Early Fluid-Free Status and Long-Term BCVA Outcomes With Anti-VEGF Treatment in nAMD: Post Hoc Analysis of Pooled Data From HAWK & HARRIER Studies

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Disclosures

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- Employee of Novartis Pharmaceuticals Corporation

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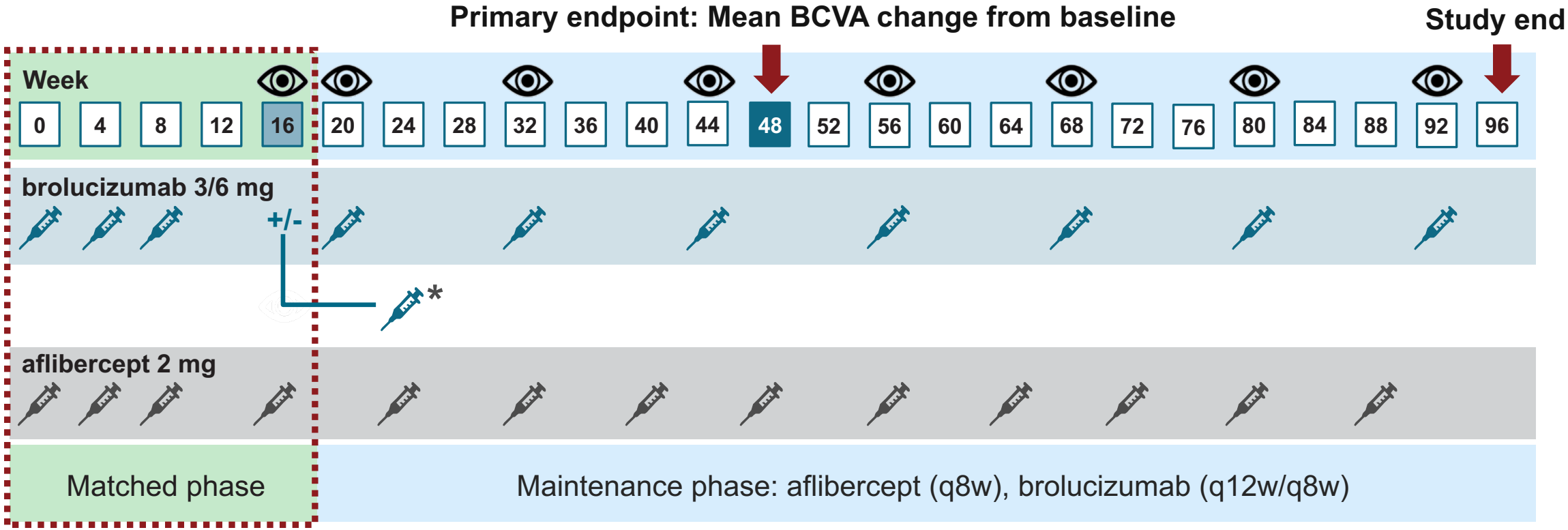
Summary

- Limited evidence exists regarding retinal fluid-free status and visual outcomes in patients with nAMD following anti-VEGF treatment.
- This post hoc analysis of the HAWK & HARRIER trials evaluates the long-term visual outcomes among patients achieving early fluid-free status (defined as intraretinal fluid (IRF) and subretinal fluid (SRF) free at Week 12), independent of treatment.
- Results suggest that patients achieving early fluid-free status following anti-VEGF treatment may have better visual outcomes than those with early fluid presence.
- This current post-hoc analysis adds to the understanding of anatomical and visual outcomes

HAWK and HARRIER: Study design and population

Study Population: Patients ≥50 years without any prior treatment for nAMD, CNV lesions secondary to nAMD with presence of IRF and SRF, and BCVA of 78-23 ETDRS letters



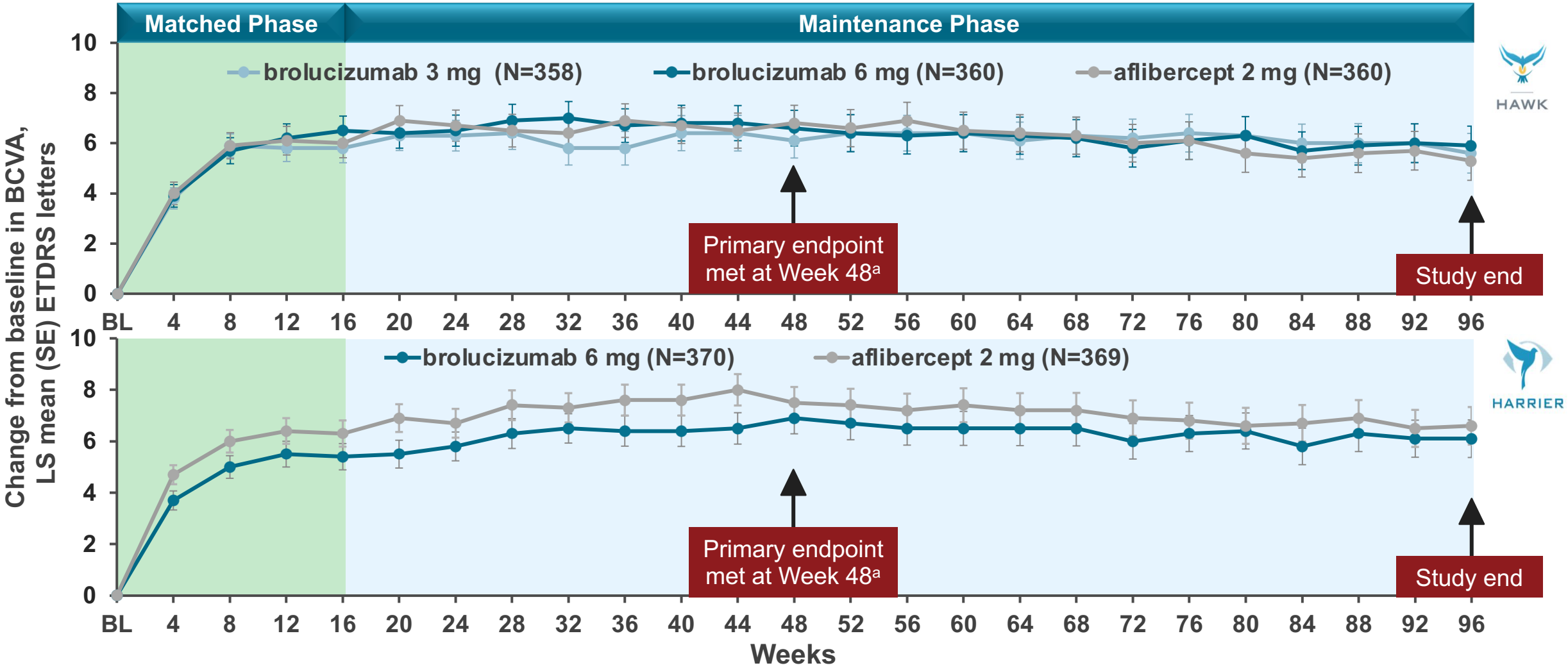
Disease activity assessment (DAA)[a]

*If disease activity was detected at any DAA visit, patients on brolucizumab q12w were adjusted to, and remained on, a q8w regimen

[a]DAAs were conducted at pre-specified visits by the masked investigator. Presence of disease activity was determined at the discretion of the masked investigator and supported by protocol guidance based on dynamic functional and anatomical characteristics. Additional assessments and potential dosing interval adjustments occurred 8 weeks after the last injection at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only. Sham injections were administered to maintain masking. Visual and anatomic assessments were made prior to injections at Weeks 16 and 48. q8w, 8-week dosing interval; q12w, 12-week dosing interval.

BCVA, best corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; SRF, subretinal fluid.

BCVA change from baseline

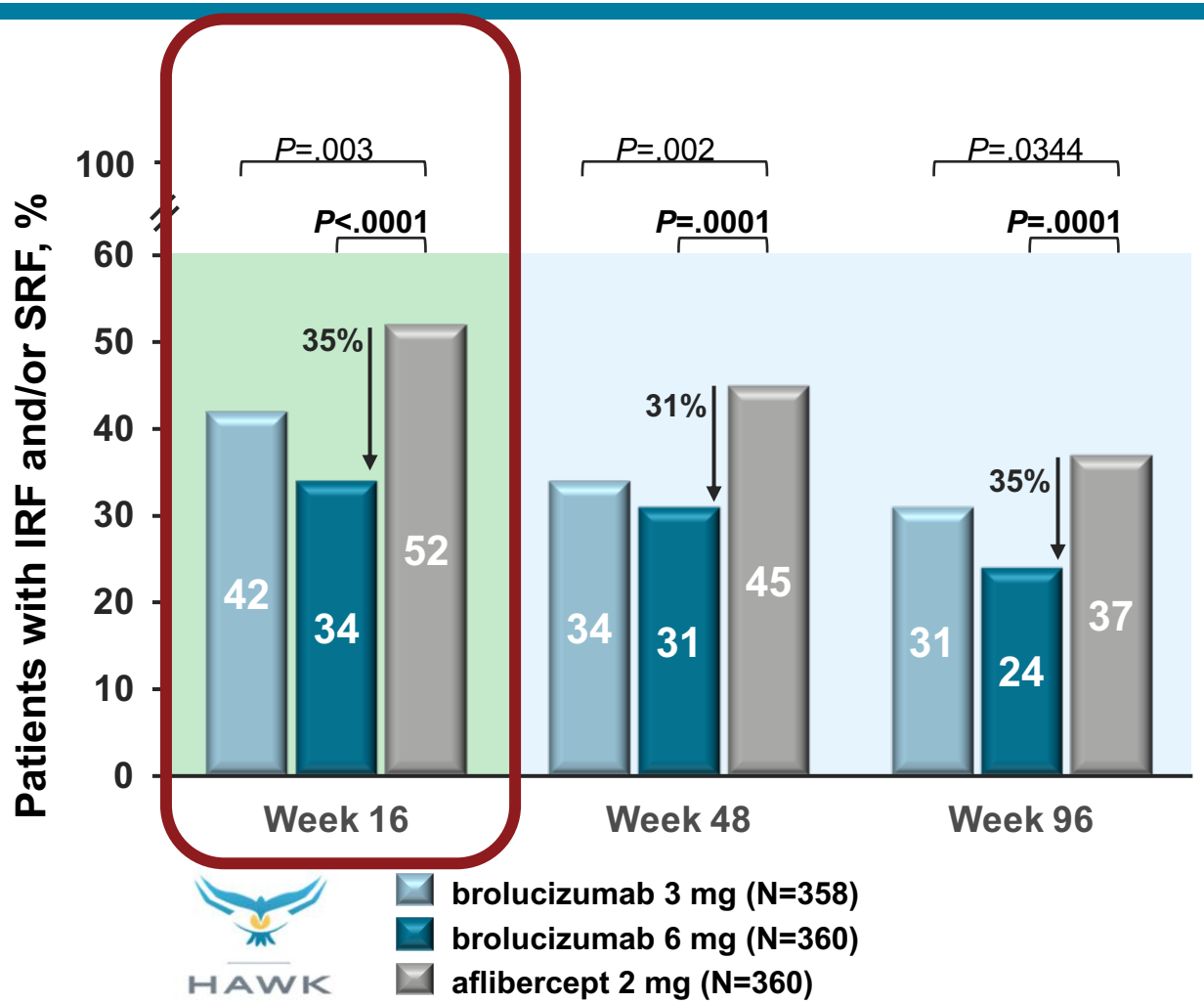


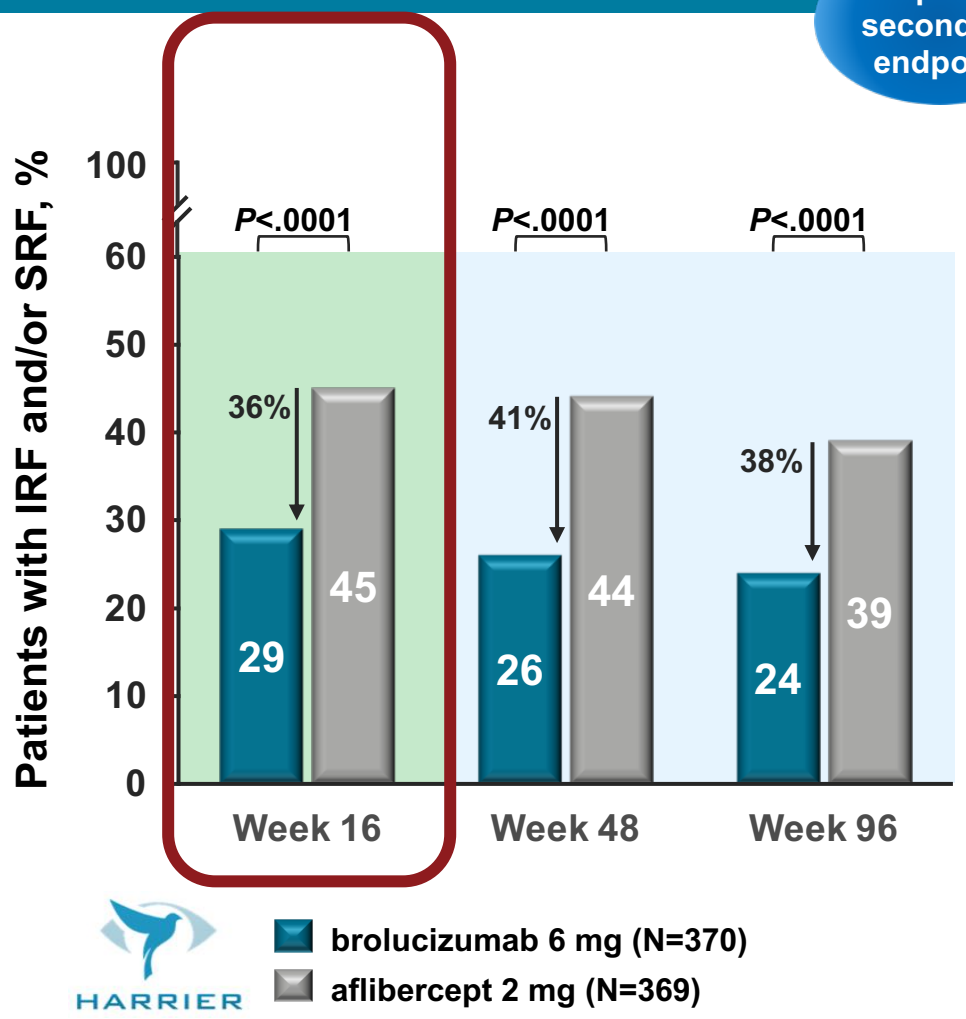
Full Analysis Set, LOCF. Mean differences in BCVA (brolucizumab–aflibercept, Δ). [a]Non-inferiority (NI) margin = 4 letters. Analyzed using ANOVA model with baseline BCVA categories (≤55, 56–70, ≥71 letters), age categories (<75, ≥75 years) and treatment as fixed-effect factors.

BCVA, best corrected visual acuity; BL, Baseline; ETDRS, Early Treatment Diabetic Retinopathy Study; LOCF, last observation carried forward; LS, least squares; SE, standard error.

IRF and/or SRF at Weeks 16,[1] 48,[1] and 96[2]

Prespecified secondary endpoint

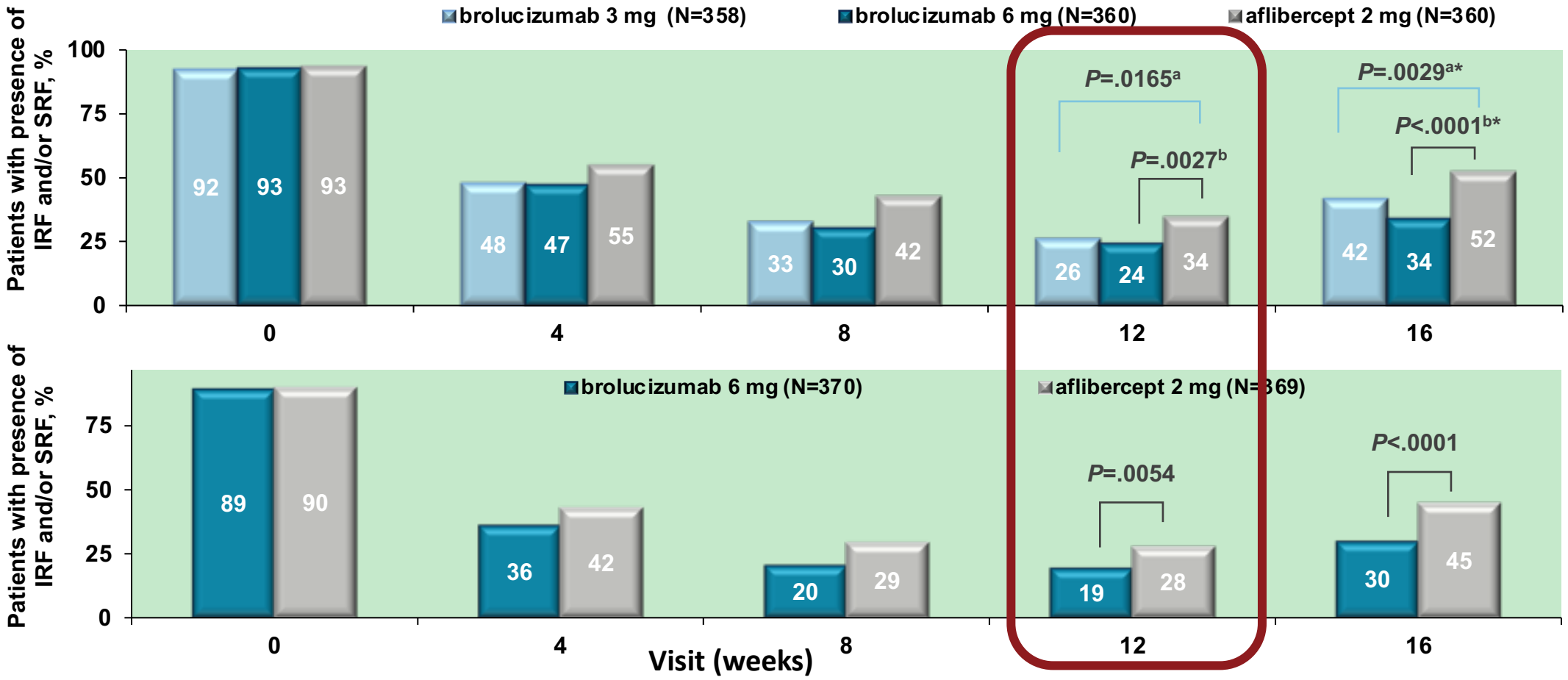




Full Analysis Set, LOCF. Prespecified secondary endpoint in both HAWK and HARRIER. Confirmatory superiority analysis at Week 16 and Week 48 in HAWK only. 1-sided *P*-values for HAWK and HARRIER. For confirmatory superiority testing in HAWK, 1-sided *P*-values below the adjusted significance level (to account for multiplicity) of *P*<.01 (for IRF and/or SRF) are regarded as statistically significant. *P*-values at Week 96 are descriptive. IRF, intraretinal fluid; LOCF, last observation carried forward. SRF, subretinal fluid.

1. Dugel PU et al. *Ophthalmology*. 2020;127(1):72-84. 2 Dugel PU et al. AAO 2018 [Oral presentation].

IRF and/or SRF presence at Week 12



FAS-LOCF; [a]brolucizumab 3 mg; [b]brolucizumab 6 mg. *Prespecified secondary endpoint in both HAWK and HARRIER with confirmatory analysis in HAWK (brolucizumab 6 mg vs aflibercept 2 mg). 1-sided *P*-values are presented. FAS, full analysis set; IRF, intraretinal fluid; LOCF, last observation carried forward; SRF, subretinal fluid.

Singh R et al. Poster presented at ARVO 2018. Poster number C0026.

Rationale for the post hoc analysis

- Retinal fluid is one of the parameters used to measure disease activity in nAMD[1-3]
- Limited evidence exists regarding early retinal fluid-free status and subsequent visual outcomes in patients with nAMD following anti-VEGF treatment
- This analysis of the HAWK and HARRIER trials evaluates the long-term visual outcomes among patients achieving early fluid-free status (defined at Week 12) independent of treatment.

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Wykoff CC et al. *J Manag Care Spec Pharm.* 2018;24(2-a):S3-S15. 2. Arnold JJ et al. *BMC Ophthalmol.* 2016;16:31. 3. Clark WL et al. *Retina Today/New Retina MD.* 2017;1-12.

HAWK and HARRIER: Post hoc pooled analysis

Early fluid-free status was defined as:

intraretinal fluid (IRF) and subretinal fluid (SRF) free at Week 12

Evaluate mean change in BCVA from baseline at Weeks:

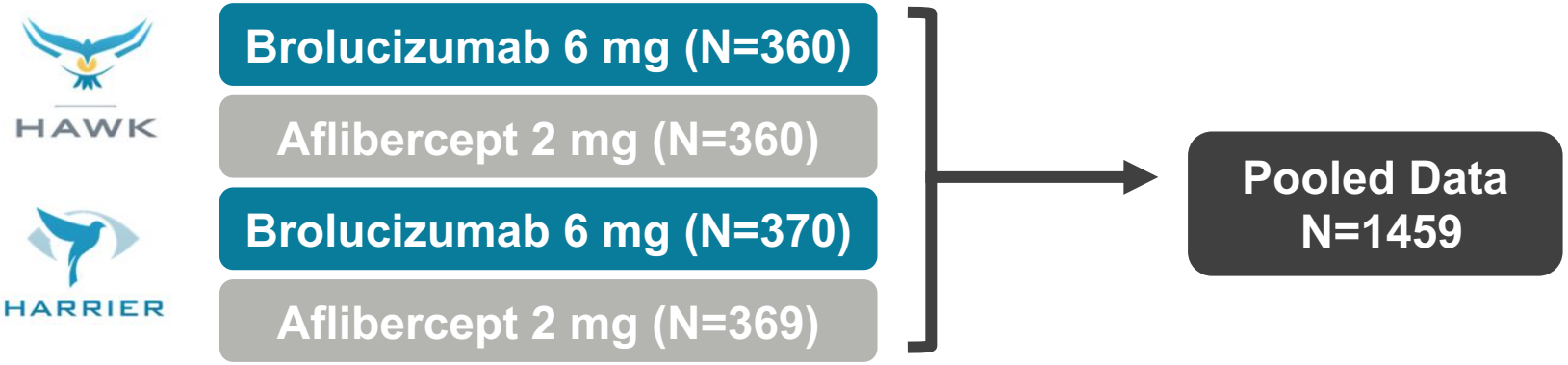
Is there an association between early retinal fluid-free status and improved long-term visual outcomes in nAMD patients following anti-VEGF treatment?

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

Methods

- The HAWK and HARRIER trials randomized eligible patients (aged ≥50 years, treatment naive, CNV lesions secondary to nAMD with presence of subfoveal fluid, BCVA of 78–23 ETDRS letters) to brolucizumab or aflibercept

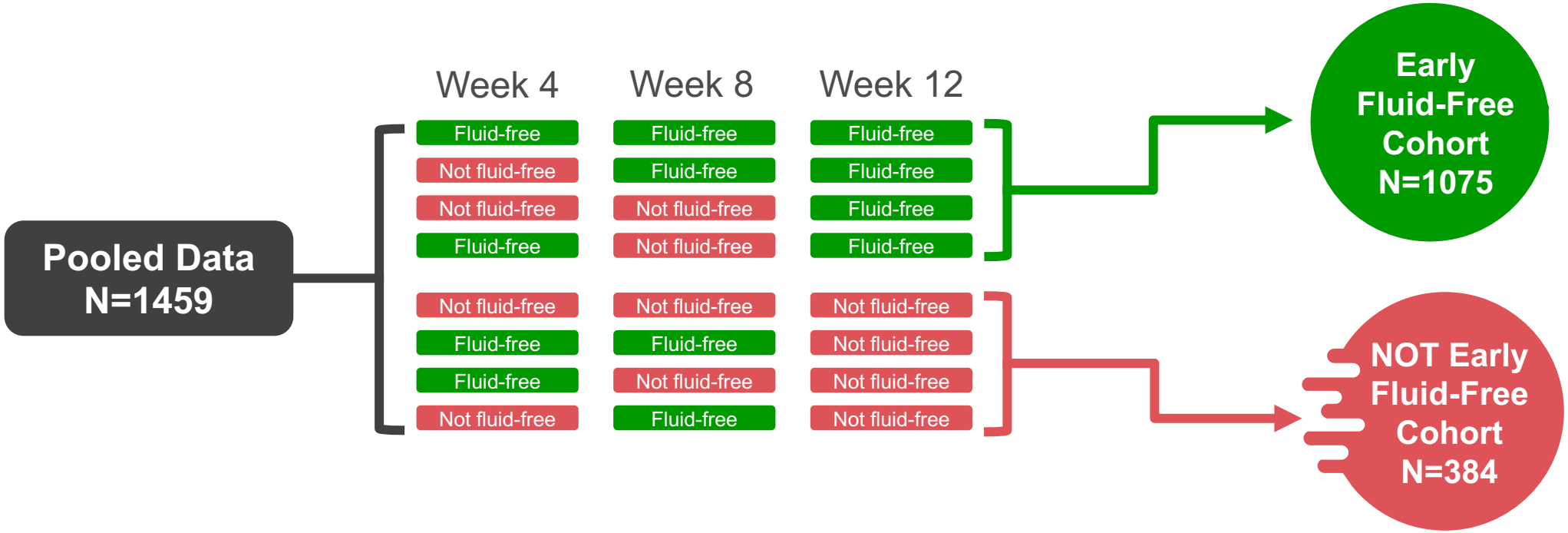
- The following data were **pooled from the HAWK and HARRIER trials**:
  - Brolucizumab 6 mg (q12/q8)
  - Aflibercept 2 mg (q8)



BCVA, best corrected visual acuity; CNV, choroidal neovascularization; ETDRS, Early Treatment Diabetic Retinopathy Study; nAMD, neovascular age-related macular degeneration.

Methods (cont)

- Patients were grouped into 2 main cohorts based on **fluid status at Week 12**, independent of treatment:



- Analyzed using ANOVA model with baseline BCVA categories (≤55, 56-70, ≥71 letters), age categories (<75, ≥75 years), and fluid-free status as fixed-effect factors

BCVA, best corrected visual acuity.

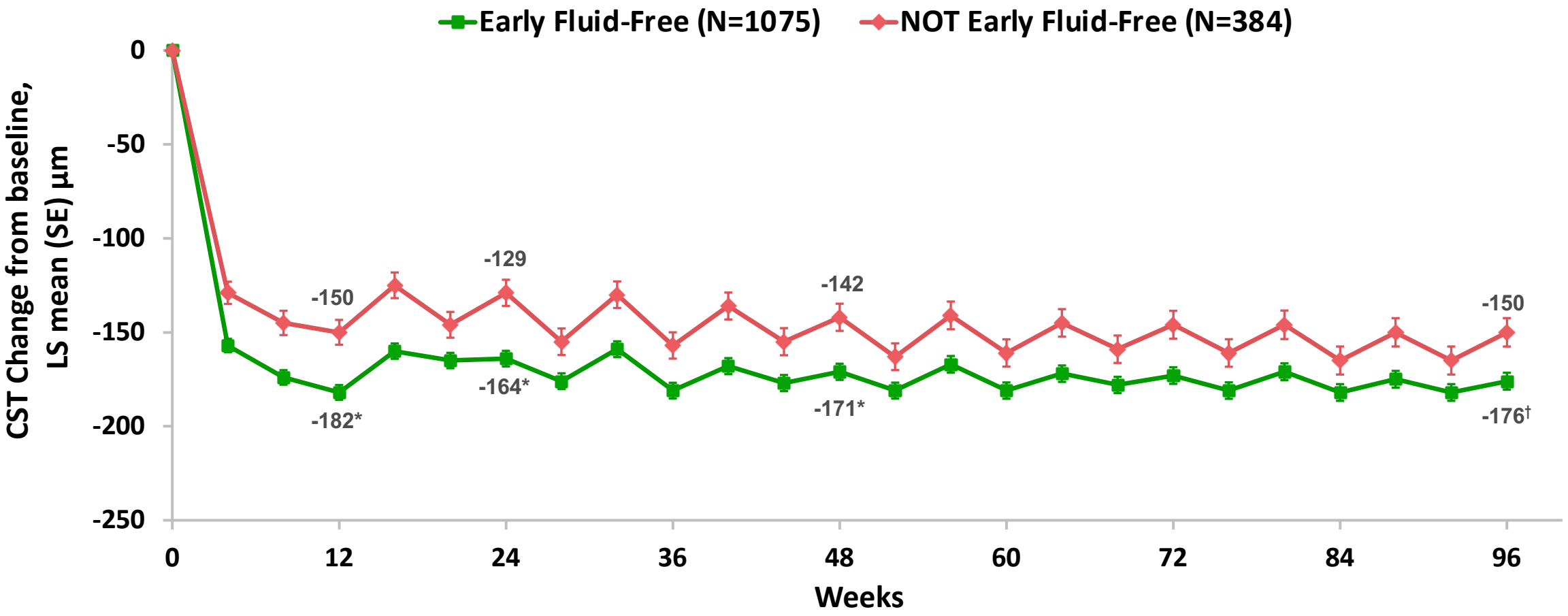
Results: Baseline Characteristics

	Early Fluid-Free (N=1075)	NOT Early Fluid-Free (N=384)
Age (years), mean ± SD	76.1 ± 8.46	74.9 ± 8.84
Female, n (%)	627 (58.3)	194 (50.5)
Time since diagnosis of nAMD <1 – 3 months, n (%)	996 (92.7)	355 (92.4)
BCVA letter score, mean ± SD	61.6 ± 12.81	58.4 ± 14.30
CST (µm), mean ± SD	455.2 ± 155.76	492.5 ± 165.65
Type of CNV, n (%)		
Predominantly classic	371 (34.7)	156 (40.6)
Minimally classic	112 (10.5)	28 (7.3)
Occult	587 (54.9)	200 (52.1)
Presence of SRF, n (%)	743 (69.1)	271 (70.6)
Presence of IRF, n (%)	497 (46.2)	179 (46.6)
Presence of sub-RPE fluid, n (%)	413 (38.4)	165 (43.0)

The BCVA and CST changes were corrected for baseline BCVA and CST differences

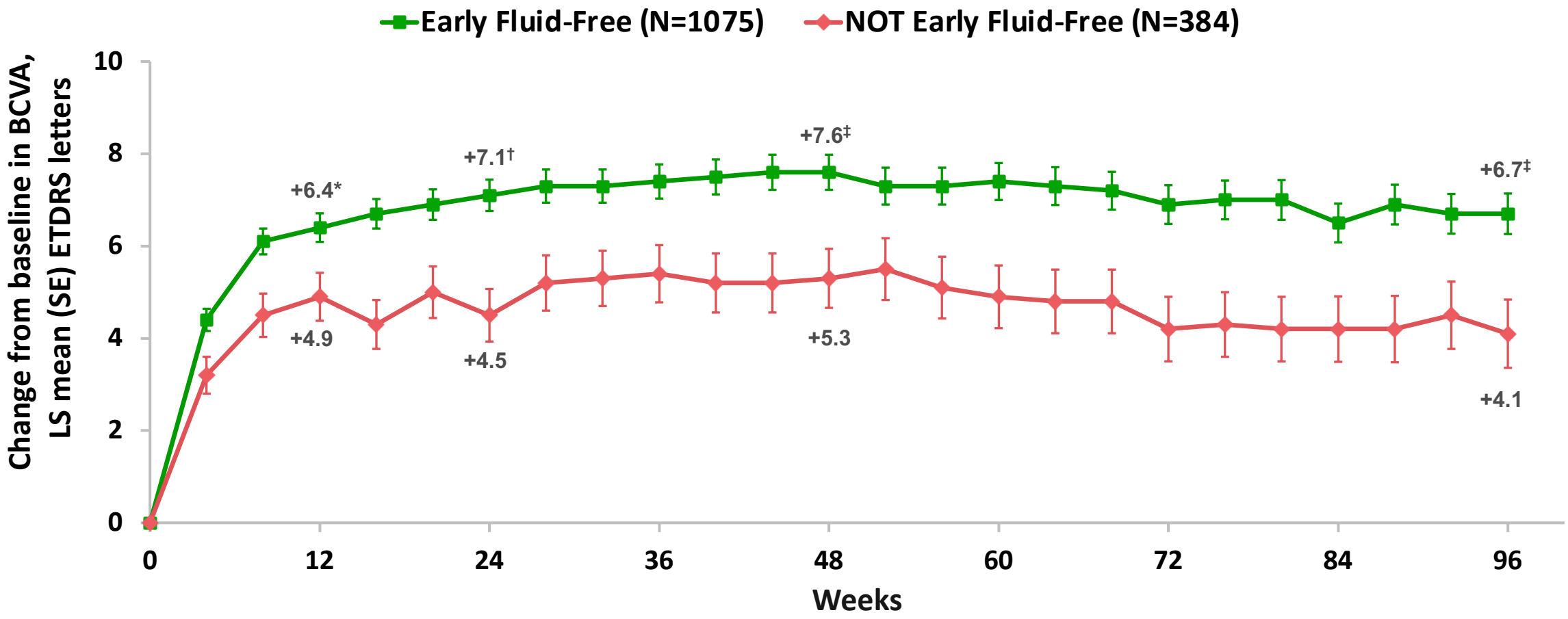
BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; IRF, intraretinal fluid; nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; SD, standard deviation; SRF, subretinal fluid.

Results: CST improvement from baseline in patients with early fluid-free status was greater than that of patients with fluid at the same time points



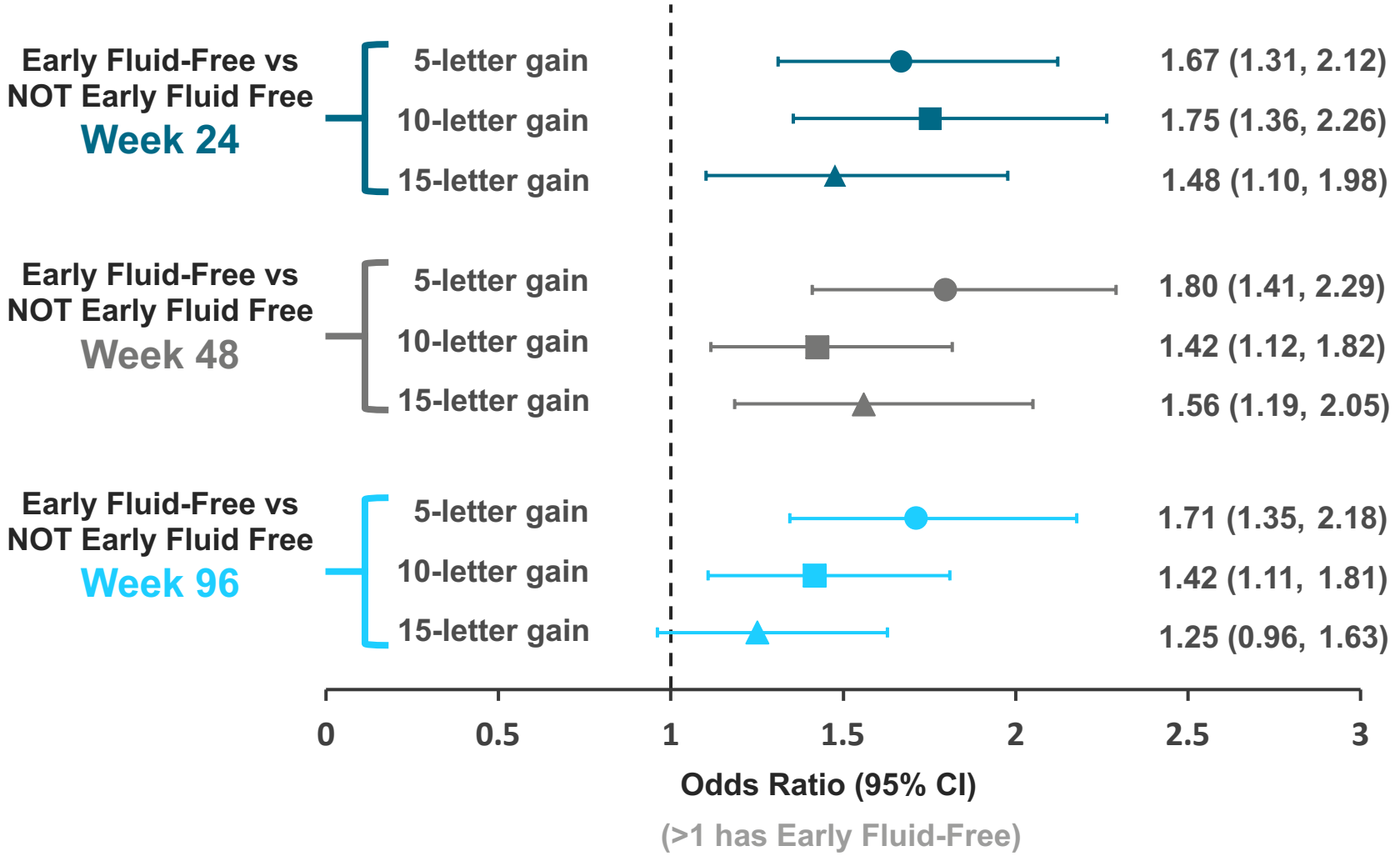
*P<.001; †P<.01; Significant difference at all time points.
Fluid status defined at Week 12.
Data pooled for brolucizumab 6 mg and aflibercept 2 mg.
CST, central subfield thickness; LS, least squares; SE, standard error.

Results: BCVA improvement from baseline in patients with early fluid-free status was greater than that of patients with fluid at the same time points



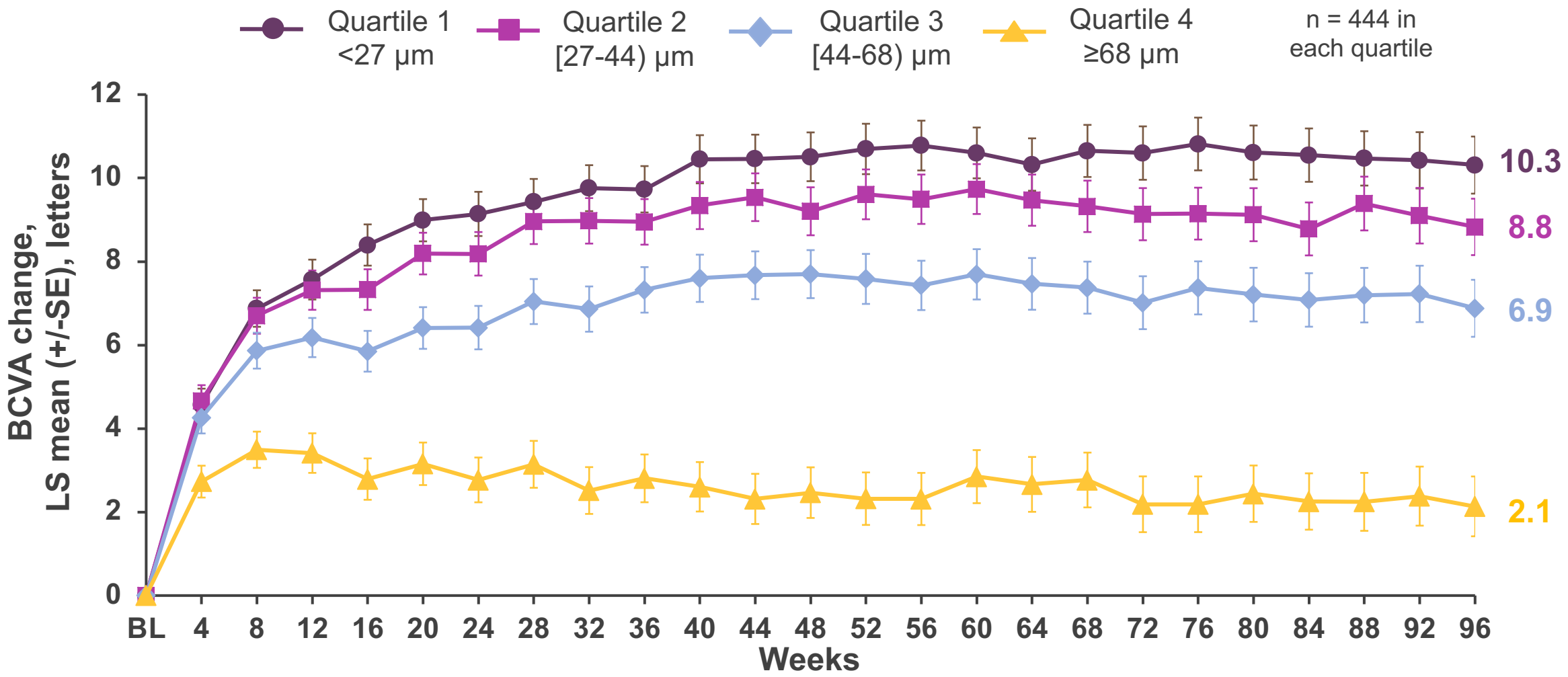
*P<.05; †P<.001; ‡P<.01; Significant difference at all time points.
Fluid status defined at Week 12.
Data pooled for brolucizumab 6 mg and aflibercept 2 mg.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; LS, least squares; SE, standard error.

Results: Odds ratio of attaining 5, 10, or 15 letter gain was greater in patients with early fluid-free status cohort at Weeks 24, 48 and 96



Fluid status defined at Week 12.
Data pooled for brolucizumab 6 mg and aflibercept 2 mg.
CI, confidence interval.

Pooled treatment and study data from HAWK and HARRIER sensitivity analysis: Higher CST variability was associated with lower BCVA gains[1]



Individual SD (CST) is for weeks 0 to 96. LS mean and SE estimates are based on an ANOVA model with baseline BCVA letters, study, treatment and CST variability quartile as fixed effect factors.
These data are combined data for brolucizumab and aflibercept. BCVA, best-corrected visual acuity; BL, baseline; CST, central subfield thickness; LS, least squares; SE, standard error; SD, standard deviation

1. Jhaveri CD, et al. Visual and anatomical outcomes for brolucizumab and aflibercept in patients with nAMD: 96-week data from HAWK and HARRIER. Podium presentation presented at: The American Society of Retina Specialists Annual Meeting; July 26-30, 2019; Chicago, USA.

Limitations - Early Fluid Resolution cohorts

- The current study was a post hoc analysis of the HAWK and HARRIER Phase 3 studies
- The BCVA changes were corrected for baseline BCVA differences, but not for other characteristics such as type of CNV

BCVA, best corrected visual acuity; CNV, choroidal neovascularization.

HAWK and HARRIER: Post hoc analysis conclusions

- The current post hoc analysis of the pooled HAWK and HARRIER studies (treatment agnostic) demonstrated:
  - Greater reduction in CST in patients with early fluid-free status compared to those with early fluid presence
  - Improvements in visual outcomes occurring as early as 4 weeks following the last loading dose (Week 12) and continuing to 96 weeks
  - Odds of gaining 5,10, 15 letters is greater in the early fluid-free cohort through 96 weeks.
- Taken together, the results suggest that patients achieving early fluid-free status following anti-VEGF treatment may have better visual outcomes than those with early fluid presence. The results of this current post-hoc analysis adds to the understanding of anatomical and visual outcomes

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