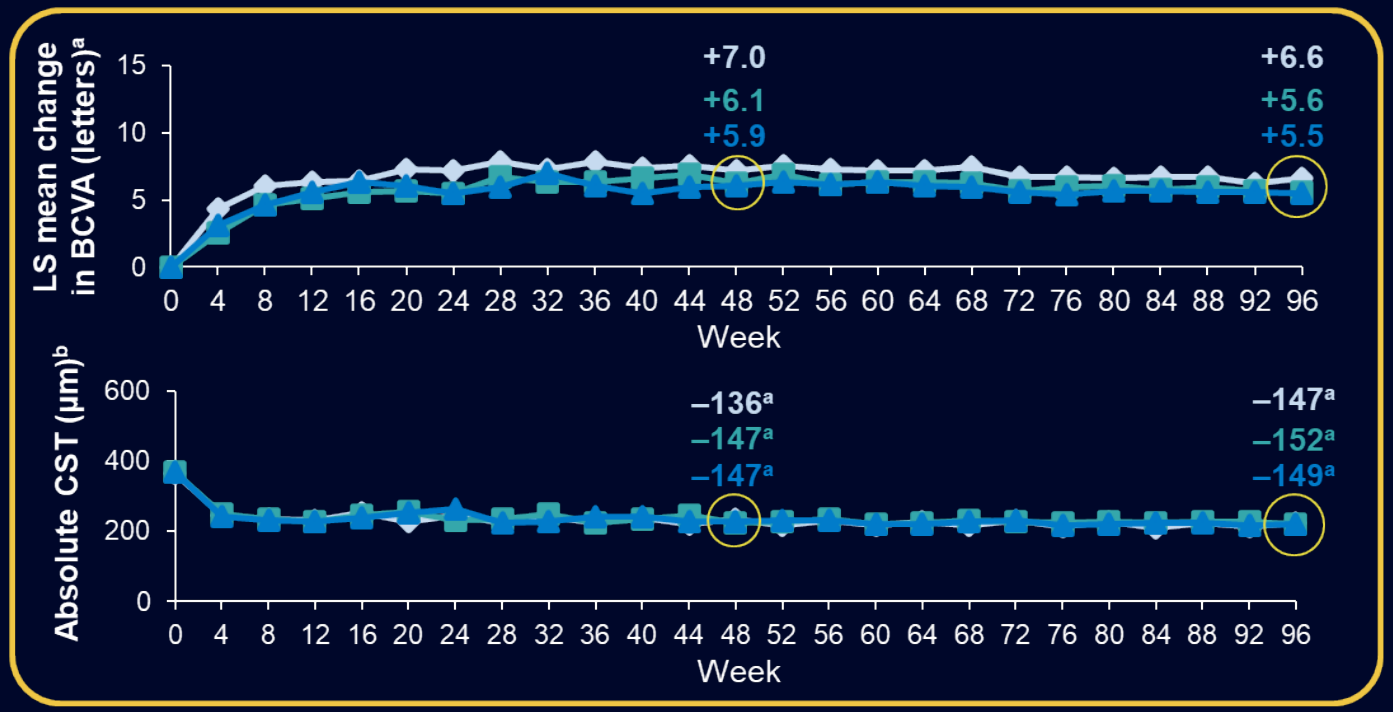
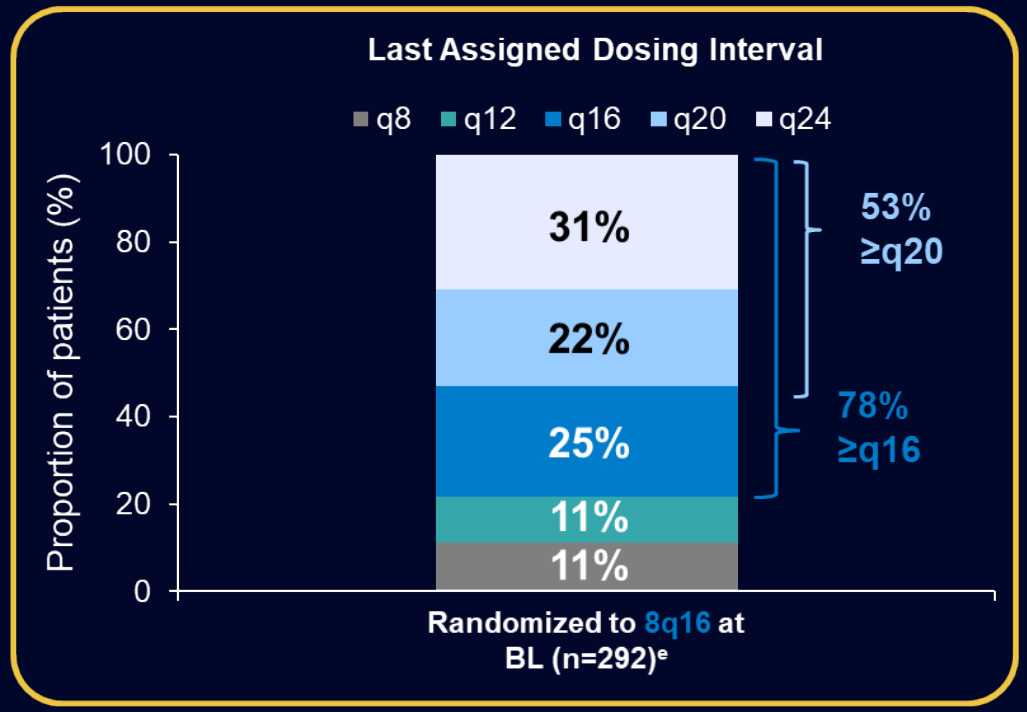
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic improvements in PULSAR for aflibercept 8 mg were maintained over time through Week 96
- At Week 96, **78%** of patients randomized to receive aflibercept 8q16 achieved ≥q16 dosing intervals and **53%** achieved ≥q20 dosing intervals
- The safety profile of aflibercept 8 mg was comparable to that of aflibercept 2 mg over 96 weeks





[a]LS mean values (data post-ICE were censored); [b]Observed values (data post-ICE were censored).