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.

Key Inclusion/Exclusion Criteria

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Inclusion Criteria

- Men or women ≥50 years of age with treatment-naïve nAMD
- Active subfoveal CNV, with a total area >50% of the total lesion area in the study eye
- Presence of IRF and/or SRF fluid in the central subfield on OCT
- BCVA of 78–24 letters (Snellen equivalent 20/32–20/320) with decreased vision due to nAMD

Exclusion Criteria

- Diabetic retinopathy, diabetic macular edema, or any retinal vascular disease other than nAMD in either eye
- Retinal pigment epithelial tears or rips, scar, fibrosis, or atrophy involving the central subfield in the study eye
- Total lesion size >12 disc areas (30.5 mm^2, including blood, scars, and neovascularization) as assessed by FA in the study eye
- Uncontrolled glaucoma (IOP >25 mmHg despite anti-glaucoma medication) in the study eye
- Extra/periocular infection or inflammation in either eye at screening/randomization
- Uncontrolled blood pressure (SBP >160 mmHg or DBP >95 mmHg)

CNV, choroidal neovascularization; **DBP**, diastolic blood pressure; **FA**, fluorescein angiography; **IOP**, intraocular pressure; **SBP**, systolic blood pressure.

PULSAR: Dosing Schedule and Regimen Modification

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Primary Endpoint

YEAR 1	Day 1	Week 4	Week 8	Week 12	Week16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 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	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	
8q12	o	X[a, b]	o	o	X[a, b]	o	o	X[a, b]	o	o	X[a, b]	
8q16	o	X[a, b]	o	o	o	X[a, b]	o	o	o	X[a, b]	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.

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 (%)	309 (91.7)	316 (94.0)	312 (92.3)	937 (92.7)
Completed Week 96, n (%)	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, %[a]				
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 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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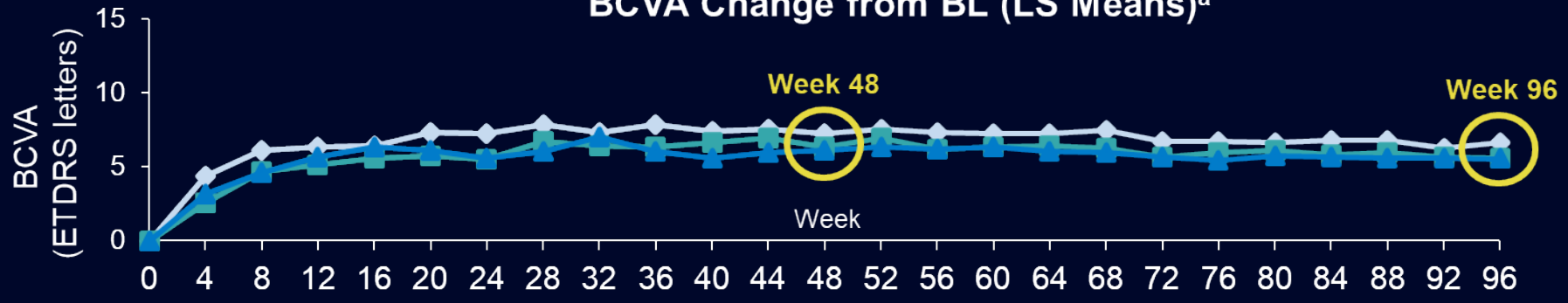
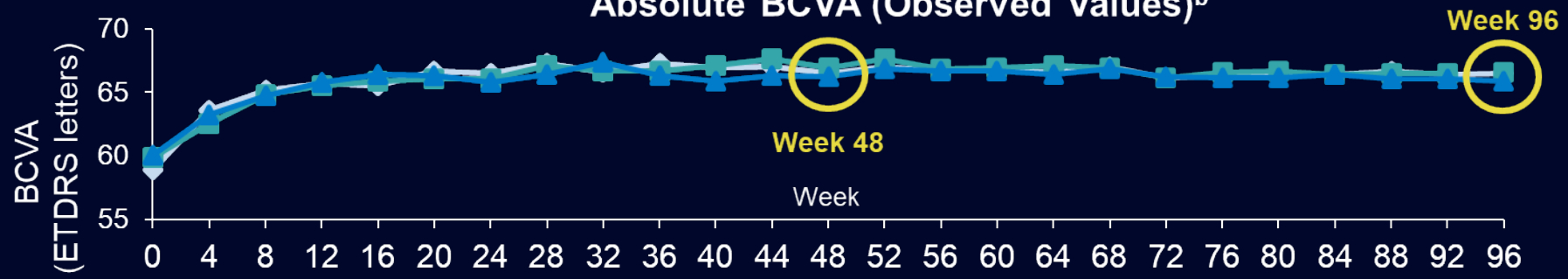
BCVA Change from BL (LS Means)[a]



	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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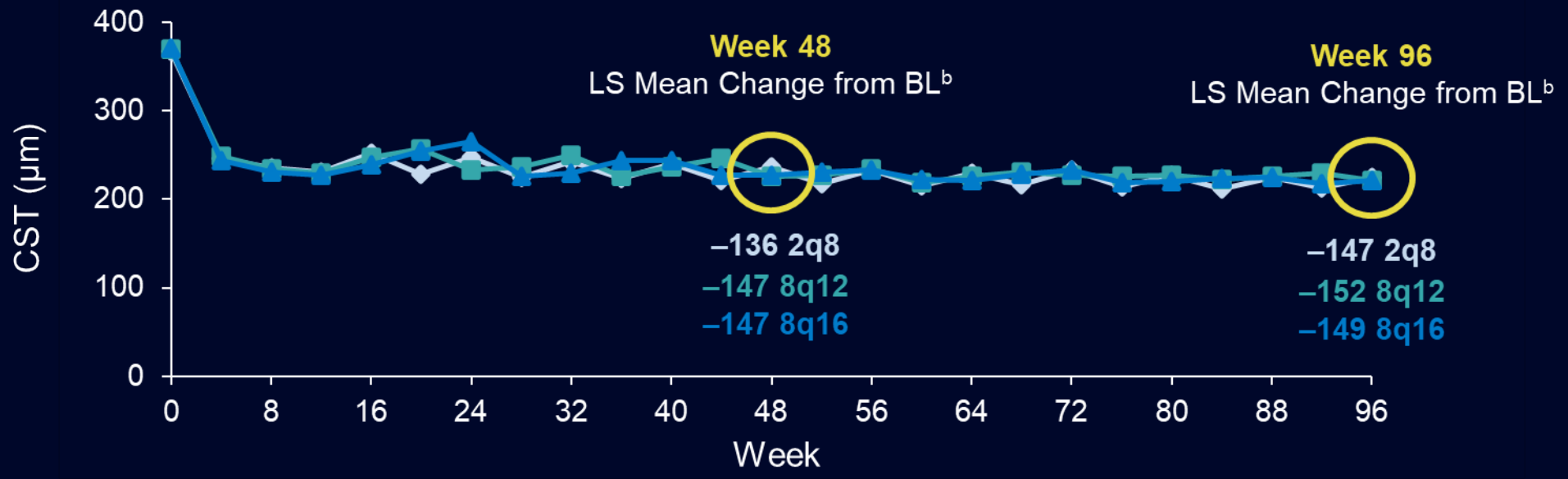
Absolute CST (Observed Values)[a]



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

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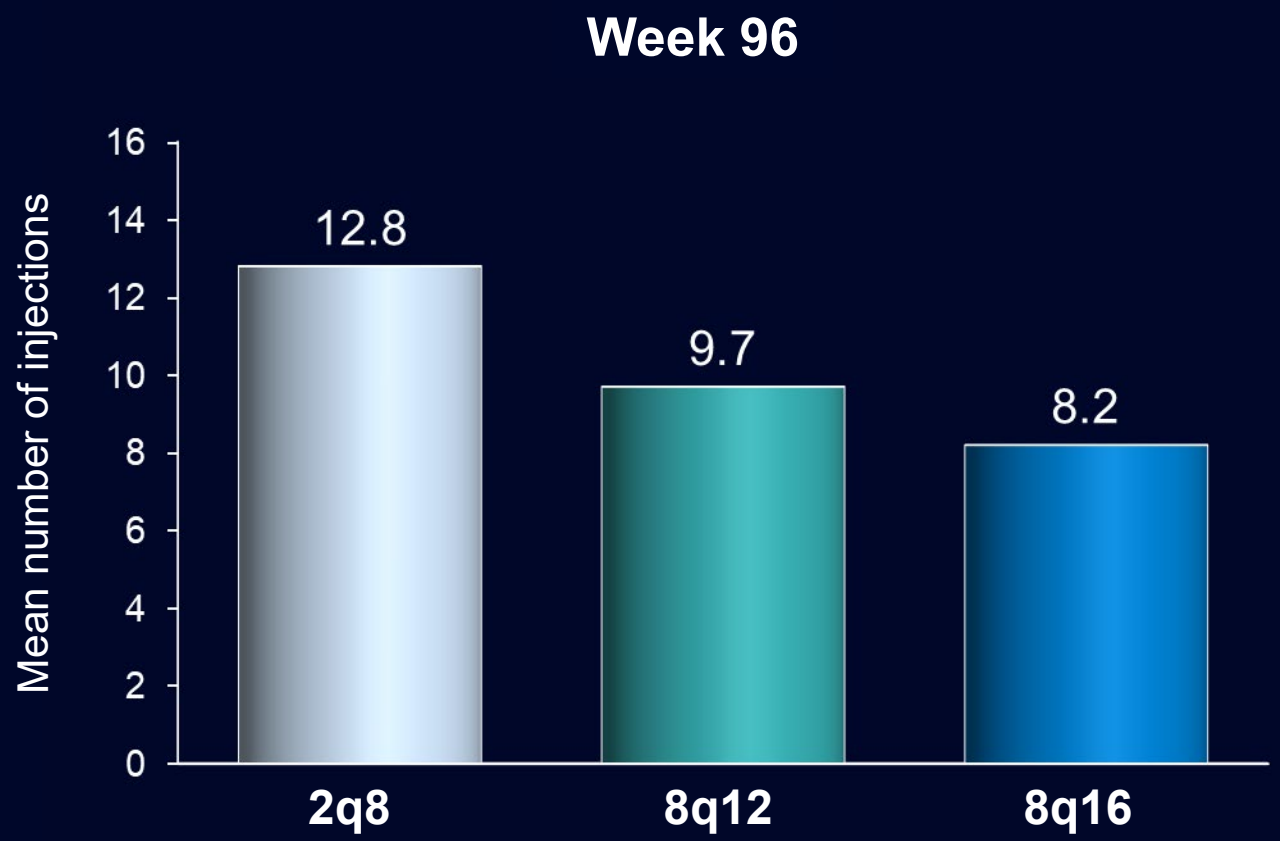
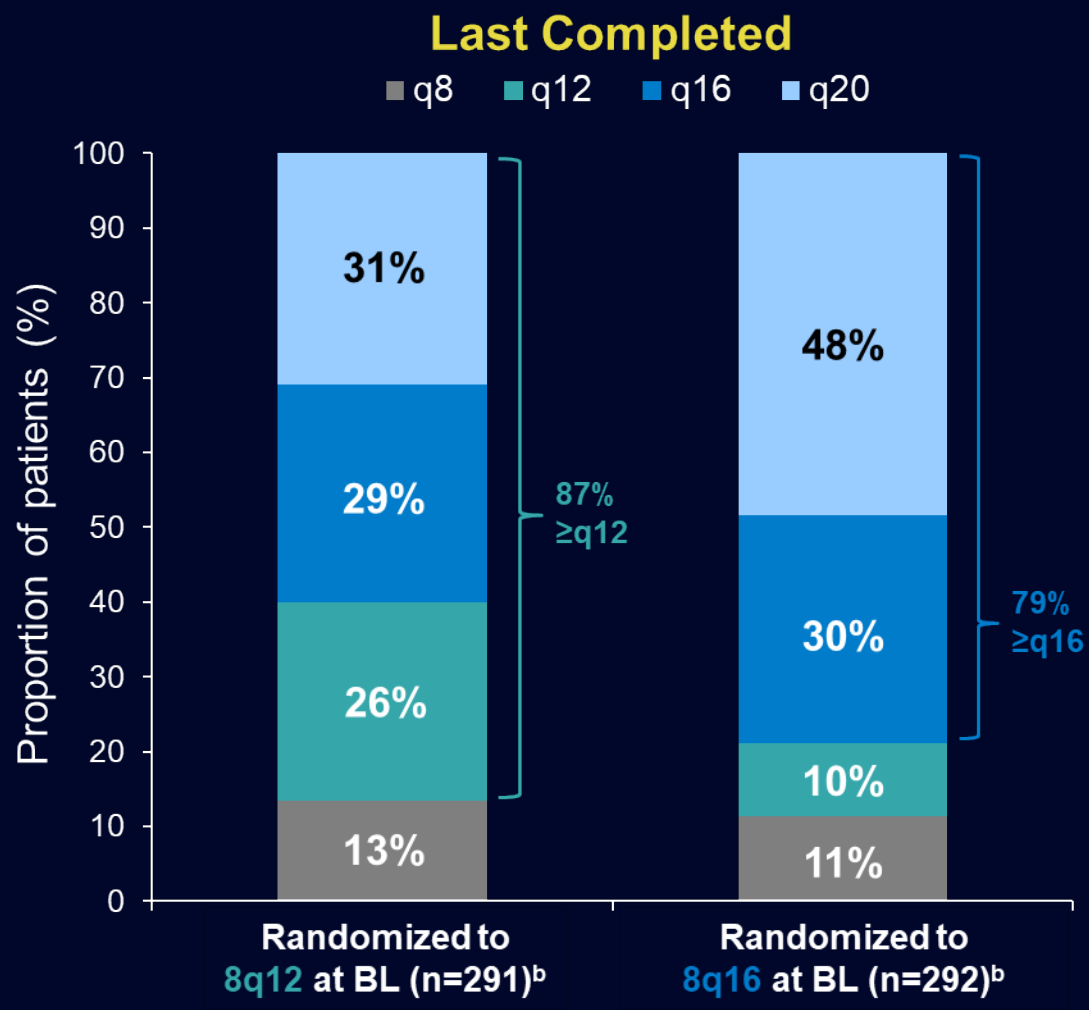
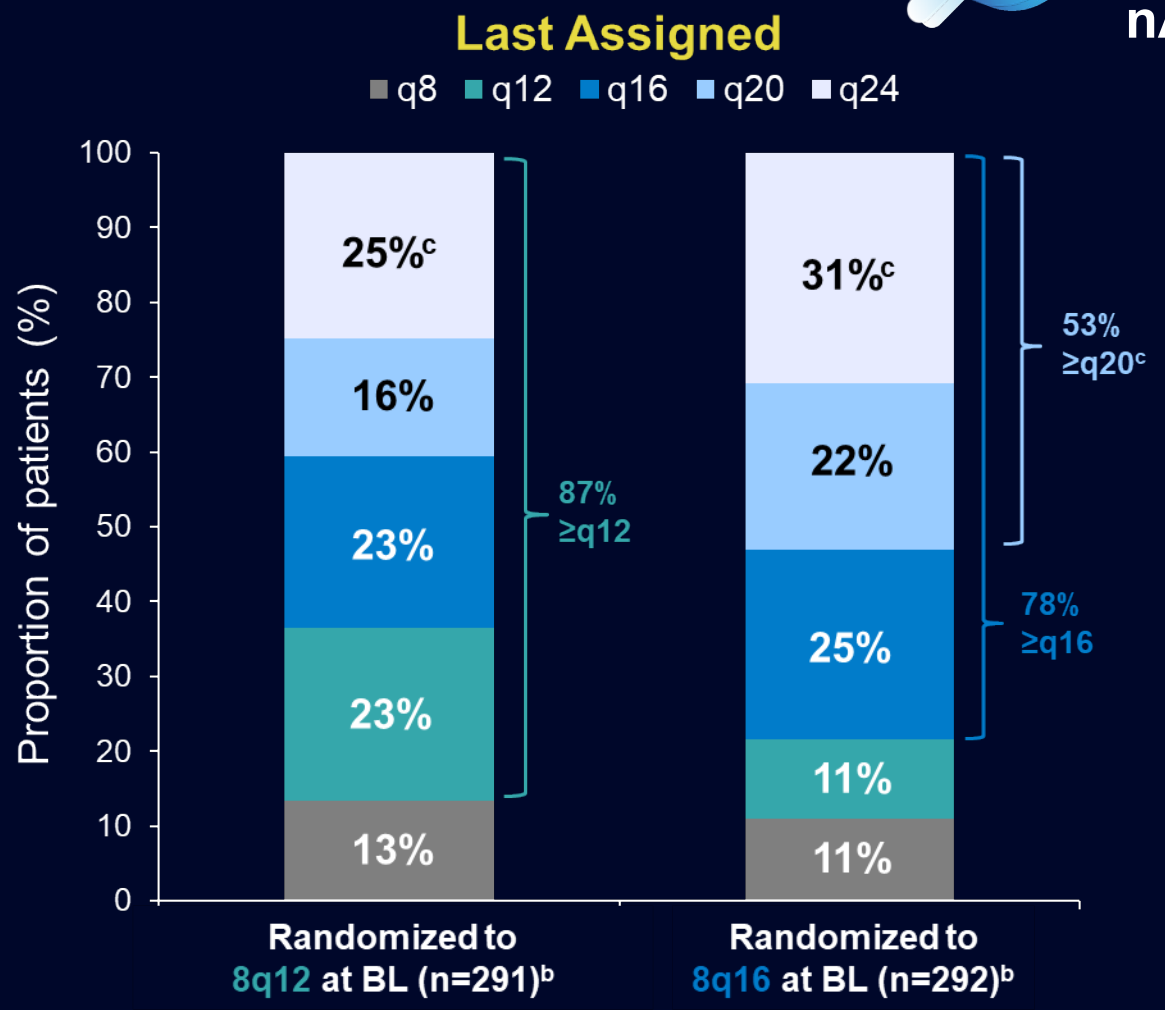


Data shown are for patients who completed Week 96 (2q8 n=286, 8q12 n=291, 8q16 n=292).

Dosing interval at Week 96[a]

nAMD





[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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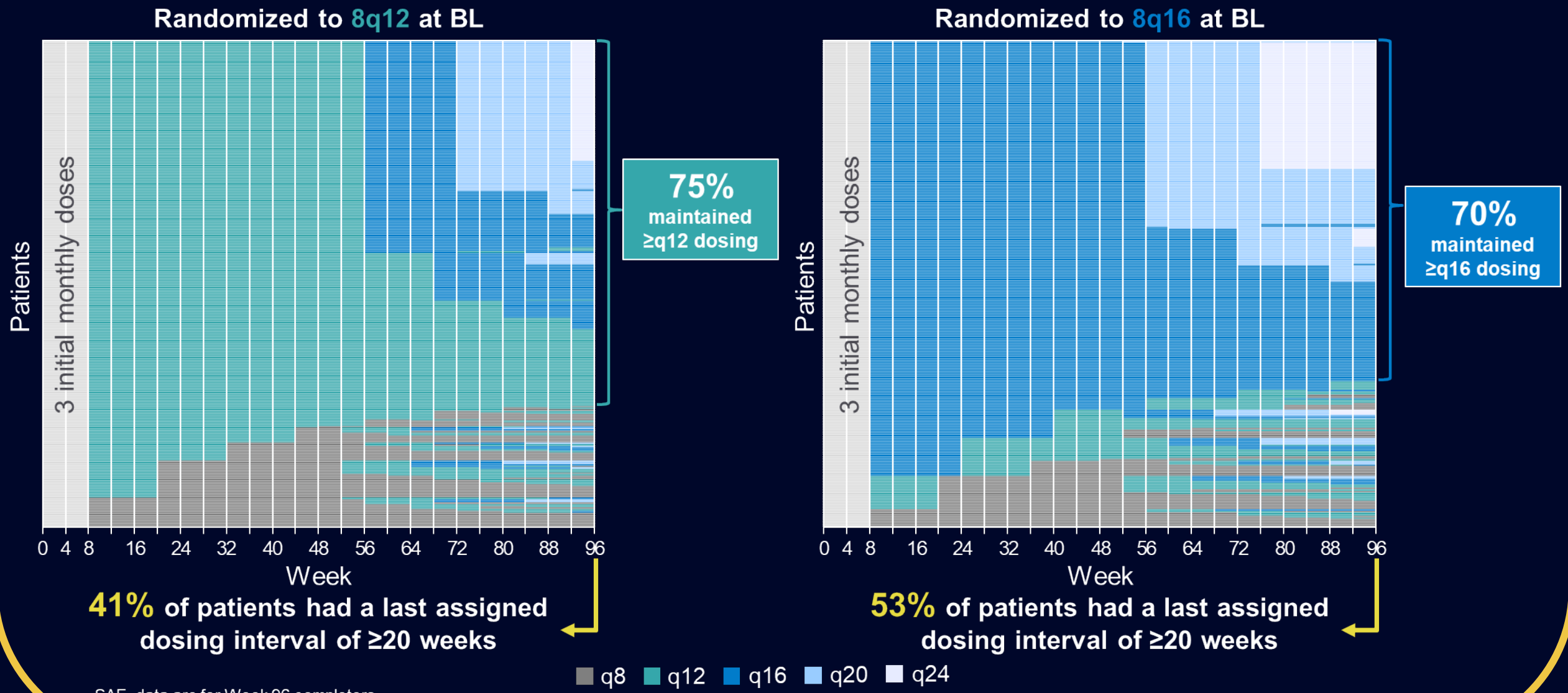

SAF, data are for Week 96 completers.
SAF, safety analysis set.

Safety Through Week 96

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Ocular TEAEs, n (%)[a]	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Non-ocular serious TEAEs, n (%)	66 (19.6)	73 (21.8)	64 (18.9)	137 (20.4)
APTC events, n (%)[b]	11 (3.3)	5 (1.5)	7 (2.1)	12 (1.8)
Hypertension events, n (%)[b]	27 (8.0)	27 (8.1)	28 (8.3)	55 (8.2)
Deaths, n (%)[c]	12 (3.6)	10 (3.0)	7 (2.1)	17 (2.5)

- Ocular TEAEs occurring in ≥5% of patients in any treatment group were cataract, retinal hemorrhage, visual acuity reduced, and vitreous floaters
- No cases of ION were reported in 8q12 and 8q16 groups, and 1 case of ION was reported in the 2q8 group

[a]Study eye; [b]Treatment-emergent events; [c]All events.
APTC, Anti-Platelet Trialists' Collaboration; **ION**, ischemic optic neuropathy; **TEAE**, treatment-emergent adverse event.

Intraocular Inflammation Through Week 96

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Patients with IOI in the study eye, n (%)	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)
Anterior chamber cell	0	1 (0.3)	0	1 (0.1)
Chorioretinitis[a]	0	1 (0.3)	0	1 (0.1)
Endophthalmitis	2 (0.6)	0	0	0
Eye inflammation	1 (0.3)	0	0	0
Hypopyon	1 (0.3)	0	0	0
Iridocyclitis	1 (0.3)	0	3 (0.9)	3 (0.4)
Iritis	0	1 (0.3)	0	1 (0.1)
Uveitis	1 (0.3)	1 (0.3)	0	1 (0.1)
Vitreal cells	2 (0.6)	1 (0.3)	0	1 (0.1)
Vitritis	0	1 (0.3)	0	1 (0.1)

- Majority of the IOI cases were reported as mild or moderate in severity

[a]Reported term was posterior uveitis.
IOI, intraocular inflammation.

IOP in the Study Eye

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Patients with IOP increase ≥10 mmHg pre-injection from baseline at any visit, n (%)	11 (3.3)	8 (2.4)	10 (3.0)	18 (2.7)
Patients with IOP ≥35 mmHg pre- or post-injection at any visit, n (%)	2 (0.6)	3 (0.9)	1 (0.3)	4 (0.6)

IOP, intraocular pressure.

PULSAR: 96-Week Results

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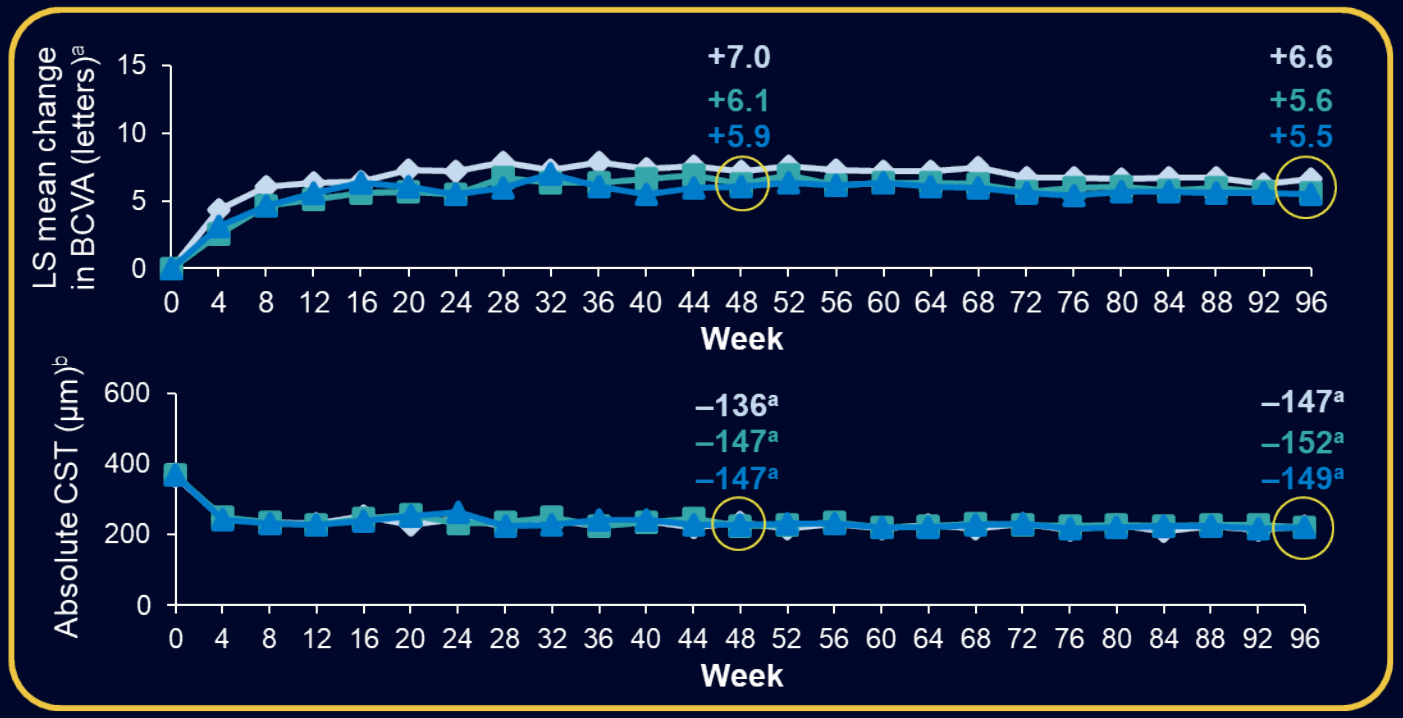
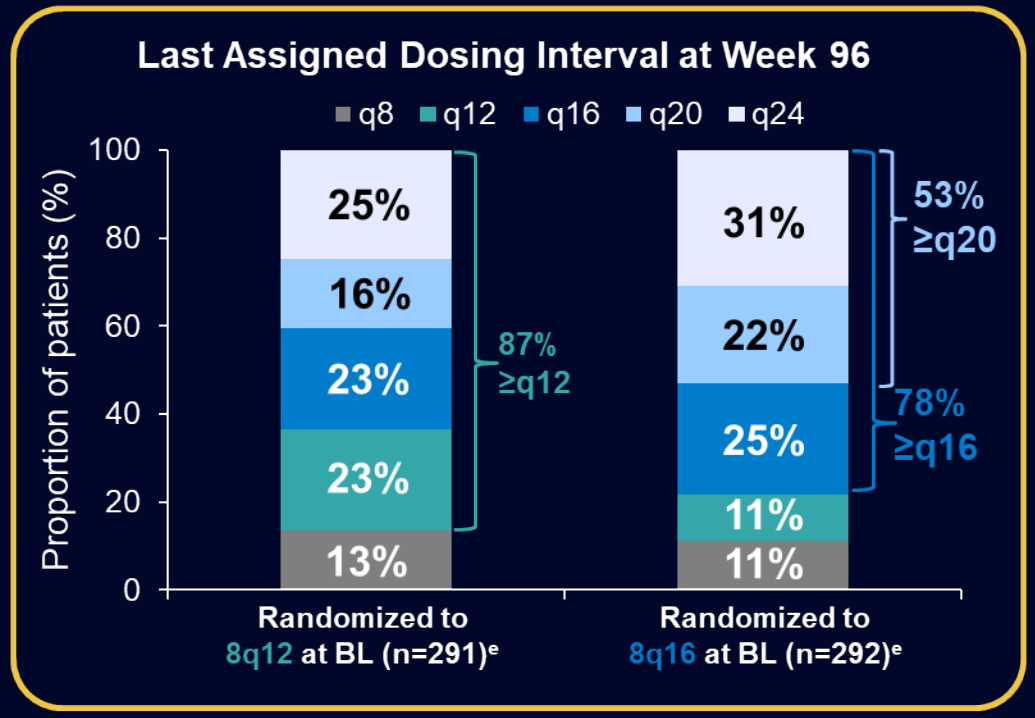
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic improvements in PULSAR for aflibercept 8 mg were maintained over time through Week 96
- At Week 96, **78%** of patients randomized to receive aflibercept 8q16 achieved ≥q16 dosing intervals 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).