High Dose Aflibercept for Neovascular AMD

February 12, 2022

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Disclosures

- This study was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY); 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

Background and Rationale for Development of Aflibercept 8 mg

- Efforts to decrease treatment burden with longer dosing intervals of current anti-VEGFs often result in suboptimal vision outcomes
- Clinical studies indicate that ~50% of patients are effectively treated with ~q12 (quarterly) dosing of aflibercept 2 mg[1-3]
- Aflibercept 8 mg (in a novel formulation) has the potential to improve anatomic and/or functional outcomes and will be investigated at dosing intervals ≥12-weeks
- Ongoing Phase 3 studies:
  - ***PHOTON***: Treatment-naïve and previously treated DME patients (Regeneron)
  - ***PULSAR***: Treatment-naïve patients with nAMD (Bayer)

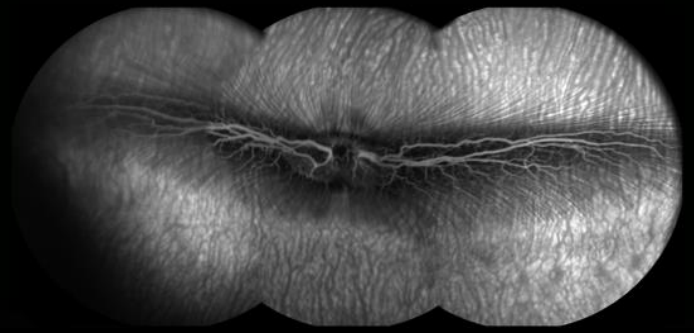
DME, diabetic macular edema; nAMD, neovascular age-related macular degeneration; q12, every 12 weeks; VEGF, vascular endothelial growth factor.

1. Khurana R, et al. *Am J Ophthalmol* 2019;200:161–168. 2. Ohji M, et al. *Adv Ther* 2020;37(3):1173–1187. 3. Mitchell P, et al. *Retina* 2021;41:1911–1920.

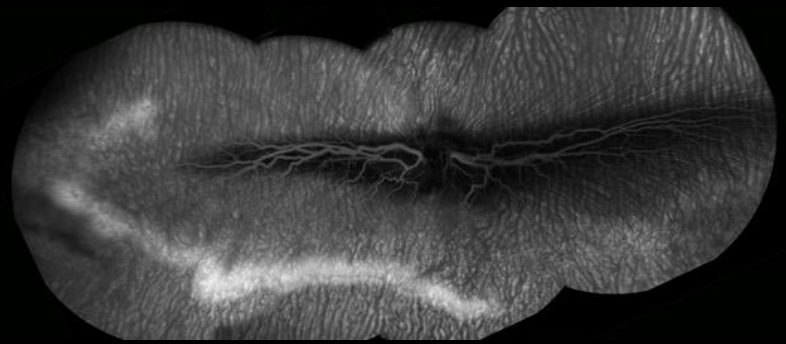
Preclinical Pharmacology Data Support Longer Treatment Intervals with Increased Aflibercept Dose

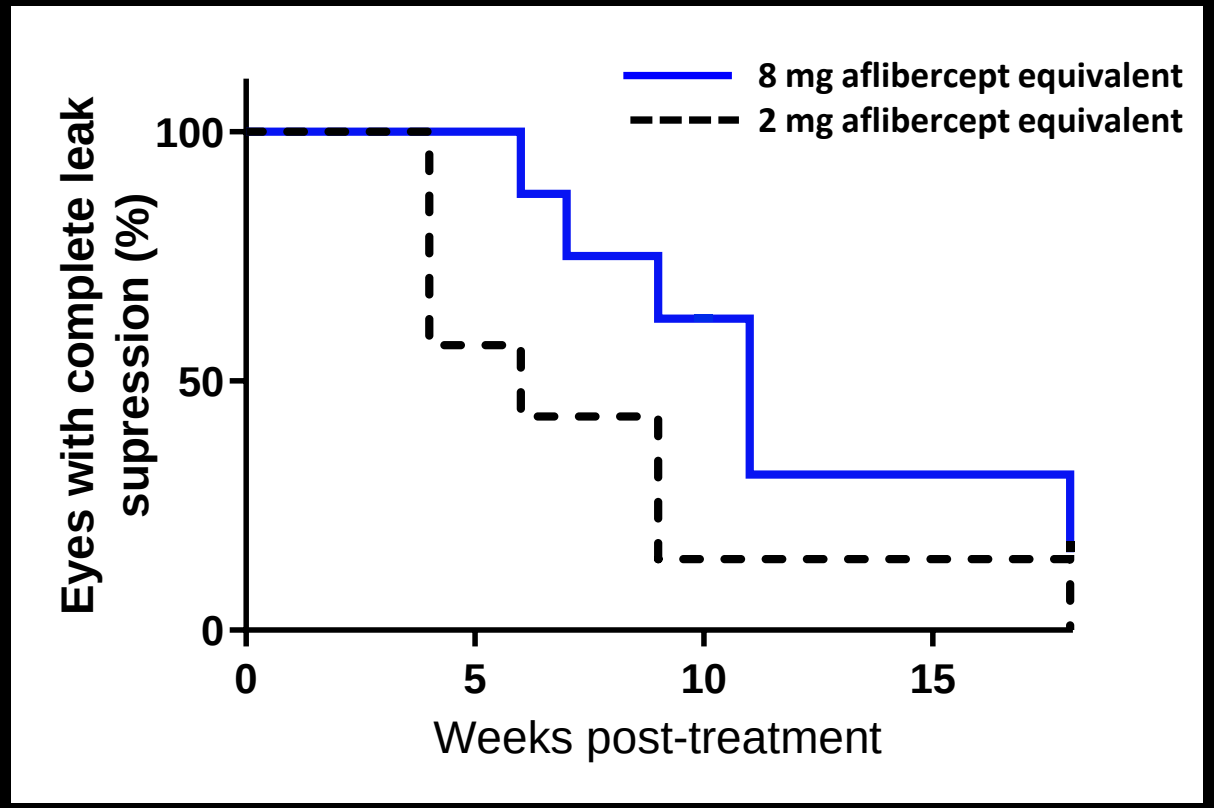
- In the DL-AAA rabbit model of chronic retinal vascular leak, the 8 mg equivalent dose of aflibercept increased duration of efficacy

Normal rabbit FA



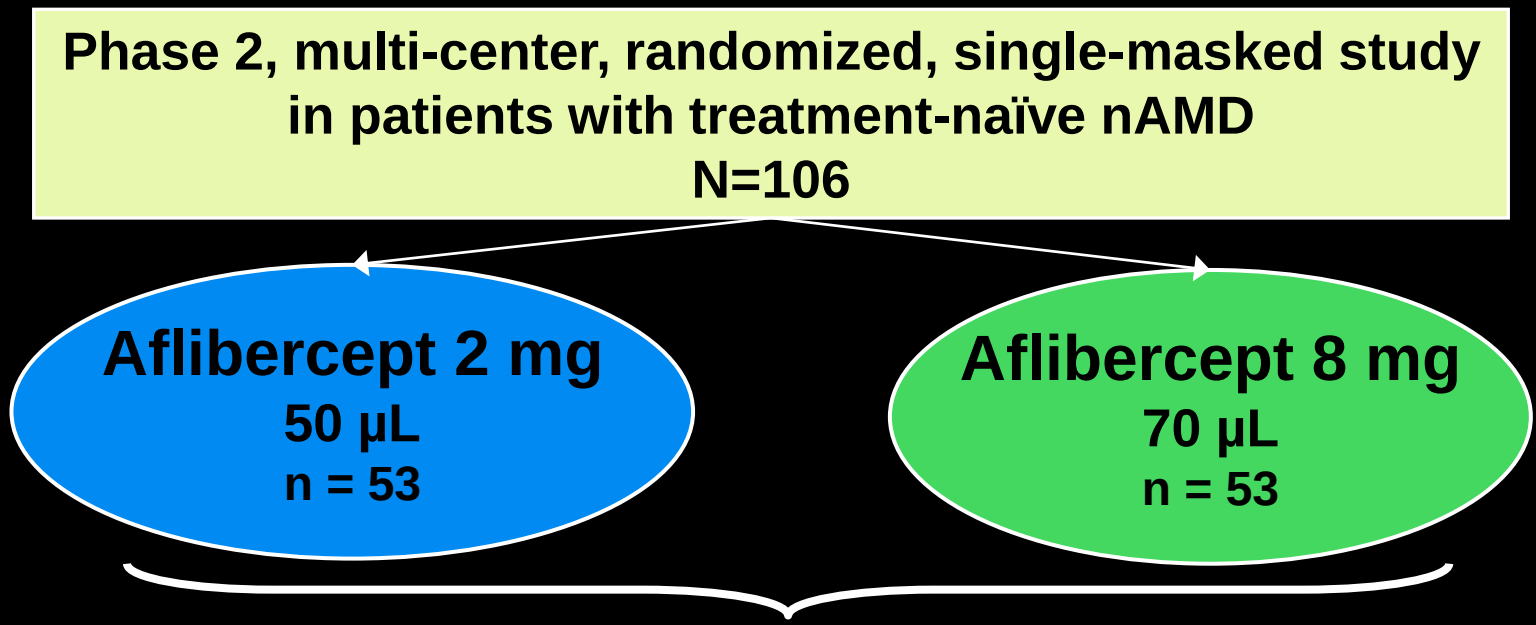
8 weeks post DL-AAA FA





DL-AAA, DL-α-aminoadipic acid; FA, fluorescein angiogram.
Regeneron, data on file.

CANDELA Study Design



EP, end point.

Key Eligibility Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
• ≥50 years of age with treatment-naïve active subfoveal CNV secondary to nAMD • ETDRS BCVA letter score of 78 to 24 (Snellen equivalent of 20/32 to 20/320) in the study eye	• Evidence of CNV due to any cause other than nAMD in either eye • Subretinal hemorrhage in the study eye that is ≥50% of the total lesion area • Uncontrolled BP (defined as systolic >140 mm Hg or diastolic >90 mm Hg)

BCVA, best-corrected visual acuity; BP, blood pressure; CNV, choroidal neovascularization; ETDRS, Early Treatment of Diabetic Retinopathy Study.

Dosing and Visit Schedule

	Screen 1 & 2	Day 1 (BL)	Wk 4	Wk 8	Wk 12	Wk 16: Primary Endpoint Wk 16*	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44 End of Study Wk 44
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	

***Week 16: Additional treatment allowed based on Investigator assessment after discussion with Sponsor; data censored after rescue (LOCF)**

BL, baseline; LOCF, last observation carried forward; PRN, pro re nata; WK, week.

PRN Dosing Criteria[a]

- To receive a PRN dose at Weeks 24, 28, 36 or 40, patients had to meet either of the following criteria:
  - Loss of ≥5 letters from Week 20 BCVA due to disease progression

OR

  - Anatomical findings that are considered vision-threatening, such as worsening or persistent retinal fluid, new or worsening retinal PED, new or persistent hemorrhage, etc.

[a]Criteria were assessed by the study investigator.
PED, pigment epithelial detachment.

Patient Disposition

	Aflibercept 2 mg	Aflibercept 8 mg	Total
Randomized patients, n	53	53	106
Patients completing Week 16, n (%)	51 (96)	53 (100)	104 (98)
Patients completing Week 44, n (%)	49 (92)	51 (96)	100 (94)

Baseline Demographics

	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)	Total (N=106)
Sex, n (%)			
Male	17 (32.1)	23 (43.4)	40 (37.7)
Female	36 (67.9)	30 (56.6)	66 (62.3)
Race, n (%)			
White	51 (96.2)	52 (98.1)	103 (97.2)
Ethnicity, n (%)			
Hispanic or Latino	4 (7.5)	2 (3.8)	6 (5.7)
Not Hispanic or Latino	49 (92.5)	51 (96.2)	100 (94.3)
Age, mean (SD), years	77.7 (8.3)	77.0 (7.7)	77.4 (8.0)

SD, standard deviation.

Baseline Characteristics – Study Eye

	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)	Total (N=106)
BCVA, mean (SD), ETDRS letters	58.2 (10.5)	57.9 (13.6)	58.0[a] (11.9)
CRT, mean (SD), µm	488.1 (204.9)	516.2 (175.6)	502.1 (190.6)
IOP, mean (SD), mm Hg	14.9 (3.4)	14.8 (3.4)	14.9 (3.4)
Lesion size, mean (SD), mm^2	7.9 (6.2)	7.7 (6.8)	7.8 (6.5)
CNV size, mean (SD), mm^2	7.9 (6.2)	7.5 (6.9)	7.7 (6.5)
FA classification, n (%)			
Occult	22 (41.5)	26 (49.1)	48 (45.3)
Minimally classic	26 (49.1)	19 (35.8)	45 (42.5)
Predominantly classic	4 (7.5)	8 (15.1)	12 (11.3)
Missing	1 (1.9)	0	1 (0.9)

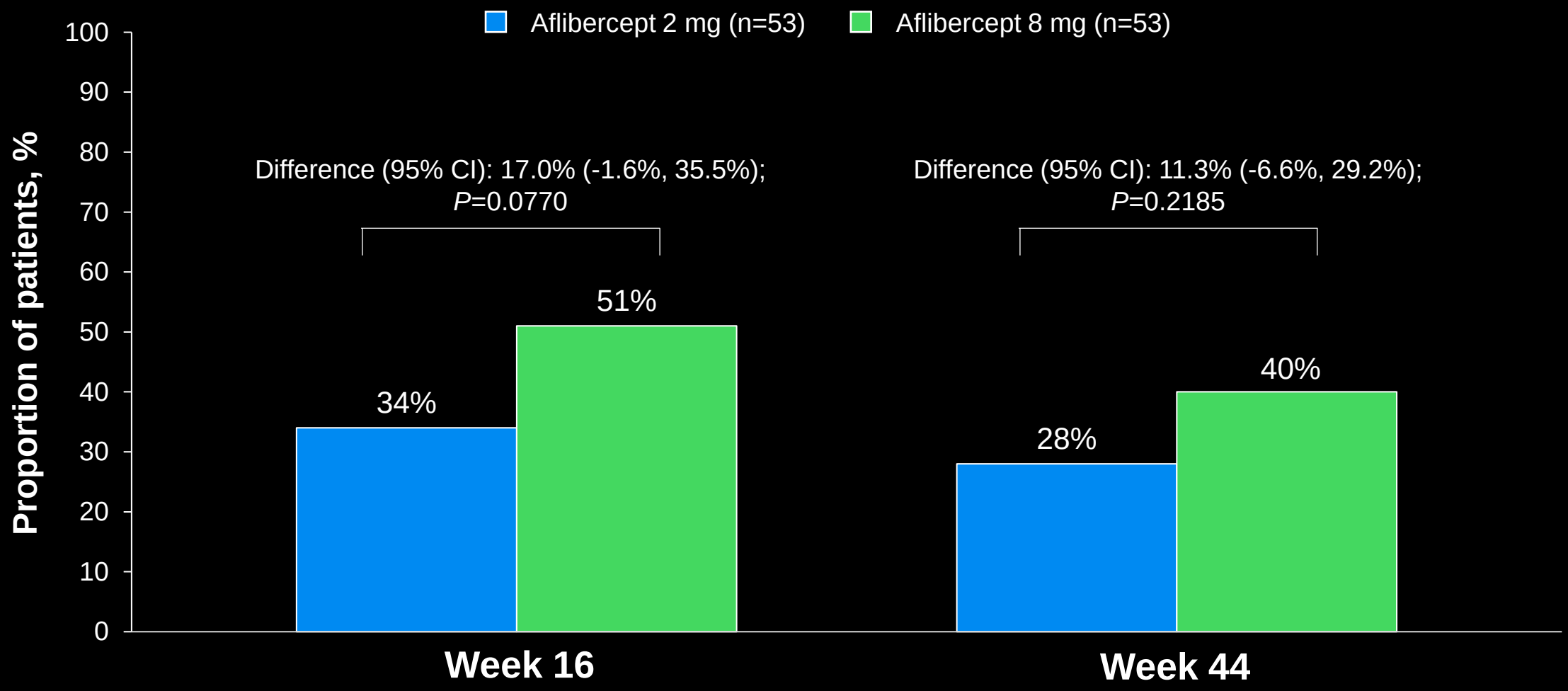
[a]58 ETDRS letters ≈ 20/60-20/70 Snellen visual acuity.
CRT, central retinal thickness; IOP, intraocular pressure.

Treatment Exposure and PRN Treatment through Week 44

Exposure	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)
Mean number of aflibercept injections through Week 44	5.8	5.8
Proportion of patients who did **NOT** receive additional or PRN treatment	24 (45%)	28 (53%)
Total number of PRN injections given	38	33

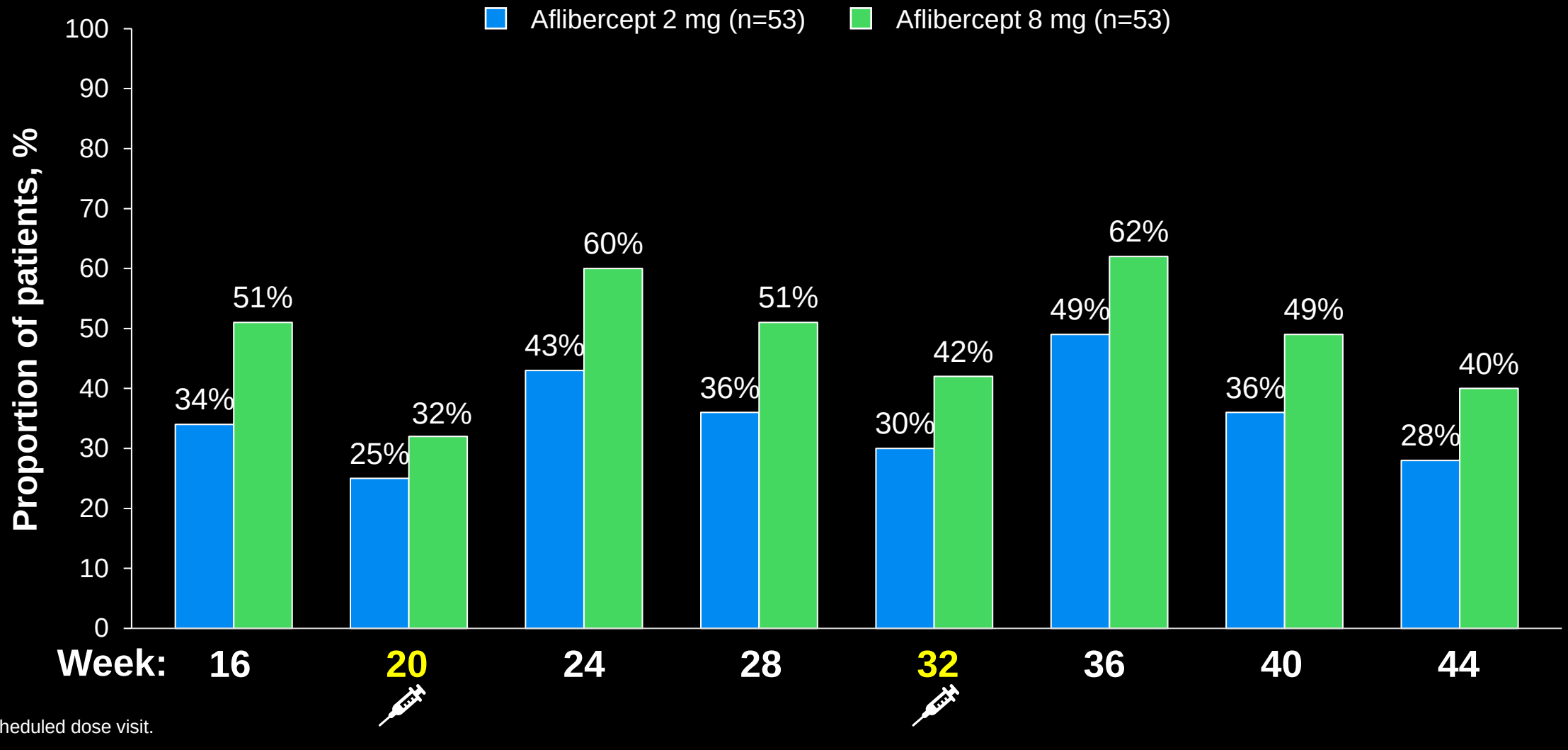
EFFICACY

Proportion of Eyes Without Fluid in the Center Subfield



FAS, LOCF.
Without fluid in central subfield defined as **no** IRF and **no** SRF in the center subfield on SD-OCT.
LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.
FAS, full analysis set; IRF, intra-retinal fluid; SD-OCT, spectral domain optical coherence tomography; SRF, sub-retinal fluid.

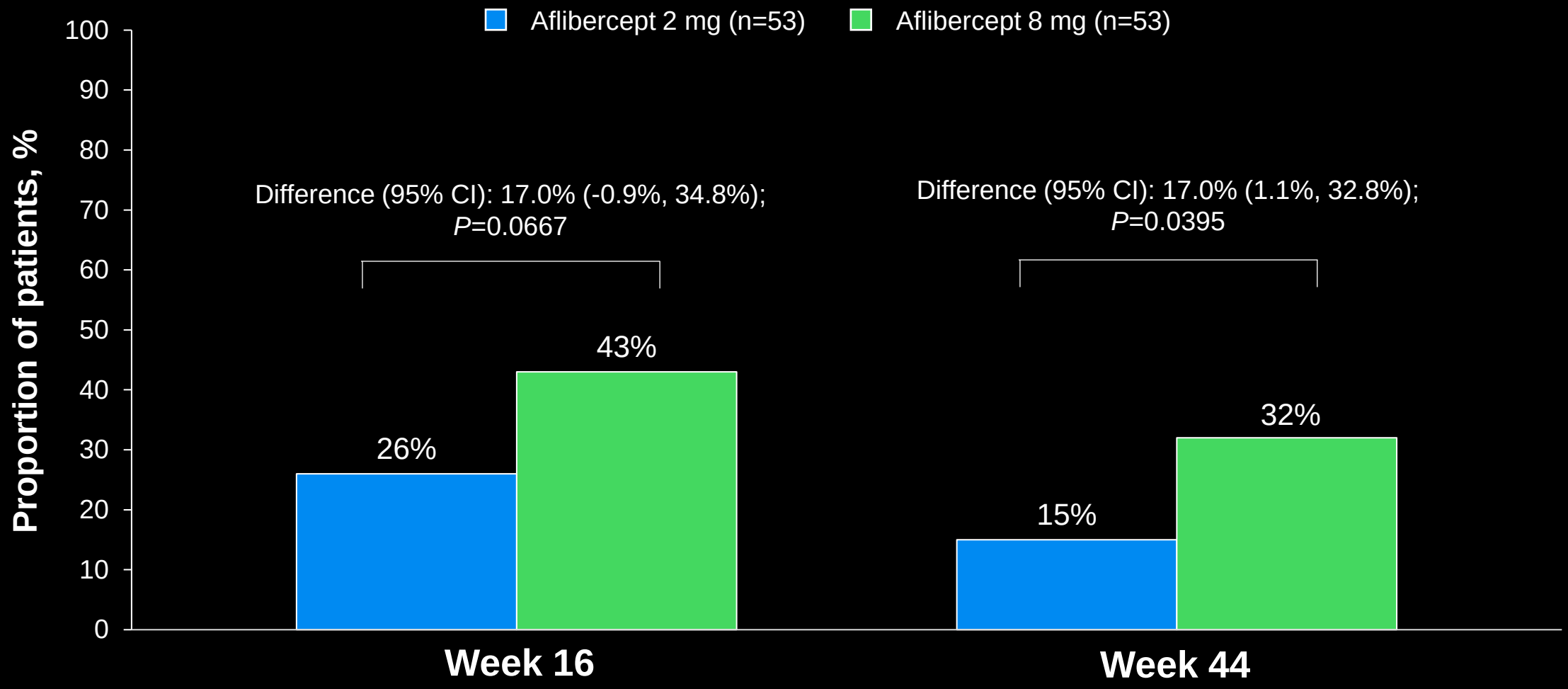
Proportion of Eyes Without Fluid in the Center Subfield



= Scheduled dose visit.

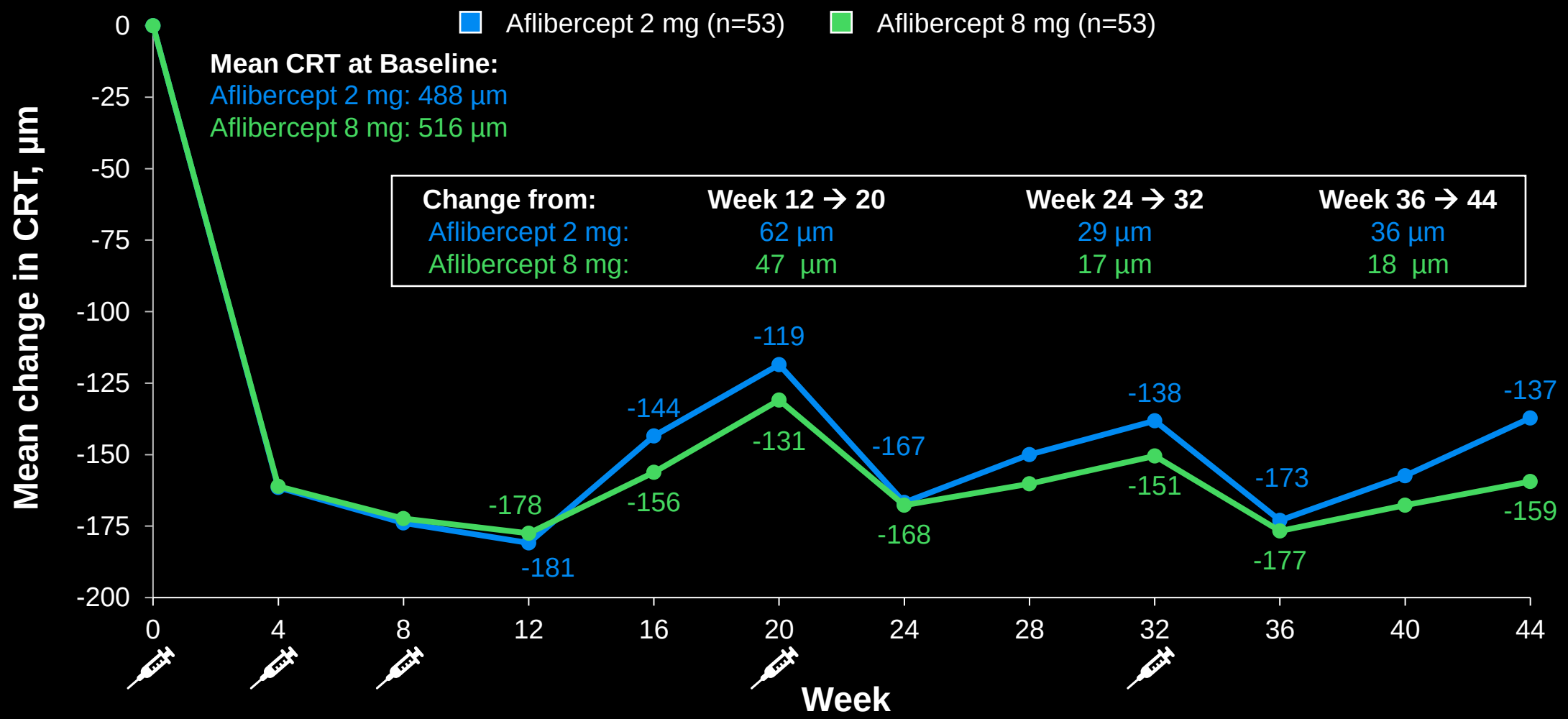
FAS, LOCF.
Without fluid in central subfield defined as **no** IRF and **no** SRF in the center subfield on SD-OCT.
LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.

Proportion of Eyes Without Fluid in the Macula



FAS, LOCF.
Without fluid in macula defined as **no** IRF and **no** SRF in the macula on SD-OCT.
LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.

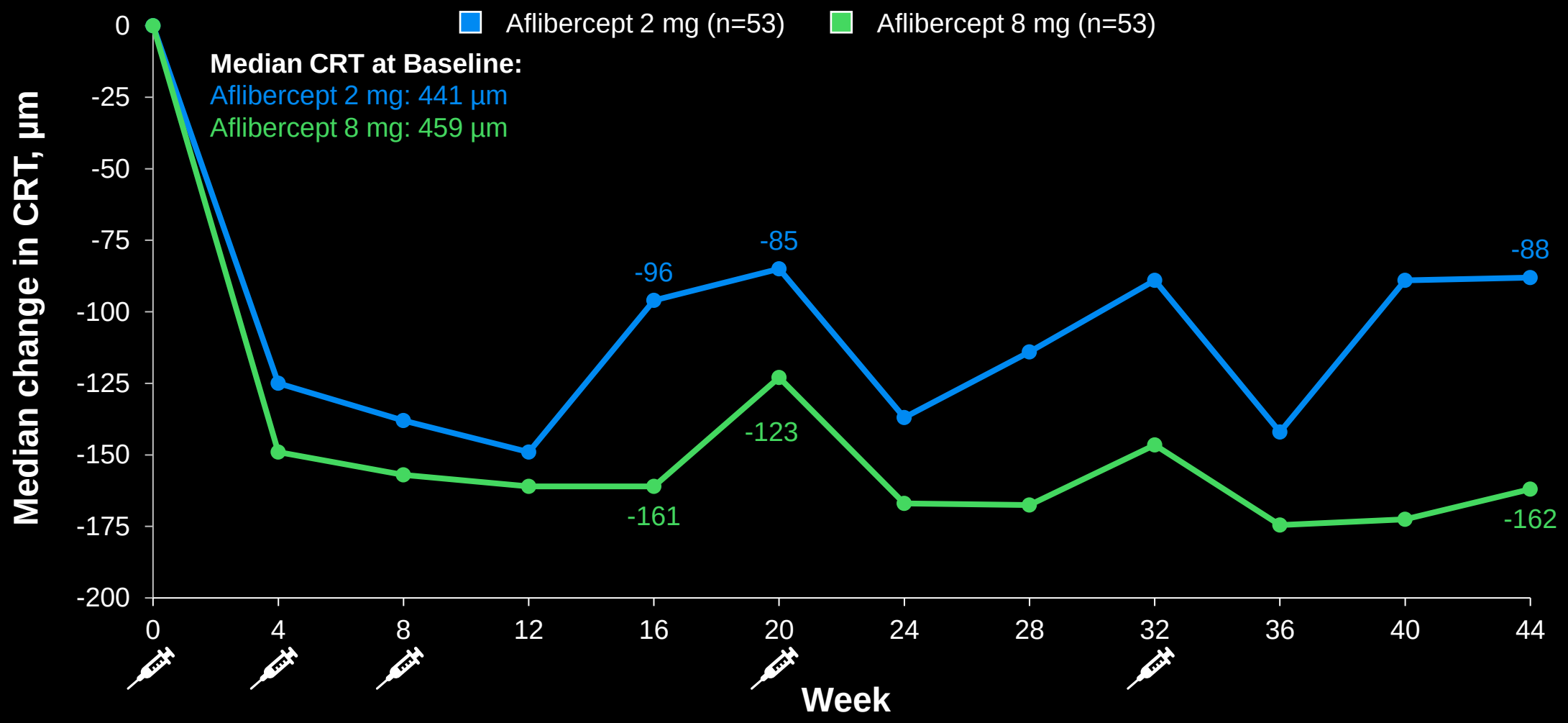
Mean Change from Baseline in CRT through Week 44



= Scheduled dose visit.

FAS, LOCF.
LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.

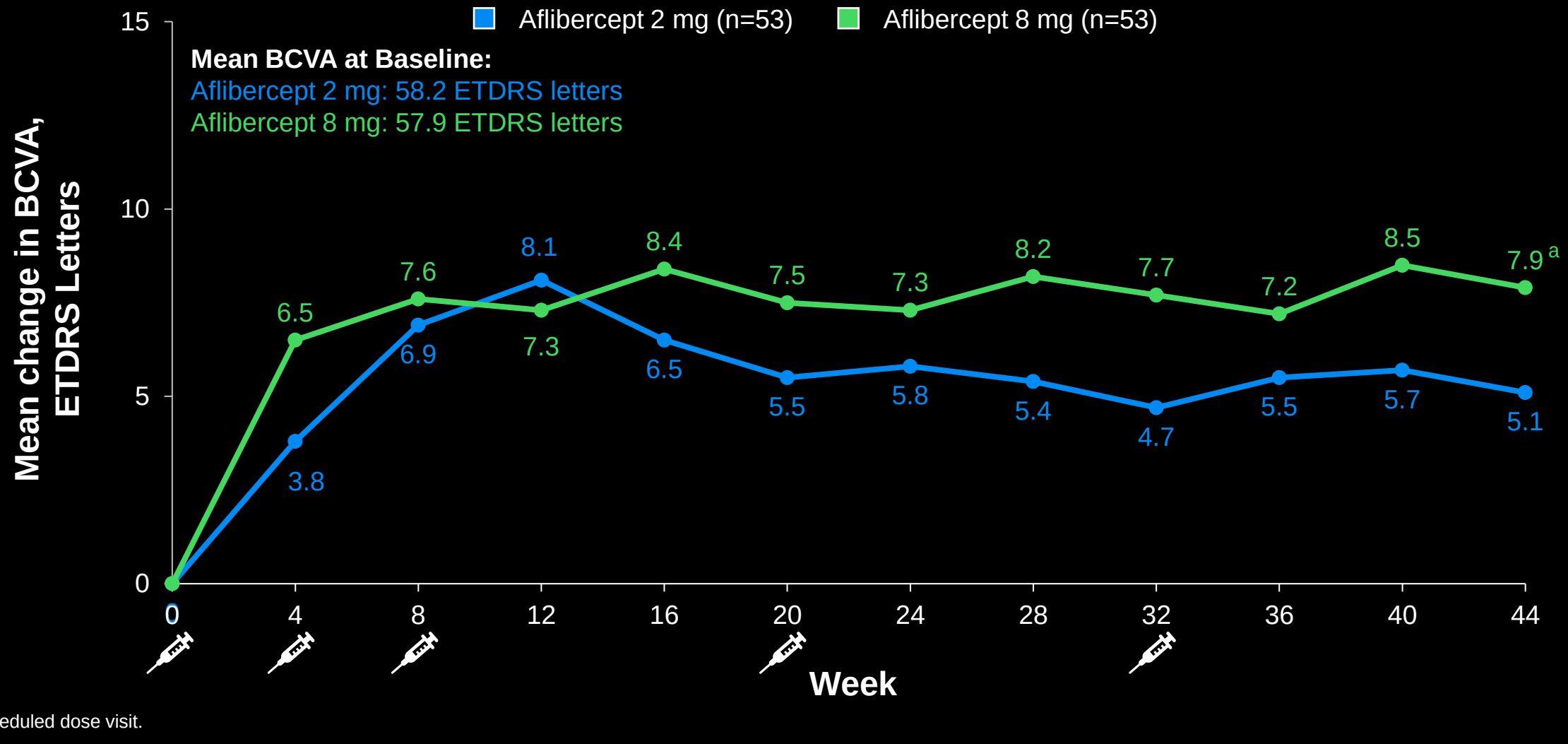
Median Change from Baseline in CRT through Week 44



= Scheduled dose visit.

FAS, LOCF.
LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.

Mean Change from Baseline in BCVA through Week 44



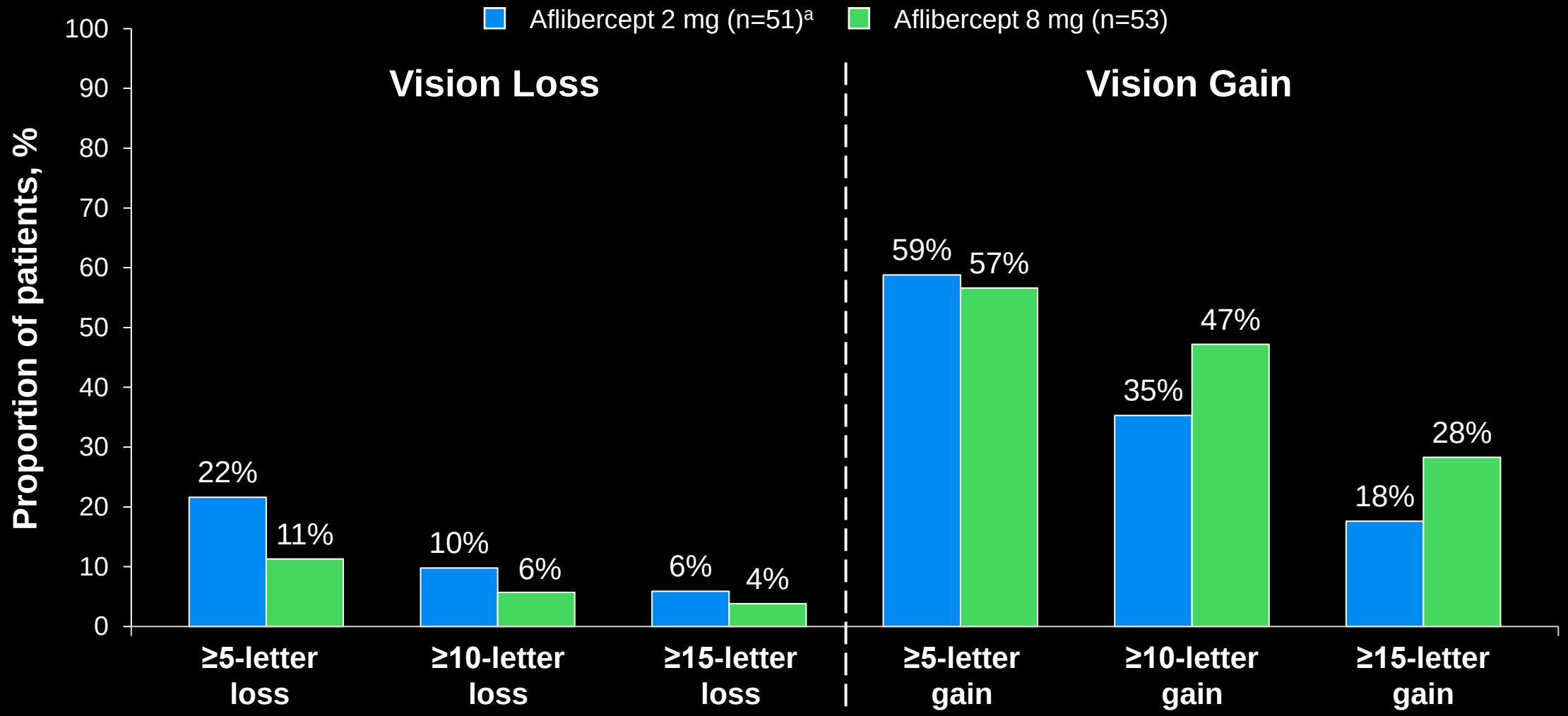
= Scheduled dose visit.

FAS, LOCF.

[a]*P* = 0.1957 vs aflibercept 2 mg at Week 44.

LOCF: Patients receiving treatment at Week 16 were considered not dry from Week 16 onward.

Proportion of Patients with Vision Loss or Gain at Week 44



FAS, LOCF.

[a]Two patients in the aflibercept 2 mg group did not have post-baseline values.

SAFETY

Ocular TEAEs in Study Eye

	Aflibercept 2 mg (n=53)	Aflibercept 8 mg (n=53)
Patients with ≥1 ocular TEAE in study eye, n (%)	20 (37.7)	20 (37.7)
Ocular TEAEs occurring in ≥2% of patients, n (%)		
Conjunctival hemorrhage	2 (3.8)	3 (5.7)
Dry eye	2 (3.8)	2 (3.8)
Neovascular age-related macular degeneration	4 (7.5)	2 (3.8)
Punctate keratitis	2 (3.8)	1 (1.9)
Retinal hemorrhage	2 (3.8)	1 (1.9)
Retinal tear	0	2 (3.8)
Visual acuity reduced	2 (3.8)	1 (1.9)
Visual impairment	2 (3.8)	1 (1.9)
Vitreous detachment	2 (3.8)	4 (7.5)

TEAE, treatment-emergent adverse event.

Safety Summary through Week 44

Ocular safety

- No vascular occlusive events
  - 1 case of iritis occurred in the aflibercept 8 mg group (mild anterior chamber cells, which resolved with topical therapy)
- No IOP increases of clinical concern occurred in either group

Non-ocular safety

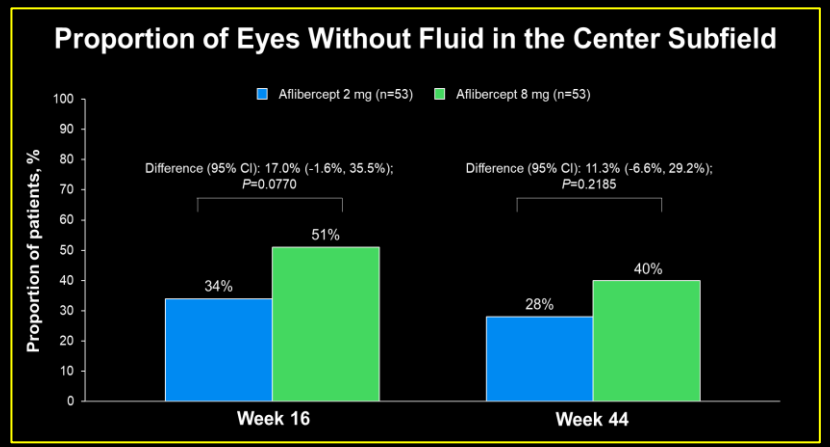
- 2 non-serious cases of worsening hypertension occurred (1 in each group)
- No APTC events
- 1 death in the aflibercept 8 mg group (glioblastoma)[a]

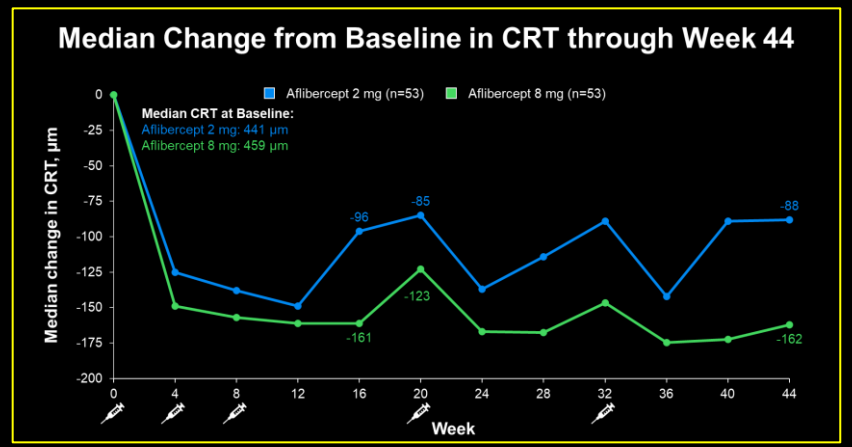
No new safety signals identified; overall safety of aflibercept 8 mg appears to be similar to aflibercept 2 mg

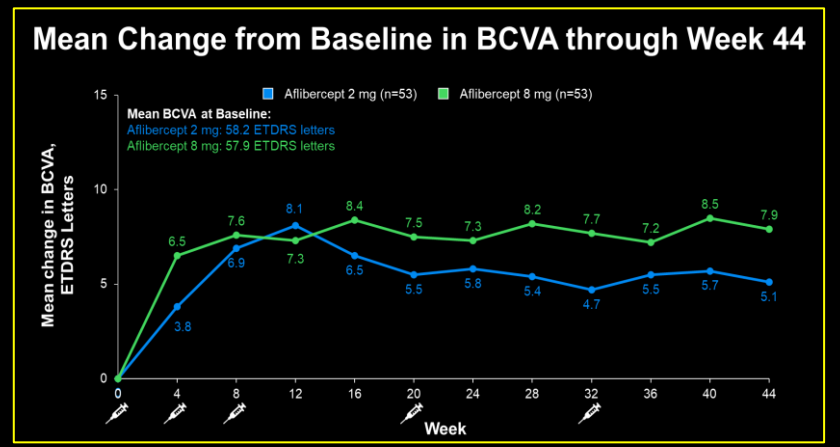
APTC, Anti-Platelet Trialists' Collaboration.
[a]Patient died after withdrawing from the study.

Week 44 Results Summary

- A higher proportion of eyes treated with aflibercept 8 mg were dry in the center subfield versus aflibercept 2 mg
  - Treatment groups followed identical dosing regimen with the 8 mg group receiving slightly fewer PRN doses
- Change from baseline in CRT suggests better anatomic outcomes with aflibercept 8 mg versus aflibercept 2 mg
- Change from baseline in BCVA favors aflibercept 8 mg (+7.9 vs +5.1 letters)
- No new safety signals were seen; safety profile for aflibercept 8 mg was similar to aflibercept 2 mg
  - One case of mild iritis in the aflibercept 8 mg group resolved with topical therapy
  - Changes from baseline in BP and IOP were similar between groups







Ongoing Phase 3 AMD and DME Studies Enrollment Complete

Multi-center, randomized, double-masked, phase 3 studies
PULSAR (AMD): Bayer sponsored
PHOTON (DME): Regeneron sponsored

2 mg aflibercept
Every 8 weeks

8 mg aflibercept

8 mg aflibercept

Dosing intervals up to 16 weeks being investigated

Primary EP at Week 48: Mean change in BCVA

End of study at Week 96

Thank you to the CANDELA Patients and Investigators