

Two-Year Results of the Phase 3 Randomized Controlled Study of Abicipar in Neovascular Age-Related Macular Degeneration

Rahul N. Khurana, MD,^{1,*} Derek Kunimoto, MD, JD,^{2,*} Young Hee Yoon, MD, PhD,³ Charles C. Wyckoff, MD, PhD,⁴ Andrew Chang, PhD, FRANZCO,^{5,6} Raj K. Maturi, MD,^{7,8} Hansjürgen Agostini, MD,⁹ Eric Souied, MD, PhD,¹⁰ David R. Chow, MD, FRCS(C),^{11,12} Andrew J. Lotery, MD, FRCOphth,¹³ Masahito Ohji, MD, PhD,¹⁴ Francesco Bandello, MD,¹⁵ Rubens Belfort, Jr., MD, PhD,¹⁶ Xiao-Yan Li, MD,¹⁷ Jenny Jiao, PhD,¹⁷ Grace Le, MD,¹⁷ Kimmie Kim, PhD,¹⁷ Werner Schmidt, MSc,¹⁷ Yehia Hashad, MD,¹⁷ on behalf of the CEDAR and SEQUOIA Study Groups[‡]

Purpose: To report the 2-year efficacy and safety of abicipar every 8 weeks and quarterly (after initial doses) compared with monthly ranibizumab in patients with treatment-naïve neovascular age-related macular degeneration (nAMD).

Design: Two multicenter, randomized, phase 3 clinical trials with identical protocols (CEDAR and SEQUOIA). Analyses used pooled trial data.

Participants: The trials enrolled 1888 patients (1 eye/patient) with active choroidal neovascularization secondary to age-related macular degeneration and best-corrected visual acuity (BCVA) of 24 to 73 Early Treatment Diabetic Retinopathy Study letters.

Methods: At enrollment, patients were assigned to study eye treatment with abicipar 2 mg every 8 weeks after initial doses at baseline and weeks 4 and 8 (abicipar Q8, n = 630), abicipar 2 mg every 12 weeks after initial doses at baseline and weeks 4 and 12 (abicipar Q12, n = 628), or ranibizumab 0.5 mg every 4 weeks (ranibizumab Q4, n = 630).

Main Outcome Measures: Efficacy measures included stable vision (<15-letter loss in BCVA from baseline) and change from baseline in BCVA and central retinal thickness (CRT). Safety measures included adverse events (AEs).

Results: For patients who completed the study, efficacy of abicipar after initial doses was maintained through week 104. At week 104, the proportion of patients with stable vision was 93.0% (396/426), 89.8% (379/422), and 94.4% (470/498); mean change in BCVA from baseline was +7.8 letters, +6.1 letters, and +8.5 letters, and mean change in CRT from baseline was −147 μm, −146 μm, and −142 μm in the abicipar Q8 (14 injections), abicipar Q12 (10 injections), and ranibizumab Q4 (25 injections) groups, respectively. The overall incidence of intraocular inflammation (IOI) AEs was 15.4%, 15.3%, and 0.3% from baseline through week 52 and 16.2%, 17.6%, and 1.3% from baseline through week 104 in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively.

Conclusions: Two-year results show efficacy of abicipar Q8 and Q12 in nAMD. First onset of IOI events with abicipar was much reduced in the second year and comparable with ranibizumab (0.8% and 2.3% vs. 1.0%). The extended duration of effect of abicipar allows for quarterly dosing and reduced treatment burden. *Ophthalmology* 2021;128:1027-1038 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at www.aaojournal.org.

Age-related macular degeneration (AMD) is a common retinal disease and a leading cause of irreversible central vision loss and blindness in adults 50 years of age or older.¹ In neovascular AMD (nAMD), an advanced stage of AMD, choroidal neovascularization (CNV) and fluid exudation from the immature vessels can result in tissue damage and severe vision loss.² Most of the legal blindness caused by AMD occurs in patients with nAMD.³

Anti-vascular endothelial growth factor (VEGF) therapy is standard care for subfoveal neovascular lesions in

nAMD.⁴ However, the frequent visits required for monitoring and intravitreal injections are a burden for patients with nAMD, physicians, and health care systems.^{5–7} An unmet need exists for longer-acting treatments that reduce the treatment burden associated with anti-VEGF therapy in nAMD.

DARPin molecules are a class of small, highly stable, synthetic binding proteins containing ankyrin repeat domains, which are one of the most common structural motifs mediating protein–protein interactions in nature.⁸

These molecules can be selected for binding to a target protein with high affinity and selectivity, and their smaller size compared with antibodies or Fab fragments potentially may improve tissue penetration, as well as allow for a higher molar dose.⁹ The DARPin molecules also are customizable and can be engineered to alter their pharmacokinetics, for example, by PEGylation for a longer half-life.⁹

Abicipar pegol (abicipar) is a DARPin anti-VEGF therapy that binds to all isoforms of VEGF-A with high affinity and specificity.¹⁰ Abicipar has a very high affinity for human VEGF-A165 (K_d of 486 fM) and has been shown to inhibit angiogenesis and vascular permeability potently in cell culture and animal models.⁸ The molecular weight of abicipar is small (34 kDa),¹¹ allowing a high molar dose by intravitreal injection, and abicipar has a long intraocular half-life. In a clinical study in patients with diabetic macular edema, the half-life of abicipar in the aqueous humor after intravitreal injection was 13 days or longer.¹⁰

The optimized combination of high affinity, high molar dose, and long half-life with abicipar may translate into an extended duration of effect after intravitreal injection. Results of 3 phase 2 studies of abicipar in patients with treatment-naïve nAMD suggested a potential for abicipar 2 mg to improve or maintain vision in patients with quarterly dosing.^{12,13} Subsequently, two 2-year phase 3 clinical trials (CEDAR and SEQUOIA) with identical protocols compared abicipar 2 mg every 8 or 12 weeks after initial doses (Q8 or Q12) with ranibizumab 0.5 mg every 4 weeks (Q4) in patients with treatment-naïve nAMD. We recently reported the pooled phase 3 study results through 1 year.¹⁴ In the individual studies as well as the pooled study analyses, both quarterly and Q8 abicipar met the primary end point of noninferiority to ranibizumab Q4 in stable vision at week 52.¹⁴ Improvements in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) after the initial doses were maintained through week 52 with each abicipar regimen.¹⁴ Intraocular inflammation (IOI) during the first study year was more frequent with abicipar than ranibizumab (the incidence of IOI adverse events [AEs] was 15.4%, 15.3%, and 0.3% in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively) and typically occurred after one of the initial anti-VEGF injections.¹⁴

The long-term safety and efficacy of anti-VEGF regimens in nAMD is important because nAMD is a chronic disease usually requiring life long therapy.¹⁵ Here we report the pooled study 2-year safety and efficacy results of the completed CEDAR and SEQUOIA trials. In year 2 of the study, patients received 4 or 6 injections of abicipar versus 11 injections of ranibizumab.

Methods

The CEDAR (ClinicalTrials.gov identifier, NCT02462928) and SEQUOIA (ClinicalTrials.gov identifier, NCT02462486) trials were randomized, double-masked, parallel-group clinical trials with identical protocols; the data from both trials were pooled for analysis. The study design and methods were published

previously¹⁴ and are summarized here. An institutional review board or ethics committee approved the study at each site (IRB centers available online at www.aaojournal.org). The study adhered to the tenets of the Declaration of Helsinki, and all patients provided written informed consent.

Study Population, Treatment, and Masking

Study eyes (1 per patient) had active subfoveal or juxtafoveal CNV secondary to AMD and had not been treated previously for nAMD. The CNV lesion area was required to be more than 50% of the total lesion area, and BCVA was required to be between 73 and 24 Early Treatment Diabetic Retinopathy Study letters (Snellen equivalent, 20/40 and 20/320).

Patients were assigned randomly to 1 of 3 treatment groups: abicipar Q8 (2 mg abicipar administered at baseline and weeks 4 and 8, followed by administration at 8-week intervals through week 96), abicipar Q12 (2 mg abicipar administered at baseline and weeks 4 and 12, followed by administration at 12-week intervals through week 96), and ranibizumab Q4 (0.5 mg ranibizumab administered every 4 weeks from baseline through week 96; Fig S1, available at www.aaojournal.org). Each dose was administered with a 0.05-ml intravitreal injection. In the event of ocular or periocular infection, a new retinal break or retinal detachment, or intraocular pressure of 30 mmHg or higher in the study eye, dosing was withheld until the event resolved. At the investigator's discretion, dosing also could be withheld in the event of IOI in the study eye and could be resumed when the IOI resolved. Any patient who showed a loss in BCVA of 30 letters or more from baseline judged to be caused by persistent subretinal and intraretinal fluid on OCT, and not explained by a reason other than the progression of nAMD, could be treated with standard of care and exited from the study. Patients with BCVA loss of fewer than 30 letters also could be rescued and exited from the study at the discretion of the investigator.

For masking, study eyes in the abicipar groups received sham injections at study visits without scheduled abicipar treatment. Patients, reading center image graders, site personnel who collected the efficacy data, and the investigator responsible for all assessments except the postinjection safety assessment remained masked to the study group assignment until the completion of the study. After the week 52 database lock, the study was unmasked to team members directly involved in the statistical analyses and the development of the study reports and submission-related documents. To maintain the integrity of the ongoing study, Allergan personnel who were unmasked after the week 52 database lock did not participate in any masked activities during the remaining study until after the final database lock at study completion.

Assessments and Outcome Measures

Visits were scheduled every 4 weeks from baseline through week 104 or early exit. Each visit included BCVA evaluations with the Early Treatment Diabetic Retinopathy Study method¹⁶ and spectral-domain OCT. The 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) was administered at baseline and weeks 12, 24, 36, 52, 76, and 104. Safety evaluations at each visit included treatment-emergent AEs, BCVA, and full ophthalmic examinations.

The primary efficacy end point was the proportion of patients with stable vision (defined as loss of <15 letters in BCVA from baseline) in the study eye at week 52. Secondary efficacy outcome measures evaluated over 104 weeks included the proportion of patients with stable vision, the mean change in BCVA from baseline, the proportion of patients with at least 15-letter

improvement in BCVA from baseline, the mean change in CRT from baseline as evaluated by spectral-domain OCT and quantified by a central reading center, and change in the NEI-VFQ-25 composite score from baseline.

The main safety outcome measure was AEs; AEs of special interest included endophthalmitis, AEs related to IOI, and AEs potentially related to systemic VEGF inhibition such as arterial thromboembolic events, hypertension, nonocular hemorrhage, and proteinuria. The investigators determined the severity of AEs, grading them as mild (awareness of a sign or symptom but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating with inability to work or perform usual activities).

Statistical Analysis

Following the primary (week 52) database lock but before the week 104 database lock, the statistical analysis plan for the analysis of the 104-week efficacy data was modified to include a completer population. The completer population was planned to consist of all patients who completed the study (because per protocol, patients who received rescue or escape therapy were discontinued from the study) and excluded the few patients who received escape therapy and were not discontinued from the study (a protocol violation). The BCVA and CRT efficacy outcome measures were evaluated primarily using observed values from study eyes in the completer population; analyses using the intent-to-treat (ITT) population were performed as sensitivity analyses. The weighted differences between treatments (abicipar minus ranibizumab) and the 95.1% confidence intervals (CIs) for the weighted differences were calculated based on the Newcombe method using Cochran-Mantel-Haenszel weights and baseline BCVA (≤ 55 or > 55 letters) as the stratification factor. The analyses used an adjusted α level of 0.049, corresponding to a 2-sided 95.1% CI, to take into account an α value of 0.001 allocated for selected unmasked reviews during the study by the Data and Safety Monitoring Committee.¹⁴ The proportion of patients with improvement in BCVA from baseline of 15 letters or more was determined for each visit and was analyzed using the same method as for the primary end point. Change from baseline in the NEI-VFQ-25 composite score was evaluated using observed values in the ITT population.

Analyses of week 104 data aimed to show that the treatment benefits achieved during the first year were maintained through the second year. Statistical analyses applied to week 104 data were essentially the same as those used in the week 52 analyses; however, noninferiority tests for abicipar versus ranibizumab were not performed at week 104 because they were not included in the gatekeeping procedure for multiple testing and control of type 1 error. Confidence intervals for treatment group differences at week 104 are presented for reference purposes but were not intended for formal statistical conclusions.

Mean change in BCVA from baseline was evaluated with a mixed-effects model for repeated measures that included the treatment group, region, baseline BCVA, baseline CRT (≤ 400 μm or > 400 μm), baseline CNV lesion type (predominantly classic, minimally classic, or occult), visit, visit by baseline BCVA interaction, and treatment by visit interaction as fixed covariates. Mean changes in CRT and NEI-VFQ-25 composite scores from baseline were evaluated with similar mixed-effects models for repeated measures. All mixed-effects models for repeated measures used an unstructured covariance matrix. Differences in the least squares mean (LSM) between each abicipar group and the ranibizumab group (abicipar minus ranibizumab) and 95.1% CIs for the LSM differences were calculated from the models.

Safety parameters including AEs were evaluated in the safety population of all treated patients. Supplemental analyses of IOI

AEs included the number and proportion of patients with IOI onset after week 52 and a survival analysis for time to the first IOI occurrence, which used a life table approach with defined intervals of 0 to 12 weeks, 12 to 24 weeks, 24 to 48 weeks, and 48 to 104 weeks. SAS software version 9.3 (SAS Institute, Inc) was used for all statistical analyses.

Results

The CEDAR and SEQUOIA trials were conducted between June 2015 and April 2019. Of the 1888 patients enrolled, 1411 (74.7%) completed the 104-week study (Fig 1). Study completion rates were 70.8% (446/630), 70.7% (444/628), and 82.7% (521/630) in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. Ocular AEs, mostly associated with IOI, led to the discontinuation of 8.9% of abicipar-treated patients during the first year of the study¹⁴ and accounted for the difference among groups in study completion rates. During the second year of the study, the rate of study discontinuations for any reason was 10% to 12% across all treatment groups (Fig 1). Among all enrolled patients, 443 (70.3%) in the abicipar Q8 group, 442 (70.4%) in the abicipar Q12 group, and 520 (82.5%) in the ranibizumab Q4 group were included in the completer population for efficacy analysis.

Baseline characteristics of the enrolled patients and study eyes were reported previously¹⁴ and were well balanced across the treatment groups. Overall, 55.7% of patients were female, 81.4% were White, and 50.6% had occult lesions. The mean BCVA was 56.8 letters, 56.5 letters, and 56.8 letters and the mean CRT was 382.5 μm , 378.3 μm , and 380.3 μm at baseline for study eyes in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. The majority of patients (60.3%) had study eye baseline BCVA of more than 55 letters. Baseline patient and study eye characteristics in the completer population (Table S1, available at www.aaojournal.org) were similar to those in the ITT population. For the completer population, the mean BCVA at baseline in study eyes was 57.4 letters (standard deviation [SD], 12.9 letters), 56.3 letters (SD, 12.8 letters), and 56.9 letters (SD, 12.4 letters) in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively, and was comparable across treatment groups.

Efficacy Outcomes

In the completer population, the proportion of patients who had stable vision (< 15 -letter loss in BCVA from baseline in the study eye) was high and comparable among treatment groups at week 52 and remained high in each treatment group at week 104 (Fig 2). The abicipar treatment effect at week 52 was maintained throughout the second year with fewer injections compared with the ranibizumab group. During the second year, the number of intravitreal injections received by patients, as defined by the protocol, was 6 for the abicipar Q8 group, 4 for the abicipar Q12 group, and 11 for the ranibizumab Q4 group. The proportion of patients with stable vision at week 104 was 93.0% (396/426) in the abicipar Q8 group, 89.8% (379/422) in the abicipar Q12 group, and 94.4% (470/498) in the ranibizumab Q4 group; the difference in the proportion of patients with stable vision between abicipar and ranibizumab was -1.4% (95.1% CI, -4.7% to 1.7%) for abicipar Q8 and -4.6% (95.1% CI, -8.3% to -1.1%) for abicipar Q12. Results of a sensitivity analysis using the ITT patient population and the last-observation-carried-forward method for missing values confirmed maintenance of stable vision in the abicipar groups with fewer injections. In the sensitivity analysis, the proportion of patients

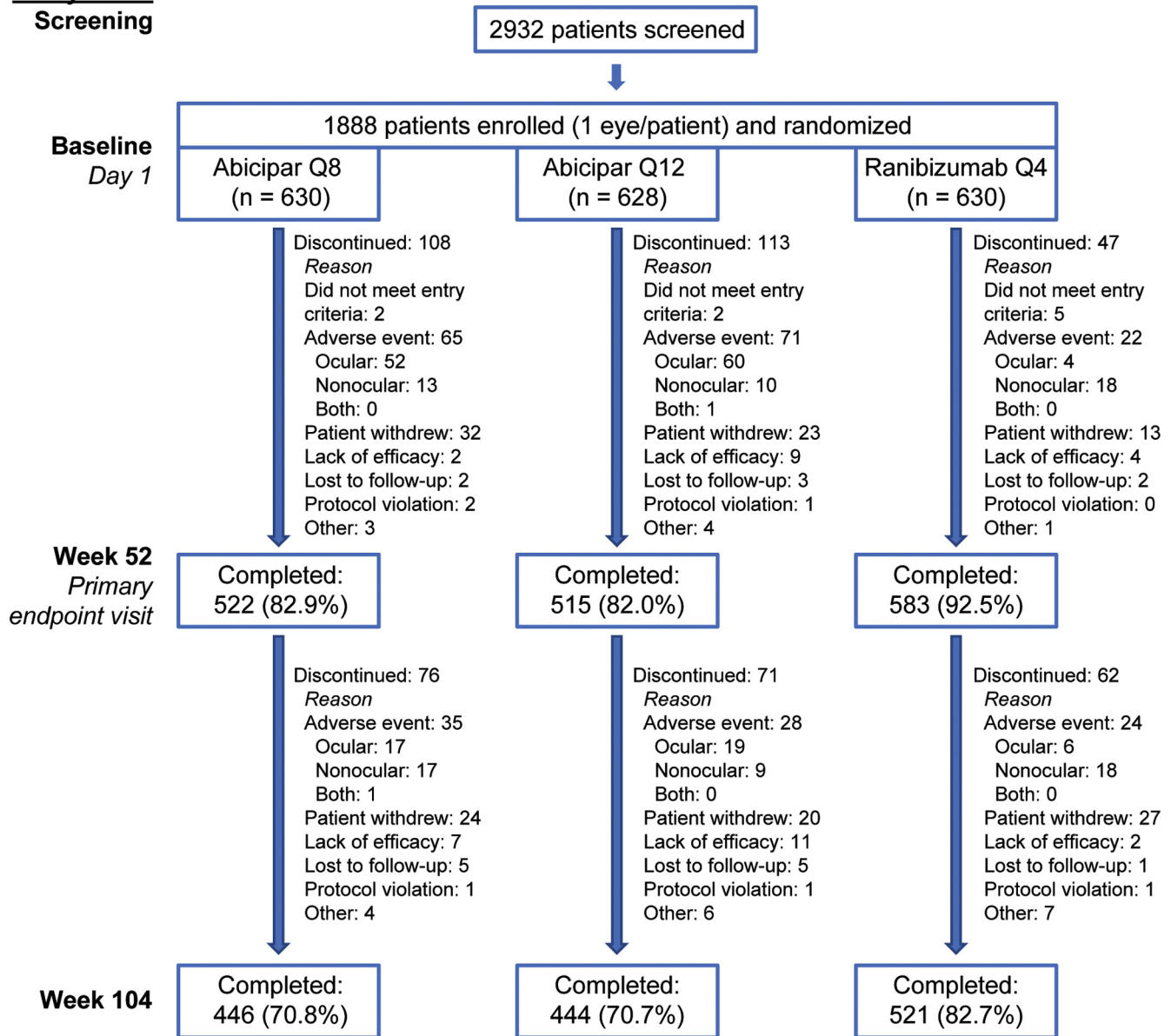
Study Visits
Screening

Figure 1. Flow diagram showing patient progress through the pooled CEDAR and SEQUOIA trials. Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

with stable vision was 91.3% (575/630), 88.5% (556/628), and 95.4% (601/630) at week 52 and 87.9% (554/630), 85.5% (537/628), and 93.3% (588/630) at week 104 in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. Other efficacy outcomes at week 104 in the ITT population are summarized in Table S2 (available at www.aaojournal.org). For comparison, Table S3 (available at www.aaojournal.org) shows outcomes in the modified ITT population that excludes patients with IOI.

Mean gains in BCVA from baseline in study eyes after initial doses were maintained in each treatment group through week 104 (Fig 3). At week 52 in the completer population, the LSM change in BCVA from baseline was +8.9 letters (standard error [SE], 0.6 letters), +7.4 letters (SE, 0.6 letters), and +9.5 letters (SE, 0.6 letters) in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. At week 104, after a

total of 14 and 10 injections in the abicipar Q8 and Q12 groups and 25 injections in the ranibizumab Q4 group, the LSM change in BCVA from baseline was +7.8 letters (SE, 0.7 letters) in the abicipar Q8 group, +6.1 letters (SE, 0.7 letters) in the abicipar Q12 group, and +8.5 letters (SE, 0.6 letters) in the ranibizumab Q4 group (Fig 3). The week 104 difference from ranibizumab Q4 was -0.7 letters (95.1% CI, -2.5 to 1.1 letters) for abicipar Q8 and -2.4 letters (95.1% CI, -4.2 to -0.6 letters) for abicipar Q12. The lower limit of each 95.1% CI was above the -5.0 limit used to determine noninferiority in the week 52 analysis.¹⁴

The proportion of patients in the completer population with a gain in BCVA from baseline of 15 letters or more was maintained from week 52 to week 104 and was similar among treatment groups (Fig 4). At week 104, 31.2% (133/426) of patients in the abicipar Q8 group achieved a gain of 15 letters or more after a total of 14

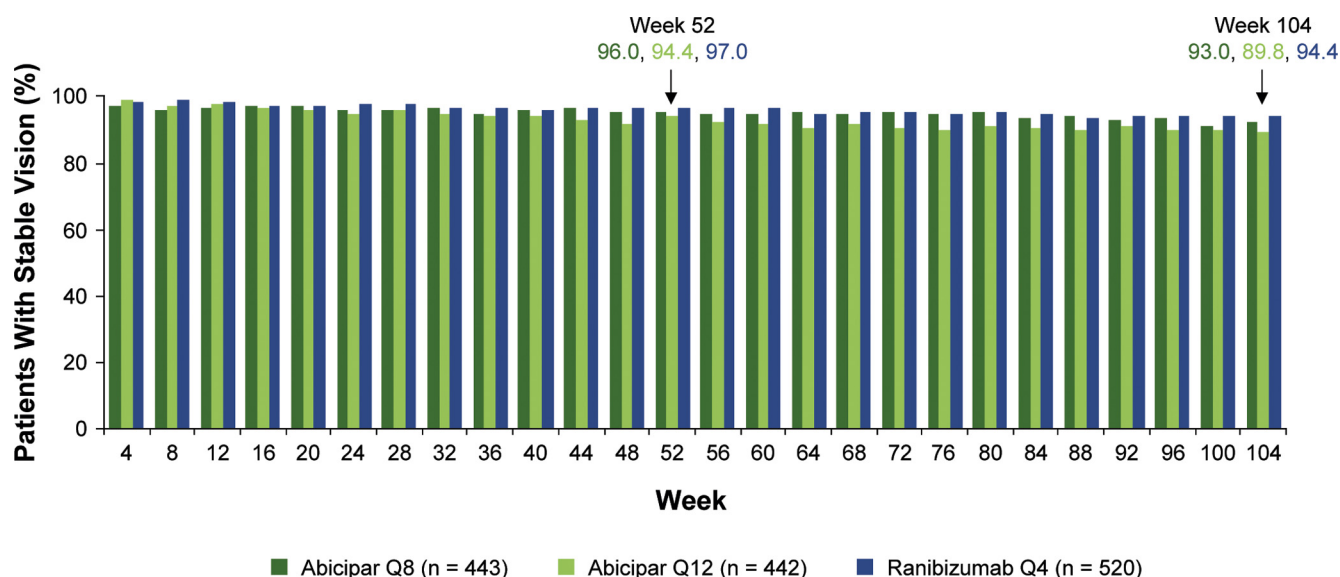


Figure 2. Proportion of patients with stable vision (<15-letter loss in best-corrected visual acuity from baseline). The analysis used observed data in the completer population. Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

injections, 26.1% (110/422) of patients in the abicipar Q12 group achieved a gain of 15 letters or more after a total of 10 injections, and 30.3% (151/498) of patients in the ranibizumab Q4 group achieved a gain of 15 letters or more after a total of 25 injections. The week 104 difference in the proportion of patients with a 15-letter or more gain between abicipar and ranibizumab Q4 was 1.1% (95.1% CI, -4.9% to 7.1%) for abicipar Q8 and -4.6% (95.1% CI, -10.4% to 1.2%) for abicipar Q12.

Baseline mean NEI-VFQ-25 composite scores were similar in the 3 treatment groups: 78.6 (SD, 14.7), 77.8 (SD, 14.7), and 77.2 (SD, 15.6) in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. The LSM change in the NEI-VFQ-25 composite score from baseline at week 104 was 2.5 (SE, 0.6) in the abicipar Q8 group, 1.4 (SE, 0.6) in the abicipar Q12 group, and 3.1 (SE, 0.6) in the ranibizumab Q4 group. The LSM

differences from the ranibizumab Q4 group at week 104 were -0.6 (95.1% CI, -2.2 to 0.9) for abicipar Q8 and -1.7 (95.1% CI, -3.3 to -0.2) for abicipar Q12. The difference in improvement in NEI-VFQ-25 composite scores between the abicipar Q12 and ranibizumab Q4 groups at week 104 is not considered to be clinically relevant.

The improvement in CRT after initial doses was maintained through week 104 in all treatment groups (Fig 5). At week 104 in the completer population, the LSM change in CRT from baseline was -146.7 μ m (SE, 3.9 μ m) in the abicipar Q8 group, -145.5 μ m (SE, 3.9 μ m) in the abicipar Q12 group, and -141.7 μ m (SE, 3.6 μ m) in the ranibizumab Q4 group (Fig 5). The week 104 difference from ranibizumab Q4 was -5.0 μ m (95.1% CI, -15.0 to 5.1 μ m) for abicipar Q8 and -3.7 μ m (95.1% CI, -13.8 to 6.3 μ m) for abicipar Q12.

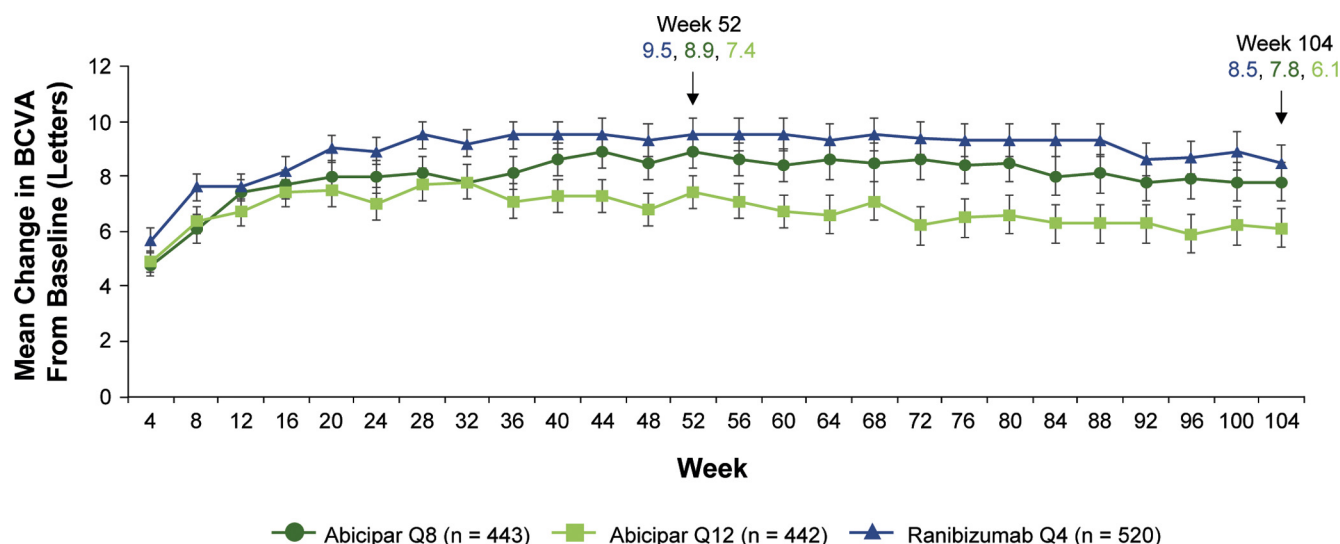


Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline. Values shown are the least squares means $\pm$ standard errors from a mixed-effects model for repeated measures using observed values in the completer population. Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

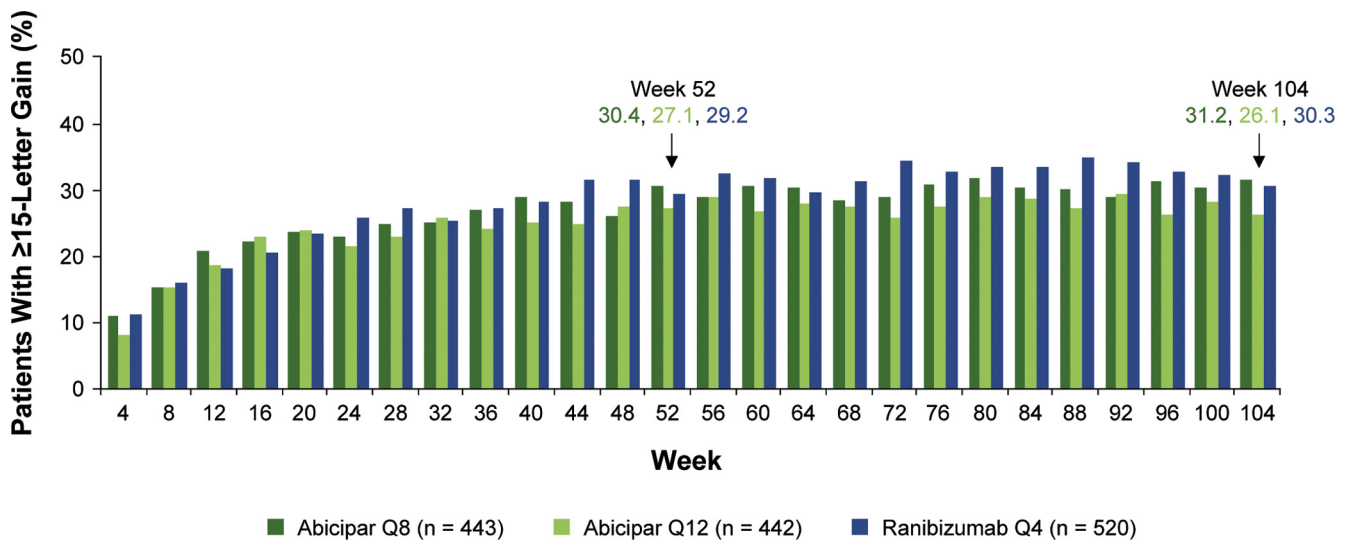


Figure 4. Proportion of patients with a 15-letter or more gain in best-corrected visual acuity from baseline. The analysis used observed data in the completer population. Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

Safety Outcomes

The overall incidence of any AE (87.7%, 88.2%, and 85.6%) and any ocular AE (66.6%, 68.4%, and 62.1%) during the 2-year study was comparable for patients in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively (Table 1). However, the incidence of study drug–related ocular AEs was clinically significantly higher in the abicipar Q8 group (17.6%) and abicipar Q12 group (22.5%) than in the ranibizumab Q4 group (6.4%) because of the occurrence of IOI. The most common IOI AEs were uveitis, vitritis and iridocyclitis (Table 2). Rates of discontinuations because of IOI AEs were 7.5% (47/625), 7.5% (47/626), and 0.2% (1/625) in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively. Among the 211 patients with IOI AEs in the abicipar groups, 195 (92.4%) received corticosteroid treatment. Topical corticosteroid alone was used for 124 patients (58.8%), and 71 patients (33.6%)

were treated with injectable or systemic (oral or intravenous) corticosteroid, or both. The outcomes of the IOI AEs in the 211 patients were reported as resolved without sequelae in 164 patients (77.7%), resolved with sequelae in 23 patients (10.9%), resolving in 9 patients (4.3%), and not resolved in 15 patients (7.1%). Severe vision loss (loss of ≥ 30 letters in BCVA from baseline) at the last visit (week 104 or early exit visit, including data after early exit if available) occurred in a larger proportion of patients in the abicipar Q8 and Q12 groups (5.3% and 5.9%, respectively) than in the ranibizumab Q4 group (2.2%) because of the occurrence of IOI and endophthalmitis in the abicipar groups.

As reported previously, the incidence of IOI and endophthalmitis AEs over the first 52 weeks of the study was higher in the abicipar groups than in the ranibizumab group (Fig 6A).¹⁴ However, the incidence of IOI AEs from week 52 to week 104 in patients without an IOI AE during the first 52 weeks was not

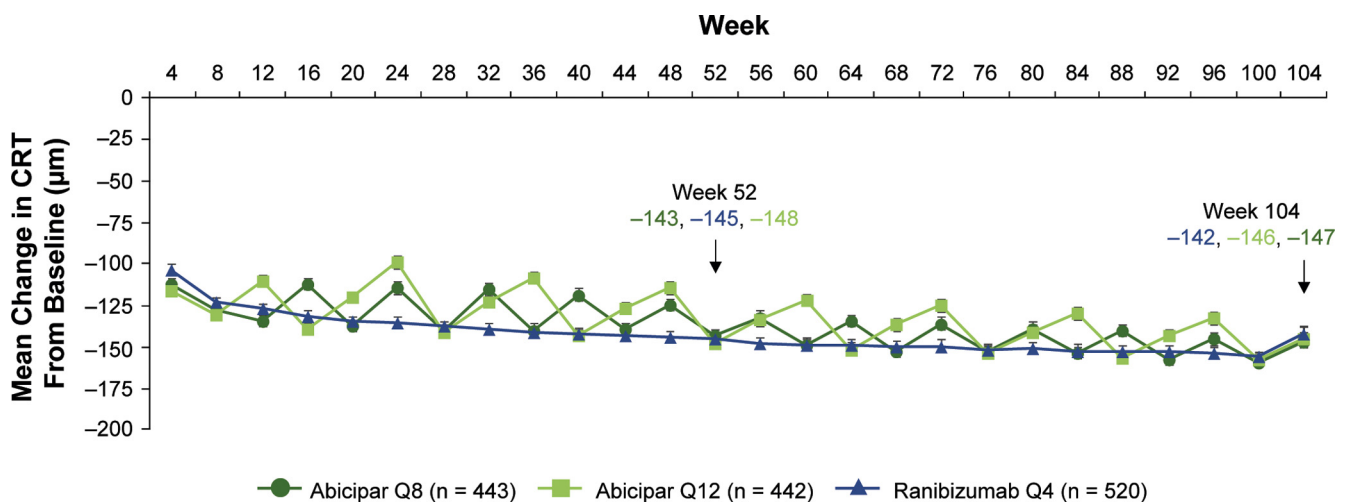


Figure 5. Mean change in central retinal thickness (CRT) from baseline. Values shown are the least squares means $\pm$ standard errors from a mixed-effects model for repeated measures using observed values in the completer population. Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

Table 1. Adverse Event Summary (Safety Population)

Adverse Event	Abicipar Q8 (n = 625)	Abicipar Q12 (n = 626)	Ranibizumab Q4 (n = 625)
Overall (any AE)	548 (87.7)	552 (88.2)	535 (85.6)
Ocular	416 (66.6)	428 (68.4)	388 (62.1)
Nonocular	418 (66.9)	435 (69.5)	465 (74.4)
Treatment-related AE*	237 (37.9)	257 (41.1)	196 (31.4)
Ocular	232 (37.1)	253 (40.4)	190 (30.4)
Study drug	110 (17.6)	141 (22.5)	40 (6.4)
Study procedure	171 (27.4)	184 (29.4)	177 (28.3)
Serious AE	186 (29.8)	184 (29.4)	173 (27.7)

AE = adverse event; Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses..

Data are n (%).

*An AE was determined by the investigator to be treatment related if there was a reasonable possibility that it was caused by the treatment.

notably different among treatment groups (0.8%, 2.3%, and 1.0% in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively; Table 3; Fig 6A). Life table analysis of the first occurrence of an IOI AE in the pooled abicipar Q8 and Q12 groups confirmed that the risk of IOI decreased rapidly over time (Fig 6B). The risk of IOI was highest, with an estimated monthly rate of 2.95%, during the first 12 weeks of the study. The risk for patients who did not have an IOI AE by week 12 was reduced to an estimated monthly rate of 1.13% in the next 12-week period (weeks 12–24), representing a relative reduction in the IOI rate of more than 60%, and continued to decrease in subsequent periods to a monthly rate of 0.21% in the second year (weeks 48–104). The IOI AEs that occurred during year 2 were mostly mild or moderate in severity. There were 3 new cases of severe IOI after week 52 (2 in the abicipar Q8 group, autoimmune uveitis and vitritis, which were treated with topical corticosteroid; none in the abicipar Q12 group; and 1 in the ranibizumab Q4 group, anterior chamber inflammation, which was treated with intravitreal triamcinolone). The last BCVA measurements available for these patients were 31 letters, 63 letters (improved from 58 letters at baseline), and 33 letters, respectively. There were no new reports of retinal vasculitis after week 52.

Endophthalmitis with onset after week 52 was reported for no patient in the abicipar Q8 group, 1 patient in the abicipar Q12 group, and 2 patients in the ranibizumab Q4 group. Adverse events potentially related to systemic VEGF inhibition were reported in a comparable percentage of patients in each treatment group (Table 4).

Discussion

Abicipar is a DARPIn anti-VEGF therapy optimized for duration by balancing high-affinity binding, a long half-life in the vitreous, and high molar dose. The results of the pooled phase 3 CEDAR and SEQUOIA trials reported here show efficacy of a quarterly abicipar regimen in improving or stabilizing vision and reducing CRT through 2 years. The incidence of first onset of IOI events was reduced in the second year of treatment.

More than 70% of abicipar-treated patients and 80% of ranibizumab-treated patients completed the second year of the study. The 2-year study completion rate for the ranibizumab group was consistent with study completion rates reported in other phase 3 studies of anti-VEGF therapy in nAMD, including the pHase 3, 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 in patients with subfoveal neOvasculaR age-related macular degeneration (HARBOR)¹⁷ and VEGF trap-eye: Investigation of Efficacy and safety in Wet age-related macular degeneration (VIEW)¹⁸ studies. The completion rates were lower for the abicipar groups because of the larger number of discontinuations due to IOI during the first year of the study.

Table 2. Intraocular Inflammation Adverse Events in the Study Eye at Any Time during the Study (Safety Population)

Intraocular Inflammation Adverse Event	Abicipar Q8 (n = 625)	Abicipar Q12 (n = 626)	Ranibizumab Q4 (n = 625)
Overall (any IOI AE)	101 (16.2)	110 (17.6)	8 (1.3)
Uveitis	35 (5.6)	34 (5.4)	0
Vitritis	27 (4.3)	30 (4.8)	0
Iridocyclitis	23 (3.7)	35 (5.6)	4 (0.6)
Iritis	20 (3.2)	11 (1.8)	0
Retinal vasculitis	12 (1.9)	10 (1.6)	0
Keratic precipitates	9 (1.4)	15 (2.4)	0
Vitreous cells	7 (1.1)	3 (0.5)	1 (0.2)
Vitreous haze	5 (0.8)	8 (1.3)	2 (0.3)
Autoimmune uveitis	3 (0.5)	7 (1.1)	0

AE = adverse event; IOI = intraocular inflammation; Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses. Data are n (%).

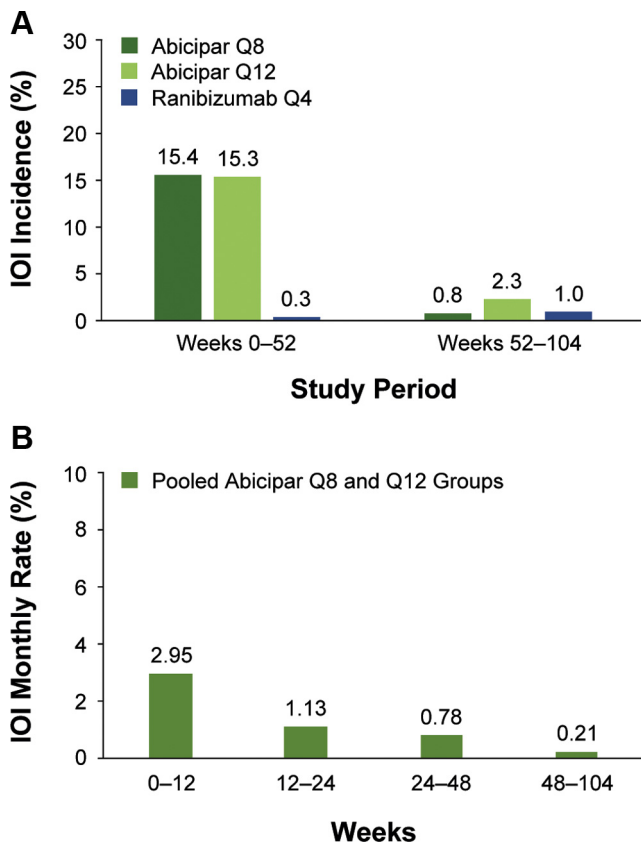


Figure 6. Timing of the onset of intraocular inflammation (IOI) adverse events. **A**, Incidence rates of first IOI episode during the first and second years of the study. **B**, Estimated monthly rates of IOI based on the life table method, which assumed a constant rate within each defined interval (0–12, 12–24, 24–48, and 48–104 weeks). Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

The demographic and baseline disease characteristics of patients in the completer population were well balanced among treatment groups, and a high proportion of patients in each group, ranging from 89.8% to 94.4%, showed stable vision at week 104 after a total of 14, 10, and 25 injections

in the abicpar Q8, abicpar Q12, and ranibizumab Q4 groups, respectively. Because of potential bias in analysis using the completer population, a sensitivity analysis was performed for the ITT population using last observation carried forward for missing values. The sensitivity analysis confirmed the maintenance of stable vision in the abicpar groups through week 104 with fewer injections.

These phase 3 studies were designed to demonstrate noninferiority of abicpar to ranibizumab at the primary end point of week 52 with the prespecified noninferiority margins for stable vision and BCVA change from baseline. The primary reason for analyses of week 104 efficacy data was to determine whether treatment benefits achieved during the first year were maintained through the second year with 8-week and 12-week dosing intervals. Formal statistical testing for comparisons between treatment groups at week 104 was not a prespecified hypothesis in the study design or stated in the analysis plan; however, CIs for group differences are provided for reference purposes only.

The improvement in BCVA after initial doses was maintained through week 104 in each treatment group. From week 52 to week 104, all treatment groups exhibited a small decrease in the mean BCVA gain, ranging from 1.0 to 1.3 letters across treatment groups. These results indicate that visual gains achieved by the end of the first year of treatment were maintained as effectively with 4 injections of abicpar as with 11 injections of ranibizumab during the second year. The proportion of patients with improvement in BCVA from baseline of 15 letters or more at week 104 was similar among treatments (31.2% after 14 injections in the abicpar Q8 group, 26.1% after 10 injections in the abicpar Q12 group, and 30.3% after 25 injections in the ranibizumab Q4 group).

During the initial dose phase of the study, abicpar Q8 and Q12 achieved more rapid and complete drying of intraretinal and subretinal fluid compared with ranibizumab Q4.¹⁴ This is thought to be important because the persistence of intraretinal and subretinal fluid compartments seems to affect vision.^{19,20} For example, in the Comparison of Age-Related Macular Degeneration Treatments Trials, patients with residual intraretinal fluid after ranibizumab or bevacizumab treatment had worse visual acuity outcomes than patients without residual

Table 3. Intraocular Inflammation Adverse Events in the Study Eye during the Second Year in Patients with No Intraocular Inflammation Adverse Event in the Study Eye during the First Year

Intraocular Inflammation Adverse Event	Abicpar Q8 (n = 474)	Abicpar Q12 (n = 474)	Ranibizumab Q4 (n = 580)
Overall (any IOI AE)	4 (0.8)	14 (3.0)	6 (1.0)
Iritis	2 (0.4)	4 (0.8)	0
Uveitis	1 (0.2)	1 (0.2)	0
Chorioretinitis	1 (0.2)	0	0
Vitreal cells	1 (0.2)	0	0
Iridocyclitis	0	5 (1.1)	3 (0.5)
Vitritis	0	3 (0.6)	0
Anterior chamber inflammation	0	1 (0.2)	1 (0.2)
Autoimmune uveitis	0	1 (0.2)	0
Keratic precipitates	0	1 (0.2)	0
Vitreous haze	0	0	2 (0.3)

AE = adverse event; IOI = intraocular inflammation; Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses. Data are n (%).

Table 4. Adverse Events Potentially Related to Systemic Vascular Endothelial Growth Factor Inhibition

Adverse Event	Abicipar Q8 (n = 625)	Abicipar Q12 (n = 626)	Ranibizumab Q4 (n = 625)
Overall	80 (12.8)	84 (13.4)	104 (16.6)
Hypertension	43 (6.9)	44 (7.0)	44 (7.0)
Blood pressure increased	9 (1.4)	8 (1.3)	13 (2.1)
Hypertensive crisis	4 (0.6)	1 (0.2)	2 (0.3)
Hematuria	3 (0.5)	1 (0.2)	6 (1.0)
Cerebrovascular accident	2 (0.3)	5 (0.8)	6 (1.0)
Epistaxis	2 (0.3)	1 (0.2)	2 (0.3)
Deep vein thrombosis	2 (0.3)	1 (0.2)	1 (0.2)
Death	2 (0.3)	0	1 (0.2)
Cerebral infarction	2 (0.3)	0	0
Hemoptysis	2 (0.3)	0	0
Myocardial infarction	1 (0.2)	5 (0.8)	2 (0.3)
Gastrointestinal hemorrhage	1 (0.2)	3 (0.5)	4 (0.6)
Acute myocardial infarction	1 (0.2)	3 (0.5)	3 (0.5)
Peripheral ischemia	1 (0.2)	2 (0.3)	0
Thrombosis	1 (0.2)	1 (0.2)	5 (0.8)
Pulmonary embolism	1 (0.2)	1 (0.2)	4 (0.6)
Rectal hemorrhage	1 (0.2)	1 (0.2)	3 (0.5)
Proteinuria	1 (0.2)	0	2 (0.3)
Hematoma	0	5 (0.8)	3 (0.5)
Blood urine present	0	2 (0.3)	0
Hypertensive cardiomyopathy	0	2 (0.3)	0
Protein urine present	0	1 (0.2)	4 (0.6)
Renal failure	0	1 (0.2)	2 (0.3)
Subdural hematoma	0	1 (0.2)	2 (0.3)

Q4 = every 4 weeks; Q8 = every 8 weeks after initial doses; Q12 = every 12 weeks after initial doses.

Data are n (%). All adverse events potentially related to systemic vascular endothelial growth factor inhibition that were reported in more than 1 patient in any treatment group are listed.

intraretinal fluid.²¹ The 2-year study results show that the CRT improvement after initial doses was maintained to week 104 and was similar between quarterly or Q8 abicipar and ranibizumab. The week 104 mean changes in CRT from baseline ranged from -142 to -147 μm across treatment groups, after a total of 14, 10, and 25 injections in the abicipar Q8, abicipar Q12, and ranibizumab Q4 groups, respectively.

In patients who received quarterly or Q8 abicipar, there was some fluctuation in the mean CRT reduction from baseline at 8 and 12 weeks after dosing, but an optimal level of CRT reduction was always achieved after the next dose. Furthermore, the magnitude of the fluctuations decreased to less than 30 μm during the second year of the study (Fig 5). The exact reasons for the decrease in fluctuations are unknown, but it could reflect a decrease in CNV activity over time, that is, the magnitude of the fluctuations may have decreased in the second year because CNV decreased, so there was less of an increase in CRT when the anti-VEGF effect diminished. In the pooled data analysis of the VIEW trials, fluctuations in the mean CRT reduction from baseline occurred with 8-week dosing intervals of the anti-VEGF agent aflibercept; these fluctuations were not associated with fluctuations in the BCVA gain from baseline, and their magnitude similarly decreased in the second year of treatment.²² Importantly, in the pooled CEDAR and SEQUOIA trials, fluctuations in CRT reductions likewise did not result in fluctuations in BCVA

gains from baseline (Fig 3), and the BCVA improvement after initial doses was maintained through week 104.

The overall incidence of treatment-emergent AEs during the study was comparable among treatment groups, and there was no pattern of cardiovascular or other AEs potentially associated with systemic VEGF inhibition. During the first year of the study, abicipar-treated patients had higher risk of developing IOI and endophthalmitis compared with ranibizumab-treated patients.¹⁴ However, the incidence of IOI AEs over 2 years was only minimally higher than the 1-year incidence in each treatment group (by 0.8% in the abicipar Q8 group, 2.3% in the abicipar Q12 group, and 1.0% in the ranibizumab Q4 group), and the incidence of new IOI and endophthalmitis during the second study year was not notably different between abicipar and ranibizumab. The IOI AEs that occurred during the second year of the study mostly were mild or moderate in severity, and there were no new cases of severe IOI in the abicipar Q12 group. Retinal vasculitis was an unexpected AE that occurred in 22 abicipar-treated patients during the first year of the study and was reported to have resolved without sequelae in 11 patients, to have resolved with sequelae in 8 patients, and to be ongoing in 3 patients.¹⁴ Retinal vasculitis (mostly occlusive) also has been reported in patients treated with the anti-VEGF brolucizumab.²³ There were no new cases of retinal vasculitis in the abicipar treatment groups during the second year of the CEDAR and SEQUOIA trials.

After the initiation of the CEDAR and SEQUOIA trials, the manufacturing process for abicipar was modified to optimize the removal of host-derived impurities. The formulation of abicipar remained the same throughout the CEDAR and SEQUOIA trials. However, abicipar produced with the modified manufacturing process was evaluated in the open-label MAPLE study ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03539549) identifier, NCT03539549), in which it demonstrated a reduced incidence of IOI (8.9% over 28 weeks and 5 injections) with no reports of retinal vasculitis or endophthalmitis (Albini T. Paper entitled “Abicipar Phase 2 MAPLE Trial Demonstrates Improved Safety for Patients with nAMD Following a Modified Manufacturing Process” presented at: Retina Society Virtual Meeting, September 21–22, 2020). A full report of the MAPLE study results is forthcoming.

Abicipar is the only anti-VEGF therapy that has been shown to achieve stable vision and CRT gains at 1 year with a fixed quarterly dosing regimen, unadjusted for disease activity.¹⁴ The phase 3 studies of brotacizumab used initial quarterly dosing, but the dosing interval was adjusted to 8 weeks when disease activity was present, and the probability of patients showing disease activity and not remaining on quarterly dosing through week 48 was 49% and 44% in the studies.²⁴ The 2-year results of CEDAR

and SEQUOIA show that improvements in vision and CRT at 1 year appeared to be maintained through the second year of treatment with quarterly abicipar and confirm a long duration of effect of abicipar. We expect that this long duration of effect will enable less frequent dosing of abicipar compared with other anti-VEGF agents when used in clinical practice in fixed-dosing, pro re nata, and treat-and-extend treatment paradigms. Less frequent dosing will result in reduced treatment burden associated with the injection procedure, and for patients without IOI, fewer office visits and reduced costs for patients and health care systems.

In conclusion, for patients who completed the CEDAR and SEQUOIA trials, visual and anatomic changes occurring in the first year of abicipar treatment were maintained in the second year. The increased risk of IOI AEs with abicipar seen in the first year of the study was not sustained, and the incidence of IOI in patients with no previous IOI was low and comparable across treatment groups after week 52. Abicipar demonstrated noninferiority to monthly ranibizumab when used in an unadjusted, quarterly regimen in patients with nAMD. It has potential to help fulfill the unmet need for a long-acting anti-VEGF that decreases the treatment burden for patients with nAMD.

Footnotes and Disclosures

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¹ Northern California Retina Vitreous Associates, Mountain View, California.

² Retinal Consultants of Arizona, Phoenix, Arizona.

³ Asan Medical Center, University of Ulsan, Seoul, South Korea.

⁴ Retina Consultants of Houston, Houston, Texas.

⁵ Sydney Retina Clinic, Sydney, Australia.

⁶ Save Sight Institute, University of Sydney, Sydney, Australia.

⁷ Midwest Eye Institute, Indianapolis, Indiana.

⁸ Department of Ophthalmology, Indiana University School of Medicine, Indianapolis, Indiana.

⁹ Eye Center, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany.

¹⁰ Centre Hospitalier Creteil, Service Universitaire d'Ophthalmologie, Creteil, France.

¹¹ St Michael's Hospital, University of Toronto, Toronto, Canada.

¹² Toronto Retina Institute, North York, Canada.

¹³ University of Southampton, Southampton, United Kingdom.

¹⁴ Department of Ophthalmology, Shiga University of Medical Science, Shiga, Japan.

¹⁵ University Vita-Salute Scientific Institute, Hospital San Raffaele, Milan, Italy.

¹⁶ Vision Institute, Federal University of São Paulo, São Paulo, Brazil.

¹⁷ Allergan, an AbbVie company, Irvine, California.

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*Both authors contributed equally as first authors.

†Members of the CEDAR and SEQUOIA Study Groups are listed in the Supplemental Appendix at www.aaojournal.org.

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A.J.L.: Advisory board — Allergan (an AbbVie company), Bayer; Financial support — Allergan (an AbbVie company), Bayer; Lecturer — Novartis
M.O.: Consultant — Alcon, Allergan (an AbbVie company), Bausch + Lomb, Bayer, Hoya, Novartis, Pfizer, Santen; Financial support — Alcon, Bayer, Novartis, Otsuka, Pfizer, Santen, Senju
F.B.: Consultant — Allergan (an AbbVie company), Bayer, Boehringer Ingelheim, Fidia Soffit, Hoffmann-La Roche, Novartis, NTC Pharma, SIFI, Thrombogenics, Zeiss
R.B.: Consultant — Allergan (an AbbVie company)
X.-Y.L.: Employee and stock ownership — AbbVie, Inc.
J.J.: Employee and stock ownership — AbbVie, Inc.
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K.K.: Employee and stock ownership — AbbVie, Inc.
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No animal subjects were included in this study.

Author Contributions:

Conception and design: Schmidt, Hashad

Analysis and interpretation: Khurana, Kunimoto, Yoon, Wyckoff, Chang, Maturi, Agostini, Souied, Chow, Lotery, Ohji, Bandello, Belfort, Li, Jiao, Le, Kim, Schmidt, Hashad

Data collection: Khurana, Kunimoto, Yoon, Wyckoff, Chang, Maturi, Agostini, Souied, Chow, Lotery, Ohji, Bandello, Belfort

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Overall responsibility: Khurana, Kunimoto, Yoon, Wyckoff, Chang, Maturi, Agostini, Souied, Chow, Lotery, Ohji, Bandello, Belfort, Li, Jiao, Le, Kim, Schmidt, Hashad

Abbreviations and Acronyms:

AE = adverse event; **AMD** = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CRT** = central retinal thickness; **IOI** = intraocular inflammation; **ITT** = intention-to-treat; **LSM** = least squares mean; **nAMD** = neovascular age-related macular degeneration; **NEI-VFQ-25** = 25-item National Eye Institute Visual Functioning Questionnaire; **SD** = standard deviation; **SE** = standard error; **VEGF** = vascular endothelial growth factor.

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Abicipar, Anti-VEGF, Choroidal neovascularization, DARPIn therapeutic, Intravitreal injection, Neovascular age-related macular degeneration, Ranibizumab, Treatment burden, Visual acuity.

Correspondence:

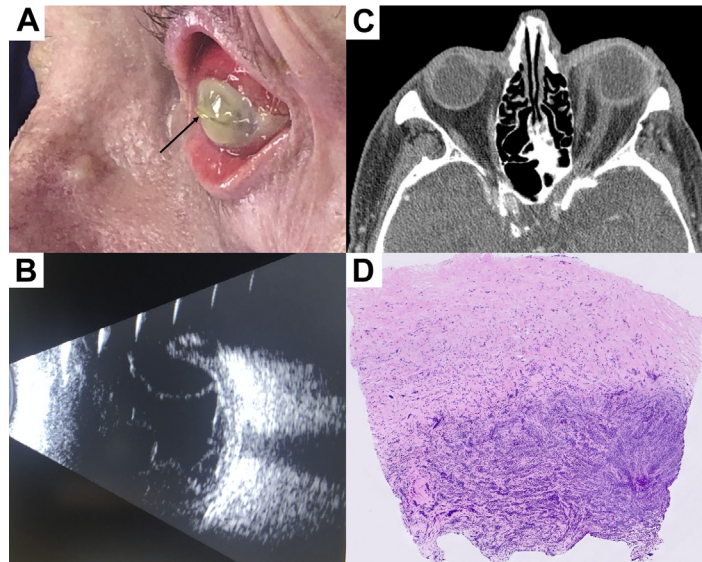
Rahul N. Khurana, MD, Northern California Retina Vitreous Associates, 2495 Hospital Drive, No. 545, Mountain View, CA 94040. E-mail: nkhurana@gmail.com.

References

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5:e1221–e1234.
2. Yonekawa Y, Kim IK. Clinical characteristics and current treatment of age-related macular degeneration. *Cold Spring Harb Perspect Med*. 2015;5:a017178.
3. Ferris 3rd FL, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol*. 1984;102:1640–1642.
4. Schmidt-Erfurth U, Chong V, Loewenstein A, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). *Br J Ophthalmol*. 2014;98:1144–1167.
5. Amoaku W, Blakeney S, Freeman M, et al. Action on AMD. Optimising patient management: act now to ensure current and continual delivery of best possible patient care. *Eye (Lond)*. 2012;26(Suppl 1):S2–S21.
6. Prenner JL, Halperin LS, Rycroft C, et al. Disease burden in the treatment of age-related macular degeneration: findings from a time-and-motion study. *Am J Ophthalmol*. 2015;160:725–731.e1.
7. Brown MM, Brown GC, Lieske HB, et al. Societal costs associated with neovascular age-related macular degeneration in the United States. *Retina*. 2016;36:285–298.
8. Rodrigues GA, Mason M, Christie LA, et al. Functional characterization of abicipar-pegol, an anti-VEGF DARPIn therapeutic that potently inhibits angiogenesis and vascular permeability. *Invest Ophthalmol Vis Sci*. 2018;59:5836–5846.
9. Plückthun A. Designed ankyrin repeat proteins (DARPins): binding proteins for research, diagnostics, and therapy. *Annu Rev Pharmacol Toxicol*. 2015;55:489–511.
10. Campochiaro PA, Channa R, Berger BB, et al. Treatment of diabetic macular edema with a designed ankyrin repeat protein that binds vascular endothelial growth factor: a phase I/II study. *Am J Ophthalmol*. 2013;155:697–704. e1–2.
11. Souied EH, Devin F, Mauguet-Faysse M, et al. Treatment of exudative age-related macular degeneration with a designed ankyrin repeat protein that binds vascular endothelial growth factor: a phase I/II study. *Am J Ophthalmol*. 2014;158:724–732.e2.
12. Callanan D, Kunimoto D, Maturi RK, et al. Double-masked, randomized, phase 2 evaluation of abicipar pegol (an anti-VEGF DARPIn therapeutic) in neovascular age-related macular degeneration. *J Ocul Pharmacol Ther*. 2018;34:700–709.
13. Kunimoto D, Ohji M, Maturi RK, et al. Evaluation of abicipar pegol (an anti-VEGF DARPIn therapeutic) in patients with neovascular age-related macular degeneration: studies in Japan and the United States. *Ophthalmic Surg Lasers Imaging Retina*. 2019;50:e10–e22.
14. Kunimoto D, Yoon YH, Wyckoff CC, et al. Efficacy and safety of abicipar in neovascular age-related macular degeneration: 52-week results of phase 3 randomized controlled study. *Ophthalmology*. 2020;127:1331–1344.

15. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the Comparison of Age-Related Macular Degeneration Treatments Trials. *Ophthalmology*. 2016;123:1751–1761.
16. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol*. 2001;119:1417–1436.
17. Ho AC, Busbee BG, Regillo CD, et al. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:2181–2192.
18. Richard G, Monés J, Wolf S, et al. Scheduled versus pro re nata dosing in the VIEW trials. *Ophthalmology*. 2015;122:2497–2503.
19. Golbaz I, Ahlers C, Stock G, et al. Quantification of the therapeutic response of intraretinal, subretinal, and subpigment epithelial compartments in exudative AMD during anti-VEGF therapy. *Invest Ophthalmol Vis Sci*. 2011;52:1599–1605.
20. Sulzbacher F, Roberts P, Munk MR, et al. Relationship of retinal morphology and retinal sensitivity in the treatment of neovascular age-related macular degeneration using aflibercept. *Invest Ophthalmol Vis Sci*. 2014;56:1158–1167.
21. Jaffe GJ, Martin DF, Toth CA, et al. Macular morphology and visual acuity in the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2013;120:1860–1870.
22. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121:193–201.
23. Bauman CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brodalumab. *Ophthalmology*. 2020;127:1345–1359.
24. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brodalumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127:72–84.

Pictures & Perspectives



Inside-out: Infectious Endophthalmitis with Secondary Corneal Perforation

A 98-year-old man with exudative age-related macular degeneration receiving intravitreal aflibercept injections was referred for worsening left eye endophthalmitis. Prior vitreous culture grew *Streptococcus pneumoniae*. He received two rounds of intravitreal vancomycin and ceftazidime. Examination revealed corneal necrosis with intraocular lens extrusion (Fig A, arrow). Ultrasound revealed multiple, loculated collections with heterogeneous echogenicity (Fig B). Computed tomography demonstrated thickened posterior sclera without retro-orbital extension (Fig C). Following evisceration, histopathologic analysis demonstrated severe neutrophilic infiltration of the posterior cornea (Fig D). Although infectious keratitis may infrequently develop into secondary endophthalmitis, primary endophthalmitis leading to secondary corneal perforation is very rare (Magnified version of Fig A-D is available online at www.aaojournal.org).

BENYAM KINDE, MD, PhD¹

M. REZA VAGEFI, MD¹

GERAMI D. SEITZMAN, MD^{1,2}

¹Department of Ophthalmology, University of California - San Francisco, San Francisco, California; ²Francis I. Proctor Foundation, Department of Ophthalmology, University of California, San Francisco, California