



Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen

FLUID Study 24-Month Results

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Purpose: To test the hypothesis that tolerating some subretinal fluid (SRF) in patients with neovascular age-related macular degeneration (nAMD) treated with ranibizumab using a treat-and-extend (T&E) regimen can achieve similar visual acuity (VA) outcomes as treatment aimed at resolving all SRF.

Design: Multicenter, randomized, 24-month, phase 4, single-masked, noninferiority clinical trial.

Participants: Participants with treatment-naïve active subfoveal choroidal neovascularization (CNV).

Methods: Participants were randomized to receive ranibizumab 0.5 mg monthly until either complete resolution of SRF and intraretinal fluid (IRF; intensive arm: SRF intolerant) or resolution of all IRF only (relaxed arm: SRF tolerant except for SRF >200 µm at the foveal center) before extending treatment intervals. A 5-letter noninferiority margin was applied to the primary outcome.

Main Outcome Measures: Mean change in best-corrected VA (BCVA), and central subfield thickness and number of injections from baseline to month 24.

Results: Of the 349 participants randomized (intensive arm, n = 174; relaxed arm, n = 175), 279 (79.9%) completed the month 24. The mean change in BCVA from baseline to month 24 was 3.0 letters (standard deviation, 16.3 letters) in the intensive group and 2.6 letters (standard deviation, 16.3 letters) in the relaxed group, demonstrating noninferiority of the relaxed compared with the intensive treatment ($P = 0.99$). Similar proportions of both groups achieved 20/40 or better VA (53.5% and 56.6%, respectively; $P = 0.92$) and 20/200 or worse VA (8.7% and 8.1%, respectively; $P = 0.52$). Participants in the relaxed group received fewer ranibizumab injections over 24 months (mean, 15.8 [standard deviation, 5.9]) than those in the intensive group (mean, 17 [standard deviation, 6.5]; $P = 0.001$). Significantly more participants in the intensive group never extended beyond 4-week treatment intervals (13.5%) than in the relaxed group (2.8%; $P = 0.003$), and significantly more participants in the relaxed group extended to and maintained 12-week treatment intervals (29.6%) than the intensive group (15.0%; $P = 0.005$).

Conclusions: Patients treated with a ranibizumab T&E protocol who tolerated some SRF achieved VA that is comparable, with fewer injections, with that achieved when treatment aimed to resolve all SRF completely. *Ophthalmology* 2019;126:723-734 © 2018 by the American Academy of Ophthalmology



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Treat-and-extend (T&E) protocols using anti-vascular endothelial growth factor (VEGF) for the management of neovascular age-related macular degeneration (nAMD) provide clinical benefits that are comparable with those of monthly injections¹⁻⁴ and better than those of pro re nata regimens.^{3,5-7} Typically, these protocols mandate at least 3 consecutive monthly doses that are continued until the retina is dry and there are no other signs of disease activity, after which the interval between visits and injections can be extended based on the

clinician's assessment of the patient's disease activity.^{1,8,9} Treat-and-extend protocols aim to resolve all subretinal fluid (SRF) and intraretinal fluid (IRF) to achieve a completely dry retina before interval extension, because it has been assumed that persistent fluid, especially early in the treatment history, adversely influences the visual outcome.¹⁰

However, it is unclear whether it is always necessary to dry the retina completely to achieve the same visual outcome. In the Comparison of Age-Related Macular

Degeneration Treatments Trials (CATT) study, a doubling of the proportion of patients who achieved a dry retina (ranibizumab pro re nata arm, 22.3% patients vs. ranibizumab monthly arm, 45.5% patients) did not change the proportion of patients who gained more than 15 letters (ranibizumab pro re nata arm, 30.7% patients vs. ranibizumab monthly arm, 32.8% patients).¹¹ Similarly, the 96-week VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) study results revealed little difference in the proportion of patients who gained 15 letters or more (ranibizumab monthly arm, 34.9% patients vs. aflibercept monthly arm, 29.4% patients) or the number of letters gained (ranibizumab monthly arm, 9.4 letters vs. aflibercept monthly arm, 7.6 letters), despite a notable difference in the proportion of patients achieving a dry retina (ranibizumab monthly arm, 60.4% patients vs. aflibercept monthly arm, 80.3% patients).¹²

Whereas persistent IRF is associated with lower baseline visual acuity (VA),^{13–15} delayed response to treatment,¹⁶ and poorer outcomes,^{13–15,17} it is possible that some SRF may be tolerated without compromising visual outcomes, as indicated by post hoc analyses of the CATT¹³ and VIEW¹⁸ studies, and even has been associated with greater improvements in VA.^{13,19} These data suggest that completely resolving SRF may not be necessary for achieving the best visual outcomes and likely will require more frequent, possibly unnecessary, anti-VEGF injections administered to patients.

Another possible consequence of treating nAMD with a goal of completely drying the retina, requiring more injections, is to increase the risk of macular atrophy, which was a major cause of poor long-term outcomes in the SEVEN-UP (Seven-Year Observational update of macular degeneration patients post-MARINA/ANCHOR and HORIZON trials) and CATT studies.^{20,21} Several studies have reported an association among more injections, the development of macular atrophy, and the rate of atrophy enlargement,^{22–24} although the HARBOR (pHase III double-masked, multicenter, randomized, Active-treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis [PRN] in patients with subfoveal neOvascular age-related macular degeneration) study reported no such correlation.²⁵ Although IRF was associated with macular atrophy in both the CATT and HARBOR studies, the presence of SRF was associated with a lower risk of macular atrophy and better VA outcome.^{25,26} These data suggest there is a need to explore further the criteria for making extension decisions when using a T&E protocol because it may be possible to tolerate some SRF, but not IRF, potentially achieving similar visual results with fewer injections.

The randomized, single-masked, 24-month FLUID (Comparison of treatment regimens using ranibizumab: Intensive [resolution of intra- and subretinal fluid] vs relaxed [resolution of primarily intraretinal fluid] treatment) study aimed to determine whether SRF must be resolved completely when treating nAMD eyes with ranibizumab 0.5 mg (Lucentis; Novartis Pharma AG, Basel Switzerland, and Genentech, Inc., South San Francisco, CA). The study tested

the hypothesis that tolerating some SRF achieves similar VA outcomes as not tolerating any SRF using a ranibizumab T&E regimen. The rationale, design, methodology, and protocol amendments have been published previously.²⁷ Herein, we report the baseline characteristics of the FLUID study cohort and 24-month results. The study is registered at clinicaltrials.gov (identifier, NCT01972789).

Methods

As described previously,²⁷ participants were recruited from 16 sites across Australia from October 30, 2013, through March 3, 2015. Written informed consent was obtained from all participants by the principal investigator or subinvestigator after full disclosure of the study and before any study-related assessment or investigation being initiated. The study was designed, implemented, and reported in accordance with the International Conference on Harmonization/Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. Institutional review board or ethics committee approval (Bellberry Limited Human Research Ethics Committee for 13 sites [in New South Wales, Victoria, South Australia, Western Australia, Tasmania], Macquarie University Human Research Ethics Committee for one site [in New South Wales], The Royal Victorian Eye and Ear Hospital Human Research Ethics Committee for one site [in Victoria] and The Alfred Ethics Committee for one site [in Victoria]) was obtained from all sites involved in the study. An independent data safety monitoring committee reviewed data at 6-month intervals.

Study Population, Randomization, and Treatment

Inclusion and exclusion criteria have been described previously.²⁷ In brief, the FLUID study recruited participants with treatment-naïve subfoveal choroidal neovascularization (CNV) secondary to nAMD in 1 eye (study eye) without restriction of lesion size and with best-corrected visual acuity (BCVA) of 23 letters (Snellen equivalent, 20/320) or more. Subfoveal CNV was defined on multimodal imaging as eyes with CNV classified as subfoveal or as juxtafoveal or extrafoveal on fluorescein angiography (FA), but with fluid (IRF or SRF) or subretinal hyperreflective material involving the fovea on spectral-domain (SD) OCT.

At baseline, participants were randomized 1:1 to either an intensive retinal fluid treatment regimen (SRF-intolerant group) or a relaxed retinal fluid treatment regimen (SRF-tolerant group). All participants received 3 consecutive monthly intravitreal injections of ranibizumab 0.5 mg followed by a T&E regimen allowing treatment extension by 2 weeks (up to a maximum extension interval of 12 weeks), dependent on disease activity.²⁷ In both arms, disease activity was defined as a loss of BCVA of 5 letters or more than the best BCVA recorded since baseline, new retinal hemorrhage, presence of fluid on SD OCT, or a combination thereof. For the intensive arm, fluid was defined as the presence of any IRF (resulting from disease activity as judged by the investigator), any SRF, or both. For the relaxed arm, fluid was defined as the presence of any IRF (resulting from disease activity as judged by the investigator) and any SRF of more than 200 μ m in height at the subfoveal center (as measured by calipers on SD OCT). Subfoveal SRF of 200 μ m or less or any SRF elsewhere was tolerated and by itself did not prohibit extension. If disease activity was detected, the treatment interval was shortened by 2 weeks to a minimum of 4 weeks for 1 sign

of activity and returned to 4 weeks for 2 or more signs of activity. In situations in which a patient's disease activity continued to recur after a second attempt at treatment interval extension, the maximum treatment interval permitted for the remainder of the study was 2 weeks less than the interval at which activity previously recurred (referred to as the break point).²⁷

Reading Center Assessments

Participants underwent assessment of BCVA with refraction on a logarithm of the minimum angle of resolution chart, SD OCT, color fundus photography, FA, and fundus autofluorescence in both the study and fellow eyes.²⁷ Both participants and BCVA assessors were masked to the participants' treatment allocation; investigators were not masked. A central reading center (Bern Photographic Reading Center, INSELSPITAL, Universitätsspital Bern, Universitätsklinik für Augenheilkunde, Bern, Switzerland), which was masked to treatment allocation to avoid investigator bias, evaluated all images as follows: the color fundus photography and FA images to determine the presence and type of nAMD and area of leakage of the CNV, the fundus autofluorescence images to determine presence and change in area of macular atrophy, and the OCT images to assess presence of SRF and IRF.

Throughout the study, the investigator made the assessment of disease activity based on change in BCVA related to CNV activity, new hemorrhage, and presence of IRF resulting from disease activity, whereas the central reading center made an assessment on the presence and subfoveal height of SRF, which then was provided to the site to inform treatment extension decisions. Arnold *et al*²⁷ outline protocol amendments that were implemented during the study, notably relating to the transition of responsibility for adjudication of IRF from the central reading center to the investigator site. Results presented herein are based on the central reading center measurements unless indicated otherwise. All BCVA results are based on investigator assessments.

Outcome Measures

The full set of primary and secondary end points has been described previously.²⁷ The primary end point was the mean change in BCVA from baseline to month 24. Secondary end points included the mean change in BCVA from baseline to month 12, mean change in central subfield thickness (CST) from baseline to months 12 and 24, number of ranibizumab injections at months 12 and 24, proportion of participants who achieved 20/40 or better BCVA at months 12 and 24, proportion of participants who progressed to 20/200 or worse BCVA at months 12 and 24, and the proportion of participants who did not achieve resolution of SRF, IRF, or both.

Statistical Analyses

Analyses were performed on the randomized set, consisting of all randomized participants; the safety set, consisting of all participants who received at least 1 ranibizumab injection and underwent at least 1 safety assessment after baseline; and the full analysis set (FAS), consisting of all participants who underwent at least 1 efficacy value after baseline for the primary end point. Continuous data were summarized using mean, median, standard deviation, minimum, and maximum. The *t* test or analysis of variance was used to test the null hypothesis of no difference between the means of the treatment groups. Discrete data were summarized using frequency counts and percentages, and a Fisher exact test was used to test the null hypothesis of no association between treatment groups and variable categories. Statistical testing was 2 sided with a 5% significance level. A 5-letter noninferiority margin was

applied to the primary end point. The relaxed treatment arm was considered noninferior if the upper limit of the 95% 2-sided confidence interval (CI) for the difference in changes from baseline BCVA between the 2 groups was less than 5, representing a clinically meaningful change in vision. Additional analysis using a 4- and 3.5-letter noninferiority margin also was conducted to align with the more recent anti-VEGF studies HAWK and HARRIER (Prospective, randomized, double-masked, 2-year ongoing studies to evaluate the efficacy and safety of brodalumab for the treatment of nAMD)²⁸ and the HARBOR²⁹ and IVAN (alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularization)³⁰ studies. A standard deviation of 15 letters and an expected drop-out rate of 15% during the 24-month study duration aligned with the CATT study.¹¹

The data presented are based on the FAS. The last observation was carried forward on the FAS for missing data (including data for those participants who discontinued before month 24 completion), except for those analyses relating to SRF or IRF and ranibizumab injections. Additional sensitivity analyses were performed on the primary end point of mean change in BCVA from baseline to month 24 as follows: per protocol (PP), last observation carried forward on PP, and mixed-model analysis on both the FAS and PP to adjust for any observed differences between treatment groups in baseline demographics or characteristics that may cause potential confounding. Only data for the primary end point were adjusted for multiple testing. Locally weighted scatterplot smoothing was performed for postbaseline (i.e., week 4 onward) values of absolute change in BCVA values. The baseline values were not included in the smoothing because the value at baseline of the change from baseline is (by definition) zero.

Results

Participants

A total of 349 participants were randomized to the study (intensive arm, *n* = 174; relaxed arm, *n* = 175). Two randomized participants, 1 in each treatment group, did not receive study treatment and were excluded from the safety set (347 participants; intensive arm, *n* = 173; relaxed arm, *n* = 174). Two participants did not have correctly measured BCVA at baseline and were excluded from the FAS (345 participants; intensive arm, *n* = 172; relaxed arm, *n* = 173; Fig 1).

Based on central reading center grading, 332 of the 347 participants in the safety set met the inclusion criteria (95.7%). Of those who did not, 1 demonstrated CNV secondary to non-AMD (macular telangiectasia), 4 demonstrated a juxtafoveal lesion with no subfoveal component or fluid on SD OCT, 9 showed no CNV confirmed, and 1 was ungradable because of poor-quality images.

A total of 279 participants (79.9%) completed the 24-month study (intensive arm, *n* = 134; relaxed arm, *n* = 145), with 70 participants (20.1%) discontinuing before the 24-month time point. Two hundred forty-two participants (70.1%) experienced at least 1 protocol deviation (intensive arm, *n* = 120 [69.8%]; relaxed arm, *n* = 122 [70.5%]), the most common deviation (193 participants [55.9%]) being a visit performed out of window (intensive arm, *n* = 93 [54.1%]; relaxed arm, *n* = 100 [57.8%]). The PP set consisted of 329 participants (94.3%; intensive arm, *n* = 167 [96.0%]; relaxed arm, *n* = 162 [92.6%]) who completed the study without clinically significant protocol deviations identified and documented before the database lock. A detailed outline of the a priori definitions for clinically significant protocol deviations are available in Supplement 1 (available at www.aaojournal.org).

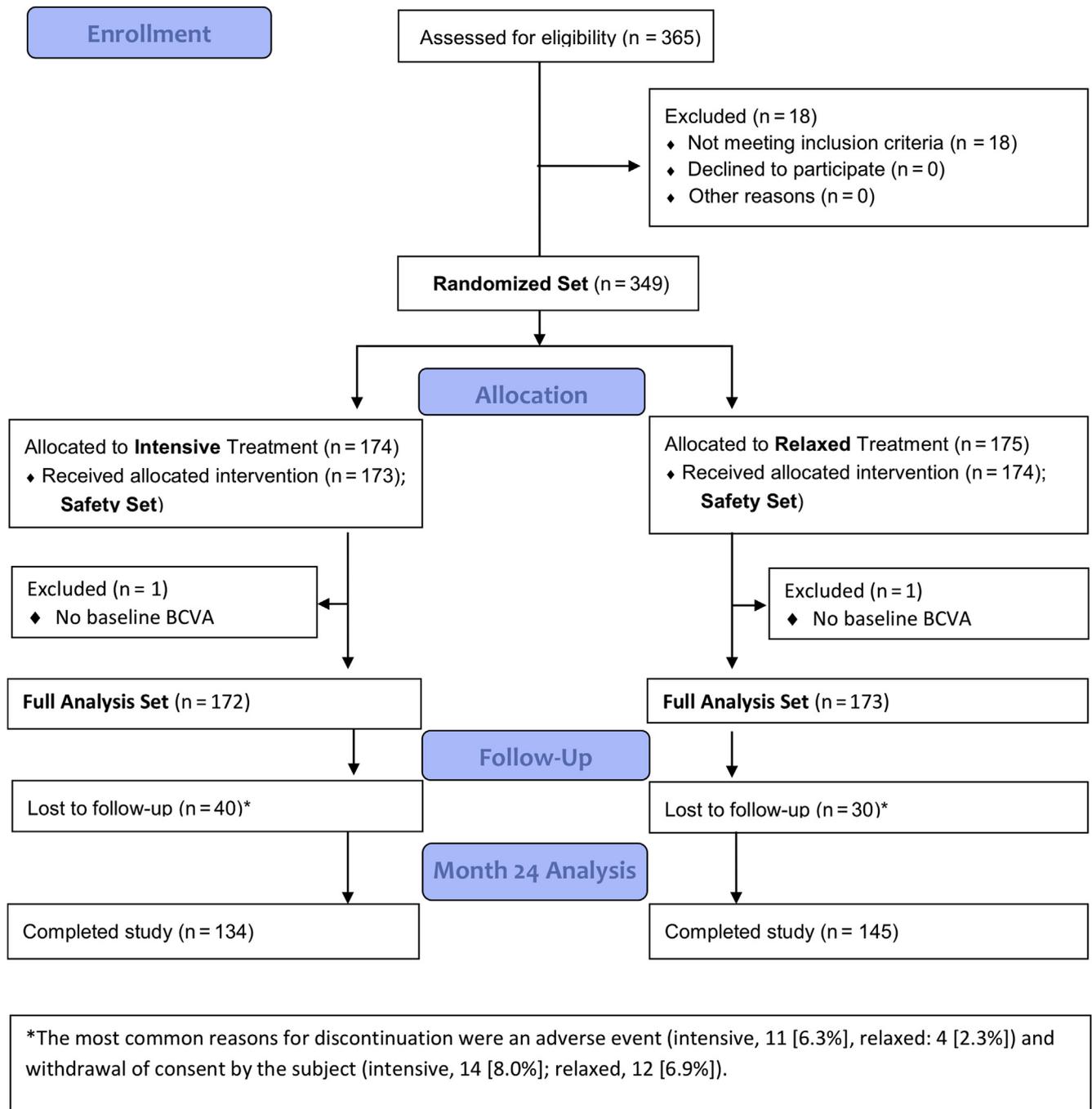


Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. BCVA = best-corrected visual acuity.

Baseline Characteristics

Overall, treatment groups were well balanced at baseline for participant demographic, visual, and ocular characteristics except area of lesion and area of CNV, both of which were larger in the intensive group (Table 1). The average age of participants was 79 years (standard deviation, 8.1 years), 95.7% were white, 9.2% currently smoked, and 24.2% had undergone previous nAMD treatment in the fellow eye. Importantly, baseline BCVA logarithm of the minimum angle of resolution score (intensive arm, 62.3±15.2 letters [Snellen equivalent, 20/60]; relaxed arm,

64.2±12.6 letters [Snellen equivalent, 20/50]) and the proportion of participants demonstrating BCVA of 70 letters or more (intensive arm, 60.1%; relaxed arm, 59.2%) was balanced, as was the proportion of participants demonstrating SRF as assessed by the central reading center (intensive arm, 83.2%; relaxed arm, 81.6%) and IRF (intensive arm, 59%; relaxed arm, 64.4%; Table 1). There was relative consistency between the masked central reading center and investigators for the assessment of proportion of participants with SRF at baseline (investigators: intensive arm, 76.9%; relaxed arm, 79.3%) but not for the proportion of participants with IRF at baseline, because the

Table 1. Baseline Characteristics of Participants in the Safety Set by Treatment Group

	Intensive Treatment (n = 173)	Relaxed Treatment (n = 174)	Total (n = 347)
Investigator site assessments			
Age, yrs (SD)	79.3 (8.1)	78.8 (8.2)	79.0 (8.1)
Gender, no. (%)			
Female	100 (57.8)	89 (51.1)	189 (54.5)
Male	73 (42.2)	85 (48.9)	158 (45.5)
Race, no. (%)*			
White	162 (93.6)	170 (97.7)	332 (95.7)
Asian	9 (5.2)	3 (1.7)	12 (3.5)
Aboriginal/Torres Strait Islander	1 (0.6)	1 (0.6)	2 (0.6)
History of thromboembolic events, no. (%)	20 (11.6)	25 (14.4)	45 (13.0)
Family history of AMD, no. (%)	36 (20.9)	38 (21.8)	74 (21.4)
Smoking history, no. (%)			
Current smoker	20 (11.6)	12 (6.9)	32 (9.2)
Smoked in the past	81 (46.8)	76 (43.7)	157 (45.2)
Previous nAMD treatment of nonstudy eye, no. (%)	39 (22.5)	45 (25.9)	84 (24.2)
Study eye, no. (%)			
Right	95 (54.9)	88 (50.6)	183 (52.7)
Visual acuity score			
logMAR letters, mean (SD)	62.3 (15.2)	64.2 (12.6)	63.2 (14.0)
<70 letters, no. (%)	104 (60.1)	103 (59.2)	207 (59.7)
≥70 letters, no. (%)	69 (39.9)	71 (40.8)	140 (40.3)
Central reading center assessments			
Central subfield foveal thickness on OCT (μm), mean (SD)	454.1 (180.2)	444.9 (164.0)	449.5 (172.1)
Central subfield volume on OCT (mm ³), mean (SD)	0.4 (0.1)	0.4 (0.3)	0.4 (0.2)
Retinal fluid components on OCT, no. (%)			
SRF	144 (83.2)	142 (81.6)	286 (82.4)
IRF	102 (59.0)	112 (64.4)	214 (61.7)
Absence of any SRF and/or IRF	5 (2.9)	7 (4.0)	12 (3.5)
Area of lesion on FA (μm ²), mean (SD)	6.8 (6.1)	5.5 (4.8)	6.2 (5.5)
Area of CNV on FA (μm ²), mean (SD)	6.1 (5.3)	4.5 (3.7)	5.3 (4.7)
CNV type, no. (%) [†]			
Predominant classic	23 (13.5)	30 (18.1)	53 (15.7)
Occult	139 (81.3)	131 (78.9)	270 (80.1)
Other	4 (2.3)	2 (1.2)	6 (1.8)
CNV location on FA [‡]			
Subfoveal	147 (85.0)	135 (77.6)	282 (81.3)
Juxtafoveal [§]	14 (8.1)	18 (10.3)	32 (9.2)
Extrafoveal	8 (4.6)	11 (6.3)	19 (5.5)
Hemorrhage on CFP, no. (%)	71 (41.0)	73 (42.0)	144 (41.5)
Macular atrophy on AF, no. (%)	29 (16.8)	27 (15.5)	56 (16.1)
Area of macular atrophy on AF (mm ²), mean (SD)	3.5 (6.3)	2.7 (3.9)	3.1 (5.2)
Fibrosis on CFP, no. (%) [¶]	12 (7.0)	6 (3.4)	18 (5.2)

AF = autofluorescence; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CFP = color fundus photography; CNV = choroidal neovascularization; FA = fluorescein angiography; IRF = intraretinal fluid; logMAR = logarithm of the minimum angle of resolution; nAMD = neovascular age-related macular degeneration; SD = standard deviation; SRF = subretinal fluid.

*No assignment of race for 1 patient in the intensive group. Race categories are as follows: Asian (Asian, Indian), Caucasian (Afghan, Caucasian, Egyptian, El Salvador, Greek, Hispanic, Israeli, Italian, Maltese, Middle Eastern, South American, Turkish, and Yugoslavian); Aboriginal, and Torres Strait Islanders (Aboriginal and Torres Strait Islanders).

[†]Images could not be graded because of poor image quality for 5 patients and 3 patients in the intensive and relaxed groups, respectively.

[‡]Images could not be graded because of poor image quality for 2 patients in each of the intensive and relaxed groups. No CNV complex was evident in 2 patients and 7 patients in the intensive and relaxed groups, respectively.

[§]Patients in each of the intensive and relaxed groups showed juxtafoveal lesions in the absence of central fluid.

^{||}Refers to any hemorrhage; not necessarily limited to the lesion. Images for 1 patient in the intensive group were not available for grading.

[¶]Images not available for grading for 1 patient.

investigators assessed more participants as showing IRF (investigators: intensive arm, 79.2%; relaxed arm, 75.3%).

Visual Acuity Changes

The results of BCVA assessments are shown in Table 2. There was no significant difference between the intensive group (3.0±16.32

letters) and the relaxed group (2.6±16.31 letters) for the mean change in BCVA from baseline to month 24 ($P = 0.99$; Fig 2). The relaxed group was noninferior to the intensive group (based on the 5-letter noninferiority margin) for this primary end point measure (treatment effect, 0.01; 95% CI, -2.79 to 2.81). Additional post hoc analysis for noninferiority based on a 4- and 3.5-letter margin also showed noninferiority (the upper limit of

Table 2. Visual Acuity of Participants Treated with an Intensive Retinal Fluid Retreatment Protocol Compared with a Relaxed Retinal Fluid Retreatment Protocol

	Intensive Treatment (n = 172)	Relaxed Treatment (n = 173)	Treatment Effect or Odds Ratio (95% CI)	P Value
Mean change in BCVA (letters)				
Month 12			TE, -0.69 (-3.49 to 2.11)	0.63
Mean (SD)	4.0 (14.37)	4.3 (12.71)		
Median (minimum–maximum)	4.0 (-41, 46)	4.0 (-42, 42)		
Month 24			TE, -0.01 (-2.79 to 2.81)	0.99
Mean (SD)	3.0 (16.32)	2.6 (16.31)		
Median (minimum–maximum)	4.0 (-69, 46)	4.0 (-59, 42)		
Participants with $\geq 20/40$ VA, no. (%)				
Month 12	88 (51.2)	103 (59.5)	OR, 0.71 (0.43–1.20)	0.20
Month 24	92 (53.5)	98 (56.6)	OR, 0.97 (0.60–1.58)	0.92
Participants with $\leq 20/200$ VA, no. (%)				
Month 12	12 (7.0)	9 (5.2)	OR, 0.86 (0.32–2.35)	0.78
Month 24	15 (8.7)	14 (8.1)	OR, 0.76 (0.33–1.76)	0.52
Participants with ≥ 15 -letter gain, no. (%)				
Month 12	29 (16.9)	28 (16.2)	OR, 0.86 (0.47–1.59)	0.64
Month 24	28 (16.3)	28 (16.2)	OR, 0.76 (0.40–1.44)	0.40
Participants with < 15 -letter loss, no. (%)				
Month 12	158 (91.9)	159 (91.9)	OR, 1.07 (0.49–2.35)	0.86
Month 24	150 (87.2)	152 (87.9)	OR, 0.98 (0.52–1.88)	0.96

BCVA = best-corrected visual acuity; CI = confidence interval; OR = odds ratio; SD = standard deviation; TE = treatment effect; VA = visual acuity.

treatment effect at month 24 was 2.81 letters). This outcome was supported by sensitivity analyses, specifically PP analysis (treatment effect on PP: -0.29; 95% CI, -3.19 to 2.61; $P = 0.84$), adjustment for the baseline imbalance between groups in area of CNV (treatment effect on FAS: 1.52; 95% CI, -1.50 to 4.54; $P = 0.32$; treatment effect on PP: 1.11; 95% CI, -2.02 to 4.24; $P = 0.49$), and adjustment for the baseline imbalance between groups in area of lesion (treatment effect on FAS: 0.70; 95% CI, -2.27 to 3.67; $P = 0.64$; treatment effect on PP: 0.33; 95% CI, -2.77 to 3.42; $P = 0.84$).

Similarly, there was no difference between the intensive and relaxed groups for the mean change in BCVA from baseline to month 12 ($P = 0.63$), proportion of participants who achieved a BCVA of 20/40 or better at month 12 ($P = 0.20$) and month 24 ($P = 0.92$), or proportion of participants with BCVA 20/200 or worse at month 12 ($P = 0.78$) and month 24 ($P = 0.52$). Treatment groups were not significantly different for the proportion of participants who gained 15 letters or more at month 12 ($P = 0.64$) and month 24 ($P = 0.40$) or who lost fewer than 15 letters at month 12 ($P = 0.86$) and month 24 ($P = 0.96$; Table 2). The overall loss of BCVA was no greater in the relaxed group relative to the intensive group (Fig 3).

Anatomic Changes: Central Subfield Thickness

There was no significant difference in mean reduction in CST from baseline to month 12 in the intensive group ($145.2 \pm 161.4 \mu\text{m}$) relative to the relaxed group ($123.1 \pm 131.9 \mu\text{m}$; $P = 0.12$). However, by month 24, the intensive group showed a trend toward a greater reduction in CST ($153.1 \pm 161.3 \mu\text{m}$) relative to the relaxed group ($127.3 \pm 136.6 \mu\text{m}$; $P = 0.06$).

Intraretinal and Subretinal Fluid Changes

There was a decline in the proportion of eyes with SRF (based on reading center assessment) over the 24-month study, with a notable decrease from baseline (intensive arm, 83.1%; relaxed arm, 82.1%)

occurring by month 2 (intensive arm, 23.5%; relaxed arm, 30.8%) for both treatment groups; thereafter, the proportion remained relatively stable at both months 12 and 24 (Table 3). There was no significant difference between groups at baseline or months 2, 12, and 24. Similarly, there was a decline in the proportion of eyes with IRF (based on reading center assessment; defined as either IRF or intraretinal cysts) over the 24-month study, with a notable decrease from baseline (intensive arm, 59.3%; relaxed arm, 64.2%) occurring by month 2 (intensive arm, 20.6%; relaxed arm, 28.5%) for both treatment groups; thereafter, the proportion remained relatively stable at both months 12 and 24 (Table 3). There was no significant difference between groups at baseline or month 24; however, there was significantly more IRF in the relaxed group at month 2 ($P = 0.048$) and month 12 ($P = 0.043$). The investigators graded more patients with IRF at baseline than the central reading center. However, similar to observations of the central reading center, the proportion of participants with IRF graded by the investigators declined by month 2 in both treatment groups and remained stable thereafter (Table 3). There was no significant difference between groups in this parameter at baseline or months 2, 12, and 24.

Of the participants who demonstrated SRF at baseline (intensive arm, $n = 143$; relaxed arm, $n = 142$), more in the relaxed group (19.2%) than in the intensive group (12.3%) did not achieve resolution of SRF up to month 12 (odds ratio [OR], 0.62; 95% CI, 0.31–1.24; $P = 0.18$) and month 24 (relaxed arm, 15%; intensive arm, 9.5%; OR, 0.62; 95% CI, 0.28–1.39; $P = 0.25$). There was no difference between the relaxed group (15.7%) and intensive group (16.7%) for the proportion of participants who showed IRF at baseline (intensive arm, $n = 102$; relaxed arm, $n = 111$) and who did not achieve resolution of IRF at month 12 (OR, 0.83; 95% CI, 0.37–1.87; $P = 0.66$). By month 24, more participants in the relaxed group (14.8%) than the intensive group (7.5%) did not achieve resolution of IRF (OR, 0.35; 95% CI, 0.12–1.04; $P = 0.06$).

Of the participants who demonstrated fluid at baseline (SRF, IRF, or both) and completed 12 months of treatment (intensive

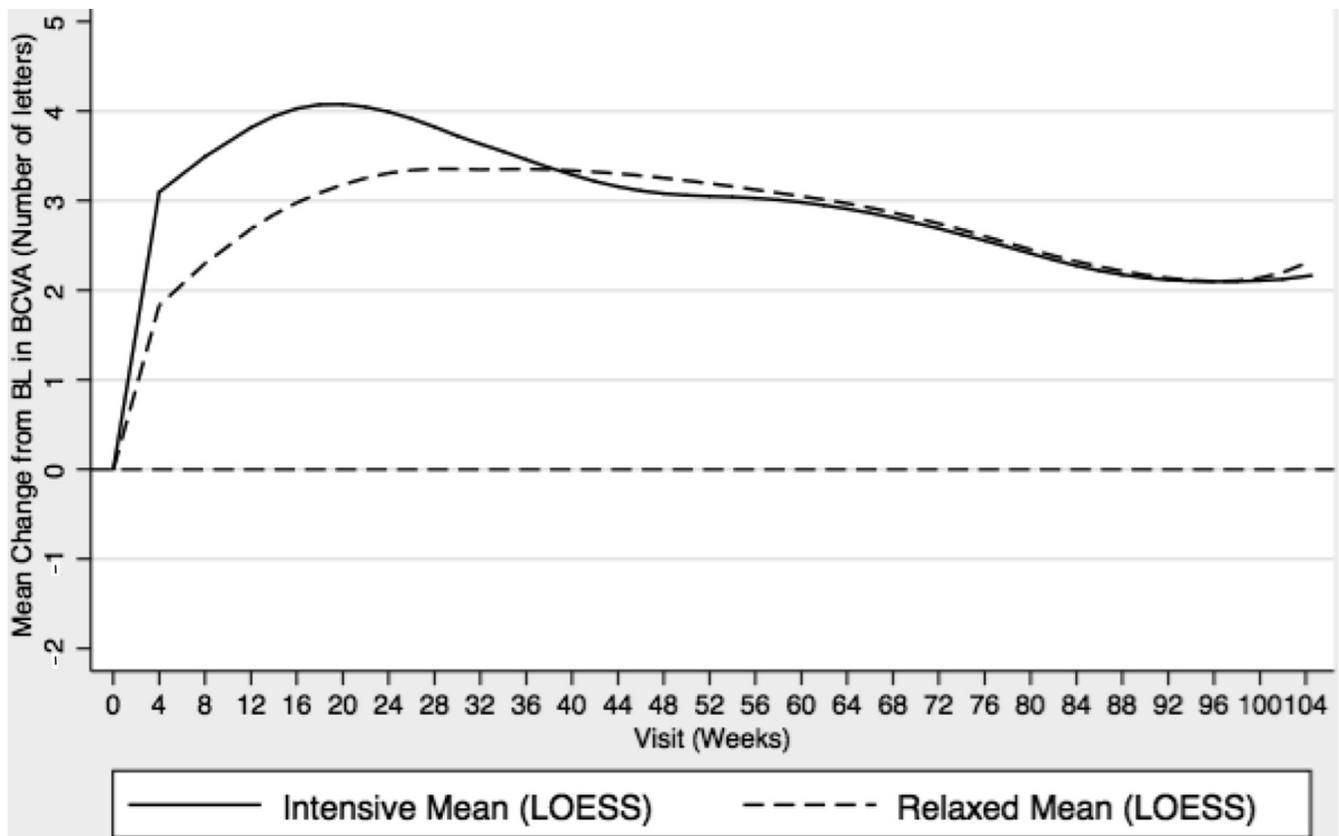


Figure 2. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline over time to month 24 in participants treated with an intensive subretinal fluid retreatment regimen compared with a relaxed subretinal fluid retreatment regimen. LOESS = locally weighted smoothing.

arm, $n = 149$; relaxed arm, $n = 146$), more participants in the relaxed group (29.5%) than in the intensive group (21.5%) did not achieve resolution of all baseline fluid at any visit to month 12 (OR, 0.63; 95% CI, 0.37–1.08; $P = 0.09$). Of the participants with baseline fluid (SRF, IRF, or both) who completed 24 months of treatment (intensive arm, $n = 128$; relaxed arm, $n = 135$), significantly more in the relaxed group (24.4%) than in the intensive group (14.1%) did not achieve resolution of all baseline fluid at any visit to month 24 (OR, 0.49; 95% CI, 0.26–0.93; $P = 0.03$).

Ranibizumab Treatment

The mean number of ranibizumab injections per participant was significantly lower in the relaxed group (8.9 ± 2.25) than the intensive group (9.5 ± 2.60) from baseline to month 12 ($P = 0.001$), from month 12 to month 24 (relaxed arm, 7.6 ± 3.62 ; intensive arm, 8.4 ± 3.64 ; $P = 0.005$), and for the full 24-month period (relaxed arm, 15.8 ± 5.91 ; intensive arm, 17 ± 6.48 ; $P = 0.001$).

Significantly fewer participants who completed the 12-month time point (intensive arm, $n = 152$; relaxed arm, $n = 155$) remained consistently at 4-week treatment intervals (for every visit throughout the entire study with no interval extension) in the relaxed group (9.0%) than in the intensive group (20.4%; OR, 2.58; 95% CI, 1.31–5.07; $P = 0.006$). Similarly, of those participants who completed the 24-month time point (intensive arm, $n = 133$; relaxed arm, $n = 142$), significantly fewer in the relaxed group (2.8%) remained consistently at 4-week treatment intervals than in the intensive group (13.5%; OR, 5.40; 95% CI, 1.78–16.41; $P = 0.003$). In addition, of those participants who completed the 24-month time point (intensive arm, $n = 133$; relaxed arm, $n =$

142), significantly more were extended to, and maintained, 12-week treatment intervals in the relaxed group (29.6%) than in the intensive group (15.0%; OR, 2.37, 95% CI, 1.31–4.31; $P = 0.005$). The mean number of times a participant was on a monthly treatment regimen during the 24-month study (either remained on monthly, or returned to monthly, treatment because of disease activity excluding the initial 3 loading doses) was significantly lower in the relaxed group (7.6 ± 8.09) than the intensive group (10.6 ± 8.34 ; $P = 0.03$).

There was no significant difference in the proportion of participants in whom SRF was the only sign of disease activity present (and treatment extension occurred at least once) between the intensive group (120 [69.4%] participants) and relaxed group (120 [68.6%] participants; $P = 0.87$), indicating that SRF alone was a common scenario. Further, in the relaxed group (in which the height of SRF was considered in determining disease activity), SRF larger than $200 \mu\text{m}$ at the foveal center was observed in only 4 participants (at 5 visits); at 3 of those visits, IRF also was observed to be present.

Safety

There was no difference in the number of adverse events and serious adverse events, for either all body systems or the ocular system, between the intensive and relaxed groups. No new safety signals were observed for ranibizumab. Summaries of adverse events and serious adverse events for the intensive and relaxed groups are available in Supplement 2 (available at www.aaojournal.org).

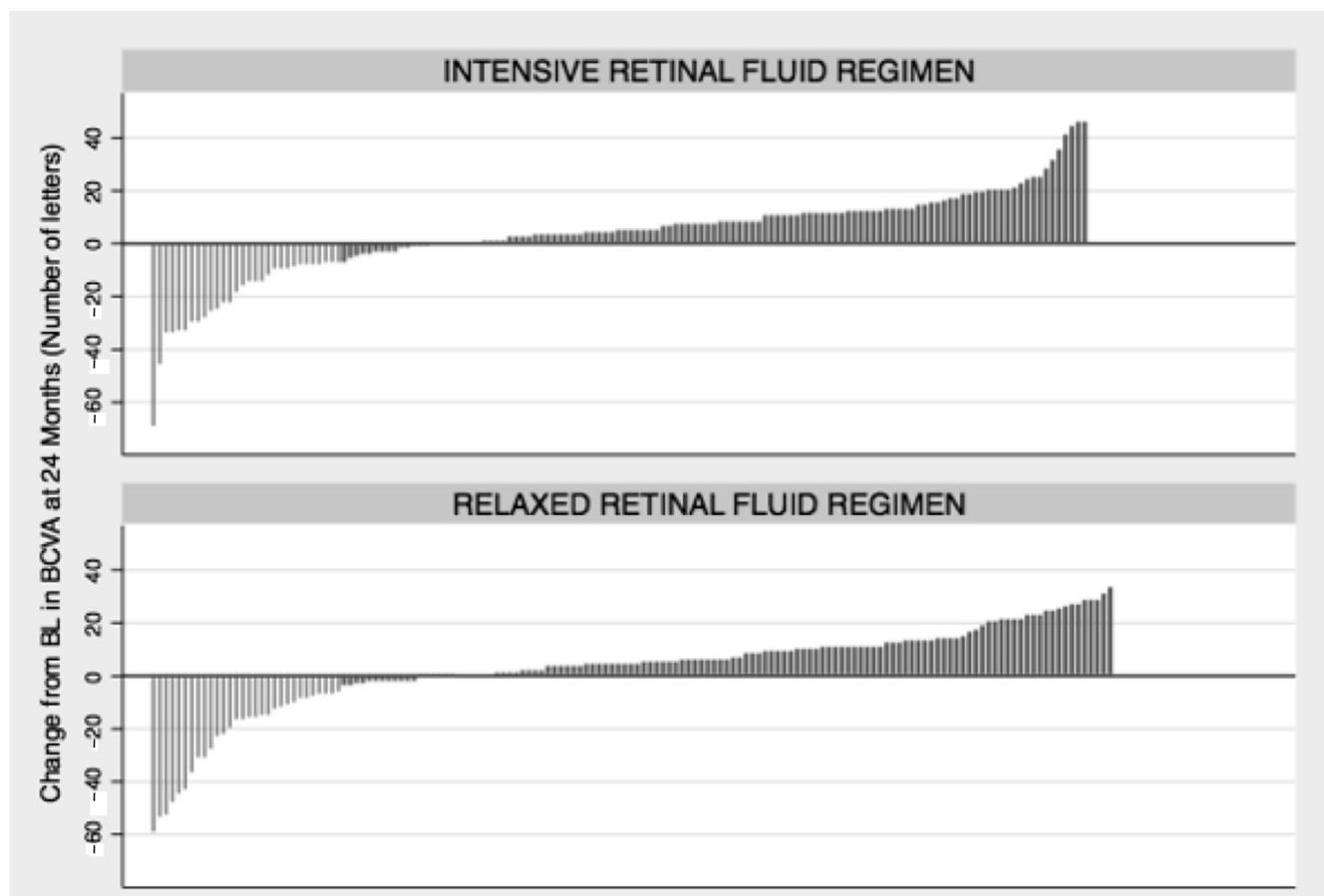


Figure 3. Graph showing mean change in best-corrected visual acuity (BCVA) from baseline to month 24 or early discontinuation in participants treated with an intensive subretinal fluid regimen compared with a relaxed subretinal fluid regimen. BL = baseline.

Discussion

The current article reports the VA outcomes of eyes with nAMD after 24 months of ranibizumab treatment using T&E protocols differing only in the tolerance of a degree of SRF. We found that visual outcomes were not inferior after 24 months, with fewer ranibizumab treatments, if SRF was tolerated, unless it was larger than 200 μm under the fovea center. The inclusion criteria for lesion characteristics applied in the study were designed to reflect the type of nAMD patient typically treated with ranibizumab in standard clinical practice so that results of the study would be applicable to a broad patient population. There was relative alignment between study site and central reading center assessment of participant inclusion criteria (95.7%), noting that eligibility decisions lay with investigators in accordance with the protocol, a finding consistent with the CATT study.³¹ The proportion of participants completing the 24-month FLUID study (79.9%) was not too dissimilar to that of other anti-VEGF studies at 24 months, notably ANCHOR (81.1%),³² MARINA (85.9%),³³ VIEW 1 and 2 (84% at 96 weeks),¹² and CATT (86.9%).¹¹

Treatment groups were balanced at baseline for participant demographics, visual characteristics, and ocular characteristics, except area of lesion and area of CNV, both of

which were larger on average in the intensive treatment group. These imbalances were accounted for statistically in the 12- and 24-month analyses on visual outcomes because larger CNV area is a known predictor of less BCVA gain.^{34,35} Importantly, all other baseline characteristics known to predict visual outcome, namely age, lesion type, CST, VA,³⁶ and IRF,^{14,15,37} were well balanced between treatment groups, as was the presence of SRF.

At 24 months, we found a BCVA improvement in the intensive group of 3.0 ± 16.3 letters and in the relaxed group of 2.6 ± 16.3 letters, which is not as high as that seen in pivotal anti-VEGF studies. However, the mean baseline BCVA observed in the FLUID cohort (63.2 letters) was better than that in the CATT study (range, 59.9–61.6 letters for all treatment groups)³¹ and the Australian Fight Retinal Blindness study (range, 48.4–56.5 letters),² with notably more participants having better baseline vision of 70 letters or more (40.3%) than in the Fight Retinal Blindness study (range, 17.1%–27.3%).² This better baseline BCVA in the FLUID cohort is likely to have influenced the degree of vision improvement observed by 24 months because of a ceiling effect. Regardless of the small level of BCVA gained by the FLUID cohort, the study clearly demonstrated that the mean change in BCVA from baseline to month 24 in the relaxed (SRF-tolerant)

Table 3. Subretinal Fluid and Intraretinal Fluid in Participants Treated with an Intensive Retinal Fluid Retreatment Protocol Compared with a Relaxed Retinal Fluid Retreatment Protocol

	Intensive Treatment (n = 172)	Relaxed Treatment (n = 173)	P Value
Central reading center assessment			
Participants with SRF, no. (%)			
Baseline	143 (83.1)	142 (82.1)	0.86
Month 2	40 (23.5)	53 (30.8)	0.13
Month 12	39 (25.3)	42 (27.6)	0.79
Month 24	38 (27.0)	43 (29.5)	0.78
Participants with IRF, no. (%)			
Baseline	102 (59.3)	111 (64.2)	0.19
Month 2	35 (20.6)	49 (28.5)	0.05
Month 12	35 (22.7)	48 (31.6)	0.04
Month 24	52 (36.9)	59 (40.4)	0.38
Investigator site assessment:			
Participants with IRF, no. (%)*			
Baseline	137 (79.7)	129 (74.6)	0.33
Month 2	52 (30.6)	52 (30.1)	0.89
Month 12	38 (24.7)	44 (28.4)	0.35
Month 24	37 (25.2)	38 (25.5)	0.89

IRF = intraretinal fluid; SRF = subretinal fluid.

*Determined by study investigator to be the result of disease activity.

group was noninferior to that in the intensive (SRF-intolerant) group, a finding that is supported by multiple sensitivity analyses. The noninferiority margin for the primary end point of mean change in BCVA from baseline to month 24 was set a priori at 5 letters to align with the CATT study¹¹; however, when we used post hoc a noninferiority margin of 4 letters to align with HAWK, HARRIER,²⁸ and HARBOR,²⁹ and even 3.5 letters to align with IVAN,³⁰ the relaxed arm remained noninferior to the intensive arm (the upper limit of treatment effect at month 24 was 2.81 letters). Most encouragingly, there was no difference in the percentages of participants maintaining 20/40 BCVA or better nor losing BCVA to 20/200 or worse. This suggests that a T&E ranibizumab protocol that allows a degree of SRF can achieve similar visual outcomes to a protocol that does not tolerate any SRF. Further, by tolerating SRF, significantly more participants were extended beyond 4-week treatment intervals and even out to 12-week intervals and required significantly fewer ranibizumab injections at 12 and 24 months. It is important to note that, in the relaxed group, larger amounts of SRF were tolerated, except at the fovea, where only SRF of 200 μm or less was tolerated. This exception to the height at the fovea was defined to provide study investigators with confidence that patient safety was not being compromised. Larger than 200-μm SRF at the foveal centerpoint was observed at only 5 visits (4 participants); at 3 of those visits, IRF also was detected. Of note, approximately 69% of participants (in both the relaxed and intensive groups) demonstrated SRF as the only sign signifying disease activity.

Adjudication of SRF by a reading center masked to participant randomization and treatment (information subsequently provided to investigators to inform clinical decisions) was considered an important aspect of the study's design to ensure that no bias was introduced when

investigators made decisions on treatment extension. Although the reading center also read the IRF component, a protocol amendment partway through the study allowed the investigator to add their own interpretation of disease activity resulting from the presence of intraretinal cyst and its impact on their decision for extension. Similar to the CATT study (in which there was an approximately 71% to 74% discrepancy between reading center and investigators for as-needed ranibizumab and bevacizumab retreatment decisions, with approximately 91% to 93% of such discrepancies being related to fluid detection on OCT¹¹), there were many occasions in the present study when the presence of IRF was interpreted not to mean disease activity, and extensions were permitted at the investigators' discretion. Often this was the result of small, persistent amounts of IRF being interpreted by the investigator as degenerative rather than indicative of lesion activity, and thus, extensions occurred. Until the protocol amendment, all reading center IRF was to be taken as being indicative of activity, and as such, the ability to extend was curtailed significantly, hence the required change in protocol. The rationale for this change was to allow greater alignment with standard clinical practice. There was a significant number of participants in both groups who demonstrated IRF throughout the study, but it is important to note that the IRF data presented herein reflect the central reading center assessment, not the investigators' opinion on IRF signifying activity.

Significantly more participants in the relaxed group never achieved resolution of baseline SRF, IRF, or both at any visit compared with the intensive group ($P = 0.029$) throughout the study. Approximately two-thirds more participants in the relaxed group did not achieve resolution of baseline SRF, which was as expected given the protocol rules, in which total resolution of SRF was not the treatment aim in this group. However, the relaxed group did show a

trend of not achieving resolution of baseline IRF as assessed by the reading center by 24 months ($P = 0.06$), which was not an expected finding, given that IRF should have been interpreted the same way in both groups. There was no difference in investigator assessment of the percent of participants showing IRF because of lesion activity between the 2 groups at 12 months (intensive arm, 24.7% vs. relaxed arm, 28.4%) and 24 months (intensive arm, 25.2% vs. relaxed arm, 25.5%). The trend of a lower reduction of CST in the relaxed group relative to the intensive group ($P = 0.06$) is supportive evidence that the study protocol was implemented successfully.

Ambiguity still exists regarding how to interpret the presence of fluid-related signs in nAMD patients and highlights the need for better markers of neovascular activity.⁵⁸ The FLUID study was designed to assess the clinical importance of total SRF resolution on visual outcomes up to 24 months in response to ranibizumab therapy. We found that participants treated with a ranibizumab T&E protocol that tolerates a degree of SRF achieved BCVA that was noninferior to that achieved when the treatment protocol aimed to resolve all SRF completely. By tolerating a degree of SRF, there will be a larger number of people who can have their treatment interval extended beyond 4 weeks, resulting in fewer ranibizumab injections with equivalent visual outcomes and no safety concerns. A limitation of the study is that it was only a 24-month study, and as such, it is not possible to know what the longer-term outcomes of tolerating this degree of SRF will be. Therefore, longer studies are encouraged. This study will help ophthalmologists make evidence-based re-treatment decisions using our current disease activity criteria. However, it is clear we have yet to define the parameters of true neovascular activity that requires relentless treatment and to discover further additional biomarkers that could indicate true ongoing disease activity.

It is recognized that the OCT appearance of SRF could result from a nonexudative process.³⁹ Although all participants in the FLUID study were assessed and confirmed to have neovascular CNV on FA, it is possible that a subretinal space may exist long after active exudation has ceased, with failure of the retina to adhere firmly back to the retinal pigment epithelium through interdigitations. It is also possible that the active CNV could be quiescent and result in a small amount of SRF being present that does not require treatment. Indeed, others have suggested that such residual SRF may be beneficial to reduce rates of atrophy.^{25,26} Newer techniques using OCT angiography are revealing quiescent CNV or abnormal choroidal vascular complexes that may never need treatment, at least in the short to medium term, and could from time to time result in small amounts of asymptomatic SRF that may protect from atrophy. As such, there is still much to learn regarding the best treatment protocols for nAMD.

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Footnotes and Financial Disclosures

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A complete listing of the FLUID Investigators is available at www.aao-journal.org (Supplement 3).

HUMAN SUBJECTS: Human subjects were included in this study. The study was designed, implemented, and reported in accordance with the International Conference on Harmonization / Harmonized Tripartite Guidelines for Good Clinical Practice with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. Institutional Review Board/Ethics Committee approval was obtained from all sites involved in the study. All participants provided informed consent.

No animal subjects were included in this study.

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Abbreviations and Acronyms:

BCVA = best-corrected visual acuity; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CST** = central subfield thickness; **FA** = fluorescein angiography; **FAS** = full analysis set; **FLUID Study** = Tolerating Subretinal Fluid in Neovascular Age-Related Macular Degeneration Treated with Ranibizumab Using a Treat-and-Extend Regimen; **HARBOR Study** = One-Year Results of Efficacy and Safety of 2.0 mg versus 0.5 mg Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration; **IRF** = intraretinal fluid; **nAMD** = neovascular age-related macular degeneration; **OR** = odds ratio; **PP** = per protocol; **SD** = spectral-domain; **SRF** = subretinal fluid; **T&E** = treat and extend; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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