Purpose: The purpose of this study was to compare intravitreal nesvacumab (anti-angiopoietin 2) plus aflibercept with intravitreal aflibercept injection (IAI) in diabetic macular edema.

Methods: The eyes (n = 302) were randomized (1:2:3) to nesvacumab 3 mg + aflibercept 2 mg (LD combo), nesvacumab 6 mg + aflibercept 2 mg (HD combo), or IAI 2 mg at baseline, Weeks 4 and 8. LD combo continued every 8 weeks (q8w). HD combo was rerandomized at Week 12 to q8w or every 12 weeks (q12w); IAI to q8w, q12w, or HD combo q8w through Week 32.

Results: Week 12 best-corrected visual acuity gains for LD and HD combo versus IAI were 6.8, 8.5, and 8.8 letters; Week 36 changes were similar. Central subfield retinal thickness reductions at Week 12 were −169.4, −184.0, and −174.6 μm (nominal P = 0.0183, HD combo vs. IAI); Week 36 reductions for LD combo and HD combo q8w and q12w versus IAI were −210.4, −223.4, and −193.7 versus −61.9 μm (nominal P < 0.05). At Week 12, 13.3% and 21.3% versus 15.2% had ≥2-step Diabetic Retinopathy Severity Scale improvement (LD and HD combos vs. IAI) and 59.6% and 66.3% versus 53.7% had complete foveal center fluid resolution. Safety was comparable across groups.

Conclusion: Nesvacumab + aflibercept demonstrated no additional visual benefit over IAI. Anatomic improvements with HD combo may warrant further investigation.
antibodies can be individually optimized, ensuring a specific dose of each component is delivered. A bi-
specific antibody does not allow for flexibility to dose at different ratios, and binding is limited to a single
ligand, either VEGF or Ang-2, per molecule.

The Phase 2 Anti-vascularR Endothelial Growth Factor pLUs Anti-angiopoietin 2 in Fixed comBination therapY: Evaluation for the Treatment of Diabetic Macular Edema (RUBY) study compared the efficacy and safety of intravitreal nesvacumab + aflibercept combination therapy with IAI monotherapy in patients with DME.

Methods

Study Design

RUBY (NCT02712008) was a Phase 2, randomized, double-masked, multiple-dose, active-controlled, 36-week study investigating the efficacy and safety of intravitreal nesvacumab + aflibercept versus IAI monotherapy in patients with center-involved DME. RUBY was conducted at 53 sites in the United States between March 2016 and July 2017 in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. Approvals were obtained from institutional review board/ethics committee at each study site. Written informed consent was obtained from all patients before participation. Study investigators are listed in Supplemental Digital Content 1 (see Table, http://links.lww.com/IAE/B651).

Eligible patients were aged 18 years or older with Type 1 or 2 DM and center-involved DME (central subfield on spectral domain optical coherence tomography [SD-OCT]) and best-corrected visual acuity (BCVA) of 73 to 24 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/40–20/320 Snellen equivalent) in the study eye. Key exclusion criteria included evidence of macular edema because of any cause other than DME in either eye, anti-VEGF treatment within 12 weeks of screening, panretinal or macular laser photoocoagulation within 3 months of screening, or any history of stage ≥2 macular hole in the study eye and any prior treatment with angiopoietin inhibitors or intravenous anti-VEGF.

One eye per eligible patient was randomized (1:2:3) through an interactive voice/web response system (IXRS) to intravitreal low-dose nesvacumab 3 mg +

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The RUBY study was funded by Regeneron Pharmaceuticals, Inc., Tarrytown, New York, and Bayer HealthCare, Berlin, Germany. The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of the manuscript.

These data were presented at the American Society of Retina Specialists (ASRS), 36th Annual Meeting, Vancouver, BC, Canada, July 20 to 25, 2018; the Club Jules Gonin Congress, Jersey, Channel Islands, July 11 to 14, 2018; the Biennial Meeting of the World Ophthalmology Congress, Barcelona, Spain, June 16 to 19, 2018; and the Annual meeting of the Association for Research in Vision and Ophthalmology Congress, Honolulu, Hawaii, April 29 to May 3, 2018.

D. M. Brown: Consultant for and has received research funding from Adverum, Allergan, Chengdu Kanghong Biotechnology, Clearside Biomedical, Genentech/Roche, Heidelberg, Novartis, OHR, Regeneron Pharmaceuticals, Inc., RegenXBio, Santen, and Samsung. He is also a consultant for Bayer, Biotime, Kodiak, Optos, and Senju outside of the submitted work. D. S. Boyer: Consultant for Genentech, Regeneron Pharmaceuticals, Inc., Roche, Bayer, Allergan, Chengdu Kanghong Biotechnology, Clearside Biomedical, Boehringer Ingelheim, Kodiak, Novartis, Adverum, RegenXBio, and Graybug. K. Csaky: Consultant for Genentech, Roche, Allergan, Novartis, and Regeneron Pharmaceuticals, Inc. R. Vitti, L. Perlee, K. W. Chu, and Y. Cheng: Employees of and stockholders in Regeneron Pharmaceuticals, Inc. F. Asmus: Employee of Bayer AG at the time of the study. T. Schmelter: Employee of and stockholder in Bayer AG. O. Zeitz: Consultant and speaker for Allergan, Bayer, Boehringer Ingelheim, and Novartis; a consultant for Omeicos and Oculur; and receives research support from Bayer, Boehringer-Ingeheim, and Novartis. Employment with Bayer ended September 30, 2016. S. Leal: Employee of and stockholder in Bayer Consumer Care AG. J. S. Heier: Consultant for 4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Avicenda, Beaver-Visitec, Bionic Vision Technologies, DTx, Elexx, Galimedix, Genentech, Graybug, Gyroscope, Horizon Therapeutics, iRenix, Iveric, JCyte, Chengdu Kanghong Biotechnology, LensGen, NGM, Notal Vision, Novartis, Ocular Theraputix, OccuTerra, Oxurion, Palatin, Regeneron Pharmaceuticals, Inc., RegenXBio, Stealth, Thea, Verseon, Vinci, and Voyant and has received research grants from Aerpio, Aldeyra, Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hermera, Iveric, Jansen R&D, JCyte, Chengdu Kanghong Biotechnology, Kodiak, Novartis, Regeneron Pharmaceuticals, Inc., RegenXBio, and Stealth.

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afibercept 2 mg (LD combo), high-dose nesvacumab 6 mg + afibercept 2 mg (HD combo), or IAI 2 mg at baseline, Weeks 4 and 8 (Figure 1). Information regarding the nesvacumab + afibercept drug formulation is presented in Supplemental Digital Content 2 (see Text. http://links.lww.com/IAE/B651). LD combo treatment was continued every 8 weeks (q8w) from Week 16 to 32. The HD combo group was rerandomized (1:1) to HD combo q8w from Week 16 or every 12 weeks (q12w) from Week 20, until Week 32. The IAI group was rerandomized (1:1:1) to IAI q8w from Week 16, IAI q12w from Week 20, or HD combo q8w from Week 16 through Week 32. For rerandomization, patients were stratified by change in BCVA between baseline and Week 12 (<5, 5 to <10, 10 to <15, or ≥15 letters). To maintain masking, sham injections were administered at non-treatment visits. Last dose of study treatment was administered at Week 32 with a follow-up at Week 36.

Starting at Week 12, additional treatment with IAI 2 mg could be administered if, in the investigator’s judgment, the patient could not adhere to the protocol-specified dosing interval because of persistent or worsening disease. Patients requiring additional interim treatment continued to receive randomized treatment at subsequent visits and remained masked to dosing interval.

Outcome Measures

The primary efficacy end point was BCVA change from baseline in ETDRS letters at Weeks 12 and 36. Secondary efficacy end points were change from baseline in central subfield retinal thickness (CST) by SD-OCT and proportion of eyes with ≥2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) score from baseline at Weeks 12 and 36. Other efficacy end points included retinal fluid resolution (both subretinal and intraretinal) by SD-OCT and normalization of macular thickness (CST ≤300 μm) at Weeks 12 and 36. Both SPECTRALIS (Heidelberg Engineering, Inc, Franklin, MA) and CIRRUS (Carl Zeiss Meditec, Inc, Dublin, CA) were used for SD-OCT; the same SD-OCT machine was used for each patient for the study duration. The DRSS was graded by the Digital Angiography Reading Center (DARC, New York, NY) using ETDRS seven-standard fields on fundus photography. Overall safety was assessed by adverse events (AEs), vital signs, electrocardiograms, and laboratory tests. Ocular safety was assessed by ophthalmic examinations, including intraocular pressure measurements, slit-lamp examination, and indirect ophthalmoscopy. BCVA, SD-OCT, and safety evaluations were performed at each study visit, which occurred every 4 weeks.

Statistical Analysis

Assuming a normal distribution for change in BCVA score from baseline to Week 12, a mean between-group difference of 5 (standard deviation [SD], 9.5) letters, a dropout rate of 20%, and a sample size of 50, 100, and 150 patients in the LD combo, HD combo, and IAI groups, respectively, was needed to provide ≥80% probability that the 95% confidence interval (CI) for treatment difference would exclude zero for one of the combo groups. The sample size calculation was computed using the two-group Satterthwaite11 t test of unequal sample size of ratio 1:2:3 by clinical assumption with equal variances using nQuery Advisor 7.0 software (Statsols, Cork, Ireland).

The full analysis set, which included all randomized patients who received any study treatment and had both a baseline and at least one postbaseline measurement of BCVA, was used to analyze all efficacy variables through Week 12. The secondary randomization set included all patients in the full analysis set who completed the study through Week 12, had received any study treatment after either Week 12 (patients originally randomized to LD combo) or rerandomization (patients originally randomized to HD combo or IAI monotherapy), and had a Week 12 and at least one post-Week 16 measurement of BCVA; the secondary randomization set was used to analyze all efficacy variables through Week 36. The assessment of outcomes from Week 12 through Week 36 included qualitative assessment of effect over these visits to determine the overall interpretation of benefit.

The primary efficacy end point at Week 12 was analyzed using an analysis of covariance (ANCOVA) model, with treatment as fixed effect and baseline BCVA score as covariate. Least-square (LS) mean and two-sided 95% CI of the difference (LD or HD combo minus IAI) were calculated. After Week 12, primary efficacy end point was analyzed by ANCOVA model, with baseline BCVA score as covariate and treatment group and BCVA stratification variable as fixed factors. Change from baseline in CST was analyzed as for the primary efficacy end point. Proportions of eyes with a ≥2-step improvement in DRSS score, resolution of retinal fluid, and normalization of macular thickness were summarized using descriptive statistics. For categorical variables, nominal P values for comparison of either LD or HD combo with IAI were calculated using the two-sided Cochran–Mantel–Haenszel test; after Week 12, calculations were adjusted by BCVA stratification variable. No adjustment for multiplicity testing was made; all reported P values are nominal. For all efficacy analyses, missing data were imputed using last observation carried forward.
The safety analysis set, which included all patients who received at least one dose of any study drug, was used to analyze safety through Week 36. The secondary safety randomization set included all patients who had completed the study through Week 12 and had received any study treatment after either Week 12 (patients originally randomized to LD combo) or rerandomization (patients originally randomized to HD combo or IAI monotherapy). Safety data were summarized using descriptive statistics.

**Results**

**Patients**

In total, 302 eyes were randomized to LD combo (n = 50), HD combo (n = 100), or IAI (n = 152). Patient disposition details are in Supplemental Digital Content 3 (see Figure, http://links.lww.com/IAE/B651). Overall, 92.0% to 97.4% of patients completed the first 12 weeks of this study. Baseline characteristics were generally balanced across all treatment groups (Table 1). At baseline, the mean age across groups was 59.5 to 62.4 years, most participants had type 2 DM (93.9%), the mean hemoglobin A1c was 7.8% to 8.5%, and the mean duration of DM was 15.8 to 17.6 years. The mean BCVA was 57.7 to 60.6 letters, and the mean CST was 484.2 to 520.1 μm. Approximately half the patients had moderately severe to severe nonproliferative diabetic retinopathy (DRSS score 47–53) at baseline.

Baseline characteristics in the secondary randomization set are summarized in Supplemental Digital Content 4 (see Table, http://links.lww.com/IAE/B651). The rates of completion at Week 36 across the six treatment groups in the secondary randomization set were 89.6% to 100.0%.

Over the 32-week treatment period, the mean (SD) number of intravitreal injections administered was 7.2 (0.92), LD combo q8w; 5.9 (0.35), HD combo q8w; 5.1 (0.58), HD combo q12w; 5.9 (0.45), IAI q8w; 4.8 (0.63), IAI q12w; and 5.8 (0.44), IAI monotherapy → HD combo q8w. A programming error in the IXRS system affected the dosing schedules for LD combo q8w and HD combo q12w, resulting in a reduced proportion of eyes being dosed per protocol after rerandomization (patients either received additional doses or doses were not timed as intended). Approximately 10% and 50% of eyes were dosed per protocol with LD combo q8w and HD combo q12w, respectively. The treatment schedules for all other treatment groups were unaffected. Details regarding this operational error and patients receiving additional treatment are detailed in Supplemental Digital Content 5 (see Text, http://links.lww.com/IAE/B651).

**Efficacy**

Mean (SD) changes in BCVA from baseline to Week 12 for LD and HD combo versus IAI groups were 6.8 (7.30) and 8.5 (6.89) versus 8.8 (9.71) letters, respectively, with LS mean differences between LD combo versus IAI of −2.09 letters (95% CI −4.84, 0.67; nominal P = 0.1368) and between HD combo versus IAI of 0.04 letters (95% CI −2.10, 2.18; nominal P = 0.9716; Figure 2A); changes were similar at Week 36 (Figure 3A).
Mean (SD) changes in CST from baseline to Week 12 were $-169.4$ (155.86) and $-184.0$ (143.69) versus $-174.6$ (160.36) $\mu m$, respectively (nominal $P = 0.1105$, LD combo vs. IAI; nominal $P = 0.0183$, HD combo vs. IAI; Figure 2B); changes at Week 36 for LD combo and HD combo q8w and q12w versus IAI were $-210.4$, $-223.4$, and $-193.7$ versus $-61.9$ $\mu m$, respectively (all nominal $P < 0.05$ vs. IAI; Figure 3B).

The proportions of eyes with complete resolution of fluid at the foveal center at Week 12 in the LD and HD combo versus IAI groups were 59.6% and 66.3% versus 53.7% (nominal $P = 0.0489$, HD combo vs. IAI; Figure 2C; proportions at Week 36 are shown in Figure 3C).

The proportion of eyes with normalization of macular thickness (CST $\leq 300$ $\mu m$) at Week 12 in the LD and HD combo versus IAI groups was 40.4% and 57.6% versus 35.3%, respectively (nominal $P = 0.0006$, HD combo vs. IAI; Figure 2D; Week 36 results are shown in Figure 3D).

The proportion of eyes with a $\geq$2-step improvement in DRSS score at Week 12 in the LD and HD combo versus IAI groups was 13.3% and 21.3% versus 15.2% (Figure 4A); proportions were generally greater at Week 36 across all groups (Figure 4B).

### Safety

Throughout the 36-week study duration, 30.0% (15/50), 31.0% (31/100), and 25.7% (39/152) of patients in the LD combo, HD combo, and IAI monotherapy groups, respectively, experienced one or more ocular AE in the study eye, most commonly conjunctival hemorrhage (LD combo, 8.0% [4/50];

#### Table 1. Baseline Characteristics by Original Treatment Randomization

|                          | Intravitreal Nesvacumab 3 mg + Aflibercept 2 mg (LD Combo) (n = 47) | Intravitreal Nesvacumab 6 mg + Aflibercept 2 mg (HD Combo) (n = 99) | IAI Monotherapy 2 mg (n = 150) | Total (N = 296) |
|--------------------------|------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------|-----------------|
| Mean (SD) age, years     | 62.1 (8.90)                                                      | 62.4 (10.37)                                                     | 59.5 (10.24)                  | 60.9 (10.15)    |
| Female, n (%)            | 20 (42.6)                                                        | 49 (49.5)                                                        | 67 (44.7)                     | 136 (45.9)      |
| Race, n (%)              |                                                                  |                                                                  |                               |                 |
| White                    | 35 (74.5)                                                        | 86 (86.9)                                                        | 119 (79.3)                    | 240 (81.1)      |
| Black/African American   | 11 (23.4)                                                        | 8 (8.1)                                                          | 19 (12.7)                     | 38 (12.8)       |
| Asian                    | 0                                                                | 2 (2.0)                                                          | 4 (2.7)                       | 6 (2.0)         |
| Other*                   | 1 (2.1)                                                          | 1 (1.0)                                                          | 6 (4.0)                       | 8 (2.7)         |
| Not reported             | 0                                                                | 2 (2.0)                                                          | 2 (1.3)                       | 4 (1.4)         |
| Mean (SD) BMI, kg/m^2    | 33.0 (7.46)                                                      | 32.0 (6.58)                                                      | 32.8 (7.64)                   | 32.6 (7.26)     |
| Diabetes type, n (%)     |                                                                  |                                                                  |                               |                 |
| Type 1                   | 2 (4.3)                                                          | 5 (5.1)                                                          | 11 (7.3)                      | 18 (6.1)        |
| Type 2                   | 45 (95.7)                                                        | 94 (94.9)                                                        | 139 (92.7)                    | 278 (93.9)      |
| Mean (SD) duration of diabetes, years | 17.6 (10.93) | 17.5 (11.22) | 15.8 (10.69) | 16.7 (10.90) |
| Mean (SD) HbA1c, %       | 8.5 (1.86)                                                        | 7.8 (1.61)                                                        | 8.1 (1.86)                    | 8.0 (1.79)      |
| DRSS score, n (%)        |                                                                  |                                                                  |                               |                 |
| $\leq$43                 | 20 (42.6)                                                        | 32 (32.3)                                                        | 55 (36.7)                     | 107 (36.1)      |
| 47-53                    | 22 (46.8)                                                        | 53 (53.5)                                                        | 81 (54.0)                     | 156 (52.7)      |
| $\geq$61 (PDR)           | 5 (10.6)                                                         | 13 (13.1)                                                        | 13 (8.7)                      | 31 (10.5)       |
| Missing                  | 0                                                                | 1 (1.0)                                                          | 1 (0.7)                       | 2 (0.7)         |
| Prior treatment for DME/DR, $^\dagger$ n (%) | 27 (57.4) | 40 (40.4) | 58 (38.7) | 125 (42.2) |
| Prior focal or grid laser, n (%) | 19 (40.4) | 27 (27.3) | 36 (24.0) | 82 (27.7) |
| Prior intravitreal anti-VEGF, n (%) | 12 (25.5) | 28 (28.3) | 27 (18.0) | 67 (22.6) |
| Prior intravitreal steroids, n (%) | 4 (8.5) | 7 (7.1) | 7 (4.7) | 18 (6.1) |
| Mean (SD) BCVA in the study eye, letters | 57.7 (11.13) | 60.6 (11.11) | 58.7 (10.78) | 59.2 (10.96) |
| Mean (SD) CST, $\mu m$   | 484.2 (152.78)                                                   | 497.8 (151.77)                                                   | 520.1 (151.80)                | 507.0 (151.80) |

Data shown are for the full analysis set, which included all randomized patients who received any study treatment, and had both a baseline and at least one postbaseline measurement of BCVA.

$^*$Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and individuals who self-identified as “other.”

$^\dagger$Patients could have received more than one treatment for DME/DR.

BCVA, best-corrected visual acuity; BMI, body mass index; CST, central subfield retinal thickness; DME, diabetic macular edema; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; HbA1c, glycated hemoglobin; PDR, proliferative diabetic retinopathy; SD, standard deviation; VEGF, vascular endothelial growth factor.
HD combo, 2.0% [2/100]; and IAI monotherapy, 7.2% [11/152]) (Table 2). Two serious ocular AEs were reported, both in the HD combo group (iritocyclitis, n = 1 and retinal artery occlusion, n = 1); both were considered related to study treatment.

Serious nonocular AEs occurred in 12.0% (6/50), 17.0% (17/100), and 20.4% (31/152) of patients in the LD combo, HD combo, and IAI groups, respectively (Table 2). The only serious nonocular AE to occur in ≥3% of patients in any group was congestive cardiac failure (HD combo, 3.0% [3/100] and IAI, 2.0% [3/152]). Antiplatelet Trialists’ Collaboration-defined arterial thromboembolic events (myocardial infarction, stroke, or death from vascular/unknown causes) occurred in 10.0% (5/50), 2.0% (2/100), and 2.0% (3/152) of patients in the LD combo, HD combo, and IAI groups, respectively. Nine patients died during this study (LD combo, n = 5 and IAI, n = 4); no death was considered related to study treatment. Note that safety assessment in the IAI group included 49 patients treated with HD combo after rerandomization. Secondary safety randomization set data are in the Supplemental Digital Content 6 (see Table, http://links.lww.com/IAE/B651).

**Discussion**

In the primary efficacy analysis of this exploratory Phase 2 study, dual inhibition of Ang2 and VEGF with a fixed-dose combination of intravitreal nesvacumab + aflibercept (either LD or HD) in patients with DME did not lead to improvements in the mean BCVA score at Week 12 or 36 relative to IAI monotherapy. Nesvacumab + aflibercept produced similar outcomes for patients with neovascular age-related macular degeneration (AMD), which was studied in the Anti-angiOpoetin 2 Plus Anti-vascular eNdothelial Growth
Factor as a therapy for Neovascular Age Related Macular Degeneration: Evaluation of a fixed Combination Intravitreal Injection (ONYX) trial. IAI monotherapy demonstrated clinically meaningful improvements in both visual and anatomic outcomes consistent with those reported previously.

Despite similar BCVA outcomes, the combination of Ang2 and VEGF blockade demonstrated improved anatomic outcomes, with some improvements achieving nominal statistical significance. Reduction of DME, based on CST changes from baseline, was better for HD combo than IAI, with nominally significant P values. Greater proportions of eyes had complete resolution of retinal fluid in the foveal center and normalization of CST in the combination treatment groups compared with IAI, particularly for the HD combo. Although changes in fluid resolution and CST demonstrate additional anatomic benefit from combination therapy, this did not translate into nominally statistically significant BCVA improvements during the 36-week study. In addition, improvements in these parameters were not observed in the IAI monotherapy group relative to the IAI q8w group. For ≥2-step improvement in DRSS score, nominal statistical significance was not seen for any combination group when compared with IAI monotherapy.

Although Ang2 is upregulated in patients with DME and has been shown to play a role in pathological neovascularization, VEGF seems to be the key cytokine in this process, hence the substantial clinical efficacy demonstrated with anti-VEGF agents, including IAI. In addition, the mechanism by which VEGF induces neovascularization and leakage is better

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**Fig. 3.** Visual and anatomic outcomes through Week 36 by treatment assignment at Week 12. 

A. The absolute mean BCVA score from baseline through Week 36. 
B. The absolute mean CST from baseline through Week 36. 
C. Proportion of eyes with complete resolution of retinal fluid at Week 36. 
D. Proportion of eyes with normalization of macular thickness (CST ≤ 300 μm) at Week 36. 

Data shown are for the secondary randomization set (last observation carried forward). Nominal P values for continuous variables were based on an ANCOVA model, with baseline measurement as a covariate and treatment group and BCVA stratification variable as fixed factors. Nominal P values for categorical variables were calculated using the two-sided Cochran–Mantel–Haenszel test adjusted by BCVA stratification variable. ANCOVA, analysis of covariance; BCVA, best-corrected visual acuity; CST, central subfield thickness; HD combo, high-dose combination nesvacumab 6 mg + aflibercept 2 mg; IAI, intravitreal aflibercept injection; LD combo, low-dose combination nesvacumab 3 mg + aflibercept 2 mg; q8w, every 8 weeks; q12w, every 12 weeks; SD, standard deviation.
understood compared with Ang2 which situationally acts as both an agonist and antagonist to its receptor, tyrosine kinase (Tie-2).\textsuperscript{14} In vitreous samples collected from patients newly diagnosed with neovascular AMD, retinal vein occlusion, diabetic retinopathy (DR), or proliferative DR, Ang2 levels were elevated compared with samples from patients with macular hole.\textsuperscript{15} Levels of Ang2 in patients with DR were the most elevated relative to neovascular AMD and retinal vein occlusion, indicating a potential role for Ang2 inhibition in DR and DME. However, because VEGF inhibition is likely to be responsible for most of the observed benefit, it is possible that the RUBY study was not sufficiently powered to detect a difference attributable to the inhibition of Ang2.

In contrast to RUBY, the BOULEVARD study (NCT02699450) of faricimab\textsuperscript{10} demonstrated significantly greater improvements versus 0.5 mg ranibizumab in the mean BCVA score from baseline at Week 24 (adjusted mean difference +3.6 letters; 80% CI 1.53, 5.61; \(P = 0.03\)) in treatment-naive patients with DME,\textsuperscript{10} with greater central retinal thickness reductions and greater proportions achieving ≥2-step DRSS improvement in both treatment-naive patients and those previously treated with anti-VEGF.\textsuperscript{10} Approximately 40% of patients in RUBY were previously treated for DME. Differences in results between BOULEVARD and RUBY may be attributable to differences in distribution of treatment-naive patients across treatment groups and variability in BCVA and other characteristics. Because faricimab represents a higher molar dose of anti-VEGF (~5 times higher than 0.5 mg ranibizumab), the effect seen in BOULEVARD could simply be due to higher concentration of anti-VEGF and not to the combined inhibition. Furthermore, although patients in BOULEVARD were randomized to 0.3 mg ranibizumab as active comparator, the comparator in RUBY...
was aflibercept which has demonstrated superiority versus 0.3 mg ranibizumab.16

Overall, the ocular and systemic safety profile of both nesvacumab + aflibercept combination therapy groups were consistent with that of IAI monotherapy,1,2 with no new or unexpected safety signals for IAI observed.

This study’s limitations include its relatively small sample size, particularly after rerandomization at Week 12. Because it was an exploratory study, there was no correction for multiplicity and all P values were considered nominal. Dosing errors affecting the LD combo q8w and HD combo q12w groups limited interpretation of any dosing interval benefit, although the mean number of doses received in those groups was not very different from the number intended. It is possible that further improvement in anatomic end points, particularly in the IAI monotherapy → HD combo q8w group, would have been seen with a study design tailored to demonstrate anatomic improvement, such as by DRSS score, with continued treatment and a longer follow-up. With a longer follow-up, the improvement in anatomy may have resulted in improved visual acuity.

In conclusion, the RUBY study did not show additional benefits in vision with intravitreal nesvacumab + aflibercept over IAI monotherapy in patients with DME. However, there were some indications of additional anatomic benefit with combination therapy particularly in OCT-measured end points, including reduction in CST, patients with resolution of fluid in the foveal center, and patients achieving macular thickness ≤300 μm and a trend toward more patients demonstrating improvement in DRSS scores. The indication of positive anatomic effects may warrant further investigation of the role of anti-Ang2 agents in combination with anti-VEGF therapy.

Key words: vascular endothelial growth factor, diabetic macular edema, prospective study, randomized controlled trial, investigational clinical trials.

Acknowledgments

The authors thank the study investigators and patients involved in this study. Medical writing support was provided by Tiffany DeSimone, PhD, and Nila Bhana, MSc, of Prime (Knutsford, United Kingdom), in accordance with the Good Publication Practice guidelines (Link), and funded by Regeneron Pharmaceuticals, Inc. The authors were involved in the study design and collection, analysis, and interpretation of data. All authors had full access to all the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.
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