Additional Visual and Anatomic Outcomes of Intravitreal Aflibercept Injection 8 mg Versus 2 mg: A Post Hoc Analysis of the Phase 2 CANDELA Study

Priya S Vakharia, MD[1]
on behalf of the CANDELA study investigators

[1]*Retina Vitreous Associates of Florida, Palm Harbor, Florida*

Presented at the American Society of Retina Specialists (ASRS) Annual Meeting, July 28–August 1, 2023

Disclosures

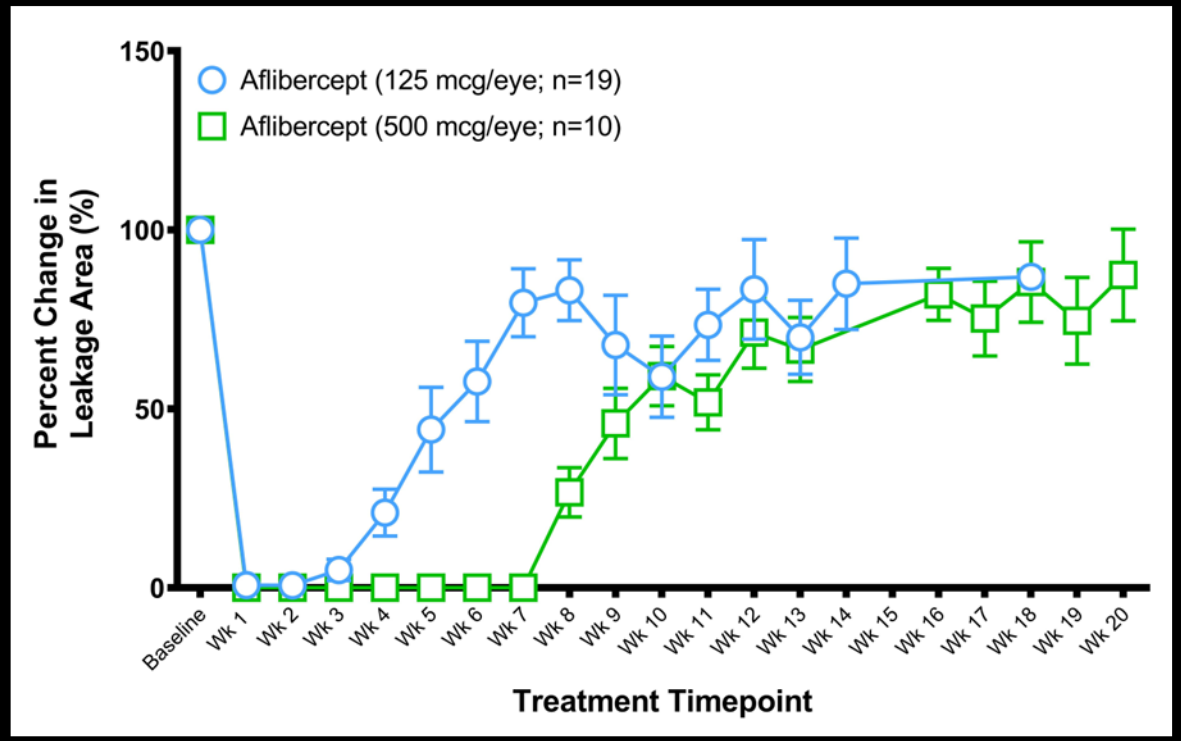
- Dr Vakharia is a consultant and investigator for Regeneron Pharmaceuticals, Inc.
- This study was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, New York); the sponsor participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
- Study disclosures: This study includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- Medical writing support was provided by Rob Campbell, PhD, of Core, London, United Kingdom, in accordance with Good Publication Practice guidelines, and funded by Regeneron Pharmaceuticals, Inc.

Background

- Higher molar doses of intravitreal anti-VEGF agents may improve visual and anatomic outcomes and lengthen duration of effect[1–3]

- In a preclinical DL-AAA rabbit model, aflibercept dose-dependently increased the duration of leakage inhibition[4]
  - A **4-fold higher dose**, aflibercept 500 µg versus 125 µg, **extended** the duration of complete leakage inhibition by **5 weeks** (from 2 to 7 weeks)

Dose-dependent Duration of Leak Inhibition



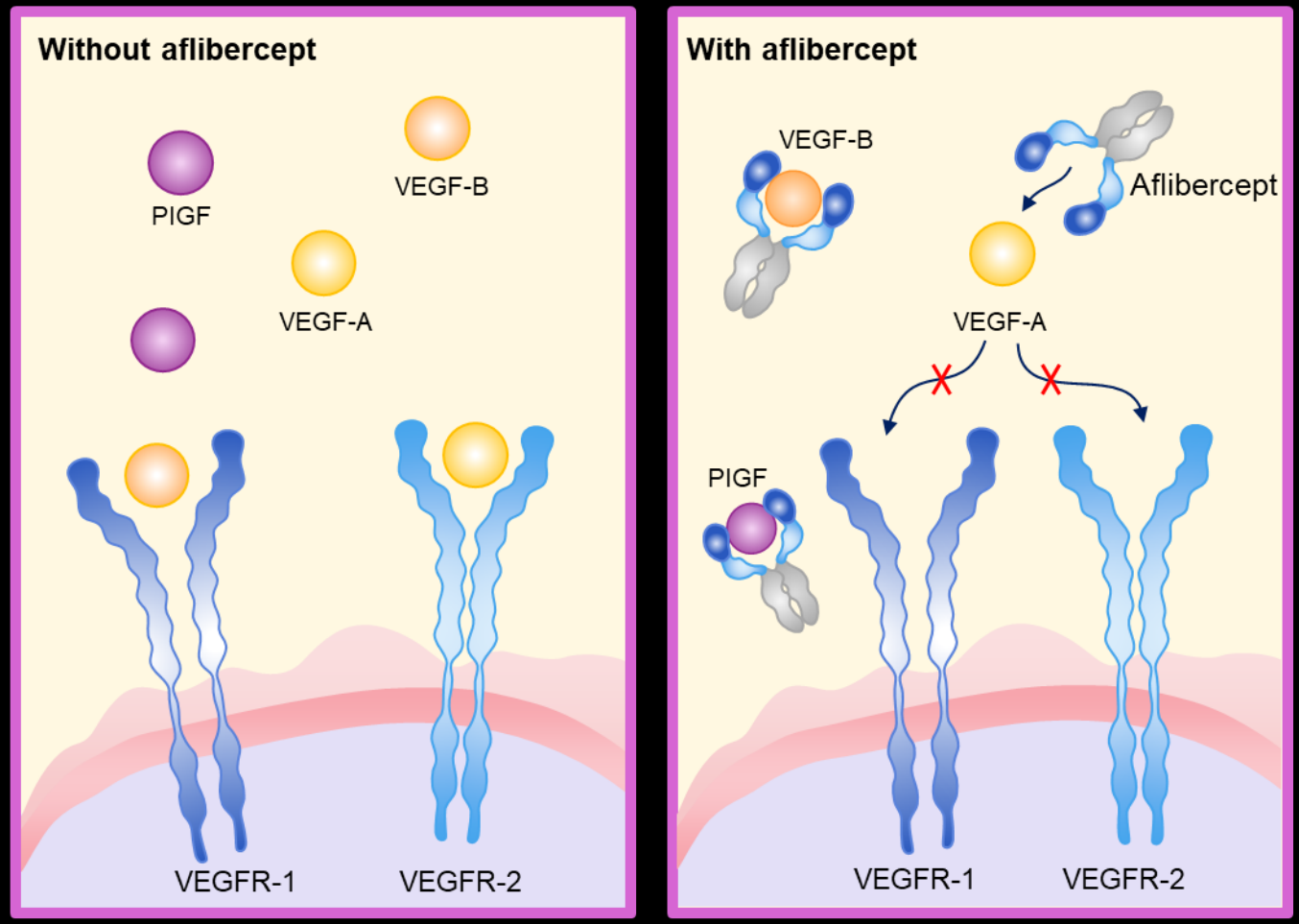
Data shown represent mean ±1 standard error measurement.

DL-AAA, DL-α-aminoadipic acid; mcg, microgram; VEGF, vascular endothelial growth factor; Wk, Week.

1. Brown DM et al. *Ophthalmology*. 2013;120:349–354. 2. Dugel PU et al. *Ophthalmology*. 2020;127:72–84. 3. Brown DM. Angiogenesis 2020, Miami, Florida. 4. Cao J et al. *Invest Ophthalmol Vis Sci*. 2018;59:1033–1044.

Aflibercept 8 mg Overview

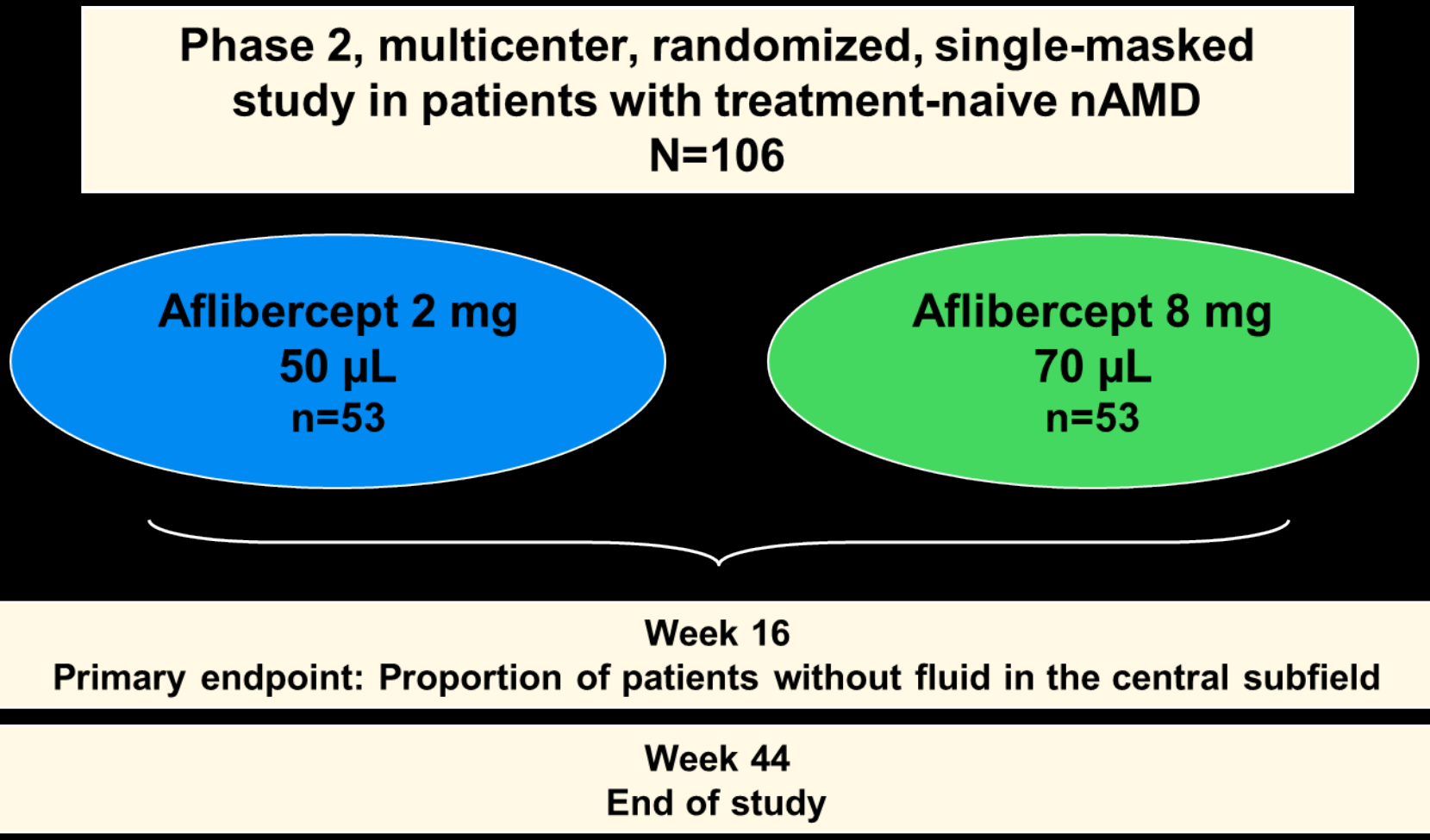
- Aflibercept is a fully human recombinant fusion protein that binds VEGF-A, VEGF-B and PlGF, thereby inhibiting the activation of the cognate VEGF receptors[1-3]
- **Aflibercept 8 mg** is a novel intravitreal formulation delivering a **4-fold higher molar dose** than aflibercept 2 mg, in a 70-µL injection
- Aflibercept 8 mg has demonstrated improved functional and anatomic outcomes at dosing intervals of ≥12 weeks in ongoing clinical trials in nAMD, DME, and DR[4,5]



PlGF, placental growth factor; VEGFR, vascular endothelial growth factor.

1. Semeraro F et al. *Drug Des Devel Ther*. 2013;7:711-22. 2. Holash J et al. *Proc Natl Acad Sci USA*. 2002;99:11393–11398. 3. Rudge JS et al. *Proc Natl Acad Sci USA*. 2007;104:18363–18370.
4. Lanzetta P. Intravitreal aflibercept injection 8 mg for nAMD: results from the phase 3 PULSAR trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL.
5. Brown DM. Intravitreal aflibercept injection 8 mg for DME: results from the phase 2/3 PHOTON trial. Presented at: American Academy of Ophthalmology; September 30, 2022; Chicago, IL.

CANDELA Study Design



Dosing and Visit Schedule

Week 16: Primary EP

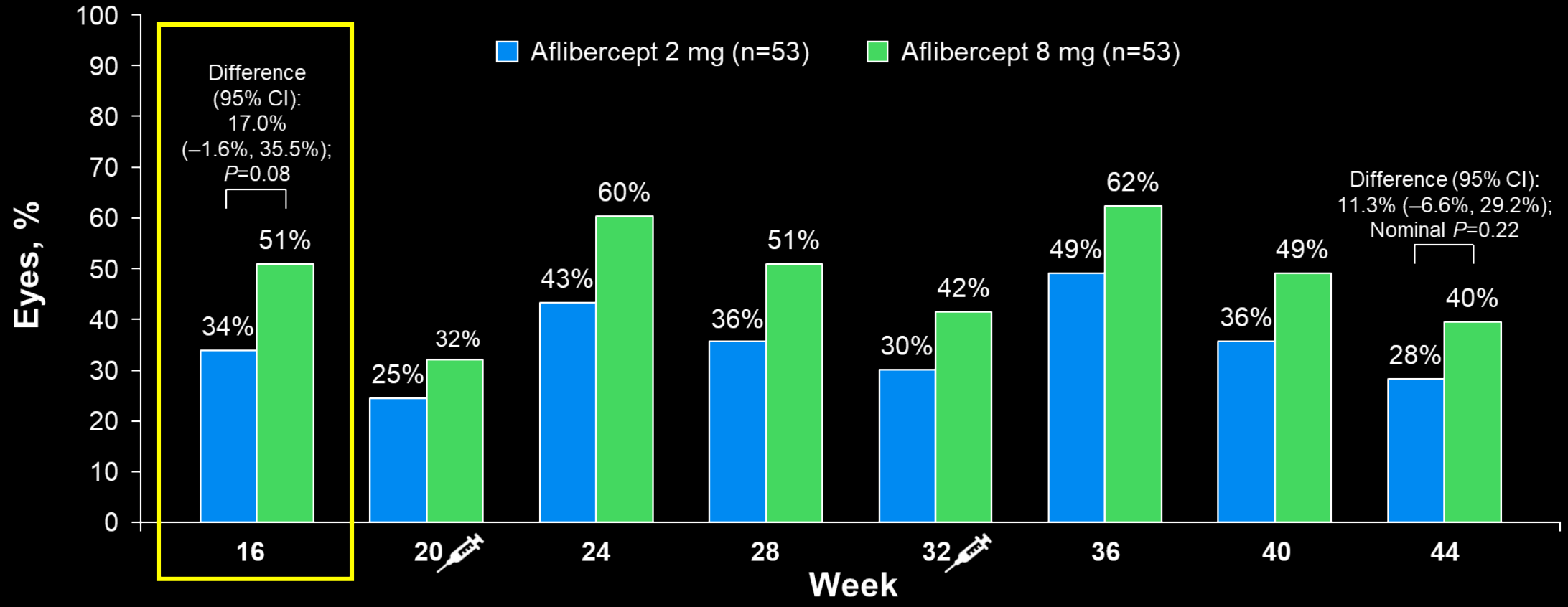
	Screen 1 and 2	Day 1 (baseline)	Week 4	8	12	16	20	24	28	32	36	40	44 (EOS)
Aflibercept 2 mg (50 µL)		X	X	X			X	PRN	PRN	X	PRN	PRN	
Aflibercept 8 mg (70 µL)		X	X	X			X	PRN	PRN	X	PRN	PRN	

Additional treatment allowed based on investigator assessment after discussion with sponsor; data censored after rescue (LOCF)

- **PRN Dosing:** Permitted (at Weeks 24, 28, 36, or 40) if patients lost ≥5 letters from Week 20 due to disease progression or anatomic findings that were considered vision threatening (e.g., worsening/persistent retinal fluid, new/worsening retinal pigment epithelial detachment, new/persistent hemorrhage)
- Intervals longer than 12 weeks were not investigated

EOS, end of study; LOCF, last observation carried forward; PRN, pro re nata.

Primary Efficacy Endpoint: Proportion of Eyes Without Retinal Fluid in the Central Subfield



Mean number of injections

Aflibercept 2 mg	Aflibercept 8 mg
5.8	5.8

= Scheduled dose visit.

Without fluid defined as no IRF and no SRF.

FAS, LOCF. For patients receiving additional treatment at Week 16, measurements past Week 16 were imputed using the LOCF prior to additional treatment.

FAS, full analysis set; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

Objective and Methods

Objective:

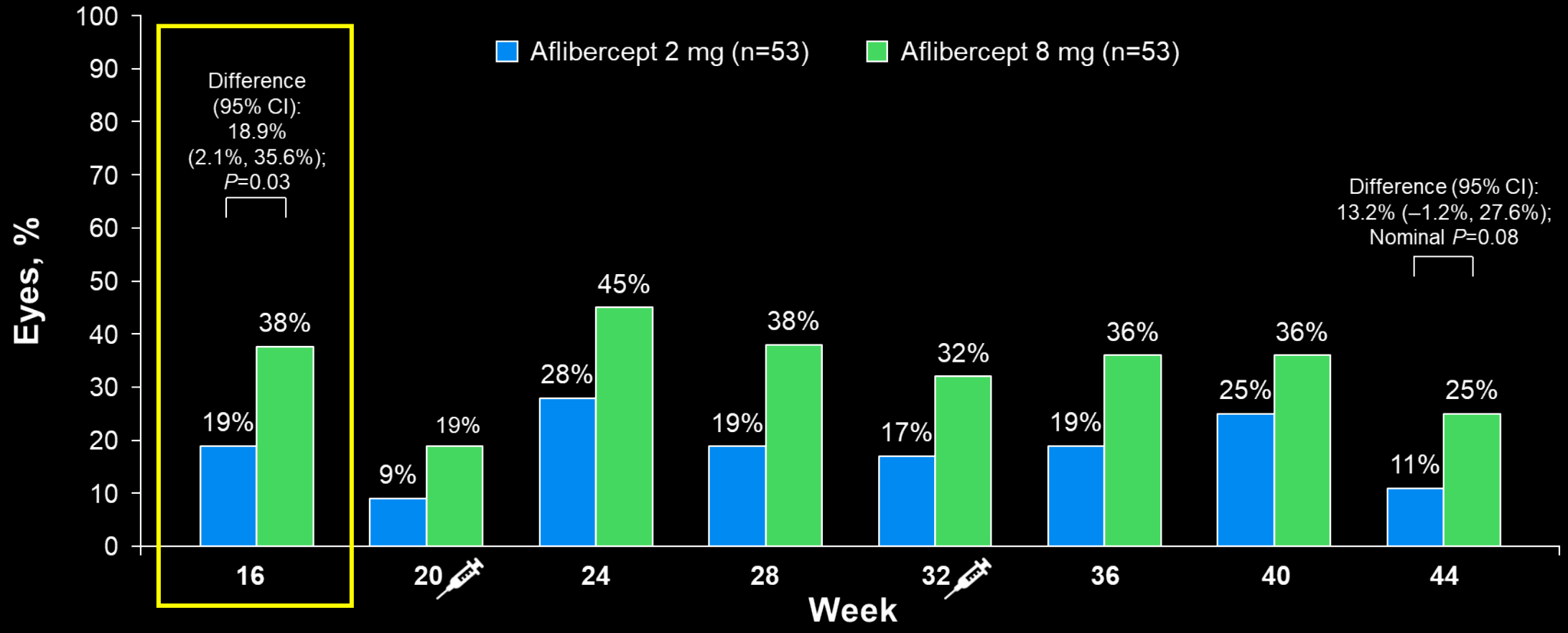
- To further evaluate the effect of aflibercept 8 mg on visual and anatomic outcomes in patients with nAMD

Methods:

- This post hoc analysis of the CANDELA trial assessed the following outcomes:
  - Proportion of eyes without IRF, SRF, or sub-RPE fluid in the central subfield through Week 44
  - Proportion of eyes with CST change at Week 44 by quartiles
  - Proportion of eyes with BCVA changes at Week 44
  - Proportion of eyes that achieved BCVA of ≥20/40 and ≥20/20 at Week 44
  - Proportion of eyes with baseline BCVA <20/40 that achieved ≥10- and ≥15-letter gains at Week 44

Sub-RPE, subretinal pigment epithelium.

Proportion of Eyes Without IRF, SRF, or Sub-RPE Fluid in the Central Subfield

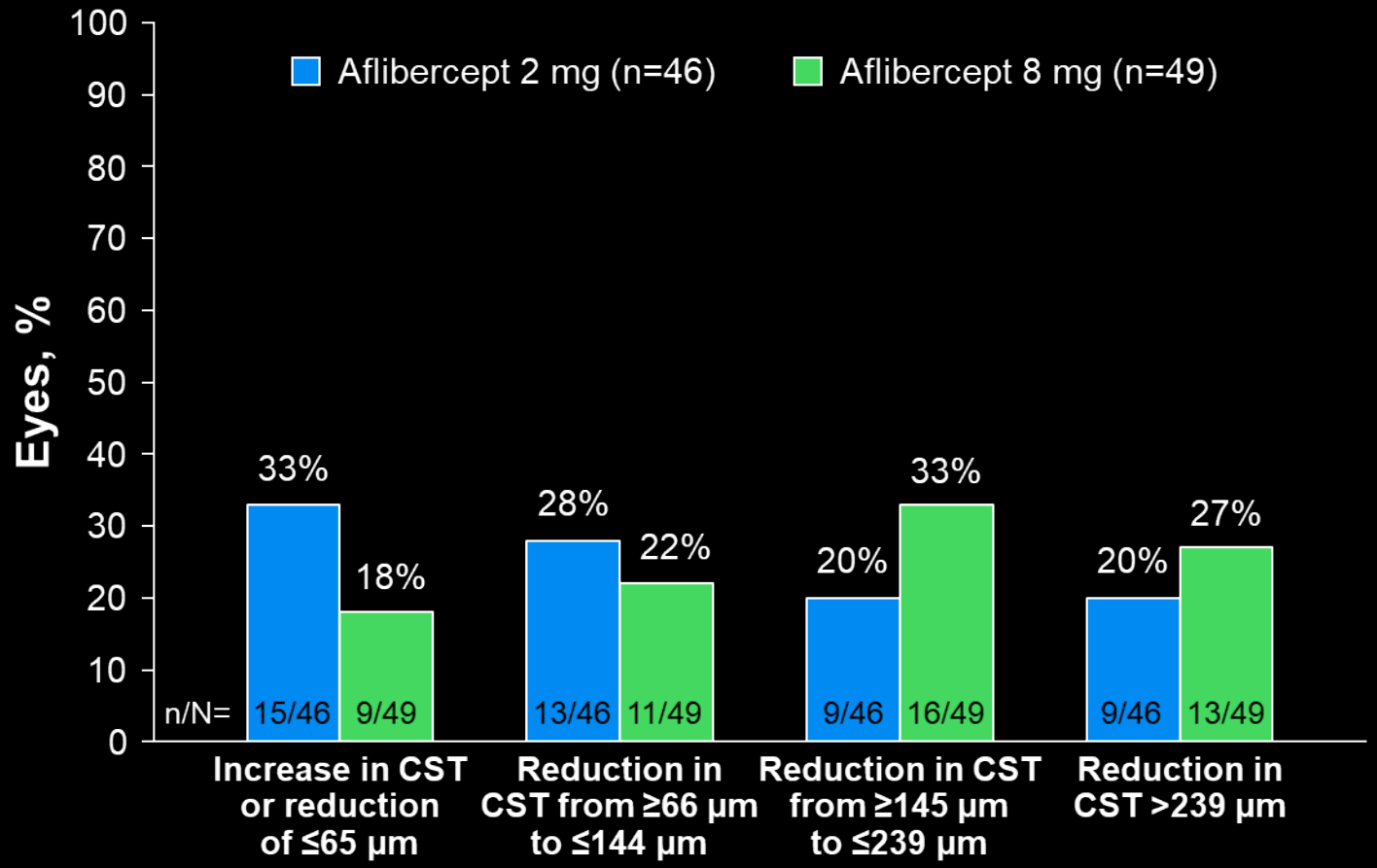


= Scheduled dose visit.

FAS, LOCF.

For patients receiving additional treatment at Week 16, measurements past Week 16 were imputed using the LOCF prior to additional treatment.

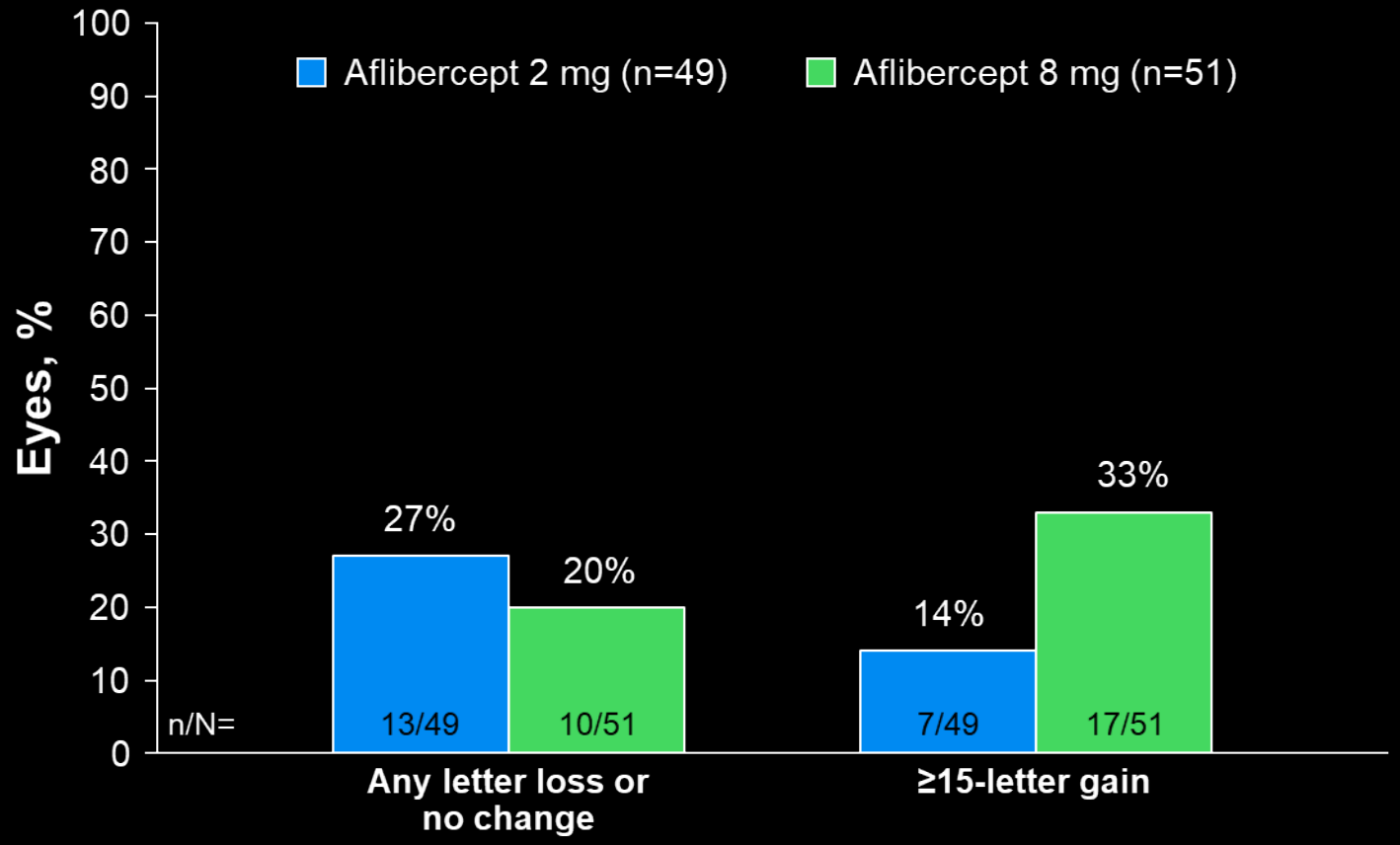
Proportion of Eyes With CST Change by Quartiles and Baseline Characteristics of Eyes With CST Reductions >239 µm at Week 44



Baseline characteristics of eyes with CST reductions of >239 µm		
	Aflibercept 2 mg	Aflibercept 8 mg
BCVA, letters		
Mean	47.1	47.5
Median	50.0	54.0
Range (min, max)	33, 59	23, 74
CST, µm		
Mean	788.2	702.2
Median	650.0	688.0
Range (min, max)	485, 1271	510, 990

FAS, patients who had evaluable CST at the Week 44 visit.
All observed values used for analysis.

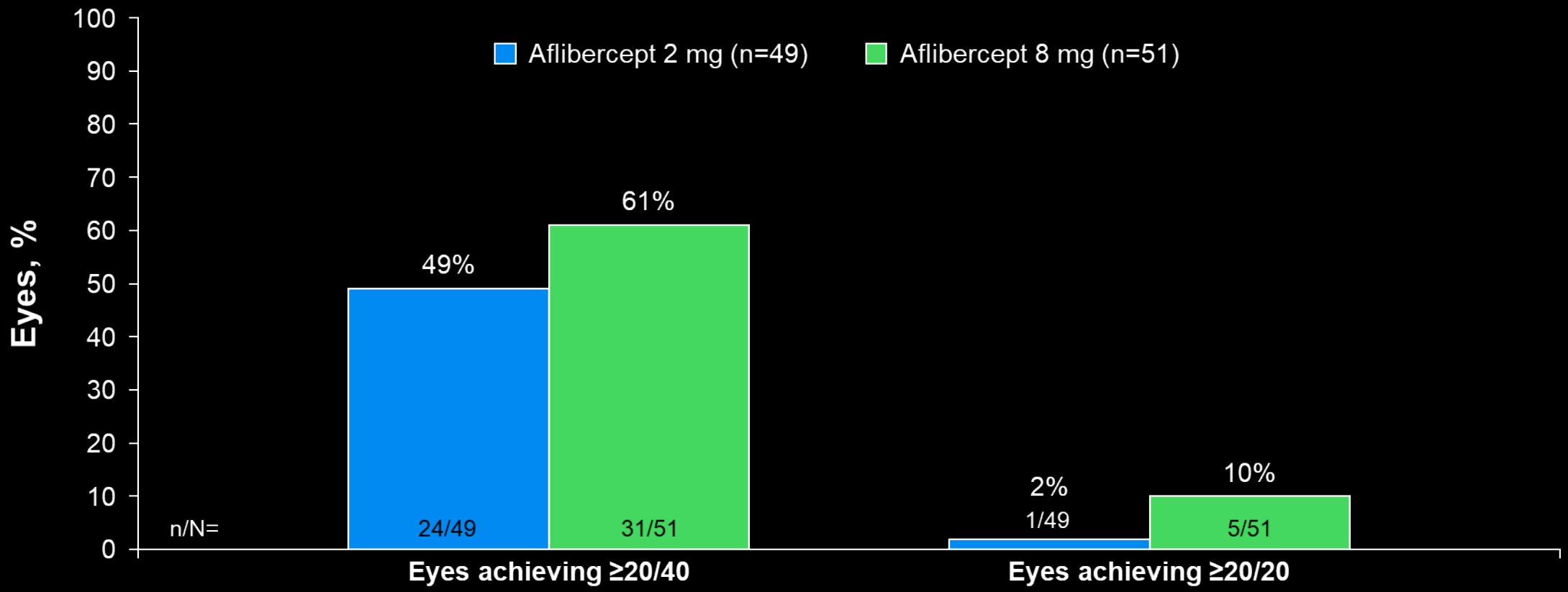
Proportion of Eyes With BCVA Changes and Baseline Characteristics of Eyes With ≥15-Letter Gains at Week 44



Baseline characteristics of eyes with ≥15-letter gains at Week 44		
	Aflibercept 2 mg	Aflibercept 8 mg
BCVA, letters		
Mean	55.4	53.8
Median	56.0	56.0
Range (min, max)	43, 63	23, 72
CST, µm		
Mean	579.0	554.9
Median	567.0	557.0
Range (min, max)	360, 819	371, 990

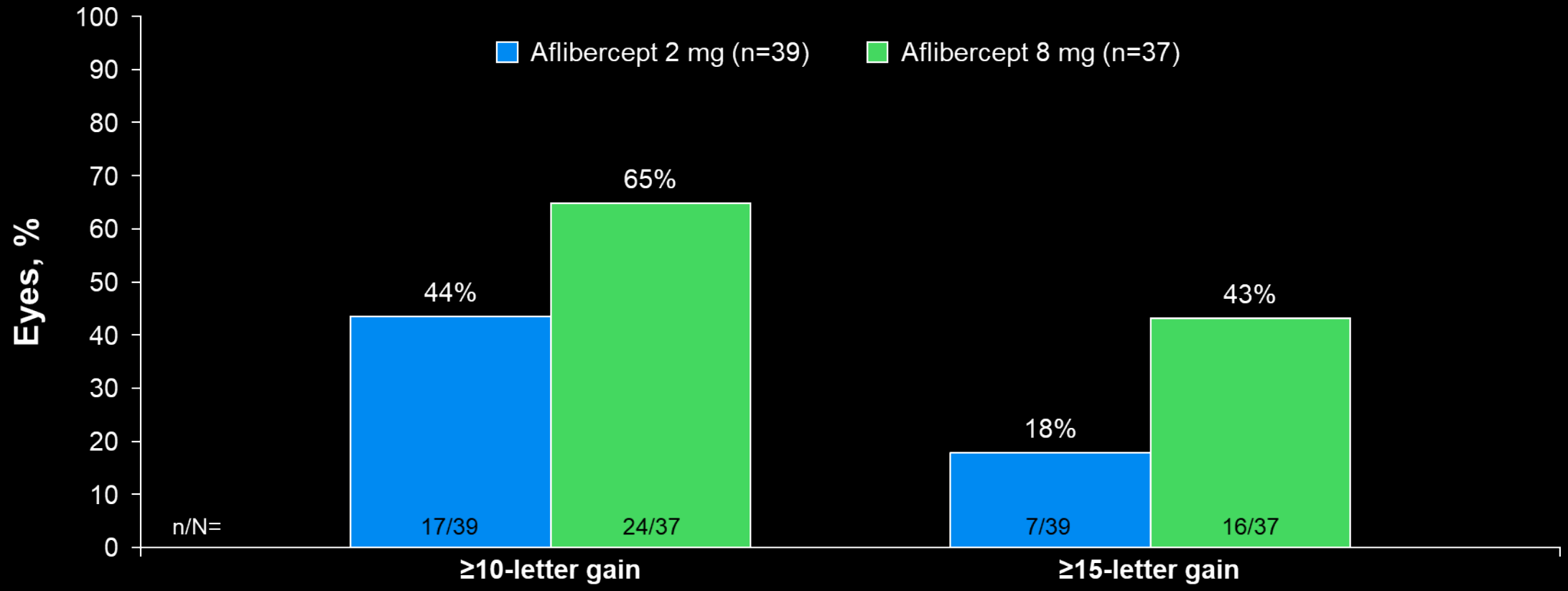
FAS, observed cases.
Analysis limited to patients who completed Week 44 visit.

Proportion of Eyes Achieving BCVA ≥20/40 and ≥20/20 at Week 44



FAS, observed cases.
Analysis limited to patients who completed Week 44 visit.

Proportion of Eyes With Baseline BCVA <20/40 and ≥10- and ≥15-Letter Gains at Week 44



FAS, observed cases.
Analysis limited to patients who completed Week 44 visit and with BCVA <20/40 at baseline.

Conclusions

- A greater proportion of eyes treated with aflibercept 8 mg versus aflibercept 2 mg had no IRF, SRF, or sub-RPE fluid in the central subfield at every visit starting at Week 16
- More eyes treated with aflibercept 8 mg in the quartiles of greater BCVA and CST improvement from baseline to Week 44; these benefits were not driven by baseline imbalances
- More eyes treated with aflibercept 8 mg achieved the clinically meaningful BCVA thresholds of ≥20/40 and ≥20/20 at Week 44