PULSAR Extension: 156-week retinal fluid and PED outcomes in patients with nAMD receiving aflibercept 8mg

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PULSAR Extension Design

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PULSAR (BL–W96)
(Masked)

Patients with treatment-naïve nAMD

2q8 group (n=336)
Aflibercept 2 mg every 8 weeks after 3 initial monthly injections

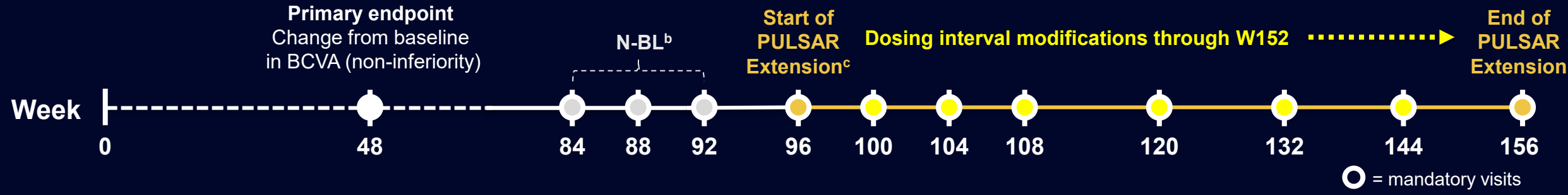
8q12 group (n=335)
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections

8q16 group (n=338)
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections

PULSAR Extension (W96–W156)
(Open label and optional)[a]

2q8→8mg group (n=208)
Patients originally assigned to 2q8 switched to aflibercept 8 mg every 12 weeks

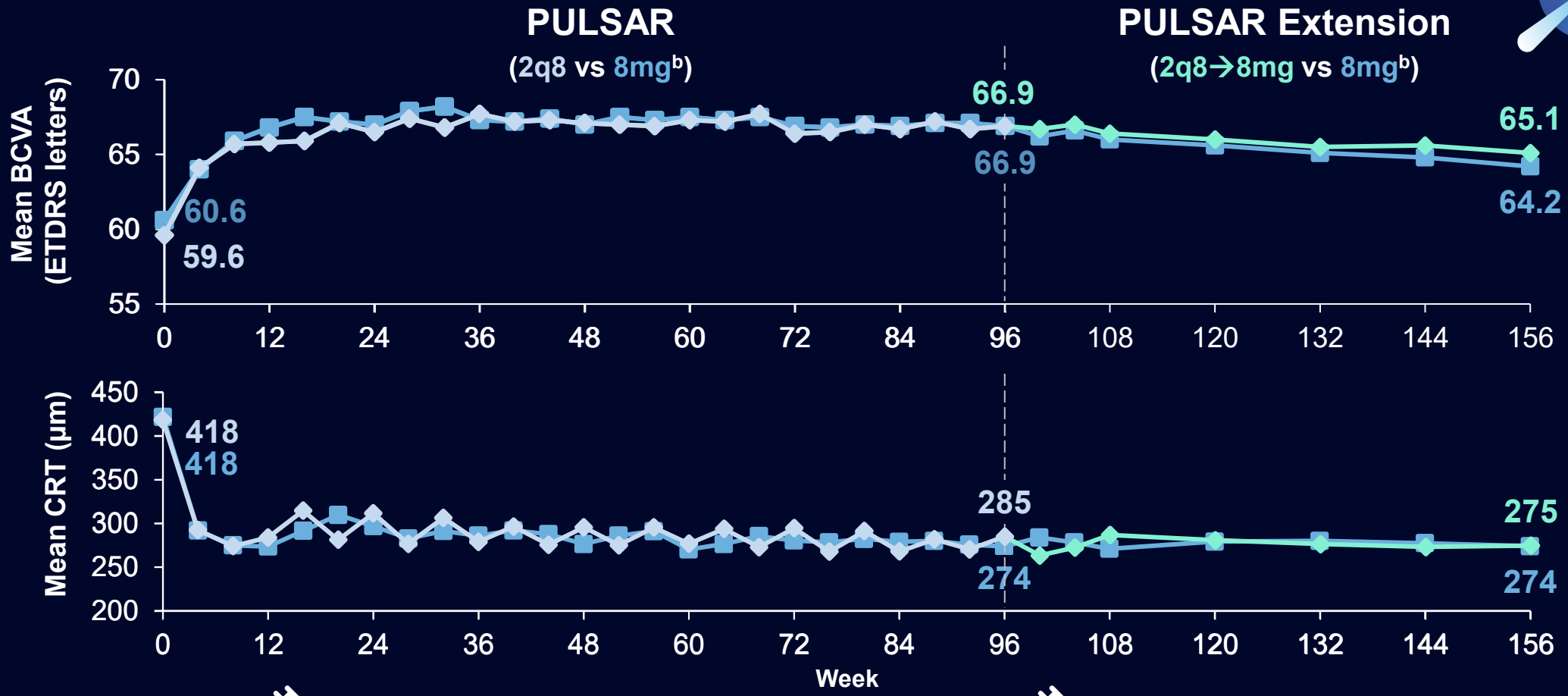
8mg group (n=417)
Patients originally assigned to 8q12 or 8q16 continued aflibercept 8 mg on last assigned dosing interval



[a]To be eligible for PULSAR Extension, patients were required to have ≥1 BCVA and CRT assessments between Week 84 and Week 92. Masked transition period (W96–108) was followed by open-label part (W108–W156). [b]N-BL was an average of values from W84, W88, and W92. [c]Optional phase added while PULSAR was ongoing; therefore, not all patients were able to enroll due to time constraints.

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; **BL,** baseline; **CRT**, central subfield retinal thickness; **nAMD**, neovascular age-related macular degeneration; **N-BL**, new baseline; **W**, week.

Mean BCVA and CRT Through Week 156[a]



Mean number of injections from baseline to Week 96 (96 weeks)[c]
2 mg: 12.8
8 mg: 9.0

Mean number of injections from Week 96 to Week 156 (60 weeks)[c]
8 mg: 4.9
8 mg: 3.9

No new safety signals were identified through 156 weeks. The safety profile remained consistent with previous findings.

Note: At Week 156, the 2q8→8mg group (n=208) and 8mg group (n=417) reported LS mean (95% CI) changes from BL (MMRM) in BCVA of +4.6 (2.6, 6.6) letters and +3.4 (1.9, 4.9) letters, respectively, and in CRT of −145 (−155, −136) µm and −148 (−156, −140) µm, respectively. MMRM was used to generate BCVA/CRT LS means for the eFAS with BL BCVA/CRT as a covariate; treatment group (aflibercept 8q12, 8q16, 2q8), visit, and stratification variables (geographic region [Japan vs rest of the world] and BL BCVA [<60 vs ≥60 letters]) as fixed factors; and terms for the interaction between visit and BL BCVA/CRT and the interaction between visit and treatment. [a]eFAS (observed cases). [b]Patients who were randomly assigned to the 8q12 or 8q16 groups at the beginning of the PULSAR study and continued treatment with aflibercept 8 mg through the PULSAR Extension. [c]eSAF (156-week completers; 2q8→8mg, n=186; 8q12, n=185; 8q16, n=190; 8mg, n=375). **CI**, confidence interval; **eSAF**, safety analysis set in the PULSAR Extension; **ETDRS**, Early Treatment Diabetic Retinopathy Study; **LS**, least squares; **MMRM**, mixed model for repeated measures.

Fluid Resolution: Patients with No Intraretinal and Subretinal Fluid at Week 156

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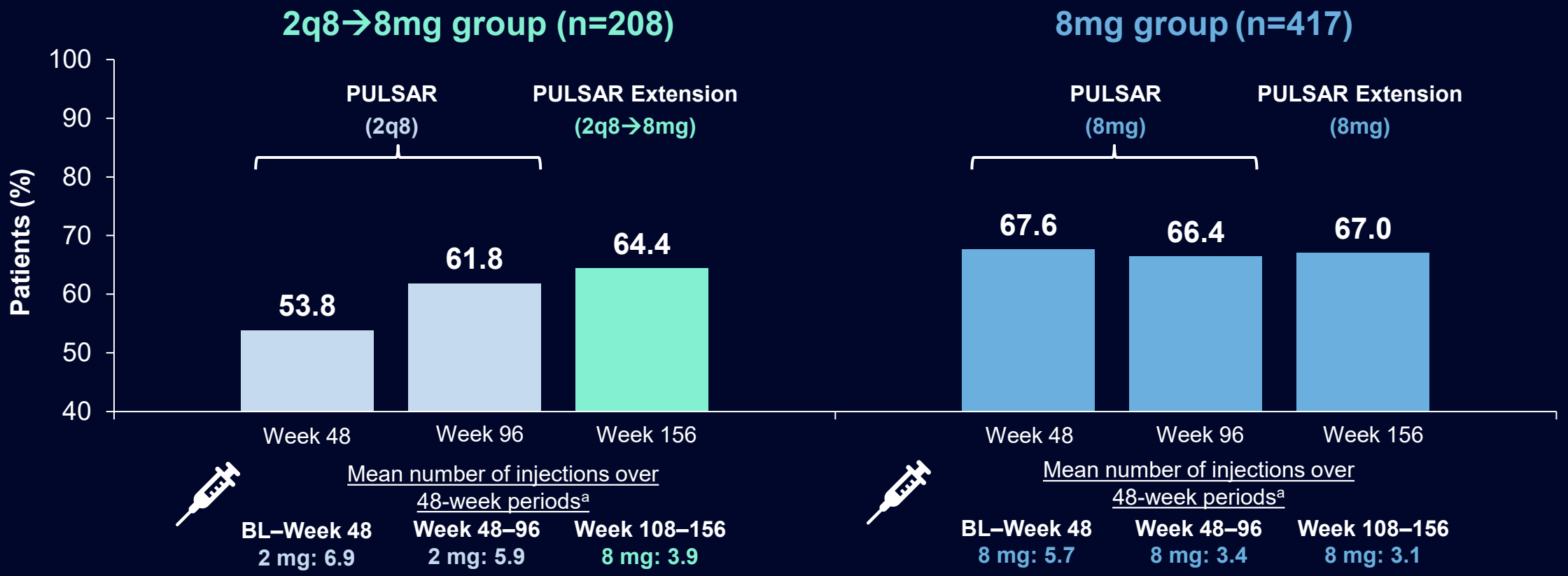

- The proportion of patients with fluid resolution was maintained in the **aflibercept 2q8→8mg** group through 96 weeks and was **sustained after switching to 8 mg** through Week 156
- **Long-term fluid resolution** was observed in the 8mg group with extended dosing intervals through Week 156
- The proportion of patients with fluid resolution was **similar in the 2q8→8mg and 8mg groups** at Week 156

eFAS (LOCF). Fluid resolution defined as no IRF and no SRF in central subfield. Fluid status was evaluated pre-injection. eFAS (LOCF). [a]eSAF (156-week completers; 2q8→8mg, n=186; 8mg, n=375).
IRF, intraretinal fluid; **LOCF**, last observation carried forward; **SRF**, subretinal fluid.

2q8→8mg Group: Patients with Fluid Resolution 4 and 8 Weeks After Active Injections

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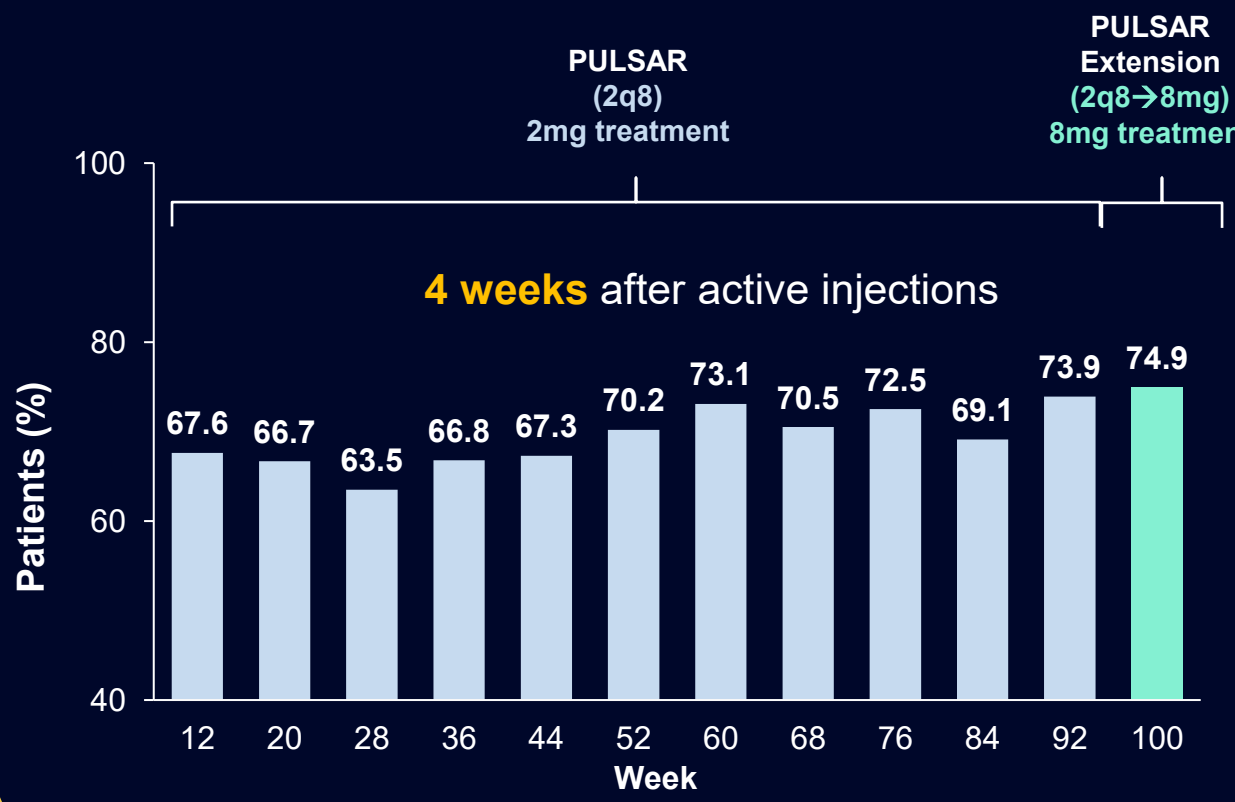
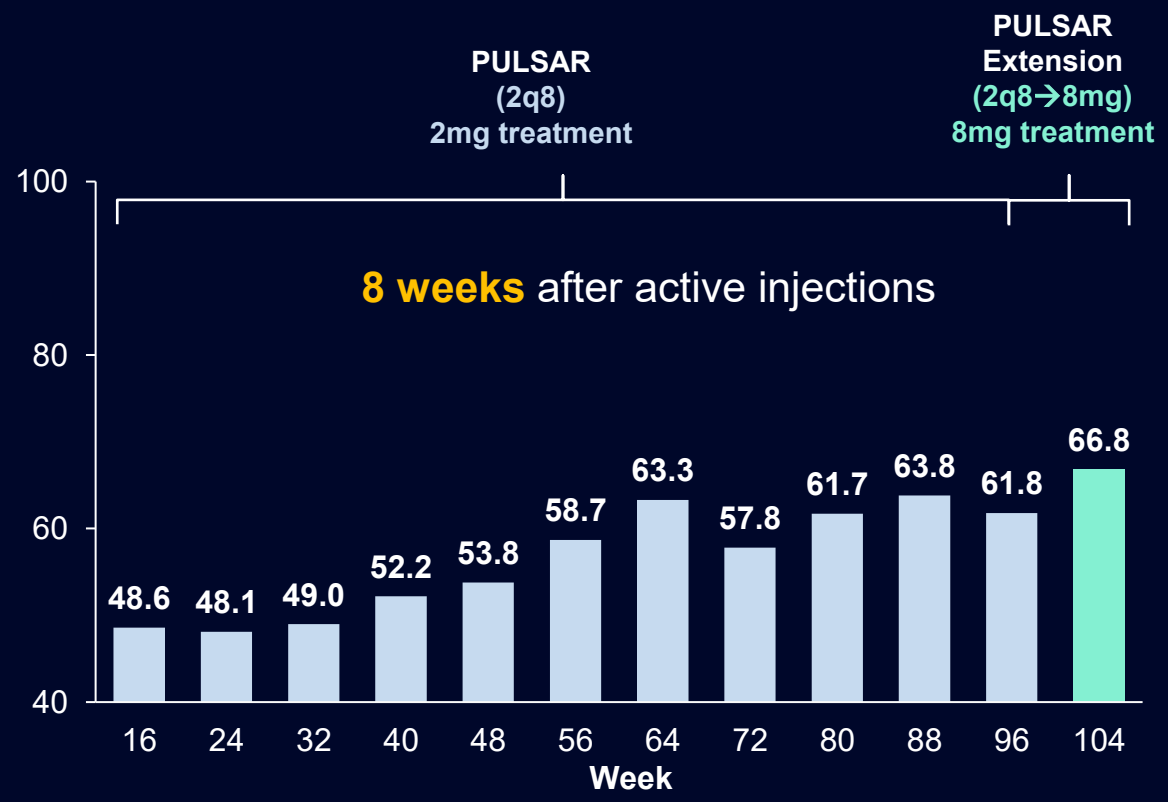
Aflibercept 2q8 dosing regimen through Week 96 of PULSAR																							
Day 1	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96
X	X	X		X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X	o	X





Stippled boxes = initial treatment phase; X = active injection; o = sham injection.
eFAS (LOCF). Patients entering the PULSAR extension: 2q8→8mg group (n=208). Presence of fluid was evaluated prior to active injection administration. Aflibercept 2 mg injections were given at Weeks 0, 4 and 8, and then 8-weekly from Week 16 to Week 88. The first aflibercept 8 mg injection was administered at Week 96.

2q8→8mg Group: Proportion of Patients with Fluid Resolution 4 and 8 Weeks After Aflibercept 2 mg and 8 mg Injections

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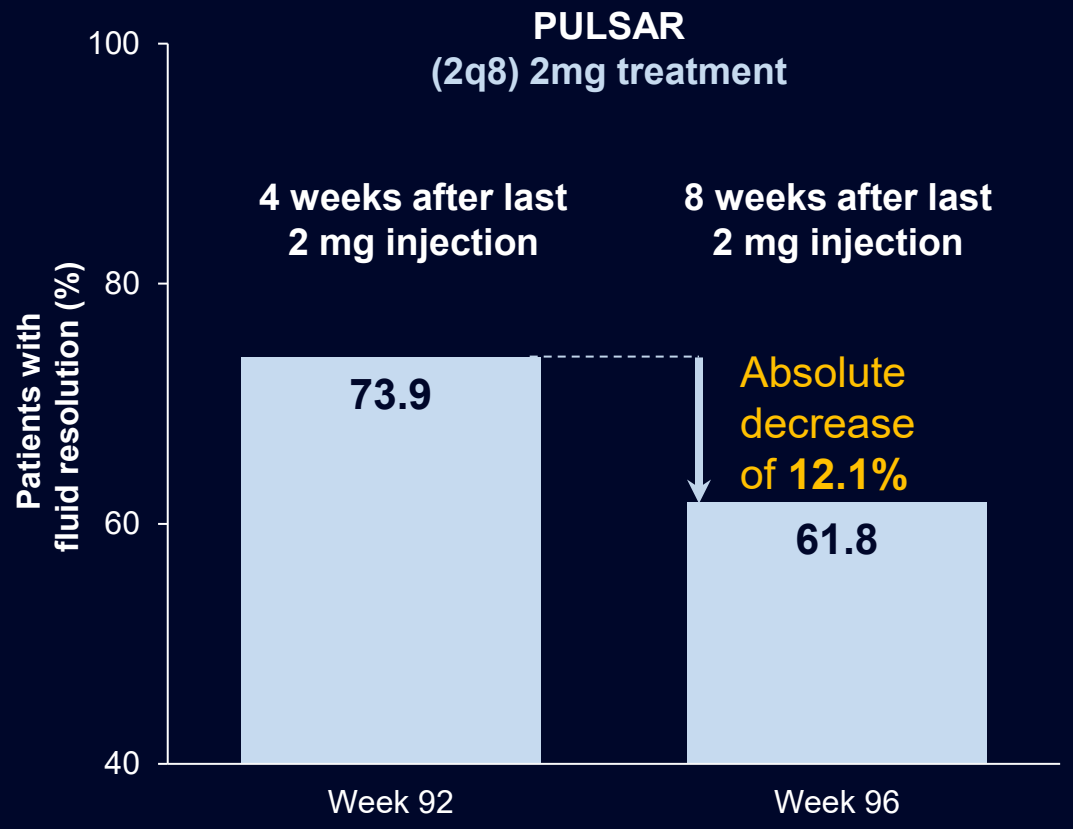
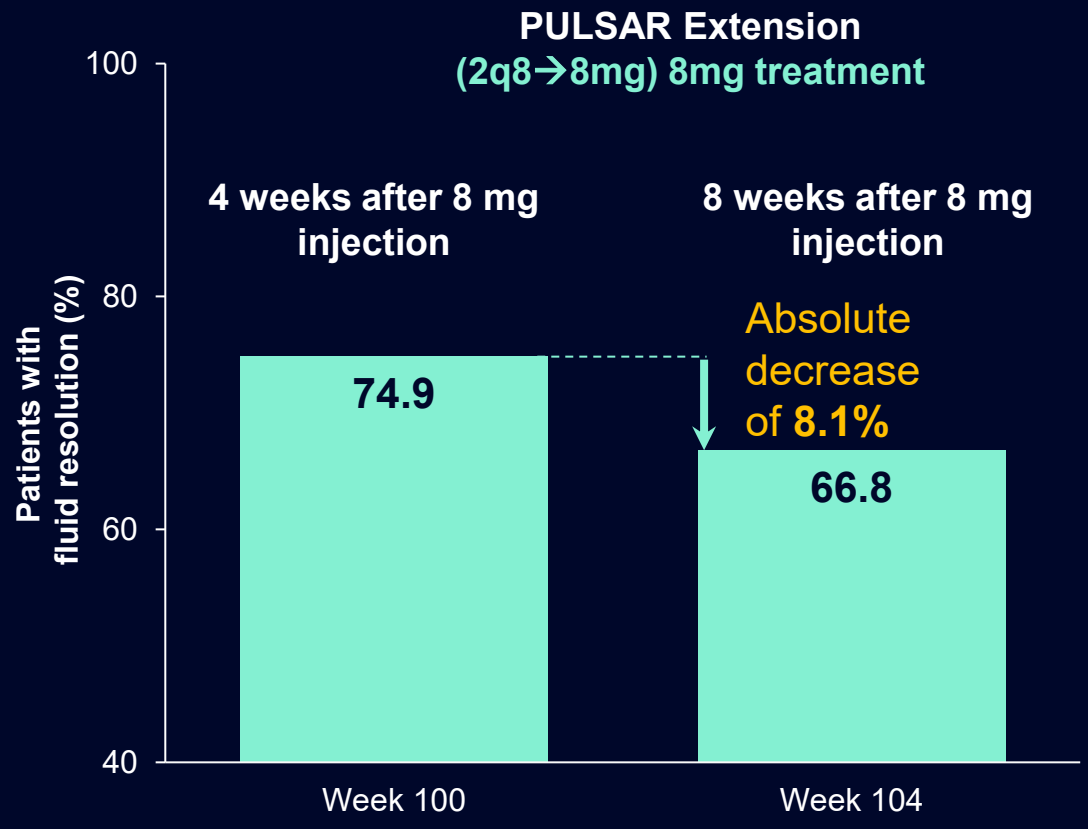
Difference in Proportion of Patients with Fluid Resolution 4 and 8 Weeks After the Last 2 mg Injection



Difference in Proportion of Patients with Fluid Resolution 4 and 8 weeks After the First 8 mg Injection



eFAS (LOCF). Patients entering the PULSAR extension: 2q8→8mg group (n=208).

Sub-RPE Fluid: PED Outcomes

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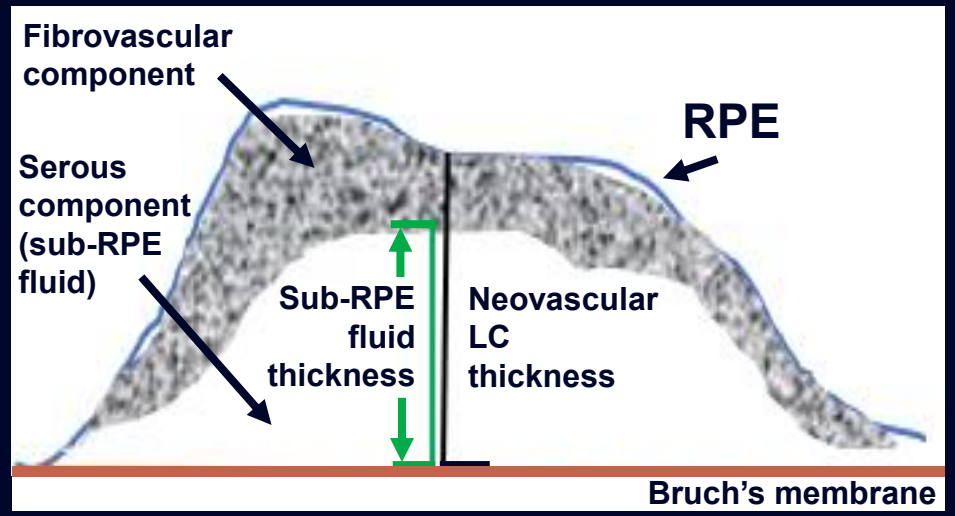
- Pigment epithelial detachment (PED) is characterized by the separation of the RPE from the Bruch's membrane, resulting in a space that can be filled with fluid, blood, drusen, or fibrovascular material
- The neovascular lesion complex (LC) is comprised of the serous (sub-RPE fluid) and fibrovascular component



Objective:

To assess sub-RPE fluid over 156 weeks in patients who switched from aflibercept 2 mg to 8 mg, and who stayed on aflibercept 8 mg

Outcome measures[a]:

- Proportion of patients with sub-RPE fluid
- Mean thickness of sub-RPE fluid in patients with serous component of PED involving the foveal center

PED characteristics at PULSAR baseline[b]	2q8→8mg (n=208)	All 8mg (n=417)
Patients with sub-RPE fluid, n (%)	110 (52.9)	210 (50.4)
Patients with sub-RPE fluid with involvement of foveal center, n (%)	24 (11.5)	52 (12.5)

[a]Assessed using SD-OCT at Wisconsin Reading Center. [b]eFAS. **eFAS**, extension full analysis set; **RPE**, retinal pigment epithelium; **SD-OCT**, spectral-domain optical coherence tomography

Patients with Presence of Sub-RPE Fluid Through Week 156[a]

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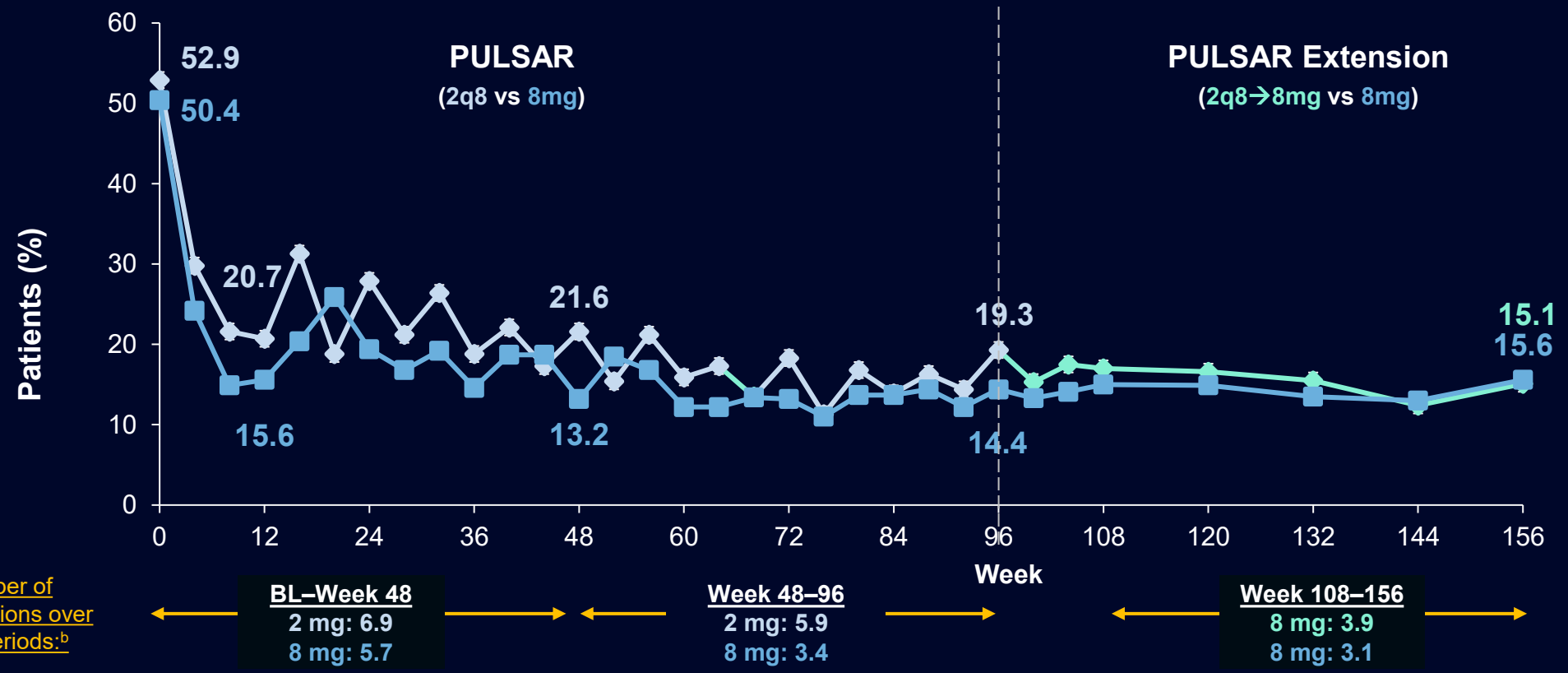

Mean number of actve injections over 48-week periods:[b]

BL–Week 48	Week 48–96	Week 108–156
2 mg: 6.9	2 mg: 5.9	8 mg: 3.9
8 mg: 5.7	8 mg: 3.4	8 mg: 3.1

- At **Week 96**, a **lower proportion** of patients had presence of sub-RPE fluid **with aflibercept 8 mg** than with aflibercept 2 mg
- At **Week 156**, the **proportion of patients** with presence of sub-RPE fluid was **generally maintained in the 8mg group**
- Results in the **2q8→8mg** group were **comparable to those of the 8mg group,** with **fewer aflibercept 8 mg injections** (following the switch) compared with previous aflibercept 2 mg injections over the same time periods

[a]eFAS, observed cases (2q8→8mg, n=208; 8mg, n=417); [b]eSAF (156-week completers; 2q8→8mg, n=186; 8mg, n=375).

Reduction of Proportion of Patients with Presence of Sub-RPE Fluid at Key Timepoints

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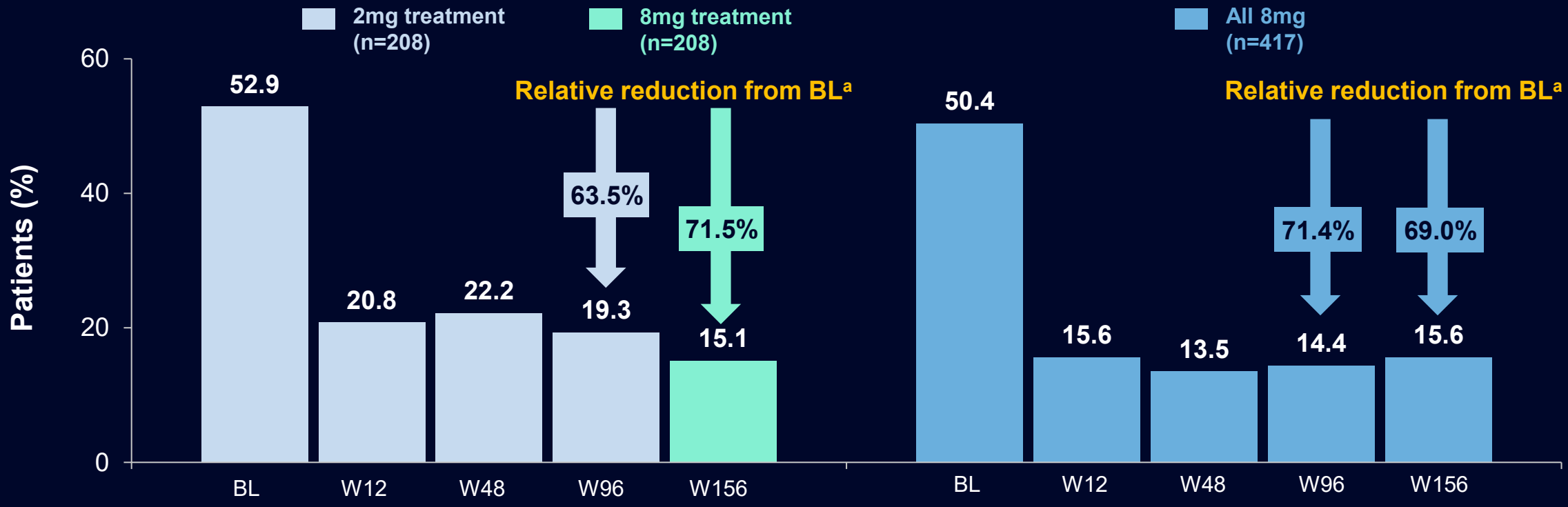
Patients with presence of sub-RPE fluid



- At Week 96, the proportion of patients with presence of **sub-RPE fluid decreased from 52.9% to 19.3% and from 50.4% to 14.4% at W96** in patients receiving **aflibercept 2 mg and 8 mg**, respectively
- From **W96 to W156**, the proportion of patients with presence of sub-RPE fluid in the **2q8→8mg group decreased further following switch to aflibercept 8 mg,** while the proportion of patients in the 8mg group remained stable

eFAS, observed cases (2q8→8mg, n=208; 8mg, n=417). [a]Calculated as change in proportion of patients with presence of sub-RPE fluid from BL at a particular timepoint divided by the BL value, then multiplied by 100.

Thickness of Sub-RPE Fluid Involving the Foveal Center through Week 156

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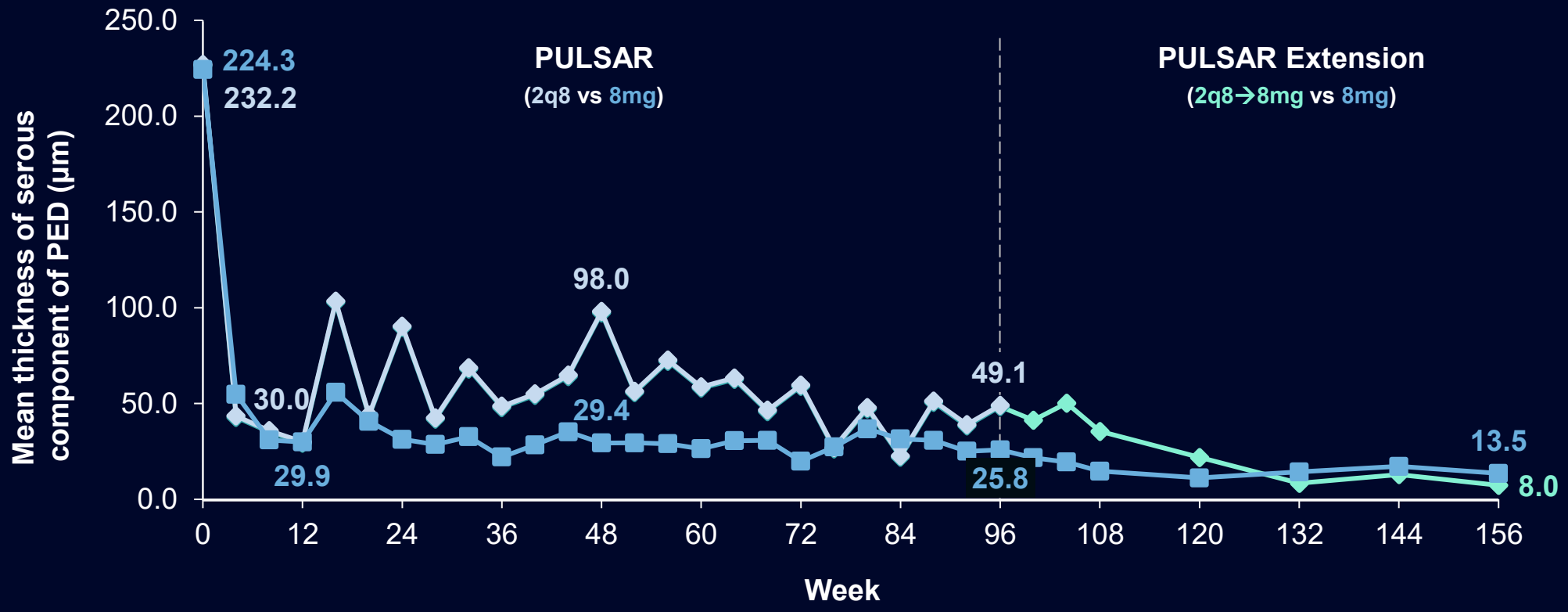

- **Marked reductions** in **thickness of sub-RPE fluid** involving the foveal center were achieved with **aflibercept 2 mg and 8 mg** at **Week 12 and sustained** through **Week 96**
- **Further reductions** were observed **at Week 156** in patients who **switched** from **aflibercept 2 mg to 8 mg** and in patients who continued to receive **aflibercept 8 mg**

Patients with sub-RPE fluid presence at center point, observed cases (2q8→8mg, n=24; 8mg, n=52).

Reductions in Thickness of Sub-RPE Fluid Involving the Foveal Center at Key Timepoints

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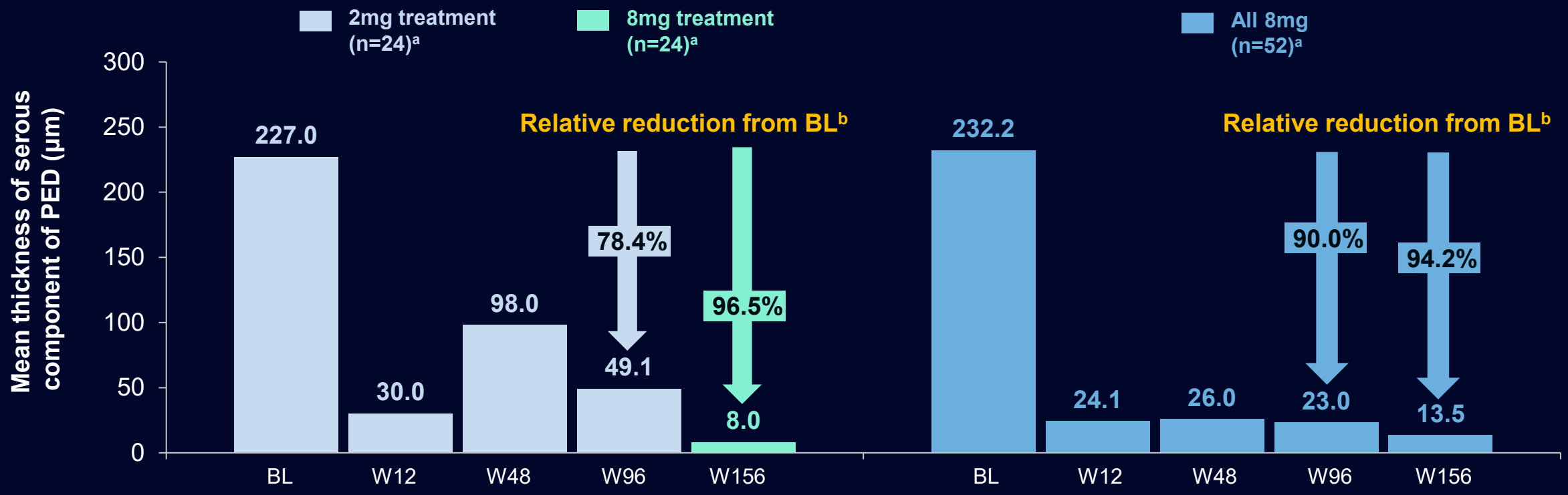

- From **BL to Week 96**, the **thickness in sub-RPE fluid involving the foveal center decreased** by **78.4% and 90.0%** in patients **who received aflibercept 2 mg and 8 mg, respectively**
- **At Week 156,** these values **decreased further** to **96.5%** in patients who **switched from aflibercept 2 mg to 8 mg,** and to **94.2%** in those **who received aflibercept 8 mg throughout**

[a]Patients with sub-RPE fluid presence at center point, observed cases. [b]Calculated as the mean change from BL in thickness of sub-RPE fluid presence at center point at a particular timepoint divided by the BL value, then multiplied by 100.

Conclusions

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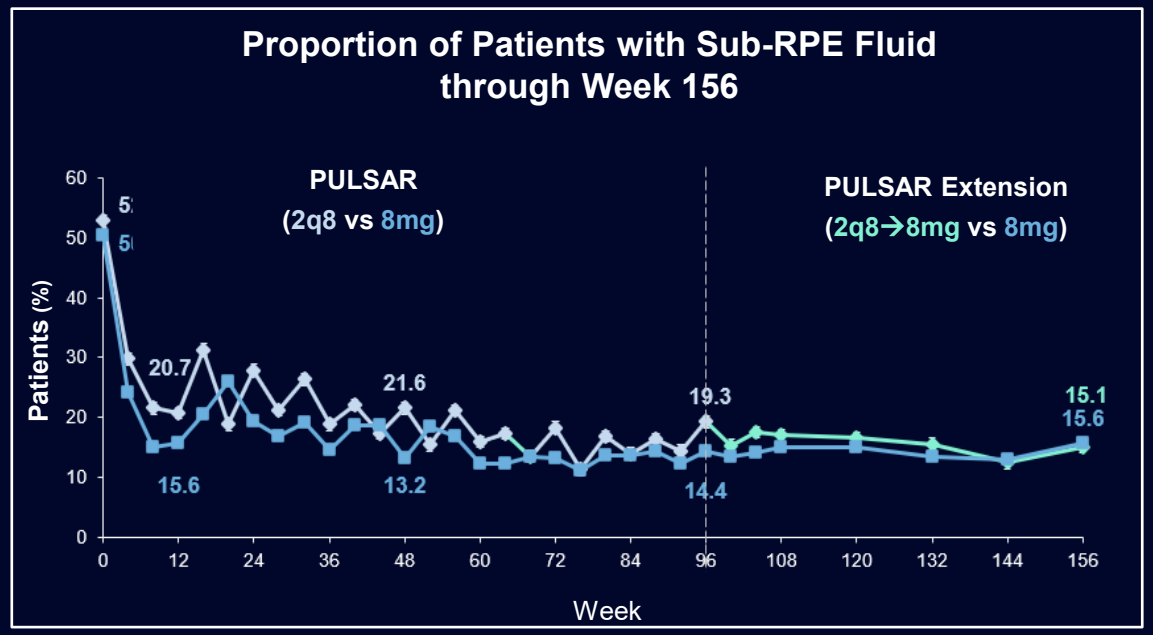
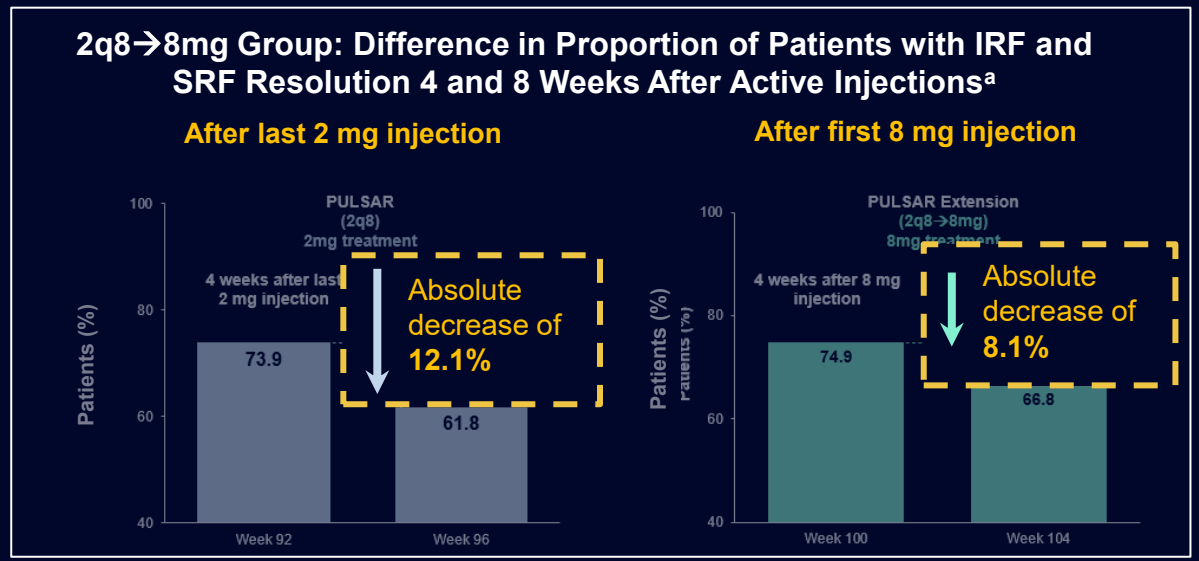
- Early **improvements in fluid and PED outcomes** were **generally maintained through Week 96** and **sustained or improved from Week 96 to Week 156** in the following patient groups:
  - **2q8→8mg** group following switch from aflibercept 2 mg to aflibercept 8 mg, with **fewer injections**
  - **8mg** group who had been receiving aflibercept 8 mg over **extended dosing intervals**
- At Week 156, the proportion of patients with IRF, SRF, and sub-RPE **fluid resolution** was **comparable in both groups**
  - In the **2q8→8mg** group, IRF and SRF **re-accumulation** between 4 and 8 weeks was **lower after the first 8 mg** injection in the PULSAR extension compared with after the last 2 mg injection in PULSAR





[a]eFAS (LOCF).