Early Fluid Resolution Association with Treatment Interval Maintenance at Week 48 in Patients with Treatment-Naïve Neovascular Age-Related Macular Degeneration Receiving Aflibercept 8 mg: Post Hoc Analysis of the Phase 3 PULSAR Trial

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Disclosures

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PULSAR Study Design and Dosing Schedule

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96-week, multicenter, randomized, double-masked study in patients with treatment-naïve nAMD
Randomized at baseline 1 (2q8) : 1 (8q12) : 1 (8q16)

Key secondary endpoint: Proportion of patients without IRF and SRF in the central subfield

Primary endpoint: Mean change in BCVA (non-inferiority)

	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 (n=336)	X	X	X		X	o	X	o	X	o	X	o	X
8q12 (n=335)	X	X	X		o	X	o	o	X	o	o	X	o
8q16 (n=338)	X	X	X		o	o	X	o	o	o	X	o	o

DRM Criteria for Shortening Dosing Interval

- >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

DRM in Year 1

- Intervals can only be shortened
- Multiple opportunities to shorten interval
- Minimum interval for all patients was Q8

Week 16 and 20: Patients on 8q12 and 8q16 meeting DRM criteria shortened to Q8

Week 24: Patients on 8q16 meeting DRM criteria shortened to Q12

Week 32 and 44 for 8q12 and Week 40 for 8q16: Treatment interval shortened by 4 weeks for patients meeting DRM criteria

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.
2q8, aflibercept 2 mg every 8 weeks after 3 initial monthly injections; **8q12**, aflibercept 8 mg every 12 weeks after 3 initial monthly injections; **8q16**, aflibercept 8 mg every 16 weeks after 3 initial monthly injections; **BCVA**, best-corrected visual acuity; **CST**, central subfield thickness; **DRM**, dose regimen modification; **IRF**, intraretinal fluid; **nAMD**, neovascular age-related macular degeneration; **Q8**, every 8 weeks; **Q12,** every 12 weeks; **SRF**, subretinal fluid; **Wk**, week.

48-Week Visual and Anatomic Outcomes

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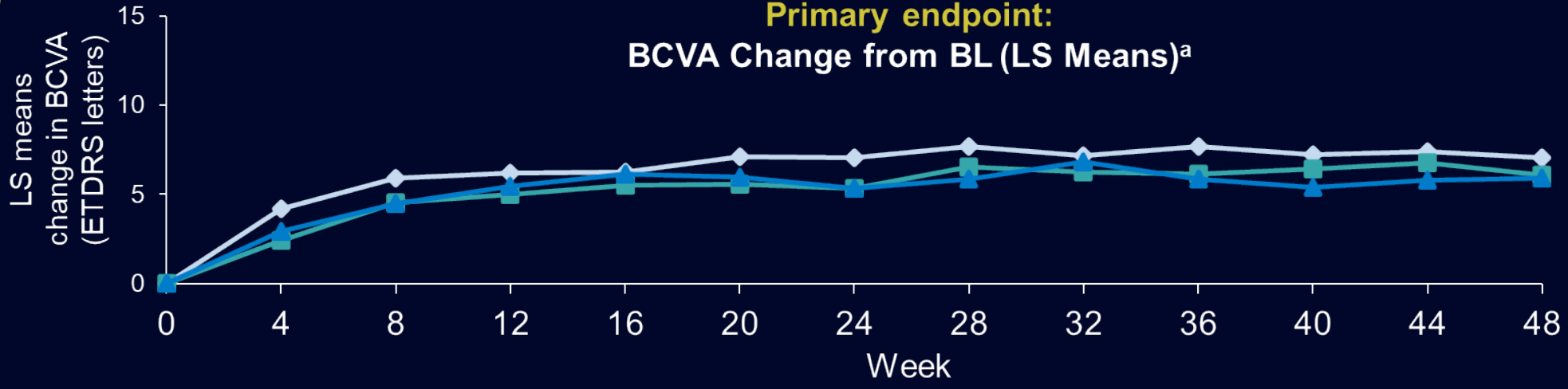
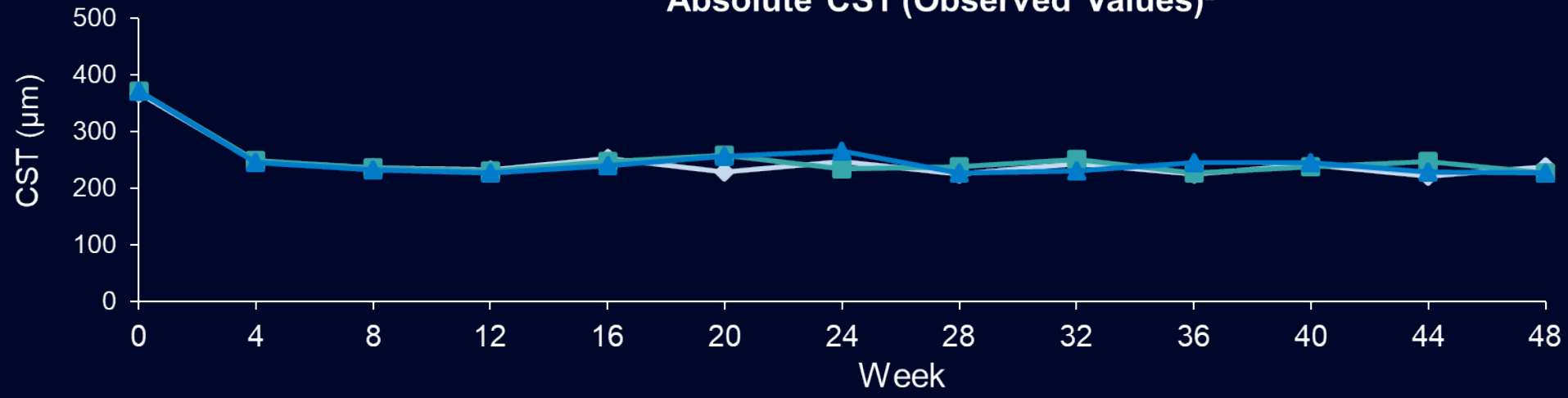
Primary endpoint:

BCVA Change from BL (LS Means)[a]



BCVA Change from BL at Week 48 (LS means; ETDRS letters)
+7.0 2q8
+6.1 8q12
+5.9 8q16

Absolute CST (Observed Values)[b]



CST Change from BL at Week 48 (LS means;[a] µm)
–147 8q16
–147 8q12
–136 2q8

[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; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **FAS**, full analysis set; **ICE**, intercurrent event; **LS**, least squares; **MRMM**, mixed model for repeated measures.

Analysis of Early Fluid Resolution Associated with Dosing Interval

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Objective:

To evaluate if early fluid resolution during the initial treatment phase may serve as a biomarker to predict the likelihood of patients with nAMD achieving extended dosing intervals with aflibercept 8 mg

Methods:

The presence of fluid at Weeks 4, 8, and 12 was analyzed in patients who received intravitreal aflibercept injections, after 3 initial monthly injections. Patients were categorized depending on their fluid status up to Week 12. In this analysis, we focus on the aflibercept 8q16 treatment group

	Day 1	Week 4	Week 8	Week 12
Aflibercept 8q16				
Patients who were fluid free at Week 4		Fluid free 	/	/
Patients who were fluid free at Weeks 4 and 8		Fluid free 	Fluid free 	/
Patients who were fluid free at Weeks 4, 8, and 12		Fluid free 	Fluid free 	Fluid free 
Patients who were never fluid free during the initial treatment phase		Fluid presence 	Fluid presence 	Fluid presence 

Fluid status was not assessed on Day 1. Fluid is defined as IRF and SRF in the central subfield. Fluid free is defined as absence of IRF and SRF in central subfield. / = patients who were either fluid free, not fluid free, or with unknown fluid status.

Early Fluid Resolution: A Potential Biomarker

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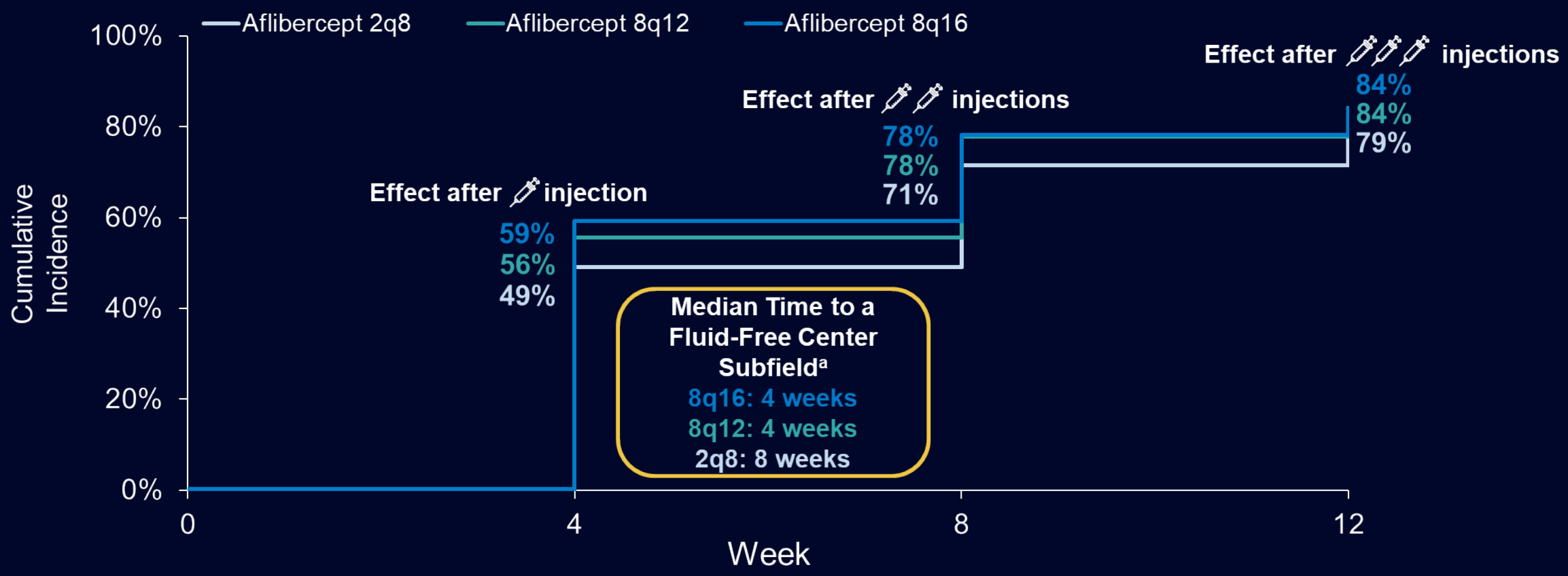
Time to a Fluid-Free Central Subfield



FAS, 2q8 n=336; 8q12 n=335; 8q16 n=338. Time to fluid-free central subfield is defined as the time of first injection until the time where a patient did not have any IRF or SRF in the central subfield for the first time (regardless of whether any retinal fluid was found again after that). [a]Time to fluid-free retina was analyzed using the Kaplan–Meier method, using the study visits (i.e., multiples of 4 weeks) and not the calendar time as unit.

Patients Maintaining ≥Q12- and Q16-Week Dosing Intervals at Week 48 Based on Early Fluid Status: Aflibercept 8q16 Treatment Group

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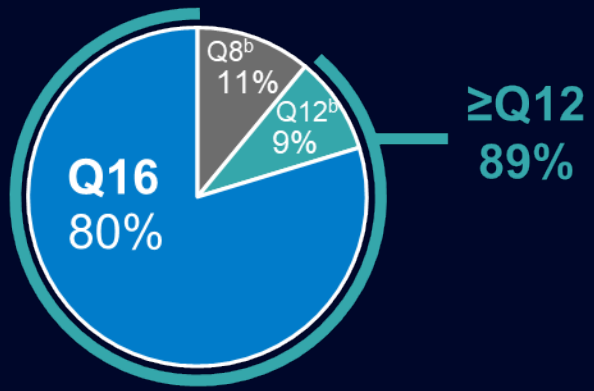
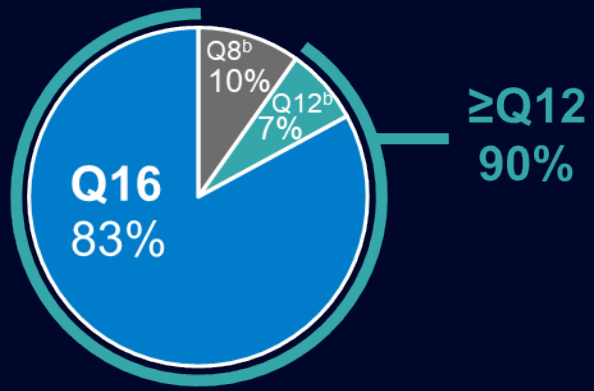
Fluid Free at Week 4 (n=182[a])



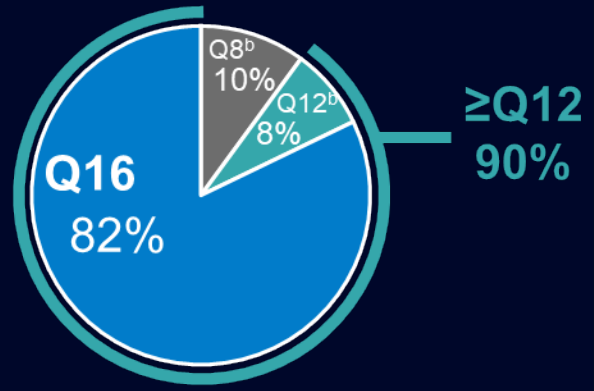
FAS, LOCF (n=200)	BCVA (ETDRS letters)	CST (µm)
Baseline	60.9	342
Week 48	66.1	221

Fluid Free at Weeks 4 and 8 (n=164[a])



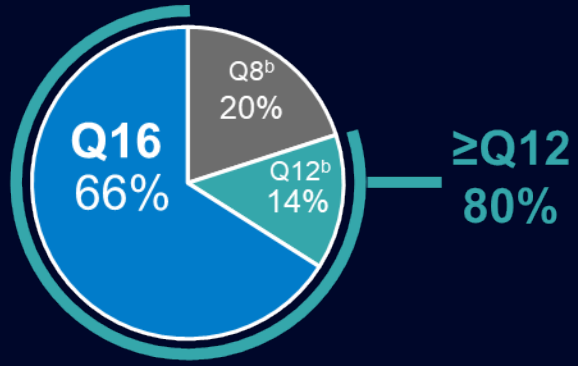
FAS, LOCF (n=179)	BCVA (ETDRS letters)	CST (µm)
Baseline	61.3	335
Week 48	67.1	219

Fluid Free at Weeks 4, 8, and 12 (n=159[a])



FAS, LOCF (n=172)	BCVA (ETDRS letters)	CST (µm)
Baseline	61.5	336
Week 48	67.2	219

Patients Who Were Never Fluid Free During the Initial Treatment Phase (n=50[a])



FAS, LOCF (n=52)	BCVA (ETDRS letters)	CST (µm)
Baseline	57.6	432
Week 48	62.1	249

[a]Patients completing Week 48. [b]Patients shortened based on DRM assessments at some point through Week 48. **LOCF**, last observation carried forward.

Conclusions

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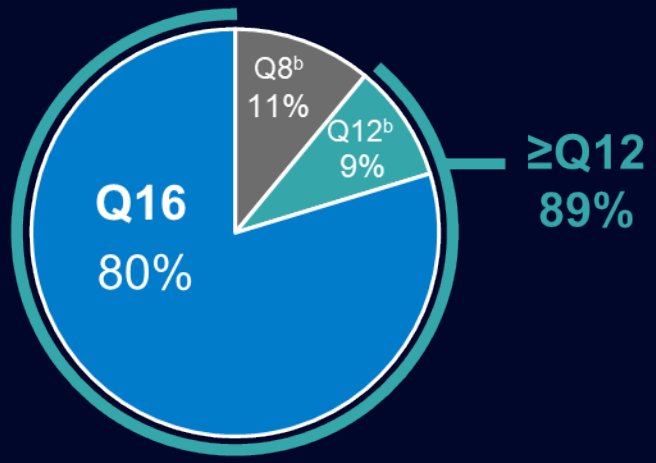
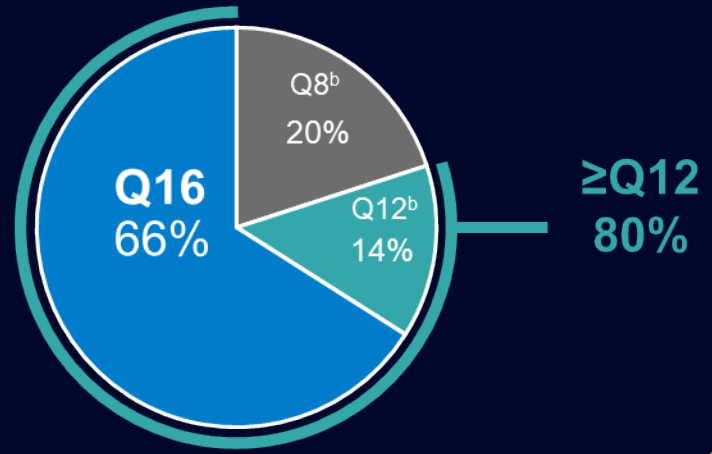
Fluid Free at Week 4 (n=182[a])



Patients who were Never Fluid Free During the Initial Treatment Phase (n=50[a])



- Approximately **80% of patients** who were **fluid free at Week 4 maintained a Q16 interval** until Week 48 compared with **66% of patients** who had **never been fluid free** during the initial treatment phase
- These results suggest that early fluid resolution during the initial treatment phase may serve as a biomarker to predict the likelihood of patients with nAMD achieving extended dosing intervals with aflibercept 8 mg

[a]Patients completing Week 48. [b]Patients shortened based on DRM assessments at some point through Week 48.