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

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Presented at the 47th Annual Macular Society Meeting, Palm Springs, California, February 7–10, 2024

Disclosures

- **MS:** Consultant fees from Adverum, Aerie, Alimera, Allergan, Biogen Bausch, Eyepoint, Genentech, Novartis, Ocular Therapeutics, and Regeneron Pharmaceuticals, Inc.; served on speakers bureau for Allergan, Apellis, Biogen, Eyepoint, Genentech, and Regeneron Pharmaceuticals, Inc.; contracted research for Adverum, Aerie, Alimera, Allergan, Ashvanta, Clearside, DRCR, Genentech, Icon, Ionis, Kalvista, Kodiak, Jansen, Novartis, Ocuterra, Opthea, Optos, Oysterpoint, Recens, Regeneron Pharmaceuticals, Inc., Rezolute Medical, Ribomic, Santen, Senju, and Sydnexis; and holds equity in Aviceda, Inflammasome, Nanoscope, and Olives
  - **AL:** Consultant fees from Allergan, Bayer, ForSight Labs, Kanghong, Notal Vision, Novartis, and Roche
  - **PL:** Consultant fees from Aerie, Allergan, Apellis, Bausch + Lomb, Bayer, Biogen, Boehringer Ingelheim, Genentech, I-Care, Novartis, Ocular Therapeutix, Outlook Therapeutics, and Roche
  - **JFK:** Consultant fees from AbbVie, Apellis, Bayer, Carl Zeiss Meditec AG, Janssen, Nano Retina, Roche, and Théa Pharmaceuticals; member of a data safety monitoring board or advisory board for Alexion, Novo Nordisk, and Oxular
- The PULSAR study (NCT04423718) 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
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- The data in this presentation were originally presented at the 23rd European Society of Retina Specialists (EURETINA) Congress, Amsterdam, The Netherlands, October 5–8, 2023
- Medical writing support, under the direction of the author, was provided by ApotheCom and funded by Bayer Consumer Care AG (Basel, Switzerland), in accordance with Good Publication Practice (GPP) guidelines (*Ann Intern Med* 2022;175:1298–1304)

PULSAR: A 3-Arm Randomized, Double-Masked, Phase 3 Study

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)

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; **nAMD**, neovascular age-related macular degeneration.

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	–
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 CRT compared with Week 12, **OR** new foveal neovascularization, **OR** new 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 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.
q8, every 8 weeks; **q24**, every 24 weeks; **CRT**, central retinal 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 (%)	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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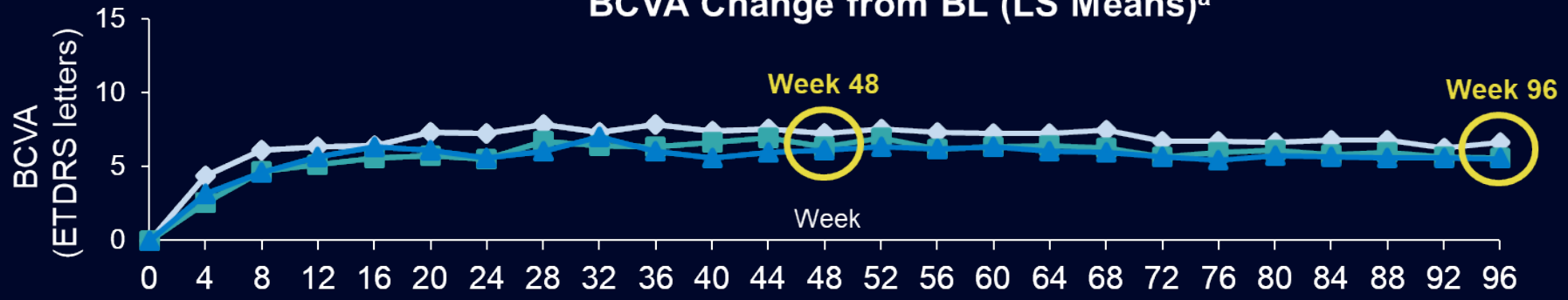
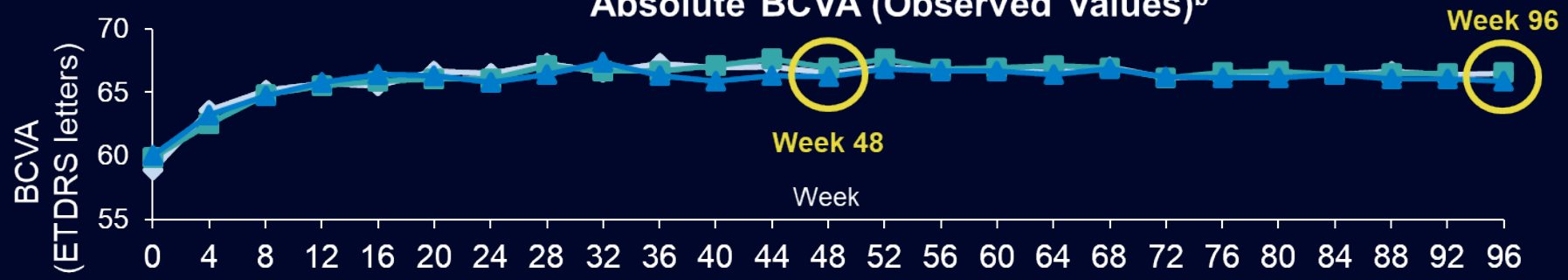
BCVA Change from BL (LS Means)[a]



	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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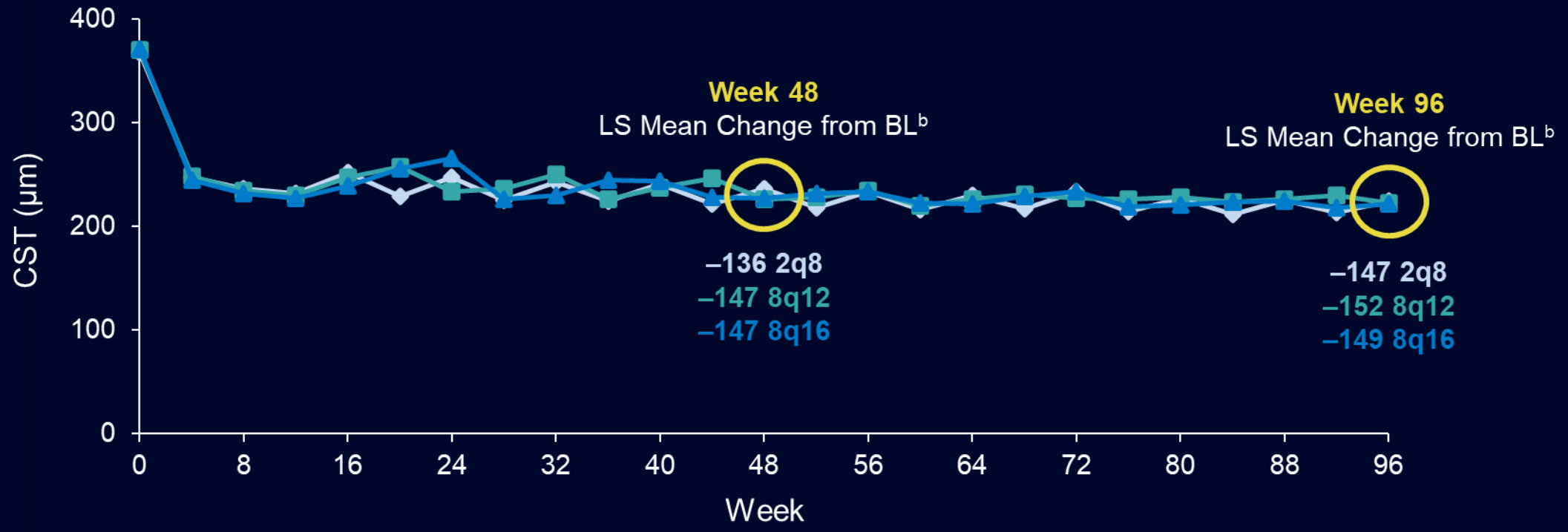
Absolute CST (Observed Values)[a]

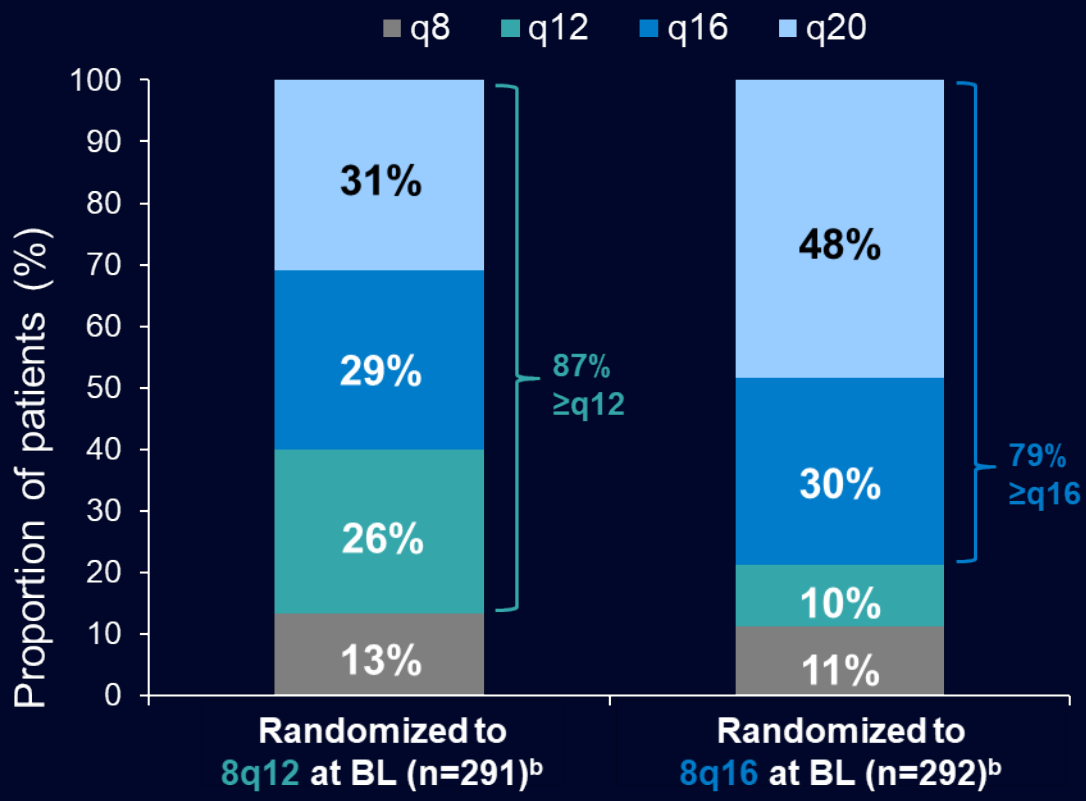


FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at BL). [a]Observed values (data post-ICE were censored). [b]LS mean values (data post-ICE were censored); LS means were generated using MRMM, with BL CST measurement as a covariate, and treatment group (aflibercept 2q8, 8q12, 8q16), visit, and stratification variables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

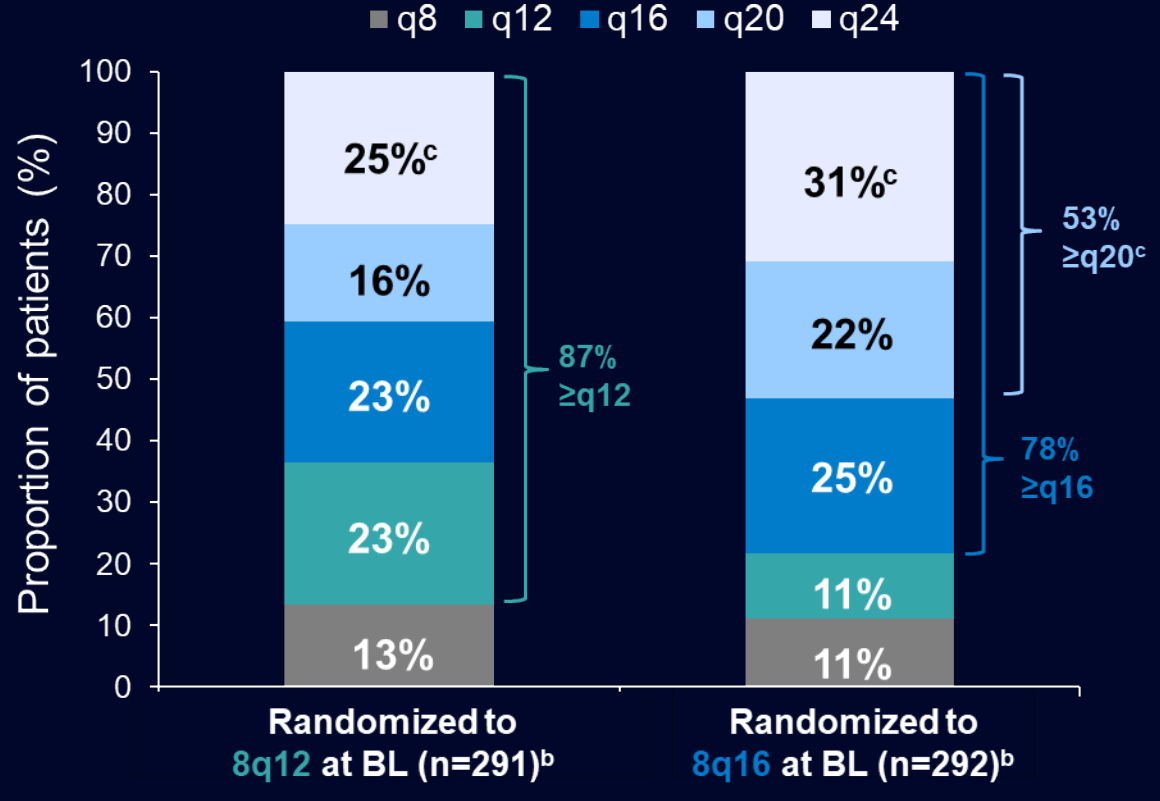
Dosing Interval Extension in Year 2[a]

nAMD

Last Completed



Last Assigned



Mean number of injections by Week 96[b]:
2q8: 12.8 **8q12: 9.7** **8q16: 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 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.
q12, every 12 weeks; **q16**, every 16 weeks; **q20**, every 20 weeks.

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

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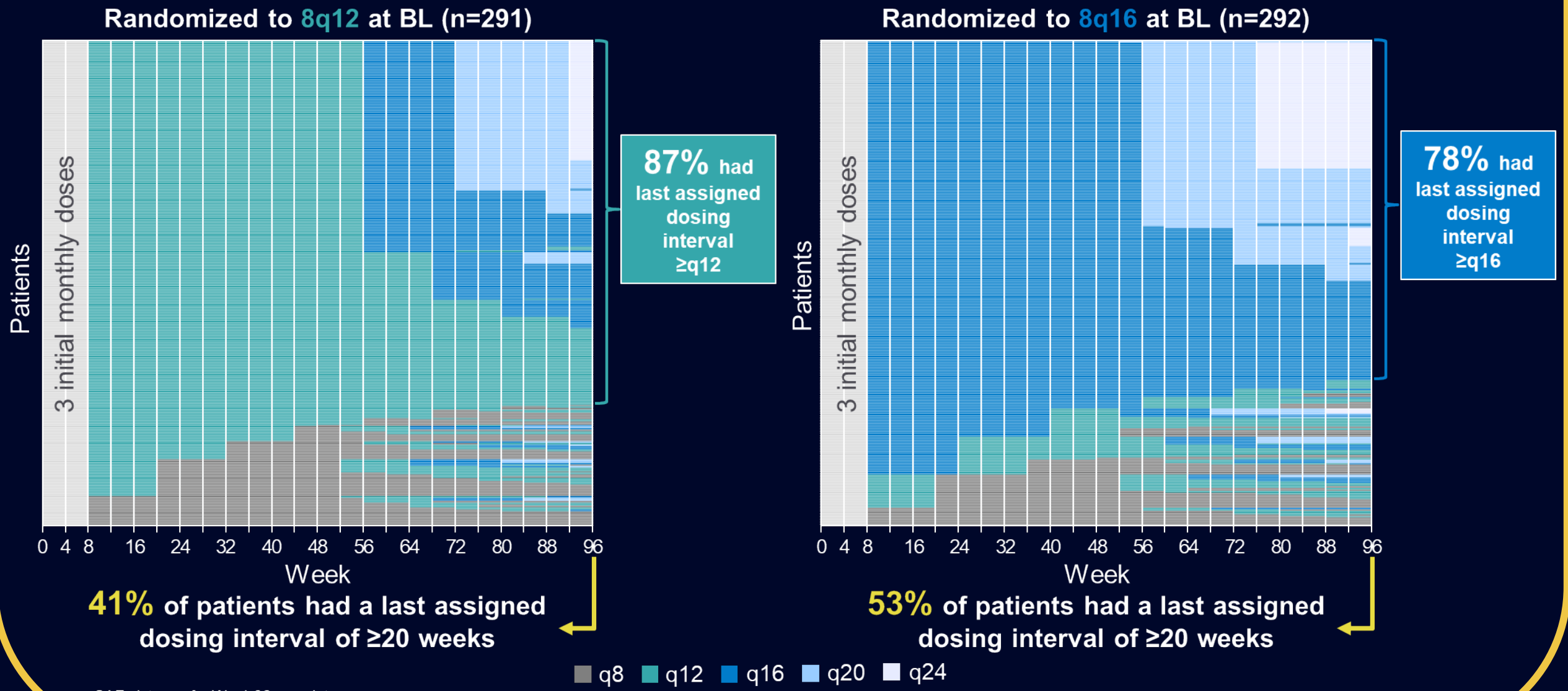

SAF, data are for Week 96 completers.
SAF, safety analysis set.

96-Week Safety Profile of Aflibercept 8 mg: Similar to Aflibercept 2 mg

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	2q8	8q12	8q16	All 8 mg
SAF, n	336	335	338	673
Ocular Safety				
Ocular TEAEs, n (%)[a]	181 (53.9)	171 (51.0)	174 (51.5)	345 (51.3)
Patients with IOI, n (%)[a,b]	7 (2.1)	6 (1.8)	3 (0.9)	9 (1.3)
Pre-injection IOP increase from baseline ≥10 mmHg, n (%)[c]	11 (3.3)	8 (2.4)	10 (3.0)	18 (2.7)
Pre- or post injection IOP ≥35 mmHg, n (%)[c]	2 (0.6)	3 (0.9)	1 (0.3)	4 (0.6)
Non-ocular Safety				
Non-ocular serious TEAEs, n (%)	66 (19.6)	73 (21.8)	64 (18.9)	137 (20.4)
APTC events, n (%)[d]	11 (3.3)	5 (1.5)	7 (2.1)	12 (1.8)
Hypertension events, n (%)[d]	27 (8.0)	27 (8.1)	28 (8.3)	55 (8.2)
Deaths, n (%)[e]	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
- All IOI cases were mild or moderate in severity, except for one case of severe endophthalmitis with 2q8
- 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]Reported IOI terms were iridocyclitis (n=3), anterior chamber cell, chorioretinitis (reported term was posterior uveitis), iritis, uveitis, vitreal cells, and vitritis (all n=1) in the 8 mg arm, and endophthalmitis, vitreal cells (both n=2), eye inflammation, hypopyon, iridocyclitis, and uveitis (all n=1) in the 2 mg arm; [c]At any visit; [d]Treatment-emergent events; [e]All events.
APTC, Anti-Platelet Trialists' Collaboration; **IOI**, intraocular inflammation; **ION**, ischemic optic neuropathy; **IOP**, intraocular pressure; **TEAE**, treatment-emergent adverse event.

PULSAR: 96-Week Results

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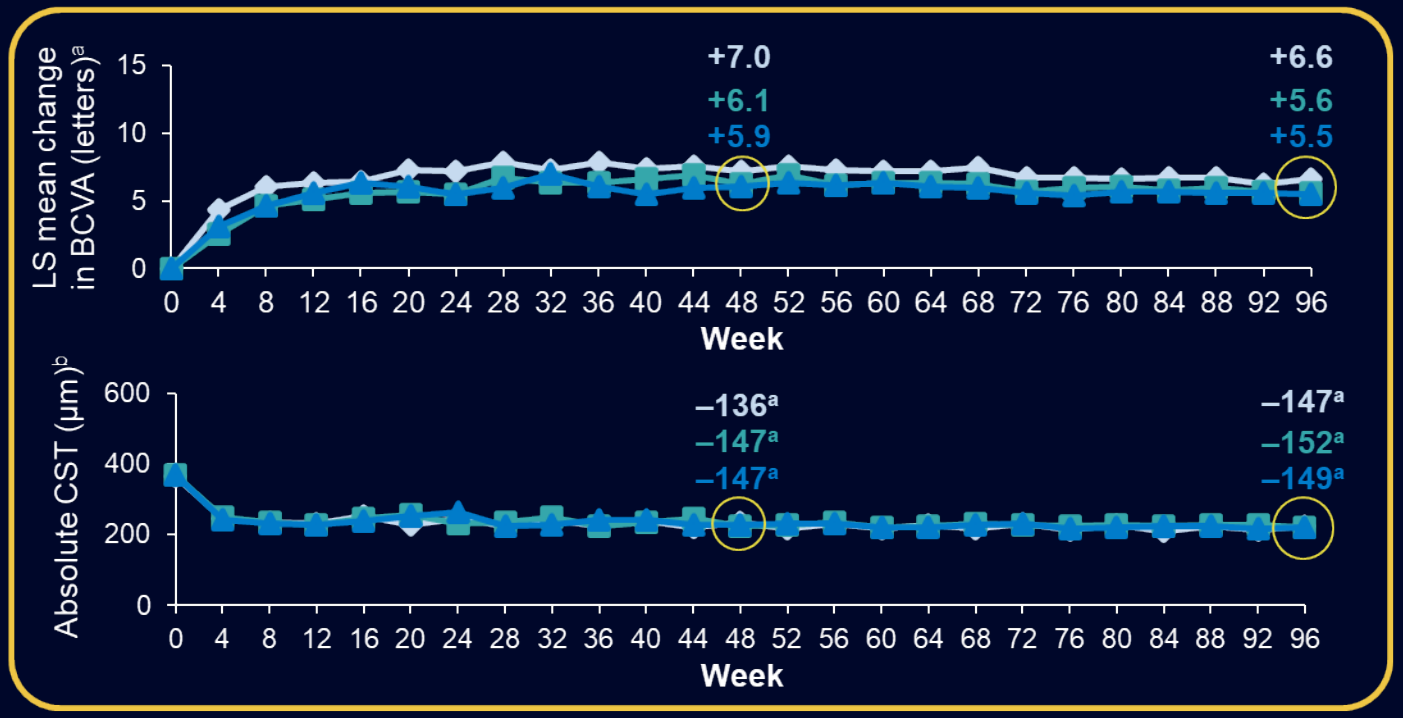
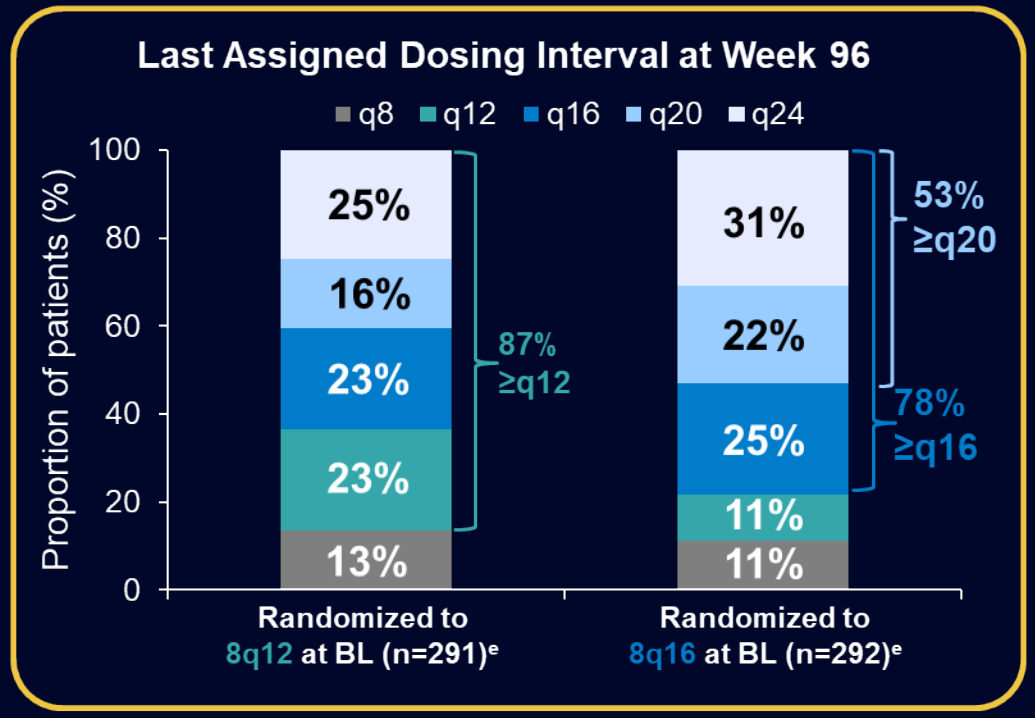
- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic improvements in PULSAR for aflibercept 8 mg were maintained over time through Week 96
- At Week 96, **78%** of patients randomized to receive aflibercept 8q16 achieved ≥q16 dosing intervals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

Thank you!