Early Residual Fluid-Free Status and Long-Term BCVA Outcomes: A Treatment Agnostic, Post Hoc Analysis of Pooled HAWK and HARRIER Data

CHIRAG JHAVERI, CHARLES C. WYKOFF, ARSHAD M. KHANANI, CHIARA M. EANDI, ANDREW CHANG, GURUPRASAD B, KINFEMICHAEL A. GEDIF, AND MICHAEL SINGER

• PURPOSE: The aim of this study was to determine associations between early residual fluid (ERF)—free status and improved long-term visual outcomes.
• DESIGN: This was a retrospective clinical cohort study from a post hoc analysis of 2 phase III clinical trials' data.
• METHODS: Independent of treatment allocation, patients from the multicenter, prospective, randomized, double-masked HAWK and HARRIER trials who received either brolucizumab 6 mg or aflibercept 2 mg were split into 2 cohorts depending on the presence or absence of ERF at week 12. In addition, similar analyses were performed on the presence or absence of early residual intraretinal fluid (IRF) and subretinal fluid (SRF) at week 12. The 2 groups, ERF-free (n = 1051) and ERF (n = 366) patients were compared. Changes from baseline in best corrected visual acuity (BCVA) and central subfield thickness (CST) were determined.
• RESULTS: From week 12 to 96, patients who were ERF free had greater least squares (LS) mean increases from baseline for BCVA and CST compared to ERF patients. Greater LS mean differences in BCVA from week 12 to 96 were noted between ERF-free and ERF patients. A greater proportion of patients in the ERF-free cohort reported a ≥5, ≥10, or ≥15 letter improvement, and a higher proportion reported BCVA ≥70 letters from baseline to week 96 compared to patients with fluid.
• CONCLUSIONS: Improvements in visual outcomes in ERF-free patients were greater than in ERF patients occurring as early as 4 weeks (week 12) after the last loading dose and continued to week 96. Therefore, ERF status may be a useful indicator of anti—vascular endothelial growth factor treatment response. (Am J Ophthalmol 2022;236: 12–19. © 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/))

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Retina Consultants of Austin (C.J.), Austin Research Center for Retina, Austin, Texas, USA; Dell Medical School (C.J.), University of Texas at Austin, Austin, Texas, USA; Retina Consultants of Texas (C.C.W.), Retina Consultants of America; Blanton Eye Institute (C.C.W), Houston Methodist Hospital, Houston, Texas, USA; Sierra Eye Associates (A.M.K.), Reno, Nevada, USA; Reno School of Medicine (A.M.K.), The University of Nevada, Reno, Nevada, USA; Department of Surgical Science (C.M.E.), University of Torino, Torino, Italy; Department of Ophthalmology (C.M.E.), University of Lausanne, Jules-Gonin Eye Hospital, Fondation Asile des Aveugles, Lausanne, Switzerland; Sydney Retina Clinic (A.C.); Sydney Eye Hospital; Save Sight Institute, University of Sydney, Sydney, Australia; Novartis Pharmaceuticals (G.B, K.A.G.), East Hanover, New Jersey, USA; Medical Center Ophthalmology Associates (M.S), University of Texas Health Center, San Antonio, Texas, USA

Inquiries to Michael Singer, 9157 Huebner Road, San Antonio, TX 78240, USA.; e-mail: msinger11@me.com

Since their introduction in 2004, anti—vascular endothelial growth factor (anti-VEGF) agents have revolutionized the treatment of patients with neovascular age-related macular degeneration (nAMD), leading to substantially improved visual outcomes.[1-3] Brolucizumab was approved by the Food and Drug Administration and the European Medicines Agency following the completion of the phase III HAWK and HARRIER trials.[4-7] Brolucizumab demonstrated noninferiority for visual acuity (VA) outcomes compared with aflibercept in these trials. In HAWK, 56% and in HARRIER, 51% of patients treated with brolucizumab maintained an every 12 weeks dosing regimen after the loading phase until week 48. Of the patients who received brolucizumab 6 mg and were on an every 12 weeks dosing regimen at week 48, >75% successfully remained on the every 12 weeks regimen until week 96. These trials also demonstrated greater fluid resolution in patients receiving brolucizumab compared with aflibercept, with significantly less intraretinal fluid (IRF) and/or subretinal fluid (SRF) at weeks 16 and 48. Furthermore, superior anatomical outcomes, including a reduction in disease activity and central subretinal thickness, were observed up to week 96. These findings suggest that brolucizumab leads to greater inhibition of vascular leakage and therefore, compared with aflibercept, is more effective at both reducing retinal thickness and resolving retinal fluid.[6,7]

In patients with nAMD, the accumulation of fluid, including both IRF and SRF, is an important marker of

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disease activity, with a recent cross-sectional analysis implicating IRF more than SRF to be associated with worse vision outcomes.[8,9] The reduction of retinal fluid has also been used to determine treatment decisions for individual patients.[9-12] As reported by Toth et al,[9] the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) group designed a trial to assess an "as-needed treatment" approach versus a fixed monthly regimen based on the amount of retinal fluid present on a monthly optical coherence tomography (OCT) scan. Anti-VEGF injections were administered following the determination of IRF, SRF, or sub-retinal pigment epithelium (RPE) fluid. In addition, Jaffe et al showed, in the CATT study, that when analyzed cross-sectionally, the presence of IRF was associated with worse vision, whereas the presence of SRF was associated with better concurrent vision compared to that in the patients who were SRF-free.[13] Another study that has also investigated retinal fluid in determining choice of dosing regimen for individual patients was the FLUID study.[14-16] In the FLUID study, a treat-and-extend approach with ranibizumab was tested, in which treatment extension was allowed without complete resolution of SRF (SRF ≤200 µm) in patients with nAMD. The study demonstrated noninferiority of this method when compared with a treat-and-extend protocol requiring complete resolution of both IRF and SRF after comparing visual outcomes over a 24-month period.

Limited evidence exists regarding early residual fluid (ERF)—free status, the fluid that remains after the loading phase and subsequent visual outcomes through the medium-term follow-up of 2 years or more in patients with nAMD following anti-VEGF treatment in a clinical study. This has led to analysis such as that by Ohji et al, who investigated links between early fluid-free status and visual outcomes at year 2 after treatment with aflibercept.[17] In this Japanese study, aflibercept was administered at variable treat-and-extend intervals in patients with nAMD. The findings showed that patients who did not have fluid at week 16 had superior best corrected visual acuity (BCVA) outcomes, greater reduction in central retinal thickness, and longer treatment intervals at the end of the study, leading to the hypothesis that fluid status after the loading phase could be a prognostic factor in determining visual and anatomic outcomes. However, further studies are needed to support this association with fluid status.

Here we present pooled data from the phase III HAWK and HARRIER studies, which were analyzed in a treatment agnostic manner to determine whether there is an association between ERF-free status and improved long-term visual and anatomic outcomes in patients with nAMD after anti-VEGF treatment. Because the current analysis is treatment agnostic and the aflibercept arm was an administered dose in a fixed 8-weekly interval (Q8), the impact of the ERF status on longer treatment intervals could not be evaluated.

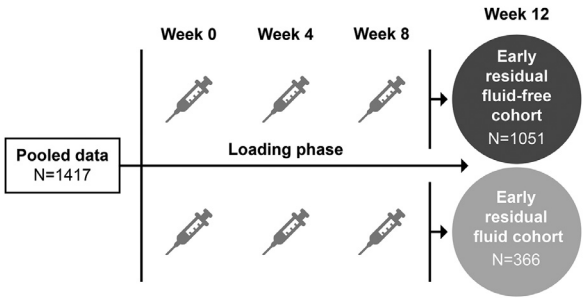

FIGURE 1. Patient cohorts used in this analysis based on fluid status from HAWK and HARRIER at weeks 4, 8, and 12.

METHODS

• **STUDY DESIGN:** The phase III HAWK (NCT02307682) and HARRIER (NCT02434328) trials (registration location in Texas, USA) randomized eligible patients (aged ≥50 years, treatment naive, choroidal neovascular [CNV] lesions secondary to nAMD with presence of subfoveal fluid, BCVA of 78-23 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) to receive brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg in a 1:1:1 ratio. These studies were approved by an Independent Ethics Committee/Institutional Review Board and were conducted according to the principles in the Declaration of Helsinki and the International Conference on Harmonization E6 Good Clinical Practice Consolidated Guideline. Written informed consent was provided by all patients before screening and other study procedures.

In the HAWK study, a total of 1082 patients were randomized 1:1:1 to receive brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. In the HARRIER study, a total of 743 patients were randomized 1:1 to receive either brolucizumab 6 mg or aflibercept 2 mg. In both the HAWK and HARRIER studies, following the 3-monthly loading phase injections at weeks 0, 4, and 8, intravitreal brolucizumab was administered every 12 weeks, unless disease activity was present and the regimen was adjusted to every 8 weeks. In contrast, aflibercept was continued every 8 weeks, per label, after the loading phase.[6,7]

In this post hoc, treatment agnostic analysis, data from only the brolucizumab 6 mg and aflibercept 2 mg treatment arms from the 2 studies were pooled. Only the brolucizumab 6 mg arm was used, as it is the only approved dose across geographies. Patients were grouped into 2 cohorts, designated as ERF-free and ERF, based on fluid status at week 12 (4 weeks after the end of the loading phase), independent of treatment allocation. A similar analysis was also performed defining the cohorts based on the presence and absence of IRF and SRF, respectively, at week 12 (Figure 1). These were ERF (IRF) and ERF- (IRF) free for patients with and without IRF, respectively, and ERF (SRF) and ERF- (SRF) free

for patients with and without SRF, respectively. Sub-RPE fluid was not investigated in this post hoc analysis, as it is not typically used as an indicator of disease activity in clinical practice.

• **FLUID ASSESSMENTS:** Anatomical assessments carried out every 4 weeks from the HAWK and HARRIER trials were used for this analysis, including SRF and IRF assessments, and central subfield thickness (CST) measurements using spectral domain OCT.[6] Anatomical assessments were carried out at a masked central reading center (HAWK: Duke Reading Center, Duke University, Durham, NC; HARRIER: Vienna Reading Center, Medical University of Vienna, Vienna, Austria). The CST evaluated by the central reading center in this study represented the average retinal thickness (Bruch membrane to inner limiting membrane) of the circular area within 1 mm diameter around the foveal center on the spectral domain—OCT (SD-OCT).

IRF was defined as the hyporeflective space within the retina, not including those spaces with a hyperreflective border that corresponded to outer retinal tubulation. SRF was defined as the hyporeflective space bound internally by the photoreceptor outer segment tips and externally by the RPE.

• **VISUAL ASSESSMENTS:** BCVA data were obtained using ETDRS testing charts, at a distance of 4 m, at week 12 up to week 96, as described previously.[6]

Baseline characteristics, including ocular characteristics, for both cohorts were determined. The number and percentage of patients in both cohorts with retinal fluid was calculated at each timepoint. BCVA (letters read) was analyzed as change from baseline, ≥15/≥10/≥5 letter improvement, percentage of patients with ≥70 letter vision, and vision loss from baseline using the full analysis set. A subgroup analysis of BCVA data was carried out for patients with and without SRF at week 12, and with and without IRF at week 12. CST was presented as change from baseline by visit.

• **STATISTICAL ANALYSES:** BCVA data were analyzed using analysis of variance with baseline BCVA categories (≤55, 56-70, ≥71 letters), age categories (<75, ≥75 years), and fluid-free status as fixed-effect factors. Ninety-five percent confidence intervals, based on *t* distribution, were presented as descriptive statistics. The odds ratio for BCVA (letters read) was determined from a statistical model using logistic regression adjusting for BCVA categories, age categories, and treatment as fixed-effect factors, and 95% CIs for the treatment difference were estimated using the bootstrap method. The CST measurements were analyzed with analysis of variance using baseline CST categories (<400, ≥400 μm), age categories (<75, ≥75 years), and treatment as fixed effects, and 95% CIs for binomial proportions were based on the Clopper—Pearson exact method.

RESULTS

• **STUDY POPULATION:** In this post hoc analysis, data were pooled from 360 patients treated with brolucizumab 6 mg and 360 patients treated with aflibercept 2 mg from the HAWK study, and 370 patients treated with brolucizumab 6 mg and 369 patients treated with aflibercept 2 mg from the HARRIER study. In total from both studies, data from 1417 patients were analyzed. The study populations were split into 2 cohorts that were designated as either ERF free (n = 1051) or ERF (n = 366).

Patient baseline characteristic disposition was well balanced between the fluid and fluid-free cohorts for patients in the ERF-free, ERF, ERF- (SRF) free, ERF (SRF), ERF- (IRF) free, and ERF (IRF) cohorts at week 12. This included the percentage of patients treated and randomized and the percentage of patients who completed at week 96 and discontinued prior to week 96. For patients in the ERF cohort, the most common reason for discontinuation of study treatment prior to week 96 was withdrawal by subject followed by adverse event. Withdrawal by subject and adverse event were also the most common reasons for study treatment discontinuation between the ERF-free, ERF- (SRF) free, ERF (SRF), and ERF- (IRF) free cohorts. In the ERF (IRF) cohort, the most common reasons were withdrawal by subject, death, and loss to follow-up.

• **PATIENT BASELINE CHARACTERISTICS:** Overall, the patient baseline characteristics were fairly balanced between the ERF-free and ERF cohorts with similar proportions of female patients, time since diagnosis of nAMD, and SRF, IRF, and sub-RPE fluid at baseline (Table 1). Most patients in both cohorts had SRF at baseline (69.4% in the ERF-free cohort and 71.0% in the ERF cohort). The mean (± standard deviation [SD]) BCVA letter score and CST between the cohorts was also similar. At baseline, most patients had BCVA of 56 to 70 letters and mean CST-total of ≥400 μm.

• **BEST CORRECTED VISUAL ACUITY:** At every week from week 4 to week 96, greater least squares (LS) mean changes from baseline in BCVA were observed in the ERF-free cohort compared with the ERF cohort (Figure 2). The LS mean (SE) change from baseline in BCVA was 7.2 (0.34) at week 24, 7.7 (0.39) at week 48, and 6.8 (0.44) at week 96 in the ERF-free cohort, and was 4.6 (0.58) at week 24, 5.4 (0.66) at week 48, and 4.1 (0.76) at week 96 in the ERF cohort. The differences between the cohorts were statistically significant at every week ($P \leq 0.0255$).

A subgroup analysis of BCVA was carried out on 1188 and 229 patients who were ERF- (SRF) free and ERF (SRF), respectively, and 1244 and 171 patients who were ERF (IRF) free and ERF (IRF), respectively (Figure 3, A and B). IRF data were not available for 2 patients who were excluded from the IRF subgroup analysis. Numerically greater

TABLE 1. Baseline Characteristics of Pooled HAWK and HARRIER Patients

Characteristic	Early Residual Fluid Free (n = 1051)	Not Early Residual Fluid Free (n = 366)
Age, y, mean ± SD	76.1 ± 8.47	74.7 ± 8.81
Female, n (%)	610 (58.0)	184 (50.3)
Time since diagnosis of nAMD <1-3 mo, n (%)	975 (92.8)	339 (92.9)
BCVA letter score, mean ± SD	61.6 ± 12.81	58.3 ± 14.25
CSFT (μm), mean ± SD	455.7 ± 156.59	492.5 ± 165.23
Type of CNV, n (%)		
Predominantly classic	364 (34.8)	150 (41.0)
Minimally classic	111 (10.6)	25 (6.8)
Occult	571 (54.6)	191 (52.2)
Presence of SRF, n (%)	729 (69.4)	260 (71.0)
Presence of IRF, n (%)	482 (45.9)	166 (45.4)

BCVA = best corrected visual acuity; CNV = choroidal neovascular; CSFT = central subfield thickness; IRF = intraretinal fluid; nAMD = neovascular age-related macular degeneration; SRF = subretinal fluid.

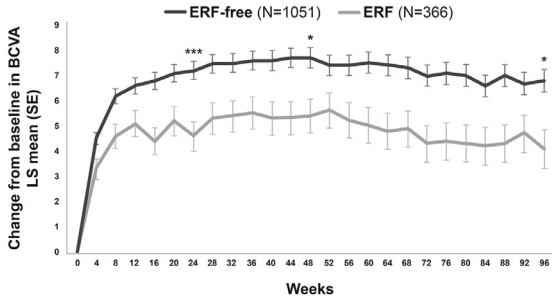

FIGURE 2. BCVA changes from baseline in patients with and without early residual fluid-free status. BCVA = best corrected visual acuity; ERF = early residual fluid; LS = least squares. *LS mean difference, *P* < .01; ***LS mean difference, *P* < .0001.

LS mean changes from baseline in BCVA were observed from week 12 to 96 in patients from the ERF- (SRF) free cohort compared with the ERF (SRF) cohort (Figure 3, A) but did not achieve statistical significance. The LS mean (SE) change from baseline in BCVA was 6.8 (0.32) at week 24, 7.3 (0.36) at week 48, and 6.2 (0.42) at week 96 in the ERF- (SRF) free cohort and 5.2 (0.74) at week 24, 6.0 (0.83) at week 48, and 5.3 (0.96) at week 96 in the ERF (SRF) cohort. The LS mean (SE) difference between the ERF- (SRF) free and ERF (SRF) cohorts was –1.5 (0.80; $P = 0.0557$) at week 24, –1.3 (0.91; $P = .1641$) at week 48, and –0.9 (1.04; $P = .3848$) at week 96. Significantly greater LS mean changes from baseline in BCVA were observed from week 12 to week 96 in patients from the ERF- (IRF) free cohort compared with the ERF (IRF) cohort (Figure 3, B). The LS mean (SE) change from baseline in BCVA was 7.0 (0.31) at week 24, 7.5 (0.36) at week 48, and 6.7 (0.41) at week 96 in the ERF- (IRF) free cohort and 3.0 (0.85) at week 24, 3.8 (0.97) at week 48, and 1.8 (1.11) at week 96 in the ERF (IRF) cohort. The LS mean (SE) difference between the ERF- (IRF) free and ERF (IRF) cohorts was –4.1 (0.91; $P < .0001$) at week 24, –3.7 (1.04; $P = .0003$) at week 48, and –4.9 (1.19; $P < .0001$) at week 96.

A greater percentage of patients reported BCVA of ≥70 letters in the ERF-free cohort compared with the ERF cohort. This was observed at each time point from weeks 12 to 96. The odds ratio was 0.5 ($P < .0001$) at weeks 24 and 48 and 0.6 ($P = .0002$) at week 96. This indicates that the ERF-free cohort had higher odds of gaining ≥70 letters than the ERF cohort (Figure 4).

A greater percentage of patients in the ERF-free cohort reported a ≥5, ≥10, or ≥15 letter improvement from baseline compared with the ERF cohort. This was observed from weeks 24 to 96 in all 3 letter categories. When comparing ERF versus ERF-free cohorts, for ≥15 letter improvement, the odds ratio was 0.7 ($P = .0068$) at week 24, 0.6 ($P = .0011$) at week 48, and 0.8 ($P = .0748$) at week 96; for ≥10 letter improvement, the odds ratio was 0.6 ($P < .0001$) at week 24, 0.7 ($P = .0028$) at week 48, and 0.7 ($P = 0.0036$) at week 96; for ≥5 letter improvement, the odds ratio was 0.6 ($P < .0001$) at week 24, 0.5 ($P < .0001$) at week 48, and 0.6 ($P < .0001$) at week 96. This indicates that the ERF-free cohort has higher odds of gaining ≥5, ≥10, or ≥15 letters than the ERF cohort (Figure 5). Similarly, a greater percentage of patients in the ERF cohort reported a loss of ≥5, ≥10, and ≥15 letters from baseline compared with the ERF-free cohort. When comparing ERF versus ERF-free cohorts, for ≥15-letter loss, the odds ratio was 1.4 ($P = .2318$) at week 24, 1.3 ($P = .2592$) at week

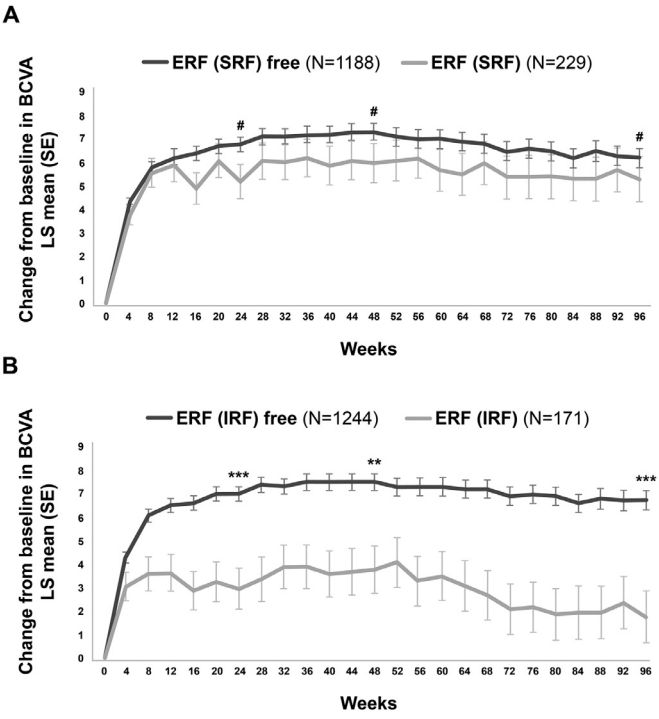

FIGURE 3. BCVA (letters read) LS mean (SE) change from baseline to week 96 for patients with and without SRF (A) and IRF (B). BCVA = best corrected visual acuity; ERF = early residual fluid; IRF = intraretinal fluid; LS = least squares; SRF = subretinal fluid. #LS mean difference, *P* > .05, **LS mean difference, *P* < .001, ***LS mean difference, *P* < .0001.

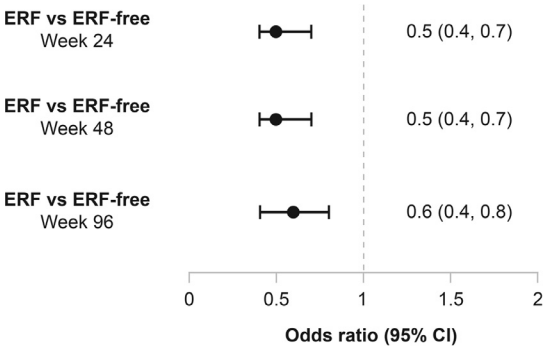

FIGURE 4. Odds ratio of attaining ≥70 letter gain. ERF = early residual fluid.

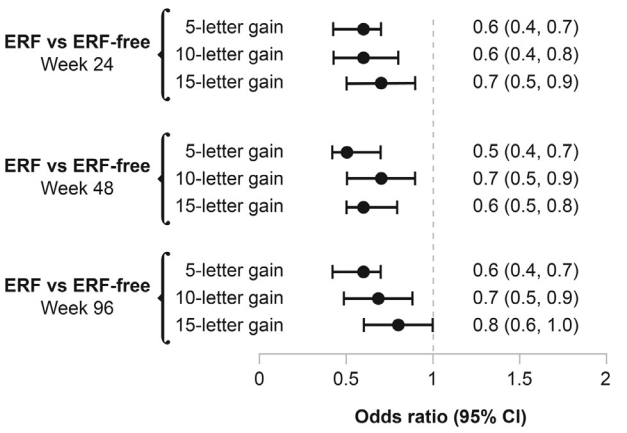

FIGURE 5. odds ratio of attaining ≥5, ≥10, or ≥15 letter gain. ERF = early residual fluid.

48, and 1.5 (*P* = .0817) at week 96; for ≥10-letter loss, the odds ratio was 1.7 (*P* = .0276) at week 24, 1.4 (*P* = .1071) at week 48, and 1.6 (*P* = .0052) at week 96; for ≥5-letter loss, the odds ratio was 1.9 (*P* = .0001) at week 24, 1.6 (*P* = .0070) at week 48, and 1.4 (*P* = .0300) at week 96. This indicates that the ERF cohort has higher odds of losing ≥5, ≥10, or ≥15 letters than the ERF (free) cohort.

• **CENTRAL SUBFIELD THICKNESS:** From weeks 12 to 96, patients in the ERF-free cohorts had a greater reduction in CST compared with patients in the ERF cohort (Figure 6).

The LS mean (SE) change from baseline in CST was –166.1 (3.87) at week 24, –173.3 (4.02) at week 48, and –178.2 (4.22) at week 96 in the ERF-free cohort and –126.7 (6.58) at week 24, –141.4 (6.84) at week 48, and –149.6 (7.17) at week 96 in the ERF cohort. Overall, CST largely decreased in both cohorts from baseline to week 12. From weeks 12 to 96, CST remained low in comparison to baseline in both cohorts, with slight variations.

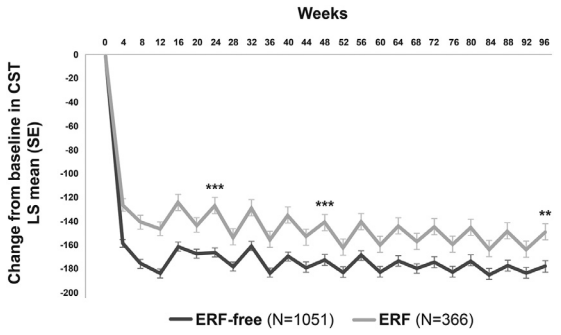

FIGURE 6. CST changes from baseline in ERF-free patients and those with ERF. CST = central subfield thickness; ERF = early residual fluid; LS = least squares. **LS mean difference, $P < .001$, ***LS mean difference, $P < 0.0001$.

DISCUSSION

An association between early fluid-free status and improved visual outcomes has been reported in the literature, but limited evidence exists to support this theory. This post hoc analysis of the 2-year, phase III HAWK and HARRIER trials has demonstrated that patients who were SRF and IRF fluid free at week 12, regardless of the anti-VEGF agent administered, have improved BCVA and CST over a 2-year period compared with those who were not. In addition, the current study also demonstrates similar findings with the absence of IRF at week 12 in comparison to the presence of IRF.

Persisting exudation may contribute to long-term vision loss, and clinical research has been conducted to investigate links between fluid-free status and visual outcome. This includes a recent study by Singer et al, which showed that in nAMD eyes treated with anti-VEGFs, patients with early persistent retinal dryness for IRF through week 12 had greater clinical improvement in visual function at week 24 compared to those who did not achieve persistent retina dryness.[18] Brown et al, in a post hoc analysis from the PIER study, observed the anatomical features of ranibizumab-treated eyes over 2 years to determine whether this was predictive of BCVA outcome.[20] At month 24, they found no difference in BCVA outcomes between ranibizumab-treated subgroups, defined by baseline fundus fluorescein angiography lesion size and composition. However, eyes with leakage at months 5 and 8 had lost initial visual gains obtained through ranibizumab treatment during the loading phase. In addition, a net vision loss from baseline to month 24 was observed in eyes with leakage, whereas eyes with OCT and fundus fluorescein angiography inactivity maintained visual gains. A phase III study by Dugel et al used fluid resolution as an indicator of efficacy, and the authors reported a greater proportion of eyes without both SRF and IRF after treatment with brolucizumab versus aflibercept. They concluded that brolucizumab was comparable to aflibercept in relation to BCVA but found more stable CST reductions and fewer unscheduled treatments in brolucizumab-treated patients.[7] In the HAWK and HARRIER studies, it was reported that there was less fluid, including both SRF and IRF, in brolucizumab-treated eyes at week 16 (when dose frequency was matched) and week 48.[19]

This post hoc analysis was unique in that it was treatment agnostic, focusing on the impact of anti-VEGF treatment overall. It showed that regardless of whether patients were treated with aflibercept or brolucizumab, a complete resolution of retinal fluid, including SRF and IRF, was associated with improved visual outcomes.

Like our study, superior visual outcomes with IRF resolution have been demonstrated in an analysis of the CATT study. Although the CATT study showed that SRF was associated with concurrent better vision, the current analysis did not show the same findings.[14] In contrast, it was seen that the ERF- (SRF) free cohort was associated with numerically higher vision in comparison to the ERF (SRF) cohort. The reason for this observation could be the fact that this analysis constructs the cohorts at a specific point (week 12) and follows them over time. Subsequent fluid status does not have a bearing, unlike in the CATT study, in which the analysis was performed cross-sectionally, showing concurrent associations between fluid status and vision. In addition, the CATT study had pro re nata (PRN) arms, which could have influenced the findings, as the treatment, even in patients with good vision and good response, would be deferred until the appearance of fluid. The other possibility could be the fact that the nature of the ERF (SRF) and SRF remaining or appearing late (>12 months) can be different between patients. The differential visual gains between the SRF-present and SRF-absent cohorts, especially in year 2 of the CATT study, could support this hypothesis. This shows the potential for early complete resolution of retinal fluid to be used as an indicator in clinical practice for both disease progression and clinical improvement, as well as treatment effectiveness. Ohji et al, have also studied the impact of fluid status at week 16 on vision, anatomy, and treatment interval through week 96.[17] However, the current study also analyzes ERF status of both SRF and IRF at week 12 and its potential impact on vision.

As this was a post hoc analysis of the HAWK and HARRIER phase III studies, limitations associated with this analysis may affect conclusions obtained from these data. BCVA changes were corrected for baseline BCVA differences, but not for other lesion characteristics such as the type of CNV, presence of pigment epithelial detachment, and other factors. All of the *P* values presented in this post hoc analysis were not adjusted for multiplicity. However, the large sample size gives strength to these data.

Looking ahead, it is important to consider emerging sources of data to further investigate and to fully under-

stand the association between treatment outcomes after anti-VEGF treatment. There is a need for real-world data in order to further understand the link between anatomical and visual improvement after treatment for nAMD with anti-VEGF agents.

In summary, the improvement in visual outcomes in ERF-free patients occurred as early as 4 weeks following the last loading dose (at week 12) and continued to 96 weeks. In addition, the post hoc analysis also showed an improvement in CST in patients who were ERF free compared to those with ERF. These results suggest that patients achieving ERF-free status following anti-VEGF treatment may have better long-term visual and anatomic outcomes than those with the presence of ERF.

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