BCVA gains with aflibercept 8 mg maintained through Week 96 in PULSAR with extended treatment intervals in patients with nAMD

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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

pulsar nAMD
Primary Endpoint

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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nAMD

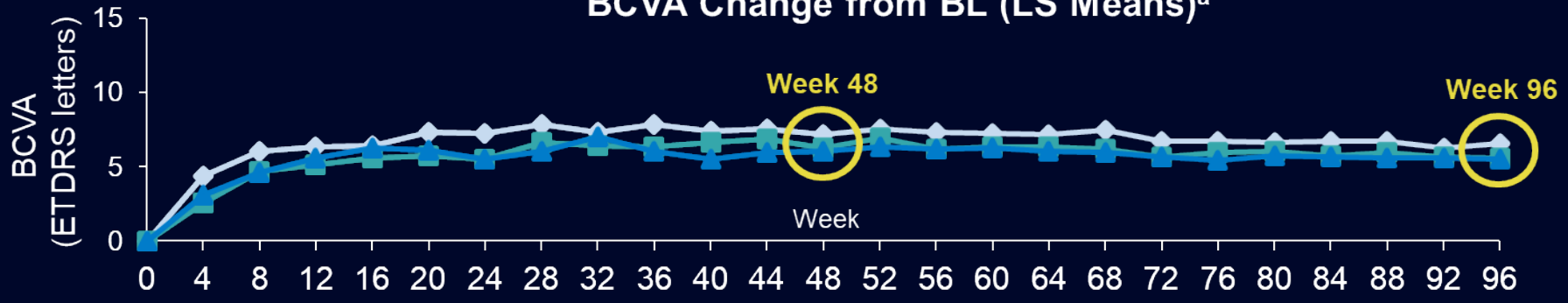
	2q8	8q12	8q16	Total
Randomized, n	337	337	338	1012
Treated, n	336	335	338	1009
Completed Week 48, n (%)	309 (91.7)	316 (94.0)	312 (92.3)	937 (92.7)
Completed Week 96, n (%)	286 (84.9)	291 (86.4)	292 (86.4)	869 (85.9)
Age, years	74.2 (8.8)	74.7 (7.9)	74.5 (8.5)	74.5 (8.4)
Female, %	56.0	54.3	53.3	54.5
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)
CRT, 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 Through Week 96: Comparable Gains Observed with Aflibercept 8 mg and 2 mg

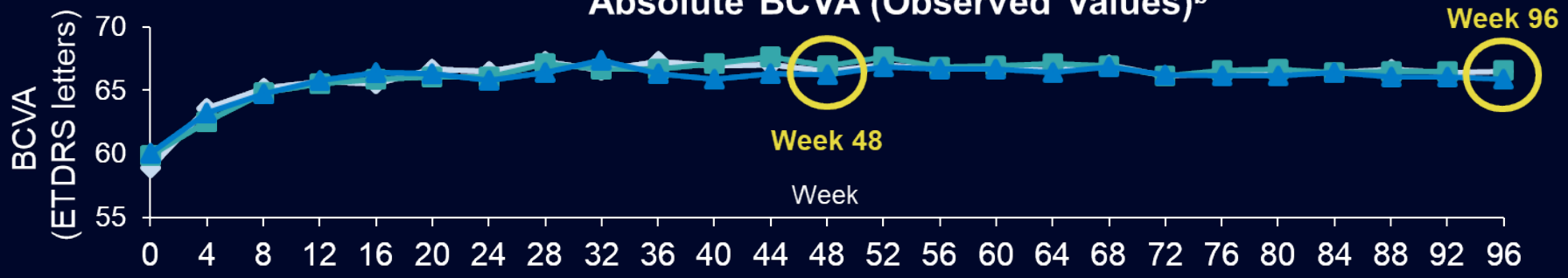
pulsar nAMD

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.

Exploratory Analysis of Patients Who Met DRM Criteria for Additional Theoretical Interval Shortening Through Week 96

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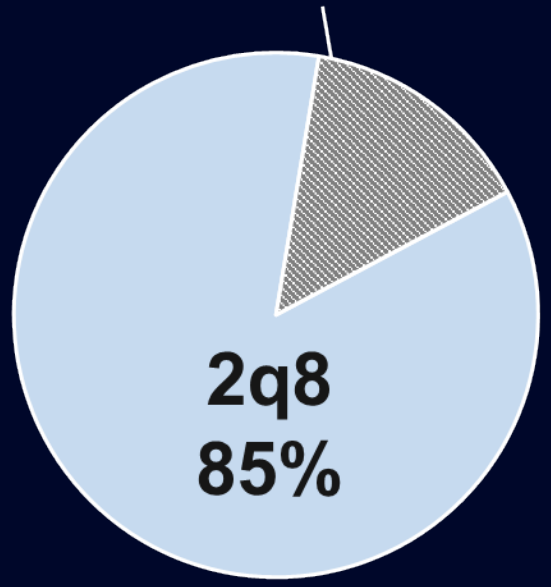
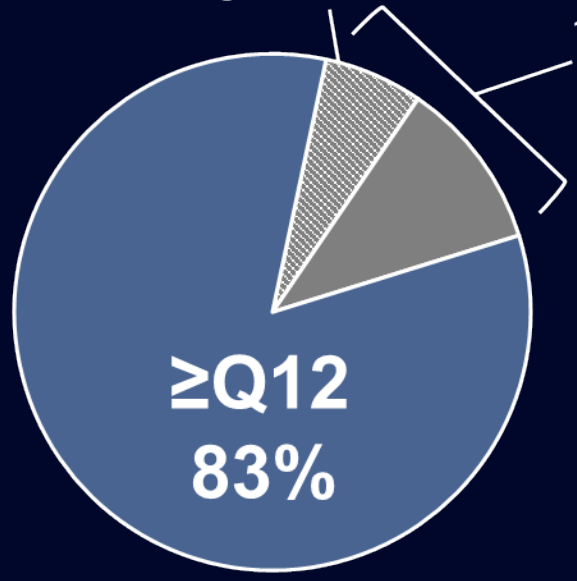
14.6% of patients in the 2q8 group would have met DRM criteria for shortening to Q4[a] at Week 48,



2q8
(n=309)[c]

6.2% of all 8 mg patients would have met DRM criteria for shortening to Q4 at Week 48



All 8 mg
(n=628)[c]

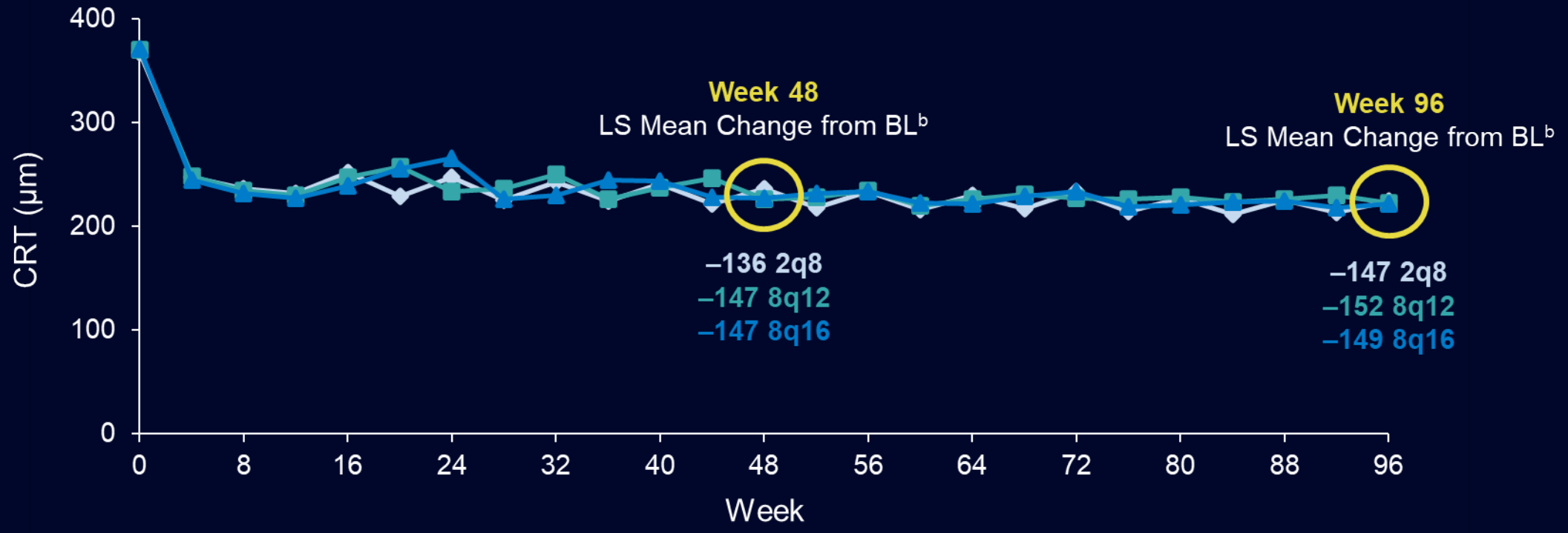
At Week 96, **22.4%** of 2q8 patients versus **10.5%** of all 8 mg patients would have met DRM criteria for shortening to Q4[d]

In this exploratory analysis, eyes in the 2q8 group and the all 8 mg group with dosing intervals that were shortened to Q8 through Week 48 were further evaluated to determine if the study-specified DRM criteria would have been met for further shortening to a Q4 interval. DRM criteria for interval shortening were defined as >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 the presence of new foveal neovascularization or hemorrhage.
Values may not add up to 100 due to rounding.
[a]Patients in the 2q8 group who met the DRM criteria for shortening at any active dosing visit through Week 48. [b]Patients whose dosing intervals were shortened based on DRM assessments at any dosing visit through Week 48. [c]Patients completing Week 48. [d]Patients in the 2q8 group who met the DRM criteria for shortening dosing interval at any active dosing interval up to Week 96 and patients in the 8 mg group who were shortened to Q8 and met the DRM criteria for shortening at any dosing visit again without being extended in the meantime (patients completing Week 96).

CRT Through Week 96: Comparable Improvements Observed with Aflibercept 8 mg and 2 mg

pulsar nAMD

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 CRT 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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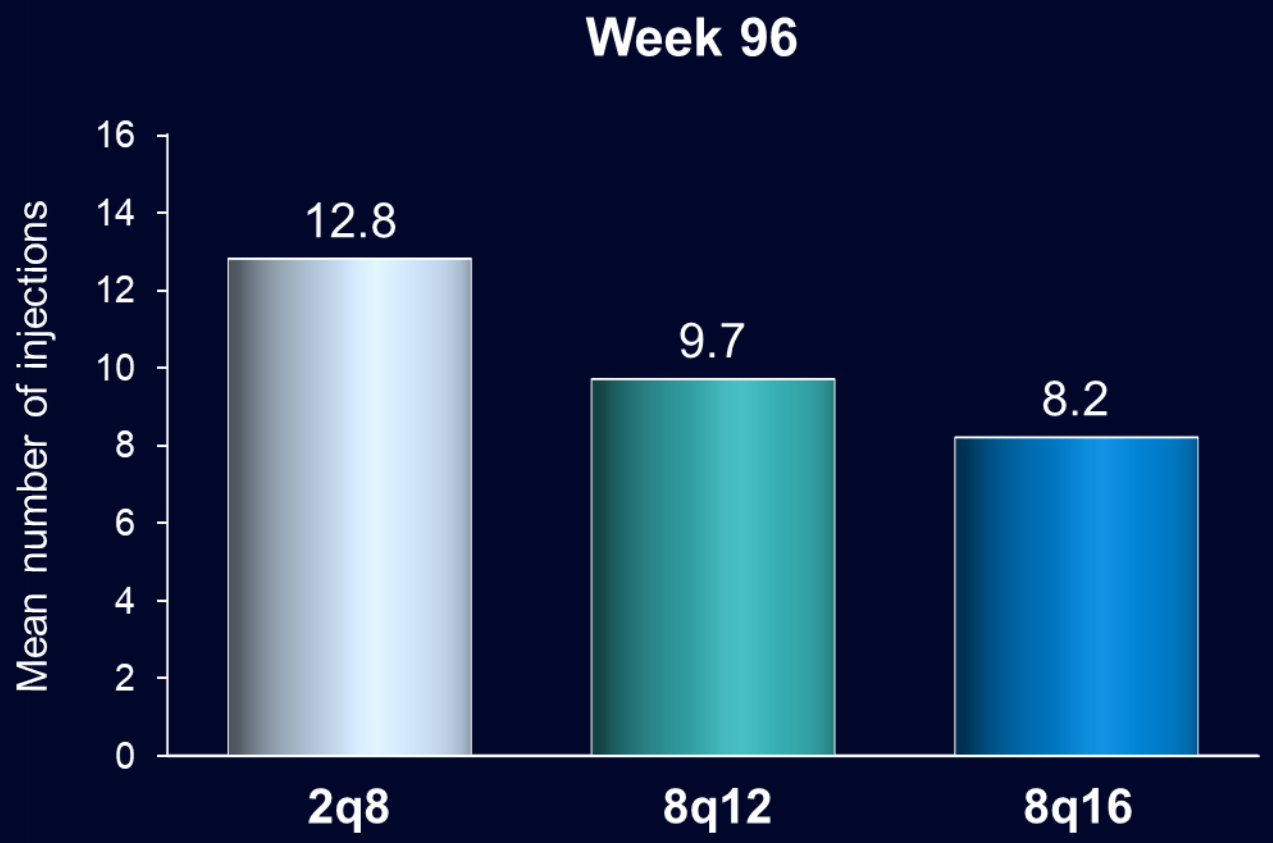
nAMD

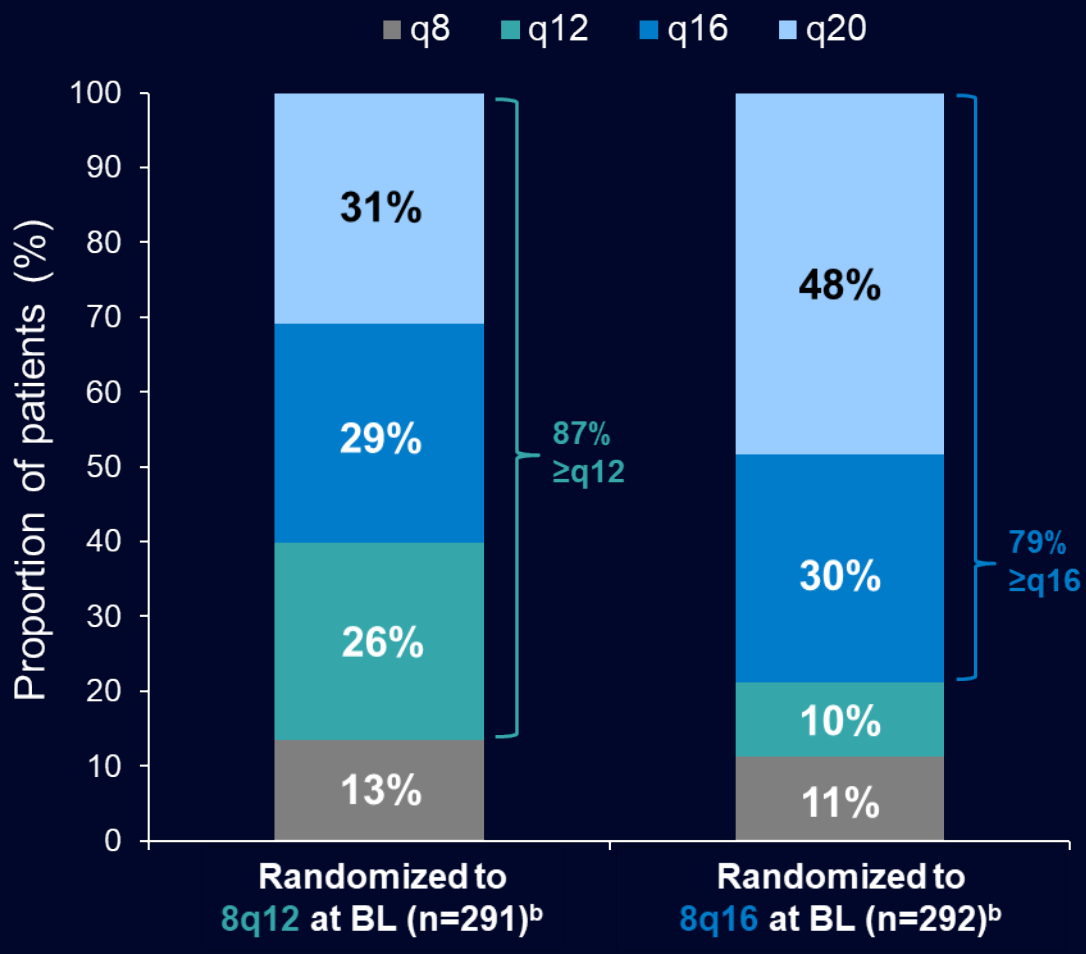


Data are shown for patients who completed Week 48 (2q8 n=309, 8q12 n=316, 8q16 n=312) and Week 96 (2q8 n=286, 8q12 n=291, 8q16 n=292).

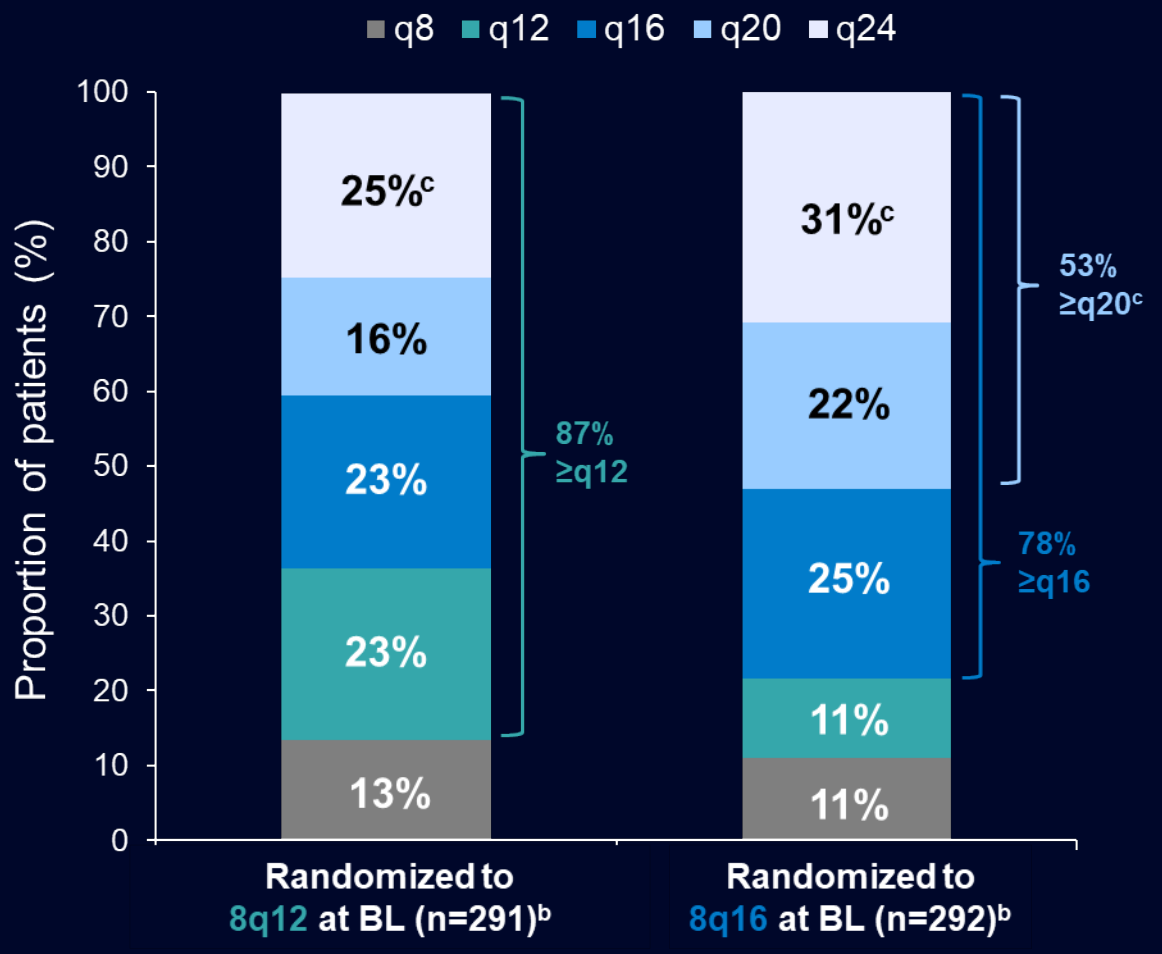
Dosing Interval Extension in Year 2[a]: Large Proportion of Patients Qualified for Extension

nAMD

Last Completed



Last Assigned

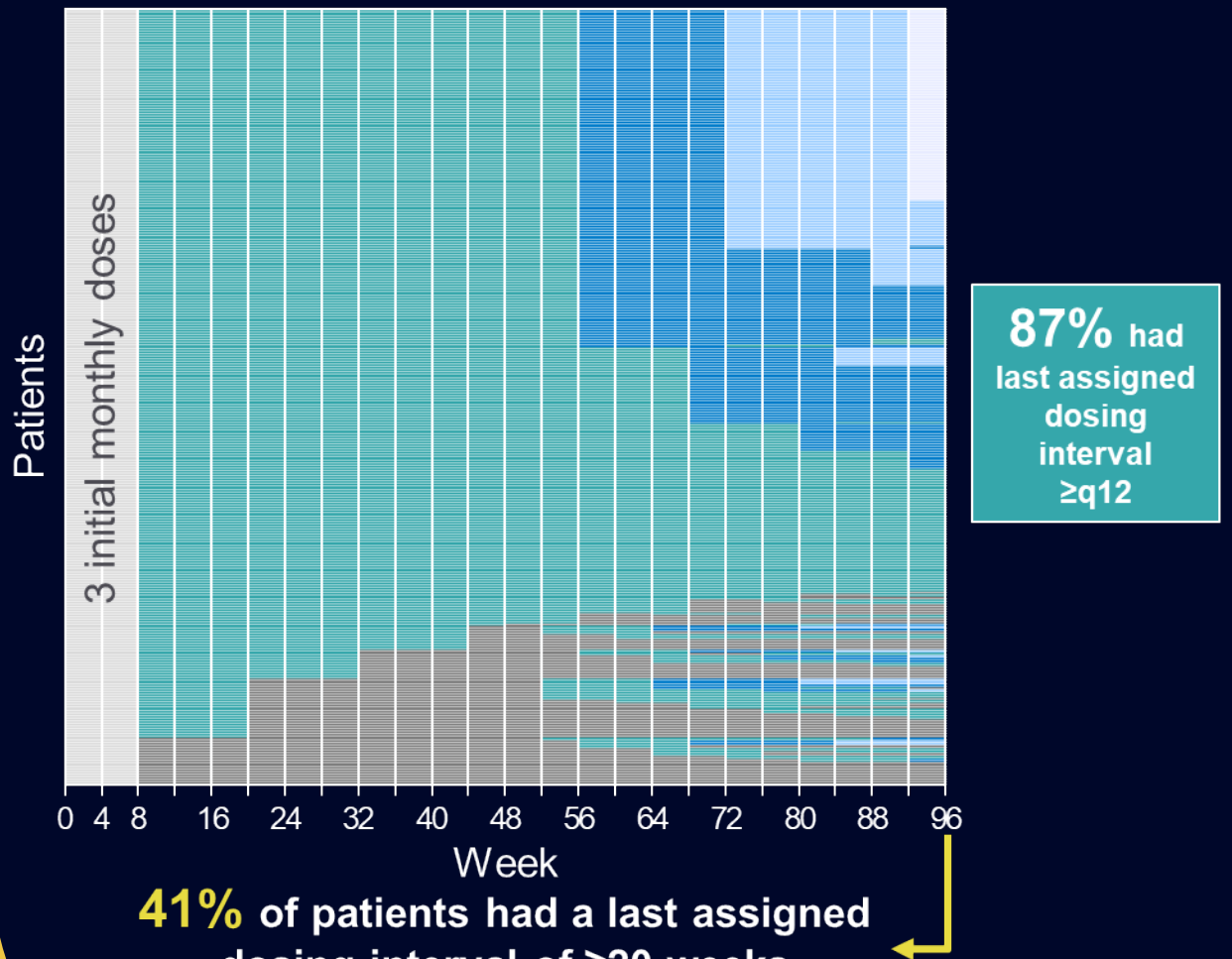


[a]Dosing intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 **AND** no fluid at the central subfield **AND** no new foveal hemorrhage or neovascularization.
[b]Patients completing Week 96. [c]Patients assigned to a 24-week dosing interval did not have enough time to 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.

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

pulsar
nAMD

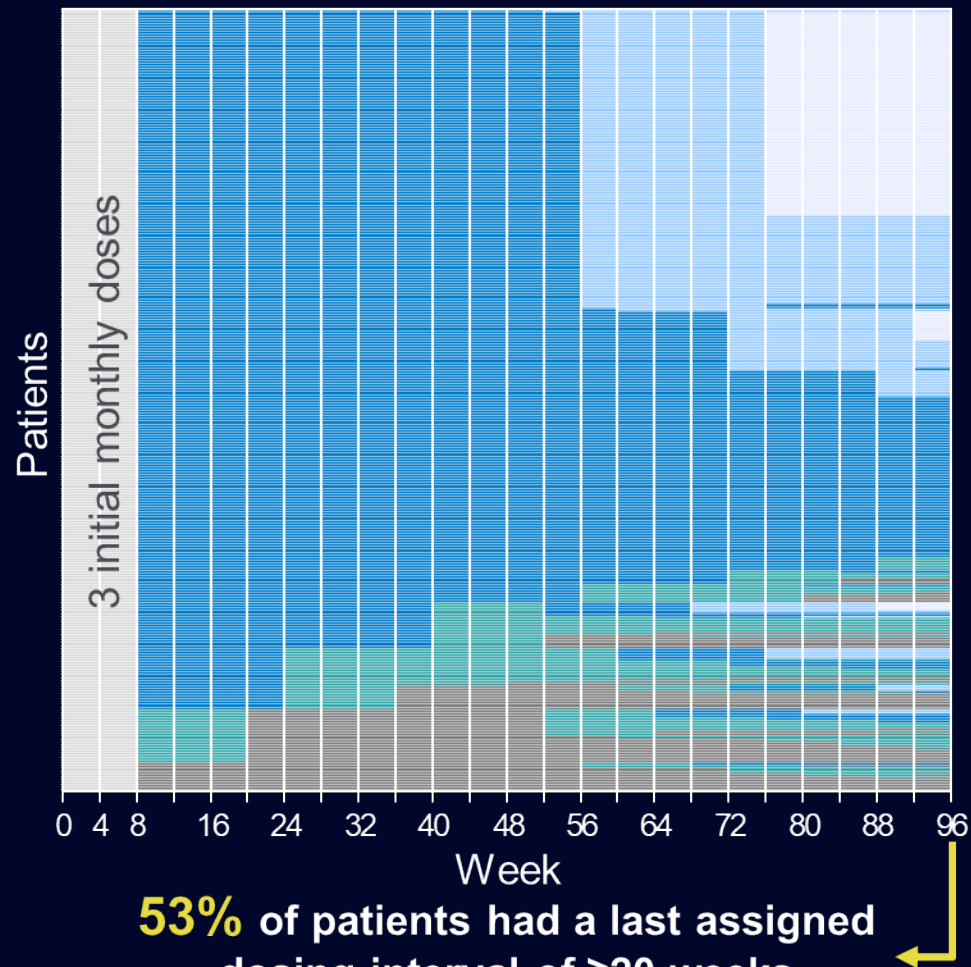
Randomized to 8q12 at BL (n=291)



87% had last assigned dosing interval ≥q12

41% of patients had a last assigned dosing interval of ≥20 weeks

Randomized to 8q16 at BL (n=292)



78% had last assigned dosing interval ≥q16

53% of patients had a last assigned dosing interval of ≥20 weeks

q8 q12 q16 q20 q24

Data are for Week 96 completers.

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

pulsar nAMD

	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; **SAF**, safety analysis set; **TEAE**, treatment-emergent adverse event.

Intraocular Inflammation Through Week 96

pulsar
nAMD

	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)

- All IOI cases were mild or moderate in severity, except for one case of severe endophthalmitis

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

Intraocular Pressure in the Study Eye

pulsar
nAMD

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

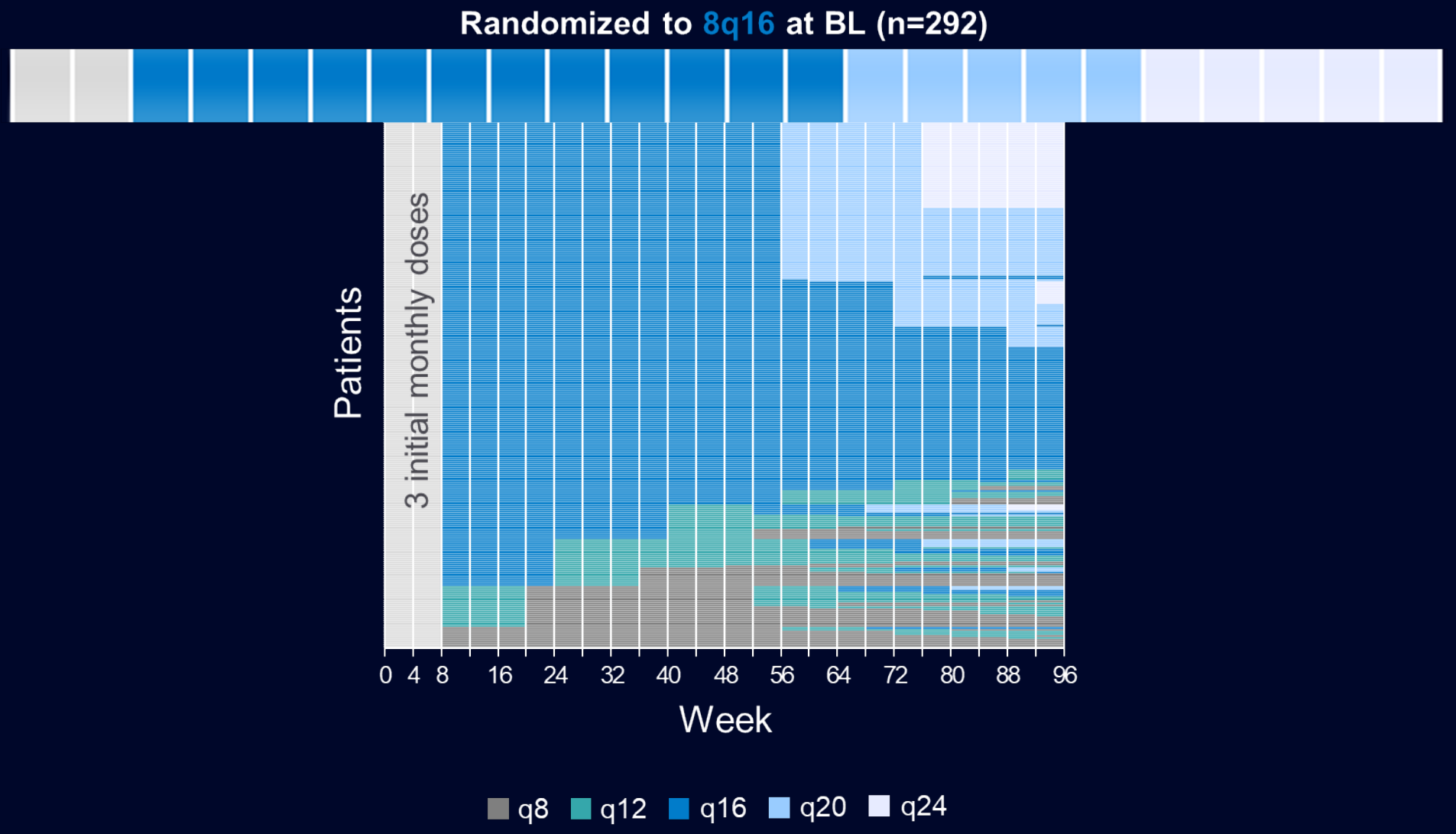
[a]At any visit.
IOP, intraocular pressure.

pulsar
nAMD

Case Studies with Aflibercept 8 mg

Case 1: Increasing Treatment Intervals Through Week 96

nAMD



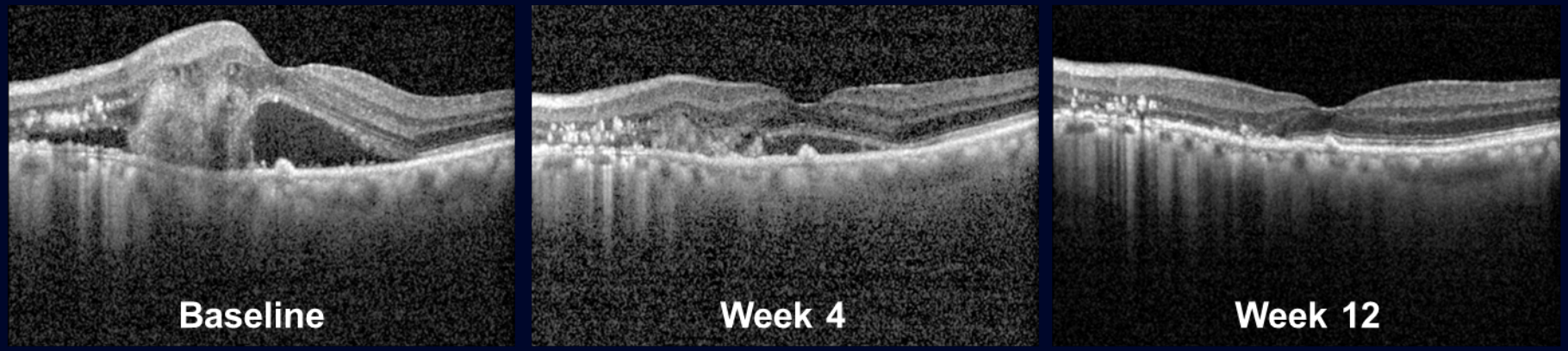
SAF, data are for Week 96 completers.

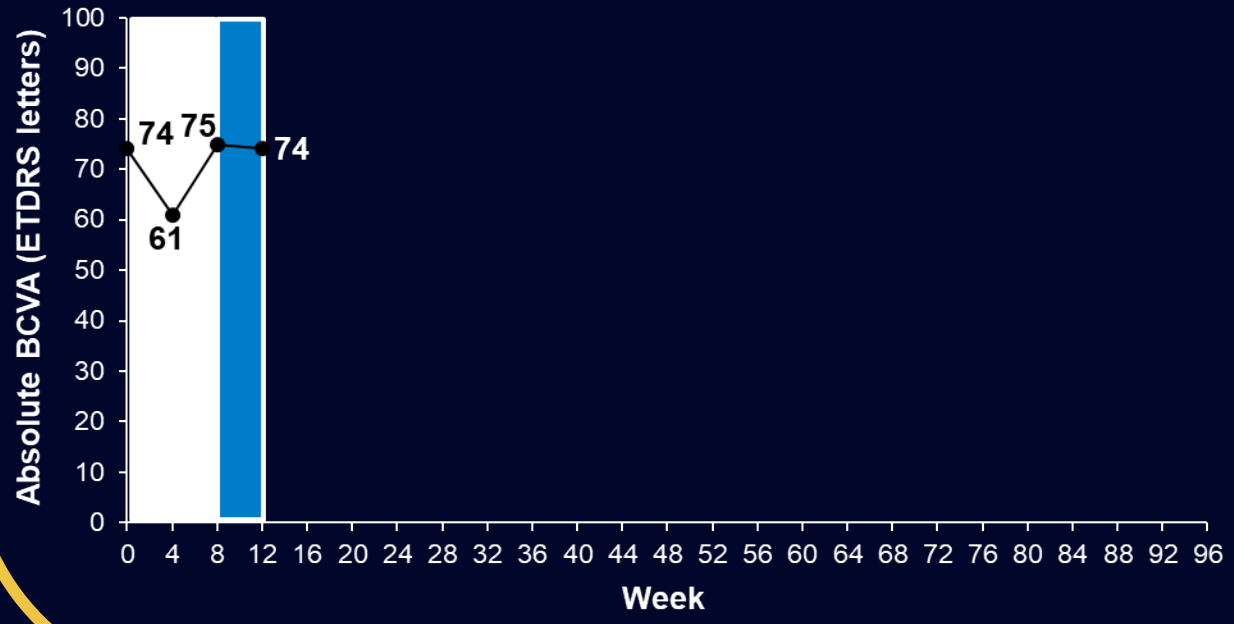
Case 1

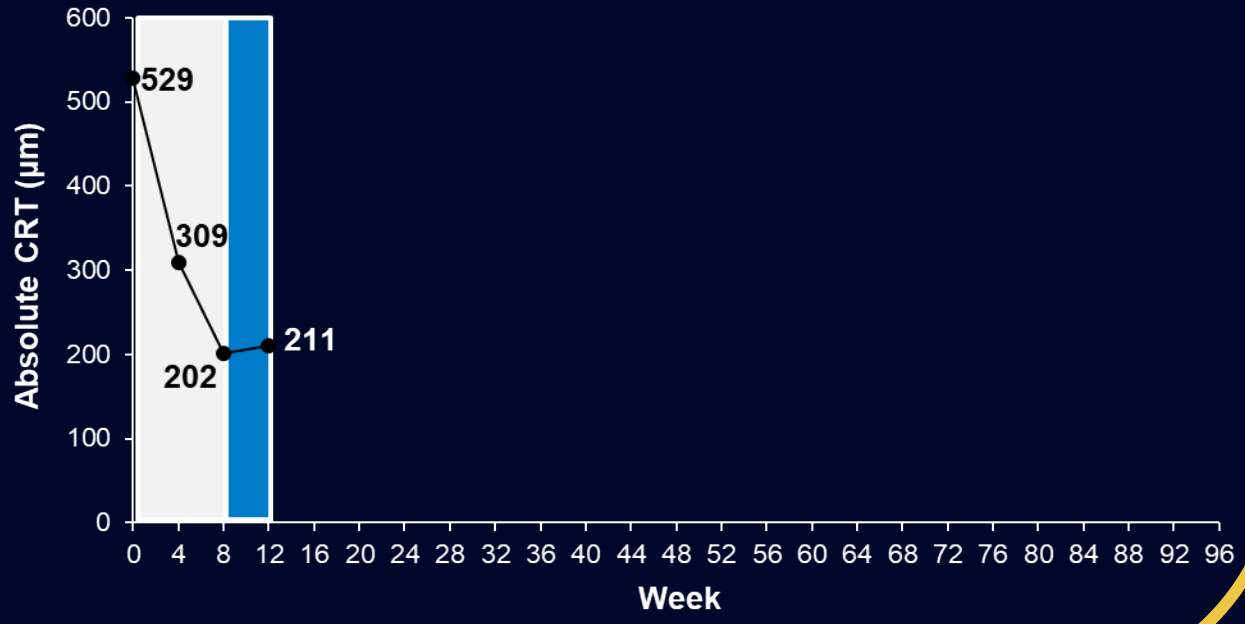
BCVA Through Week 12

pulsar nAMD

Age range (years)	70–80
Sex	Male
Treatment arm	8q16
Baseline BCVA (ETDRS letters)	74
Baseline CRT (µm)	529





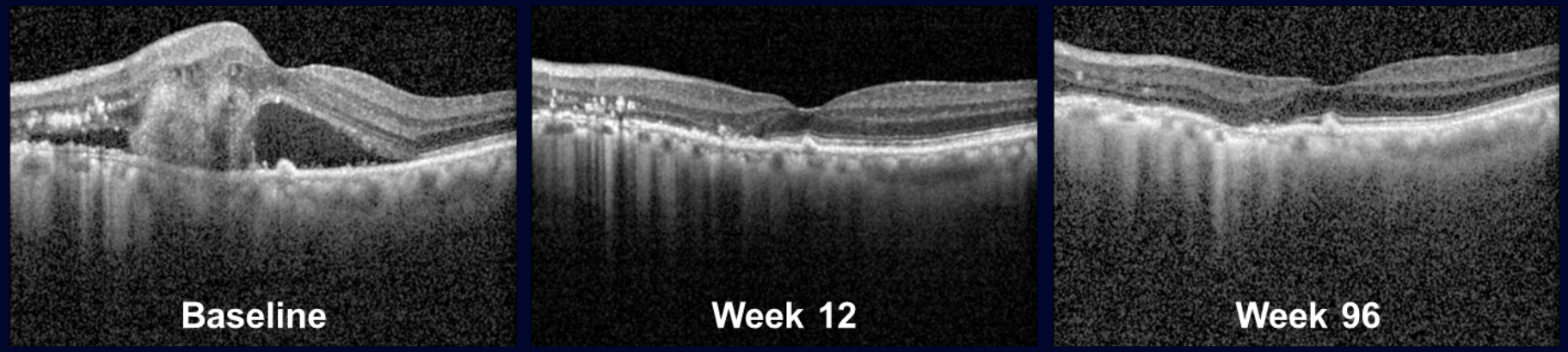


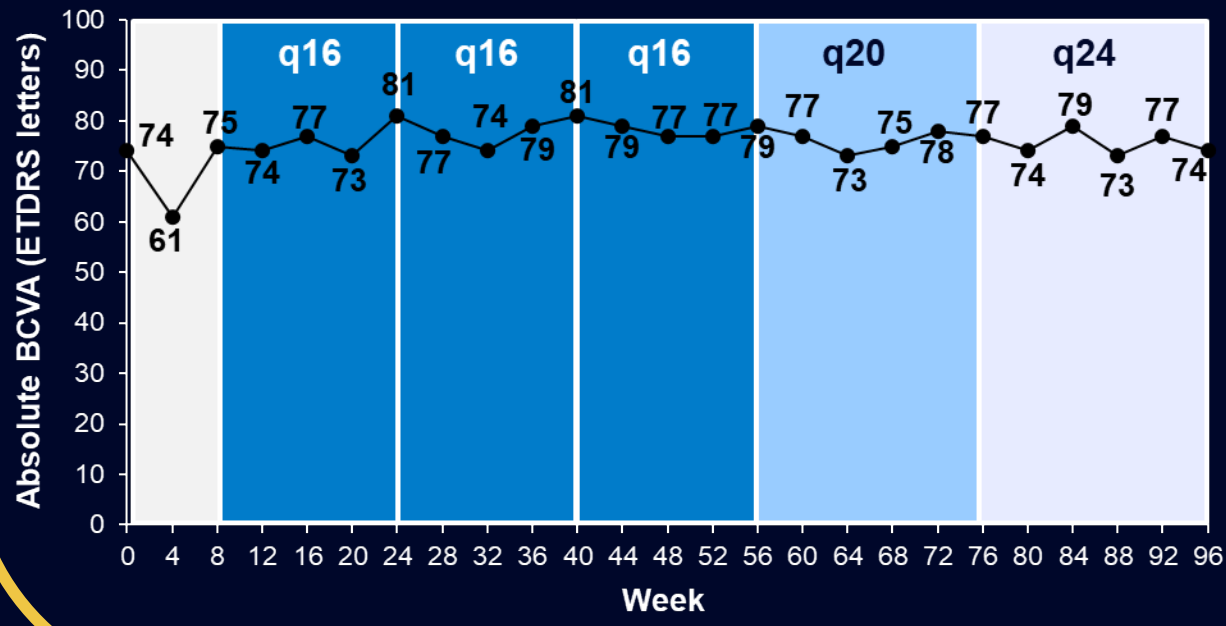
Case 1

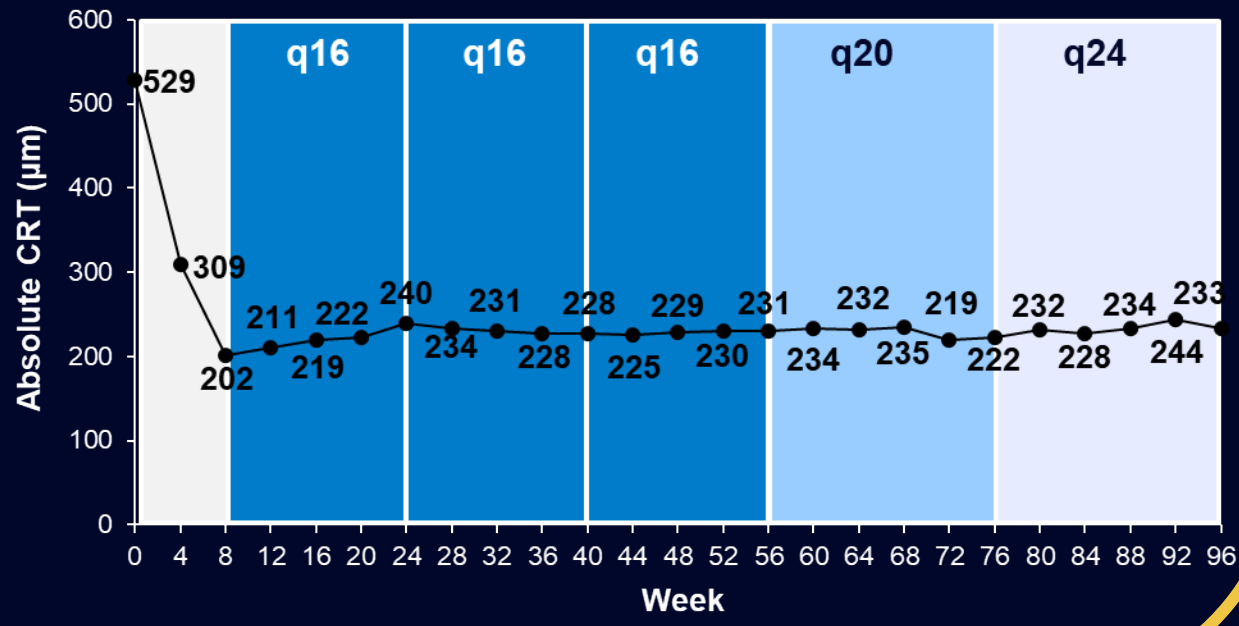
BCVA Through Week 96 (end of study)

pulsar nAMD

Age range (years)	70–80
Sex	Male
Treatment arm	8q16
Baseline BCVA (ETDRS letters)	74
Baseline CRT (µm)	529

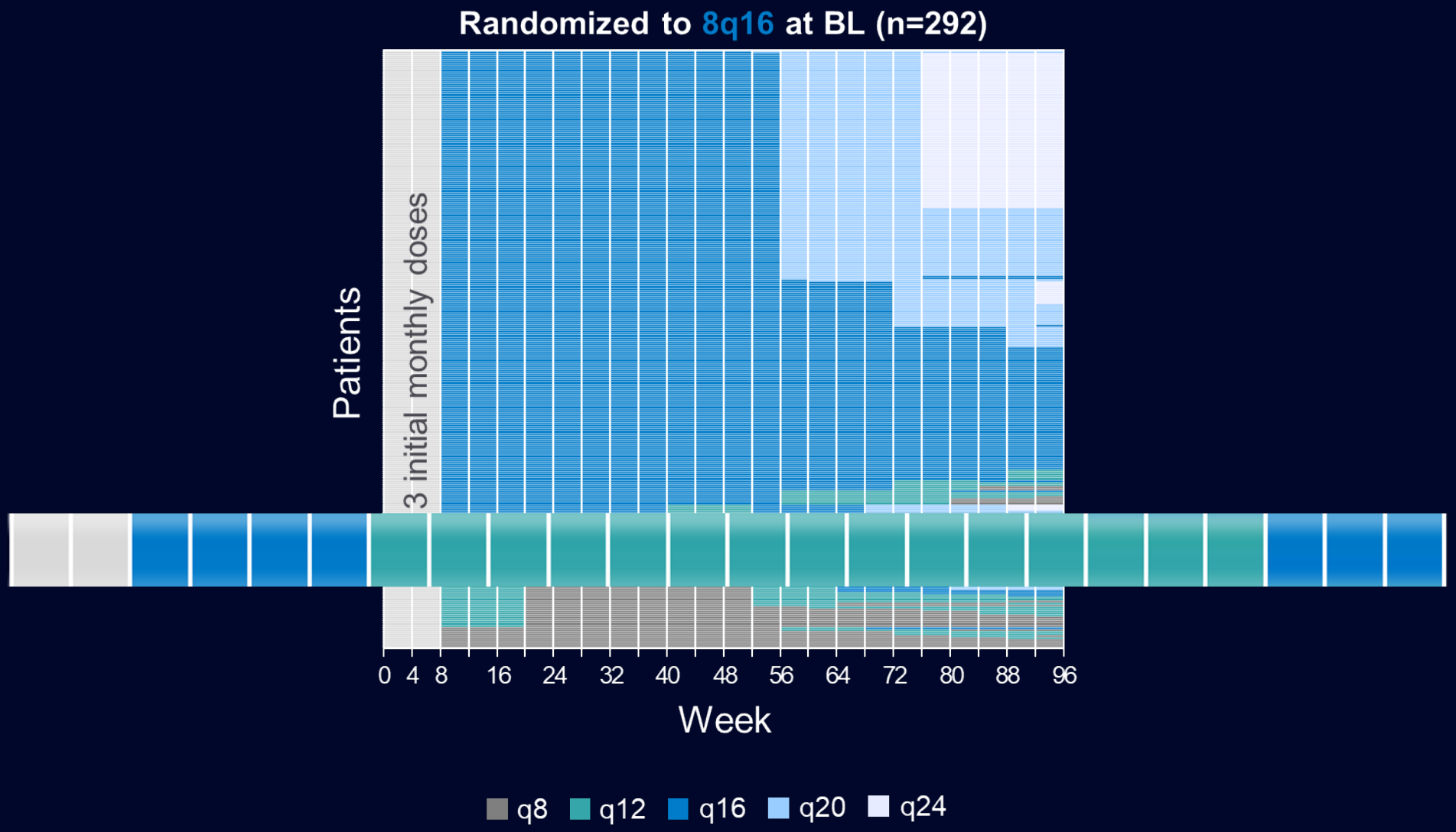






Case 2: Treatment Interval Shortening/Extension Through Week 96

nAMD



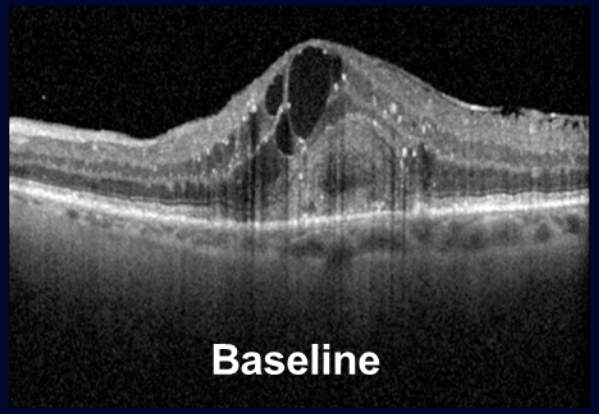
SAF, data are for Week 96 completers.

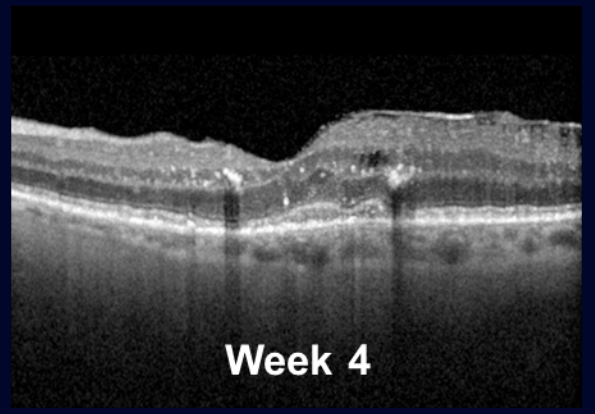
Case 2

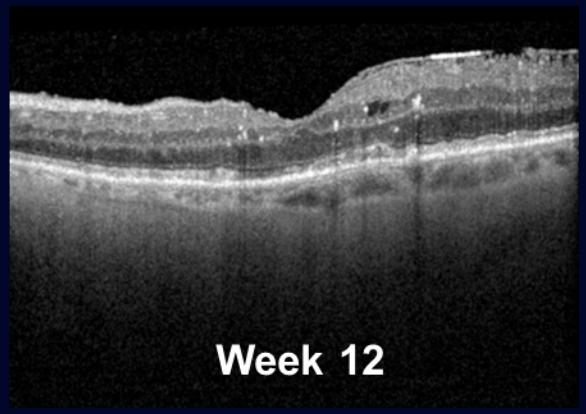
BCVA Through Week 12

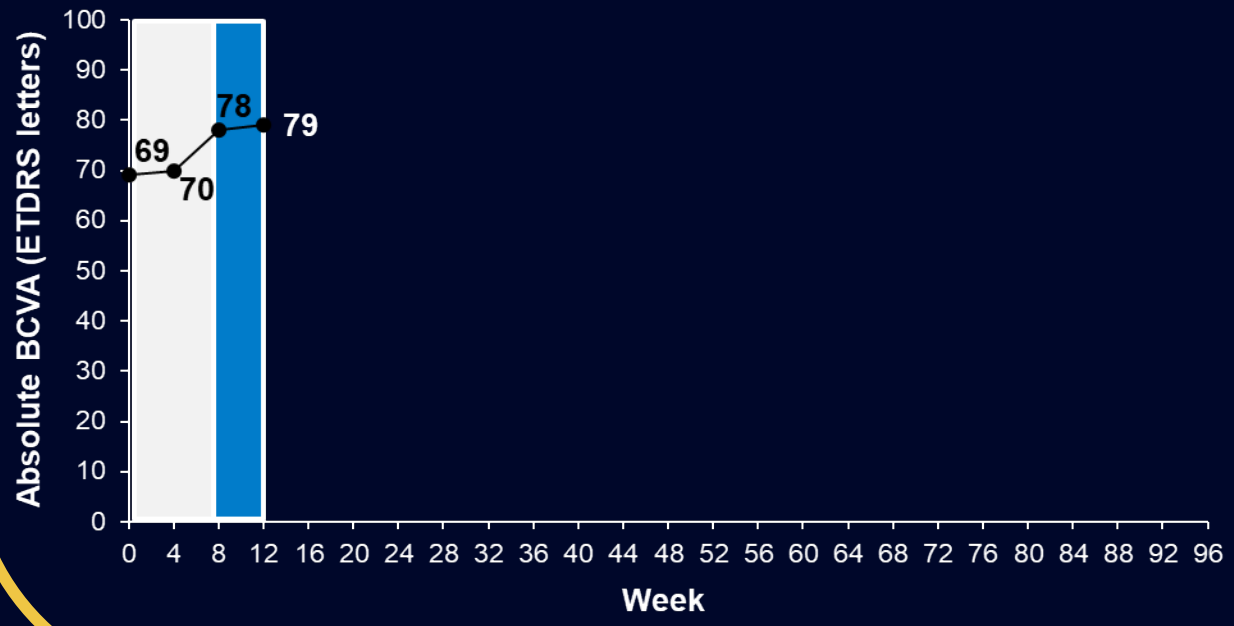
pulsar nAMD

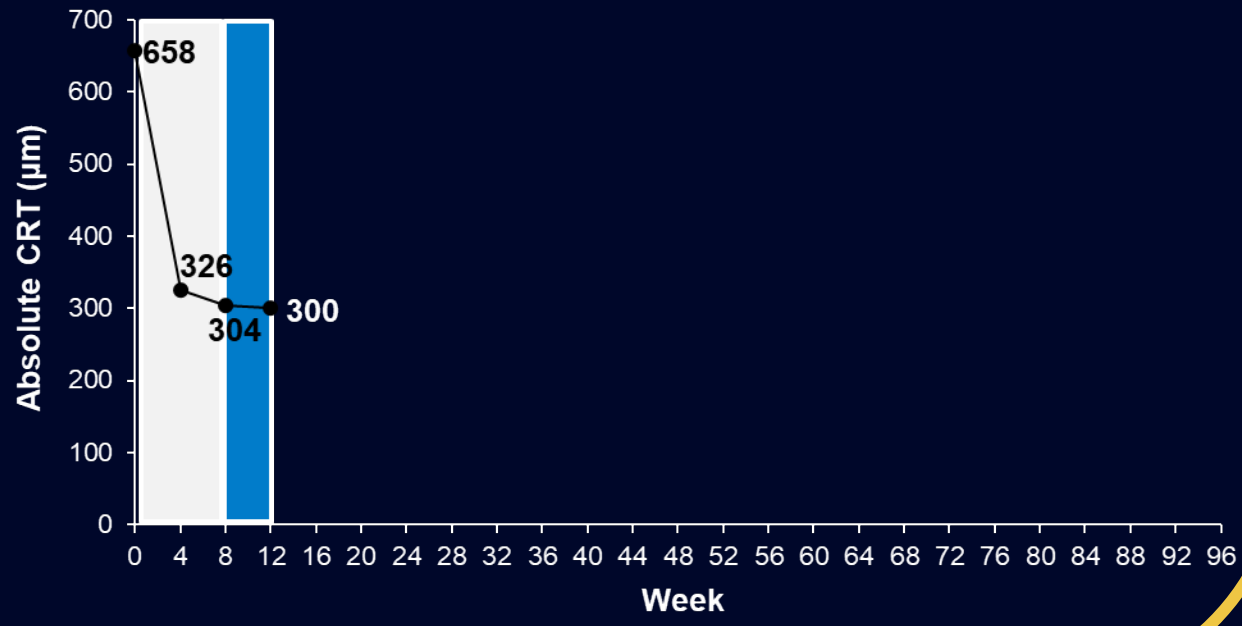
Age range (years)	80–90
Sex	Female
Treatment arm	8q16
Baseline BCVA (ETDRS letters)	69
Baseline CRT (µm)	658









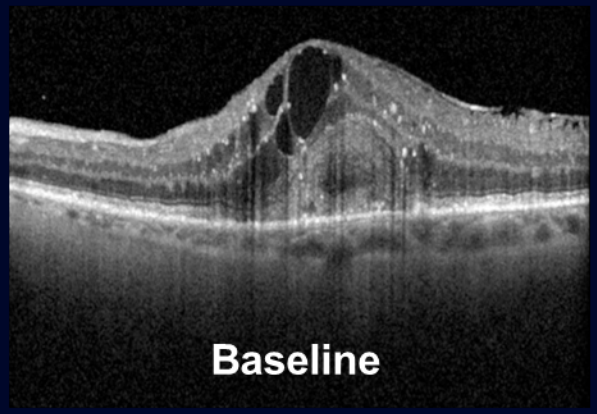


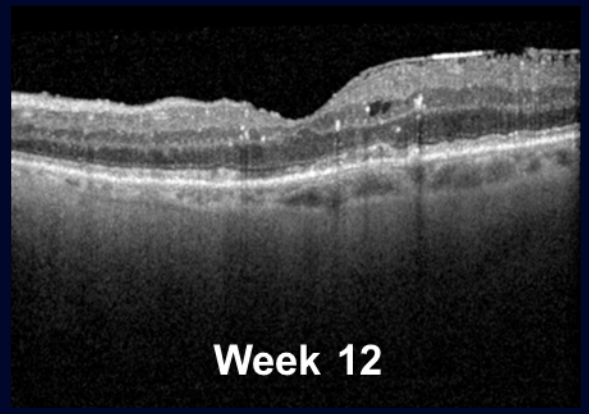
Case 2

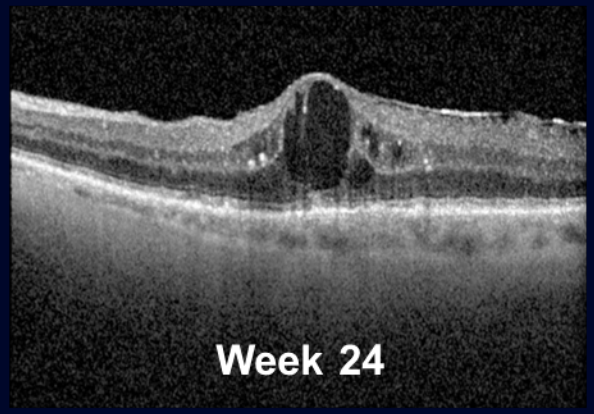
BCVA Through Week 24

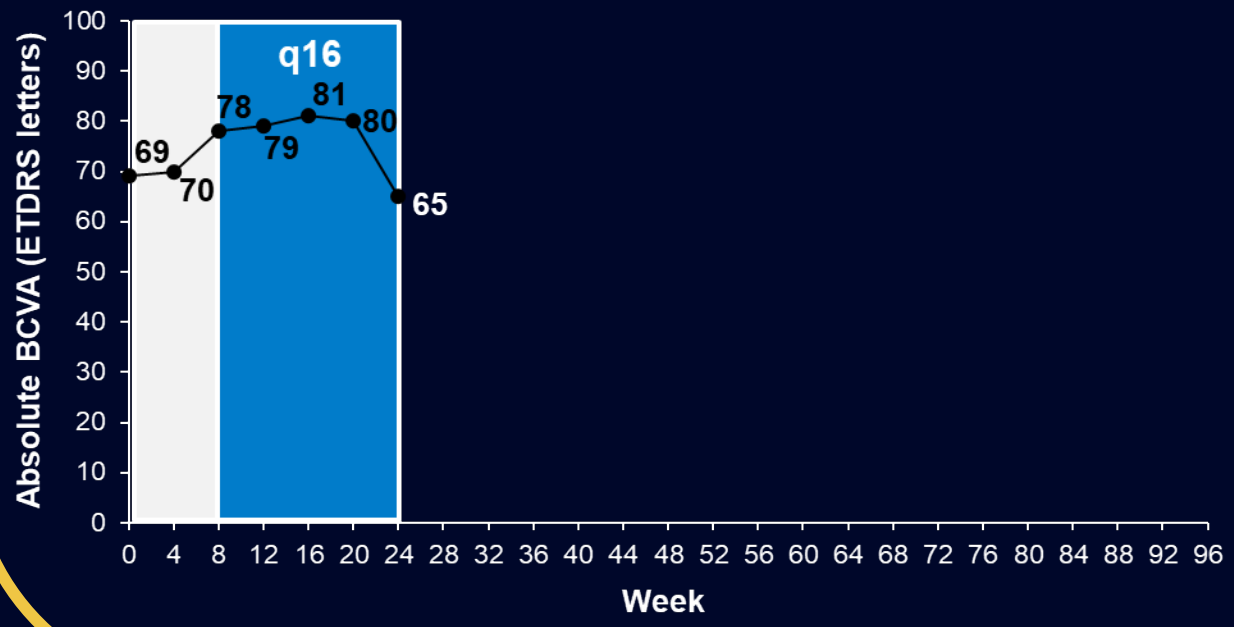
pulsar nAMD

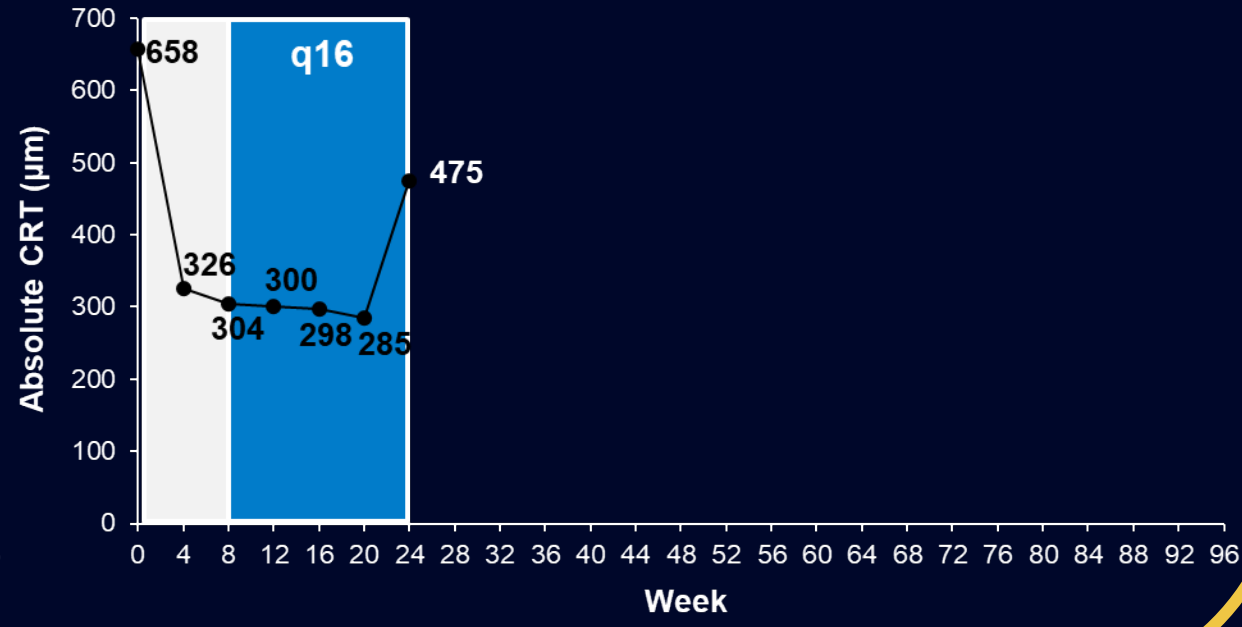
Age range (years)	80–90
Sex	Female
Treatment arm	8q16
Baseline BCVA (ETDRS letters)	69
Baseline CRT (µm)	658









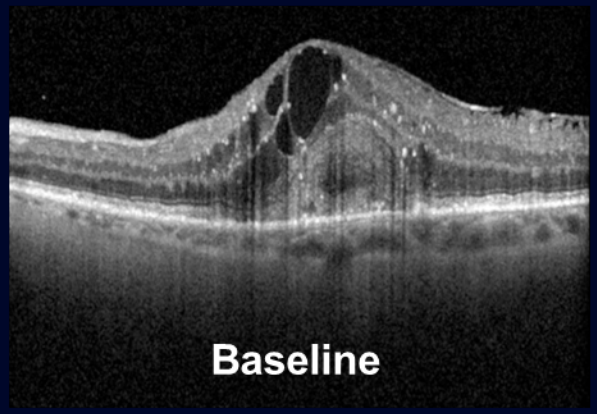


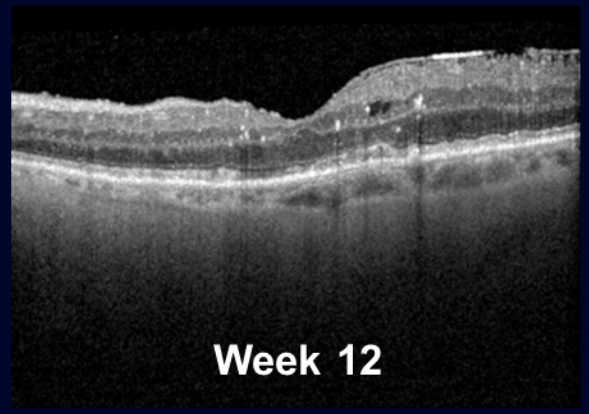
Case 2

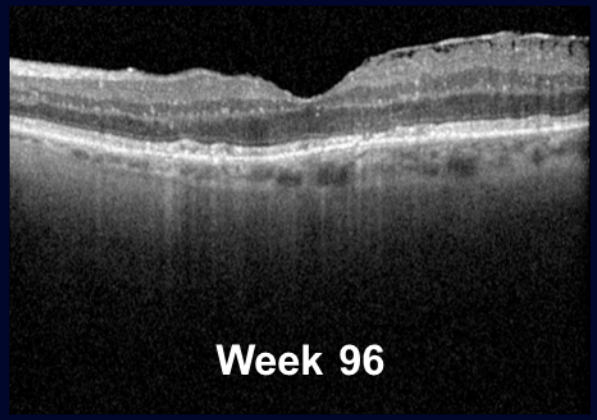
BCVA Through Week 96 (end of study)

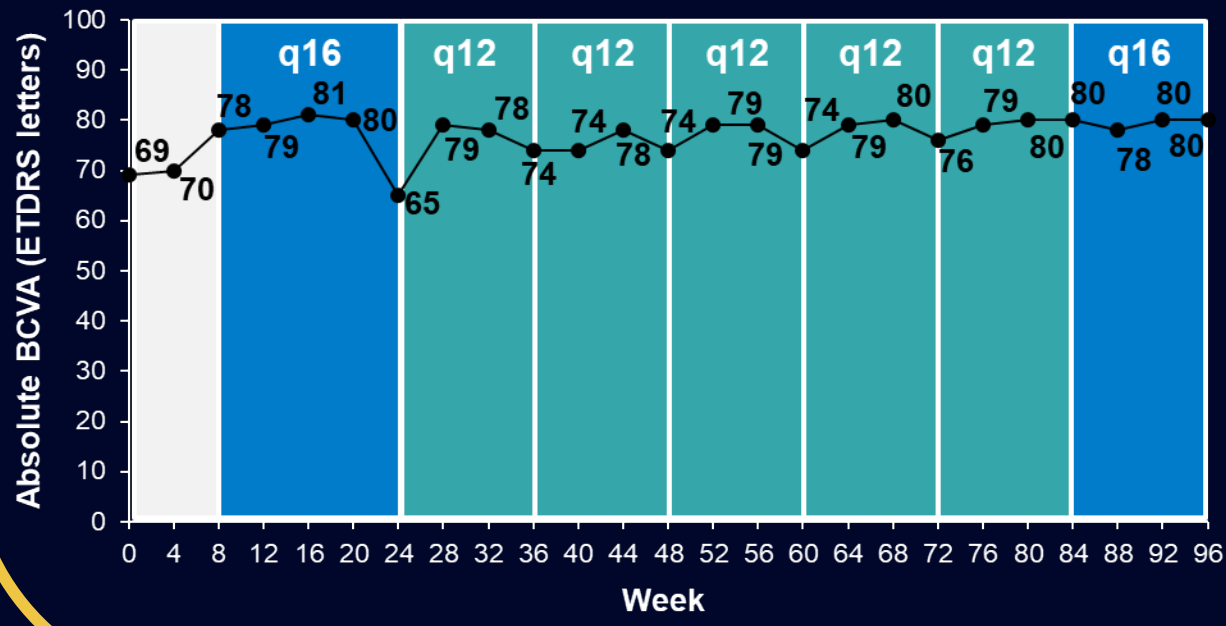
pulsar nAMD

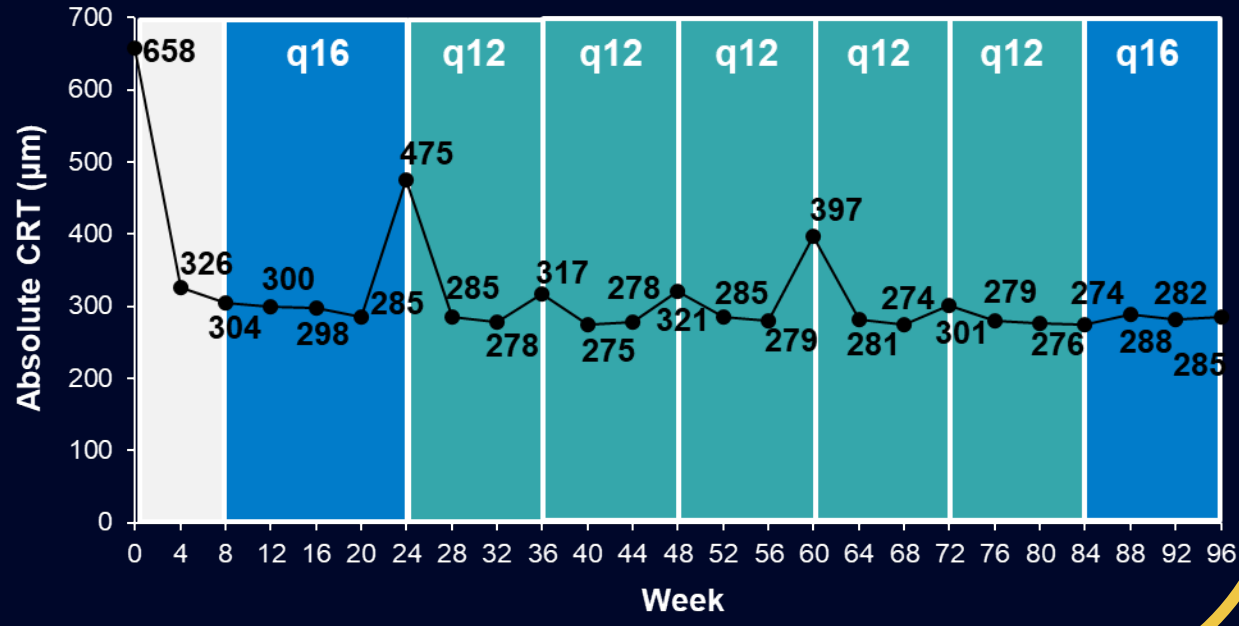
Age range (years)	80–90
Sex	Female
Treatment arm	8q16
Baseline BCVA (ETDRS letters)	69
Baseline CRT (µm)	658







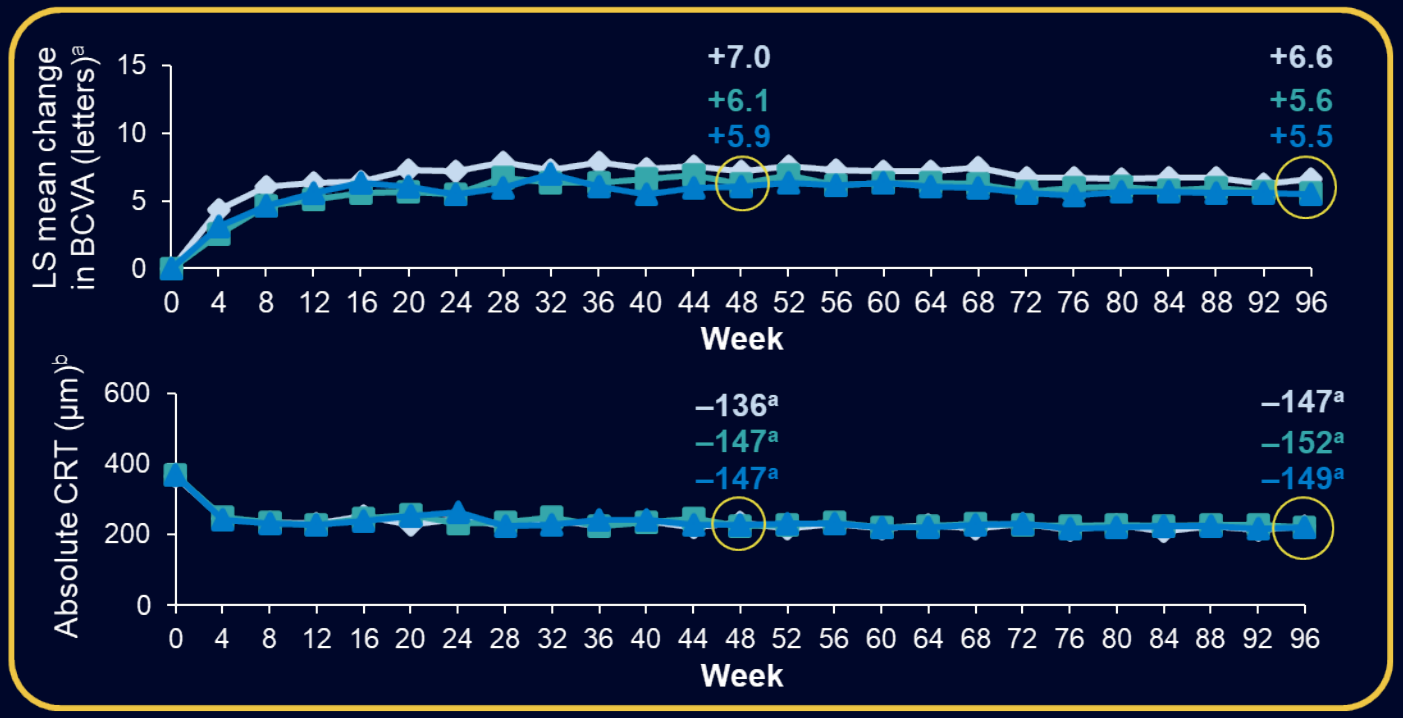


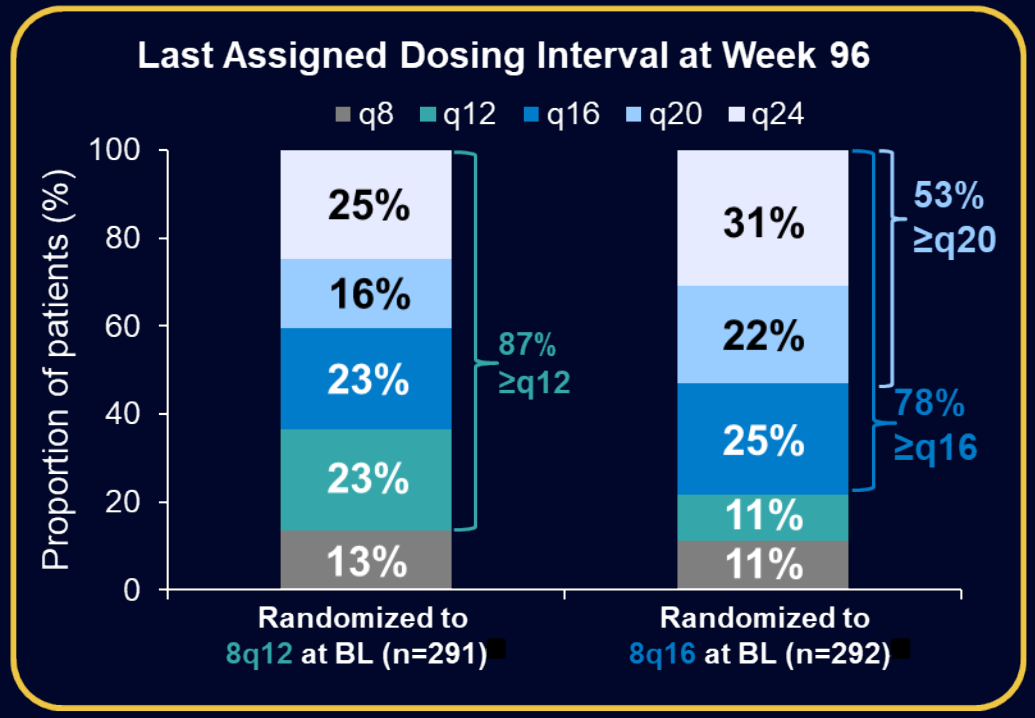


PULSAR: 96-Week Results

pulsar nAMD

- Aflibercept 8 mg groups achieved similar BCVA gains compared with the aflibercept 2 mg group at Week 96
- Anatomic 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).

pulsar
nAMD

Thank you!

- 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
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